

Bone and Joint Infections

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KEYWORDS

• Septic arthritis • Osteomyelitis • Arthrocentesis • Trepanation • Clindamycin

KEY POINTS

- The treatment of childhood acute osteoarticular infections can be simplified.
- For the treatment of uncomplicated childhood osteoarticular infections, in which fever and symptoms resolve rapidly, 2 to 4 days of intravenous antibiotics can be followed by high-dose oral antibiotics, for a total antibiotic course of 3 weeks for osteomyelitis and 2 weeks for septic arthritis.
- Oral antibiotics should be well absorbed, provide good bone penetration, and be given in sufficiently high doses. Clindamycin or first-generation cephalosporins should be given 4 times a day.
- Serum C-reactive protein measurements are reliable and inexpensive in the diagnosis and follow-up of osteomyelitis and septic arthritis.

INTRODUCTION

In contrast to developing countries, acute osteoarticular infections (AOI) of children, osteomyelitis (OM), septic arthritis (SA), and OM with adjacent SA (OM+SA), are rare diseases in high-income settings.¹⁻³ The annual incidence of AOI varies regionally between 10 and 25 per 100,000 population, of which OM constitutes two-thirds.^{1,4,5} The incidence is increased in immunocompromised patients and those with sickle-cell disease. The infection is considered acute if the time from the onset of symptoms to the presentation to a hospital is less than 2 weeks. Most cases are hematogenous in origin, although direct inoculation from trauma or spread from an adjacent tissue occurs as well. Boys predominate girls with an approximate ratio of 2:1.^{1,4,5}

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Cultures frequently fail to disclose the causative agent, but when tested positive, almost all cases show only a single organism.^{1,4,6} Overwhelmingly, the most common agent is *Staphylococcus aureus*, followed by respiratory pathogens *Streptococcus pyogenes*, *Streptococcus pneumoniae* (pneumococcus), and *Haemophilus influenzae* type b (Hib).^{7–13} *Kingella kingae* is a common cause of OM and SA in some areas and requires special culture techniques or real-time polymerase chain reaction for diagnosis.¹⁴ Current vaccinations have caused decreased incidence of Hib and pneumococcus in some countries.^{12,13} *Salmonella* spp are a common agent in the tropics and in children with sickle-cell disease,¹⁵ and neonates may be affected by bacteria such as *Streptococcus agalactiae*.¹

PATIENT HISTORY

The classical presentation of AOI is a locally swollen, warm limb or joint combined with high fever with no prior history of trauma. In a high-income setting the time from onset of symptoms is 2 to 5 days, and rarely more than a week.^{6,16–19} Focal symptoms are not always remarkable, especially in OM, and fever of unknown origin may be the only remarkable sign present in an OM patient visiting the emergency department.²⁰ Prior trauma is documented in one-third of the cases.⁵

PHYSICAL EXAMINATION

The limb or joint may be too painful to allow thorough palpation or testing of joint motion, but plenty of useful information may be obtained from the disease history and mere observation of the patient. The child may be limping or refuse to use an extremity. Newborns may be irritable and may present as pseudoparalytic, whereas older children show more clear signs such as focal tenderness.¹ Fever may be absent or high, up to 40°C.^{5,21} Generally, children with SA are clinically more ill than those with OM, which has a more insidious onset. Mild reddish color with no swelling may be the only visible focal sign in OM. Gonococcal arthritis, previously more common than today in the western settings, may present in the newborn only with unspecific irritability and poor feeding.¹

Focal symptoms and signs vary according to localization, causative organism, and the age of the child (**Table 1**). *S aureus* causes clear focal symptoms compared with the insidious onset of *K kingae*, and culture-negative cases tend to present milder symptoms.^{6,14} Spinal osteomyelitis may manifest as unspecific back pain. The diagnosis of pelvic osteomyelitis is difficult; the mean diagnostic delay in 1 study was 12 days.²² OM in a long bone of a child beyond the neonatal age might show local pinpoint tenderness, which can be provoked by percussing the bone away from the affected area. Calcaneal osteomyelitis is characterized by slowly developing symptoms, and thus, late presentation.²³ Sacroiliitis may present as pain in the sacrum or lower back, provoked by digital dorsal compression in rectal examination.¹ The swelling in hip arthritis of a neonate may pass detection unless the child has sought a characteristic position, with the affected hip flexed and externally rotated. Pain is elicited by compression of the head of the femur into the acetabulum.

DIAGNOSTIC EVALUATION

Further evaluation is warranted whenever an acute AOI is suspected. **Box 1** summarizes the commonly performed tests, and **Box 2** lists some of the examinations to be considered in the differential diagnosis. Blood tests are used to assess the extent of inflammation. Blood leukocyte count (white blood cell count) is unspecific

Table 1
Characteristics of osteomyelitis (OM) versus septic arthritis (SA), diseases caused by *Staphylococcus aureus* versus *Kingella kingae*, and symptoms and signs of newborns versus older children

| | OM | SA |
|------------------------------|----------------------------------|---------------------------------|
| Fever >38.5°C | Suggestive if present | Suggestive |
| Malaise | Usually | Usually |
| Swollen joint/limited motion | Not unless concurrent arthritis | Nearly always |
| Edema overlying bone | Often | Absent |
| Back pain | Suggestive of spinal OM | Rare |
| Difficulty weight-bearing | Lower limb affected | Lower limb affected |
| | <i>S aureus</i> | <i>K kingae</i> |
| Age | Any age group | Often <4 y |
| Fever | >38°C | Afebrile on admission |
| CRP | Elevated | May be normal |
| WBC | Elevated | May be normal |
| | Neonates | Children and Adolescents |
| Systemic effects | Poor feeding/irritability | Malaise and fever |
| Pain | Nonspecific limp/pseudoparalysis | Often focal |
| Joint involvement | Common | Possible |

Abbreviations: CRP, C-reactive protein; WBC, white blood cell count.

and elevated only in 20% of cases.^{24,25} Erythrocyte sedimentation rate with a cutoff of 20 mm/h is sensitive in the diagnostics, but is inferior to C-reactive protein (CRP) measurements in monitoring the course of the illness because of slow normalization.²⁵ Procalcitonin is more useful in OM than SA,²⁶ but is considerably more costly than CRP and does not offer more information. CRP with a cutoff of 20 mg/L is sensitive in the diagnosis of OM and SA.²⁵ The levels of CRP not only

Box 1

Diagnostic armamentarium for childhood acute osteoarticular infections

- Parameters of inflammation/infection: C-reactive protein, procalcitonin, erythrocyte sedimentation rate, white blood cell count
- Plain X ray
- Ultrasound
- Scintigram
- Magnetic resonance imaging
- Blood cultures
- Synovial fluid cytology
- Synovial fluid/bone sample; Gram-staining, culture

Box 2**Differential diagnoses of osteomyelitis and septic arthritis***Osteomyelitis*

- Traumatic fracture
- Septicemia
- Rheumatic fever
- Cellulitis
- Thrombophlebitis
- Pyomyositis
- Leukemia
- Benign/malignant tumors
- Child abuse
- Scurvy
- Stress fracture

Septic arthritis

- Transient synovitis
- Viral arthritis
- Tuberculosis
- Henoch-Schönlein purpura
- Perthes disease
- Septic bursitis
- Slipped capital femoral epiphysis
- Reactive arthritis
- Juvenile rheumatoid arthritis
- Sickle cell anemia

increase rapidly (doubling time is 6 hours) but also descend quickly enough (the level is halved in 24 hours if the recovery is uneventful) to be useful later in the monitoring of the patient.²⁵ CRP is especially high in OM complicated by SA, but because of considerable overlapping, OM, SA, and OM+SA cannot be distinguished from each other with CRP alone.^{25,27}

In OM, plain radiographs are notoriously normal on admission in most cases because the characteristic “rat bites” appear only in 2 to 3 weeks in long bones and even after 6 weeks in flat bones. Traditional radiographs are still of value in ruling out other pathologic abnormalities, such as a fracture, Perthes disease, or slipped capital femoral epiphysis.⁵

In SA, radiographs are of lesser importance and may at most show an enlarged joint space. Instead, ultrasound (US) may find joint effusion, but, conditions permitting, magnetic resonance imaging (MRI) is the most accurate diagnostic tool especially useful in OM.^{28–30} Contrast enhancement does not improve sensitivity or specificity of MRI in OM, but increases reader confidence if bone or soft tissue edema is found on unenhanced images.³¹ Computed tomography is another valuable option, along with technetium 99 bone scintigraphy (bone scan), which is still useful, especially in major long bones, or if the symptoms are poorly localized.^{32–34}

The symptoms, signs, routine blood tests, and vaccination history against Hib or pneumococcus may give a hint toward the possible causative organism.^{12,13} *S aureus* OM or SA often develops in a short time and causes high fever, which is not typical of *K kingae* infection (see **Table 1**).^{14,21} These generalizations may be valuable in the primary evaluation, but bacterial culture or other identification (polymerase chain reaction) remains pivotal in terms of the choice of treatment and for an antibiogram. In SA, the aspirated synovial fluid sample before treatment is essential for bacteriology.¹⁷ Spontaneous clotting, high white blood cell count, and low glucose concentration suggest SA, but values overlap with other types of arthritides causing problems with interpretation.³⁵

Joint puncture is always recommended in SA, although even 70% of synovial cultures may remain culture-negative.⁶ In OM the need for a bone sample is more contentious because the diagnosis by MRI is reliable.^{30–32} The authors strive to identify the agent also in OM and emphasize the importance of blood cultures, which yield bacteria in one-third of the cases.¹⁹ A sample for bacteriology is obtainable by needle aspiration of soft tissue in neonates, subperiosteal aspiration in infants, or drilling in older children.^{1,6}

TREATMENT

Choosing the Antibiotic

The major role of *S aureus* among the agents causing AOIs^{1,8,9} influences the choice of the initial antibiotic, provided the local resistance pattern is known.^{1,19,36} **Table 2** summarizes some current recommendations for methicillin-sensitive *S aureus* and methicillin-resistant *S aureus* (MRSA).^{16,19,36–39} *S pyogenes* and pneumococcus do not pose a similar challenge, because both are sensitive to first-generation cephalosporins and clindamycin. The authors prefer to use clindamycin for staphylococcal infection, but anti-staphylococcal penicillins are also widely used.^{16,19} Of note, *K kingae* is resistant to clindamycin and vancomycin, but sensitive to cephalosporins and penicillins.^{14,40} In countries where Hib is still common in SA (Hib rarely causes OM), an unvaccinated child should receive concomitant ampicillin or amoxicillin (200 mg/kg/d divided in 4 equal doses) until the agent is identified.¹³ Gonococcal arthritis can be treated with ceftriaxone or cefotaxime.^{39,41} These agents are also appropriate for salmonella AOIs. In developing countries one may have to resort to cheaper agents such as chloramphenicol or possibly trimethoprim-sulfamethoxazole.⁴² An antibiogram would be of paramount importance in these situations.

Duration of Intravenous and Oral Treatment

For decades recommendations stated that the medication for AOIs should start with a long intravenous phase and treatment lasting a minimum of 4 to 6 weeks.^{43,44} A lack of prospective trials led to stagnation until in the last decade more than 1 study showed that a short intravenous period suffices.^{16,45,46} In the authors' largest to date, prospective, and randomized trial, the intravenous administration was only 2 to 4 days, after which the treatment was switched to oral medication, provided the first signs of recovery were observed and level of CRP began to descend.^{17–19}

Fig. 1 demonstrates the short antibiotic courses tested in recent trials on OM and SA. The entire course of antibiotic was approximately 3 weeks for uncomplicated OM,¹⁸ and 10 to 14 days for SA.¹⁷ The key points of this treatment have been exceptionally high doses (see **Table 2**) of well-absorbed first-generation cephalosporins or clindamycin, antibiotics that penetrate bone and soft tissue well, in intravenous and oral administration, and equal doses 4 times a day, because time-dependent

| Local Resistance | Antibiotic | Dose | Reference |
|---|----------------------|----------------------------------|--|
| >90% of strains in community MSSA ^a | 1st gen. CEPH | ≥150 mg/kg/d q.i.d. ^b | Peltola et al, ¹⁹ 2011 |
| | Or | | |
| | Flucloxacillin | ≥200 mg/kg/d q.i.d. | Jadogzinski et al, ¹⁶ 2009 |
| | Or | | |
| | Clindamycin | ≥40 mg/kg/d q.i.d. ^b | Peltola et al, ¹⁹ 2012 |
| >10% of strains MRSA ^c + Clindamycin resistance <10% | Clindamycin | ≥40 mg/kg/d q.i.d. | Liu et al, ³⁸ 2011 |
| >10% of strains MRSA + Clindamycin resistance 10%–25% | Vancomycin | ≥40 mg/kg/d q.i.d. | Liu et al, ³⁸ 2011 |
| | Or | | |
| | Clindamycin | ≥40 mg/kg/d q.i.d. ^b | Harik and Smeltzer, ³⁶ 2010 |
| | Or | | |
| | TMP-SMX ^d | ≥16 mg/kg/d b.i.d. ^e | Messina et al, ³⁹ 2011 |
| >10% of strains MRSA + Clindamycin resistance >25% | Vancomycin | ≥40 mg/kg/d q.i.d. | Harik and Smeltzer, ³⁶ 2010 |
| | Or | | |
| | TMP-SMX | ≥16 mg/kg/d b.i.d. | Messina et al, ³⁹ 2011 |
| Resistant to vancomycin/ TMP-SMX | Linezolid | ≥30 mg/kg/d t.i.d. | Chen et al, ³⁷ 2007 |

Abbreviations: b.i.d., divided into 2 equal doses each per 24 hours; 1st gen. CEPH, first-generation cephalosporin; q.i.d., divided into 4 equal doses each per 24 hours; t.i.d., divided into 3 equal doses each per 24 hours.

^a Methicillin-sensitive strains.

^b Author's choice.

^c Methicillin-resistant strains.

^d Trimethoprim-sulfamethoxazole.

^e Dosage of trimethoprim component.

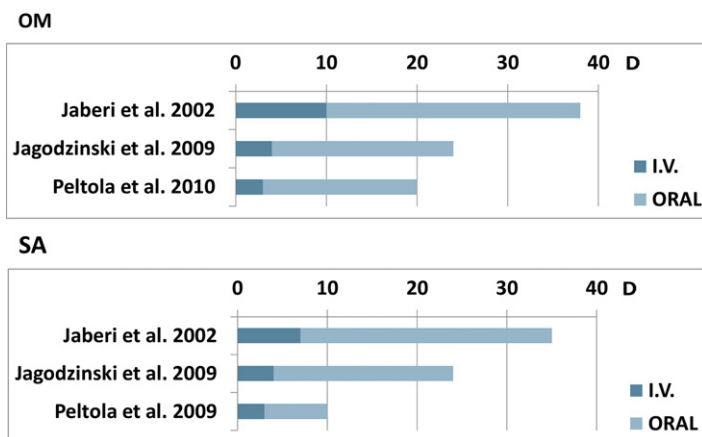


Fig. 1. Short courses of antibiotic for osteoarticular infections that have been tried successfully in the last 10 years. D, days; I.V., intravenous; OM, osteomyelitis; SA, septic arthritis. (Data from Refs. ^{16–18,45})

antibiotics do better with shorter intervals between doses.⁴⁷ For convenience and to ensure good compliance of the parents, the treatment was modified slightly so that the day's last dose is given before bedtime and the first at wake up. The efficiency of the approach in the past decades has been widely documented in both OM and SA.¹⁷⁻¹⁹

Adjuvant Medication

Nonsteroidal anti-inflammatory agents are given at the clinician's discretion and in large enough doses to relieve pain and fever.^{17,18} A 4-day course of low-dose dexamethasone provides some relief in the symptoms of SA without a shown effect in the rate of sequelae.^{48,49} A potential effect of large-dose adjuvant paracetamol has not been studied in AOs, but in bacterial meningitis it seems to be beneficial.⁵⁰

Surgical Treatment

No consensus prevails in the timing, procedures, extent, or even the overall need for surgical intervention in OM.⁵¹ In 1 patient series with aggressive surgical approach, 17% of the patients went on to develop chronic OM.⁵² On the other hand, conservative treatment with antibiotics has cured as many as 90% the patients with an early OM.^{51,53} Surgery may benefit the patient if an abscess or a sequestra has already developed, but the issue is unclear even in cases in which pus has elevated the periosteum, as subperiosteal collections greater than 3 mm wide have resolved spontaneously with adequate antibiotic treatment.^{44,54,55} In pelvic osteomyelitis an abscess greater than 20 mm may benefit from surgery.²⁹ The decision to drain a collection cannot be based solely on size but on the clinical grounds, which take into account the response to antibiotic therapy.⁵ Persistent fevers and persistent elevation of the CRP in a patient with a periosteal abscess are indications for surgical drainage. Patients whose treatment has been instituted after more than a week from the onset of symptoms seem more likely to require open trepanation.^{44,53,54,56} Thus, the need for surgery in a resource-poor environment is more likely than in the standard western setting.

A septic joint can be drained by aspiration (under US or fluoroscopic control, conditions permitting), arthroscopy, or open arthrotomy.^{28,57-59} Traditionally, routine open arthrotomy has been considered essential in shoulder and hip arthritis.^{57,58} Arthroscopy and repeated US-guided aspirations have been introduced more recently.^{28,58} Eighty-one percent of children in the authors' series of 62 children with SA of the hip were treated without arthrotomy with uneventful recovery in all cases.⁵⁹

Some caveats should be noted in applying minimally invasive surgery or a conservative approach in SA. Patients presenting in the early stages of disease usually recover uneventfully with no surgery at all, but the outcome starts to worsen if the history is 5 days or more.⁵⁷⁻⁵⁹ There are no good data on success without surgical intervention in neonates, who are deemed to be at greater risk of sequelae than older children.⁵⁷

PREVENTION

Hib was the second most common pathogen in SA of young children through the 1980s, but practically vanished from regions where large-scale Hib vaccination has been adopted. Hib vaccination had implications for treatment because adjuvant ampicillin or amoxicillin for children less than 5 years was no longer used.¹³ Similar success might be expected with the *S pneumoniae* conjugate vaccines,¹² but the path has not been as smooth as with Hib vaccination. For example, the incidence of AOI caused by

nonvaccine serotype 19A increased significantly in France after the use of the heptavalent pneumococcal vaccine was started.¹² This snag may be averted with newer vaccines that cover the serotype in question.

TREATMENT RESISTANCE AND COMPLICATIONS

Increased pneumococcal resistance to penicillin has not led to an increase in the rate of complications, but the rise of MRSA in many, although not all, countries has had an impact in the treatment of bone and joint infections.^{7–11} Staphylococcal infections are no more problematic in terms of treatment and outcomes than other AOIs when caused by methicillin-sensitive *S aureus*.⁶⁰ In contrast, MRSA seems to associate somewhat more frequently with complications.^{7–10,61} In the United States, the strain USA300 is predominant and is associated with a longer duration of fever.^{9,62} The patient seems to be at an elevated risk of a pathologic fracture when OM is caused by the USA300–0114 pulsotype.⁶² Fortunately, most MRSA strains are still susceptible to clindamycin, but this resistance pattern needs to be monitored constantly⁶³ as some areas are reporting increased clindamycin resistance in MRSA. The Panton-Valentine leukocidin–coding gene is associated with MRSA and causes more severe local symptoms and somewhat greater systemic inflammatory response.⁶⁴

Surprisingly the old-fashioned, and very cheap, antibiotic trimethoprim-sulfamethoxazole is experiencing a renaissance in the treatment of clindamycin-resistant cases, because this agent has excellent bioavailability, and, in many areas, 99% of the MRSA strains are susceptible.³⁹ In contrast to the pre-antibiotic era, death from AOI is rare in an immunocompetent host in high-income countries.^{6–10,16–19} However, deep vein thrombosis (DVT) may be life-threatening. A recent review on AOI identified 93 children with DVT from 28 studies, and risk factors for DVT were OM, male sex, and MRSA.⁶⁵

Relapse or chronic infection occurs if the eradication of the infection has failed.³ Also reinfections caused by dissimilar agents, in contrast to recurrences, are possible, although very rare events.^{17,66} Chronic OM is a major health problem among children in the resource-poor settings, where it is the commonest cause of pathologic fracture.² In SA, avascular necrosis of the femoral head and joint cartilage destruction are feared sequelae.^{57–59} Unsurprisingly, patients who present after many days of symptoms are more prone to these complications than those arriving early in the disease process.^{57,58}

EVALUATION OF OUTCOME

Rates of recrudescence and sequelae are used as the yardsticks of the quality of treatment.^{17–19} In this regard, reinfections should not be interpreted as treatment failures.^{17,66} Much more common are sequelae, which, however, may pass unnoticed if the follow-up is not long enough.^{1,18,57} Therefore, the authors recommend a late checkup for all cases of AOIs approximately 12 months after hospitalization, with intermediate checkups at 2 weeks and 3 months from discharge.^{17–19} A thorough clinical investigation is the key, combined with CRP measurements and, when needed, radiography.^{17–19,25,59,60}

SUMMARY

Early diagnosis and prompt treatment remain pivotal in avoiding complications in acute bacterial bone and joint infections.⁶⁷ Causative agents and the resistance pattern vary in different regions and should dictate the choice of antibiotics. In

uncomplicated OM or SA, in which fever and symptoms quickly resolve, initial intravenous treatment for 2 to 4 days, followed by high-dose oral antibiotics, leads to outcomes as good as or better than those with longer intravenous treatment. Exceptionally large doses of a well-absorbing and penetrating agent, and administration of equal doses 4 times a day are likely pivotal in the parenteral and oral treatment. The authors' prospective and randomized trials showed 3 weeks and 2 weeks to be safe in uncomplicated OM and SA, respectively.¹⁷⁻¹⁹ CRP is useful in the diagnosis and monitoring the cause of illness and in quick detection of pending complications.^{25,27} Overall, the treatment of most cases of childhood OM, SA, and OM+SA can still be much simplified from the regimen practiced in many hospitals.^{68,69}

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