EUROPEAN SOCIETY for PAEDIATRIC INFECTIOUS DISEASES

BONE AND JOINT INFECTIONS

Guideline Authors

Jesús Saavedra (Chair), Spain
Oana Falup-Pecurariu, Romania
Saul Faust, United Kingdom
Hermann Girschick, Germany
Nico Hartwig, Netherlands
Sheldon Kaplan, United States
Mathie Lorrot, France
Elpis Mantadakis, Greece
Heikki Peltola, Finland
Pablo Rojo, Spain
Theoklis Zaoutis, United States/Greece
Anton LeMair, Netherlands

Contents

Tables

1 Introduction

The *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 or osteoarticular infection), including general paediatricians and family practice physicians. Although BJI can include a diverse range of presentations, these guidelines will focus on **acute, haematogenous 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. Since 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.

The *ESPID Guidelines* are based on medical scientific literature, existing practice guidelines and regional best-practice standards. All available sources were used in the guidelines to develop a balanced approach for providing optimal care to paediatric patients with BJI in the average European health practice. The chosen methodology for *ESPID Guidelines* was based on consensus development among experts at the highest possible level of evidence.

The ESPID Review Team (RT) for this guideline comprised a panel of clinical experts, including specialists in paediatric infectious diseases, paediatric rheumatology and surgery. The RT members were required to disclose any financial or other interest to avoid any actual, potential, or apparent conflict. See the Appendix for relevant information on the individual RT members.

Literature searches were performed monthly and delivered to the RT members as alerts. Based on the alerts, the RT scanned the literature and identified new insights and evidence for the next guideline update. Revisions were made on an ‘as needed’ basis and were determined by the guideline chair.

The authors of these *ESPID Guidelines* have made considerable efforts to ensure 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.

2 Summary of BJI recommendations

2.1 Main practice statements

There is a paucity of clinical trial or prospective cohort study data to inform the diagnosis and management of BJI in children. Most data is 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**). Future versions will address evidence quality as new trial results are published.

1. BJI more frequently affects children younger than 5 years of age, and the infection more often involves joints of the lower extremities. [IIA]
2. S*taphylococcus 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 (ESR) have a high sensitivity for the diagnosis of BJI, which is slightly increased by combining the two tests, whereas the specificity is low. [IIB]
4. Ultrasound has a high sensitivity for the diagnosis of septic arthritis 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 radiological 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 microbiological 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 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. Septic arthritis (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 therapy followed by oral therapy is appropriate in most children with uncomplicated BJI based on absence of complications and favourable 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 septic arthritis and 3-4 weeks for osteomyelitis. [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 intravenous (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 orthopaedic 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: Randomised placebo controlled trials; other studies appropriately randomized; good meta-analysis and systematic reviews of randomised 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; C = Weak recommendation**

2.2 BJI diagnostic recommendations

Table 1 – Diagnostic options for childhood BJI

Type	Tests	Notes/remarks
LABORATORY TESTS (1–4)	**C-reactive protein (CRP)**	– Easy, inexpensive, and rapid test in diagnostics and follow-up – High sensitivity for diagnosis of BJI (2,5) – Normal rate is reached quickly (in 3-8 days) during recovery of BJI (6,7)
	Erythrocyte sedimentation rate (ESR)	– This test may be more difficult in children: larger sample blood volume needed and possible laboratory errors due to handling problems – Some studies have shown high sensitivity (8). 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 weeks or more) during recovery of BJI (7)
	Complete blood count (CBC)	– Useful in conjunction with ESR and CRP – White blood cell, haemoglobin and platelet count may still be very useful for differential diagnosis of BJI (leukaemia, for example)
IMAGING	**X-ray imaging**	– Always at baseline (often normal at baseline but useful for later re-imaging comparison and to rule out other diseases) – Plain radiography often misses joint effusion, especially in the hip joint (9) – If clinical presentation is not severe and clinical outcome on therapy is appropriate, an additional imaging study may not always be necessary
	Ultrasound (US) sonography	– Identify joint effusion in septic arthritis (very sensitive) – Subperiostic abscess (low sensitivity for osteomyelitis but may be very useful)

Type	Tests	Notes/remarks
		– Doppler may detect elevated blood flow in osteomyelitis (OM) and help in early diagnosis (10)
	Scintigraphy/ Tc bone scan	– In several European countries, scintigraphy has become unpopular due to 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 localised – Not always needed in every child, especially if the diagnosis is clear and the child improves in a short period (2-3 days) – Provides excellent definition of soft tissues and bone marrow – Whole body MRI for multifocal processes has proven very useful (11), e.g., in cases of severe CA-MRSA
	CT scan	– Reserved for diagnostic dilemma in most centres, although local variation exists even within countries – much higher radiation than any other imaging test* – It may be more frequently used in centres 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 *S. 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 non-infectious processes – Drainage, e.g., of purulent fluid or abscess, may also serve as an important form of therapy
	Bacterial PCR (when available)	– Including molecular detection of *K. kingae, S. aureus* or others by using eubacterial rRNA amplification in tissue sample or synovial fluid (12). It may significantly increase the yield of a microorganism in SA, especially in previous use of antibiotics. Specific primers may be more sensitive (13,14)

Notes

- **Procalcitonin (PCT) has not been proven to be of value for the diagnosis of BJI in children because of its low sensitivity (15–17) and the wide availability of the existing tests CRP and ESR.**
- **In some settings (for example, high rates of MRSA), initial bone puncture for diagnosis may be appropriate to better adjust therapy. This procedure may be performed under CT direction (18).**
- *** = Radiation dose** (19–21)
  - **Conventional X-ray: Thorax one dimension post-anterior 0.02 mSv; Thorax 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-X rays)**

2.3 BJI management recommendations

Table 2 – Principle scheme for management of simple or uncomplicated and complex BJI

See text for details

Suspected diagnosis ▶ ▼Management components	Uncomplicated OM or SA	Complex[$] OM or SA
1. Hospitalisation	Yes	Yes
2. Blood tests	CBC, CRP, ESR	
3. Bacteriology	Blood culture – Generally, 4 ml minimum, 2 ml for neonates (22) 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	
4. Imaging	**OM** – Always plain X-ray. Consider MRI **SA** – US, MRI to document suspected OM in SA and perifocal disease	**OM** – Always plain X-ray. MRI, US **SA**– US, MRI, consider ^{99}Tc bone scan if no MRI is available
5. 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
6. Antibiotic treatment	**See Chapter 7**	
7. Monitoring	When **pathogen is not known**: • Switch to oral antibiotic monotherapy following local microbiological or clinical infectious diseases standards • Choose oral antibiotic spectrum similar to IV if initial IV response was favourable	
		Consider 2nd line or additional antibiotics, especially as long as gram-negative bacteria or MRSA are not ruled out
8. Switch IV to oral treatment		
– Criteria for time to switch – **pathogen is unknown**	Afebrile 24-48 hrs, improved clinical condition (reduction of **pain**, mobility, inflammation) **>24 hrs** and **significantly decreased CRP (30-50%** of highest value)	Similar parameters but consider a **minimum of 1 week of IV therapy**
– Up to 3 months old – time to switch and duration	Consider switch after **14-21 days,** especially under 1-month age; some experts consider switching earlier →**OM** and **SA** – **4-6 wks** total antibiotic treatment	Consider switch after **21 days** →**OM** and **SA** – **4-6 wks to several months** oral antibiotic treatment based on individual response
– 3 months and older – time to switch and duration	Consider switch after **24-48 hrs of improvement** →**OM** – minimum 3-4 weeks total →**SA** – minimum 2-3 weeks total*	Consider 10-14 days of IV antibiotics depending on severity and outcome, but may be switched to PO earlier. →**OM** and **SA** – 4-**6 wks up to several months** oral antibiotic treatment based on individual response and other specific characteristics
9. 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 • X-ray, 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 • Orthopaedic follow up at end of course of treatment more important than PID to address any ongoing sequelae of the bone or joint infection.	

Notes

- **CBC=Complete blood count. CRP=C-reactive protein. ESR=Erythrocyte sedimention rate. OM=Osteomyelitis. SA=Septic arthritis. PID=Pediatric infectious disease specialist.**
- **Consultation and treatment should <u>not</u> be delayed while waiting for a bone scan or MR in suspected OM**
- **Arthrocentesis or arthrotomy should be promptly performed in suspected SA before antibiotic therapy**
- **IV = intravenous administration, PO = oral administration**
- **$ = Complex disease = if any one of the following features are present: – significant bone destruction – resistant or unusual pathogen – immunocompromised patient – sepsis or shock – venous thrombosis or other major complications (e.g. important abscess).**
- *** = Some studies showed that 10 days of treatment may be enough for non-complicated SA**
- **# = Some symptoms may not be related to infection or inflammatory cause but to sequelae (e.g., limping, pain, limit range of motion). Consultation with Orthopaedics may be considered.**

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 (23,24). Acute haematogenous BJI in children may clinically manifest as osteomyelitis (OM), septic arthritis (SA), both combined (OM-SA), or as pyomyositis. Paediatric spondylodiscitis is uncommon and accounts for 1–2% of all children with OM. It is characterised by infection involving the intervertebral disc and adjacent vertebrae. Pyomyositis may complicate or accompany BJI, and it can also be a primary infection by itself without the coexistence of bone or joint infection.

- **Acute OM** is an inflammatory process in the bone accompanied by bone destruction (25) usually due to bacterial infection (26), and it is most commonly seen in the long bones of lower and, less frequently, upper extremities (8,27). 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 (8,27). Half of the children with acute haematogenous OM are under the age of 5 years (23).
- **SA** is an acute infection of the joint that occurs most commonly in young children, mainly monoarticular, and is frequently localized in the knee and hip joints (27,28) (see **Chapter 5**).
- **Spondylodiscitis** forms part of a continuum of spinal infections including vertebral OM and soft tissue collections. Early in the disease, differentiation between discitis and vertebral OM may be difficult. The pathogens implicated in discitis are similar to those in SA and OM (26). It occurs mainly in children < 5 years of age (24,29). Vertebral OM is more common in older children and usually involves the anterior body of the vertebra (29). In these instances, infectious agents such as *M. tuberculosis* and *Salmonella* should be considered as well.
- **Pyomyositis** is frequently seen with pelvic involvement and may be related to MRSA or PVL production (30–34).

3.1 European guidelines

Europe is a group of countries, and as such differs greatly 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.

Therefore, there may be important differences in terms of epidemiology, diagnosis and treatment in relation to the topic of this guideline. Where possible, this guideline describes regional variations in management.

To deal with variations in resource availability, this document aims to provide choices of diagnostic tools, options for treatment and investigation in "best practice order" where, for example, "state of the art" solutions are not available.

3.2 Incidence, prevalence

- Acute BJI incidence is higher in children than in adults (24).
- In developed countries, recent reports of OM rates are 2 to 13 per 100,000 children/year (35,36) and it is considerably more common in developing countries (37).
- Overall, OM is often more common than SA (8,36).
- The incidence is increased in immunocompromised patients and those with sickle cell disease (SCD), among others. However, not all immunodeficiencies have the same risk; chronic granulomatous disease (CGD) is a very typical example with increased risk.
- Boys are 1.2–3.7 times more likely to be affected by BJI than girls (8,24).

Table 3 – BJI incidence in European countries (Author input)

Country/region	BJI incidence	Remarks
Finland	OM: 4.5/100,000/year SA: <2/100,000/year	Reference (38)
France-Northern France	7.1/100,000 child/year 22/100,000/year	Children <16 years of age Nat. Hosp. Discharge Database (39)
Germany-Berlin	10-20/100,000 child/year	Spondylodiscitis: 1/100,000 child/year
Romania	5/100,000/year	Children Clinic Hospital Brasov
Spain$	4/100.000/year	BJI incidence increased from 2 (2002-2007) to 6 (2008-2012) cases/100,000 persons/year (40,41)
UK-England (26)	OM: 4.8-7.0/100,000 child/year	Child admission rates 0-18 yrs old
UK-Newcastle (26)	OM: 11/100,000/year SA: 7/100,000/year	1991 to 1999
UK-Southampton	1.4-10.5/100,000/year (42)	1979 to 1997
UK-'Dinosaur study'	Incidence reported less than previously	Results due for publication

Notes

- **It is unknown whether the reported differences in BJI incidence between European countries are based on dissimilar capacity to reach aetiological diagnoses and surveillance methods or truly different "incidence rates".**
- **$ = Data based on a retrospective, single centre study in Madrid (40,41).**

3.3 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 (*Kingella kingae*) (43–45)
- Preceding trauma (46) – such as blunt injury or a fall; some recent papers question this, since trauma is very common in children (47)
- Wounds (26), erosions, varicella infection (for Group A *Streptococcus* –GAS) (26)
- Sickle cell disease (*Salmonella* spp.) (26,37)
- Immunodeficiency – e.g., CGD (*Serratia*, *Aspergillus*) (48,49)

- Penetrating wounds – e.g., through the sole of a shoe or sandal (anaerobes and *Pseudomonas*) (24)
- Living conditions, occupation – e.g., animal handling and laboratory work in cases of infection due to *Brucella*, *Coxiella* spp. (50–53)
- Contact with pulmonary tuberculosis or living in endemic areas (tuberculosis BJI)
- Newborns: prematurity, skin infections, bacteraemia or candidaemia, previous central venous catheter (54,55).

4 Aetiology and pathogenesis

4.1 Introduction

- Most BJI in children are of a haematogenous origin
- Although less frequently in children than in adults, there are special BJI groups such as BJI in presence of prosthetic material or post-trauma cases
- In part due to practical reasons, "acute", "subacute", and "chronic" cases are those with a history of < 2 weeks, 2 weeks – 3 months, and > 3 months, respectively.

Note

- **Subacute and chronic are not consistently differentiated in the literature due to clinical and diagnostic similarities.**

4.2 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 (see **Table 14**). As one example, a common pathogen of BJI is community-acquired MRSA (CA-MRSA), which has emerged in some countries. **Table 4** illustrates the most common pathogens by age in acute BJI.

- OM and SA are most commonly caused by *Staphylococcus aureus;* then, depending on age and other risk factors, or geographical location, *K. kingae* or GAS.
- Pathogens involved less frequently in these infections are *S. pneumoniae*, *Pseudomonas*, *Haemophilus influenzae* type b (Hib), *Salmonella*, among others.
- Group B *Streptococcus* (GBS) and *Escherichia coli* are important pathogens in newborns.
- In certain areas, a variable but considerable number of cases are caused by CA-MRSA.
- Rates of CA-MRSA in children vary across European countries (see **Table 14**). A recent European pediatric study of invasive *S. aureus* disease has shown a prevalence of 8% of MRSA (56).
- In many European countries/regions, *K. kingae* should be considered in young children with culture negative skeletal infections. In some studies, it is the second (or even the first) most common aetiology after *S. aureus* in children < 5 years where real-time polymerase chain reaction (PCR) has been performed (8,13,40,57–59).

Table 4 – Most common pathogens by age in acute BJI.

Age group	Pathogen
Infant <3 months old	*S. aureus* *E. coli* and other gram negative bacteria GBS *Candida albicans* *Neisseria gonorrhoeae* (newborns)

Young child **3 months up to 5 yrs old**	*S. aureus* *K. kingae* GAS *S. pneumoniae* (especially under 2 yrs old) *H. influenzae* type b (exceptional in well immunised populations)
Older child **>=5 yr old**	*S. aureus* GAS *N. gonorrhoeae* (in sexually-active adolescents)

Note
- **References: (26,27,36,37)**

5 Clinical features

The "classical presentation" of BJI is the sick child with fever[$], localizing signs of swelling, pain or redness, and limitation of movement or limping. This chapter provides an overview of the general and location-specific symptoms as well as age and frequency information (see **Tables 5** and **6**).

Note
- **$ = While common, up to 30-40% of children may not initially develop fever (8,23,28,60)**

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. Pyomyosistis of the psoas may also be very difficult to diagnose. Other symptoms follow.

- Limping or non-weight bearing
- Refusal to use limb and/or decreased range of motion (28)
- Acute or subacute onset of complaints: SA 2-4 days (7,8,61) and OM 6-7 days (7,8)
- Fever and other systemic complaints or symptoms, such as malaise. In newborns and young infants only non-specific symptoms could be present such as irritability, vomiting or refusal to eat.

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 (8,27,28) (see **Table 5**). Single site infection is most common, but multifocal OM is seen in 5-10% of infants (especially in newborns and young infants) (28,35,62). Pain in OM tends to be more localised and is often characterised by tenderness, redness, and swelling; these symptoms are more common in SA. Pyomyositis, when it involves muscles around the hip joint, can mimic septic arthritis (63).

A 2012 systematic literature review (60) of paediatric studies of patients with OM reported the following distribution of symptoms.

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

Table 5 - Skeletal distribution of BJI in children

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

Notes
- **$ = Foot bones 26% (8)**
- **Table references (23,24,30,37).**

Table 6 - 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 localise on examination • Bone or limb swelling • Erythema • Pseudoparalysis • May have no local signs, especially when flat bones affected
OM	**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		• Limp • Pain – more localised • Bone or limb swelling • Erythema • Older children tend to localise more the symptomatology
SA	**All**		• Hot, swollen, immobile peripheral joint • Refusal to bear weight • Pain on passive joint movement
Spondylo-discitis	**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 neurological signs (64,65)
Pyomyositis	**All**	• Fever • Frequently no increase of CPK • Abdominal pain (psoas and muscles around)	• May have no local signs • Refusal to bear weight • Limp • Bone or limb swelling • Pain – more localised

Note

- **Based on: 2012 Faust SN et al. Managing bone and joint infection in children (26)**

6 Diagnosis

See **Chapter 2** for a summary of recommendations for the diagnosis of paediatric BJI.

6.1 Laboratory tests

In case of suspected BJI, the following tests are normally recommended:

- Complete blood count (CBC)
- C-reactive protein (CRP)
- Erythrocyte sedimentation rate (ESR, or blood viscosity test)

At this time, there lacks clear evidence of the clinical benefit of procalcitonin (15–17) to justify widespread introduction and replacement of CRP, a test more accessible and available. Gram staining can be very informative, both for synovial fluid and the potentially obtained bone aspirate. This test is especially important because the culture may be negative. Synovial fluid cytology may be performed but is not considered mandatory for the diagnosis because its findings overlap with other diseases.

6.2 Microbiology

Blood culture with appropriate volume should always be performed. Furthermore, it is important to obtain diagnostic specimens prior to antibiotics.

Use of blood culture vials (BCV) for culturing synovial fluid and bone exudates in recent years has resulted in the recognition of *K. kingae*, a commensal bacterium of the respiratory tract, as one of the most common cause of BJI in children < 5 years of age in selected regions or countries (66,67). The determination of bacterial PCR (discussed below) from biological samples may replace this technique.

In recent years, nucleic acid amplification methods (e.g., conventional and real-time PCR) have also improved the detection of bacteria not isolated by culture (57,66,68). 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 (13,40,43,44,57,59,66,67). *K. kingae* is identified mainly via eubacterial PCR using rRNA primers targeting the 16S rRNA gene. More specific primers may increase the sensitivity of PCR to detect *Kingella* (14,43,44). Specific for *K. kingae* quantitative polymerase chain reaction (qPCR) assays show no cross reactivity with other common osteoarticular pathogens, and exhibit 10-fold higher sensitivity compared to older semi-nested broad-ranged 16S rRNA gene PCR (14,58).

- Real-time PCR identified *K. kingae* in 24/53 culture-negative cases of SA in a French study, and in another study in the same centre, *K. kingae* was identified in 69% of 75 children diagnosed with SA (69).
- In a Madrid cohort, after PCR implementation, the aetiology of SA was identified in 68%; *K. kingae* was the causing agent in 48% of the proven etiologies (40).

An aetiological diagnosis is highly recommended even though *S. aureus* is so common that an empirical anti MSSA/MRSA treatment would usually perform well, and may be acceptable for children >= 5 years of age, but less acceptable for younger children. Although most culture-negative cases of BJI can be successfully treated with empirical antibiotics, it is important to establish a microbiological diagnosis to tailor therapy to the responsible pathogen, thereby limiting the use of unnecessary broad-spectrum antibiotics. This may specially apply to regions with high rates of MRSA (18).

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. For most uncomplicated OM, bone aspiration does not seem to affect the outcome of these infections (27,36).

6.3 Imaging studies

X-ray imaging is considered the most important baseline test in all patients for comparison of subsequent change if disease does not rapidly improve, and to rule out other underlying conditions.

- **Acute OM** – normal in most baseline films. Repeat imaging shows late appearance of osteolytic changes or periosteal elevation: occur mostly 10–21 days after onset of symptoms (26) – once apparent, bony changes provide good correlation with disease severity.
- **Subacute OM** – changes frequently seen can be confused with malignancies, e.g. Ewing's sarcoma or osteoid osteoma (70) which usually requires 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 localised rarefication ('thinning') of a single vertebral body, then anterior bone destruction. Magnetic resonance imaging (MRI) may be indicated in suspected spondylodiscitis and vertebral or pelvic OM.

Magnetic resonance imaging 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 and sequestra, and can help the orthopaedic 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. In general, clinicians may wait for 2-3 days to determine the antibiotic response before an imaging study, additional to plain X-ray is performed in acute OM, unless the child is very sick, there are reasonable doubts about the diagnosis, or when a complication is suspected.

- **OM** – high sensitivity and specificity (71), it may also demonstrate subperiosteal abscesses, pyomyositis, evidence of contiguous venous thrombosis; more sensitive than bone scan for *S. aureus* OM (72).
- **SA** – may reveal valuable additional information, such as bone oedema (or even involvement, i.e. associated OM) and perifocal myositis – MRI is not generally indicated for SA. However, it may be valuable if OM-SA is suspected. Thus, in a recent study (18), 35% of children with acute OM had a contiguous SA.

- **Spondylodiscitis** and vertebral OM – for detailing bone and soft tissue involvement, discriminate between vertebral OM, epidural abscess and tumour; MRI is a necessary test if these infections are suspected.
- **Pyomyositis** – high sensitivity and specificity, especially useful for the hip and pelvis.
- Availability and access – although not (immediately/timely) available in each and every medical centre, most European centres will have access to an MRI.
- Disadvantages of MRI include long scan times, susceptibility to motion artefacts which necessitate sedation or anaesthesia in young children, and is a contraindication in some patients with metallic foreign bodies and certain types of implanted hardware (11).
- Whole body MRI may be considered as an alternative to bone scan in settings where it is possible and affordable (11,73).

Computerized tomography (CT scan) is not generally recommended; it is less sensitive compared to MRI in detecting early osseous lesions and exposes children to high radiation doses (19). It may be performed in settings where MRI is not feasible.

- **Chronic OM** – effectively demonstrates air, sequestra, cortical destruction (74)
- **Discitis** – non-specific results
- Valuable for guided procedures, such as aspiration or drainage (18,75)
- The advantages over MRI may be its widespread availability and less need for general anaesthesia in young children due to the short time needed for the procedure.

Sonography or ultrasound (US) is most indicated for SA since it has a high sensitivity for the diagnosis of joint effusion, although with a lower specificity. In many cases it cannot discriminate between SA and other inflammatory conditions. 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, and it may provide guidance for diagnostic or therapeutic aspiration and/or drainage. Along with X-ray, US may be performed to rule out OM, although it requires radiologic expertise and it is much less sensitive than other imaging modalities such as bone scan or MRI (76). Doppler US may provide early detection of a high vascular flow in the infected bone (10).

- A disadvantage of US modality is that it cannot always differentiate between purulent and non-purulent material (77).
- US may distinguish infection from other extraarticular causes of similar symptoms such as cellulitis, bursitis, appendicitis, orchitis, or psoas abscess that may lead to referred hip pain.

Bone scintigraphy or 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 (78). In some centres, bone scan is still faster and more accessible than MRI, but may not be ordered routinely as it involves a significant amount of radiation exposure (20,21). And although the absolute risks are small, the radiation dose* should be kept as low as possible, as guided by the clinical benefits.

- **OM** – high sensitivity but less specificity (79), triple-phase bone scintigraphy using ^{99m}Tc-methylene diphosphonate (^{99m}Tc-MDP) can demonstrate evidence of infection as soon as 24 hours after onset and has the advantage of being able to depict multiple sites of infection (11). The specificity is lower than sensitivity, and both are lower in neonates;

specificity may increase with Gallium scan or In-labelled leukocytes (80), although these techniques have more complexity and add radiation exposure to the procedure.

- **SA** – to exclude underlying OM
- May give false negative results in infancy, and with virulent pathogens such as MRSA (72).
- * = Dose range equal to 200-750 chest X-rays; see also **Section 2.2** and the American Nuclear Society website (http://www.ans.org/)

Table 7 – BJI diagnosis: summary of recommended imaging studies for SA and OM

BJI	Imaging test recommendations
All patients	Always perform an X-ray study as baseline and to rule out other possible conditions
SA	– Ultrasonography is the most sensitive (but less specific) and an easy test to apply. – Other tests should be ordered in case of diagnostic doubts or if complications are suspected.
OM	– Focal symptoms/clear location: MRI – Systemic or less focal symptoms: consider bone scan (Tc^{99} scintigraphy). Some institutions may use total body MRI. – If MRI is not available, apply bone scan or CT-scan, the latter in case of focal disease – In less severe cases with favourable initial outcome no additional imaging test may be needed

Notes

- **Not all technical options are equally accessible throughout Europe.**
- **Regionally, radiation exposure reduction programs and availability of different imaging studies may influence the choice of imaging options.**
- **When needed, it is encouraged that individual cases are discussed with an experienced radiologist.**

6.4 Differential diagnosis

Table 8 – Differential diagnosis of BJI

Differential diagnosis	
OM	**SA**
– Traumatic or stress fracture	– Transient synovitis
– Cellulitis, pyomyositis	– Viral arthritis
– Septicaemia (newborns)	– Reactive arthritis
– Rheumatic fever	– Juvenile idiopathic arthritis
– Thrombophlebitis	– Tuberculosis
– Leukaemia	– Henoch-Schoenlein purpura
– Benign/malignant tumours	– Perthes disease
– Sickle cell infarction	– Septic bursitis
– Child abuse	– Slipped capital femoral epiphysis
– Chronic recurrent multifocal osteomyelitis	– Sickle cell anaemia, infarction
– Tuberculosis and other chronic infections	– Malignancy
– Scurvy	– Arthralgia
– Other bone inflammatory processes such as hypophosphatasia,	

Note

- **Based on: Pääkkönen M, Peltola H. Bone and joint infections (27) and Faust et al. Managing bone and joint infection in children (26)**

7 Management

See **Chapter 2** for a summary of recommendations for the management of paediatric 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 (7,9,81,82). Early diagnosis and prompt treatment are needed to avoid complications (8,83). 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 culture and other microbiological studies including antibiotic susceptibility testing, 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 of the aspirate, and other clinical and epidemiological considerations, including prevalence of MRSA in the community.
- Suggested treatment of uncomplicated (rapid resolution of fever and other symptoms) childhood BJI could include a short IV therapy followed by a high dose oral antibiotics for an average total duration of 3-4 weeks for OM and 2-3 weeks for SA. Treatment of less than 3 (OM) and 2 (SA) weeks is not advised.
- This may not be the case for the management of:
  - Complex infections
  - Significant bone destruction or complications, such as abscesses
  - Resistant or unusual pathogens (MRSA, PVL+, *Salmonella*)
  - Sepsis or in immunocompromised children
  - Neonates and very young infants (i.e., < 3 months).
- Oral antibiotics should be well absorbed, provide good bone penetration and be given in sufficiently high doses; beta-lactams at least 2-3 times the regular doses (30,81,84–86).
- Suspect PVL-positive *S. aureus* (including MRSA) disease if infection fails to respond to empirical treatment, is recurrent, multifocal, or associated with a necrotising process.

Note

- **See the Appendix for a summary of antibiotic recommendations.**

7.2 Hospitalisation

Most children are hospitalised at the start of the infection as intravenous therapy is generally used. It is recommended that children with suspected BJI be admitted at the start of therapy and generally started on intravenous therapy except in exceptional circumstances. 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.

Children should be given IV therapy until clinical improvement, including disappearance of fever and decreased inflammation and pain. A decrease of CRP is also an important parameter to follow. Furthermore, blood cultures may prove to be sterile if initially positive. Oral switch may be done after 2-4 days, unless risk factors are present (7,26,30,81,87).

An alternative approach used by some centres, when IV antibiotics are still needed for specific situations, is the insertion of a peripheral inserted central (PIC) line for once/daily antibiotic treatment at home – outpatient parenteral antimicrobial therapy (OPAT) (88,89), with the care being managed by PID teams. This is becoming increasingly available and is patients' preference: staying under hospital IV care but being at home. Nevertheless, one should keep in mind that prolonged IV therapy may be associated with catheter-associated

complications. Moreover, oral therapy does not seem to be associated with a higher risk of treatment failure compared to prolonged intravenous therapy in children with BJI (90,123).

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 antibiotic therapy.

Local, up-to-date resistance patterns are required to decide the best initial empirical therapy (see **Chapter 3 and Table 14**). The clinical condition of the patient at presentation is also important: the level of severity may lower the threshold to initiate anti-MRSA therapy or other adjuvant measures.

Table 9 – Empirical therapy preferences in different Europeans countries

Country	Author reported empirical therapy preferences
Finland	Clindamycin or 1st generation cephalosporin for 2-4 days IV, then the same doses orally.
France	2nd G cephasporins or amoxicillin-clavulanate. Cloxacilin in children over 5 years old. 3rd G cephalosporins (cefotaxime) + gentamicin in children under 3 months of age.
Greece	Ceftriaxone or cefotaxime plus clindamycin (due to high risk of CA-MRSA BJI). In the very sick child with multifocal disease and/or lung involvement: ceftriaxone or cefotaxime plus vancomycin
Netherlands	No use of first generation cephalosporins (restricted to surgical prophylaxis). First choice is flucloxacillin; when risk factors present: 2nd or 3rd generation cephalosporins.
Spain	1st and 2nd G cephalosporins (<= 2 years old). Cloxacillin in >= 5 years old. Few cases of CA-MRSA to influence antibiotic resistance in the community. Well tolerated and given in 3 doses PO.
United Kingdom	Cefuroxime most commonly used <=5 years old Flucloxacillin high dose first line in children >= 6 years old. Ceftriaxone has been used successfully in some centres against *S. aureus* in BJI

Other considerations regarding empirical therapy are:

- Beta-lactams, such as 1st generation cephalosporins and cloxacillin or other anti-staphylococcal penicillins, are the drugs of choice for good experience and tolerance (30,36,81,91,92). Clindamycin is also a suitable treatment, especially in settings with high rate of CA-MRSA (93).
- Amoxicillin-clavulanate may be an option although no published data is available and has a higher reported rate of adverse events (91,92).
- Antimicrobials with activity against *Kingella* should be considered in children < 5 years of age, especially in areas with high rates.

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

Clindamycin can be used if CA-MRSA is a possible cause (93–96). Although some authors recommend caution in the case of bacteraemic patients (95), others have good experience with clindamycon in this situation (97). Endocarditis and deep venous thrombosis (DVT), as well as inducible macrolide-lincosamide-streptogramin (MLS) resistance, may be ruled out before treating children with CA-MRSA BJI with clindamycin (94). Some experts may consider if MRSA is sensitive to clindamycin treat with clindamycin ± rifampin. Clindamycin may be combined with a beta-lactam to cover MSSA until antibacterial sensitivity is available.

In case of severe infection where CA-MRSA or clindamycin-resistance strains are a concern, vancomycin is recommended by the US guidelines (IDSA)(94) at high dose: 60 mg/kg/day qid – (no good data for trough levels in children and, in general, clinical outcome should be the most important outcome) (98). Nevertheless, there is not much evidence of the efficacy of vancomycin in BJI (99–101) and other antibiotic may be used (daptomaycin or linezolid), especially if no initial response or minimum inhibitory concentration (MIC) to vancomycin ≥ 2 mcg/ml (94,101–104). Rifampin may be added to all three (101) but with little evidence. Other options may be quinolones or cotrimoxazole (little experience in children) (105) ± rifampin.

In severe cases or special circumstances, adding a toxin inhibitor antibiotic such as clindamycin, rifampin (100), or linezolid (106), may be considered (107). Although data are sparse (101,108), this strategy is considered for adults in IDSA guidelines (94), and in children and adults with PVL *S. aureus* in British guidelines (109). In case of MSSA PVL+ infections, treatment with first generation cephalosporins or anti-staphylococcal penicillins (ASP) *plus* clindamycin might be suitable. Nevertheless, in most situations the clinicians do not have the PVL results to guide the therapy of BJI and it may need to be a test that is specifically requested

There are some reports and *in vitro* studies of the use of IVIG on severe PVL + *S. aureus* BJI infections but there is not enough evidence to support its general use (110,111). It may be considered in severe infections suspected to be caused by MRSA or PVL + *S. aureus*.

Table 10 – Initial empirical therapy and rate of methicillin-resistant *S. aureus* (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 3rd 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 (112) or linezolid (MRSA-IDSA guidelines) (94) • Always consider adding a beta-lactam until MRSA is confirmed • IVIG may be added where toxin-mediated systemic symptoms (i.e., toxic shock syndrome) is suspected.

Notes

- *** = Consider covering other agents such as *Kingella*, especially in children < 5 years of age.**
- **$ = Much less experience with 3rd G cephalosporins in children and less *in vitro* activity than the other options, although some studies in adults showed appropriate clinical outcome (113).**
  # = There is no evidence of rifampin benefit in otherwise healthy children with BJI.

Table 11 – Empirical therapy by age

Age	Empirical IV antibiotic treatment*
Up to 3 months old	Cefazolin (or ASP) + gentamicin; (ASP + cefotaxime may be an alternative) (30,71)
3 months to 5 yrs old	&Cefazolin or $cefuroxime Clindamycin in regions of non-*Kingella*; Alternatives: #Amoxicillin-clavulanate or ampicillin-sulbactam (114) or $ceftriaxone or %ASP
5 yrs and older	IV ASP or cefazolin or clindamycin (high MRSA prevalence) When risk factors present (e.g., SCD): other options may be considered such as ceftriaxone (± ASP or clindamycin)

Notes

- *** = High rate of MRSA, cover this by adding clindamycin (< 2 years of age) or clindamycin alone (above 2 years of age) – see specific section.**
- **& = Under 2-5 years of age there may be risk of *S. pneumoniae* or *H. influenzae* type b BJI in unvaccinated children, thus 1st G cephalosporins may be suboptimal.**
- **$ = Both cefuroxime and ceftriaxone have better coverage for *S. pneumoniae* and *H. influenzae*, but may be inferior to 1st G cephalosporins or ASP in *S. aureus* infections (115). There is experience with cefuroxime (Saavedra J, personal communication)(8) and ceftriaxone (some UK and Greece sites)**
- **# = The amoxicillin-clavulanate PK/PD profile may be suitable for BJI (116). Furthermore, there is a broad experience in BJI in children and has an appropriate activity for MSSA.**
- **% = Narrow spectrum ASP are not appropriate for treatment of *K. kingae* BJI (117).**
- **ASP = anti-staphylococcal penicillins. SCD=sickle cell disease. MRSA = Methicillin-resistant *S. aureus*.**

7.3.3 Targeted therapy

Table 12 – Pathogens and antibiotic treatment (according to local resistance patterns)

Pathogen	Antibiotic considerations
Staphylococcus aureus	• ASP, 1st generation (G) cephalosporins (30,36) • 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 (105)
Streptococcus pyogenes	• Penicillin, ampicillin, or amoxicillin
Streptococcus pneumoniae	• Ampicillin, amoxicillin or 2nd-3rd G cephalosporins • In the very unusual situation of high beta-lactam resistance may use vancomycin, linezolid or levofloxacin
Haemophilus influenza type b	• 2nd G cephasporins or amoxicillin-clavulanate (or ampicillin-sulbactam). • Some strains may be resistant to 2nd G cephalosporins and/or amoxicillin-clavulanate: 3rd G cephalosporins may be used
Kingella kingae	• Sensitive to cephalosporins and penicillins (58) • Resistant to clindamycin, vancomycin, linezolid, daptomycin; ASP not optimum • Rarely produces beta-lactamases (118)
***Salmonella* species**	• Ceftriaxone or cefotaxime • PO: amoxicillin or quinolones (119), according to sensitivity
***Escherichia coli* and other enterobacteria**	• According to sensitivity – amoxicillin-clavulanate or 2nd/ 3rd G cephalosporins or others
Pseudomonas aeruginosa	• According to sensitivity – ciprofloxacin PO
Neisseria gonorrhoeae	• Ceftriaxone or cefotaxime (or PO third generation cephalosporins)

Notes

- **Based on: Pääkkönen M, Peltola H. Bone and joint infections (27)**
- **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 p-OPAT 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 TMP/SMX efficacy in the treatment of *S. aureus* OM/SA in children, especially as initial therapy (105); It may be combined with rifampin (108,120).**
- **ASP = anti-staphylococcal penicillins.**

7.3.4 Allergy

In case of allergy to beta-lactams the options are: clindamycin, glycopeptides, quinolones, linezolid and cotrimoxazole. The best alternatives to cover the possibility of *Kingella* infection are cotrimoxazole and quinolones (levofloxacin may be superior to ciprofloxacin). Cotrimoxazole and quinolones may be suboptimal for *S. pyogenes*, although recent studies have indicated a better *in vitro* susceptibility to the former antibiotic (121,122).

7.3.5 Oral therapy

Oral therapy has been used as equivalent to prolonged IV therapy and may be associated with fewer complications (90,123).

Switching to PO therapy after IV treatment

Early oral switch has been used (30,81,82,97) if the child is showing clinical improvement (although there is limited evidence and variable practice) which may include:

- Afebrile or clear decreased temperature for 24-48 hours
- Improvement of symptoms
- 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, especially, MRSA or PVL+.
- Negative blood cultures.

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 cotrimoxazole, quinolones or linezolid, according to local resistance patterns.
- **In low MRSA regions:** first/second generation cephalosporin. Clindamycin is a good alternative especially in > 2 years. 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 12**.

According to reviewed sources, there is no good data for how long younger infants and neonates need IV therapy. The younger the infant, the less clinicians are likely to choose to treat orally. Most experts would treat (in particular) newborns and young infants (e.g., < 3 months) with IV therapy and for a longer total duration (4 to 6 weeks). Nevertheless, there is some personal experience in switching to PO after a minimum duration of IV therapy (e.g., 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 (124)

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

- MRSA or PVL+
- Newborns and young infants
- Slow/poor response or complications
- Involvement of pelvis or spinal column (125)

Before stopping treatment, most symptoms should have disappeared and the CRP should be normal (e.g., < 2 mg/dl). Many do not repeat CRP again in simple disease once it is reducing

towards normal, symptoms have completely resolved and the child is on oral therapy. However, children with complex disease, underlying problems, 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 agents (NSAID) in large enough doses during the acute phase while signs of inflammation are present is of benefit (7).

Although some studies (126,127), including a randomized, placebo controlled trial (128) 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 non-infectious 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 (7,36,129,130). Surgery is usually not needed (except if aspiration/drainage is required, for instance in the case of abscess formation) and could in some cases prolong recovery. However, surgery should be considered if the patient has not responded within a few days to antibiotic therapy or a complication is suspected.

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 (60): e.g., persistence of fever > 72-96 hours or its reappearance
- Surgical drainage may be indicated in patients with a 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 (27)
- Sequestration
- Identification of MRSA or PVL+ *S. aureus* may increase the need for surgery (56,131)
- Chronic OM or presence of prosthetic material.

Surgical interventions in SA (27,30,132–139)

- **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 favourable prognosis according to some studies (30,136,139), and as soon as possible after the diagnosis is suspected. Drainage may be even more important in neonates and infants under 18 months of age with SA of the hip or shoulder joint.
- In SA, the goal of drainage is to remove pus.
- 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 to arthrotomy. Some orthopaedic surgeons prefer arthrotomy to closed needle aspiration because more complete pus removal can be achieved. However, few small studies, one prospective and the others retrospective, have shown some evidence that arthrocentesis may be an

appropriate approach for SA therapy in children, even when shoulder and hip are involved (133–137).

- **Arthrotomy** should may be considered in some SA involving the hip or shoulder (especially if experience with arthrocentesis is lacking) in young children (3-6 months) (8), longer duration of symptoms at presentation (5-7 days), and with more virulent pathogens (MRSA or PVL+) since the rate of developing complications and sequelae may be higher (34,83,131,140–142). Some studies have associated SA of the hip with higher developping of sequelae (8,143) and, therefore, some authors suggest arthrotomy when this join is involved (143).
- In some institutions, many episodes of SA such as those in the knee and ankle, and hip SA without risk factors (134,137), are managed by repeated **closed needle aspirations and lavage** in older children – consider surgery if more than 2-3 interventions have to be performed (136,137). If closed needle aspiration is selected, it should be performed with a sterile procedure (144). Benefits include avoidance of surgery but it may require general anesthesia in young children
- **Arthroscopy** has been associated with shorter lengths of hospital stay, and may provide improved visualization of the joint space for prognostic purposes (139,145,146)
- Generally, even after arthrotomy, there is no need for **immobilisation** except for pain control or upon risk of fracture, although some orthopaedic 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 a period as possible.

Notes

- **In general, inflammation in the follow-up does not per se mean infection. Repetitive surgical interventions should be discussed by an interdisciplinary approach.**

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 mobilisation 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, such as a soft removable cast, boot case, and instructions to avoid weight bearing for some period, 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 - though clearly for some toddlers it is harder to enforce; back slabs/splints may be used to make this easier.
- Supportive devices (i.e., corsets) in case of spondylodiscitis may be recommended.
- BJI management is often a multidisciplinary approach with orthopaedics or paediatric orthopaedics (in larger centres) and adjunctive therapy should be discussed on a case-by-case basis with them.

7.7 Follow-up & 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 (24). Common sequelae are: limping, dismetry, chronic pain, rigidity and chronic inflammation in the absence of an infectious agent.

- Experienced orthopaedic surgeons should follow children for a variable duration of time depending on the severity of the infection, age, and the area affected.
- After hospitalisation, follow up by orthopaedics and paediatricians 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. Infants and younger children may be followed longer, as well.
- Pain-free normal activity is an important end point prior to 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* (147), MRSA or PVL+ bacteria may be related with higer rate of complications and/or sequelae. Recent studies show that morbidity associated with MRSA BJIs in children may be significantly higher than that caused by MSSA, and this reflects on type and duration of therapy (131,140,141). Other studies, however, did not see this difference (56,96). PVL positive (PVL +) *S. aureus* (MSSA or MRSA) may also be associated with higher morbidity in paediatric BJI (34,56,96,142,148). Some authors claim that MRSA virulence may be related to PVL (or other toxin) production since PVL is more commonly found in MRSA than in MSSA (96,107,142). Therefore, when this bactery is isolated, a closer, and probably longer, follow up should be completed.

It is important to look out for DVT in severe *S. aureus* OM and especially MRSA/PVL+ infection (149,150). In case of DVT, it is recommended to discuss the best treatment options with a paediatric haematologist (151). Low molecular weight heparin may be started and maintained until the DVT is resolved; no prophylaxis is recommended. For patients with DVT, antibiotics are typically administered for longer periods of time. Some authors claim for 6 weeks of IV and then orally until the thrombosis has resolved as demonstrated by Doppler examination. This often requires 4 or more months of therapy (152). Nevertheless, there is no evidence for this recommendation and, thus, the most appropriate length of therapy for this situation is unclear.

Table 13 – Clinical outcome BJI: possible complications and sequelae.

Outcome & complications	Notes/remarks
Persistent fever	• Look out for complications or resistant pathogen
OM-SA	• In certain *S. aureus* infections – relatively common in < 18 months and hip/shoulder* • It may be associated with higher rate of complications or sequelae (8)
Pyomyositis	• More frequent in pelvic involvement and with MRSA/PVL+
Discitis/vertebral OM	• Supportive corset might be beneficial
Abscess, sequestrum	• Surgery may be needed
Deep vein thrombosis (DVT)	• May be life-threatening and high risk of pulmonary thromboembolism • Risk factors: femoral OM, male sex, MRSA/PVL+ (150,152) • Some experts may recommend low-weight molecular heparin until resolved
Relapse or chronic infection	• If eradication of infection failed (153)

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 (154)
Reinfections with another agent (not recurrence)	• Possible but very unusual (155) • Not a sign of treatment failure
Bone deformity, e.g., avascular necrosis of the femoral head, joint cartilage destruction in SA	• Feared sequelae • More frequent if patient presents late after symptoms (139)
Decreased movement, residual pain, rigidity	• Physical therapy may be needed
Mortality	• Very unusual in an immunocompetent host in high-income countries

Note

– **OM-SA = osteomyelitis-associated septic arthritis.**

– *** = Some studies have shown that OM-SA may be more common in older children (8,156)**

8 Appendix

8.1 Etiology in BJI – summary

Table 14 – Summary of pathogens in BJI with geographical prevalence.

Microorganism	Regional data	Remarks
***S. aureus*, methicillin sensitive (MSSA)**	• UK: 44-80% (26) • Spain: 62% (8) • Greece: common • Romania: common • France: 11-61% • Finland[$]: >90%	• By far most common cause of BJI
Methicillin-resistant *S. aureus* (MRSA)	• UK: rare (26) • US: 40-50% (26) • Spain: 2.5% (8) • Germany: sporadic in children • Romania and Greece: common • France: 8.5%	• Resistant to beta-lactams (except ceftaroline) • Associated more frequently with complications (131,140,141)
Coagulase-negative *Staphylococcus*		• Special situations, such as prosthetic material
PVL producing *S. aureus* (148)	• PVL toxin was reported to be produced by less than 2% of *S aureus* (PVL-SA) but new data points to higher percentages in some European countries (56,157)	• PVL-*S. aureus* poses a serious risk – severe osteoarticular infection, sometimes multifocal • Associated with myositis, thrombophlebitis and deep venous thrombosis, and/or pneumonia • More common in MRSA (depending on the location)(34,96,107)
Group A *streptococcus*	• France: 7%(158) - 9%(69) • Spain: 7-10% (8)	• Toxic shock, rash – In general very purulent • More common in > 3-5 years
Streptococcus pneumoniae	• Spain: rare • France: 3-7.5%% (158,159)	• Vaccination not yet as successful as in Hib due to non-vaccine serotypes (160) • First two years of life (161)
***H. influenzae* type b**	• Germany: rare • Romania, Greece, Spain: none	• In 1980s second most common cause of SA in young children – now largely eliminated by vaccination (only in non-immunized or immunodeficient children) • Rarely causes OM

Microorganism	Regional data	Remarks
K. kingae	• Common in the UK (26), Spain (8,40), France (45,69,158,159), Israel • Occasional in Germany • Rare in Scandinavian countries • Greece: first BJI case (162) reported • Romania: no data	• Gram-negative coccobacillus respiratory pathogen • Seems an emerging pathogen – common cause of OM and SA in some areas (40,58) • May cause bacteraemia in infants and endocarditis in school-aged children • *K. kingae* infection diagnosis can be increased by using PCR • *K. kingae* is highly susceptible to β-lactam antibiotics – a recent paper described for the first time a *K. kingae* beta-lactamase-producing strain in continental Europe (163).
***E. coli*, *Klebsiella* spp., other Gram negative bacilli**	Variable rates	• Neonates (< 3 months) and immunocompromised children
Fusobacterium		• Often multifocal. Very rare
Group B *streptococci*		• Neonates (164)
***Aspergillus, Serratia* and other catalase-positive microorganisms**		• Chronic granulomatous disease (CGD)(48,49)
Mycobacteria		• Non-tuberculosis: associated with defects of IFNg/IL12 pathway • Immunocompromised hosts – patients under immunomodulation/suppression (e.g. anti-TNF drugs) (165) • Usually older children – develops 2 years from primary infection
Neisseria gonorrhoeae		• Adolescents and newborns
Neisseria menigitidis		• Adolescents
Pseudomonas aeruginosa		• Usually inoculation injuries (i.e. through sport shoe soles) – therefore >1 year old
***Salmonella* spp**		• Common agent in tropics and in SCD (166) • (147)
Brucella		• Sacroiliitis – endemic areas around the Mediterranean, occupational disease in people working with farm animals
Bartonella henselae		• Kitten exposure
Coxiella		• Associated with chronic OM • Domestic animals – very rare
C. albicans		• Neonate, damaged bone, nosocomial, immunodeficiencies

Notes
- **PVL = panton-valentine leucocidin; SCD = sickle cell disease; TB = tuberculosis**
- **$ = and most of Scandinavian countries**

8.2 Antibiotic recommendations in BJI – summary

It is important to know the different concentration, formulation, and availability for each antibiotic for each country. The use of a narrow-spectrum antibiotic is recommended and empiric antibiotic treatment must target common pathogens (*S. aureus*, *K. kingae* and group A beta-haemolytic *streptococcus*) considering their local prevalence and antibiotic resistance.

Table 15 – Paediatric BJI and most common Antibiotic Treatment

Antibiotic Empirical treatment	Dose mg/kg/day	Maximum daily dose†	Bone Penetration‡
First generation cephalosporin, if prevalence of MRSA in community is < 10-15%§			
Cefazolin IV	100-150, 3-4 doses	4-6 g	6-7%
Cefadroxil PO	75-150, in 3-4 doses	3-4 g	
Cephalexin PO	75-120, 3-4 doses	3-4 g	
Antistaphylococcal penicillin if prevalence of MRSA in community <10-15%			
Oxacillin/nafcillin IV	150-200, 4-6 doses	6-12 g	15–17% (PO not recommended for low oral biodisponibility, especially for cloxacillin)
Dicloxacillin PO	100, 4 doses	12 g	
Flucloxacillin IV	200, 4 doses	12 g	
Cloxacillin IV	100-200, 4-6 doses	6-12 g	
Clindamycin, if prevalence of MRSA in community >10-15% and prevalence of clindamycin resistant *S. aureus* <10%			
Clindamycin IV	30-40; 3-4 doses	2.7-4.8 g	65–78%
Clindamycin PO	30-40; 3-4 doses	1.2-1.8 g	
If MRSA prevalence in community >10-15% and prevalence of clindamycin-resistant S. aureus ≥10%			
Vancomycin	45-60; 4 doses	2-4 g	5–67%
Teicoplanin	10; 1 dose-first 3 doses bid	0.4 g	12-48%
Linezolid if no response to vancomycin	30, 3 doses >12 yrs: 600 mg bid	1.2 g	40–51%
	For 28 days maximum – some reports use up to 3 months; be cautious and monitor		
Daptomycin IV	6-10; one dose a day Not approved in children – adult dose: 4-6 mg/kg in one dose a day		
Trimethoprim/Sulfamethoxazole PO	6-12 (of TMP), 2 doses	320 mg (of TMP)	
Other antibiotics that may be used in BJI			
Cefuroxime IV	150-200, 3-4 doses	6 g	
Cefuroxime PO	75-100, 3 doses @	1.5-3 g	may be suboptimal PO
Ceftriaxone	80-100, 1-2 doses	4 g	<15%
Cefotaxime	150-200, 3-4 doses	12 g	
Amoxicillin-clavulanic acid IV	100 amoxicillin, 3-4 doses	6-8 g amoxicillin per day 200 mg clavulanic acid per dose	
Amoxicillin-clavulanic acid PO	120 amoxicillin, 3-4 doses	3 g amoxicillin per day 125 mg clavulanic acid per dose	
Ampicillin-sulbactam IV	200 ampicillin, 4 doses	8 g	
Alternatives for specific agents			
Ampicillin or amoxicillin for group A (or group B) beta-hemolytic streptococcus, *Haemophilus influenzae* type b (beta-lactamase–negative strains), and *S. pneumoniae*			
Ampicillin	150–200, 4 doses	12 g	3–31%

Antibiotic Empirical treatment	Dose mg/kg/day	Maximum daily dose†	Bone Penetration‡
Amoxicillin PO	80-120, 3-4 doses	3-6 g	
Amoxicillin IV	200-300/4-6 dose	12 g	
Chloramphenicol if safer agents not available or affordable	50-100‖, 4 equal doses	2–4 g	39%

Notes

- **Table references: (30,37,91,92,158,159,167)**
- **See Peltola/Pääkkönen N Engl J Med 2014 (37) for dose information references.**
- **When relevant and suitable, the same dose may be used parenterally and orally. For 1st and 2nd generation PO cephalosporins some RT may go up to ≥150 mg/kg/day (maximum 6 gr/day) whereas others would use up to 90-100 mg/kg/day (neutropenia may be more common with higher doses). Oral cephalexin had good tolerance and achieved optimal pharmacokinetics and pharmacodynamics in children with BJI at 120 mg/kg/day (168). In addition, children with osteoarticular infections had a good outcome on oral cefadroxil at 150 mg/kg/day in a prospective, quasi-randomized study (93).**
- **According to some reports PO cefuroxime may not be suitable for BJI (116) although there is good clinical experience**
- **For the switch IV-oral, antibiotics compliance is mandatory for which an acceptable taste is very important. Most of the RT think that t.i.d. dosing is appropriate whereas some would consider a q.i.d. dosing during the day-time (maintaining 8 hours sleep at night) more appropriate for these infections.**
- **PO Trimethoprim/Sulfamethoxazole (TMP-SMX) is a possible choice for culture negative OM in younger children in whom *S. aureus* and *Kingella kingae* are possible; French recommendations consider TMP-SMX as alternative treatment of *S aureus*, and group A beta-haemolytic *streptococcus;* Occasionally, consider TMP-SMX in MRSA infections, even though knowledge is limited.**
- **PO Amox-clav: max dose 125 mg of clavulanic. We may add more amoxicillin up to 3 gr per day or more, according to tolerance.**
- **† = The maximal daily dose is not always well defined – in general, the maximal adult dose should not be exceeded, although e.g. 1st generation cephalosporins or amoxicillin are very well tolerated.**
- **‡ = Bone penetration is the ratio of the bone concentration to the serum concentration.**
- **§ = Data on antistaphylococcal penicillins, first-generation cephalosporins, and clindamycin are from prospective studies involving children; the remaining data were derived from case series, studies involving adults or from experimental models.**
- **¶ = Cephalothin and cefazolin are administered intravenously, cephalexin and cefadroxil are administered orally, and cephradine is administered by either route. If no parenteral first-generation agent is available, cefuroxime can be used for parenteral administration.**
- **‖ = Chloramphenicol at a dose of 100 mg per kilogram of body weight per day in four equal doses is generally used in bacterial meningitis.**
- **@ = although not well known, some authors would recommend a dose similar to what is recommended for 1st G cephalosporins**
- **MRSA denotes methicillin-resistant *Staphylococcus aureus***

8.3 Abbreviations & definitions

Table 16 – List of abbreviations

Abbreviation	
ASP	anti-staphylococcal penicillins
BID	Given in 2 equal doses per 24 hours
CA-MRSA	Community-acquired MRSA
CGD	Chronic granulomatous disease
CoNS	Coagulase-negative *Staphylococcus*
CRMO	Chronic recurrent multifocal osteomyelitis
CRP	C-reactive protein
DVT	Deep vein thrombosis
GAS	Group A *streptococci*
GBS	Group B *streptococci*
Hib	*Haemophilus influenza* type b
hrs	Hours

IV	Intravenous administration
JIA	Juvenile idiopathic arthritis
LMWH	Low-Molecular-Weight Heparin
MRSA	Methicillin-resistant *Staphylococcus aureus*
MSA	Monoarticular septic arthritis
MSSA	Methicillin-sensitive *Staphylococcus aureus*
OAI	Osteoarticular infection
OM	Osteomyelitis
OMSA	OM adjacent with SA
PO	Oral administration ('per os')
PVL	Panton-Valentine leukocidin
QD	Once a day
PVL-SA	*S aureus* producing Panton Valentine leukocidin toxin
QID	Given in 4 equal doses per 24 hours
SA	Septic arthritis
SCD	Sickle cell disease
Spp	Species (microbes)
TID	Given in 3 equal doses per 24 hours
WBC	White blood cell count
Yr	Year

8.4 Review team members' information and disclosures

Table 17 – ESPID Guideline Review Team members

Name	First	Country	Activities	Guideline making
Saavedra	Jesus	Spain	Paediatric Infectious disease based in a hospital Medical education Clinical research	Several Spanish guidelines including bone and joint infection (chair), community-acquired pneumonia, periodic fever, congenital CMV.
Faust	Saul	UK	Clinical research (investigation/trials) and Clinical PID	Current Chair of UK NICE Sepsis Guideline Development Group (adults and children); Lead author UK BJI guidelines (BPAIIG) (also 3-4 other national guidelines)
Girschick	Hermann	Germany	Ped. Rheumatology/Osteology/ Immunology/Infectious diseases	Yes
Hartwig	Nico	Netherlands	Clinical Med. Education	CBO on varicella infections, asplenia and vaccination
Heikki	Peltola	Finland	Professor of Infectious Diseases, Former Head of Paediatric Infectious Diseases, General Surgeon, University of Helsinki	
Kaplan	Sheldon	US	Clinical, research, teaching, administration	IDSA
Lorrot	Mathie	France	Paediatric Infectious diseases and rheumatology, teaching hospital, medical education, clinical research	French Guidelines for the treatment of paediatric infections
Mantadakis	Elpis	Greece	Clinical research, teaching	Extensive experience with systematic reviews
Falup-Pecurariu	Oana	Romania	Clinical and researcher in PID	No

Rojo	Pablo	Spain	Clinical and researcher in PID	Different PID Spanish Guidelines. Also PENTA HIV Guidelines
Zaoutis	Theoklis	US, Greece	Research/Clinical	Yes
LeMair	Anton	Netherlands	Guideline development consultant	Guideline process and methodology specialist

Table 18 – Author-relevant financial disclosures

Name	First	Financial affiliations (past 5 yrs)
Saavedra	Jesus	Gilead grants and talks. Astellas, talks and conferences financial support. Pfizer and Merck: talks and educational material financial support. Roche, MSD, Pfizer and GSK clinical trials.
Faust	Saul	As NICE GDG Chair will not participate in any infection/sepsis related pharma advisory boards Jan 2014-July 2016, previous advisory boards for vaccine (GSK, Novartis, Pfizer, Sanofi) and antimicrobial manufactures. Participation in disease-specific generic advisory board for C Difficile infection (Astellas/Cubist/Actelion) and EMEA PDCO meeting on same topic. Current CI for UK NIHR HTA funded (public) feasibility study for bone and joint infections in children (due to report Q1-2 2015). Cubist Phase 3 daptomycin trial investigator.
Girschick	Hermann	No related conflict
Hartwig	Nico	Abbvie: talks and support conference. GSK: talks
Heikki	Peltola	Consulting pharmaceutical firm re. antibiotics
Kaplan	Sheldon	Grants from Pfizer, Cubist, Cerexa, Optimer
Lorrot	Mathie	GSK, Sanofi, Novartis: talks and financial support to attend meetings
Mantadakis	Elpis	GSK, Sanofi, Pfizer: Educational material financial support.
Falup-Pecurariu	Oana	Pfizer, Sanofi, GSK, Cubist: talks and educational material, financial support to attend meetings
Rojo	Pablo	None
Zaoutis	Theoklis	MERCK Consultant and grant support, Cubist grant support
LeMair	Anton	None

8.5 References

1. Lorrot M, Fitoussi F, Faye A, Mariani P, Job-Deslandre C, Penneçot G-F, et al. [Laboratory studies in pediatric bone and joint infections]. Arch Pediatr. 2007 Oct;14 Suppl 2:S86-90.

2. Pääkkönen M, Kallio MJT, Kallio PE, Peltola H. C-reactive protein versus erythrocyte sedimentation rate, white blood cell count and alkaline phosphatase in diagnosing bacteraemia in bone and joint infections. J Paediatr Child Health. 2013 Mar;49(3):E189-192.

3. Basmaci R, Ilharreborde B, Bonacorsi S, Kahil M, Mallet C, Aupiais C, et al. [Septic arthritis in children with normal initial C-reactive protein: clinical and biological features]. Arch Pediatr. 2014 Nov;21(11):1195–9.

4. Unkila-Kallio L, Kallio MJ, Peltola H. The usefulness of C-reactive protein levels in the identification of concurrent septic arthritis in children who have acute hematogenous osteomyelitis. A comparison with the usefulness of the erythrocyte sedimentation rate and the white blood-cell count. J Bone Joint Surg Am. 1994 Jun;76(6):848–53.

5. Basmaci R, Ilharreborde B, Lorrot M, Bidet P, Bingen E, Bonacorsi S. Predictive score to discriminate Kingella kingae from Staphylococcus aureus arthritis in France. Pediatr Infect Dis J. 2011 Dec;30(12):1120–1.

6. Kallio MJ, Unkila-Kallio L, Aalto K, Peltola H. Serum C-reactive protein, erythrocyte sedimentation rate and white blood cell count in septic arthritis of children. Pediatr Infect Dis J. 1997 Apr;16(4):411–3.

7. Peltola H, Pääkkönen M, Kallio P, Kallio MJT, Osteomyelitis-Septic Arthritis Study Group. Short- versus long-term antimicrobial treatment for acute hematogenous osteomyelitis of childhood: prospective, randomized trial on 131 culture-positive cases. Pediatr Infect Dis J. 2010 Dec;29(12):1123–8.

8. Calvo C, Núñez E, Camacho M, Clemente D, Fernández-Cooke E, Alcobendas R, et al. Epidemiology and Management of Acute, Uncomplicated Septic Arthritis and Osteomyelitis: Spanish Multicenter Study. Pediatr Infect Dis J. 2016 Jul 22;

9. Trujillo M, Nelson JD. Suppurative and reactive arthritis in children. Semin Pediatr Infect Dis. 1997 Oct;8(4):242–9.

10. Collado P, Naredo E, Calvo C, Crespo M. Role of power Doppler sonography in early diagnosis of osteomyelitis in children. J Clin Ultrasound JCU. 2008 May;36(4):251–3.

11. Pugmire BS, Shailam R, Gee MS. Role of MRI in the diagnosis and treatment of osteomyelitis in pediatric patients. World J Radiol. 2014 Aug 28;6(8):530–7.

12. Fenollar F, Lévy P-Y, Raoult D. Usefulness of broad-range PCR for the diagnosis of osteoarticular infections. Curr Opin Rheumatol. 2008 Jul;20(4):463–70.

13. Chometon S, Benito Y, Chaker M, Boisset S, Ploton C, Bérard J, et al. Specific real-time polymerase chain reaction places Kingella kingae as the most common cause of osteoarticular infections in young children. Pediatr Infect Dis J. 2007 May;26(5):377–81.

14. Cherkaoui A, Ceroni D, Emonet S, Lefevre Y, Schrenzel J. Molecular diagnosis of Kingella kingae osteoarticular infections by specific real-time PCR assay. J Med Microbiol. 2009 Jan;58(Pt 1):65–8.

15. Faesch S, Cojocaru B, Hennequin C, Pannier S, Glorion C, Lacour B, et al. Can procalcitonin measurement help the diagnosis of osteomyelitis and septic arthritis? A prospective trial. Ital J Pediatr. 2009;35(1):33.

16. Butbul-Aviel Y, Koren A, Halevy R, Sakran W. Procalcitonin as a diagnostic aid in osteomyelitis and septic arthritis. Pediatr Emerg Care. 2005 Dec;21(12):828–32.

17. Paosong S, Narongroeknawin P, Pakchotanon R, Asavatanabodee P, Chaiamnuay S. Serum procalcitonin as a diagnostic aid in patients with acute bacterial septic arthritis. Int J Rheum Dis. 2015 Mar;18(3):352–9.

18. McNeil JC, Forbes AR, Vallejo JG, Flores AR, Hultén KG, Mason EO, et al. Role of Operative or Interventional Radiology-Guided Cultures for Osteomyelitis. Pediatrics. 2016 May;137(5).

19. Manssor E, Abuderman A, Osman S, Alenezi SB, Almehemeid S, Babikir E, et al. Radiation doses in chest, abdomen and pelvis CT procedures. Radiat Prot Dosimetry. 2015 Jul;165(1–4):194–8.

20. Brix G, Nekolla E, Griebel J. [Radiation exposure of patients from diagnostic and interventional X-ray procedures. Facts, assessment and trends]. Radiol. 2005 Apr;45(4):340–9.

21. Lin EC. Radiation risk from medical imaging. Mayo Clin Proc. 2010 Dec;85(12):1142–1146; quiz 1146.

22. Baron EJ, Miller JM, Weinstein MP, Richter SS, Gilligan PH, Thomson RB, et al. A guide to utilization of the microbiology laboratory for diagnosis of infectious diseases: 2013 recommendations by the Infectious Diseases Society of America (IDSA) and the American Society for Microbiology (ASM)(a). Clin Infect Dis. 2013 Aug;57(4):e22–121.

23. Gutierrez K. Bone and joint infections in children. Pediatr Clin North Am. 2005 Jun;52(3):779–794, vi.

24. Krogstad P, Cherry J, Harrison G, Kaplan S. Osteomyelitis. In: Feigin and Cherry's Textbook of Pediatric Infectious Diseases, Chapter 55, 711-727.e5 [Internet]. 7th ed. Philadelphia: Elsevier Health Sciences Division; 2014 [cited 2016 May 4]. Available from: https://www.clinicalkey.com/#!/content/book/3-s2.0-B9781455711772000558

25. Lew DP, Waldvogel FA. Osteomyelitis. Lancet Lond Engl. 2004 Jul 24;364(9431):369–79.

26. Faust SN, Clark J, Pallett A, Clarke NMP. Managing bone and joint infection in children. Arch Dis Child. 2012 Jun;97(6):545–53.

27. Pääkkönen M, Peltola H. Bone and joint infections. Pediatr Clin North Am. 2013 Apr;60(2):425–36.

28. Saavedra-Lozano J, Calvo C, Huguet Carol R, Rodrigo C, Núñez E, Pérez C, et al. [SEIP-SERPE-SEOP Consensus Document on aetiopathogenesis and diagnosis of uncomplicated acute osteomyelitis and septic arthritis]. An Pediatría Barc Spain 2003. 2015 Sep;83(3):216.e1-10.

29. Fernandez M, Carrol CL, Baker CJ. Discitis and vertebral osteomyelitis in children: an 18-year review. Pediatrics. 2000 Jun;105(6):1299–304.

30. Saavedra-Lozano J, Calvo C, Huguet Carol R, Rodrigo C, Núñez E, Obando I, et al. [SEIP-SERPE-SEOP Consensus document on the treatment of uncomplicated acute osteomyelitis and septic arthritis]. Pediatr Barc. 2015 Apr;82(4):273.e1-273.e10.

31. Pannaraj PS, Hulten KG, Gonzalez BE, Mason EO, Kaplan SL. Infective pyomyositis and myositis in children in the era of community-acquired, methicillin-resistant Staphylococcus aureus infection. Clin Infect Dis. 2006 Oct 15;43(8):953–60.

32. Moriarty P, Leung C, Walsh M, Nourse C. Increasing pyomyositis presentations among children in Queensland, Australia. Pediatr Infect Dis J. 2015 Jan;34(1):1–4.

33. Llorente Otones L, Vázquez Román S, Iñigo Martín G, Rojo Conejo P, González Tomé MI. [Pyomyositis in children: not only a tropical disease]. Pediatr Barc. 2007 Dec;67(6):578–81.

34. Shallcross LJ, Fragaszy E, Johnson AM, Hayward AC. The role of the Panton-Valentine leucocidin toxin in staphylococcal disease: a systematic review and meta-analysis. Lancet Infect Dis. 2013 Jan;13(1):43–54.

35. Gafur OA, Copley LAB, Hollmig ST, Browne RH, Thornton LA, Crawford SE. The impact of the current epidemiology of pediatric musculoskeletal infection on evaluation and treatment guidelines. J Pediatr Orthop. 2008 Nov;28(7):777–85.

36. Dodwell ER. Osteomyelitis and septic arthritis in children: current concepts. Curr Opin Pediatr. 2013 Feb;25(1):58–63.

37. Peltola H, Pääkkönen M. Acute osteomyelitis in children. N Engl J Med. 2014 Jan 23;370(4):352–60.

38. Peltola H, Vahvanen V. A comparative study of osteomyelitis and purulent arthritis with special reference to aetiology and recovery. Infection. 1984 Apr;12(2):75–9.

39. Mitha A, Boutry N, Nectoux E, Petyt C, Lagrée M, Happiette L, et al. Community-acquired bone and joint infections in children: a 1-year prospective epidemiological study. Arch Dis Child. 2015 Feb;100(2):126–9.

40. Hernandez-Ruperez B, Suarez M, Santos M, Villa A, Sainz T, Navarro M. Kingella kingae as the main cause of septic arthritis in a cohort of children in Spain. ESPID 2014 Abstr 021. 2014;

41. Hernandez-Ruperez M, Suarez-Arrabal M, Santos Sebastián M, Navarro Gómez M, Hernandez-Sampelayo T, Gonzalez J. Acute osteomyelitis in children: searching a better management. ESPID Conf 2014 Abstr 562. 2014;

42. Weichert S, Sharland M, Clarke NMP, Faust SN. Acute haematogenous osteomyelitis in children: is there any evidence for how long we should treat? Curr Opin Infect Dis. 2008 Jun;21(3):258–62.

43. Bidet P, Collin E, Basmaci R, Courroux C, Prisse V, Dufour V, et al. Investigation of an outbreak of osteoarticular infections caused by Kingella kingae in a childcare center using molecular techniques. Pediatr Infect Dis J. 2013 May;32(5):558–60.

44. Ceroni D, Dubois-Ferriere V, Cherkaoui A, Gesuele R, Combescure C, Lamah L, et al. Detection of Kingella kingae osteoarticular infections in children by oropharyngeal swab PCR. Pediatrics. 2013 Jan;131(1):e230-235.

45. El Houmami N, Minodier P, Dubourg G, Martin-Laval A, Lafont E, Jouve J-L, et al. An outbreak of Kingella kingae infections associated with hand, foot and mouth disease/herpangina virus outbreak in Marseille, France, 2013. Pediatr Infect Dis J. 2015 Mar;34(3):246–50.

46. Morrissy RT, Haynes DW. Acute hematogenous osteomyelitis: a model with trauma as an etiology. J Pediatr Orthop. 1989 Aug;9(4):447–56.

47. Pääkkönen M, Kallio MJT, Lankinen P, Peltola H, Kallio PE. Preceding trauma in childhood hematogenous bone and joint infections. J Pediatr Orthop Part B. 2014 Mar;23(2):196–9.

48. Galluzzo ML, Hernandez C, Davila MTG, Pérez L, Oleastro M, Zelazko M, et al. Clinical and histopathological features and a unique spectrum of organisms significantly associated with chronic granulomatous disease osteomyelitis during childhood. Clin Infect Dis. 2008 Mar 1;46(5):745–9.

49. Dotis J, Roilides E. Osteomyelitis due to Aspergillus species in chronic granulomatous disease: an update of the literature. Mycoses. 2011 Nov;54(6):e686-696.

50. Muñoz C, Trujillo G, Latorre C, Juncosa T, Huget R. [Osteoarticular infections in children]. Enfermedades Infecc Microbiol Clínica. 1992 May;10(5):286–9.

51. Costa PSG da, Brigatte ME, Greco DB. Questing one Brazilian query: reporting 16 cases of Q fever from Minas Gerais, Brazil. Rev Inst Med Trop São Paulo. 2006 Feb;48(1):5–9.

52. Singh K. Laboratory-acquired infections. Clin Infect Dis. 2009 Jul 1;49(1):142–7.

53. Francis JR, Robson J, Wong D, Walsh M, Astori I, Gill D, et al. Chronic Recurrent Multifocal Q Fever Osteomyelitis in Children: An Emerging Clinical Challenge. Pediatr Infect Dis J. 2016 Sep;35(9):972–6.

54. Lee SC, Shim JS, Seo SW, Lee SS. Prognostic factors of septic arthritis of hip in infants and neonates: minimum 5-year follow-up. Clin Orthop Surg. 2015 Mar;7(1):110–9.

55. Slenker AK, Keith SW, Horn DL. Two hundred and eleven cases of Candida osteomyelitis: 17 case reports and a review of the literature. Diagn Microbiol Infect Dis. 2012 May;73(1):89–93.

56. Gijón M, Bellusci M, Petraitiene B, Noguera-Julian A, Zilinskaite V, Sanchez Moreno P, et al. Factors associated with severity in invasive community-acquired Staphylococcus aureus infections in children: a prospective European multicentre study. Clin Microbiol Infect. 2016 Apr 21;

57. Ilharreborde B, Bidet P, Lorrot M, Even J, Mariani-Kurkdjian P, Liguori S, et al. New real-time PCR-based method for Kingella kingae DNA detection: application to samples collected from 89 children with acute arthritis. J Clin Microbiol. 2009 Jun;47(6):1837–41.

58. Ceroni D, Cherkaoui A, Ferey S, Kaelin A, Schrenzel J. Kingella kingae osteoarticular infections in young children: clinical features and contribution of a new specific real-time PCR assay to the diagnosis. J Pediatr Orthop. 2010 May;30(3):301–4.

59. Moumile K, Merckx J, Glorion C, Berche P, Ferroni A. Osteoarticular infections caused by Kingella kingae in children: contribution of polymerase chain reaction to the microbiologic diagnosis. Pediatr Infect Dis J. 2003 Sep;22(9):837–9.

60. Dartnell J, Ramachandran M, Katchburian M. Haematogenous acute and subacute paediatric osteomyelitis: a systematic review of the literature. J Bone Joint Surg Br. 2012 May;94(5):584–95.

61. Ballock RT, Newton PO, Evans SJ, Estabrook M, Farnsworth CL, Bradley JS. A comparison of early versus late conversion from intravenous to oral therapy in the treatment of septic arthritis. J Pediatr Orthop. 2009 Sep;29(6):636–42.

62. Dahl LB, Høyland AL, Dramsdahl H, Kaaresen PI. Acute osteomyelitis in children: a population-based retrospective study 1965 to 1994. Scand J Infect Dis. 1998;30(6):573–7.

63. Wong-Chung J, Bagali M, Kaneker S. Physical signs in pyomyositis presenting as a painful hip in children: a case report and review of the literature. J Pediatr Orthop Part B. 2004 May;13(3):211–3.

64. Brown R, Hussain M, McHugh K, Novelli V, Jones D. Discitis in young children. J Bone Joint Surg Br. 2001 Jan;83(1):106–11.

65. Nussinovitch M, Sokolover N, Volovitz B, Amir J. Neurologic abnormalities in children presenting with diskitis. Arch Pediatr Adolesc Med. 2002 Oct;156(10):1052–4.

66. Yagupsky P. Use of blood culture vials and nucleic acid amplification for the diagnosis of pediatric septic arthritis. Clin Infect Dis. 2008 May 15;46(10):1631–2.

67. Gené A, García-García J-J, Sala P, Sierra M, Huguet R. Enhanced culture detection of Kingella kingae, a pathogen of increasing clinical importance in pediatrics. Pediatr Infect Dis J. 2004 Sep;23(9):886–8.

68. Yagupsky P, Porsch E, St Geme JW. Kingella kingae: an emerging pathogen in young children. Pediatrics. 2011 Mar;127(3):557–65.

69. Aupiais C, Ilharreborde B, Doit C, Blachier A, Desmarest M, Job-Deslandre C, et al. Aetiology of arthritis in hospitalised children: an observational study. Arch Dis Child. 2015 Aug;100(8):742–7.

70. Baker ADL, Macnicol MF. Haematogenous osteomyelitis in children: epidemiology, classification, aetiology and treatment. Paediatr Child Health. 2008 Feb 1;18(2):75–84.

71. Stott NS. Review article: Paediatric bone and joint infection. J Orthop Surg Hong Kong. 2001 Jun;9(1):83–90.

72. Browne LP, Mason EO, Kaplan SL, Cassady CI, Krishnamurthy R, Guillerman RP. Optimal imaging strategy for community-acquired Staphylococcus aureus musculoskeletal infections in children. Pediatr Radiol. 2008 Aug;38(8):841–7.

73. Teixeira SR, Elias Junior J, Nogueira-Barbosa MH, Guimarães MD, Marchiori E, Santos MK. Whole-body magnetic resonance imaging in children: state of the art. Radiol Bras. 2015 Apr;48(2):111–20.

74. Jaffe H. Metabolic, Degenerative, and Inflammatory Diseases of Bones and Joints. Ann Intern Med. 1972 Dec 1;77(6):1016–1016.

75. Restrepo S, Vargas D, Riascos R, Cuellar H. Musculoskeletal infection imaging: past, present, and future. Curr Infect Dis Rep. 2005 Sep;7(5):365–72.

76. Robben SGF. Ultrasonography of musculoskeletal infections in children. Eur Radiol. 2004 Mar;14 Suppl 4:L65-77.

77. Offiah AC. Acute osteomyelitis, septic arthritis and discitis: differences between neonates and older children. Eur J Radiol. 2006 Nov;60(2):221–32.

78. Pineda C, Espinosa R, Pena A. Radiographic imaging in osteomyelitis: the role of plain radiography, computed tomography, ultrasonography, magnetic resonance imaging, and scintigraphy. Semin Plast Surg. 2009 May;23(2):80–9.

79. Blickman JG, van Die CE, de Rooy JWJ. Current imaging concepts in pediatric osteomyelitis. Eur Radiol. 2004 Mar;14 Suppl 4:L55-64.

80. Hsu W, Hearty TM. Radionuclide imaging in the diagnosis and management of orthopaedic disease. J Am Acad Orthop Surg. 2012 Mar;20(3):151–9.

81. Peltola H, Pääkkönen M, Kallio P, Kallio MJT, Osteomyelitis-Septic Arthritis (OM-SA) Study Group. Prospective, randomized trial of 10 days versus 30 days of antimicrobial treatment, including a short-term course of parenteral therapy, for childhood septic arthritis. Clin Infect Dis. 2009 May 1;48(9):1201–10.

82. Pääkkönen M, Kallio MJT, Kallio PE, Peltola H. Shortened hospital stay for childhood bone and joint infections: analysis of 265 prospectively collected culture-positive cases in 1983-2005. Scand J Infect Dis. 2012 Sep;44(9):683–8.

83. Sukswai P, Kovitvanitcha D, Thumkunanon V, Chotpitayasunondh T, Sangtawesin V, Jeerathanyasakun Y. Acute hematogenous osteomyelitis and septic arthritis in children: clinical characteristics and outcomes study. J Med Assoc Thai. 2011 Aug;94 Suppl 3:S209-216.

84. Tetzlaff TR, McCracken GH, Nelson JD. Oral antibiotic therapy for skeletal infections of children. II. Therapy of osteomyelitis and suppurative arthritis. J Pediatr. 1978 Mar;92(3):485–90.

85. Nelson JD, Bucholz RW, Kusmiesz H, Shelton S. Benefits and risks of sequential parenteral-oral cephalosporin therapy for suppurative bone and joint infections. J Pediatr Orthop. 1982 Aug;2(3):255–62.

86. Bachur R, Pagon Z. Success of short-course parenteral antibiotic therapy for acute osteomyelitis of childhood. Clin Pediatr (Phila). 2007 Jan;46(1):30–5.

87. Pääkkönen M, Peltola H. Antibiotic treatment for acute haematogenous osteomyelitis of childhood: moving towards shorter courses and oral administration. Int J Antimicrob Agents. 2011 Oct;38(4):273–80.

88. Tice AD, Rehm SJ, Dalovisio JR, Bradley JS, Martinelli LP, Graham DR, et al. Practice guidelines for outpatient parenteral antimicrobial therapy. IDSA guidelines. Clin Infect Dis. 2004 Jun 15;38(12):1651–72.

89. Esposito S, Leone S, Noviello S, Ianniello F, Fiore M, Russo M, et al. Outpatient parenteral antibiotic therapy for bone and joint infections: an italian multicenter study. J Chemother. 2007 Aug;19(4):417–22.

90. Zaoutis T, Localio AR, Leckerman K, Saddlemire S, Bertoch D, Keren R. Prolonged intravenous therapy versus early transition to oral antimicrobial therapy for acute osteomyelitis in children. Pediatrics. 2009 Feb;123(2):636–42.

91. Grimprel E, Lorrot M, Haas H, Pinquier D, Parez N, Ferroni A, et al. [Osteoarticular infections: therapeutic proposals of the Paediatric Infectious Diseases Group of the French Society of Paediatrics (GPIP)]. Arch Pediatr. 2008 Oct;15 Suppl 2:S74-80.

92. Lorrot M, Doit C, Ilharreborde B, Vitoux C, Le Henaff L, Sebag G, et al. [Antibiotic therapy of bone and joint infections in children: recent changes]. Arch Pediatr. 2011 Sep;18(9):1016–8.

93. Peltola H, Pääkkönen M, Kallio P, Kallio MJT, OM-SA Study Group. Clindamycin vs. first-generation cephalosporins for acute osteoarticular infections of childhood--a prospective quasi-randomized controlled trial. Clin Microbiol Infect. 2012 Jun;18(6):582–9.

94. Liu C, Bayer A, Cosgrove SE, Daum RS, Fridkin SK, Gorwitz RJ, et al. Clinical practice guidelines by the infectious diseases society of america for the treatment of methicillin-resistant Staphylococcus aureus infections in adults and children. Clin Infect Dis. 2011 Feb 1;52(3):e18-55.

95. Martínez-Aguilar G, Hammerman WA, Mason EO, Kaplan SL. Clindamycin treatment of invasive infections caused by community-acquired, methicillin-resistant and methicillin-susceptible Staphylococcus aureus in children. Pediatr Infect Dis J. 2003 Jul;22(7):593–8.

96. Martínez-Aguilar G, Avalos-Mishaan A, Hulten K, Hammerman W, Mason EO, Kaplan SL. Community-acquired, methicillin-resistant and methicillin-susceptible Staphylococcus aureus musculoskeletal infections in children. Pediatr Infect Dis J. 2004 Aug;23(8):701–6.

97. Pääkkönen M, Kallio PE, Kallio MJT, Peltola H. Does Bacteremia Associated With Bone and Joint Infections Necessitate Prolonged Parenteral Antimicrobial Therapy? J Pediatr Infect Dis Soc. 2015 Jun;4(2):174–7.

98. Stockmann C, Roberts JK, Yu T, Constance JE, Knibbe CAJ, Spigarelli MG, et al. Vancomycin pharmacokinetic models: informing the clinical management of drug-resistant bacterial infections. Expert Rev Anti Infect Ther. 2014 Nov;12(11):1371–88.

99. Dombrowski JC, Winston LG. Clinical failures of appropriately-treated methicillin-resistant Staphylococcus aureus infections. J Infect. 2008 Aug;57(2):110–5.

100. Norden CW, Shaffer M. Treatment of experimental chronic osteomyelitis due to staphylococcus aureus with vancomycin and rifampin. J Infect Dis. 1983 Feb;147(2):352–7.

101. Nguyen HM, Graber CJ. Limitations of antibiotic options for invasive infections caused by methicillin-resistant Staphylococcus aureus: is combination therapy the answer? J Antimicrob Chemother. 2010 Jan;65(1):24–36.

102. Jobson S, Moise PA, Eskandarian R. Retrospective observational study comparing vancomycin versus daptomycin as initial therapy for Staphylococcus aureus infections. Clin Ther. 2011 Oct;33(10):1391–9.

103. Ardura MI, Mejías A, Katz KS, Revell P, McCracken GH, Sánchez PJ. Daptomycin therapy for invasive Gram-positive bacterial infections in children. Pediatr Infect Dis J. 2007 Dec;26(12):1128–32.

104. Syriopoulou V, Dailiana Z, Dmitriy N, Utili R, Pathan R, Hamed K. Clinical Experience with Daptomycin for the Treatment of Gram-positive Infections in Children and Adolescents. Pediatr Infect Dis J. 2016 May;35(5):511–6.

105. Messina AF, Namtu K, Guild M, Dumois JA, Berman DM. Trimethoprim-sulfamethoxazole therapy for children with acute osteomyelitis. Pediatr Infect Dis J. 2011 Dec;30(12):1019–21.

106. Diep BA, Afasizheva A, Le HN, Kajikawa O, Matute-Bello G, Tkaczyk C, et al. Effects of linezolid on suppressing in vivo production of staphylococcal toxins and improving survival outcomes in a rabbit model of methicillin-resistant Staphylococcus aureus necrotizing pneumonia. J Infect Dis. 2013 Jul;208(1):75–82.

107. Rojo P, Barrios M, Palacios A, Gomez C, Chaves F. Community-associated Staphylococcus aureus infections in children. Expert Rev Anti Infect Ther. 2010 May;8(5):541–54.

108. Perlroth J, Kuo M, Tan J, Bayer AS, Miller LG. Adjunctive use of rifampin for the treatment of Staphylococcus aureus infections: a systematic review of the literature. Arch Intern Med. 2008 Apr 28;168(8):805–19.

109. Panton-Valentine Leukocidin (PVL): guidance, data and analysis - GOV.UK [Internet]. Public Health England, Infectious diseases. [cited 2016 May 5]. Available from: https://www.gov.uk/government/collections/panton-valentine-leukocidin-pvl-guidance-data-and-analysis

110. Gauduchon V, Cozon G, Vandenesch F, Genestier A-L, Eyssade N, Peyrol S, et al. Neutralization of Staphylococcus aureus Panton Valentine leukocidin by intravenous immunoglobulin in vitro. J Infect Dis. 2004 Jan 15;189(2):346–53.

111. Yanagisawa C, Hanaki H, Natae T, Sunakawa K. Neutralization of staphylococcal exotoxins in vitro by human-origin intravenous immunoglobulin. J Infect Chemother. 2007 Dec;13(6):368–72.

112. Liang SY, Khair HN, McDonald JR, Babcock HM, Marschall J. Daptomycin versus vancomycin for osteoarticular infections due to methicillin-resistant Staphylococcus aureus (MRSA): a nested case-control study. Eur J Clin Microbiol Infect Dis. 2014 Apr;33(4):659–64.

113. Wieland BW, Marcantoni JR, Bommarito KM, Warren DK, Marschall J. A retrospective comparison of ceftriaxone versus oxacillin for osteoarticular infections due to methicillin-susceptible Staphylococcus aureus. Clin Infect Dis. 2012 Mar 1;54(5):585–90.

114. Löffler L, Bauernfeind A, Keyl W, Hoffstedt B, Piergies A, Lenz W. An open, comparative study of sulbactam plus ampicillin vs. cefotaxime as initial therapy for serious soft tissue and bone and joint infections. Rev Infect Dis. 1986 Dec;8 Suppl 5:S593-598.

115. Paul M, Zemer-Wassercug N, Talker O, Lishtzinsky Y, Lev B, Samra Z, et al. Are all beta-lactams similarly effective in the treatment of methicillin-sensitive Staphylococcus aureus bacteraemia? Clin Microbiol Infect. 2011 Oct;17(10):1581–6.

116. Cohen R, Grimprel E. [Pharmacokinetics and pharmacodynamics of antimicrobial therapy used in child osteoarticular infections]. Arch Pediatr. 2007 Oct;14 Suppl 2:S122-127.

117. Yagupsky P. Antibiotic susceptibility of Kingella kingae isolates from children with skeletal system infections. Pediatr Infect Dis J. 2012 Feb;31(2):212.

118. Banerjee A, Kaplan JB, Soherwardy A, Nudell Y, Mackenzie GA, Johnson S, et al. Characterization of TEM-1 β-lactamase producing Kingella kingae clinical isolates. Antimicrob Agents Chemother. 2013 Jun 24;

119. Anand AJ, Glatt AE. Salmonella osteomyelitis and arthritis in sickle cell disease. Semin Arthritis Rheum. 1994 Dec;24(3):211–21.

120. Euba G, Murillo O, Fernández-Sabé N, Mascaró J, Cabo J, Pérez A, et al. Long-term follow-up trial of oral rifampin-cotrimoxazole combination versus intravenous cloxacillin in treatment of chronic staphylococcal osteomyelitis. Antimicrob Agents Chemother. 2009 Jun;53(6):2672–6.

121. Imöhl M, van der Linden M. Antimicrobial Susceptibility of Invasive Streptococcus pyogenes Isolates in Germany during 2003-2013. PloS One. 2015;10(9):e0137313.

122. Bowen AC, Lilliebridge RA, Tong SYC, Baird RW, Ward P, McDonald MI, et al. Is Streptococcus pyogenes resistant or susceptible to trimethoprim-sulfamethoxazole? J Clin Microbiol. 2012 Dec;50(12):4067–72.

123. Keren R, Shah SS, Srivastava R, Rangel S, Bendel-Stenzel M, Harik N, et al. Comparative effectiveness of intravenous vs oral antibiotics for postdischarge treatment of acute osteomyelitis in children. JAMA Pediatr. 2015 Feb;169(2):120–8.

124. McMullan BJ, Andresen D, Blyth CC, Avent ML, Bowen AC, Britton PN, et al. Antibiotic duration and timing of the switch from intravenous to oral route for bacterial infections in children: systematic review and guidelines. Lancet Infect Dis. 2016 Aug;16(8):e139-152.

125. Park K-H, Chong YP, Kim S-H, Lee S-O, Choi S-H, Lee MS, et al. Clinical characteristics and therapeutic outcomes of hematogenous vertebral osteomyelitis caused by methicillin-resistant Staphylococcus aureus. J Infect. 2013 Dec;67(6):556–64.

126. Harel L, Prais D, Bar-On E, Livni G, Hoffer V, Uziel Y, et al. Dexamethasone therapy for septic arthritis in children: results of a randomized double-blind placebo-controlled study. J Pediatr Orthop. 2011 Mar;31(2):211–5.

127. Fogel I, Amir J, Bar-On E, Harel L. Dexamethasone Therapy for Septic Arthritis in Children. Pediatrics. 2015 Oct;136(4):e776-782.

128. Odio CM, Ramirez T, Arias G, Abdelnour A, Hidalgo I, Herrera ML, et al. Double blind, randomized, placebo-controlled study of dexamethasone therapy for hematogenous septic arthritis in children. Pediatr Infect Dis J. 2003 Oct;22(10):883–8.

129. Herring JA, Copley LAB. Tachdjian's Pediatric Orthopaedics: From the Texas Scottish Rite Hospital for Children [Internet]. 1024–78: Elsevier Health Sciences; 2013 [cited 2016 May 5]. 2663 p. Available from: https://books.google.nl/books?id=fBkyAgAAQBAJ&pg=PA1078-IA1&dq=Copley+L,+Herring+J.+Infections+of+the+musculoskeletal+system.+In:&hl=en&sa=X&redir_esc=y#v=onepage&q=infections%20of%20the%20musculoskeletal%20system&f=false

130. Peltola H, Unkila-Kallio L, Kallio MJ. Simplified treatment of acute staphylococcal osteomyelitis of childhood. The Finnish Study Group. Pediatrics. 1997 Jun;99(6):846–50.

131. Saavedra-Lozano J, Mejías A, Ahmad N, Peromingo E, Ardura MI, Guillen S, et al. Changing trends in acute osteomyelitis in children: impact of methicillin-resistant Staphylococcus aureus infections. J Pediatr Orthop. 2008 Aug;28(5):569–75.

132. Kocher MS, Mandiga R, Murphy JM, Goldmann D, Harper M, Sundel R, et al. A clinical practice guideline for treatment of septic arthritis in children: efficacy in improving process of care and effect on outcome of septic arthritis of the hip. J Bone Joint Surg Am. 2003 Jun;85–A(6):994–9.

133. Smith SP, Thyoka M, Lavy CBD, Pitani A. Septic arthritis of the shoulder in children in Malawi. A randomised, prospective study of aspiration versus arthrotomy and washout. J Bone Joint Surg Br. 2002 Nov;84(8):1167–72.

134. Pääkkönen M, Kallio MJT, Peltola H, Kallio PE. Pediatric septic hip with or without arthrotomy: retrospective analysis of 62 consecutive nonneonatal culture-positive cases. J Pediatr Orthop Part B. 2010 May;19(3):264–9.

135. Journeau P, Wein F, Popkov D, Philippe R, Haumont T, Lascombes P. Hip septic arthritis in children: assessment of treatment using needle aspiration/irrigation. Orthop Traumatol Surg Res. 2011 May;97(3):308–13.

136. Givon U, Ganel A. Re: Treatment of early septic arthritis of the hip in children: comparison of results of open arthrotomy versus arthroscopic drainage. J Child Orthop. 2008 Dec;2(6):499.

137. Givon U, Liberman B, Schindler A, Blankstein A, Ganel A. Treatment of septic arthritis of the hip joint by repeated ultrasound-guided aspirations. J Pediatr Orthop. 2004 Jun;24(3):266–70.

138. Pääkkönen M, Peltola H, Kallio M, Kallio P. [Pediatric septic shoulder arthritis. Is routine arthrotomy still necessary?]. Duodecim Lääketieteellinen Aikakauskirja. 2011;127(7):716–9.

139. El-Sayed AMM. Treatment of early septic arthritis of the hip in children: comparison of results of open arthrotomy versus arthroscopic drainage. J Child Orthop. 2008 Jun;2(3):229–37.

140. Kini AR, Shetty V, Kumar AM, Shetty SM, Shetty A. Community-associated, methicillin-susceptible, and methicillin-resistant Staphylococcus aureus bone and joint infections in children: experience from India. J Pediatr Orthop Part B. 2013 Mar;22(2):158–66.

141. Hawkshead JJ, Patel NB, Steele RW, Heinrich SD. Comparative severity of pediatric osteomyelitis attributable to methicillin-resistant versus methicillin-sensitive Staphylococcus aureus. J Pediatr Orthop. 2009 Feb;29(1):85–90.

142. Bocchini CE, Hulten KG, Mason EO, Gonzalez BE, Hammerman WA, Kaplan SL. Panton-Valentine leukocidin genes are associated with enhanced inflammatory response and local disease in acute hematogenous Staphylococcus aureus osteomyelitis in children. Pediatrics. 2006 Feb;117(2):433–40.

143. Chapman MW, Griffin P, editors. Bone and Joint Infection in Children. In: Chapman's Comprehensive Orthopaedic Surgery [Internet]. 3rd ed. Philadelphia: Lippincott Williams & Wilkins; 2001. 2001:4470-84. (G. MOSSER TAYLOR COLLECTION). Available from: http://catalog.llu.edu/record=b1174079

144. Donatto KC. Orthopedic management of septic arthritis. Rheum Dis Clin North Am. 1998 May;24(2):275–86.

145. Jayakumar P, Ramachandran M, Youm T, Achan P. Arthroscopy of the hip for paediatric and adolescent disorders: current concepts. J Bone Joint Surg Br. 2012 Mar;94(3):290–6.

146. Eberhardt O. Hip Arthroscopy in Children under the Age of Ten. Open J Orthop. 2013;3(1):41–8.

147. Gill A, Muller M, Pavlik D, Eldredge J, Johnston J, Eickman M, et al. Non-Typhoidal Salmonella Osteomyelitis in Immunocompetent Children without Hemoglobinopathies: A Case Series and Systematic Review of the Literature. Pediatr Infect Dis J. 2017 Jan 26;

148. Dohin B, Gillet Y, Kohler R, Lina G, Vandenesch F, Vanhems P, et al. Pediatric bone and joint infections caused by Panton-Valentine leukocidin-positive Staphylococcus aureus. Pediatr Infect Dis J. 2007 Nov;26(11):1042–8.

149. Hollmig ST, Copley LAB, Browne RH, Grande LM, Wilson PL. Deep venous thrombosis associated with osteomyelitis in children. J Bone Joint Surg Am. 2007 Jul;89(7):1517–23.

150. Mantadakis E, Plessa E, Vouloumanou EK, Michailidis L, Chatzimichael A, Falagas ME. Deep venous thrombosis in children with musculoskeletal infections: the clinical evidence. Int J Infect Dis. 2012 Apr;16(4):e236-243.

151. Bouchoucha S, Benghachame F, Trifa M, Saied W, Douira W, Nessib MN, et al. Deep venous thrombosis associated with acute hematogenous osteomyelitis in children. Orthop Traumatol Surg Res. 2010 Dec;96(8):890–3.

152. Gonzalez BE, Teruya J, Mahoney DH, Hulten KG, Edwards R, Lamberth LB, et al. Venous thrombosis associated with staphylococcal osteomyelitis in children. Pediatrics. 2006 May;117(5):1673–9.

153. Mantero E, Carbone M, Calevo MG, Boero S. Diagnosis and treatment of pediatric chronic osteomyelitis in developing countries: prospective study of 96 patients treated in Kenya. Musculoskelet Surg. 2011 Apr;95(1):13–8.

154. Akinyoola AL, Orimolade EA, Yusuf MB. Pathologic fractures of long bones in Nigerian children. J Child Orthop. 2008 Dec;2(6):475–9.

155. Uçkay I, Assal M, Legout L, Rohner P, Stern R, Lew D, et al. Recurrent osteomyelitis caused by infection with different bacterial strains without obvious source of reinfection. J Clin Microbiol. 2006 Mar;44(3):1194–6.

156. Carrillo-Marquez MA, Hulten KG, Hammerman W, Mason EO, Kaplan SL. USA300 is the predominant genotype causing Staphylococcus aureus septic arthritis in children. Pediatr Infect Dis J. 2009 Dec;28(12):1076–80.

157. Ritz N, Curtis N. The role of Panton-Valentine leukocidin in Staphylococcus aureus musculoskeletal infections in children. Pediatr Infect Dis J. 2012 May;31(5):514–8.

158. Ferroni A, Al Khoury H, Dana C, Quesne G, Berche P, Glorion C, et al. Prospective survey of acute osteoarticular infections in a French paediatric orthopedic surgery unit. Clin Microbiol Infect. 2013 Sep;19(9):822–8.

159. Brehin C, Claudet J, Debuisson C, Prère M, Vial J, Doston C, et al. Epidemiology of 377 paediatric osteoarticular infections and evaluation of management protocol. ESPID 2015 Conference [abstract #0175]. ESPID 2015 Conf Abstr 0175. 2015;

160. Lemaître C, Ferroni A, Doit C, Vu-Thien H, Glorion C, Raymond J, et al. Pediatric osteoarticular infections caused by Streptococcus pneumoniae before and after the introduction of the heptavalent pneumococcal conjugate vaccine. Eur J Clin Microbiol Infect Dis. 2012 Oct;31(10):2773–81.

161. Bradley JS, Kaplan SL, Tan TQ, Barson WJ, Arditi M, Schutze GE, et al. Pediatric pneumococcal bone and joint infections. The Pediatric Multicenter Pneumococcal Surveillance Study Group (PMPSSG). Pediatrics. 1998 Dec;102(6):1376–82.

162. Grivea IN, Michoula AN, Basmaci R, Dailiana ZH, Tsimitselis G, Bonacorsi S, et al. Kingella kingae sequence type-complex 14 arthritis in a 16-month-old child in Greece. Pediatr Infect Dis J. 2015 Jan;34(1):107–8.

163. Basmaci R, Bidet P, Jost C, Yagupsky P, Bonacorsi S. Penicillinase-encoding gene blaTEM-1 may be plasmid borne or chromosomally located in Kingella kingae species. Antimicrob Agents Chemother. 2015 Feb;59(2):1377–8.

164. Dessì A, Crisafulli M, Accossu S, Setzu V, Fanos V. Osteo-articular infections in newborns: diagnosis and treatment. J Chemother Florence Italy. 2008 Oct;20(5):542–50.

165. Sri JC, Tsai CL, Deng A, Gaspari AA. Osteomyelitis occurring during infliximab treatment of severe psoriasis. J Drugs Dermatol JDD. 2007 Feb;6(2):207–10.

166. Lavy CBD, Thyoka M, Pitani AD. Clinical features and microbiology in 204 cases of septic arthritis in Malawian children. J Bone Joint Surg Br. 2005 Nov;87(11):1545–8.

167. American Academy of Pediatrics, Committee on Infectious Diseases, Kimberlin DW, Brady MT, Jackson MA, Long SS. Red book: 2015 report of the Committee on Infectious Diseases [Internet]. 2015 [cited 2016 Dec 23]. Available from: http://online.statref.com/Document.aspx?FxId=76&DocID=1&grpalias=

168. Autmizguine J, Watt KM, Théorêt Y, Kassir N, Laferrière C, Parent S, et al. Pharmacokinetics and pharmacodynamics of oral cephalexin in children with osteoarticular infections. Pediatr Infect Dis J. 2013 Dec;32(12):1340–4.