Bone and Joint Infections

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1. INTRODUCTION

The *European Society for Paediatric Infectious Diseases (ESPID) Bone and Joint Infection Guidelines* (*ESPID Guidelines*) are intended for use by health providers who take care of children with bone and joint infection (BJI). Although BJI can include a diverse range of presentations, these guidelines will focus on "acute, hematogenous BJI in children," with an emphasis on bacterial infections.

ESPID Guidelines are consensus-based practice recommendations developed in a systematic manner that aim to be clear, valid and reliable, and presented with clinical applicability. Because evidence from large randomized controlled trials is rare or lacking, practice statements and recommendations provided here frequently reflect our expert consensus process based on best current practice.

Although these guidelines include evidence-based and opinion-based recommendations for the diagnosis and management of children with BJI, these guidelines may not provide the best clinical solution and are not intended to serve as a substitute for the clinical judgment of physicians in individual cases or to establish a protocol valid for all children with these infections. Consequently, they do not represent the "only" appropriate approach for children with this kind of infection.

We kindly refer to the full version available online (Supplemental Digital Content, http://links.lww.com/INF/C729) for more information on sources used, literature search strategies, guideline development methodology and the ESPID Review Team.

The authors of these *ESPID Guidelines* have made considerable efforts to ensure that the information upon which they are based is accurate and up-to-date. Users of these guidelines are strongly recommended to confirm that the information contained within them, especially drug doses, is correct by way of independent sources. ESPID and the authors of these guidelines accept no responsibility for any inaccuracies, information perceived as misleading or the outcome of any treatment regimen detailed in the guidelines.

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2. SUMMARY OF BJI RECOMMENDATIONS

There is a paucity of clinical trial or prospective cohort study data to inform the diagnosis and management of BJI in children. Most data are derived from retrospective, observational studies of variable quality. Therefore, ESPID decided to apply a simple grading of the practice statements in this guideline (see notes below).

1. BJI more frequently affects children younger than 5 years of age, and the infection more often involves joints and bones of the lower extremities (IIA).
2. *Staphylococcus aureus* is the most prevalent microorganism involved in BJI in children at all ages. In addition, *Kingella kingae* is a common causative pathogen in children <5 years old in some regions (IIA).
3. C-reactive protein (CRP) and erythrocyte sedimentation rate for the diagnosis of BJI have a high sensitivity, which is slightly increased by combining the 2 tests, whereas the specificity is low (IIB).
4. Ultrasound (US) has a high sensitivity for the diagnosis of septic arthritis (SA), whereas magnetic resonance imaging (MRI) is the most reliable imaging study for the diagnosis of BJI overall (IIA).
5. The isolation of a microorganism from the bone, joint or blood with a clinical or radiologic syndrome compatible with BJI is the gold standard for diagnosis in children (IIA).
6. Empirical antibiotic therapy should be started as soon as possible after collecting appropriate samples for microbiologic analysis upon suspecting BJI in children (IIA).
7. Empirical therapy should include an antibiotic with appropriate coverage against methicillin-sensitive *S. aureus* (MSSA) and against methicillin-resistant *S. aureus* (MRSA) in geographical areas with more than 10%–15% prevalence of this bacterium (IIA).
8. Empirical therapy in young children needs to include appropriate coverage for *K. kingae* in relevant areas (IIA).
9. First-generation cephalosporins, anti-staphylococcal penicillins (ASPs) and clindamycin are the antibiotics most studied in BJI in children (IIA).
10. If MRSA infection is suspected and the patient is not critically ill, empirical therapy should include clindamycin if the rate of clindamycin-resistant *S. aureus* is less than 10%–15%. A glycopeptide or other appropriate antibiotic for MRSA, such as linezolid, should be included if local clindamycin-resistant MRSA rates are high (IIIB).
11. SA in children should be treated with joint drainage by arthrocentesis, arthrotomy or arthroscopy, depending on the preference and experience of the treating clinicians and surgeons. Arthrocentesis may be appropriate as the only invasive procedure in most uncomplicated cases of SA in children (IIB).
12. Short intravenous (IV) therapy followed by oral therapy is appropriate in the majority of children with uncomplicated BJI based on absence of complications and favorable outcome (IA).
13. Follow-up oral antibiotic therapy should be guided by the antibiotic susceptibilities of the bacteria if isolated; if susceptible,

the antibiotics of choice are first-generation cephalosporins and clindamycin (IIA).
14. The minimum total duration of antibiotic therapy should be 2–3 weeks for SA and 3–4 weeks for osteomyelitis (OM) (IA).
15. Complicated or high-risk BJI such as those produced by *Salmonella*, MRSA or Panton–Valentine leukocidin (PVL)-positive strains, developing in young infants, or with slow clinical improvement, may need to receive longer duration of both IV and oral therapy (IIB).
16. Risk factors associated with sequelae include young infants and newborns, infections caused by MRSA or PVL-positive strains, longer duration of symptoms before initiation of therapy and hip involvement. Thus, children with BJI who have any of these risk factors should be followed more closely and for a longer time to rule out or treat sequelae (IIB).
17. A multidisciplinary team should follow children with BJI until osteoarticular function is restored and sequelae are resolved. If bone growth is the only concern, an orthopedic specialist will suffice. Infants with BJI in hip or with any physis involvement should be followed for extended periods of time (IIB).

Notes

– Quality of evidence
  I = Good evidence: Randomized placebo controlled trials; other studies appropriately randomized; good meta-analysis and systematic reviews of randomized controlled trials.
  II = Moderate evidence: Well designed but not randomized studies, cohort and case control studies.
  III = Poor evidence: Expert opinion, case series.

– Strength of recommendation—team consensus based on calculation of votes for A, B or C by the team members: A = strong recommendation; B = moderate recommendation and C = weak recommendation.

3. EPIDEMIOLOGY

Musculoskeletal infections involve bones, muscles and joints and are a significant cause of morbidity, and mortality in certain circumstances or settings, in children worldwide.[1,2] Acute hematogenous BJI in children may clinically manifest as OM, SA, both combined (OM-SA) or pyomyositis. Pediatric spondylodiscitis is uncommon and accounts for 1%–2% of all children with OM. Pyomyositis may complicate BJI and can also be a primary infection without the coexistence of BJI.

- **Acute OM** is an inflammatory process in the bone with bone destruction usually resulting from bacterial infection.[3] In high-income settings, the time from onset of symptoms to presentation for medical care is usually <5 days, and rarely more than a week.[4,5] Half of the children with acute hematogenous OM are under 5 years of age.[1]
- **SA** is an acute infection of the joint that occurs most commonly in young children, mainly monoarticular.[4,6] (See Section 5 "Clinical Features.")
- **Spondylodiscitis** is characterized by infection involving the intervertebral disc and adjacent vertebrae. Early in the disease, differentiation between discitis and vertebral OM may be difficult. The pathogens implicated in discitis are similar to those in other BJI.[3] It occurs mainly in children <5 years of age.[2,7] Vertebral OM is more common in older children and usually involves the anterior vertebral body.[7] In these instances, infectious agents such as *Mycobacterium tuberculosis* and *Salmonella* should be considered.
- **Pyomyositis** is frequently seen with pelvic involvement and may be related to MRSA or PVL production.[8–11]

3.1. European Guidelines

Europe is a group of countries with great differences in population, culture, wealth and health services. All variations of disease are impacted by differing epidemiology of pathogens and bacterial resistance, differences in presentation of reported cohorts between regions, medical approaches of infectious diseases, possibilities of medical care, etc.

To deal with variations in resource availability, this document aims to provide choices of diagnostic tools and options for treatment. Perhaps, see Table 3 in the full, online version (Supplemental Digital Content, http://links.lww.com/INF/C729) for BJI incidence in several European countries (between 1.4 and 22 per 100,000 people). Differences in incidence may also be related to dissimilar capacity to reach etiologic diagnoses and surveillance methods.

3.2. Predispositions/Risk Factors

Most BJI do not have a predisposed condition and occur in primarily healthy children. In specific situations, the following associations have been described.

- Upper respiratory infection (*K. kingae*)[12,13]
- Preceding trauma,[14] although some recent papers question this since trauma is very common in children[15]
- Wounds,[3] erosions and varicella infection (group A *Streptococcus*)[3]
- Sickle cell disease (*Salmonella* spp.)[3,16]
- Immunodeficiency—for example, chronic granulomatous disease (*Serratia* and *Aspergillus*)[17]
- Penetrating wounds—for example, through the sole of a shoe or sandal (anaerobes and *Pseudomonas*)[2]
- Living conditions, occupation—for example, animal handling and laboratory work in cases of infection caused by *Brucella* and *Coxiella* spp.[18,19]
- Contact with pulmonary tuberculosis or living in endemic areas (tuberculosis BJI)
- Newborns: prematurity, skin infections, bacteremia or candidemia and previous central venous catheter[20,21]

4. ETIOLOGY AND PATHOGENESIS

- Most BJI in children are of a hematogenous origin, and it is the focus of these guidelines. Much less frequently than in adults, BJI in children can be secondary to an adjacent infection, prosthetic material or traumatism.
- For practical reasons, "acute" and "subacute" are usually considered those BJI with a history of <2 weeks and 2 weeks to 3 months, respectively.

4.1. Causative Agents and Bacterial Resistance

- The prevalence of different pathogens encountered in various European countries is the main factor influencing the antibiotic regimen in BJI (Table 14, Supplemental Digital Content, http://links.lww.com/INF/C729). Some important points are a higher incidence of community-acquired MRSA (CA-MRSA) in some countries such as Romania or Greece, or important differences in *K. kingae* incidence within some countries (ie, very low in Scandinavia and quite high in Spain, France or United Kingdom). A recent European pediatric study of invasive *S. aureus* disease has shown a prevalence of 8% of MRSA.[22]

  Table 1 illustrates the most common pathogens by age in acute BJI.

- OM and SA are most commonly caused by *S. aureus*, followed by *K. kingae* or group A *Streptococcus* depending on age and other risk factors, or geographical location. In some studies, *K. kingae* is the second (or even the first) most common etiology after *S.*

TABLE 1. Most Common Pathogens by Age in Acute BJI[3,4,16,23]

Age Group	Pathogen
Infant: <3 mo old	*Staphylococcus aureus* *Escherichia coli* and other Gram-negative bacteria GBS *Candida albicans* *Neisseria gonorrhoeae* (newborns)
Young child: 3 mo to 5 yr old	*S. aureus* *Kingella kingae* GAS *Streptococcus pneumoniae* (especially under 2 yr old) *Haemophilus influenzae* type b (exceptional in well-immunized populations)
Older child: ≥5 yr old	*S. aureus* GAS *N. gonorrhoeae* (in sexually active adolescents)

GAS indicates group A *Streptococcus*; GBS, group B *Streptococcus*.

aureus in children <5 years of age where real-time polymerase chain reaction (PCR) has been performed.[5,24–27]

- Pathogens involved less frequently in these infections are *Streptococcus pneumoniae*, *Pseudomonas*, *Salmonella*, *Haemophilus influenzae* type b (Hib), among others.
- Group B *Streptococcus* and *Escherichia coli* are important pathogens in newborns.
- In certain areas, a variable but considerable number of cases are caused by CA-MRSA.

5. CLINICAL FEATURES

The "classical presentation" of BJI is fever, localizing signs of swelling or pain and limitation of movement or limping. Table 2 shows a summary of the most frequent signs and symptoms of children with BJI.

5.1. General Symptoms

There is considerable overlap in the symptoms of OM, SA and pyomyositis: OM frequently has a more insidious onset; SA presents more frequently with fever, swelling and decreased range of motion, except when in occult joints, such as sacroiliac or vertebra; and pyomyositis of the psoas may also be very difficult to diagnose. Other symptoms are as follows:

- Limping or non-weight bearing
- Refusal to use limb and/or decreased range of motion[6]
- Acute or subacute onset of complaints: SA 2–4 days[5,29] and OM 6–7 days[5,29]
- Fever is present in 30%–40% of cases.[1,5,6,30]
- In newborns and young infants only nonspecific symptoms

A 2012 systematic literature review[30] of pediatric studies of OM showed:

- 81% pain
- 70% localized signs and symptoms
- 62% fever
- 50% reduced range of motion
- 50% reduced weight bearing.

TABLE 2. Clinical Features of BJI by Age and Location

BJI	Age	Systemic Symptoms	Local Symptoms
OM	Neonate	• Fever (frequently not present) • Irritability • Poor feeding • May be difficult to distinguish from other infections at this age	• Widespread limb pain difficult to localize on examination • Bone or limb swelling • Erythema • Pseudoparalysis • May have no local signs, especially when flat bones affected
	Young child	• In young infants: vomiting, poor feeding, irritability • Fever: not always present, but may be the only symptom • Systemic symptoms in SA are usually more severe	• May have no local signs • Refusal to bear weight or sit down • Limping • Bone or limb swelling • Erythema
	Older child	Same as OM, Young child.	• Limp • Pain—more localized • Bone or limb swelling • Erythema • Older children tend to localize more the symptomatology
SA	All	• In young infants: vomiting, poor feeding, irritability • Fever: not always present, but may be the only symptom • Systemic symptoms in SA are usually more severe	• Hot, swollen, immobile peripheral joint • Refusal to bear weight • Pain on passive joint movement
Spondylodiscitis	All	• Fever is uncommon or low grade • No systemic illness • BJI of the pelvis or sacroiliitis may have similar symptoms	• Insidious onset back pain • Refusal to sit, stand, walk or limping • Refusal to flex the spine • Constipation or abdominal pain • Loss of lordosis, local tenderness or paraspinal muscle spasm • Rarely neurologic signs[28]
Pyomyositis	All	• Fever • Frequently no increase of creatine phosphokinase • Abdominal pain (psoas and muscles around)	• May have no local signs • Refusal to bear weight • Limp • Bone or limb swelling • Pain—more localized

Based on Faust et al.[3]

TABLE 3. Skeletal Distribution of BJI in Children[1,2,6,16]

	%
Bones	
Femur	20–30
Tibia	19–26
Humerus	5–13
Pelvis	3–14
Calcaneus	4–11*
Fibula	4–10
Radius	1–4
Clavicle	1–3
Metatarsal, hand, ulna, metacarpal, spondylodiscitis	1–2
Mandible, sternum, ribs, skull, maxilla, scapula, patella, talus	<1
Joints	
Knee	35–56
Hip	25–30
Ankle	12–15
Elbow	5–10
Shoulder	4–5

*Foot bones 26%.[5]

5.2. Location-specific Symptoms

In children with BJI, the infection can affect any bone, muscle or joint. Most commonly the long bones and joints of the lower limbs are involved[4–6] (Table 3). Multifocal OM is seen in 5%–10% of infants (especially newborns and young infants).[6,31] Pain in OM tends to be more localized. Tenderness, redness and swelling are more common in SA. Pyomyositis, when it involves muscles around the hip joint, can mimic SA.[32]

6. DIAGNOSIS

See Table 4 for a summary of recommendations for the diagnosis of pediatric BJI.

6.1. Laboratory Tests

In case of suspected BJI, the following tests are normally recommended: complete blood count, CRP and erythrocyte sedimentation rate.

At this time, there lacks clear evidence of the clinical benefit of procalcitonin.[39–41] Gram staining can be very informative, both for synovial fluid and the potentially obtained bone aspirate/biopsy. This

TABLE 4. Diagnostic Options for Childhood BJI

Type	Tests	Notes/Remarks
Laboratory tests[33–35]	CRP	– Easy, inexpensive and rapid test in diagnostics and follow-up – High sensitivity for diagnosis of BJI[34,36] – Normal rate is reached quickly (in 3–8 d) during recovery of BJI[29]
	ESR	– This test may be more difficult in children: larger sample blood volume needed and possible laboratory errors because of handling problems – Some studies have shown high sensitivity.[5] Sensitivity may be higher with measurement of both CRP and ESR. – Low specificity for diagnosis of BJI – Normal rate is reached a long time (2–3 wk or more) during recovery of BJI[29]
	CBC	– Useful in conjunction with ESR and CRP – White blood cell, hemoglobin and platelet count may still be very useful for differential diagnosis of BJI (eg, leukemia)
Imaging	Radiograph imaging	– Always at baseline (often normal at baseline but useful for later reimaging comparison and to rule out other diseases) – Plain radiography often misses joint effusion, especially in the hip joint – If clinical presentation is not severe and clinical outcome on therapy is appropriate, an additional imaging study may not always be necessary
	US sonography	– Identify joint effusion in septic arthritis (very sensitive) – Subperiostic abscess (low sensitivity for OM but may be very useful) – Doppler may detect elevated blood flow in OM and help in early diagnosis[37]
	Scintigraphy/ Tc bone scan	– In several European countries, scintigraphy has become unpopular because of high radiation dose* – In others, it is still frequently used in the diagnosis of OM – It may be useful in ill-defined locations or if multiple foci are suspected
	MRI	– MRI is expensive and not always available – Best test for OM, especially if symptoms are localized – Not always needed in every child, especially if the diagnosis is clear and the child improves in a short period (2–3 d) – Provides excellent definition of soft tissues and bone marrow – Whole body MRI for multifocal processes has proven very useful,[38] for example, in cases of severe CA-MRSA
	CT scan	– Reserved for diagnostic dilemma in most centers, although local variation exists even within countries—much higher radiation than any other imaging test* – It may be more frequently used in centers where MRI is not readily available
Microbiology	Blood culture	– Should always be obtained despite a possible low yield (10%–40%) – In neonates and young infants with OM, blood culture may be positive on suspected sepsis without local signs – The presence of *Staphylococcus aureus* in the blood should prompt a consideration of occult BJI
	Synovial fluid/bone sample: Gram staining, culture	– If sample taken, obtain it before initiation of antibiotic treatment (especially for synovial fluid) – Bone sample not always required; to be considered if subperiostal pus is present or infection is not improving as expected – Important also for the diagnosis of noninfectious processes – Drainage, for example, of purulent fluid or abscess, may also serve as an important form of therapy
	Bacterial PCR (when available)	– Including molecular detection of *Kingella kingae*, *S. aureus* or others by using eubacterial ribosomal RNA amplification in tissue sample or synovial fluid. It may significantly increase the yield of a microorganism in SA, especially in previous use of antibiotics. Specific primers may be more sensitive.[24]

PCT has not been proven to be of value for the diagnosis of BJI in children because of its low sensitivity[39–41] and the wide availability of the existing tests CRP and ESR. In some settings (eg, high rates of MRSA), initial bone puncture for diagnosis may be appropriate to better adjust therapy. This procedure may be performed under CT direction.[42]

*Radiation dose.[43,44] Conventional radiograph: thorax in 1 dimension postanterior 0.02 mSv; thorax in 2 dimensions 0.1–0.2 mSv; knee in 2 dimensions 0.001–0.01 mSv, CT scan: thorax 3–5 mSv; abdomen 5–8 mSv; extremity 4–5 mSv; spine 8–10 mSV. Bone scintigram using Tc-99m: 3–6 mSv (same as 200–750 chest radiographs).

CBC indicates complete blood count; CT, computerized tomography; ESR, erythrocyte sedimentation rate; PCT, procalcitonin.

test is especially important because the culture may be negative. Synovial fluid cytology is not considered mandatory because its findings overlap with other diseases.

6.2. Microbiology

Blood culture with appropriate volume should always be performed before antibiotics.

Use of blood culture vials for culturing synovial fluid and bone exudates in recent years has resulted in the recognition of *K. kingae* as one of the most common causes of BJI in children <5 years of age in selected regions or countries.[45]

In recent years, nucleic acid amplification methods (eg, conventional and real-time PCR) have also improved the detection of bacteria not isolated by culture.[25,45] This may be very important when prior use of antibiotics (synovial fluid PCR remains diagnostic up to 6 days after antibiotic initiation) or for a pathogen in which conventional diagnostic methods remain suboptimal.[12,13,24–26,45] *K. kingae* is identified mainly via eubacterial PCR using ribosomal RNA primers targeting the 16S ribosomal RNA gene. More specific primers may increase the sensitivity of PCR to detect *Kingella*.[12,13,24]

An etiologic diagnosis is highly recommended even though *S. aureus* is so common that an empirical anti MSSA/MRSA treatment would usually perform well, especially for children ≥5 years of age. Although most culture-negative cases of BJI can be successfully treated with empirical antibiotics, it is important to establish a microbiologic diagnosis to adjust therapy and to rule out noninfectious causes of the disease.

Whereas arthrocentesis has a therapeutic aim in SA (see "Section 7.5"), the need for a bone aspiration for a suspected uncomplicated OM is more controversial because this procedure does not seem to affect the outcome of these infections.[4,23]

See Table 4 for a summary of microbiologic approach to BJI.

6.3. Imaging Studies

Radiograph Imaging

Radiograph imaging is considered an important baseline test in all patients for comparison of subsequent change if disease does not rapidly improve and to rule out other underlying conditions. See Table 4 for a summary of diagnostic procedures.

- Acute OM: Frequently normal at baseline. Repeat imaging shows appearance of osteolytic changes or periosteal elevation, mostly 10–21 days after onset of symptoms.[3]
- Subacute OM: Changes frequently seen can be confused with malignancies,[46] which usually require operative biopsy for definitive diagnosis.
- SA: Limited usefulness; soft tissue swelling
- Discitis: Lateral spine radiographs show late changes at 2–3 weeks into illness, especially decreased intervertebral space and/or erosion of the vertebral plate.
- Vertebral OM: Initially shows localized rarefication (thinning) of a single vertebral body, then anterior bone destruction. MRI may be indicated in suspected spondylodiscitis and vertebral or pelvic OM.

MRI

MRI is the most informative imaging modality for OM, because it can detect abnormalities within 3–5 days of disease onset. Moreover, it reveals details of the bone and soft tissue involvement, including the formation of abscesses, sequestra or associated pyomyositis or contiguous venous thrombosis, and can help the orthopedic surgeon to plan the most appropriate surgery for diagnostic and/or therapeutic purposes. MRI may not be necessary in certain situations where other clinical and diagnostic tools are strongly suggestive of the diagnosis. It may be indicated in severe clinical conditions, there are reasonable doubts about the diagnosis, or when a complication is suspected. Other indications may be as follows:

- SA: Although not generally indicated, it may be valuable if OM-SA is suspected. Thus, in a recent study,[42] 35% of children with acute OM had a contiguous SA.
- Spondylodiscitis and vertebral OM: MRI may be a necessary test if these infections are suspected for detailing bone and soft tissue involvement and to rule out epidural abscess and tumor.
- Pyomyositis: High sensitivity and specificity, especially useful for the hip and pelvis.

MRI disadvantages may be as follows: long scan times, need of sedation or anesthesia in young children and is a contraindication with some metallic foreign bodies and certain types of implanted hardware.[38]

Computerized Tomography

Computerized tomography is not generally recommended: it is less sensitive compared with MRI in detecting early osseous lesions and exposes children to high radiation doses.[43] It may be performed in settings where MRI is not feasible.

- Valuable for guided procedures, such as aspiration or drainage,[42] and may not need sedation because of the short time needed.

Sonography

Sonography or US is most indicated for SA because it has a high sensitivity for the diagnosis of joint effusion, although with a lower specificity. It should be performed in all suspected SA unless easily diagnosed by physical examination. US may be useful for OM, mainly in the diagnosis of abscess formation and surrounding soft tissue abnormalities (pyomyositis, cellulitis, etc.), and it may provide guidance for diagnostic or therapeutic aspiration and/or drainage. Doppler US may provide early detection of a high vascular flow in the infected bone.[37]

Bone Scintigraphy or Bone Scan

Technetium radionuclide scan (^{99m}Tc) is used to identify multifocal osseous involvement and to document the site of OM when local skeletal symptoms are ill defined.[47] It has a high sensitivity but less specificity,[48] and both are lower in neonates. It may also give false negative results in infancy and with virulent pathogens (MRSA).[49] SPET-CT may increase the sensitivity of bone scintigraphy when the spine is involved. In some centers, bone scan is still faster and more accessible than MRI. This technique involves a significant amount of radiation exposure[44] [Dose range equals to 200–750 chest radiographs; see also Section 2.2 in Supplemental Digital Content, http://links.lww.com/INF/C729 and the American Nuclear Society website (http://www.ans.org/)]. Its specificity may increase with Gallium scan or Indium-labeled leukocytes.[50]

Finally, when needed, individual cases may be discussed with an experienced radiologist. See Table 7, Supplemental Digital Content, http://links.lww.com/INF/C729 for a summary of imaging studies in BJI in children.

6.4. Differential Diagnosis

Multiple infections and noninfectious diseases may have similar clinical syndromes to BJI and, therefore, should be ruled out, especially when the infection does not progress appropriately and no infectious etiology is isolated. Other types of infection, rheumatologic disease or neoplasias are among the most common or important entities that may mimic BJI. See Table 8, Supplemental Digital Content, http://links.lww.com/INF/C729 for the most common differential diagnosis of BJI.

TABLE 5. Principle Scheme for Management of Simple or Uncomplicated and Complex BJI (See Text for Details)

Management Components	Suspected Diagnosis	
	Uncomplicated OM or SA	Complex* OM or SA
Hospitalization	Yes	Yes
Blood tests	CBC, CRP, ESR	
Bacteriology	Blood culture—Generally, 4 mL minimum, 2 mL for neonates[51] Culture of any possible material, especially joint fluid; consider bone sample in certain circumstances (it may be crucial in complex BJI); PCR from synovial fluid, abscesses or tissue when feasible	
Imaging	OM—Always plain radiograph. Consider MRI SA—US. MRI to document suspected OM in SA and perifocal disease	OM—Always plain radiograph. MRI, US SA—US, MRI, consider ^{99}Tc bone scan if no MRI is available
Surgery	Avoid if possible—Indications include need for pus or effusion drainage, bone destruction Always arthrocentesis/arthrotomy for SA	Consider—Indications include need for pus or effusion drainage, bone destruction or diagnostic purposes
Antibiotic treatment	See Section 7	
Monitoring	When pathogen is not known: • Switch to oral antibiotic monotherapy following local microbiologic or clinical infectious disease standards • Choose antibiotic spectrum similar to IV if initial IV response was favorable	Consider second line or additional antibiotics, especially as long as Gram-negative bacteria or MRSA are not ruled out
Switch IV to oral treatment		
Criteria for time to switch—pathogen is unknown	Afebrile or clearly decreased temperature 24–48 hr, improved clinical condition (reduction of pain, mobility, inflammation) >24 hr and significantly decreased CRP (30%–50% of highest value)	Similar parameters but consider a minimum of 1 wk of IV therapy
Up to 3 mo old—time to switch and duration	Consider switch after 14–21 d, especially under 1 mo of age; some experts consider switching earlier →OM and SA—4–6 wk total antibiotic treatment	Consider switch after 21 d; it may be earlier in certain favorable circumstances →OM and SA—4–6 wk or longer (up to several months) oral antibiotic treatment based on individual response
3 mo old and older—time to switch and duration	Consider switch after 24–48 hr of improvement →OM—minimum 3–4 wk total →SA—minimum 2–3 wk total†	Consider 10–14 d of IV antibiotics depending on severity and outcome, but may be switched to PO earlier →OM and SA—4–6 wk or longer (up to several months) oral antibiotic treatment based on individual response and other specific characteristics
Follow-up	• CRP measurements—reliable and inexpensive in the follow-up of OM and SA. No need to repeat inflammatory markers once normalized unless new clinical findings • Long-term beta-lactam therapy may produce leukopenia, usually mild to moderate • Clinical investigation—longer follow-up: infants, physis involvement and complex disease • Radiograph, sonography or MRI may be needed • End-point therapy: Normal CRP, asymptomatic or minor symptoms‡ and after minimum length of treatment—see above. The end-point may be more difficult to determine in complex OM/SA • Orthopedic follow-up at end of course of treatment more important than PID to address any ongoing sequelae of the bone or joint infection	

Consultation and treatment should "not" be delayed while waiting for a bone scan or MRI in suspected OM. Arthrocentesis or arthrotomy should be promptly performed in suspected SA before antibiotic therapy.

*Complex disease = if any one of the following features is present: (1) significant bone destruction; (2) resistant or unusual pathogen; (3) immunocompromised patient; (4) sepsis or shock and (5) venous thrombosis or other major complications (eg, important abscess).

†Some studies showed that 10 days of treatment may be enough for noncomplicated SA.

‡Some symptoms may not be related to infection or inflammatory cause but to sequelae (eg, limping, pain, limit range of motion). Consultation with orthopedics may be considered.

CBC indicates complete blood count; ESR, erythrocyte sedimentation rate; PID, pediatric infectious disease specialist.

7. MANAGEMENT

See Table 5 for a summary of recommendations for the management of pediatric BJI.

7.1. Introduction

The treatment in most cases of childhood OM, SA and OM-SA can be simplified from the regimen reportedly practiced in many hospitals.[29,52,53] Early diagnosis and prompt treatment are needed to avoid complications.[5,54] Key factors in the management approach are regional prevalence of CA-MRSA and age of the patient.

- Initial management includes adequate drainage of pus, collection of specimens for microbiologic studies and prompt initiation of empiric antibiotic therapy.
- The choice of empiric antimicrobial therapy is based on the most likely causative pathogens according to patient age, immunization status, underlying disease, Gram stain and other clinical and epidemiologic considerations, including prevalence of MRSA.

7.2. Hospitalization

Most children are hospitalized at the start of the infection as IV therapy is generally used. This may be especially important in regions with a high rate of MRSA or PVL-positive *S. aureus*, worse clinical severity and in high-risk patients such as infants and immunocompromised patients. There is no evidence that BJI can be treated with oral therapy (PO) during the whole course of the disease, although children with milder infections without risk factors for a worse outcome may have a favorable outcome on PO antibiotics. Nevertheless, with the current evidence, we cannot recommend this latter approach.

TABLE 6. Empirical Therapy by Age

Age	Empirical IV Antibiotic Treatment*
Up to 3 mo old	Cefazolin (or ASP) + gentamicin; ASP + cefotaxime may be an alternative[8]
3 mo to 5 yr old	Cefazolin† or cefuroxime‡ Clindamycin in regions of non-*Kingella*; alternatives: amoxicillin§–clavulanate or ampicillin–sulbactam or ceftriaxone‡ or ASP¶
5 yr old and older	IV ASP or cefazolin or clindamycin (high MRSA prevalence) When risk factors present (eg, SCD), other options may be considered such as ceftriaxone (± ASP or clindamycin)

*High rate of MRSA, cover this by adding clindamycin (<2 years of age) or clindamycin alone (above 2 years of age)—see Section 7.3.2.

†Under 2–5 years of age, there may be risk of *Streptococcus pneumoniae* or *Haemophilus influenzae* type b BJI in unvaccinated children, thus first G cephalosporins may be suboptimal.

‡Both cefuroxime and ceftriaxone have better coverage for *S. pneumoniae* and *H. influenzae*, but may be inferior to first G cephalosporins or ASP in *Staphylococcus aureus* infections.[62] There is experience with cefuroxime (some Spanish sites)[5] and ceftriaxone (some UK and Greece sites).

§The amoxicillin–clavulanate pharmacokinetic/pharmacodynamic profile may be suitable for BJI.[63] Furthermore, there is a broad experience in BJI in children and has an appropriate activity for MSSA.

¶Narrow spectrum ASP is not appropriate for treatment of *Kingella kingae* BJI.[64]

ASP indicates anti-stapylococcal penicillin; SCD, sickle cell disease.

An alternative approach used by some centers when IV antibiotics are still needed for specific situations is the insertion of a peripheral-inserted central line for once/daily antibiotic treatment at home—outpatient parenteral antimicrobial therapy.[55,56] Nevertheless, prolonged IV therapy may be associated with catheter-associated complications and, moreover, oral therapy does not seem to be linked with a higher risk of treatment failure compared with prolonged IV therapy in children with BJI.[57,58]

7.3. Antibiotic Therapy

7.3.1. Empirical IV Therapy

Any empirical therapy should include coverage of *S. aureus.* When CA-MRSA prevalence is 10%–15% or higher, this pathogen should be included in the choice of empiric therapy.

Local, up-to-date resistance patterns are required to decide the best initial empirical therapy [Table 14 (Supplemental Digital Content, http://links.lww.com/INF/C729) shows a summary of pathogens with geographical prevalence]. The level of severity may also lower the threshold to initiate anti-MRSA therapy or other adjuvant measures.

See Table 9 in the full, online version (Supplemental Digital Content, http://links.lww.com/INF/C729) for empirical therapy preferences in different European countries.

Other considerations regarding empirical therapy are as follows:

- Beta-lactams, such as first-generation cephalosporins and cloxacillin or other ASPs, are the drugs of choice for good experience and tolerance.[8,23,52,59,60] Clindamycin is a suitable treatment, especially in settings with high rate of CA-MRSA.[61]
- Amoxicillin–clavulanate may be an option, although no published data are available and had a higher reported rate of adverse events.[59,60]
- Antimicrobials with activity against *Kingella* should be considered in children <5 years of age, especially in areas with high rates.

Table 6 shows empirical therapy for BJI according to age.

TABLE 7. Initial Empirical Therapy and Rate of MRSA (Beyond 3 Months of Age)

Regional Rate of MRSA—Low/High at 10%–15%	Recommended Initial Empirical Therapy*
Low rate of MRSA or culture-negative infections	• First or second generation cephalosporins • Alternatives: Anti-staphylococcal penicillins or third G cephalosporins†
High rate of MRSA	• Clindamycin ± rifampin‡ ± anti-staphylococcal beta-lactam
High rate of MRSA plus severe infection without preliminary results or high-rate clindamycin resistance or in case of failure to respond to initial therapy	• Vancomycin or teicoplanin ± rifampin‡ ± clindamycin • Alternative: Daptomycin or linezolid (MRSA-IDSA guidelines)[65] • Always consider adding a beta-lactam until MRSA is confirmed • Intravenous immunoglobulin may be added where toxin-mediated systemic symptoms (ie, toxic shock syndrome) are suspected

*Consider covering other agents such as *Kingella*, especially in children <5 years of age. Clindamycin may be an option as well.

†Much less experience in children and less in vitro activity than the other options, although some studies in adults showed appropriate clinical outcome.[75]

‡There is no evidence of rifampin benefit in otherwise healthy children with BJI.

7.3.2. Treatment of MRSA or MSSA PVL-positive *S. aureus*

Clindamycin can be used if CA-MRSA is a possible cause.[61,65–67] Although some authors recommend caution in the case of bacteremic patients,[66] others have good experience with clindamycin in this situation.[68] Endocarditis and deep venous thrombosis (DVT), as well as inducible macrolide-lincosamide-streptogramin resistance, may be ruled out before treating children with CA-MRSA BJI with clindamycin.[65] Some experts may consider treatment of BJI with clindamycin ± rifampin even if MRSA is sensitive to clindamycin. Clindamycin may be combined with a beta-lactam to cover MSSA until bacterial sensitivity is available. It is important to suspect PVL-positive *S. aureus* (including MRSA) disease if infection fails to respond to empirical treatment, is recurrent, multifocal or associated with a necrotizing process.

In case of severe infection where CA-MRSA or clindamycin-resistance strains are a concern, vancomycin is recommended by the Infectious Disease Society of America (IDSA) Guidelines[65] at high dose: 60 mg/kg/d qid—no good data for trough levels in children and, in general, clinical outcome should be followed.[69] Nevertheless, evidence of the efficacy of vancomycin in BJI is scarce,[70,71] and other antibiotic may be used (daptomycin or linezolid), especially if no initial response or minimum inhibitory concentration to vancomycin ≥2 μg/mL.[65,71–73] Rifampin may be added to all 3[71] but with little evidence. Other options may be quinolones or trimethoprim-sulfamethoxazole (little experience in children)[74] ± rifampin. Table 7 shows the empirical therapy according to rate or MRSA.

In severe cases or special circumstances, adding a toxin inhibitor antibiotic such as clindamycin, rifampin or linezolid[76] may be considered.[77] Although data are sparse,[71,78] this strategy is considered for adults in IDSA guidelines[65] and in children and adults with PVL *S. aureus* in British guidelines.[79] In case of MSSA PVL-positive (PVL+) infections, treatment with first-generation cephalosporins or ASPs "plus" clindamycin might be suitable. Nevertheless, in most situations, the clinicians do not have the PVL results to guide the therapy of BJI.

There are some reports and in vitro studies about the use of intravenous immunoglobulin on severe PVL+ *S. aureus* BJI infections, but there is not enough evidence to support its general use.[80,81]

TABLE 8. Pathogens and Antibiotic Treatment (According to Local Resistance Patterns)

Pathogen	Antibiotic Considerations
Staphylococcus aureus	• ASP, first-generation (G) cephalosporins[8,23] • Clindamycin—if sensitive MRSA isolated (it may also be used for MSSA) • Trimethoprim-sulfamethoxazole*—in clindamycin-resistant cases, 99% of the MRSA strains are susceptible[74]
Streptococcus pyogenes	• Penicillin, ampicillin or amoxicillin
Streptococcus pneumoniae	• Ampicillin, amoxicillin or second to third G cephalosporins • In the very unusual situation of high beta-lactam resistance may use vancomycin, linezolid or levofloxacin
Haemophilus influenzae type b	• Second G cephalosporins or amoxicillin–clavulanate (or ampicillin–sulbactam) • Some strains may be resistant to second G cephalosporins and/or amoxicillin–clavulanate: third G cephalosporins may be used
Kingella kingae	• Sensitive to cephalosporins and penicillins[27] • Resistant to clindamycin, vancomycin, linezolid, daptomycin; ASP not optimum • Rarely produces beta-lactamases
Salmonella species	• Ceftriaxone or cefotaxime • PO: amoxicillin or quinolones,[82] according to sensitivity
Escherichia coli and other enterobacteria	• According to sensitivity—amoxicillin–clavulanate or second/third G cephalosporins or others
Pseudomonas aeruginosa	• According to sensitivity—ciprofloxacin PO
Neisseria gonorrhoeae	• Ceftriaxone or cefotaxime (or PO third generation cephalosporins)

Based on Pääkkönen and Peltola.[4] Resources, policies and resistance patterns are different across countries and regions; consequently, scenarios may not be "pan-European." Always sensitivity of the strain should be performed. Where pediatric outpatient parenteral antimicrobial therapy is implemented, once/daily regimens such as ceftriaxone (high dose, >80 mg/kg/qd IV) have been found to be useful and effective.

*There is experience with but little published information on trimethoprim-sufamethoxazole efficacy in the treatment of *S. aureus* OM/SA in children, especially as initial therapy[74]; it may be combined with rifampin.[78,83]

p-OPAT indicates paediatric outpatient parenteral antimicrobial therapy.

7.3.3. Targeted Therapy

Targeted therapy should be always used once a microorganism has been isolated and its sensitivity determined. Table 8 shows most suitable antibiotic therapy according to specific bacterial isolates.

7.3.4. Allergy

In case of allergy to beta-lactams, the options are as follows: clindamycin, glycopeptides, quinolones, linezolid and trimethoprim-sulfamethoxazole. The best alternatives to cover the possibility of *Kingella* infection are trimethoprim-sulfamethoxazole and quinolones (levofloxacin may be superior to ciprofloxacin). Trimethoprim-sulfamethoxazole and quinolones may be suboptimal for *Streptococcus pyogenes*, although recent studies have indicated a better in vitro susceptibility to the former antibiotic.[84]

7.3.5. Oral Therapy

Oral therapy following initial IV treatment has been used as equivalent to prolonged IV therapy and may be associated with fewer complications.[57,58]

Switching to PO Therapy After IV Treatment Early oral switch has been used[8,52,53,68] if the child is showing clinical improvement (although there is limited evidence and variable practice), which may include the following:

- Afebrile or clear decreased temperature for 24–48 hours
- Improvement of symptoms, with decreased inflammation and pain
- Decrease in CRP of about 30%–50% from maximum value
- No signs of complications, such as metastatic foci (endocarditis, pneumonia, etc.) or DVT
- Absence of virulent pathogens, such as *Salmonella*, MRSA or PVL+
- Negative blood cultures if initially positive

Culture-negative Infections In culture-negative infections, the recommendation is to continue with an oral antibiotic similar to the class used in IV treatment.

- In high MRSA regions: clindamycin ± cephalosporin (the latter in younger children)—alternatives for clindamycin may be trimethoprim-sulfamethoxazole, quinolones or linezolid.
- In low MRSA regions: first/second generation cephalosporin. Clindamycin is a good alternative especially in children >2 years old. Amoxicillin–clavulanate may be an alternative option, but thorough evidence is lacking and the tolerance is worse.

Culture-positive Infections In culture-positive infections, follow the recommendations listed in Table 8.

According to reviewed sources, there are no good data for how long younger infants and neonates need IV therapy. Most experts would treat newborns, in particular, and young infants, for example, <3 months old, with IV therapy and for a longer total duration (4–6 weeks). Nevertheless, there is some personal experience in switching to PO after a minimum duration of IV therapy (eg, 10–14 days) beyond the neonatal period.

7.3.6. Duration of Therapy

The length of total therapy, IV plus PO, should be on average of 2–3 weeks for SA and 3–4 weeks for OM. Although the evidence is lower for pyomyositis, 2–6 weeks of total therapy (with a few days of IV therapy) may be appropriate for this infection.[85]

In the following situations, longer therapy may be required (although practice varies, some centers may go up to 4–6 weeks):

- Resistant or unusual pathogens (eg, MRSA, PVL+ and *Salmonella*)
- Newborns and young infants (ie, <3 months)
- Slow/poor response or complications; complex infections
- Involvement of pelvis or spinal column[86]
- Sepsis or in immunocompromised children

Before stopping treatment, most symptoms should have disappeared and the CRP should be normal (eg, <2 mg/dL). Children with complex disease, underlying problems, ongoing symptoms or immunodeficiency need careful consideration.

7.4. Adjuvant Treatment

One trial has suggested that symptomatic therapy for pain and fever with nonsteroidal anti-inflammatory drugs (NSAID) in large enough doses during the acute phase while signs of inflammation are present is of benefit.[29]

Although some studies,[87] including a randomized, placebo controlled trial,[88] appear to have shown a faster recovery in children with SA, widespread adoption of steroids is not recommended until larger prospective studies are performed. Corticosteroids may delay the diagnosis of noninfectious arthritis.

7.5. Surgical Interventions

Surgical Interventions in OM

Studies show that up to 90% of patients with an early OM can be cured with conservative treatment of antibiotics, especially when antibiotics are initiated during the first days of the onset of symptoms.[23,29] Surgery is usually not needed (except if aspiration/drainage is required, for instance in the case of abscess) and could in some cases prolong recovery.

Consensus is lacking on the need, extent, timing and procedures for surgical drainage. In the decision process, the following is important:

- Clinical response to antibiotic therapy[30]: for example, persistence of fever >72–96 hours or its reappearance
- Periosteal abscess and persistent fever and CRP elevation
- Size and position of the abscess, such as in close proximity to a growth plate–although even abscesses >3 mm may have good outcome with only antibiotics[4]
- Sequestration or other suspected complications
- Identification of MRSA or PVL+ *S. aureus* may increase the need for surgery[22,89]
- Chronic OM or presence of prosthetic material

Surgical Interventions in SA[4,8,90–96]

- Joint drainage and irrigation is recommended after the diagnosis of SA is suspected. A delay in effective therapy, including drainage, may be associated with worse outcomes. Drainage and antibiotic therapy should be initiated within 5–7 days of the onset of SA to achieve a more favorable prognosis according to some studies.[8,93,96] Drainage may be more important in neonates and infants <18 months of age with SA of the hip or shoulder joint.
- Classically, surgical drainage by arthrotomy has been performed, but arthrocentesis or arthroscopy, depending on the local expertise, may be effective in a number of cases of SA. Both these procedures are minimally invasive compared with arthrotomy. Some orthopedic surgeons prefer arthrotomy because more complete pus removal can be achieved. However, few small studies, 1 prospective and the others retrospective, have shown that arthrocentesis may be an appropriate approach for SA therapy in children, even when shoulder and hip are involved.[90–94] In some institutions, many episodes of SA such as those in the knee and ankle, and hip without risk factors,[91,94] are managed by arthrocentesis, sometimes with repeated "closed needle aspirations and lavage"—consider surgery if more than 2–3 interventions have to be performed.[93,94]
- Arthrotomy may be considered in some SA involving the hip or shoulder in young children (3–6 months),[5] longer duration of symptoms at presentation (5–7 days) and with more virulent pathogens (MRSA or PVL+), because the rate of developing complications and sequelae may be higher.[11,54,89,97,98] Some studies have found an association between SA of the hip and higher development of sequelae[5,99] and, therefore, some authors suggest arthrotomy when this joint is involved.[99]
- Arthroscopy has been associated with shorter lengths of hospital stay and may provide improved visualization of the joint space for prognostic purposes.[96,100]
- Generally, even after arthrotomy, there is no need for "immobilization" except for pain control or upon risk of fracture, although some orthopedic surgeons recommend this, especially after hip SA to avoid a potential luxation of the joint.
- There is little evidence to leave a drain in place routinely. If considered due to the extent of infection or difficulty in debridement, drains should be inserted for as short as possible.

TABLE 9. Clinical Outcome BJI: Possible Complications and Sequelae

Outcome and Complications	Notes/Remarks
Persistent fever	• Look out for complications or resistant pathogen
OM-SA	• In certain *Staphylococcus aureus* infections—relatively common in <18 months and hip/shoulder* • It may be associated with higher rate of complications or sequelae[5]
Pyomyositis	• More frequent in pelvic involvement and with MRSA/PVL+
Discitis/vertebral OM	• Supportive corset might be beneficial
Abscess, sequestrum	• Surgery may be needed
DVT	• May be life-threatening and high risk of pulmonary thromboembolism • Risk factors: femoral OM, male sex, MRSA/PVL+[101,102] • Some experts may recommend low-weight molecular heparin until resolved
Relapse or chronic infection	• If eradication of infection failed
Chronic OM	• Important early diagnosis and therapy to avoid it • Surgery and prolonged antibiotic therapy frequently needed • Major health problem in the resource-poor settings • Most common cause of pathologic fracture
Reinfections with another agent (not recurrence)	• Possible but very unusual • Not a sign of treatment failure
Bone deformity, for example, avascular necrosis of the femoral head, joint cartilage destruction in SA	• Feared sequelae • More frequent with late diagnosis and therapy[96]
Decreased movement, residual pain, rigidity	• Physical therapy may be needed
Mortality	• Very unusual in an immunocompetent host in high-income countries

*Some studies have shown that OM-SA may be more common in older children.[5,103]

7.6. Physical Therapy

Rehabilitation is a very important part in the management of BJI, and especially so in SA and after surgery. Although injury to the area involved should be avoided, prompt mobilization is crucial for the prevention of complications such as rigidity.

- Depending on the site and severity of the OM, some type of support and/or protection device may help prevent the development of a pathologic fracture.
- Non-weight bearing is considered essential in the early management for pain control for the short and longer term.
- Supportive devices (ie, corsets) in case of spondylodiscitis may be recommended.
- BJI management is often a multidisciplinary approach with orthopedics and adjunctive therapy should be discussed on a case-by-case basis with them.

7.7. Follow-up and Outcome, Complications/Sequelae

Early diagnosis and appropriate treatment are associated with excellent outcome and successful prevention of chronic inflammation

and development of sequestra and fistulae.[2] Common sequelae are as follows: limping, dismetry, chronic pain, rigidity and chronic inflammation in the absence of an infectious agent (Table 9).

- After hospitalization, follow-up by orthopedics and pediatricians with musculoskeletal experience (and especially infants, hips and physis involvement) is recommended at about 2 weeks, 4–6 weeks, 3 months and 12 months after discharge.
- Consider longer follow-up in children with involvement of the pelvis, the spinal column and hip, or if the physis is affected, especially infants and younger children.
- Pain-free normal activity is an important end-point before discharge from follow-up.
- Check-up should include: clinical investigation, CRP, US—radiography only when indicated.
- Provide NSAID or analgesia as needed.

The identification of *Salmonella*,[82] MRSA or PVL+ bacteria may be related with higher rate of complications and/or sequelae,[89,97] although not all studies have shown this.[22,67] PVL+ *S. aureus* (MSSA or MRSA) may also be associated with higher morbidity in pediatric BJI.[11,22,67,98] Some authors claim that MRSA virulence may be related to PVL (or other toxin) production, because PVL is more commonly found in MRSA than in MSSA.[67,77,98]

It is important to look out for DVT in severe *S. aureus* OM and especially MRSA/PVL+ infection.[101] In case of DVT, it is recommended to discuss the best treatment options with a pediatric hematologist.[104] Low molecular weight heparin may be started and maintained until the DVT is resolved. For patients with DVT, antibiotics are typically administered for longer periods of time,[102] although there is no evidence of which would be the most appropriate length of therapy for this situation.

Please refer to the full, online version (Supplemental Digital Content, http://links.lww.com/INF/C729) of this guideline for the following:

- Summary of pathogens in BJI with geographical prevalence (Table 14)
- Summary of antibiotic recommendations in BJI
- Abbreviations and definitions used in this guideline
- Review team members' information and disclosures

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