OSTEOMYELITIS

CHI Formulary Indication Review

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Council of Health Insurance

INDICATION UPDATE

ADDENDUM – November 2023

To the CHI Original Osteomyelitis-Issued March 2020

Contents

Related Documents

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Abbreviations

AHO	Acute Hematogenous Osteomyelitis
CA	Community-Acquired
CADTH	Canadian Agency for Drugs and Technologies in Health
CHI	Council of Health Insurance
CNS	Coagulase-Negative Staphylococci
CPG	Clinical Practice Guideline
CRP	C-Reactive Protein
DAIR	Debridement, Antibiotics, and Implant Retention
EMA	European Medicines Agency
ESBL	Extended-Spectrum Beta-Lactamase
FDA	Food and Drug Administration
GNB	Gram-Negative Bacteria
GR	Grade of Recommendation
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HAS	Haute Autorité de Santé (French National Authority for Health)
HTA	Health Technology Assessment
IDF	CHI Drug Formulary
IDSA	Infectious Diseases Society of America
IM	Intramuscular
IM	Intramuscular
IQWIG	Institute for Quality and Efficiency in Health Care (Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen in German)
IV	Intravenous
IV	Intravenous
LE	Levels of Evidence
MIC	Minimum Inhibitory Concentration
MLSb	Macrolide, Lincosamide, Streptogramin B
MRSA	Methicillin-Resistant Staphylococcus Aureus

MSSA	Methicillin-Sensitive Staphylococcus Aureus
N/A	Not Applicable
NICE	National Institute for Health and Care Excellence
NTM	Non-Tuberculous Mycobacteria
OAI	Osteoarticular Infection
OPAT	Outpatient Parenteral Antibiotic Therapy
PBAC	Pharmaceutical Benefits Advisory Committee
PCR	Polymerase Chain Reaction
PIDS	Pediatric Infectious Diseases Society
PIOC	Positive Intraoperative Cultures
PJI	Prosthetic Joint Infection
PO	Per Os
SA	Septic Arthritis
SAT	Suppressive Antibiotics Therapy
SEIMC	Sociedad Española de Enfermedades Infecciosas y Microbiología Clínica (Spanish Society of Infectious Diseases and Clinical Microbiology)
SFDA	Saudi Food and Drug Authority
SFR	Société Française de Rhumatologie (French Society of Rheumatology)
SNC	Staphylococcus Non-Cultivable
SPILF	Société de Pathologie Infectieuse de Langue Française (French Infectious Diseases Society)
US	United States

Executive Summary

Osteomyelitis is a condition characterized by inflammation or swelling of bone tissue, typically arising from an infection. This condition can emerge from a bacterial bloodstream infection, also known as bacteremia or sepsis, which then spreads to the bone. The predominant source of the blood infection is typically *Staphylococcus aureus*, although it may also be triggered by different types of bacteria or fungal organisms. Osteomyelitis may also result from infections in close proximity, stemming from traumatic injuries, repeated medication injections, surgical procedures, or the use of prosthetic devices. Additionally, individuals with diabetes who develop foot ulcers are at an elevated risk. In all these scenarios, the infecting organism gains direct access to the affected bone[1].

Smokers, people with chronic diseases or weakened immune systems, and individuals undergoing immunosuppressive treatments like chemotherapy or steroid therapy, are more susceptible to developing osteomyelitis. The onset of osteomyelitis can be acute (sudden, gradual, and mild), or it can become a chronic issue, depending on the source of the infection[1].

Most common symptoms of osteomyelitis are fever, pain, redness or swelling in the affected area, and difficulty in movement, bearing weight or walking. Complications may include bone death, septic arthritis, impaired growth, and even skin cancer[2].

In the pediatric population, the most common manifestation is acute hematogenous osteomyelitis (AHO). It is particularly common in children < 5 years of age and typically affects the metaphysis because of the rich but slow blood flow of the growing bone[3].

The overall incidence of osteomyelitis in the United States (US) is mostly unknown, but reports show it to be as high as 1 in 675 US hospital admissions each year or about 50,000 cases annually. Other studies show an overall incidence of osteomyelitis of 21.8 cases per 100,000 person-years[4].

The management of this disease is costly, hence, the importance of early detection to prevent complications. Mainstay treatment of osteomyelitis include antibiotic therapy, surgery (debridement, draining or amputation), and supportive care.

CHI issued Osteomyelitis clinical guidance after thorough review of renowned international and national clinical guidelines in March 2020. Updating clinical practice guidelines (CPGs) is a crucial process for maintaining the validity of recommendations.

This report functions as an addendum to the prior CHI Osteomyelitis clinical guidance and seeks to offer guidance for the effective management of Osteomyelitis. It provides an **update on the Osteomyelitis Guidelines** for CHI Formulary with the ultimate objective of updating the IDF (CHI Drug Formulary)

while addressing **the most updated best available clinical and economic evidence related to drug therapies.**

Main triggers for the update are summarized, being **the issuance of the new guidelines that are added to the report**, the Clinical Practice Guideline by the Pediatric Infectious Diseases Society (PIDS) and the Infectious Diseases Society of America (IDSA): **2021** Guideline on Diagnosis and Management of Acute Hematogenous Osteomyelitis in Pediatrics, SPILF (French Society of Infectious Pathology) update on bacterial arthritis in adults and children **2023**, and the management of prosthetic joint infections, clinical practice guidelines by the Spanish Society of Infectious Diseases and Clinical Microbiology (SEIMC) **2017.**

Guidelines on the management of vertebral osteomyelitis were included in the previous CHI report and no updates have been issued since. The main treatment options for osteoarticular manifestation of human brucellosis are mentioned briefly where applicable; however, a detailed review of brucellosis is undertaken in a separate report. Finally, options for the treatment of septic arthritis, meaning an infection in the joint fluid and joint tissues were included.

After carefully examining clinical guidelines and reviewing the SFDA drug list, it is important to note that it is recommended to delist **Benzylpenicillin and Doripenem** from the CHI formulary. Additionally, there have been **no newly approved drugs** for the treatment of Osteomyelitis, however, there have been **updates** regarding certain previously mentioned drugs in terms of drug information and prescribing edits since March 2020.

All recommendations are well supported by reference guidelines, Grade of Recommendation (GoR), Level of Evidence (LoE) and Strength of Agreement (SoA) in all tables reflecting specific drug classes' role in the therapeutic management of Osteomyelitis.

Below is a table summarizing the major changes based on the different Osteomyelitis treatment guidelines used to issue this report:

Table 1. General Recommendations for the Management of Osteomyelitis

Management of Osteomyelitis		
General Recommendations	**Level of Evidence/ Grade of Recommendation**	**Reference**
Pediatric patients		
In children with suspected acute hematogenous osteomyelitis (AHO), empiric antimicrobial therapy	Strong recommendation,	PIDS/IDSA 2021[5]

active against *Staphylococcus aureus* is recommended.	moderate certainty of evidence	
Antimicrobials with activity against community-acquired methicillin-resistant *S. aureus* (CA-MRSA) should be considered based on local susceptibility data and patient history with regard to previous CA-MRSA infections and/or colonization.	Not graded	PIDS/IDSA 2021[5]
In the presence of a clinical presentation, physical examination, exposure history, or other risk factors that either are inconsistent with *S. aureus* infection or suggest need for coverage for other organisms, additional empiric antimicrobial coverage for pathogens other than *S. aureus* may be warranted (such as younger age for *Kingella kingae* or children with underlying hemoglobinopathies who have increased risk for *Salmonella* spp. infection).	Not graded	PIDS/IDSA 2021[5]
In children with suspected AHO without an identified bacterial cause, selection of a definitive antibiotic regimen should be based on the principles of selecting an effective agent based on the most likely causative organism(s), with a spectrum comparable to that on which the patient demonstrated clinical and laboratory improvement, and with the lowest adverse effect profile and most favorable host tolerance.	Good Practice Statement	PIDS/IDSA 2021[5]
For children with suspected or documented AHO who respond to initial intravenous antibiotic therapy, we recommend transition to an oral antibiotic regimen rather than outpatient parenteral antibiotic therapy (OPAT) when an appropriate (active against the confirmed or presumed pathogen(s)) and well-tolerated oral antibiotic option is available.	Strong recommendation, low certainty of evidence	PIDS/IDSA 2021[5]
In children with AHO presumed or proven to be caused by *S. aureus* who have had an uncomplicated course and responded to initial therapy, we suggest a 3- to 4-week duration of antibiotics rather than a longer course.	Conditional recommendation, very low certainty of evidence	PIDS/IDSA 2021[5]
For children either experiencing primary treatment	Good practice	PIDS/IDSA

failure or early or late recurrence of AHO: • Clinicians should assess the adequacy of the antimicrobial regimen (spectrum of activity, dosage, and penetration to the site of infection, and adherence) before deciding on the need to broaden the spectrum or to restart antimicrobials. • Clinicians should reassess the need for surgical intervention for therapeutic and/or diagnostic purposes.	statement	2021[5]
• 1st or 2nd-generation or IV amoxicillin/clavulanic acid at 3 months of age (oxacillin or cloxacillin possible from 4 years). • If severe sepsis and/or toxic shock: add clindamycin or linezolid. Total treatment duration is 2 weeks.	Not graded	SPILF 2023[6]
Adult patients		
Treatment durations: • *S. aureus*, and enterobacterials: 6 weeks • *Streptococcus* spp.: 4 weeks • *Neisseria gonorrhoeae*: 7 days • Early arthritis (evolution < 4 weeks), by direct inoculation of the small joints of the hands, following proper surgical hand washing: 14 days in the absence of osteolysis	Not graded	SPILF 2023[6]
Initial methicillin-sensitive *Staphylococcus aureus* (MSSA) treatment: IV cefazolin or IV penicillin M (cloxacillin, oxacillin), is the recommended initial treatment of MSSA arthritis.	Not graded	SPILF 2023[6]
MSSA oral relay: • The molecule for oral relay is chosen according to antimicrobial susceptibility. • If monotherapy, clindamycin is proposed as first-line treatment in the event of sensitivity without inducible Macrolide, Lincosamide, Streptogramin B (MLSb) phenotype, meaning a strain sensitive to clindamycin and erythromycin. • Without complications, total treatment	Not graded	SPILF 2023[6]

duration is six weeks.		
MRSA treatment: • Daptomycin in monotherapy is recommended as first-line initial treatment, with vancomycin or teicoplanin as possible alternatives. • Without complications, total treatment duration is six weeks.	Not graded	SPILF 2023[6]
Pseudomonas treatment: • Initial intravenous (IV) treatment on microbiological documentation • Initial antibiotic treatment: ceftazidime or cefepime on *Pseudomonas aeruginosa*-infected native joint • Oral relay of antibiotic treatment of septic arthritis on Pseudomonas aeruginosa-affected native joint only once the infection is under control and after at least 14 days of treatment by intravenous beta-lactams. The first-line molecule is ciprofloxacin.	Not graded	SPILF 2023[6]
Prosthetic joint infections		
The main medical and surgical strategies to be considered in a patient with prosthetic joint infection (PJI) are: • Attempted eradication with implant retention and antibiotics (debridement, antibiotics, and implant retention or DAIR). • Attempted eradication with implant removal and antibiotics: o With prosthesis replacement (in a 1-step or a 2-step exchange procedure). o Without prosthesis replacement (arthrodesis or resection arthroplasty). • Implant retention and long-term suppressive antibiotics (SAT), without attempted eradication	Not graded	SEIMC 2017[7]
• For acute staphylococcal PJI managed with rifampin and levofloxacin, an 8-week schedule of treatment after debridement appears sufficient for most patients (B-I). • For PJI caused by other microorganisms	-	SEIMC 2017[7]

treated with antibiotics with good activity against biofilm-embedded bacteria (i.e., ciprofloxacin for PJI caused by GNB, 8 weeks is also a reasonable duration) (B-III). • In other clinical scenarios, the most appropriate duration of treatment remains uncertain. A variable period between 8 and 12 weeks may be adequate (B-III).		
Staphylococcal infections: • Initial treatment (antibiotics against planktonic bacteria): o Methicillin-susceptible strains: cloxacillin (or cefazolin) (B-II), or cloxacillin + daptomycin (C-III). o Methicillin-resistant strains: daptomycin + cloxacillin, or daptomycin + fosfomycin (C-III), or vancomycin (B-II). Streptococcal infections: • For initial treatment (planktonic phase): penicillin or ceftriaxone (B-II).	-	SEIMC 2017[7]

At the end of the report, a **key recommendation synthesis section** is added highlighting the latest updates in **Osteomyelitis clinical and therapeutic management.** Additionally, **appendices** are provided for treatment algorithms and further information on the topic.

Section 1.0 Summary of Reviewed Clinical Guidelines & Evidence

This section is divided into two parts: the first includes recommendations from **updated versions of guidelines** mentioned in the previous CHI Osteomyelitis report, while the second includes **newly added guidelines** that have helped generate this report.

1.1 Revised Guidelines

This section contains the **updated versions** of the guidelines mentioned in the March 2020 CHI Osteomyelitis Report and the corresponding recommendations:

Table 2. Guidelines Requiring Revision

Guidelines Requiring Revision	
Old Versions	**Updated versions**
1.1.1. **Infectious Diseases Society of America (IDSA)** Clinical Practice Guidelines for the Diagnosis and Treatment of Native Vertebral Osteomyelitis in adults **2015**	N/A*
1.1.2. Diagnosis and Management of Prosthetic Joint Infection: Clinical Practice Guidelines by the **Infectious Diseases Society of America [2013]**	N/A*

*****: *No updated versions available*

1.2 Additional Guidelines

This part includes the added guidelines to the previous CHI Osteomyelitis report, along with their recommendations.

Table 3. List of Additional Guidelines

Additional Guidelines
Clinical Practice Guideline by the **Pediatric Infectious Diseases Society and the Infectious Diseases Society of America: 2021** Guideline on Diagnosis and Management of Acute Hematogenous Osteomyelitis in Pediatrics
SPILF (French Society of Infectious Pathology) Update on Bacterial Arthritis in Adults and Children (**2023**)
Management of prosthetic joint infections. Clinical practice guidelines **by the**

Spanish Society of Infectious Diseases and Clinical Microbiology (SEIMC) 2017

1.2.1 Pediatric Infectious Diseases Society (PIDS)/Infectious Diseases Society of America (IDSA): Guideline on Diagnosis and Management of Acute Hematogenous Osteomyelitis in Pediatrics (2021)

This clinical practice guideline for the diagnosis and treatment of acute hematogenous osteomyelitis (AHO) in children was developed by a multidisciplinary panel representing Pediatric Infectious Diseases Society (PIDS) and the Infectious Diseases Society of America (IDSA). This guideline is intended for use by healthcare professionals who care for children with AHO, including specialists in pediatric infectious diseases, orthopedics, emergency care physicians, hospitalists, and any clinicians and healthcare providers caring for these patients. A standardized methodology for rating the certainty of the evidence and strength of recommendation using the GRADE (Grading of Recommendations Assessment, Development and Evaluation) approach was followed[5].

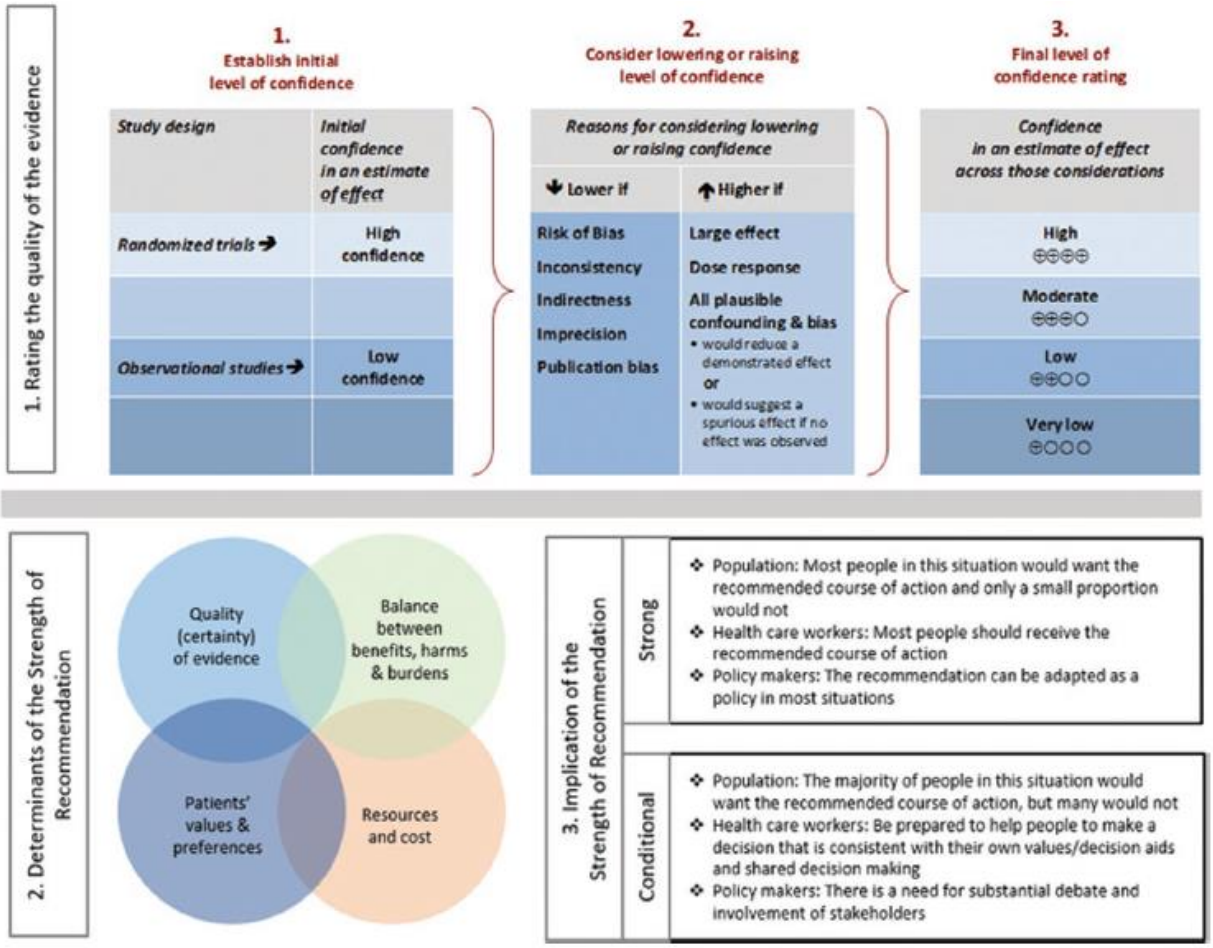


Figure 1. *GRADE Approach – Rating the Quality of Evidence and Strength of Recommendations (Retrieved from the PIDS/IDSA 2021 Guideline)*

The main recommendations are summarized below.

Table 4. Characteristics of Uncomplicated vs Complicated Osteomyelitis (Adapted from the PIDS/IDSA 2021 Guideline)

Characteristic	Uncomplicated	Complicated
Sites of infection	Single bone	• 2 or more bones involved • Additional soft tissue sites of infection beyond the bone (e.g., muscle [myositis or pyomyositis], pneumonia, and liver abscess)
Clinical response to medical and surgical treatment	Rapid (within 3-5 days), including signs of sepsis or septic shock	• Slow, prolonged response, or lack of clinical response • Need for more than 1 surgery for source control
Course of bacteremia when present	Rapid resolution of bacteremia (serial blood cultures become negative when obtained within 1-2 days after the initiation of therapy and source control)	Prolonged bacteremia (3 or more days), suggestive of uncontrolled infection/distant site(s) of infection
Acute sequelae of infection	None	• Venous thrombosis or septic thrombophlebitis • Endocarditis
Late sequelae of infection	No findings that suggest risk of physis injury or other short- or long-term osteoarticular sequelae of infection	• Findings concerning for physeal injury with potential impacts on bone growth with long-term sequelae

		• Presence of or concern for pathologic fracture

The set of criteria detailed in the table above is consensus-based with a primary focus on clinical findings and course. It may be reasonable to include additional laboratory tests such as the serum C-reactive protein (CRP) in making a determination of an uncomplicated vs complicated course. Concepts such as:

- Rapid fall of the CRP concentration within 48 h of initiation of treatment

  or

- A 50% or more decline from peak CRP concentration within 3 to 5 d of admission or first surgical debridement may be considered.
- **Noninvasive diagnostic laboratory tests**
- In children with suspected AHO, we recommend performing blood culture prior to the administration of antimicrobial therapy (strong recommendation and moderate certainty of evidence).
- In children with suspected AHO, we suggest performing a serum C-reactive protein (CRP) on initial evaluation (conditional recommendation and very low certainty of evidence). Comment: Serum CRP has a low accuracy to establish the diagnosis of AHO, but in situations where AHO is confirmed, the serum CRP performed on initial evaluation can serve as the baseline value for sequential monitoring.
- In children with suspected AHO, we suggest against using serum procalcitonin (PCT) (conditional recommendation and low certainty of evidence).

Imaging studies

- In children with suspected AHO, we recommend obtaining plain radiography of the potentially infected bone(s) rather than not performing plain radiographs (strong recommendation and moderate certainty of evidence).

  Comment:

  Despite the low sensitivity of plain radiography for detecting AHO on initial presentation, other important diagnoses may be ruled out by this simple, quick, safe, and relatively inexpensive imaging test.
- In children with suspected AHO requiring further imaging studies to confirm the diagnosis, we suggest magnetic resonance imaging (MRI) rather than

scintigraphy (bone scan), computerized tomographic (CT) scan, or ultrasound (US) (conditional recommendation and very low certainty of evidence).

Comment:

For children suspected to have uncomplicated AHO, imaging may not be required to establish or confirm the diagnosis. However, if a child does not respond to medical therapy within 24 to 48 hours or signs and symptoms suggest a potential role for surgical debridement, MRI may be performed to better define the location and extent of infection or to evaluate for an alternative diagnosis such as a malignancy. In children with suspected AHO who have associated joint effusion or other concern for the spread of infection into an adjacent joint (or soft tissues), US evaluation may provide valuable diagnostic guidance for further management.

Invasive procedures

- In children with suspected AHO, we suggest performing invasive diagnostic procedures to collect aspirates and/ or biopsy specimens of bone and/or associated purulent fluid collections for routine microbiological studies (aerobic bacteriologic culture and Gram stain) rather than only performing noninvasive diagnostic tests (conditional recommendation and moderate certainty of evidence).

  Comment:

  This recommendation places a high value on confirming the microbiological diagnosis to allow optimization of the spectrum and duration of antimicrobial therapy. The decision to implement this recommendation and its timing may be influenced by factors such as local feasibility of obtaining invasive diagnostic procedures (by interventional radiology [IR] or in the operating room), individual clinical situations (eg, need for therapeutic surgical intervention and concerns regarding procedural risks or sedation), positive results of prior noninvasive diagnostic tests (eg, blood culture), and duration of any prior antimicrobial therapy.

Empiric antimicrobial therapy

- In children with presumed acute hematogenous osteomyelitis (AHO) who are ill-appearing or have rapidly progressive infection, we recommend starting empiric antimicrobial therapy (table 5) immediately rather than withholding antibiotics until invasive diagnostic procedures are performed (strong recommendation and moderate certainty of evidence).

Comment:

The yield of positive cultures from specimens collected by invasive diagnostic procedures (bone biopsy and aspirate), when obtained within 24 to 48 hours after initiation of antibiotic therapy, is similar to the yield when these cultures are obtained prior to the administration of antibiotics.

- In children with presumed AHO who are not clinically ill and for whom an aspirate or biopsy by invasive diagnostic procedure is being planned prior to initiating antibiotics, we suggest withholding antibiotics for no more than 48 to 72 hours (conditional recommendation and very low certainty of evidence).

  Comment:

  The decision to implement this recommendation incorporating a reasonable delay may be influenced by local accessibility to experts and resources to perform invasive diagnostic procedures or the time required for transport to a higher level of care if appropriate.

  For children likely to have AHO, it is advisable that children remain hospitalized for observation while withholding antibiotics until cultures can be obtained.

- In children with suspected AHO, we recommend using empiric antimicrobial therapy active against *Staphylococcus aureus* (strong recommendation and moderate certainty of evidence).

  Comment:

  Antimicrobials with activity against community-acquired methicillin-resistant *S. aureus* (CA-MRSA) should be considered based on local susceptibility data and patient history with regard to previous CA-MRSA infections and/or colonization.

  In the presence of a clinical presentation, physical examination, exposure history, or other risk factors that either are inconsistent with *S. aureus* infection or suggest need for coverage for other organisms, additional empiric antimicrobial coverage for pathogens other than *S. aureus* may be warranted (such as younger age for *Kingella kingae* or children with underlying hemoglobinopathies who have increased risk for *Salmonella* spp. infection).

Invasive therapeutic procedures

- In children with AHO who present with sepsis or have a rapidly progressive infection, we recommend debridement of the infected bone and any associated abscesses as soon as possible after diagnosis, rather than treating with medical therapy alone (strong recommendation and moderate certainty of evidence).

- In a child with AHO who is clinically stable but is documented to have a substantial abscess (greater than 2 cm), we suggest debridement rather than treating with medical therapy alone (conditional recommendation and very low certainty of evidence).
- In children with AHO requiring a surgical procedure, we recommend against routine use of surgical-site (i.e., instilled or implanted) antimicrobial agents (strong recommendation and very low certainty of evidence).

  Comment:

  This recommendation places a high value on avoiding unnecessary harm and cost associated with this intervention.

Definitive parenteral and oral therapy

- In children with confirmed AHO, selection of a definitive antibiotic regimen should be based on the principles of selecting an effective agent against the identified pathogen, with the narrowest spectrum, lowest adverse effect profile, and most favorable host tolerance (Good Practice Statement).
- In children with suspected AHO without an identified bacterial cause, selection of a definitive antibiotic regimen should be based on the principles of selecting an effective agent based on the most likely causative organism(s), with a spectrum comparable to that on which the patient demonstrated clinical and laboratory improvement, and with the lowest adverse effect profile and most favorable host tolerance (Good Practice Statement).

Response to treatment

- In children with suspected or confirmed AHO receiving antimicrobial therapy, we suggest performing sequential monitoring of CRP in addition to serial clinical evaluation to assess response to therapy, rather than relying solely on clinical evaluation (conditional recommendation and low certainty of evidence).

  Comment:

  Serial clinical examinations that assess the febrile response, pain, and musculoskeletal function are important clinical parameters to monitor response to treatment.
- For children with suspected or documented AHO who respond to initial intravenous antibiotic therapy, we recommend transition to an oral antibiotic regimen rather than outpatient parenteral antibiotic therapy (OPAT) when an appropriate (active against the confirmed or presumed pathogen(s)) and well-

tolerated oral antibiotic option is available (strong recommendation and low certainty of evidence).

Comment:

This recommendation places a high value on avoidance of harms and costs as well as on the improvement of acceptability, feasibility, and equity.

- For children with suspected or documented AHO who respond to initial parenteral antibiotic therapy but for whom oral antimicrobial therapy is not feasible, we suggest transition to OPAT, rather than remaining in an acute-care hospital for the total duration of therapy (conditional recommendation and very low certainty of evidence).

  Comment:

  This recommendation places a high value on avoiding harms and costs associated with unnecessary and prolonged hospital stay. The decision to implement this recommendation and the selection of the type of OPAT (home, intermediate care facility, and clinic) may be influenced by the availability of local resources.

Duration of treatment

- In children with AHO presumed or proven to be caused by S. aureus who have had an uncomplicated course and responded to initial therapy, we suggest a 3- to 4-week duration of antibiotics rather than a longer course (conditional recommendation and very low certainty of evidence).

  Comment:

  Although the optimal duration of therapy is best described for uncomplicated courses of AHO due to methicillin-susceptible S. aureus (MSSA), longer duration may be necessary for other pathogens, including more virulent strains of *S. aureus* (such as USA 300 and Panton Valentine leucocidin + [PVL+], whether CA-MRSA or MSSA), and for complicated courses

Treatment failure/recurrence

- For children either experiencing primary treatment failure or early or late recurrence of AHO:
    - Clinicians should assess the adequacy of the antimicrobial regimen (spectrum of activity, dosage, and penetration to the site of infection, and adherence) before deciding on the need to broaden the spectrum or to restart antimicrobials (Good practice statement).

- Clinicians should reassess the need for surgical intervention for therapeutic and/or diagnostic purposes (Good practice statement).

Comment:

The accuracy of the diagnosis of AHO may need to be reconsidered, especially in culture-negative cases.

Long-term follow-up

- In children with AHO who are determined to be at risk of long-term adverse outcomes, we suggest a follow-up period of at least 1 year by specialists with experience treating children with AHO (conditional recommendation and low certainty of evidence).

Table 5 details the empiric parenteral therapy for children with acute hematogenous osteomyelitis (AHO) based on local epidemiology of resistance in bone isolates of s. aureus to methicillin and clindamycin:

Table 5. Empiric Parenteral Therapy for Children with Acute Hematogenous Osteomyelitis (AHO) Based on Local Epidemiology of Resistance in Bone Isolates of *S. Aureus* to Methicillin and Clindamycin (Adapted from the PIDS/IDSA 2021 Guideline)

Clindamycin Resistance Rate				
		<10% to 20%	>10% to 20%	
MRSA rate	<10% to 20%	Cefazolin or oxacillin/nafcillin	Cefazolin or oxacillin/nafcillin	
	>10% to 20%	Clindamycin	Options for clinically stable, nontoxic patient: vancomycin, cefazolin, or oxacillin/nafcillin	Options for clinically moderate to severely ill patient: vancomycin, daptomycin, ceftaroline, or linezolid

Table 6 lists the antibiotic choices and duration of therapy for uncomplicated pediatric AHO caused by Staphylococcus aureus:

Table 6. Antibiotic Choice and Duration of Therapy for Uncomplicated Pediatric Acute Hematogenous Osteomyelitis (AHO) Caused by Staphylococcus aureus (Adapted from the PIDS/IDSA 2021 Guideline)

Pathogen	Parenteral Therapy	Oral Convalescent Therapy	Duration
Staphylococcus aureus, methicillin susceptible	Preferred: Cefazolin Semi-synthetic penicillin (e.g., oxacillin and nafcillin)	Preferred: Cephalexin	3 to 4 weeks if uncomplicated
	Alternatives: Clindamycin Vancomycin Ceftaroline	Alternative: Clindamycin	3 to 4 weeks if uncomplicated
S. aureus, methicillin-resistant, susceptible to clindamycin	Preferred: Clindamycin	Preferred: Clindamycin	3 to 4 weeks if uncomplicated
	Alternatives: Vancomycin Daptomycin Ceftaroline Linezolid	Alternative: Linezolid	No data
S. aureus, methicillin-resistant, resistant to clindamycin	Preferred: Vancomycin	Preferred: Linezolid	No data
	Alternatives: Daptomycin Ceftaroline Linezolid	Alternatives: Insufficient clinical data for the treatment of AHO to recommend other oral antibiotics with in vitro activity against S. aureus	No data

The suggested duration of therapy should be based on clinical course (pace of resolution of fever and clinical signs and symptoms, noting the need for surgical intervention(s) required, if any), supported by decline of inflammatory markers.

Preferred and alternative agents are selected based on published data regarding in vitro activity, clinical efficacy, and safety. Agents are generally listed in order of preference.

Many of the beta-lactamase-stable penicillins cause significant phlebitis in peripheral veins with infusion; administration through a central venous catheter is preferred.

Alternative antibiotics that may display in vitro activity against *S. aureus* have not been evaluated prospectively in AHO. However, linezolid has been evaluated in prospective, controlled clinical trials for invasive methicillin resistant *S. aureus* nosocomial pneumonia in adults and is more likely to provide adequate therapy of invasive *S. aureus* AHO, compared with trimethoprim/sulfamethoxazole, which is not recommended for children with AHO by the Infectious Diseases Society of America (IDSA) Clinical Practice Guidelines for Treatment of Methicillin-Resistant Staphylococcus aureus Infections in Adults and Children.

Table 7 outlines the antibiotic dosages for pediatric AHO (dose adjustment may be needed in children with renal or hepatic failure).

For children receiving linezolid for more than 2 weeks, weekly screening for thrombocytopenia and neutropenia is recommended.

Table 7. IDSA/PIDS 2021 - Antibiotic Dosages for Pediatric Acute Hematogenous Osteomyelitis (Adapted from the PIDS/IDSA 202 Guideline)

Antibiotic	Dosage	Maximum Daily Adult Dosage	Comments
Parenteral Administered Antibiotics			
Cefazolin	100-150 mg/kg/d in divided doses every 8 hours	12 g/day	Higher end of dosing range for more serious, invasive infection.
Ceftaroline	45 mg/kg/d in divided doses every 8 hours, each dose infused over 1-2 h, max 600 mg/dose	1.8 g/day	Dose designed for the phase 2 treatment of pediatric acute osteomyelitis, including MRSA.
Clindamycin	30-40 mg/kg/day in divided doses every 6 to 8 hours	2.7 g/day	-
Daptomycin	Age-adjusted doses: 12-17 years: 7 mg/kg 7-11 years: 9 mg/kg 1-6 years: 12 mg/kg	-	Not recommended for children under 1 year of age based on safety concerns in animal models of infection.
Linezolid	30 mg/kg/d in divided doses every 8 h for children < 12 years and 20 mg/kg/d in divided doses every 12 h for children ≥12 years	Daily dose 1200 mg	Doses provided were studied prospectively for pneumococcal pneumonia, and uncomplicated skin infections, including MRSA.
Nafcillin	100-200 mg/kg/d in divided doses every 6 hours	12 g/day	Doses as high as 200 mg/kg/d have been used for meningitis.
Oxacillin	100-200 mg/kg/d in divided doses every 6 hours	12 g/day	Doses as high as 200 mg/kg/d have been used for meningitis.
Vancomycin	40-60 mg/kg/d in divided doses every 6 to 8 hours	No mg/kg maximum but	For MRSA: dosing to achieve an AUC/MIC of >400; associated with less

		follow for renal toxicity	renal toxicity than trough concentrations of 15-20 mcg/mL. Monitor serum concentrations.
Telavancin, dalbavancin, and oritavancin	-	-	Insufficient data exist for these agents for the treatment of bone infections caused by MRSA in adults to make recommendations for children.
Combination therapy for serious invasive *S. aureus* infections with multiple antibiotics, including gentamicin +/− rifampin, has not been evaluated prospectively. Please consult an infectious diseases specialist.			
Orally Administered Antibiotics			
Amoxicillin	50-100 mg/kg/d in divided doses every 8 hours	4 g/day	Not studied for AHO caused by pneumococcus or group A Streptococcus in children; doses in the higher end of the range may be needed to achieve adequate exposure in necrotic bone or abscesses, even for fully susceptible organisms.
Cephalexin	75-100 mg/kg/d in divided doses three or four times per day	4 g/day	Some experts recommend up to 6 g/d in divided doses four times per day
Clindamycin	30-40 mg/kg/d in divided doses three or four times per day	1.8 g/day	Some experts recommend up to 2.7 g/d in divided doses three times per day
Levofloxacin, if susceptible	16-20 mg/kg/d in divided doses two times per day for children 6 months to 5 years and 8-10 mg/kg/d once daily for children 5 to 16 years	750 mg/day	Use if no other active oral antibiotic therapy available

Linezolid	30 mg/kg/d in divided doses three times per day for children < 12 years and 20 mg/kg/d in divided doses two times per day for children ≥ 12 years	1200 mg/day	
Trimethoprim-sulfamethoxazole	Only evaluated prospectively for uncomplicated skin infections, with very limited retrospective data for osteomyelitis; therefore, no recommendation for osteomyelitis can be made at this time.		

1.2.2 French Society of Infectious Pathology (SPILF) Update on Bacterial Arthritis in Adults and Children (2023)

In 2020 the French Society of Rheumatology (SFR) published an update of the 1990 recommendations for management of bacterial arthritis in adults. The French Society of Infectious Pathology (SPILF) fully endorsed this update, and this 2023 publication expands on the SFR guideline and provides further information about specific antibiotic treatments. It focuses on antibiotics with good distribution in bone and joint. Dosages proposed in this update are high, with the optimized mode of administration for intravenous beta lactams (continuous or intermittent infusion)[6]. The main recommendations are summarized below.

Principles of antibiotic treatment

- The usual regulations for management of osteoarticular infections (OAI) must be followed in coordination with the antibiotic specialists of the establishment. The following rules are relevant:
    - Bacteriological sampling before initiation of antibiotic therapy or subsequent to a time lapse without antibiotic therapy, ideally 14 days, except in cases of therapeutic urgency.
    - Probabilistic antibiotherapy secondarily adapted to bacteriological results, to those pertaining the molecular biology of synovial fluids, and to antibiotic tolerance.
    - The shortest possible treatment duration,
    - Monitoring of the tolerance and efficacy of antibiotic therapy.

Treatment duration

- Treatment duration depends on the responsible pathogens:
    - *S. aureus*, and enterobacterials: 6 weeks
    - *Streptococcus* spp: 4 weeks
    - *Neisseria gonorrhoeae*: 7 days
    - Early arthritis (evolution < 4 weeks), by direct inoculation of the small joints of the hands, following proper surgical hand washing: 14 days in the absence of osteolysis.

Probabilistic antibiotherapy

- Probabilistic antibiotherapy should begin when:

- Direct examination with positive results and/or synovial fluid culture and/or positive hemoculture (after having ruled out contamination)
    - Antibiotic therapy adapted to Gram stain and/or bacterial culture
- Sepsis with widespread repercussions, or septic shock
    - Antibiotic therapy adapted to Gram stain and/or bacterial culture if infection is documented
    - Cefazolin* or penicillin M (cloxacillin, oxacillin), + amikacin (24–48 h)

      *In case of beta-lactam allergy, daptomycin or, by default, a glycopeptide (vancomycin or teicoplanin) is used.
- Purulent synovial fluid (with negative or unavailable direct examination results) + anamnesis compatible with the septic arthritis diagnosis + expert advice
    - Cefazolin* or penicillin M (cloxacillin, oxacillin), +/- broadened spectrum if anamnesis suggests a specific bacterium.

      *In case of beta-lactam allergy, daptomycin or, by default, a glycopeptide (vancomycin or teicoplanin) is used.

Septic gram-positive bacterial arthritis

- Initial MSSA Treatment
    - IV cefazolin or IV penicillin M (cloxacillin, oxacillin), is the recommended initial treatment of MSSA arthritis
    - Association with an aminoglycoside is not recommended in the absence of septic shock or sepsis with widespread repercussions
    - In case of beta-lactam allergy, daptomycin or, by default, a glycopeptide (vancomycin or teicoplanin) is used.
- MSSA Oral Relay
    - The molecule for oral relay is chosen according to antimicrobial susceptibility.
    - Only with certain molecules is monotherapy possible.
    - If monotherapy, clindamycin is proposed as first-line treatment in the event of sensitivity without inducible MLSb phenotype, that is to say a strain sensitive to clindamycin and erythromycin.
    - The levofloxacin/rifampicin or levofloxacin/clindamycin associations may likewise be proposed as first-line treatment.

    - In the event of resistance to clindamycin or of an inducible MLSb phenotype, doxycycline, an oxazolidinone (linezolid, tedizolid) or cotrimoxazole may be proposed.
    - Levofloxacin and rifampicin must be used in association with one another.
    - Without complications, total treatment duration is six weeks.
- Initial MRSA treatment
    - Daptomycin in monotherapy is recommended as first-line initial treatment, with vancomycin or teicoplanin as possible alternatives.
    - Following expert advice, dalbavancin, ceftaroline or ceftobiprole may be considered.
    - Oral relay should be determined by MRSA-sensitivity profile; the MSSA proposals remain applicable.
    - Without complications, total treatment duration is 6 weeks.
- Streptococci sensitive to penicillin
    - Amoxicillin is the initial first-line treatment for streptococcal-associated arthritis.
    - In the event of non-severe allergy to amoxicillin: cefazolin or ceftriaxone or cefotaxime
    - In the event of severe beta-lactam allergy: daptomycin
    - Oral relay: amoxicillin or, if allergy, clindamycin in the absence of inducible MLSb phenotype (strain sensitive to erythromycin)
    - If resistance to clindamycin: oxazolidinone (linezolid, tedizolid)
    - Without complications, the total treatment duration is 4 weeks.
- Penicillin-resistant (MIC > 0.250 mg/L) streptococci
    - If sensitive to cephalosporins: cefotaxime or ceftriaxone
    - If cephalosporin-resistant: daptomycin
- Enterococci sensitive to amoxicillin
    - Initial treatment: High-dose IV amoxicillin in monotherapy
    - If allergy: vancomycin or teicoplanin
    - Oral relay: amoxicillin or, if allergy, oxazolidinones (linezolid, tedizolid)
    - Without complications, total treatment duration is 4 weeks.
- Amoxicillin-resistant enterococci

    - Initial treatment: glycopeptide
    - Oral relay: oxazolidinone (linezolid, tedizolid)
    - Expert advice required
- Vancomycin-resistant enterococci
    - Expert advice required
- Cutibacterium acnes
    - Initial treatment: IV amoxicillin, IV clindamycin in cases of beta-lactam allergy and in the event of a sensitive strain
    - Oral relay: amoxicillin or (according to susceptibility) clindamycin or doxycycline in the event of allergy. Oxazolidinone (linezolid, tedizolid) if intolerance
    - Without complications, total duration is 4 weeks.

Gram-negative bacillary septic arthritis

- Enterobacterials
    - Initial treatment: 3rd-generation IV cephalosporin
    - In group III or group IV enterobacterials: cefepime IV
    - Oral relay: levofloxacin if sensitive, specialized advice if resistance
    - Without complications, treatment duration of 6 weeks
- Beta-lactam or carbapenemase producing enterobacterales
    - It is recommended to take the advice of an infectiologist in treatment of multidrug-resistant bacteria (ESBL and/or carbapenemase) on native joint.
- *Pseudomonas*
    - Initial intravenous (IV) treatment on microbiological documentation
    - Initial antibiotic treatment: ceftazidime or cefepime on *Pseudomonas aeruginosa*-infected native joint
    - Oral relay of antibiotic treatment of septic arthritis on *Pseudomonas aeruginosa*-affected native joint only once the infection is under control and after at least 14 days of treatment by intravenous beta-lactams. The first-line molecule is ciprofloxacin.
    - It is recommended, in the event of acquired *P. aeruginosa* resistance, to take the advice of an expert center in relation with the reference microbiologist and infectiologist.

- Neisseria
    - Initial treatment: cefotaxime or IV ceftriaxone
    - Treatment duration: 7 days

Other bacteria

- It is recommended to obtain an infectiologist's advice on antibiotic treatment of septic arthritis on native joint due to *Acinetobacter* spp, *Campylobacter* spp, *Haemophilus* spp, *Aeromonas* spp or anerobic bacilli.
- Pasteurella
    - First-line amoxicillin/clavulanic acid
    - Amoxicillin or doxycycline are possible following reception of antibiogram.
    - Treatment duration is 6 weeks, with the exception of small joint arthritis, for which, in the absence of osteolysis and after surgical washing, recommended duration is 2 weeks.
- Brucella
    - Oral route: doxycycline + rifampicin, for 6 weeks.
    - Cotrimoxazole is a possible alternative in the event of contraindication of one of the antibiotics, as is gentamicin (for 2 weeks only)
    - *For additional information on osteoarticular manifestations of human brucellosis, please refer to the "Brucellosis" report*
- Listeria
    - Initial treatment: IV amoxicillin (2 weeks) + IV gentamicin (5 days)
    - Followed by oral relay: amoxicillin
    - Alternative to amoxicillin: cotrimoxazole
    - Total treatment duration: 4 weeks
- Ureaplasma and Mycoplasma
    - Initial treatment: doxycycline
    - If unfavorable evolution, doxycycline + levofloxacin biotherapy is proposed.
    - Treatment duration: 12 weeks
- Mycobacteria
    - The therapeutic recommendations may be found in table 8:

Table 8. Antibiotic Therapy for Septic Arthritis due to Mycobacteria (Adapted from the SPILF 2023 Guideline)

Infection	Antibiotics	
	1st line treatment	2nd line treatment/ alternative
M. tuberculosis susceptible	Rifampicin 10 mg/kg PO, once a day 6 months Isoniazid 3–5 mg/kg/d PO, once a day, 6 months Ethambutol 15–20 mg/kg PO, once a day: 2 months Pyrazinamide 20–25 mg/kg/d PO, once a day, 2 months	-
M. chelonae	Azithromycin 250–500 mg*, PO, once a day AND Amikacin 10–15 mg/kg, IV/IM, once a day OR Linezolid 600 mg, PO, once or twice a day	Imipenem, Moxifloxacin, Tobramycin, Doxycycline, Ciprofloxacin, Levofloxacin, Tigecycline, Clarithromycin
M. abcessus	Cefoxitin 1–2 g, IV, twice a day OR Amikacin 10–15 mg/kg, IV/IM, once a day AND Azithromycin 250–500 mg*, PO, once a day	Linezolid, Moxifloxacin, Ciprofloxacin, Imipenem, Clarithromycin
M. fortuitum	Imipenem 1000 mg, IV, 2–3 times a day AND Amikacin 10–15 mg/kg, IV/IM, once a day AND Ciprofloxacin 500–750 mg, PO, twice a day	Cefoxitin, Cotrimoxazole, Linezolid, Azithromycin, Clarithromycin (if sensitive)
M. marinium	Rifampicin 10 mg/kg (max 600 mg) PO, once a day AND Ethambutol 15 mg/kg (max 1600 mg) PO, once a day AND Azithromycin 250–500 mg*, PO, once a day	Cotrimoxazole, Linezolid, Doxycycline (Sensitivity 50%), Ciprofloxacin (Sensitivity 50%), Clarithromycin
M. kansasii	Azithromycin 250–500 mg*, PO, once a day	Moxifloxacin, Cotrimoxazole, Clarithromycin

	AND Rifampicin 10 mg/kg (max 600 mg) PO, once a day AND Ethambutol 15 mg/kg (max 1600 mg) PO, once a day	
M. avium – intracellular	Azithromycin 250–500 mg*, PO, once a day AND Rifampicin 10 mg/kg (max 600 mg) PO, once a day AND Ethambutol 15 mg/kg (max 1600 mg) PO, once a day	Clarithromycin, Amikacin
M. xenopi	Azithromycin 250–500 mg*, PO, once a day AND Rifampicin 10 mg/kg (max 600 mg) PO, once a day AND Ethambutol 15 mg/kg (max 1600 mg) PO, once a day	Moxifloxacin, Clarithromycin
M. malmoense	Azithromycin 250–500 mg*, PO, once a day AND Rifampicin 10 mg/kg (max 600 mg) PO, once a day AND Ethambutol 15 mg/kg (max 1600 mg) PO, once a day	Moxifloxacin, Levofloxacin, Clarithromycin
* OR clarithromycin 500 mg, PO, twice a day. PO = per os. IV = intravenous. IM = intra-muscular, NTM = non-tuberculous mycobacteria		

- Coxiella
    - Initial treatment: doxycycline for 18 months
    - Addition of hydroxychloroquine has never yielded proof of effectiveness.
    - Few available clinical data on alternatives: cotrimoxazole, or doxycycline-fluoroquinolone or rifampicin-fluoroquinolone.
- Erysipelotrix
    - Initial treatment: Amoxicillin
    - Alternative and/or oral relay: levofloxacin or clindamycin
    - Treatment duration: 4 weeks

- Francisella
    - Initial treatment: oral ciprofloxacin
    - Alternative: doxycycline
    - Duration: 4 weeks

Specific situations

- Arthritis in the hands and wrist
    - It is urgently recommended to perform intraoperative lavage of the joints with microbiological sampling.
    - The route of administration of probabilistic antibiotic therapy is intravenous. Initial oral treatment is possible in less serious cases, or subsequent to early surgery.
    - Probabilistic postoperative antibiotic therapy consists in an amoxicillin/clavulanic association. If allergy: cotrimoxazole, or levofloxacin or doxycycline.
    - In the event of serious bodily harm with extension toward soft tissue and/or functional risk: piperacillin/tazobactam +/- amikacin.
    - Following surgical lavage, antibiotic therapy lasts two weeks, except in cases of osteolysis
- Pelvic arthritis
    - Initial treatment: ceftriaxone/cefotaxime + clindamycin
    - Pelvic arthritis secondary to a local pathology (bedsore, surgery), or occurring after radiation therapy: piperacillin/tazobactam + clindamycin or oxazolidinone (linezolid, tedizolid)
    - Surgical debridement must be considered
    - Treatment duration is determined according to clinical evolution and possible surgery.
- Arthritis and endocarditis
    - Endocarditis may be suspected in any case of arthritis due to Gram-positive bacteria.
    - When septic arthritis occurs in the context of endocarditis, antibiotic treatment must be based on therapeutic recommendations pertaining to endocarditis.

- Regardless of treatment duration for associated endocarditis, treatment duration for arthritis remains the same (S. aureus 6 weeks; other pyogens 4 to 6 weeks).

Pediatric specificities

- Childhood arthritis
  - Probabilistic intravenous treatment by monotherapy, as soon as aspiration is carried out
  - 1st or 2nd-generation or IV amoxicillin/clavulanic acid at 3 months of age (oxacillin or cloxacillin possible from 4 years)
  - If severe sepsis and/or toxic shock: add clindamycin or linezolid
  - If favorable evolution, oral relay from the 4th day
  - If no pathogenic agent is found, the oral relay antibiotic therapy consists in amoxicillin-clavulanic acid or cephalexin
  - If identified MSSA, the oral relay antibiotic therapy consists in amoxicillin-clavulanic acid, cefalexin or cotrimoxazole in children under 6 years of age and, in children over 6 years of age, clindamycin (capsule) if MSSA sensitive to erythromycin or cefalexin.
  - Total treatment duration is 2 weeks.

Monitoring of clindamycin treatment

- Precautions to be taken in clindamycin treatment
  - Patients treated by clindamycin must be warned about the risk of diarrhea.
  - Diarrhea imperatively necessitates specific diagnostic and therapeutic management.
- Pediatric clindamycin
    - It is recommended to render accessible the pediatric syrup form of clindamycin.

Table 9. Modalities of Antibiotic Administration in the Context of Septic Arthritis on Adult Native Joint (Adapted from the SPILF 2023 Guideline)

Molecule	Adaptations	Total daily dosage reference for normal renal function (clearance from 60 to 90 ml/min) and normal BMI (from 18 to 30 kg/m2)	Recommended pharmacological follow-up treatment
Amoxicillin	W, R, I	***Streptococcus spp, anaerobes:*** **IV:** 100 mg/kg/d in continuous administration (stability up to 12h) after loading dose of 2g for 1h) or discontinuous in 6 administrations (infusions from 30 to 60 min every 4 h) **PO:** PO: 100 mg/kg/d in 3 to 4 doses of 2 to 3g ***Enterococcus spp:*** **IV:** 200 mg/kg/d in continuous administration (stability up to 12h) after loading dose of 2g for 1h) or discontinuous in 6 administrations (infusions from 30 to 60 min every 4 h) **PO:** 200 mg/kg/d in 3 to 4 doses of 2 to 3g	**IV:** systematic if ≥ 12 g/d **PO:** systematic if ≥ 9 g/d
Amoxicillin-clavulanate	W, R, I	**IV:** Discontinuous administration: 100 mg/kg/d amoxicillin in 4 to 6 administrations, not exceeding 1200 mg of clavulanate/d **PO:** 100 mg/kg/day amoxicillin in 3 to 4 doses of 2 to 3g	
Cloxacillin/ oxacillin	W, R, I	**IV:** 150 mg/kg/d in continuous administration (stability up to 12h) after loading dose of 2g for 1h or discontinuous in 6 administrations (infusions from 30 to 60 min every 4 h)	Systematic if ≥ 12 g/d
Cefazolin	W, R, I	**IV:** 100 mg/kg/d in continuous administration (stability up to 12h) after loading dose of 2g for 1h or	Systematic if ≥ 6 g/d

		discontinuous in 3 administrations (infusions of 60 min every 8 h)	
Ceftriaxone	W, R	**IV:** 35 mg/kg/d in 1 to 2 infusions of 2g maximum	
Cefotaxime	W, R, I	**IV:** 100mg/kg/d in continuous administration (stability up to 12h) after loading dose of 2g for 30 min or discontinuous in 3 to 4 infusions of 2g prolonged for 4h	
Ceftazidime	W, R, I	**IV:** 100mg/kg/d in continuous administration (stability up to 8h) after loading dose of 2g for 30 min or discontinuous in 3 to 4 infusions of 2g prolonged for 4h	Systematic if *P. aeruginosa*
Cefepime	W, R, I	**IV:** 80 mg/kg/d in continuous administration (stability up to 8h) after loading dose of 2g for 30 min or discontinuous in 3 to 4 infusions of 2g prolonged for 4h without exceeding 8g/d	Systematic
Aztreonam	W, R, I	**IV:** 6g/d in continuous administration (stability up to 24h) or discontinuous in prolonged infusions (4h) of 2g every 8h	Systematic if *P. aeruginosa*
Piperacillin-tazobactam	R, I	**IV:** Discontinuous administration in prolonged infusions: [4g piperacillin + 0.5g tazobactam] every 6h in infusions for 3h OR continuous infusion with dosage 12g/d	
Imipenem-cilastatin	R	**IV:** 1g every 6 h in infusions for 30 min	
Meropenem	R, I	**IV:** 2g every 8 h in infusions from 3 to 8h	
Levofloxacin	R	***Staphylococcus spp:*** **IV or PO:** 750 mg/d in a single administration ***Enterobacterales:*** **IV or PO:** 500 mg/d in a single administration	

Ciprofloxacin	W, R	***Pseudomonas spp:*** **IV:** 400 mg/ 8h **PO:** 750 mg/ 12h	
Vancomycin	W, R, I	**IV:** Continuous administration: loading dose of 30 mg/kg in infusion for 2h, followed by maintenance dose of 30 mg/kg/d (stability up to 24h)	Systematic: AUC/MIC between 400 and 600 or peak plasma concentration: 25-30 mg/L
Teicoplanin	W, R	**IV:** Loading dose of 12 mg/kg every 12h for the first 3 to 5 IV injections, followed by maintenance dose of 12 mg/kg (IV or intramuscular route) every 24h	Systematic: plasma concentration: 20 and 30 mg/L
Daptomycin	W, R	***Staphylococcus spp:*** **IV:** 10 mg/kg in infusions of 30 min in single daily dose ***Enterococcus spp:*** **IV:** 12 mg/kg in infusions of 30 min in single daily dose	Useful to evaluate hematological toxicity
Linezolid	R	**IV** or **PO**: 600 mg/12h	
Tedizolid	-	**IV** or **PO**: 200 mg/24h	
Dalbavancin	R	**IV:** 1500 mg on D1 followed by 1500 mg at D7, schema covering 6 weeks of treatment)	
Clindamycin	W	**IV** or **PO**: Weight < 70 kg: 600 mg/ 8h Weight > 70kg: 900 mg/ 8h	
Rifampicin	W, R	**IV** or **PO**: 10 mg/kg/d (900 mg/d if weight > 70 Kg)	
Metronidazole	R	**IV** or **PO**: 500 mg/ 8h	
Cotrimoxazole	W, R	**IV** or **PO**: [320 mg trimethoprim + 1600 mg sulfamethoxazole]/ 12h	
Doxycycline	W, R	**PO**: 200 mg by day in 1 or 2 doses	

Gentamicin	W, R	**IV:** 5 mg/kg in infusions of 30 min in single daily dose	Systematic: negative residual before reinjection
Amikacin	W, R	**IV**: 30 mg/kg in infusions of 30 min in single daily dose	Systematic: negative residual before reinjection
Tobramycin	W, R	**IV**: 7 mg/kg in infusions of 30 min in single daily dose	Systematic: negative residual before reinjection
W: molecule adapting to weight, use of the abxbmi.com tool and stp is recommended. **R:** molecule adapting to renal function, utilization of the "GPR" tool is recommended: http://sitegpr.com/fr/ and pharmacological therapeutic monitoring is recommended. **I:** molecules whose modalities of infusion can be adapted/modified/optimized.			

Table 10. Proposals for Treatment of Septic Arthritis on Native Joints due to Gram-Negative Bacteria (Retrieved from the SPILF 2023 Guideline)

Bacterial species	**Initial IV treatment***	**Alternative in case of contra-indication**	**Oral relay** if susceptible bacteria	**Second-line oral relay**	**Duration**
enterobacterales "susceptible"					
group 0 (*Salmonella sp, Proteus mirabilis*)	Cefotaxime or Ceftriaxone	Aztreonam	Levofloxacin	Cotrimoxazole on expert advice	42d
group 1 (*Escherichia coli, Shigella sp*)					
group 2 (*Klebsiella pneumoniae, Citrobacter koseri*)					
group 3 (*Enterobacter sp, Citrobacter freundii, Serratia sp, Morganella sp, Providencia sp*)	Cefepime	Aztreonam	Levofloxacin	Cotrimoxazole on expert advice	42d
group 4 (*Yersinia sp*)					
group 5 (*Proteus vulgaris, Proteus penneri*)	Cefotaxime or Ceftriaxone	Aztreonam	Levofloxacin	Cotrimoxazole on expert advice	42d
enterobacterales "high-dose susceptible"	Expert advice	Expert advice	Expert advice	Expert advice	
ESBL-producing enterobacterales	Meropenem or imipenem	Expert advice	Levofloxacin	Cotrimoxazole on expert advice	42d
Carbapenemase-producing enterobacterales	Expert advice	Expert advice	Levofloxacin	Cotrimoxazole on expert advice	42d
Pseudomonas aeruginosa	Ceftazidime or Cefepime	Piperacillin/tazobactam or meropenem or imipenem	Ciprofloxacin		42d
Pseudomonas aeruginosa multi-resistant	Expert advice	Expert advice	Expert advice	Expert advice	42d
Acinetobacter sp.	Expert advice	Expert advice	Expert advice	Expert advice	42d
Neisseiria gonorrheae	Cefotaxime or Ceftriaxone	Levofloxacin or ciprofloxacin	Levofloxacin or Ciprofloxacin	Expert advice	7d
Neisseiria meningitidis	Cefotaxime or Ceftriaxone	Amoxicillin	Ciprofloxacin	Expert advice	7d
Campylobacter sp	Amoxicillin/ Clavulanic acid	Imipenem	Levofloxacin	Doxycycline	42d
Anaerobic Gram-negative bacteria	Metronidazole	Amoxicillin or amoxicillin/ clavulanate or clindamycin	Metronidazole	Amoxicillin or amoxicillin/ clavulanic acid or clindamycin	42d
Haemophilus sp.	Cefotaxime or Ceftriaxone	Ciprofloxacin or levofloxacin	Ciprofloxacin or Levofloxacin	Expert advice	42d
Aeromonas sp.	Ceftriaxone or cefepime	Ciprofloxacin or Levofloxacin	Ciprofloxacin or Levofloxacin	Expert advice	42d

* addition of amikacin or tobramycin until antibiogram result if qSOFA $\geq$ 2
IV: intravenous; ESBL: extended spectrum beta-lactamase

Table 11. Probabilistic Antibiotic Therapy for Community-Acquired Childhood Septic Arthritis and Alternatives in Case of Beta-Lactam Allergy (Retrieved from the SPILF 2023 Guideline)

Clinical situation	Bacterial epidemiology	Preferred antibiotics	Alternatives	Commentaries
Septic arthritis in child > 3 months Before starting ATB (even if the child is not feverish): –**2 aerobic hemocultures** by single aspiration, to redo in operating theater (if surgery) Minimal volume to adapt to child's weight minimal volume 8 mL/ vial in adult) **- pus evacuation** (abscess, synovial fluid) Direct inoculation of pus and synovial fluid in a hemoculture vial improves the bacteriological diagnosis. **Patient with sepsis with systemic failure/ septic shock, skin rash, suggestive of SA with toxicogenic germ**	**In priority:** *Staphylococcus aureus (SA)* *Kingella kingae (KK) mostly between 6 months and 4 years* **More rarely:** *Streptococcus pyogenes (SGA)* *Streptococcus pneumoniae (pneumococcus)* Group A streptococcus S. aureus PVL + (producer of Panton Valentine leukocidin)	**Cefazolin** Duration IV antibiotic therapy: 3 days with oral relay of antibiotic therapy at D4 if favorable evolution Minimum total duration antibiotic therapy (IV + PO): 14 days **Cefazolin** **+** **Clindamycin** **+/-** **Vancomycin** ***Duration IV and PO relay:*** **Expert advice**	**In child 6 months – 4 years:** (*KK, SA, pneumococcus et SGA possible*) **Sulfamethoxazole trimethoprim** or **In child > 4 years** (mainly SA) **Vancomycin**	In child > 4 years, oxa/cloxacillin can be used *(effective only on MSSA)* **In metropolitan France, CNR SA 2022 data, children:** 5% de MRSA: Higher MRSA prevalence in some countries: Mayotte, Mediterranean region including North Africa If MSSA: -R clindamycin in 15% of cases (24% if MRSA) -R with SMZ + TMP in 12% of cases (13% if MRSA) *Kingella kingae* is sensitive to beta-lactamases and SMZ + TMP but naturally resistant to clindamycin and to vancomycin
Patient with sickle cell disease	Salmonella sp. (*Streptococcus pneumoniae and possible Staphylococcus aureu < s)*	**Cefotaxime** ***Duration IV and PO relay:*** **Expert advice**	**Expert advice**	Choice of cefotaxime over ceftriaxone because: - more active on MRSA - neither biliary toxicity nor risk of hemolytic anemia No ciprofloxacin in probabilistic initial treatment
Patient < 3 months	Group B streptococcus *Staphylococcus aureus* *E. coli*	**Cefotaxime** **+** **Gentamicin** for 48 h ***Duration IV (7to14days) and PO relay:*** ***Expert advice***	**Expert advice**	

Table 12. Adaptation of Antibiotherapy for Childhood Septic Arthritis According to the Bacteria Identified and its Antibiogram (Retrieved from the SPILF 2023 Guideline)

Bacteria	IV ANTIBIOTICS 1er CHOIX	ALTERNATIVES	PER OS RELAY Verify susceptibility on antibiogram 1st CHOICE	ALTERNATIVES
***S. aureus* meti S**	Cefazolin or Cloxacillin	**If beta-lactam allergy:** Clindamycin (if SA clinda S and erythro S)	**If < 6 years:** Amoxicillin-Ac Clav (drinkable suspension) or Cefalexin (drinkable suspension) or Cotrimoxazole (drinkable suspension) **If > 6 years:** Clindamycin (capsule*) If SA clinda S and erythro S or Cefalexin (Cp)	**If beta-lactam allergy:** **If child from 6 months to 4 years:** Cotrimoxazole (drinkable suspension) **If > 6 years:** Clindamycin (capsule*) if SA clinda S and erythro S
S. aureus* meti R** *After results of rapid tests of detection of methicillin resistance and before complete antibiogram* ***Infectiologist's advice	Vancomycin + Clindamycin	**If renal insufficiency:** Linezolid		
S. aureus* meti R** *After complete antibiogram* ***Infectiologist's advice for adaptation	**If S. aureus clinda S and erythro S:** Clindamycin	**If S. aureus erythro R:** Linezolid	**If < 6 years:** Cotrimoxazole (drinkable suspension) **If > 6 years:** Clindamycin * (if SA clinda and erythro S)	Rifampicin + Fusidic acid /Cotrimoxazole or Levofloxacin
Kingella kingae	Amoxicillin	Cefotaxime or Ceftriaxone	Amoxicillin	Ciprofloxacin Cotrimoxazole
Group A streptococcus	Amoxicillin (+Clindamycin if toxic shock)	Cefotaxime or Ceftriaxone	Amoxicillin	Cefalexin/ Clindamycin*
Group B streptococcus	Amoxicillin	Cefotaxime or Ceftriaxone	Amoxicillin	
Pneumococcus	Amoxicillin	Cefotaxime or Ceftriaxone	Amoxicillin	Clindamycin Levofloxacin
Enterobacteria (Salmonella, *E. coli*)	Cefotaxime	Ciprofloxacin (if nalidixic S)	Ciprofloxacin (if nalidixic acid S)	Cotrimoxazole
Neisseria meningitidis	Ceftriaxone	Ciprofloxacin	Amoxicillin Ciprofloxacin	
No identified germ	Cefazolin		Amoxicillin-Ac Clav or Cefalexin	Clindamycin*

*Capsules and tablets are contraindicated in children under 6 years of age. Before prescribing capsules or tablets to a child over 6 years of age, it is necessary to make sure that he is able to swallow them.

Table 13. Means of Administration of Antibiotics in Childhood Septic Arthritis on Native Joint (Adapted from the SPILF 2023 Guideline)

Molecule	Adaptations	Micro-organism	Total daily reference dose	Particularities/remarks
Amoxicillin	W, R, I	*Kingella kingae* *Streptococcus pyogenes*, *Streptococcus pneumoniae*	**IV:** 200 mg/kg/d in 4 infusions **PO:** *Kingella kingae* and *Streptococcus pyogenes*: 80 mg/kg/day in 3 oral intakes *Streptococcus pneumoniae* (if MIC of amoxicillin ≤ 1 mg/L): 150 mg/kg/d in 3 oral intakes	**IV:** maximum doses: 3 g/6 h if weight ≤ 80 kg (12 g/d) 4 g/6 h if weight > 80 kg (16 g/d) **PO:** maximum doses: 2 g/8h if weight ≤ 80 kg 3g/8h if weight > 80 kg
Amoxicillin-clavulanate	W, R	*S. aureus* meti-S	**PO:** 80 mg/kg/d amoxicillin in 3 oral intakes	**PO:** amoxicillin/ clavulanate Drinkable suspension 100 mg/12.5mg /ml: one weighted dose provided by the dosing device and divided into 3 intakes/day, corresponding to dosage of 80 mg/kg/day of amoxicillin. **Child ≥ 40 kg:** use more adapted tablet or packet (Maximum dose: 1000 mg 3 times a day)
Cloxacillin/ oxacillin	W, R, I	*S. aureus* meti-S	**IV**: 200 mg/kg/d in 4 infusions	**IV**: if ≥ 12g/d, Continuous infusion + doses
Cefazolin	W, R, I	Probabilistic antibiotic therapy	**IV**: 150 mg/kg/d in 4 infusions	No maximum dose if normal renal function

		for SA in child > 3 months (*S. aureus* meti-S and *K. kingae*) Targeted antibiotic therapy: *S. aureus* meti-S		Dosages of > 8 g/24h
Ceftriaxone	W, R	*Neisseria meningitidis, Streptococcus pneumoniae*	**IV**: 75 mg/kg/d in 1-2 perfusions	Maximum dose: 2 g/12h
Cefotaxime	W, R, I	Probabilistic antibiotic therapy for SA in child < 3 months (*Streptococcus agalactiae*, *E. coli* and *S. aureus* meti-S) in association with gentamicin.	**IV**: 200 mg/kg/d in 4 infusions	Maximum dose: 3 g/8h if weight 70-100 kg 3 g/6h if weight >100 kg
		Probabilistic antibiotic therapy for SA in sickle cell disease patients (*Salmonella sp*)	**IV**: 300 mg/kg/d in 4 infusions	
Cephalexin	W, R	*S. aureus* meti-S, *K. kingae*	**PO:** 150 mg/kg/d in 3 oral intakes	**PO**: Maximum doses: 2g/8h if weight ≤ 80 kg 3g/8h if weight > 80 kg

				Drinkable suspension 250mg/5 ml and tablet 500 and 1000 mg **Child < 6 years with weight > 10-15 kg**: high volume of drinkable suspension; amoxicillin /clavulanic acid is preferable (drinkable suspension)
Levofloxacin	W	Alternative for MRSA AS (in association with rifadin)	**PO**: < 5 years: 20 mg/kg/d in 2 oral intakes > 5 years: 10 mg/kg /d in 2 oral intakes	Drinkable suspension form (TUA) Maximum doses: 500 mg X2/d Verify absence of G6PD deficiency Drinkable suspension 25mg/ml (TUA) and divisible tablet 500 mg
Ciprofloxacin	W, R	*Salmonella sp*	**PO**: 45 mg/kg/d in 3 oral intakes	Maximum dose: 750 mg/ 12 h
Vancomycin	W, R, I	*S. aureus* meti-R	**IV**: Continuous IV after loading dose of 15 mg/kg in infusion for 1h, followed by maintenance dose of 60 mg/kg/d Or 60 mg /kg/d in 4 one-hour infusions	Hyperhydration 1500 ml/m^2/day If continuous IV: vancomycin (and creatinine) assay 24 hours before loading dose. Objective of maximum plasma concentration: 20-35 mg/L. Objective: AUC/MIC between 400 and 600. If

				discontinuous IV: vancomycin (and creatinine) assay 48 hours after initiation of vancomycin. Objective: residual concentration > 15-20 mg/L; maximum concentration: 20-40 mg/l **Infectiologist's advice of treatment prolonged for adaptation of vancomycin according to MIC**
Linezolid	W, R	*S. aureus*	**IV**: 30 mg/kg /d in 3 infusions in < 12 years of age 20/mg/kg/d in 2 infusions in > 12 years of age	Maximum dosage: 600 mg/12h No MA for child < 18 years Maximum treatment duration: 28 days
Clindamycin	W	*S. aureus* clindamycine and erythromycine S	**IV** or **PO**: 40 mg/kg/d in 3 administrations	Maximum dosage IV or PO: Weight 70 kg: 900 mg/ 8h Capsule (150 and 300 mg): contraindicated in < 6 years No drinkable suspension
Rifampicin	W, R	Alternative for MRSA SA (in association with fusidic acid, cotrimoxazole or levofloxacin)	**IV**: 20 mg/kg/d in 2 slow injections (1.5 hours) **PO**: 20 mg/kg/d in 2 oral intakes	To be administered fasting by oral route (30 minutes before meals or 2 hours after) Drinkable suspension 100mg/5 ml and capsule 300 mg
Cotrimoxazole	W, R	Alternative for AS if	**IV** or **PO**: 60 mg/kg/d of	Maximum dose IV or PO: 1600

		S. aureus, *K. kingae*	sulfamethoxazole (SMX)	mg SMX/12h Drinkable suspension 200mg SMX/5 ml, and tablets 400 SMX/80 and 800 SMX/160
Gentamicin	W, R	Probabilistic antibiotic therapy for SA in child < 3 months (*Streptococcus agalactiae*, *E. coli* and *S. aureus* meti-S) in association avec cefotaxime.	**IV**: 6 mg/kg/d in one infusion of 30 min by day	
Fusidic acid	W	Alternative for MRSA SA (in association with rifadin)	**PO:** 60 mg/kg/d	Maximum dose: 500 mg x 3/d Drinkable suspension 250mg/5 ml and 100mg/2ml, and tablet 250 and 500 mg

W: molecule adapting to weight, use of the abxbmi.com tool and stp is recommended.

R: molecule adapting to renal function, utilization of the "GPR" tool is recommended: http://sitegpr.com/fr/ and pharmacological therapeutic monitoring is recommended.

I: molecules whose modalities of infusion can be adapted/modified/optimized.

Table 14. Posology, Means of Administration by Oral Route of the Antibiotics Utilized in Treatment of Childhood Septic Arthritis (Retrieved from the SPILF 2023 Guideline)

Molecules	Product	Dosage	Posology/24 h	Nb intakes / 24 hours
Cefalexin	KEFORAL	Cp 500 and 1000 mg Drinkable suspension 250 mg (=5 ml)	C and I: 150 mg/kg Maximum dose: 6 g/d	3
Cefadroxil	ORACEFAL	Cp 1000 mg Capsule 500 mg Drinkable suspension 250 and 500 mg (=5 ml)	C and I: 150 mg/kg Maximum dose 6 g/d	3
Amoxicillin	CLAMOXYL	Cp 1000 mg Capsule 500 mg Sachet 125, 250 Drinkable suspension 125, 250 et 500 mg (=5 ml)	150 mg/kg Maximum dose: 2 g/8h if weight $\leq$ 80 kg 3 g/8h if weight > 80 kg	3
Amoxicillin/clavulanic acid	AUGMENTIN	Sachet 1000 mg amoxicillin and 125 mg clavulanic acid Cp 500 amoxicillin and 62.5 mg clavulanic acid cl Drinkable suspension 125, 250, 500 mg (=5 ml)	80 mg/kg/d amoxicillin (1 weight-appropriate dose 3 times a day) Maximum dose: 4500 mg/d	3
Clindamycin	DALACINE	Capsule 75, 150 et 300 mg Attention: capsule form unsuited for < 6 years	C: 40 mg/kg A: 40 mg/kg until 900 mg × 4	3
Rifampicin in association (AAC, SMX, fusidic acid or levofloxacin)	RIFADINE	Capsule 150 and 300 mg Drinkable suspension 2% (100 mg = 5 ml)	C, I and A: 20 to 30 mg/kg	2
Fusidic acid (in association with Rifadin)	FUCIDINE	Cp 250 and 500 mg Drinkable suspension 250 mg = 5 ml 100 mg = 2 ml	C and I: 60 mg/kg A: until 500 mg × 3	3
Ciprofloxacin	CIFLOX (If no G6PD deficiency) Must not be taken with gastric banding (Maalox) or iron, which reduces antibiotic absorption.	Cp non-divisible 250, 500 and 750 mg Drinkable suspension 500 mg/ 5 ml	PO: 30 mg/kg Drepanocyte: 45 mg/kg 2 times a day Adult: 1500 to 2250 mg/d	2–3
Levofloxacin	TAVANIC To use in association (If no G6PD deficiency)	Cp divisible 500 mg Drinkable suspension 25 ml/ml (TAU for patients not able to swallow levofloxacin tablets)	20 mg/kg < 5 years 10 mg/kg > 5 years A: 500 to 1000 mg	2
Cotrimoxazole = sulfamethoxazole (SMX) + trimethoprim (TMP)	BACTRIM (If no G6PD deficiency) Surveillance CBC-Platelet 1 time a week	Cp 800 mg SMX and 160 mg TMP (strong Bactrim) Cp 400 mg SMX et 80 mg TMP Drinkable suspension: 5 ml = 100 mg SMX and 40 mg TMP	C and I: 60 mg/kg SMX A: 2400 mg SMX/d	3
Doxycycline Minocycline	DOXYCYCLINE MINOCYCLINE CI < 8 years	Cp 100 mg Cp 100 mg	4.4 mg 4 mg Maximum dose: 200 mg/d	2

Underlined: Galenic suitable for infants.
C: child; I: infant; A: adolescent.

The galenic form of the antibiotic prescribed must be adapted to the age and preferences of the child. No clindamycin capsule for an infant or a child under 6 years of age.

1.2.3 Spanish Society of Infectious Diseases and Clinical Microbiology (SEIMC) Clinical Practice Guideline on the Management of Prosthetic Joint Infections (2017)

The guideline focuses on the management of prosthetic joint infections (PJI) by classifying all the possible therapeutic scenarios according to clinical presentation. The indications for the choice of a given surgical strategy and a particular antimicrobial therapy are specifically reviewed[7,8].

Table 15. SEIMC 2017 - Level of Evidence and Grades of Recommendation

Level of Scientific Evidence	
I	Evidence obtained from ≥1 randomized clinical trial
II	Evidence obtained from ≥1 well-designed non-randomized clinical trial, or cohort studies, or case-control-studies, especially if they have been performed in more than one center, from multiple time-series; or from dramatic results for uncontrolled experiments.
III	Evidence obtained from documents or opinions of experts, based in clinical experience descriptive studies or reports of expert committees
Grades of Recommendation	
A	Good evidence to recommend the use of a measure or practice
B	Moderate evidence to recommend the use of a measure or practice
C	Poor evidence to recommend the use of a measure or practice
D	Moderate evidence to discourage the use of a measure or practice
E	Good evidence to discourage the use of a measure or practice

Initial assessment of a patient with PJI

- Due to the complexity of patients PJI, they should be attended at multidisciplinary units (C-III).
- The main medical and surgical strategies to be considered in a patient with PJI are:
    - Attempted eradication with implant retention and antibiotics (DAIR).
    - Attempted eradication with implant removal and antibiotics:
        - With prosthesis replacement (in a 1-step or a 2-step exchange procedure).
        - Without prosthesis replacement (arthrodesis or resection arthroplasty).

- Implant retention and long-term suppressive antibiotics (SAT), without attempted eradication

Attempted eradication with implant retention (DAIR)

- The best candidates for attempting eradication treatment with implant retention are those who:
  - Have an early post-surgical (up to three months after the placement of the prosthesis) or haematogenous (either suspected or proven) infection (A-II), with a stable implant, and surrounding skin and soft tissues in good condition.
  - Have a short duration of symptoms (≤ 3 weeks) (B-II).
  - Can be treated with rifampin (staphylococcal infections) or fluoroquinolones (infections caused by GNB) (A-II).
- Some patients who do not strictly meet the above criteria may still benefit from this strategy, but its implementation should be considered on an individualized basis, since there is a higher likelihood of failure (B-II).

Attempted eradication without implant removal

- Surgical debridement must be performed promptly by an expert surgical team, with the patient in the best possible condition (CIII).
- The surgical approach must be performed by open arthrotomy. Arthroscopy should only be considered in selected cases and performed by expert surgeons (A-II).
- The surgical debridement must be aggressive, methodical, and exhaustive.
  - If feasible, the removable components of the prosthesis should be exchanged (B-II).
  - Copious irrigation (≥9 L of saline) is recommended with no additives, performed by a low-pressure system (C-III).

Removal of the prosthesis

- The prosthesis should be removed in cases of chronic PJI (A-II).
- A 2-step exchange procedure is recommended in patients with chronic PJI (A-II).
- In patients with acute PJI who are not candidates for eradication treatment with implant retention, a 2-step exchange procedure is recommended (B-II).

- The performance of a 1-step exchange procedure may be considered in non-immunosuppressed patients if they have good bone stock, if the prosthetic surrounding soft tissues are in good condition, and if the infection is caused by microorganisms susceptible to antibiotics with good activity against sessile (biofilm-embedded) bacteria (B-II).
- In patients with acute PJI in whom the removal of the prosthesis is not very complex, a 1-step exchange procedure is recommended as long as the causative microorganisms are susceptible to antibiotics with good activity against biofilm-embedded bacteria (C-III).

Implant retention without attempted eradication

- The following conditions need to be met for the indication of SAT:
    - Identification of the microorganism causing the infection.
    - Availability of oral antibiotics which are not toxic when administered over long periods of time. The use of SAT with parenteral antibiotics with long half-life has been reported, but this strategy is very rarely applied.
    - Possibility of a close follow-up of the patient
- Treatment with SAT may be considered in situations in which medical and surgical strategies are unlikely to cure the patient, and non-toxic long-term antimicrobials are available (B-II).
- Treatment with SAT is not indicated in acute PJI managed early, with appropriate debridement and optimized antimicrobial therapy (E-II).

Empirical and definitive antimicrobial treatment

- After surgical debridement, antibiotics with good activity against rapidly growing planktonic bacteria should be provided, ideally based on β-lactams, lipopeptides, or glycopeptides (B-III).
- This initial treatment must be administered intravenously for at least 7 days before switching to an optimized antimicrobial therapy focused on the treatment of biofilm-embedded bacteria (C-III).

<u>Staphylococcal infections</u>:

- Initial treatment (antibiotics against planktonic bacteria):
    - Methicillin-susceptible strains: cloxacillin (or cefazolin) (B-II), or cloxacillin + daptomycin (C-III).
    - Methicillin-resistant strains: daptomycin + cloxacillin, or daptomycin + fosfomycin (C-III), or vancomycin (B-II).

- Subsequent treatment (against biofilm-embedded bacteria):
    - Treatment of choice: rifampin + levofloxacin (A-II).
    - If fluoroquinolones cannot be used: combinations of rifampin with co-trimoxazole (B-II), linezolid (B-II), clindamycin (B-II), fusidic acid (B-II), or daptomycin (B-III).
    - If rifampin cannot be used: combinations of daptomycin with fosfomycin (B-III), cloxacillin (B-III), linezolid (B-III), co-trimoxazole (C-III), or levofloxacin (C-III); or combinations of 2 oral antibiotics or monotherapy with levofloxacin (B-III), or moxifloxacin (B-III), co-trimoxazole (BIII), or linezolid (B-III).

Streptococcal infections:

- For initial treatment (planktonic phase): penicillin or ceftriaxone (B-II).
- Subsequent treatment (biofilm-embedded bacteria): penicillin or ceftriaxone (B-II), followed by amoxicillin (B-II), either in combination with rifampin or not (B-III); alternatively, levofloxacin (B-III) either in combination with rifampin or not (B-III), or monotherapy with clindamycin or linezolid in the case of allergy to fluoroquinolones (C-III).

Infections caused by Enterococcus faecalis:

- The treatment of choice is ampicillin, followed by oral amoxicillin (B-II).
- It can be administered in combination with ceftriaxone (B-III) or rifampin (B-III).
- Teicoplanin or linezolid are possible alternatives (C-III).

Infections caused by GNB:

- For initial treatment (planktonic phase): a β-lactam (a 3rd-generation cephalosporin for Enterobacteriaceae, a carbapenem for ESBL or AmpC β-lactamase producing GNB, and an anti-pseudomonal β-lactam for P. aeruginosa) (B-III).
- Subsequent treatment (biofilm-embedded bacteria):
    - Treatment of choice: fluoroquinolone (ciprofloxacin) (A-II).
    - If fluoroquinolones cannot be used (due to resistance, toxicity…): continue treatment with a β-lactam (B-III) combined or not with colistin (B-III) or fosfomycin (C-III), or monotherapy with co-trimoxazole (C-III).

Culture-negative PJI:

- If possible, the use of antibiotics prior to a valid sampling (i.e., joint aspirate, and/or intraoperative cultures) should be avoided (B-III).

- The antimicrobial treatment must be active against the most prevalent microorganisms. The need for antibiotic activity against multi-drug resistant microorganisms must be considered in accordance with the patient's clinical and epidemiological context (C-III).
- If antibiotics have been administered prior to the sampling and they are considered as potentially responsible for the absence of microbiological diagnosis, the antimicrobial spectrum of this treatment should be considered when choosing the new antibiotic regimen (C-III).

Duration of treatment

- For acute staphylococcal PJI managed with rifampin and levofloxacin, an 8-week schedule of treatment after debridement appears sufficient for most patients (B-I).
- For PJI caused by other microorganisms treated with antibiotics with good activity against biofilm-embedded bacteria (i.e., ciprofloxacin for PJI caused by GNB, 8 weeks is also a reasonable duration) (B-III).
- In other clinical scenarios, the most appropriate duration of treatment remains uncertain. A variable period between 8 and 12 weeks may be adequate (B-III).
- Monitoring of CRP during the follow-up is advisable; the persistence of high values is suggestive of treatment failure (B-III), but its total normalization must not be a condition for deciding the end of therapy (B-II).

Follow-up

- During antimicrobial therapy, a close follow up of observance and potential adverse events of the treatment is recommended, performed by a clinician with expertise in antibiotics (C-III).
- During the first 6 months after the end of a treatment aiming at eradication, patients must be followed up closely (B-III).
- The frequency of follow-up visits may decrease afterwards. Follow-up should last at least one year (B-III).

Attempted eradication with prosthesis removal and a 2-step exchange procedure

- The two-step exchange procedure should include a targeted intravenous antimicrobial treatment for 4 to 6 weeks (A-II), or 1-2 weeks of intravenous antibiotics followed by oral antimicrobials with good bioavailability for a total duration of 6 weeks (B-II).

- In chronic PJI caused by CNS, “universal” anti-staphylococcal antimicrobial therapy (i.e., glycopeptides, daptomycin, or linezolid) may be considered after the first-step surgery (prosthesis removal), because this carries a lower rate of positive cultures during the second-step surgery (re-implantation) (C-III).
- Shortening the systemic antimicrobial treatment could be considered for cases of PJI due to low-virulent microorganisms, such as CNS or Propionibacterium acnes, as long as the first-step surgery has included a thorough and exhaustive debridement of the joint, and a cement spacer loaded with antibiotics active against the microorganism responsible for the infection has been used (B-II).
- When samples taken during the second-step surgery yield a microorganism, a new 4-6 weeks course of antibiotics is recommended (B-II).
- At present, it is not clear whether rifampin should be administered to treat staphylococcal infection managed with a two-step exchange procedure.
    - The indication of rifampin in a chronic non-inflammatory infection should be based on the thoroughness of the surgical debridement (C-III).
    - Rifampin is recommended in cases with a significant inflammatory presentation, especially those caused by S. aureus (C-III).
- Antibiotic-loaded spacers are recommended in the two-step exchange procedure (B-II).
- The dose of local antibiotic ranges between 0,5 and 4 g of vancomycin, and 0,25 and 4.8 g of gentamicin or tobramycin (per every 40 g of acrylic cement) (C-III).
- The use of combined local antibiotics (vancomycin-gentamicin) is recommended until further evidence specifically addressing this topic is available (C-III).
- In PJI caused by multi-drug resistant microorganisms, spacers may be still used as long as they are loaded with antibiotics active against these microorganisms (C-III).
- In the two-step exchange procedure, an antibiotic-free period of 2 to 8 weeks and clinical stability before the second-step surgery is recommended (C-III).
- Prophylaxis for the second-step surgery:
- Wide-spectrum antibiotic prophylaxis including nosocomial microorganisms that may potentially cause superinfection of the new prosthesis is recommended for the second-step surgery of a 2-step exchange procedure (C-III).

- “Preemptive treatment” including microorganisms that could be isolated during the second-step surgery (usually multi-drug resistant SNC) is recommended: vancomycin (or another glycopeptide or lipopeptide) during the first 5 days after re-implantation or until confirmation that the samples taken during the second-step surgery yield no microorganisms (C-III).

Attempted eradication with prosthesis removal and a 1-step exchange procedure

- Beginning an antimicrobial therapy 3 to 5 days prior to the 1-step exchange procedure is recommended if the etiological diagnosis has already been made, especially in infections caused by S. aureus or GNB (C-II).
- Regardless of the decision regarding when to start antibiotics, an appropriate antimicrobial prophylaxis throughout the procedure must be guaranteed (A-I).
- If no antimicrobial therapy has been initiated before the procedure, it should be delayed until the intraoperative sampling has been performed (C-III).
- A minimum of 7 days of intravenous antibiotics with activity against the microorganisms causing the infection is recommended, followed by oral antibiotics for a total of 4-8 weeks (B-II).
- If it has been decided to use a cemented prosthesis, a local antibiotic with activity against the microorganism causing the infection is recommended. If the etiology is unknown at the moment of the exchange procedure, the combination of vancomycin plus gentamicin is recommended (C-III).
- The positive intraoperative cultures PIOC category includes patients submitted to a 1-step exchange procedure due to the loosening of a prosthesis which was assumed to be non-infectious, but in which the samples taken during surgery finally yielded microorganisms (> or equal to 2 positive intraoperative cultures):
    - In the case of PIOC (Tsukayama’s classification) an antimicrobial treatment of 4 to 6 weeks is recommended. There is no need for further surgery. The same protocol is followed as in cases of PJI managed with a 1-step exchange procedure (B-III).
- Treatment for cases in which no new prosthesis is to be inserted after the removal of the infected one:
    - For cases in which the infected prosthesis is not to be replaced after its removal, the same antibiotics as those used for DAIR may be administered (Table 5) (B-II).

- In these cases, the length of therapy may be shortened to 4 to 6 weeks (C-III).

Implant retention and long-term suppressive antibiotics (SAT) without attempted eradication

- Surgical debridement before beginning SAT is recommended, if feasible (C-III).
- Obtaining a valid sample for culture before starting SAT is particularly important (C-III).
- For the choice of the specific antibiotic for SAT, the antimicrobial susceptibility of the microorganism causing the infection, the safety of the drug and the observance of the treatment must be considered. Except for the initial stages of SAT, these aspects must prevail over the optimization of the antimicrobial treatment (C-III).
- Except for some cases, the use of combinations (and therefore the use of rifampin) is not recommended (D-III).
- In cases undergoing surgical debridement, an initial intravenous treatment for at least 7 days is recommended. Nevertheless, prolonged intravenous treatment is not necessary when deciding on SAT management (C-III).
- If it is necessary to stop or change the antibiotics due to the occurrence of adverse events, long periods without antibiotics are not recommended (D-III).
- The prescription and control of a SAT must be performed by an expert in antimicrobial therapy, who will periodically follow up the clinical evolution of the infection and assess the possible occurrence of adverse events (B-III).
- The use of linezolid is discouraged in SAT due to high risk of toxicity, which limits its prolonged administration (E-I).
- The use of β-lactams, or low doses of co-trimoxazole, is recommended. Alternatively, other antimicrobials such as minocycline or clindamycin may be administered (C-III).

Table 16 details the empirical and targeted antimicrobial therapy in the eradicative attempt of management with implant retention:

Table 16. Empirical and Targeted Antimicrobial Therapy in the Eradicative Attempt of Management with Implant Retention (Retrieved from the SEIMC 207 Guideline)

	Recommended therapy	Alternative in patients allergic to β-lactams	Recommended duration
Initial phase of treatment (planktonic bacteria)			
Empirical treatment			
	Vancomycin or daptomycin or cloxacillin iv [&] + ceftazidime or cefepime or meropenem iv	Vancomycin or daptomycin iv + aztreonam iv	Until the results of cultures are available
Targeted treatment			
MSSA/MSSE*	(Cloxacillin or cefalozin) ± daptomycin iv	Daptomycin + fosfomycin iv	7-14 days
MRSA/MRSE*	Vancomycin (alone) or daptomycin + (cloxacillin or fosfomycin) iv	Daptomycin + fosfomycin iv	7-14 days
Streptococcus spp	Ceftriaxone or penicillin iv	Vancomycin iv	7 days
E. faecalis	Ampicillin ± ceftriaxone iv	Vancomycin or teicoplanin iv	7 days
Gram-negative bacilli	β-lactam iv ** [†]	Ciprofloxacin iv	7 days
*consider adding rifampin after the 5th day of treatment			
** consider combining an anti-pseudomonal β-lactam plus ciprofloxacin in PJI caused by P. aeruginosa			
Sequential phase treatment (biofilm-embedded bacteria)			
Staphylococcus spp			
Treatment of choice			
	Rifampin + levofloxacin po	-	Until completing 8 weeks
Alternatives without fluoroquinolones			
	Rifampin po + (daptomycin or fosfomycin) iv	-	2-4 weeks, then oral treat.
	Rifampin + (LNZ, fusidic, CMX, clindamycin, or minocyclin) po	-	Until completing 8 weeks of treat.
Alternatives without rifampin			
	Daptomycin iv + (fosfomycin or cloxacillin) iv	-	2-6 weeks, then oral treat.
	Daptomycin iv + (LNZ or CMX or levofloxacin) po	-	2-6 weeks, then oral treat.
	Levofloxacin + (LNZ, CMX, clindamycin or fusidic) po	-	Until completing 8 weeks of treat.
	LNZ + (CMX or fusidic) po	-	Until completing 8 weeks of treat.
	Clindamycin + fusidic po	-	Until completing 8 weeks of treat.
	Levofloxacin or moxifloxacin or CMX or LNZ po	-	Until completing 8 weeks of treat.
Streptococcus spp			
	(Ceftriaxone or penicillin iv) ± rifampin po	Vancomycin iv ± rifampin po	2-6 weeks, then oral treat.
	Amoxicillin ± rifampin po	Levofloxacin ± rifampin po	Until completing 8 weeks of treat.
	Levofloxacin ± rifampin po	-	Until completing 8 weeks of treat.
E. faecalis			
	Ampicillin ± ceftriaxone iv	Vancomycin or teicoplanin iv	2-6 weeks, then oral treat.
	Amoxicillin ± rifampin po	LNZ ± rifampin po	Until completing 8 weeks of treat.

E. faecium	Vancomycin or teicoplanin iv Linezolid po		2-6 weeks, then oral treat. Until completing 8 weeks of treat.
Gram-negative bacilli			
Treatment of choice			
	Ciprofloxacin po	-	Until completing 8 weeks of treat.
Alternatives without fluoroquinolones			
	β-lactam iv ± colistin iv or β-lactam iv ± fosfomycin iv	Aztreonam iv ± colistin iv	6 weeks, then oral treat.
	CMX	-	Until completing 8 weeks of treat.
Alternatives against multi-drug resistant Gram-negative bacilli			
	β -lactam (CI) iv + colistin iv β-lactam (CI) iv + fosfomycin iv	Aztreonam iv (CI) + colistin iv	6 weeks

[&] The choice of a particular anti-staphylococcal agent may be conditioned by the presence of bloodstream infection, especially in hematogenous infections.

[†] The choice of a particular β-lactam agent against Gram-negative bacilli depends on the species and mechanisms of resistance: ceftriaxone i the treatment recommended for *Enterobacteriaceae*, except if they produce chromosomal β-lactamases (i.e., AmpC) or plasmidic extended spectrum β -lactamases (ESBL); in these cases, the use of ertapenem will be preferred; in infections caused by *P. aeruginosa*, an anti-pseudomonal β-lactam is recommended.

Abbreviations: x: during; MRSA: methicillin-resistant *S. aureus*; MSSA: methicillin-susceptible *S. aureus*; MRSE: methicillin-resistant *S. epidermidis* (and other coagulase-negative staphylococci); MSSE: methicillin-susceptible *S. epidermidis* (and other coagulase-negative staphylococci). CMX: co-trimoxazole; Fusidic: fusidic acid; LNZ: linezolid; CI: continuous infusion; iv: intravenous treatment; po: *per os* (oral route); treat.: treatment.

Recommended doses (assuming normal renal function): cloxacillin, 2 g/4h iv; vancomycin, 1g/12h iv; daptomycin, 8-10 mg/kg/24h iv; ceftazidime, 2g/8h iv; aztreonam, 2g/8h iv; cefepime, 2g/8-12h iv; meropenem 1-2g/8h iv; ertapenem, 1g/24h iv; ceftriaxone 2g/24h; ampicillin: 2g/6h iv; amoxicillin, 1 g/8h po; rifampin, 600 mg/24h po; levofloxacin, 500-750 mg/24h po; moxifloxacin, 400 mg/24h po; ciprofloxacin, 400 mg/12h iv or 750-1000 mg/12h po; linezolid, 600 mg/12h po; fusidic acid, 500 mg/8h po; fosfomycin, 2 g/6h iv; colistin, 6-9 millions IU/d (8-12h) iv; co-trimoxazole 800/160 mg/8h po; clindamycin, 600 mg/6-8h po; minocycline, 200 mg/d po.

Table 17 lists the antimicrobials used in cement spacers:

Table 17. Antimicrobials Used in Cement Spacers (Adapted from the SEIMC 2017 Guideline)

Fusidic acid	Erythromycin	Cephamandole	Gentamicin	Oxacillin	Tazobactam
Amikacin	Bacitracin	Ciprofloxacin	Lincomycin	Penicillin	Ticarcillin
Amoxicillin	Cefazolin	Clindamycin	Linezolid	Piperacillin - Tazobactam	Tobramycin
Amphotericin	Ceftazidime	Colistin	Meropenem	Polymyxin B	Vancomycin
Ampicillin	Cefuroxime	Daptomycin	Novobiocin	Streptomycin	Voriconazole
Aztreonam	Cephalothin				

Table 18 details the antibiotics most frequently used as suppressive antimicrobial therapy (SAT)

Table 18. Antibiotics Most Frequently Used as Suppressive Antimicrobial Therapy (Adapted from the SEIMC 2017 Guideline)

	Experience in prolonged treatments	Precautions and main adverse events
Beta-lactams	Low toxicity in the treatment of actinomycoses. However, hypersensitivity reactions are frequent with the use of penicillin. β-lactams are the most frequently used antibiotics for SAT in various case series of PJI.	Skin rash, hypersensitivity reactions
Clindamycin	Very little experience has been reported: treatment of suppurative hidrosadenitis and bone and joint infections. Low toxicity	Skin rash. Digestive intolerance. *C. difficile* associated colitis
Co-trimoxazole	There is a great deal of experience with its use; low toxicity is reported when low doses are used as prophylaxis of opportunistic infections. The use of high doses in bone and joint infections has frequently led to discontinuation due to digestive intolerance.	Digestive intolerance, leukopenia, megaloblastic anemia, hypersensitivity reactions. Recently, cases of sudden death on patients being administered cotrimoxazole along with spironolactone or inhibitors of the renin-angiotensin system have been reported. In a study addressing the impact of antimicrobials on fecal microbiota, a transitory increase of resistance to co-trimoxazole, amoxicillin, and amoxicillin-clavulanate acid was observed.
Macrolides	There is experience of prolonged administration of macrolides for preventing infections in patients with chronic pulmonary obstructive disease, with infrequent	A higher risk of sudden death in patients under treatment with macrolides plus amoxicillin has been reported, although it has recently been questioned whether these

	adverse events.	patients may be affected by other circumstances that could prolong the QT segment.
Fluoroquinolones	There is acceptable experience with the use of levofloxacin and ofloxacin in the treatment of multi-drug resistant tuberculosis (although the number of patients is scarce).	The use of fluoroquinolones has been associated with a higher risk of tendinopathy. This risk is increased in elderly patients, renal chronic failure, and patients under treatment with corticosteroids.
Rifampin	There is experience of long treatments with rifampin for brucellosis or tuberculosis. Short treatments of rifampin are more associated with toxicity.	Rifampin must never be used alone due to a high risk of resistance. There are frequent drug-to-drug interactions.
Tetracyclines	There is experience in the treatment of acne. Adverse events are more frequent with minocycline than with doxycycline.	Minocycline: skin pigmentation, drug-induced lupus (53 cases per 100,000 treatments) and hepatitis (1 case per 10,000 treatments and month). Doxycycline: drug-induced photosensitivity, digestive adverse events, including esophageal ulcers and erosions.

Section 2.0 Drug Therapy in Osteomyelitis

This section comprises four subsections: the first contains the newly recommended drugs, the second covers drug modifications, the third outlines the drugs that have been withdrawn from the market, and the fourth briefly details drugs that have been approved by the FDA and/or EMA but are not currently SFDA-registered.

2.1 Additions

No new drugs have been approved by the FDA or EMA for the treatment of osteomyelitis since March 2020.

2.2 Modifications

Below are the modifications made to the list of Osteomyelitis drugs since the CHI report in March 2020, reflecting the changes and updates:

Table 19. Prescribing Edits (PE) Modifications of Certain Osteomyelitis Drugs

Drugs	PE modifications
PA was removed for all antibiotics	
Linezolid, Ampicillin, Cefadroxil, Ceftazidime, Cefepime, Cephalexin, cloxacillin, flucloxacillin, levofloxacin, Moxifloxacin	**MD**: this drug should be prescribed by an infectious disease specialist or orthopedic consultant
Ceftriaxone	**MD:** this drug should be prescribed by an infectious disease specialist or orthopedic consultant **CU**: can be also used as initial treatment with clindamycin for pelvic arthritis along with surgical debridement OR with amoxicillin for enterococcus faecalis **ST:** first line therapy for Neisseria
Cefazolin	**MD:** this drug should be prescribed by an infectious disease specialist or orthopedic consultant **CU:** can be used in combination with amikacin (24-46 hours) for sepsis with widespread repercussions, or septic shock

Ciprofloxacin	**MD:** this drug should be prescribed by an infectious disease specialist or orthopedic consultant **ST:** used as first line treatment for Pseudomonas and Francisella. Also, used as subsequent therapy for infections caused by GNB
Clindamycin	**ST:** PREFERRED as first line therapy in S. aureus, methicillin- resistant, susceptible to clindamycin and as MSSA oral relay first line treatment in the event of sensitivity without inducible MLSb phenotype (sensitive to clindamycin) **MD:** drug should only be used after infectious disease or orthopedic consultation [culture based] and to avoid its adr. **CU:** can be used in combination therapy for the treatment of pelvic and childhood arthritis
Doxycycline	**CU**: used with rifampicin for treatment of brucella as first line therapy was added **AGE was modified to**: Doxycycline was traditionally avoided in ages <8 years, but use has more recently been accepted for short courses (<21 days) for all ages when necessary
Rifampicin (rifampin)	**CU**: used with doxycyline for treatment of brucella as first line therapy was added
Sulfamethoxazole, Trimethoprim	**AGE modified to:** infants less than 2 months (manufacturer's labeling), not to be used in infants < 4 weeks (CDC 2009)
Vancomycin	**ST:** first line therapy for MRSA resistant to clindamycin. Alternative for MRSA sensitive to clindamycin **MD:** this drug should be prescribed by an infectious disease specialist or orthopedic consultant
Daptomycin	**MD:** this drug should be prescribed by an infectious disease specialist or orthopedic consultant **AGE:** indicated for the treatment of patients with complicated skin and skin structure infections in adult and pediatric patients 1 to 17 years of age
Amoxicillin, Amoxicillin/ clavulanic acid, Imipenem/ cilastatin, Metronidazole, Minocycline, Colistimethate sodium, Ceftaroline fosamil, Amikacin,	**These drugs were added** **MD:** this drug should be prescribed by an infectious disease specialist or orthopedic consultant

Gentamicin, Tobramycin, Fosfomycin, Teicoplanin, Ceftobiprole Medocaril sodium	
Cefotaxime	**ST:** first line therapy for Neisseria **MD:** this drug should be prescribed by an infectious disease specialist or orthopedic consultant **CU:** can be used in combination with clindamycin for treatment of pelvic arthritis
Third generations cephalosporins	**Cefdinir, Ceftriaxone, Ceftazidime, Cefoperazone, Cefixime, Cefpodoxime, Cefotaxime** **ST**: ST: first line therapy for enterobacterials infections
Piperacillin/tazobactam	**CU:** can be used with other antibacterials for the management of pelvic or hands and wrist arthritis

2.3 Delisting

After thorough review of the previous CHI drug list for osteomyelitis treatment, it is recommended to delist the below medications from CHI formulary:

- Benzylpenicillin
- Doripenem

Table 20. Delisted Drugs

Delisted Medications	Reason	Medication Status	Available Alternative
Benzyl-penicillin	Drug is no longer SFDA registered	**Guidelines** do not recommend this drug for the treatment of osteomyelitis. Not **FDA** approved for this indication[9]. **EMA** approved for treatment of bone infections (label last revised in 2021)[10].	The previously mentioned guidelines recommend the following penicillins: - Penicillin M (oxacillin and nafcillin) - Amoxicillin - Amoxicillin/clavulinic acid - Ampicillin - Cloxacillin

Doripenem	Drug is no longer SFDA registered	Can be used to treat ESBL or AmpC producing GNB infections[7]. **FDA** labeled for the treatment of complicated intra-abdominal infections and complicated urinary tract infections, including pyelonephritis[11] (FDA 2007). **Doripenem is currently discontinued in the US[12].** **EMA** originally approved for the treatment of the following infections in adults: Nosocomial pneumonia (including ventilator–associated pneumonia), complicated intra-abdominal infections, and complicated urinary tract infections (EMA 2008). **However, this medicine is now withdrawn from use in the European Union[13].**	Carbapenems acting against ESBL or AmpC producing bacteria: - Meropenem - Ertapenem - Imipenem

2.4 Other Drugs

The drugs detailed in table 21 are **not SFDA registered**. However, they have been recommended for the treatment of Osteomyelitis.

Table 21. Non-SFDA Approved Drugs for the Management of Osteomyelitis

Drug	Approval	Indication	Dose
Tedizolid	**FDA** approved in 2014 indicated in adults for the treatment of acute bacterial skin and skin structure infections **EMA** approved in 2015 for patients from 12 years of age to treat acute (short-term) bacterial infections of the skin and of skin structures.	Recommended for the treatment of bone infections caused by susceptible bacteria as an alternative agent.	Skin and soft tissue infection (alternative agent)[14]: Note: Reserve for patients with or at risk for methicillin-resistant S. aureus infection who cannot receive preferred agents. Oral, IV: 200 mg once daily. Total duration of therapy is ≥5 days; may extend up to 14 days depending on severity and clinical response
Dalbavancin	**FDA** approved for the treatment of adult (in 2014) and pediatric (in 2021) acute bacterial skin and skin structure infections **EMA** approved in 2015 for the treatment of acute bacterial skin and skin structure infections	Recommended for bone infections caused by methicillin-resistant S. aureus infection as an alternative agent.	Skin and soft tissue infection (alternative agent)[14]: Note: Reserve for patients with or at risk for methicillin-resistant S. aureus infection who cannot receive preferred agents . IV: 1.5 g as a single dose or 1 g as a single dose initially, followed by 500 mg as a single dose 1 week later; the single dose has been shown to be as effective as the two-dose regimen.

Section 3.0 Key Recommendations Synthesis

- In children with suspected AHO, we recommend using empiric antimicrobial therapy active against *Staphylococcus aureus* (strong recommendation and moderate certainty of evidence)[5].
- Antimicrobials with activity against community-acquired methicillin-resistant *S. aureus* (CA-MRSA) should be considered based on local susceptibility data and patient history with regard to previous CA-MRSA infections and/or colonization[5].
- In the presence of a clinical presentation, physical examination, exposure history, or other risk factors that either are inconsistent with *S. aureus* infection or suggest need for coverage for other organisms, additional empiric antimicrobial coverage for pathogens other than *S. aureus* may be warranted (such as younger age for *Kingella kingae* or children with underlying hemoglobinopathies who have increased risk for *Salmonella* spp. infection)[5].
- In children with confirmed AHO, selection of a definitive antibiotic regimen should be based on the principles of selecting an effective agent against the identified pathogen, with the narrowest spectrum, lowest adverse effect profile, and most favorable host tolerance (Good Practice Statement)[5].
- In children with suspected AHO without an identified bacterial cause, selection of a definitive antibiotic regimen should be based on the principles of selecting an effective agent based on the most likely causative organism(s), with a spectrum comparable to that on which the patient demonstrated clinical and laboratory improvement, and with the lowest adverse effect profile and most favorable host tolerance (Good Practice Statement). [5]
- For children with suspected or documented AHO who respond to initial intravenous antibiotic therapy, we recommend transition to an oral antibiotic regimen rather than outpatient parenteral antibiotic therapy (OPAT) when an appropriate (active against the confirmed or presumed pathogen(s)) and well-tolerated oral antibiotic option is available (strong recommendation and low certainty of evidence)[5].

  This recommendation places a high value on avoidance of harms and costs as well as on the improvement of acceptability, feasibility, and equity.
- In children with AHO presumed or proven to be caused by S. aureus who have had an uncomplicated course and responded to initial therapy, we suggest a 3- to 4-week duration of antibiotics rather than a longer course (conditional recommendation and very low certainty of evidence). [5]

- For children either experiencing primary treatment failure or early or late recurrence of AHO[5]:
    - Clinicians should assess the adequacy of the antimicrobial regimen (spectrum of activity, dosage, and penetration to the site of infection, and adherence) before deciding on the need to broaden the spectrum or to restart antimicrobials (Good practice statement).
- Clinicians should reassess the need for surgical intervention for therapeutic and/or diagnostic purposes (Good practice statement).

The suggested duration of therapy should be based on clinical course (pace of resolution of fever and clinical signs and symptoms, noting the need for surgical intervention(s) required, if any), supported by decline of inflammatory markers[5].

- Treatment durations[6]:
    - *S. aureus*, and enterobacterials: 6 weeks
    - *Streptococcus* spp: 4 weeks
    - *Neisseria gonorrhoeae*: 7 days
    - Early arthritis (evolution < 4 weeks), by direct inoculation of the small joints of the hands, following proper surgical hand washing: 14 days in the absence of osteolysis.
- Initial MSSA Treatment[6]:
    - IV cefazolin or IV penicillin M (cloxacillin, oxacillin), is the recommended initial treatment of MSSA arthritis.
- MSSA Oral Relay[6]:
    - The molecule for oral relay is chosen according to antimicrobial susceptibility.
    - If monotherapy, clindamycin is proposed as first-line treatment in the event of sensitivity without inducible MLSb phenotype, that is to say a strain sensitive to clindamycin and erythromycin.
    - Without complications, the total treatment duration is six weeks.
- MRSA[6]:
    - Daptomycin in monotherapy is recommended as first-line initial treatment, with vancomycin or teicoplanin as possible alternatives.
    - Without complications, the total treatment duration is six weeks.
- Pseudomonas[6]:
    - Initial intravenous (IV) treatment on microbiological documentation

- Initial antibiotic treatment: ceftazidime or cefepime on Pseudomonas aeruginosa-infected native joint
- Oral relay of antibiotic treatment of septic arthritis on Pseudomonas aeruginosa-affected native joint only once the infection is under control and after at least 14 days of treatment by intravenous beta-lactams. The first-line molecule is ciprofloxacin.
- It is recommended, in the event of acquired P. aeruginosa resistance, to take the advice of an expert center in relation with the reference microbiologist and infectiologist.

- Childhood arthritis[6]:
  - 1st or 2nd-generation or IV amoxicillin/clavulanic acid at 3 months of age (oxacillin or cloxacillin possible from 4 years)
  - If severe sepsis and/or toxic shock: add clindamycin or linezolid
  - Total treatment duration is 2 weeks.
- Precautions to be taken in clindamycin treatment[6]:
  - Patients treated by clindamycin must be warned about the risk of diarrhea.
  - Diarrhea imperatively necessitates specific diagnostic and therapeutic management.
- Pediatric clindamycin[6]:
  - It is recommended to render accessible the pediatric syrup form of clindamycin.
- The main medical and surgical strategies to be considered in a patient with PJI are[7]:

  a) Attempted eradication with implant retention and antibiotics (DAIR).

  b) Attempted eradication with implant removal and antibiotics:
  - With prosthesis replacement (in a 1-step or a 2-step exchange procedure).
  - Without prosthesis replacement (arthrodesis or resection arthroplasty).

  c) Implant retention and long-term suppressive antibiotics (SAT), without attempted eradication
- Staphylococcal infections[7]:
  - Initial treatment (antibiotics against planktonic bacteria):

a) Methicillin-susceptible strains: cloxacillin (or cefazolin) (B-II), or cloxacillin + daptomycin (C-III).

b) Methicillin-resistant strains: daptomycin + cloxacillin, or daptomycin + fosfomycin (C-III), or vancomycin (B-II).

- Streptococcal infections[7]:
    - For initial treatment (planktonic phase): penicillin or ceftriaxone (B-II).
- For acute staphylococcal PJI managed with rifampin and levofloxacin, an 8-week schedule of treatment after debridement appears sufficient for most patients (B-I)[7].
- For PJI caused by other microorganisms treated with antibiotics with good activity against biofilm-embedded bacteria (i.e., ciprofloxacin for PJI caused by GNB, 8 weeks is also a reasonable duration) (B-III)[7].
- In other clinical scenarios, the most appropriate duration of treatment remains uncertain. A variable period between 8 and 12 weeks may be adequate (B-III)[7].

Section 4.0 Conclusion

This report serves as **an annex to the previous CHI Osteomyelitis report** and aims to provide recommendations to aid in the management of Osteomyelitis. These recommendations should be utilized to support clinical decision-making and not replace it in the management of individual patients with Osteomyelitis. Health professionals are expected to consider this guidance alongside the specific needs, preferences, and values of their patients when exercising their judgment.

Section 5.0 References

1. John Hopkins. Osteomyelitis. Published 2023. Accessed October 19, 2023. https://www.hopkinsmedicine.org/health/conditions-and-diseases/osteomyelitis
2. mayo clinic. osteomyelitis . Published 2022. Accessed October 19, 2023. https://www.mayoclinic.org/diseases-conditions/osteomyelitis/symptoms-causes/syc-20375913
3. Thakolkaran N, Shetty AK. Acute Hematogenous Osteomyelitis in Children. *Ochsner journal*. 2019;19(2):116-122. doi:10.31486/toj.18.0138
4. Momodu &Savaliya. Osteomyelitis. Published 2023. Accessed October 19, 2023. https://www.ncbi.nlm.nih.gov/books/NBK532250/#:~:text=Osteomyelitis%20is%20a%20serious%20infection,bloodstream%2C%20fractures%2C%20or%20surgery.
5. Woods CR, Bradley JS, Chatterjee A, et al. Clinical Practice Guideline by the Pediatric Infectious Diseases Society and the Infectious Diseases Society of America: 2021 Guideline on Diagnosis and Management of Acute Hematogenous Osteomyelitis in Pediatrics. *J Pediatric Infect Dis Soc*. 2021;10(8):801-844. doi:10.1093/jpids/piab027
6. Stahl JP, Canouï E, Pavese P, et al. SPILF update on bacterial arthritis in adults and children. *Infect Dis Now*. 2023;53(4). doi:10.1016/j.idnow.2023.104694
7. Ariza Cardenal J, Cobo Reinoso J, Baraia-Etxaburu Artetxe J, et al. *Management of Prosthetic Joint Infections. Clinical Practice Guidelines by the Spanish Society of Infectious Diseases and Clinical Microbiology (SEIMC)*. http://reipi.org
8. Ariza J, Cobo J, Baraia-Etxaburu J, et al. Executive summary of management of prosthetic joint infections. Clinical practice guidelines by the Spanish Society of Infectious Diseases and Clinical Microbiology (SEIMC). *Enferm Infecc Microbiol Clin*. 2017;35(3):189-195. doi:10.1016/j.eimc.2016.08.012
9. Food and Drug Administration (FDA). Penicillin G Sodium for Injection, USP 5,000,000 Units (5 million units). https://www.accessdata.fda.gov/drugsatfda_docs/label/2012/065068s013lbl.pdf
10. *Benzylpenicillin Sodium 600mg and 1200mg Powder for Injection*. www.mhra.gov.uk/yellowcard.
11. Fda, Cder. *HIGHLIGHTS OF PRESCRIBING INFORMATION These Highlights Do Not Include All the Information Needed to Use DORIBAX ® Safely and Effectively. See Full Prescribing Information for DORIBAX ®. DORIBAX ®*

(Doripenem for Injection) Powder, For Solution for Intravenous Use Initial U.S. Approval: 2007. www.fda.gov/medwatch.

12. Hori T, Owusu YB, Sun D. US FDA-Approved Antibiotics During the 21st Century. In: *Encyclopedia of Infection and Immunity*. Elsevier; 2022:556-585. doi:10.1016/B978-0-12-818731-9.00144-0

13. Doribax | European Medicines Agency. Accessed November 13, 2023. https://www.ema.europa.eu/en/medicines/human/EPAR/doribax

14. Lexicomp. Published 2023. Accessed June 6, 2023. https://online-lexi-com.ezproxy.lau.edu.lb:2443/lco/action/home

Section 6.0 Appendices

Appendix A. Prescribing Edits Definition

I. Prescribing Edits (ensure consistent use of abbreviations, e.g., CU, ST)

Some covered drugs may have additional requirements, rules, or limits on coverage. These requirements and limits may include:

Prescribing edits Tools	Description
AGE (Age):	Coverage may depend on patient age
CU (Concurrent Use):	Coverage may depend upon concurrent use of another drug
G (Gender):	Coverage may depend on patient gender
MD (Physician Specialty):	Coverage may depend on prescribing physician's specialty or board certification
PA (Prior Authorization):	Requires specific physician request process
QL (Quantity Limits):	Coverage may be limited to specific quantities per prescription and/or time period
ST (Step Therapy):	Coverage may depend on previous use of another drug
EU (Emergency Use only):	This drug status on Formulary is only for emergency use
PE (Protocol Edit):	Use of drug is dependent on protocol combination, doses, and sequence of therapy

Appendix B. Osteomyelitis Scope

Section	Rationale/Updates
Section 1.1.1 **Clinical Practice Guideline by the Pediatric Infectious Diseases Society and the Infectious Diseases Society of America: 2021 Guideline on Diagnosis and Management of Acute Hematogenous Osteomyelitis in Pediatrics**[5]	This set of criteria is consensus based with primary focus on clinical findings and course. It may be reasonable to include additional laboratory tests such as the serum C-reactive protein (CRP) in making a determination of an uncomplicated vs complicated course. Concepts such as: • Rapid fall of the CRP concentration within 48 h of initiation of treatment **or** • A 50% or more decline from peak CRP concentration within 3 to 5 d of admission or first surgical debridement may considered. • The PIDS and IDSA published the below recommendations for the Diagnosis and Management of Acute Hematogenous Osteomyelitis in Pediatrics. The quality of evidence and strength of recommendations are defined in appendix B. • In children with presumed Acute hematogenous osteomyelitis (AHO) who are ill-appearing or have rapidly progressive infection, we recommend starting empiric antimicrobial therapy immediately rather than withholding antibiotics until invasive diagnostic procedures are performed (strong recommendation and moderate certainty of evidence). *Comment*: - The yield of positive cultures from specimens collected by invasive diagnostic procedures (bone biopsy and aspirate), when obtained within 24 to 48 hours after initiation of antibiotic therapy, is similar to the yield when these cultures are obtained prior to the administration of antibiotics. • In children with presumed AHO who are not clinically ill and for whom an aspirate or biopsy by invasive diagnostic procedure is being planned prior to initiating antibiotics, we suggest withholding antibiotics for no more than 48 to 72 hours (conditional recommendation and very low certainty of evidence). *Comment*: - The decision to implement this recommendation incorporating a reasonable delay may be influenced by local accessibility to experts and resources to perform invasive diagnostic procedures or the time required for transport to a higher level of care if appropriate. - For children likely to have AHO, it is advisable that children remain hospitalized for observation while withholding antibiotics until cultures can be obtained.

	• In children with suspected AHO, we recommend using empiric antimicrobial therapy active against Staphylococcus aureus (strong recommendation and moderate certainty of evidence). • Antimicrobials with activity against community-acquired methicillin-resistant S. aureus (CA-MRSA) should be considered based on local susceptibility data and patient history with regard to previous CA-MRSA infections and/or colonization. • In the presence of a clinical presentation, physical examination, exposure history, or other risk factors that either are inconsistent with S. aureus infection or suggest need for coverage for other organisms, additional empiric antimicrobial coverage for pathogens other than S. aureus may be warranted (such as younger age for Kingella kingae or children with underlying hemoglobinopathies who have increased risk for Salmonella spp. infection). • In children with AHO who present with sepsis or have a rapidly progressive infection, we recommend debridement of the infected bone and any associated abscesses as soon as possible after diagnosis, rather than treating with medical therapy alone (strong recommendation and moderate certainty of evidence). • In a child with AHO who is clinically stable but is documented to have a substantial abscess (greater than 2 cm), we suggest debridement rather than treating with medical therapy alone (conditional recommendation and very low certainty of evidence). • In children with AHO requiring a surgical procedure, we recommend against routine use of surgical-site (ie, instilled or implanted) antimicrobial agents (strong recommendation and very low certainty of evidence). • This recommendation places a high value on avoiding unnecessary harm and cost associated with this intervention. • In children with confirmed AHO, selection of a definitive antibiotic regimen should be based on the principles of selecting an effective agent against the identified pathogen, with the narrowest spectrum, lowest adverse effect profile, and most favorable host tolerance (Good Practice Statement). • In children with suspected AHO without an identified bacterial cause, selection of a definitive antibiotic regimen should be based on the principles of selecting an effective agent based on the most likely causative organism(s), with a spectrum comparable to that on which the patient demonstrated clinical and laboratory improvement, and with the lowest adverse effect profile and most favorable host tolerance (Good Practice Statement). • In children with suspected or confirmed AHO receiving antimicrobial therapy, we suggest performing sequential monitoring of CRP in addition to serial clinical evaluation to assess response to therapy, rather

	than relying solely on clinical evaluation (conditional recommendation and low certainty of evidence). *Comment*: • Serial clinical examinations that assess the febrile response, pain, and musculoskeletal function are important clinical parameters to monitor response to treatment. • For children with suspected or documented AHO who respond to initial intravenous antibiotic therapy, we recommend transition to an oral antibiotic regimen rather than outpatient parenteral antibiotic therapy (OPAT) when an appropriate (active against the confirmed or presumed pathogen(s)) and well-tolerated oral antibiotic option is available (strong recommendation and low certainty of evidence). *Comment*: • This recommendation places a high value on avoidance of harms and costs as well as on the improvement of acceptability, feasibility, and equity. • For children with suspected or documented AHO who respond to initial parenteral antibiotic therapy but for whom oral antimicrobial therapy is not feasible, we suggest transition to OPAT, rather than remaining in an acute-care hospital for the total duration of therapy (conditional recommendation and very low certainty of evidence). *Comment*: • This recommendation places a high value on avoiding harms and costs associated with unnecessary and prolonged hospital stay. The decision to implement this recommendation and the selection of the type of OPAT (home, intermediate care facility, and clinic) may be influenced by the availability of local resources. • In children with AHO presumed or proven to be caused by S. aureus who have had an uncomplicated course and responded to initial therapy, we suggest a 3- to 4-week duration of antibiotics rather than a longer course (conditional recommendation and very low certainty of evidence). *Comment*: • Although the optimal duration of therapy is best described for uncomplicated courses of AHO due to methicillin-susceptible S. aureus (MSSA), longer duration may be necessary for other pathogens, including more virulent strains of S. aureus (such as USA 300 and Panton Valentine leucocidin + [PVL+], whether CA-MRSA or MSSA), and for complicated courses • For children either experiencing primary treatment failure or early or late recurrence of AHO: • Clinicians should assess the adequacy of the antimicrobial regimen (spectrum of activity, dosage and penetration to the site of infection, and adherence) before deciding on the need to broaden the spectrum or

	to restart antimicrobials (Good practice statement). • Clinicians should reassess the need for surgical intervention for therapeutic and/or diagnostic purposes (Good practice statement). Comment: The accuracy of the diagnosis of AHO may need to be reconsidered, especially in culture-negative cases. • In children with AHO who are determined to be at risk of long-term adverse outcomes, we suggest a follow-up period of at least 1 year by specialists with experience treating children with AHO (conditional recommendation and low certainty of evidence). ➔ The suggested duration of therapy should be based on clinical course (pace of resolution of fever and clinical signs and symptoms, noting the need for surgical intervention(s) required, if any), supported by decline of inflammatory markers. ➔ Preferred and alternative agents are selected based on published data regarding in vitro activity, clinical efficacy, and safety. Agents are generally listed in order of preference. ➔ Many of the beta-lactamase-stable penicillins cause significant phlebitis in peripheral veins with infusion; administration through a central venous catheter is preferred. ➔ Alternative antibiotics that may display in vitro activity against S. aureus have not been evaluated prospectively in AHO. However, linezolid has been evaluated in prospective, controlled clinical trials for invasive methicillin resistant S. aureus nosocomial pneumonia in adults and is more likely to provide adequate therapy of invasive S. aureus AHO, compared with trimethoprim/sulfamethoxazole, which is not recommended for children with AHO by the Infectious Diseases Society of America (IDSA) Clinical Practice Guidelines for Treatment of Methicillin-Resistant Staphylococcus aureus Infections in Adults and Children. ➔ For children receiving linezolid for more than 2 weeks, weekly screening for thrombocytopenia and neutropenia is recommended.
Section 1.1.2 **SPILF (French Society of Infectious Pathology) update on bacterial arthritis in adults and**	• The usual regulations for management of osteoarticular infections (OAI) must be followed in coordination with the antibiotic specialists of the establishment. The following rules are relevant: o Bacteriological sampling before initiation of antibiotic therapy or subsequent to a time lapse without antibiotic therapy, ideally 14 days, except in cases of therapeutic urgency. o Probabilistic antibiotherapy secondarily adapted to bacteriological results, to those pertaining the molecular biology of synovial fluids, and to antibiotic tolerance.

children 2023[6]	o The shortest possible treatment duration, o Monitoring of the tolerance and efficacy of antibiotic therapy. • Recommendation 1 - Treatment durations: • S. aureus, and enterobacterials 6 weeks • Streptococcus spp 4 weeks • Neisseria gonorrhoeae: 7 days • Early arthritis (evolution < 4 weeks), by direct inoculation of the small joints of the hands, following proper surgical hand washing: 14 days in the absence of osteolysis • Recommendation 2 – Probabilistic antibiotherapy should begin when: o Direct examination with positive results and/or synovial fluid culture and/or positive hemoculture (after having ruled out contamination) ▪ Antibiotic therapy adapted to Gram stain and/or bacterial culture o Sepsis with widespread repercussions, or septic shock ▪ Antibiotic therapy adapted to Gram stain and/or bacterial culture if infection is documented ▪ Cefazolin* or penicillin M (cloxacillin, oxacillin), + amikacin (24–48 h) *In case of beta-lactam allergy, daptomycin or, by default, a glycopeptide (vancomycin or teicoplanin) is used. o Purulent synovial fluid (with negative or unavailable direct examination results) + anamnesis compatible with the septic arthritis diagnosis + expert advice ▪ Cefazolin* or penicillin M (cloxacillin, oxacillin), +/- broadened spectrum if anamnesis suggests a specific bacterium. *In case of beta-lactam allergy, daptomycin or, by default, a glycopeptide (vancomycin or teicoplanin) is used. • Recommendation 3 – Initial MSSA Treatment o IV cefazolin or IV penicillin M (cloxacillin, oxacillin), is the recommended initial treatment of MSSA arthritis o Association with an aminoside is not recommended in the absence of septic shock or sepsis with widespread repercussions o In case of beta-lactam allergy, daptomycin or, by default, a glycopeptide (vancomycin or teicoplanin) is used.

	• Recommendation 4 – MSSA Oral Relay:
	  o The molecule for oral relay is chosen according to antimicrobial susceptibility.
	  o Only with certain molecules is monotherapy possible.
	  o If monotherapy, clindamycin is proposed as first-line treatment in the event of sensitivity without inducible MLSb phenotype, that is to say a strain sensitive to clindamycin and erythromycin.
	  o The levofloxacin/rifampicin or levofloxacin/clindamycin associations may likewise be proposed as first-line treatment.
	  o In the event of resistance to clindamycin or of an inducible MLSb phenotype, doxycycline, an oxazolidinone (linezolid, tedizolid) or cotrimoxazole may be proposed.
	  o Levofloxacin and rifampicin must be used in association with one another.
	  o Without complications, total treatment duration is six weeks.
	• Recommendation 5 - MRSA
	  o Daptomycin in monotherapy is recommended as first-line initial treatment, with vancomycin or teicoplanin as possible alternatives.
	  o Following expert advice, dalbavancin, ceftaroline or ceftobiprole may be considered.
	  o Oral relay should be determined by MRSA-sensitivity profile; the MSSA proposals remain applicable.
	  o Without complications, total treatment duration is 6 weeks.
	• Recommendation 6 - Streptococci sensitive to penicillin
	  o Amoxicillin is the initial first-line treatment for streptococcal-associated arthritis.
	  o In the event of non-severe allergy to amoxicillin: cefazolin or ceftriaxone or cefotaxime
	  o In the event of severe beta-lactam allergy: daptomycin
	  o Oral relay: amoxicillin or, if allergy, clindamycin in the absence of inducible MLSb phenotype (strain sensitive to erythromycin)
	  o If resistance to clindamycin: oxazolidinone (linezolid, tedizolid)
	  o Without complications, total treatment duration is 4 weeks.
	• Recommendation 7 – Penicillin-resistant (MIC > 0.250 mg/L) streptococci:
	  o If sensitive to cephalosporins: cefotaxime or ceftriaxone
	  o If cephalosporin-resistant: daptomycin
	• Recommendation 8 – Enterococci sensitive to amoxicillin
	  o Initial treatment: High-dose IV amoxicillin in monotherapy

	○ If allergy: vancomycin or teicoplanin ○ Oral relay: amoxicillin or, if allergy, oxazolidinones (linezolid, tedizolid) ○ Without complications, total treatment duration is 4 weeks. • Recommendation 9 – Amoxicillin-resistant enterococci ○ Initial treatment: glycopeptide ○ Oral relay: oxazolidinone (linezolid, tedizolid) ○ Expert advice required • Recommendation 10 – Vancomycin-resistant enterococci ○ Expert advice required • Recommendation 11 – Cutibacterium acnes ○ Initial treatment: IV amoxicillin, IV clindamycin in cases of beta-lactam allergy and in the event of a sensitive strain ○ Oral relay: amoxicillin or (according to susceptibility) clindamycin or doxycycline in the event of allergy. Oxazolidinone (linezolid, tedizolid) if intolerance ○ Without complications, total duration is 4 weeks. • Recommendation 12 – Enterobacterials ○ Initial treatment: 3rd-generation IV cephalosporin ○ In group III or group IV enterobacterials: cefepime IV ○ Oral relay: levofloxacin if sensitive, specialized advice if resistance ○ Without complications, treatment duration of 6 weeks • Recommendation 13 – Beta-lactam or carbapenemase producing enterobacterales ○ It is recommended to take the advice of an infectiologist in treatment of multidrug-resistant bacteria (ESBL and/or carbapenemase) on native joint. • Recommendation 14 – Pseudomonas ○ Initial intravenous (IV) treatment on microbiological documentation ○ Initial antibiotic treatment: ceftazidime or cefepime on Pseudomonas aeruginosa-infected native joint ○ Oral relay of antibiotic treatment of septic arthritis on Pseudomonas aeruginosa-affected native joint only once the infection is under control and after at least 14 days of treatment by intravenous beta-lactams. The first-line molecule is ciprofloxacin.

	○ It is recommended, in the event of acquired P. aeruginosa resistance, to take the advice of an expert center in relation with the reference microbiologist and infectiologist. • Recommendation 15 – Neisseria ○ Initial treatment: cefotaxime or IV ceftriaxone ○ Treatment duration: 7 days • Recommendation 16 - Other gram-negative bacteria • It is recommended to obtain an infectiologist's advice on antibiotic treatment of septic arthritis on native joint due to Acinetobacter spp, Campylobacter spp, Haemophilus spp, Aeromonas spp or anerobic bacilli. • Recommendation 17 - Pasteurella • First-line amoxicillin/clavulanic acid • Amoxicillin or doxycycline are possible following reception of antibiogram. • Treatment duration is 6 weeks, with the exception of small joint arthritis, for which, in the absence of osteolysis and after surgical washing, recommended duration is 2 weeks. • Recommendation 18 - Brucella ○ Oral route: doxycycline + rifampicin, for 6 weeks. ○ Cotrimoxazole is a possible alternative in the event of contraindication of one of the antibiotics, as is gentamicin (for 2 weeks only) • Recommendation 19: Listeria ○ Initial treatment: IV amoxicillin (2 weeks) + IV gentamicin (5 days) ○ Followed by oral relay: amoxicillin ○ Alternative to amoxicillin: cotrimoxazole ○ Total treatment duration: 4 weeks • Recommendation 20: Ureaplasma and Mycoplasma ○ Initial treatment: doxycycline ○ If unfavorable evolution, doxycycline + levofloxacin biotherapy is proposed. ○ Treatment duration: 12 weeks • Recommendation 21: Mycobacteria ○ The therapeutic recommendations may be found in figure below

Antibiotic therapy for septic arthritis due to mycobacteria.

Infection		ANTIBIOTIQUES 1st-line treatment	2nd-line treatment / alternative
	M. tuberculosis susceptible	Rifampicin 10 mg/kg PO, once a day 6 months Isoniazid 3–5 mg/kg/d PO, once a day, 6 months Ethambutol 15–20 mg/kg PO, once a day: 2 months Pyrazinamide 20–25 mg/kg/d PO, once a day, 2 months	
MNT à croissance rapide	*M.chelonae*	Azithromycin 250–500 mg *, PO, once a day AND Amikacin 10–15 mg/kg, IV/IM, once a day OR Linezolid 600 mg, PO, once or twice a day	Imipenem, Moxifloxacin, Tobramycin, Doxycycline, Ciprofloxacin, Levofloxacin, Tigecycline, clarithromycin
	M.abcessus	Cefoxitin 1–2 g, IV, twice a day OR Amikacin 10–15 mg/kg, IV/IM, once a day AND Azithromycin 250–500 mg*, PO, once a day	Linezolid, Moxifloxacin, Ciprofloxacin, Imipenem, clarithromycin
	M.fortuitum	Imipenem 1000 mg, IV, 2–3 times a day AND Amikacin 10–15 mg/kg, IV/IM, once a day AND Ciprofloxacin 500–750 mg, PO, twice a day	Cefoxitin, Cotrimoxazole, Linezolid, Azithromycin, clarithromycin (if sensitive)
MNT à croissance lente	*M.marinium*[1]	Rifampicin 10 mg/kg (max 600 mg) PO, once a day AND Ethambutol 15 mg/kg (max 1600 mg) PO, once a day AND Azithromycin 250–500 mg*, PO, once a day	Cotrimoxazole, Linezolid, Doxycycline (Sensitivity 50%), Ciprofloxacin (Sensitivity 50%), clarithromycin
	M.kansasii	Azithromycin 250–500 mg*, PO, once a day AND Rifampicin 10 mg/kg (max 600 mg) PO, once a day AND Ethambutol 15 mg/kg (max 1600 mg) PO, once a day	Moxifloxacin, Cotrimoxazole, clarithromycin
	M.avium-intracellular	Azithromycin 250–500 mg*, PO, once a day AND Rifampicin 10 mg/kg (max 600 mg) PO, once a day AND Ethambutol 15 mg/kg (max 1600 mg) PO, once a day	Clarithromycin, Amikacin
	M.xenopi	Azithromycin 250–500 mg*, PO, once a day AND Rifampicin 10 mg/kg (max 600 mg) PO, once a day AND Ethambutol 15 mg/kg (max 1600 mg) PO, once a day	Moxifloxacin, clarithromycin
	M.malmoense	Azithromycin 250–500 mg*, PO, once a day AND Rifampicin 10 mg/kg (max 600 mg) PO, once a day AND Ethambutol 15 mg/kg (max 1600 mg) PO, once a day	Moxifloxacin, Levofloxacin, clarithromycin

* oR clarithromycin 500 mg, PO, twice a day.
PO = per os. IV = intravenous. IM = intra-muscular, NTM = non-tuberculous mycobacteria.
[1] évolution often favorable with medical treatment alone. surgical treatment could shortEn antibiotic therapy duration.

- Recommendation 22 Coxiella

	○ Initial treatment: doxycycline for 18 months ○ Addition of hydroxychloroquine has never yielded proof of effectiveness. ○ Few available clinical data on alternatives: cotrimoxazole, or doxycycline-fluoroquinolone or rifampicin-fluoroquinolone. • Recommendation 23: Erysipelotrix ○ Initial treatment: Amoxicillin ○ Alternative and/or oral relay: levofloxacin or clindamycin ○ Treatment duration: 4 weeks • Recommendation 24: Francisella ○ Initial treatment: oral ciprofloxacin ○ Alternative: doxycycline ○ Duration: 4 weeks • Recommendations 25: Arthritis in the hands and wrist ○ It is urgently recommended to perform intraoperative lavage of the joints with microbiological sampling. ○ The route of administration of probabilistic antibiotic therapy is intravenous. Initial oral treatment is possible in less serious cases, or subsequent to early surgery. ○ Probabilistic postoperative antibiotic therapy consists in an amoxicillin/clavulanic association. If allergy: cotrimoxazole, or levofloxacin or doxycycline. ○ In the event of serious bodily harm with extension toward soft tissue and/or functional risk: piperacillin/tazobactam +/- amikacin. ○ Following surgical lavage, antibiotic therapy lasts two weeks, except in cases of osteolysis • Recommendation 26: Pelvic arthritis ○ Initial treatment: ceftriaxone/cefotaxime + clindamycin ○ Pelvic arthritis secondary to a local pathology (bedsore, surgery), or occurring after radiation therapy: piperacillin/tazobactam + clindamycin or oxazolidinone (linezolid, tedizolid) ○ Surgical debridement must be considered ○ Treatment duration is determined according to clinical evolution and possible surgery. • Recommendation 27: Arthritis and endocarditis ○ Endocarditis may be suspected in any case of arthritis due to Gram-positive bacteria.

	○ When septic arthritis occurs in the context of endocarditis, antibiotic treatment must be based on therapeutic recommendations pertaining to endocarditis. ○ Regardless of treatment duration for associated endocarditis, treatment duration for arthritis remains the same (S. aureus 6 weeks; other pyogens 4 to 6 weeks). • Recommendation 28 Childhood arthritis ○ Probabilistic intravenous treatment by monotherapy, as soon as aspiration is carried out ○ 1st or 2nd-generation or IV amoxicillin/clavulanic acid at 3 months of age (oxacillin or cloxacillin possible from 4 years) ○ If severe sepsis and/or toxic shock: add clindamycin or linezolid ○ If favorable evolution, oral relay from the 4th day ○ If no pathogenic agent is found, the oral relay antibiotic therapy consists in amoxicillin-clavulanic acid or cephalexin ○ If identified MSSA, the oral relay antibiotic therapy consists in amoxicillin-clavulanic acid, cefalexin or cotrimoxazole in children under 6 years of age and, in children over 6 years of age, clindamycin (capsule) if MSSA sensitive to erythromycin or cefalexin. ○ Total treatment duration is 2 weeks. • Recommendation 29: Precautions to be taken in clindamycin treatment ○ Patients treated by clindamycin must be warned about the risk of diarrhea. ○ Diarrhea imperatively necessitates specific diagnostic and therapeutic management. • Recommendation 30: pediatric clindamycin • It is recommended to render accessible the pediatric syrup form of clindamycin.
Section 1.1.3 **Management of prosthetic joint infections. Clinical practice guidelines by the Spanish Society of Infectious Diseases and**	• Due to the complexity of patients with Prosthetic Joint Infections (PJI), they should be attended at multidisciplinary units (C-III). • The main medical and surgical strategies to be considered in a patient with PJI are: a) Attempted eradication with implant retention and antibiotics (DAIR). b) Attempted eradication with implant removal and antibiotics: - With prosthesis replacement (in a 1-step or a 2-step exchange procedure). - Without prosthesis replacement (arthrodesis or resection arthroplasty). c) Implant retention and long-term suppressive antibiotics (SAT), without attempted eradication

Clinical Microbiology (SEIMC) 2017[7]	• The best candidates for attempting eradication treatment with implant retention are those who:
	a) Have an early post-surgical (up to three months after the placement of the prosthesis) or haematogenous (either suspected or proven) infection (A-II), with a stable implant, and surrounding skin and soft tissues in good condition.
	b) Have a short duration of symptoms (≤3 weeks) (B-II).
	c) Can be treated with rifampin (staphylococcal infections) or fluoroquinolones (infections caused by GNB) (A-II).
	- Some patients who do not strictly meet the above criteria may still benefit from this strategy, but its implementation should be considered on an individualized basis, since there is a higher likelihood of failure (B-II).
	• Removal of the prosthesis:
	  • The prosthesis should be removed in cases of chronic PJI (A-II).
	  • A 2-step exchange procedure is recommended in patients with chronic PJI (A-II).
	  • In patients with acute PJI who are not candidates for eradication treatment with implant retention, a 2-step exchange procedure is recommended (B-II).
	  • The performance of a 1-step exchange procedure may be considered in non-immunosuppressed patients if they have good bone stock, if the prosthetic surrounding soft tissues are in good condition, and if the infection is caused by microorganisms susceptible to antibiotics with good activity against sessile (biofilm-embedded) bacteria (B-II).
	  • In patients with acute PJI in whom the removal of the prosthesis is not very complex, a 1-step exchange procedure is recommended as long as the causative microorganisms are susceptible to antibiotics with good activity against biofilm-embedded bacteria (C-III).
	• Implant retention without attempted eradication:
	  • The following conditions need to be met for the indication of SAT:
	a) Identification of the microorganism causing the infection.
	b) Availability of oral antibiotics which are not toxic when administered over long periods of time. The use of SAT with parenteral antibiotics with long half-life has been reported, but this strategy is very rarely applied.
	c) Possibility of a close follow-up of the patient
	  • Treatment with SAT may be considered in situations in which medical and surgical strategies are

	unlikely to cure the patient, and non-toxic long-term antimicrobials are available (B-II). • Treatment with SAT is not indicated in acute PJI managed early, with appropriate debridement and optimized antimicrobial therapy (E-II). • Attempted eradication without implant removal: • Surgical debridement must be performed promptly by an expert surgical team, with the patient in the best possible condition (C-III). • After surgical debridement, antibiotics with good activity against rapidly-growing planktonic bacteria should be provided, ideally based on β-lactams, lipopeptides, or glycopeptides (B-III). • This initial treatment must be administered intravenously for at least 7 days before switching to an optimized antimicrobial therapy focused on the treatment of biofilm-embedded bacteria (C-III). • Staphylococcal infections: • Initial treatment (antibiotics against planktonic bacteria): a) Methicillin-susceptible strains: cloxacillin (or cefazolin) (B-II), or cloxacillin + daptomycin (C-III). b) Methicillin-resistant strains: daptomycin + cloxacillin, or daptomycin + fosfomycin (C-III), or vancomycin (B-II). • Subsequent treatment (against biofilm-embedded bacteria): a) Treatment of choice: rifampin + levofloxacin (A-II). b) If fluoroquinolones cannot be used: combinations of rifampin with co-trimoxazole (B-II), linezolid (B-II), clindamycin (B-II), fusidic acid (B-II), or daptomycin (B-III). c) If rifampin cannot be used: combinations of daptomycin with fosfomycin (B-III), cloxacillin (B-III), linezolid (B-III), co-trimoxazole (C-III), or levofloxacin (C-III); or combinations of 2 oral antibiotics or monotherapy with levofloxacin (B-III), or moxifloxacin (B-III), co-trimoxazole (BIII), or linezolid (B-III). • Streptococcal infections: • For initial treatment (planktonic phase): penicillin or ceftriaxone (B-II). • Subsequent treatment (biofilm-embedded bacteria): penicillin or ceftriaxone (B-II), followed by amoxicillin (B-II), either in combination with rifampin or not (B-III); alternatively, levofloxacin (B-III) either in combination with rifampin or not (B-III), or monotherapy with clindamycin or linezolid in the case of allergy to fluoroquinolones (C-III). • Infections caused by Enterococcus faecalis:

	○ The treatment of choice is ampicillin, followed by oral amoxicillin (B-II). ○ It can be administered in combination with ceftriaxone (B-III) or rifampin (B-III). ○ Teicoplanin or linezolid are possible alternatives (C-III). • Infections caused by GNB: ○ For initial treatment (planktonic phase): a β-lactam (a 3rd-generation cephalosporin for Enterobacteriaceae, a carbapenem for ESBL or AmpC β-lactamase producing GNB, and an anti-pseudomonal β-lactam for P. aeruginosa) (B-III). ○ Subsequent treatment (biofilm-embedded bacteria): a) Treatment of choice: fluoroquinolone (ciprofloxacin) (A-II). b) If fluoroquinolones cannot be used (due to resistance, toxicity…): continue treatment with a β-lactam (B-III) combined or not with colistin (B-III) or fosfomycin (C-III), or monotherapy with co-trimoxazole (C-III). • Culture-negative PJI: ○ If possible, the use of antibiotics prior to a valid sampling (i.e., joint aspirate, and/or intraoperative cultures) should be avoided (B-III). ○ The antimicrobial treatment must be active against the most prevalent microorganisms. The need for antibiotic activity against multi-drug resistant microorganisms must be considered in accordance with the patient's clinical and epidemiological context (C-III). ○ If antibiotics have been administered prior to the sampling and they are considered as potentially responsible for the absence of microbiological diagnosis, the antimicrobial spectrum of this treatment should be considered when choosing the new antibiotic regimen (C-III). • For acute staphylococcal PJI managed with rifampin and levofloxacin, an 8-week schedule of treatment after debridement appears sufficient for most patients (B-I). • For PJI caused by other microorganisms treated with antibiotics with good activity against biofilm-embedded bacteria (i.e., ciprofloxacin for PJI caused by GNB, 8 weeks is also a reasonable duration) (B-III). • In other clinical scenarios, the most appropriate duration of treatment remains uncertain. A variable period between 8 and 12 weeks may be adequate (B-III). • Monitoring of CRP during the follow-up is advisable; the persistence of high values is suggestive of treatment failure (B-III), but its total normalization must not be a condition for deciding the end of therapy (B-II).

	• During antimicrobial therapy, a close follow up of observance and potential adverse events of the treatment is recommended, performed by a clinician with expertise in antibiotics (C-III). • During the first 6 months after the end of a treatment aiming at eradication, patients must be followed up closely (B-III). • The frequency of follow-up visits may decrease afterwards. Follow-up should last at least one year (B-III). • Attempted eradication with prosthesis removal and a 2-step exchange procedure: o The two-step exchange procedure should include a targeted intravenous antimicrobial treatment for 4 to 6 weeks (A-II), or 1-2 weeks of intravenous antibiotics followed by oral antimicrobials with good bioavailability for a total duration of 6 weeks (B-II). o In chronic PJI caused by CNS, "universal" anti-staphylococcal antimicrobial therapy (i.e., glycopeptides, daptomycin, or linezolid) may be considered after the first-step surgery (prosthesis removal), because this carries a lower rate of positive cultures during the second-step surgery (re-implantation) (C-III). o Shortening the systemic antimicrobial treatment could be considered for cases of PJI due to low-virulent microorganisms, such as CNS or Propionibacterium acnes, as long as the first-step surgery has included a thorough and exhaustive debridement of the joint, and a cement spacer loaded with antibiotics active against the microorganism responsible for the infection has been used (B-II). o When samples taken during the second-step surgery yield a microorganism, a new 4-6 weeks course of antibiotics is recommended (B-II). o At present, it is not clear whether rifampin should be administered to treat staphylococcal infection managed with a two-step exchange procedure. a) The indication of rifampin in a chronic non-inflammatory infection should be based on the thoroughness of the surgical debridement (C-III). b) Rifampin is recommended in cases with a significant inflammatory presentation, especially those caused by S. aureus (C-III). o Antibiotic-loaded spacers are recommended in the two-step exchange procedure (B-II). a) The dose of local antibiotic ranges between 0,5 and 4 g of vancomycin, and 0,25 and 4.8 g of gentamicin or tobramycin (per every 40 g of acrylic cement) (C-III). b) The use of combined local antibiotics (vancomycin-gentamicin) is recommended until further evidence specifically addressing this topic is available (C-III).

	c) In PJI caused by multi-drug resistant microorganisms, spacers may be still used as long as they are loaded with antibiotics active against these microorganisms (C-III). o In the two-step exchange procedure, an antibiotic-free period of 2 to 8 weeks and clinical stability before the second-step surgery is recommended (C-III). o Prophylaxis for the second-step surgery: a) Wide-spectrum antibiotic prophylaxis including nosocomial microorganisms that may potentially cause superinfection of the new prosthesis is recommended for the second-step surgery of a 2-step exchange procedure (C-III). b) "Preemptive treatment" including microorganisms that could be isolated during the second-step surgery (usually multi-drug resistant SNC) is recommended: vancomycin (or another glycopeptide or lipopeptide) during the first 5 days after re-implantation or until confirmation that the samples taken during the second-step surgery yield no microorganisms (C-III). • Attempted eradication with prosthesis removal and a 1-step exchange procedure: o Beginning an antimicrobial therapy 3 to 5 days prior to the 1-step exchange procedure is recommended if the etiological diagnosis has already been made, especially in infections caused by S. aureus or GNB (C-II). o Regardless of the decision regarding when to start antibiotics, an appropriate antimicrobial prophylaxis throughout the procedure must be guaranteed (A-I). o If no antimicrobial therapy has been initiated before the procedure, it should be delayed until the intraoperative sampling has been performed (C-III). o A minimum of 7 days of intravenous antibiotics with activity against the microorganisms causing the infection is recommended, followed by oral antibiotics for a total of 4-8 weeks (B-II). o If it has been decided to use a cemented prosthesis, a local antibiotic with activity against the microorganism causing the infection is recommended. If the etiology is unknown at the moment of the exchange procedure, the combination of vancomycin plus gentamicin is recommended (C-III). • The PIOC category includes patients submitted to a 1-step exchange procedure due to the loosening of a prosthesis which was assumed to be non-infectious, but in which the samples taken during surgery finally yielded microorganisms (> or equal to 2 positive intraoperative cultures): o In the case of PIOC (Tsukayama's classification) an antimicrobial treatment of 4 to 6 weeks is recommended. There is no need for further surgery. The same protocol is followed as in cases of PJI

	managed with a 1-step exchange procedure (B-III). • Treatment for cases in which no new prosthesis is to be inserted after the removal of the infected one: o For cases in which the infected prosthesis is not to be replaced after its removal, the same antibiotics as those used for DAIR may be administered (Table 5) (B-II). o In these cases, the length of therapy may be shortened to 4 to 6 weeks (C-III). • Implant retention and long-term suppressive antibiotics (SAT) without attempted eradication: o A surgical debridement before beginning SAT is recommended, if feasible (C-III). o Obtaining a valid sample for culture before starting SAT is particularly important (C-III). o For the choice of the specific antibiotic for SAT, the antimicrobial susceptibility of the microorganism causing the infection, the safety of the drug and the observance of the treatment must be considered. Except for the initial stages of SAT, these aspects must prevail over the optimization of the antimicrobial treatment (C-III). o Except for some particular cases, the use of combinations (and therefore the use of rifampin) is not recommended (D-III). o In cases undergoing surgical debridement, an initial intravenous treatment for at least 7 days is recommended. Nevertheless, prolonged intravenous treatment is not necessary when deciding on SAT management (C-III). o If it is necessary to stop or change the antibiotics due to the occurrence of adverse events, long periods without antibiotics are not recommended (D-III). o The prescription and control of a SAT must be performed by an expert in antimicrobial therapy, who will periodically follow up the clinical evolution of the infection and assess the possible occurrence of adverse events (B-III). o The use of linezolid is discouraged in SAT due to high risk of toxicity, which limits its prolonged administration (E-I). o The use of β-lactams, or low doses of co-trimoxazole, is recommended. Alternatively, other antimicrobials such as minocycline or clindamycin may be administered (C-III)
HTA Pharmacoeconomics Analysis	Recommendations from HTA bodies should be added under each drug therapy section as they are missing from the previous/initial document.

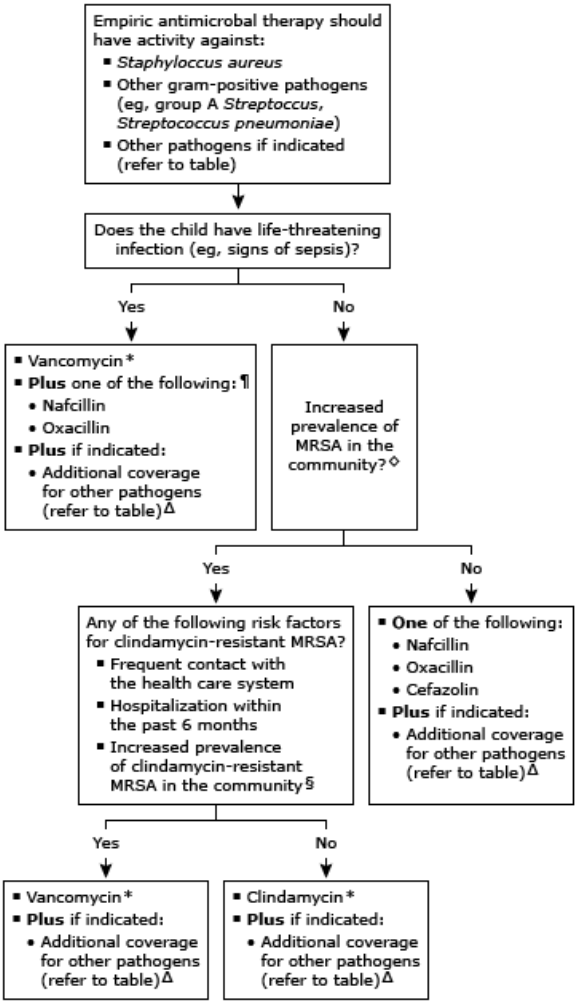
Appendix C. MeSH Terms PubMed

C.1 PubMed Search for Osteomyelitis:

Query	Filters	Search Details	Results
((((((((((Arthritis, Infectious[MeSH Terms]) OR (Infectious Arthritis[Title/Abstract])) OR (Arthritis, Viral[Title/Abstract])) OR (Viral Arthritis[Title/Abstract])) OR (Arthritis, Bacterial[Title/Abstract])) OR (Bacterial Arthritides[Title/Abstract])) OR (Arthritis, Septic[Title/Abstract])) OR (Septic Arthritis[Title/Abstract])) OR (Arthritides, Bacterial[Title/Abstract])) OR (Bacterial Arthritis[Title/Abstract])) OR (Arthritis, Suppurative[Title/Abstract])) OR (Suppurative Arthritis[Title/Abstract])	Guideline, in the last 5 years	("arthritis, infectious"[MeSH Terms] OR "infectious arthritis"[Title/Abstract] OR "arthritis viral"[Title/Abstract] OR "viral arthritis"[Title/Abstract] OR "arthritis bacterial"[Title/Abstract] OR "bacterial arthritides"[Title/Abstract] OR "arthritis septic"[Title/Abstract] OR "septic arthritis"[Title/Abstract] OR "arthritides bacterial"[Title/Abstract] OR "bacterial arthritis"[Title/Abstract] OR "arthritis suppurative"[Title/Abstract] OR "suppurative arthritis"[Title/Abstract]) AND ((y_5[Filter]) AND (guideline[Filter]))	5
(Osteomyelitis[MeSH Terms]) OR (Osteomyelitides[Title/Abstract])	Guideline, in the last 5 years	("osteomyelitis"[MeSH Terms] OR "Osteomyelitides"[Title/Abstract]) AND ((y_5[Filter]) AND (guideline[Filter]))	4

Appendix D. Treatment Algorithm of Osteomyelitis

Empiric antimicrobial therapy for children ≥3 months of age with acute hematogenous osteomyelitis



Population	Potential pathogens	Additional empiric therapy
▪ Age 6 to 36 months and in day care or history of oral ulcers before onset of musculoskeletal symptoms	▪ *Kingella kingae*	▪ Cefazolin if child is not improving as expected and is receiving vancomycin or clindamycin
▪ Incomplete Hib immunization in a child <2 years from area with low rates of Hib immunization	▪ Hib	▪ Cefotaxime or ceftriaxone
▪ Sickle cell disease$^{\Delta}$ ▪ Reptile or amphibian exposure ▪ GI symptoms	▪ *Salmonella*	▪ Cefotaxime or ceftriaxone
▪ Chronic granulomatous disease$^{\Delta}$	▪ Unusual organisms (eg, fungi, filamentous bacteria, gram-negative bacteria)	▪ Cefotaxime or ceftriaxone
▪ Recent GI surgery or complex urinary tract anatomy	▪ Enteric gram-negative organisms	Either: ▪ A third- or fourth-generation cephalosporin (eg, cefotaxime, ceftriaxone, cefepime), **or** ▪ An aminoglycoside (eg, gentamicin)
▪ Injection drug user	▪ *Pseudomonas aeruginosa*	▪ Ceftazidime

MRSA: methicillin-resistant *S. aureus*; Hib: *Haemophilus influenzae* type b; GI: gastrointestinal; MSSA: methicillin-susceptible *S. aureus*.

* Alternatives to vancomycin or clindamycin when MRSA is a concern include linezolid or daptomycin (daptomycin only if the child is ≥1 year of age and has no concomitant pulmonary involvement).

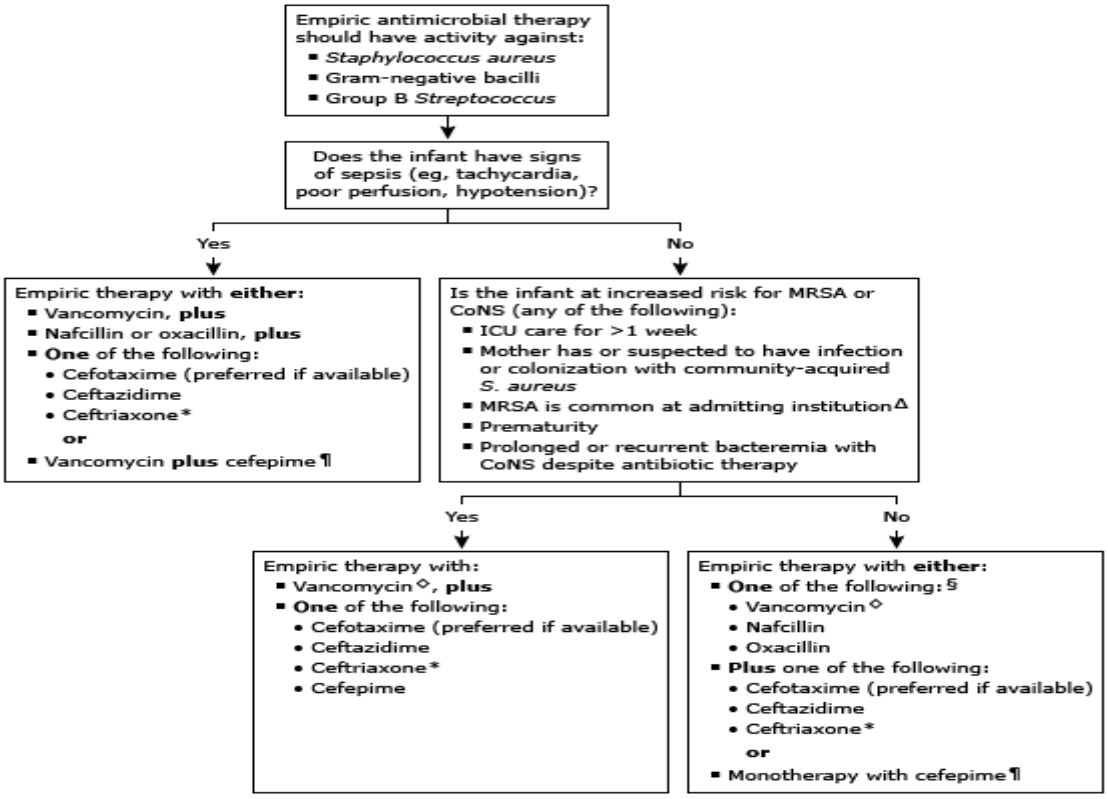
¶ For children with life-threatening infections, the combination of vancomycin plus either nafcillin or oxacillin provides bactericidal activity against both MRSA and MSSA.

Δ Consultation with an infectious disease specialist may be warranted for immunocompromised patients (eg, sickle cell disease, chronic granulomatous disease) because they may have infections with unusual pathogens or resistance profiles.

◊ We consider the prevalence of MRSA in the community to be increased if ≥10% of *S. aureus* isolates are MRSA; other experts may use a different threshold.

§ We consider the prevalence of clindamycin-resistant MRSA to be increased if ≥10% of MRSA isolates are resistant to clindamycin (constitutive and inducible); other experts may use a different threshold.

Empiric antimicrobial therapy for infants <3 months of age with acute hematogenous osteomyelitis and/or bacterial arthritis



For infants with allergy or intolerance to cephalosporins (very uncommon in this age group), we suggest consultation with an expert in pediatric infectious diseases.

MRSA: methicillin-resistant *S. aureus*; CoNS: coagulase-negative staphylococci; ICU: intensive care unit; MSSA: methicillin-susceptible *S. aureus*.

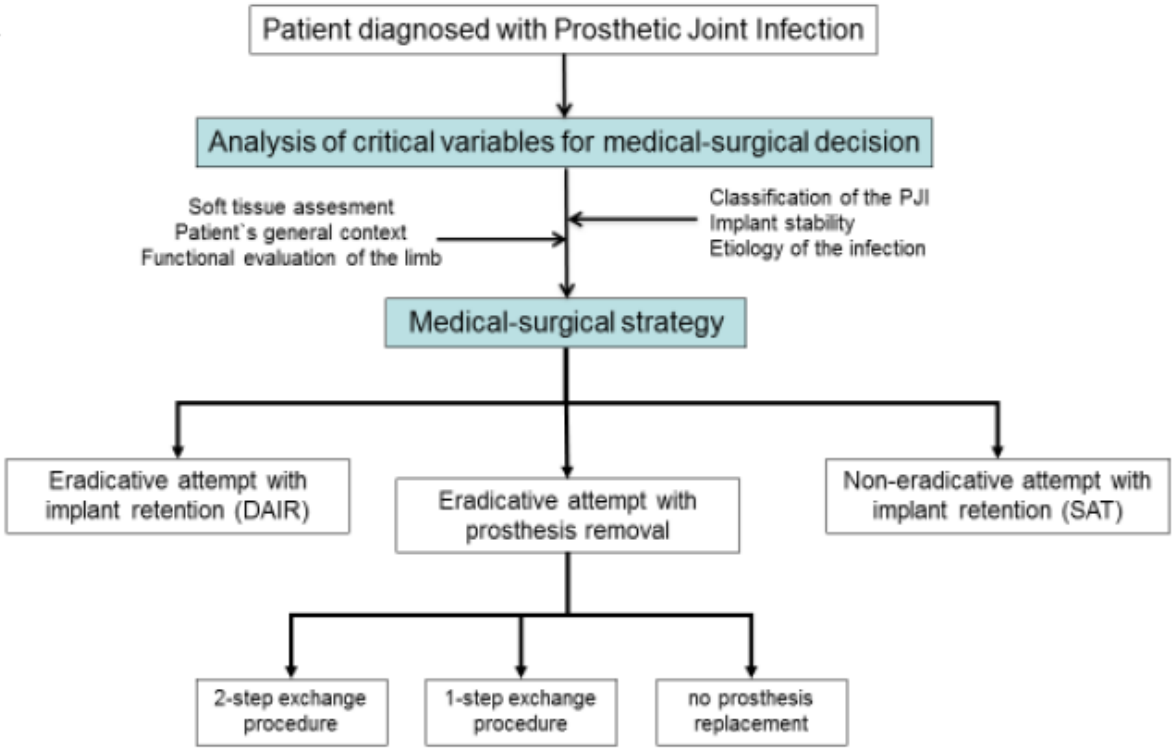
* Ceftriaxone is contraindicated in infants ≤28 days if they require or are expected to require concomitant treatment with intravenous solutions containing calcium, including parenteral nutrition.

¶ Some experts would add nafcillin or oxacillin for additional activity against MSSA.

Δ We consider MRSA to be common if ≥10% of *S. aureus* isolates are MRSA. Other experts may use a different threshold.

◊ At some institutions, clindamycin is used as an alternative to vancomycin if <10% of *S. aureus* isolates are clindamycin resistant and the infant has localized infection with no signs of sepsis.

§ Some experts also include cefazolin as an antistaphylococcal agent for infants age 1 to 3 months in whom central nervous system infection has been excluded.


Patient diagnosed with Prosthetic Joint Infection
Analysis of critical variables for medical-surgical decision
Soft tissue assesment
Patient`s general context
Functional evaluation of the limb
Classification of the PJI
Implant stability
Etiology of the infection
Medical-surgical strategy
Eradicative attempt with implant retention (DAIR)
Eradicative attempt with prosthesis removal
Non-eradicative attempt with implant retention (SAT)
2-step exchange procedure
1-step exchange procedure
no prosthesis replacement