

Acute Hematogenous Bacterial Osteoarticular Infections in Children

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Practice Gaps

Management of pediatric acute hematogenous osteoarticular infections has changed in various ways during the past decade, including the description of new pathogens and updated diagnostic and treatment strategies (such as infected source sampling and an early switch to oral therapy).

Objectives After completing this article, readers should be able to:

1. Understand what predisposes children of different age groups to acute hematogenous osteoarticular infections (OAI), particularly the role of anatomy and differing pathogenic susceptibilities.
2. Recognize the symptoms present in children with OAIs and their most common differential diagnoses.
3. Understand the most effective imaging techniques and laboratory tests/cultures to diagnose an OAI and how to interpret them.
4. Understand the benefits and limitations of therapeutic surgery and source sampling (biopsy/aspirate) and when to commence antimicrobial drug therapy.
5. Recognize the most common causative pathogens and the most effective antimicrobial drugs for their treatment.
6. Determine how long a patient should be taking intravenous and oral therapy and under what conditions they should switch from intravenous to oral antimicrobial agents.
7. Understand the recommended follow-up after diagnosis, including when to expect normalization of laboratory values in patients with uncomplicated OAIs.
8. Recognize complicated OAIs and their possible long-term sequelae.

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ABBREVIATIONS

ADE	adverse drug event
CRMO	chronic recurrent multifocal osteomyelitis
CRP	C-reactive protein
CT	computed tomography
ESR	erythrocyte sedimentation rate
MRI	magnetic resonance imaging
MRSA	methicillin-resistant <i>Staphylococcus aureus</i>
MSSA	methicillin-susceptible <i>Staphylococcus aureus</i>
OAI	osteoarticular infection
WBC	white blood cell

INTRODUCTION

Pediatric osteoarticular infections (OAI) include infections of the bones (osteomyelitis) and joints (septic arthritis). Pathogenic organisms may be introduced into these normally sterile sites via direct inoculation (eg, trauma or surgery) or via erosion from a contiguously infected source (eg, chronic ulcer), but organisms are mostly hematogenously delivered. Bacteria are the most common pathogens to cause OAIs, but mycobacteria, fungi, and viruses can also infect these tissues. If diagnosed in the first 10 to 14 days, these infections are considered acute; if diagnosed after 14 days of infection, there is a continuum from subacute to chronic osteomyelitis, with the latter often being defined by the presence of sequestra. (1)(2)(3)(4) Chronic infections are more difficult to treat due to necrotic areas of the bone and, thus, require more intensive surgical and antimicrobial drug management. In this article, we address the diagnosis and management of acute bacterial hematogenous OAIs.

The incidence of acute hematogenous OAI is approximately 1 in 10,000 children. It is most common in the first 2 decades of life, with toddler to elementary school ages predominating. It is more common in boys than in girls. It is also the most common indication for long-term (>2 weeks) outpatient antibiotic drug therapy in children.

Overall, there is a paucity of randomized controlled trials of pediatric OAIs. Treatment recommendations have, thus, evolved from retrospective case series and clinical acumen. Guidelines from the European Society for Paediatric Infectious Diseases were recently published (5) and are under development at the Infectious Diseases Society of America.

ANATOMY AND PATHOGENESIS OF INFECTION

Children are more susceptible to these infections due to the architecture of the vascular supply of growing bones. This vasculature allows for seeding during transient bacteremia. The causative bacteremia is usually subclinical, and such bacteremic events are likely common, related to trauma as minor as tooth brushing. (6)(7)(8)(9)(10) This same feature renders these infections eminently more treatable in pediatric patients compared with adults, in whom vascular flow to the skeletal system is diminished, thus limiting penetration of antibiotic agents. Although pediatric OAIs may be very severe and require long-term treatment, they generally respond well to treatment. Outcomes tend to be favorable, with full recovery in most patients.

The anatomy of the bone and its blood supply changes with age, and these changes are reflected in the clinical manifestations of the disease (Fig 1A). In the metaphysis of

long bones, the metaphyseal vessels form loops at the level of the physis and empty into venous sinusoids. It is thought that sluggish blood flow in this sinusoidal plexus provides a favorable setting for the bacteria to deposit, forming a nidus of infection. It is proposed that minor trauma resulting in a metaphyseal hematoma or small emboli in this region might predispose an otherwise well child to acute hematogenous osteomyelitis. However, studies do not demonstrate increased rates of trauma in children with OAIs compared with healthy children. (11) With bacterial replication, there is recruitment of inflammatory cells, release of inflammatory mediators, osteoblast necrosis, activation of osteoclasts, and development of an inflammatory exudate (pus). As exudate accumulates, the associated increase in pressure forces exudate through the perforating canals (Haversian and Volkmann) to the cortex. From here, the bone anatomy changes that occur throughout childhood lead to unique presentations in different age groups as the infection progresses.

In neonates, there are transphyseal vessels that connect the metaphysis to the epiphysis (Fig 1B). Thus, in neonates, infection easily tracks from the metaphysis to the epiphysis (Fig 1B – solid arrow) and subsequently erupts into the joint space (Fig 1B – hollow arrow). In fact, neonates with septic arthritis should be assumed to have contiguous osteomyelitis.

From infancy to toddlerhood (Fig 1C), endochondral ossification progresses, and a secondary ossification center develops by age 2 years. The physis becomes relatively avascular and is less likely to become infected. In these children, the inflammatory debris tends to track laterally, parallel to the physis, until it passes through the cortex (Fig 1C – solid arrow). At this age, the periosteum is thick and not yet firmly attached to the cortical bone. During infection, the periosteum is lifted off of the bone, potentially creating a subperiosteal abscess. With sufficient accumulation, the periosteum can rupture, spreading the infection into the surrounding soft tissues. In some joints (eg, the hip and shoulder), the attachment of the joint capsule is on the metaphysis (rather than the epiphysis) of the bone. Thus, if infection ruptures through the metaphysis, the patient will also develop a septic joint (Fig 1C – hollow arrow). When the blood supply to the bone is affected by detachment of the periosteum, an island of necrotic bone forms (sequestrum). New bone (involucrum) can then form in the elevated periosteum that surrounds the sequestrum. Children are at risk for these complications throughout childhood and into adolescence.

With skeletal maturity, the metaphyseal and epiphyseal vessels anastomose into a single vessel (Fig 1D). Adolescents

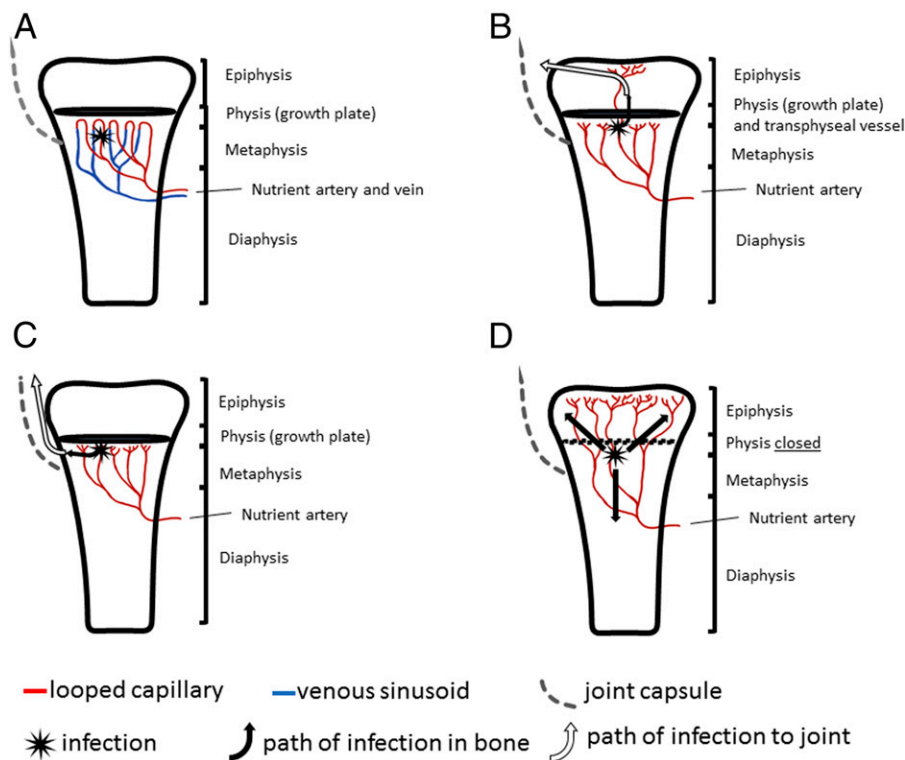


Figure 1. Pathogenesis of acute hematogenous osteoarticular infections for different age groups. A. Anatomy with initial focus of infection. B. Age 0-1 years. C. Age 1-16 years. D. Late adolescent/young adult.

continue to have increased vascular supply to bones compared with adults, but the cortex thickens and the periosteum is thinner, more adherent, and more fibrous. Thus, in adolescents, infection often remains within the bone.

Overall, osteomyelitis most commonly occurs in long bones, such as the femur, tibia, fibula, and humerus, and in the small bones of the foot. Septic arthritis is most commonly found in the hips and knees.

HISTORY AND CLINICAL EXAMINATION

As with all patients, the first step is a thorough history to establish the onset and character of symptoms such as pain, fever, swelling, redness, decreased range of motion, and refusal to bear weight as well to explore possible exposures or medical history that may alert to risk factors for unusual infectious causes (Table 1).

Pain is the most common symptom in those with OAI. In neonates and infants, this can present as pseudoparalysis (the refusal to move or use an extremity). Notably, neonates more often have multifocal infection and warrant a thorough evaluation of the entire skeleton, particularly with *Staphylococcus aureus* or *Salmonella* infections. Young toddlers may refuse to bear weight, may revert to crawling, or may seem uncomfortable with routine care, such as holding

or diaper changes. Young children may complain of generalized extremity pain and often present with a limp. Pain may be referred to contiguous areas, such as hip pain to the knee joint. In older children, the pain is often more focal and presents as point tenderness. Unlike posttraumatic pain, which often improves with rest, the pain from OAIs will occur at rest and with activity. History of fever is helpful, but fever is present in only 75% of children. Although most children present with pain and fever or malaise, it is important to recognize that children may also present systemically ill with fever, hypotension, tachycardia, and tachypnea requiring high levels of supportive care.

A careful physical examination is necessary to establish the diagnosis and location of a possible OAI; specific locations of osteomyelitis have implications for management. In neonates and young children, it is often difficult to determine a focus within an extremity. They may be irritable with any palpation or movement, but if consoled by parents, one may be able to palpate most bones and move most joints to localize the infection. Percussion over the bone distant to the focal pain will often elicit pain at the site of the infection. Passive range of motion of the joint(s) close to the site of the suspected infection can help establish the presence of a concomitant septic joint. Patients with septic arthritis typically will not tolerate short arc (<10°) of motion of the

TABLE 1. Clinical and Less Common Microbial Differential Diagnoses for Children with OAI

AGENT OR ENTITY	HISTORICAL AND CLINICAL CLUES	KEY DIAGNOSTIC CONSIDERATIONS
Noninfectious, heme/oncologic		
Bone infarction	Pain, may be multifocal, no systemic illness	MRI demonstrates changes consistent with infarction
Ewing sarcoma	Insidious onset of pain, rare to have systemic symptoms	Radiographs demonstrate a radiolucent lesion with a pronounced periosteal reaction (typically an "onion skin" or "hair on end" periosteal reaction), MRI demonstrates a bone lesion with an associated soft tissue mass biopsy of the lesion/mass
Langerhans cell histiocytosis	Insidious onset of pain, geographic radiolucent lesions in bone, rare to have elevated acute-phase reactant levels	MRI demonstrates solidly enhancing lesion in the bone, bone biopsy
Leukemia	Fatigue, weight loss, frequent infections, easy bruising/bleeding, generalized pain	CBC, peripheral blood smear, bone marrow biopsy
Lymphoma	Swollen lymph nodes, weight loss, night sweats	Imaging demonstrates lymphadenopathy, lymph node biopsy
Neuroblastoma	Painless mass, distended abdomen, weight loss, neurologic symptoms	CT or MRI demonstrates a mass, biopsy of the mass
Osteoid osteoma	Localized pain that responds well to NSAIDs	CT or MRI demonstrates small bone lesion with central nidus
Noninfectious, immune mediated		
Blood dyscrasia (hemophilia)	Family history, personal history of bleeding	Hematoma encountered instead of pus, supportive hematologic studies
Chronic recurrent multifocal osteomyelitis	Mimics subacute osteomyelitis	Bone biopsy for culture (to ensure negative) and consistent pathology, response to NSAIDs
Henoch-Schonlein purpura	Clinically consistent features	Musculoskeletal involvement usually tendonitis, but can mimic septic arthritis; distinguish on physical examination
Kawasaki syndrome	Clinical criteria for Kawasaki syndrome, with care to elicit historical symptoms	Discussed in American Heart Association Kawasaki Guidelines, supportive laboratory data (12)
Poststreptococcal arthritis	Often symmetrical arthritis, may be small to mid-size joints	Usually older children and adults, 2–3 wk after group A <i>Streptococcus</i> infection, moderate response to NSAIDs
Reactive arthritis syndrome	Arthritis, urethritis, bilateral conjunctivitis; more common in adults	Clinical diagnosis
Rheumatologic disease	Clinical criteria, usually prolonged or recurrent symptoms	Supportive laboratory data, biopsy of synovial tissue might be helpful, joint inflammation usually not >50,000 cells/mL.
Rheumatic fever	Clinical criteria Migrating polyarthritis, usually large joints	Joints resolve quickly with aspirin/ibuprofen
Serum sickness	New drug exposure Polyarthritis, often rash	Often low C3, C4
Transient synovitis	Onset of pain after a viral illness, usually large joints of lower extremities, symptoms may wax and wane	Kocher criteria may be helpful to distinguish, responds well to NSAIDs
Noninfectious, orthopedic		
Fracture	Acute pain after an injury, no systemic illness	Radiographs demonstrate the fracture

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TABLE 1. (Continued)

AGENT OR ENTITY	HISTORICAL AND CLINICAL CLUES	KEY DIAGNOSTIC CONSIDERATIONS
Legg-Calve-Perthes disease	Variable onset and acuity of pain, no systemic illness	Radiography or MRI demonstrate avascular necrosis of the femoral head
Nonaccidental trauma	Absent/inconsistent clinical history	Skeletal survey, radiographs often demonstrate multiple injuries in various states of healing
Slipped capital femoral epiphysis	Variable onset and acuity of pain, no systemic illness	Radiographs demonstrate a slip
Bacterial		
<i>Borrelia burgdorferi</i>	Exposure to ticks or travel in endemic areas within 2 mo–2 y, history of consistent rash, bland arthritis with 10,000–50,000 white blood cells	Serologic testing usually diagnostic with consistent clinical picture, PCR synovial fluid available in reference laboratories
<i>Brucella</i> species	Ingestion of unpasteurized dairy or infected meats	May grow from blood or synovial fluid, serology helpful (blood), PCR of fluid and blood available at state health departments
<i>Fusobacterium necrophorum</i>	Severe sore throat or dental abscess, neck pain, usually associated with embolic pneumonia (Lemierre syndrome)	Thrombus of internal jugular on ultrasonography or CT, embolic pulmonary findings, anaerobic blood culture positive (or aerobic supplemented with FOS)
<i>Haemophilus influenzae</i>	Usually <4 years of age, unimmunized; if nontypable, worry about immunodeficiency	Culture of infected source
<i>Mycobacterium</i> (atypical)	Immune defect in the interferon pathway	Synovial biopsy for culture and pathology helpful
<i>Mycobacterium tuberculosis</i>	Exposure to infected persons or high-risk settings or to persons with chronic cough with such exposures, unpasteurized dairy (<i>Mycobacterium bovis</i>)	Synovial biopsy for culture and pathology helpful, in addition to usual <i>M tuberculosis</i> evaluation; PCR (synovial fluid) available from reference laboratories
<i>Mycoplasma</i> and <i>Ureaplasma</i> species	Immune defect, particularly with severe immunoglobulin deficiency; insidious onset, boggy joint	Culture on special media or do PCR (synovial fluid) for various species
<i>Neisseria gonorrhoea</i>	Sexual activity, or perinatal infection	Synovial fluid positive in only 25%; screen throat/rectum/cervix
<i>Neisseria meningitidis</i>	Unimmunized	Culture of infected source
<i>Pasteurella</i> species	Bite/lick of wound from cat or dog	Culture of infected source
<i>Pseudomonas</i> species	Injection drug use, disorders of neutrophil function or number	Culture of infected source, neutropenia
<i>Salmonella</i> species	Sickle cell Amphibious pets Infants at greater risk	Culture of infected source
<i>Spirillum minus</i>	Contact with rats (Europe), often a palmar maculopapular/pustular rash	May grow from culture of blood or fluid, but add FOS
<i>Streptobacillus moniliformis</i>	Contact with rats (American continent), often palmar maculopapular/pustular rash	May grow from culture of blood or fluid, but add FOS
Fungal		
<i>Blastomyces dermatitidis</i>	Travel to central United States	Synovial biopsy for culture and pathology Serologic testing
<i>Candida</i> species	Immunocompromised, medically complex or immunodeficient, including neonates; may have diffuse maculopapular/pustular rash	May grow from culture of blood or fluid
<i>Coccidioides immitis</i>	Travel to endemic area (Arizona, Nevada, California, Texas, Utah, Mexico, Central and South America)	Synovial biopsy for culture and pathology Serologic testing

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TABLE 1. (Continued)

AGENT OR ENTITY	HISTORICAL AND CLINICAL CLUES	KEY DIAGNOSTIC CONSIDERATIONS
<i>Cryptococcus neoformans</i>	Often immunocompromised, exposure to bird droppings in soil	Synovial biopsy for culture and pathology Serologic testing
<i>Histoplasma capsulatum</i>	Travel to endemic area (central United States), exposure to birds or bird excrement	Synovial biopsy for culture and pathology Serologic testing
<i>Sporothrix schenckii</i>	Contact with plant debris, more common in the immunocompromised	Synovial biopsy for culture and pathology Serologic testing
Viral		
Chikungunya virus	Recent travel to endemic area, biphasic febrile illness	Serologic testing
Enterovirus	Associated with hypogammaglobulinemia	Enteroviral PCR (synovial fluid) if suspected
Parvovirus B19	Acute arthritis, but can last 1–2 mo Usually symmetrical, polyarticular, small joint	PCR and serology of blood
Protozoan/parasitic		
<i>Trichinella</i>	Myositis and eosinophilia, ingestions of wild/home-raised carnivore/omnivore meats	Possible to see calcifications on radiographs; eosinophilia may be present (70%), elevated muscle enzymes, pathology of muscle, serologic testing (available at the Centers for Disease Control and Prevention)
<i>Taenia</i> infections	Usually symptomatic if in nervous system, but may invade muscle	Serologic testing, pathology of lesion

CBC=complete blood cell count, CT=computed tomography, FOS=fastidious organism supplementation, MRI=magnetic resonance imaging, NSAID=nonsteroidal anti-inflammatory drug, OAI=osteoarticular infection, PCR=polymerase chain reaction.

involved joint. With the affected bone appropriately supported, it is unlikely that the joint being moved is involved in the infection if the patient has little or no pain with short arc passive range of motion. Axial loading of a joint (putting pressure through the joint) also typically elicits pain when septic arthritis is present. This is tested by lightly knocking one's fist on the distal end of the bone being examined.

If the infection has breached the cortex and involves the surrounding soft tissues, the examiner may notice edema and erythema at the involved site. There may be a focal area of fluctuance with an associated soft tissue abscess. Because of the overlap in symptoms, these children can be mistakenly diagnosed as having cellulitis or skin abscess. With concomitant septic arthritis, the joint will often be swollen. Occasionally, OAIs can lead to an associated septic thrombophlebitis, so examination of the vessels in the infected area for cording, tenderness, or redness is important.

LABORATORY EVALUATION

Laboratory testing in the evaluation for OAI should include complete blood cell count, erythrocyte sedimentation rate

(ESR), and C-reactive protein (CRP) level. It is also imperative to draw blood cultures (ideally 2) because the causative organism can often be identified in this manner. Culture of the infected source is discussed later herein. The white blood cell (WBC) count and differential count on a peripheral smear are helpful in evaluation for other conditions (ie, hematologic/oncologic), but it is not diagnostic of OAI because only 50% of patients have a WBC count greater than $10,000/\mu\text{L}$ ($>10 \times 10^9/\text{L}$) and 20% greater than $15,000/\mu\text{L}$ ($>15 \times 10^9/\text{L}$). (13) The CRP level tends to rise (and fall) faster than the ESR. The CRP level peaks at approximately 48 hours and has a half-life of 4 to 9 hours, although notably may transiently increase after surgery. (14) It is greater than 0.2 mg/L in approximately 85% of patients and greater than 0.4 mg/L in 70%. A CRP level of 0.4 mg/L is also a useful cutoff level to differentiate viral from bacterial illness. The ESR is affected by the presence of immunoglobulins and fibrinogen, 2 proteins with long half-lives; therefore, the ESR may remain elevated for more than a week after inflammation resolves. (14)(15) The ESR is greater than 20 mm/hr and greater than 30 mm/hr in 94% and 70% of patients with OAIs, respectively. (13)

Synovial fluid is important to obtain for culture and helpful in categorizing the potential source of inflammation. Normal synovial fluid has a WBC count less than $200/\mu\text{L}$ ($.2 \times 10^9/\text{L}$). Bacterial infection tends to have a WBC count greater than $50,000$ to $100,000/\mu\text{L}$ ($50 \times 10^9/\text{L}$ to $100 \times 10^9/\text{L}$). Rheumatologic causes and some infectious causes (*Borrelia burgdorferi*, mycobacteria, endemic fungi, *Brucella*) tend to have a WBC count of $5,000$ to $50,000/\mu\text{L}$ ($5 \times 10^9/\text{L}$ to $50 \times 10^9/\text{L}$), although there are exceptions. (10) Transient synovitis typically has a WBC count less than $50,000/\mu\text{L}$ ($50 \times 10^9/\text{L}$). (16) A synovial biopsy is not routine, but it is particularly helpful in infectious causes inciting granulomatous inflammation, such as mycobacterial and endemic fungal infections, and may be helpful in rheumatologic disease.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis for those presenting with focal bone pain includes trauma, infarction, benign (eg, osteoid osteoma) and malignant (eg, Ewing sarcoma) tumors, and chronic recurrent multifocal osteomyelitis (CRMO), which is a non-bacterial inflammatory bone disease. (17)(18)(19) For individuals with arthritis, the differential diagnosis includes transient synovitis, hemarthrosis, and rheumatologic disease. There is a large clinical and microbial differential diagnosis, presented in Table 1. A common clinical dilemma is the differentiation between hip septic arthritis and transient synovitis. Although independently not reliably predictive, the combination of history of fever, reluctance to bear weight, ESR greater than 40 mm/hr , and WBC count greater than $12,000/\mu\text{L}$ ($12 \times 10^9/\text{L}$) (collectively called the Kocher criteria) are relatively specific for the diagnosis of septic arthritis, which differentiates septic arthritis from transient synovitis. (20)

IMAGING

Initial imaging for suspected OAI should always begin with plain radiographs of the involved area. (21) For osteomyelitis, there may be absent or limited changes early in the course of infection, but imaging is essential to rule out other causes of pain, including tumor and fracture. If the radiographs are abnormal, they may avert the need for other studies, such as magnetic resonance imaging (MRI). Finally, they serve as a baseline to monitor for changes over time, including bone remodeling, angular deformity, and growth disturbance.

Visible changes in bone due to infection depend on the amount of bone loss over time and may take up to 2 weeks before such bone loss is detectable on radiographs. Because neonatal bone is less dense, changes are radiographically apparent sooner. Radiographic changes in osteomyelitis include areas of osteolysis, cortical expansion, thinning or destruction, periosteal elevation, and, late in the course, periosteal bone formation (Figs 2 and 3). The differential diagnosis for the most common radiologic observations in bone infection (eg, lytic lesions on radiographs, bone marrow edema on MRI) include primarily CRMO, or oncologic processes such as leukemia, lymphoma, Langerhans cell histiocytosis, neuroblastoma, and Ewing sarcoma (Table 1).

Historically, radionuclide scanning (bone scan) using technetium-99m was used to evaluate for osteomyelitis because this imaging technique was much more sensitive in detecting early osteomyelitis than were plain radiographs. This technique has largely been supplanted by MRI where available. The disadvantages of a bone scan are the relatively low specificity in ruling out other causes of increased bone turnover, difficulty in differentiating osteomyelitis from adjacent cellulitis or septic arthritis, radiation exposure,

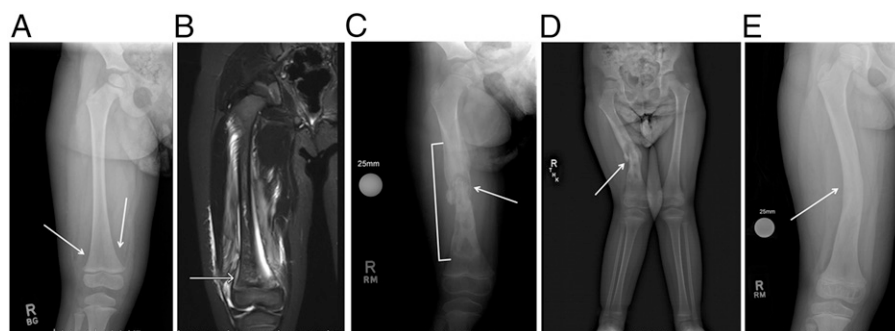


Figure 2. Two-year-old with methicillin-resistant *Staphylococcus aureus* infection of the right femur, progression over time. A. Plain radiograph on the day of presentation with fever and refusal to bear weight on the right leg. Inflammatory changes in the soft tissues about the distal thigh, no bony changes (arrows). B. Magnetic resonance image on the day of presentation showing extensive osteomyelitis of the femur with subperiosteal abscess (arrow). C. Ongoing extensive osteomyelitis (bracket) of the femur with pathologic fracture (arrow) 4 months after diagnosis. D. Healing pathologic fracture (arrow) with increased angulation after minor trauma 8 months after diagnosis. E. Resolved osteomyelitis and healed fracture (arrow) after remodeling with residual angulation 33 months after diagnosis.

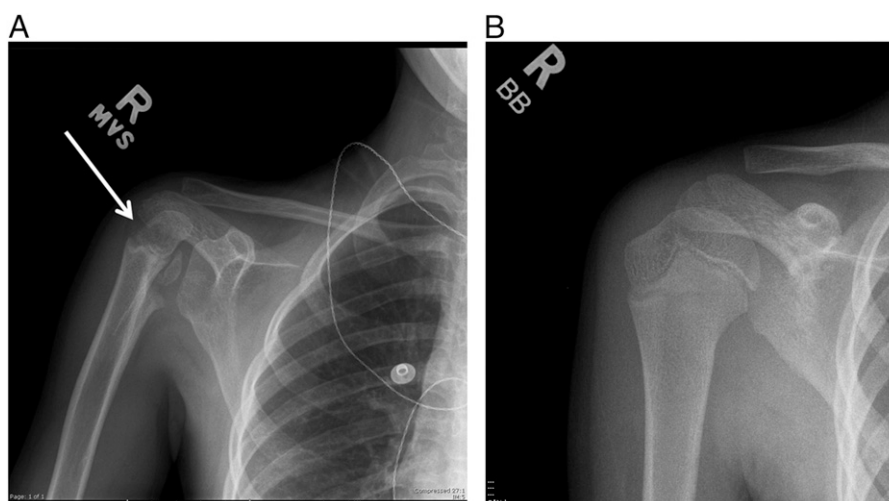


Figure 3. Fifteen-year-old with chronic deformity of the right proximal humerus (A, arrow) secondary to osteomyelitis and septic arthritis as a child; for comparison, a normal radiograph of a teenage shoulder (B).

and expense. Bone scans also lack sensitivity in neonates. Many centers no longer offer this technology.

MRI is the imaging study of choice for evaluation for osteomyelitis after plain radiographs. MRI has the greatest capacity for detecting OAI early in the disease course, when it presents as an area of edema in the bone. MRI is used to identify subperiosteal abscesses, adjacent soft tissue abscesses, myositis, and joint effusion (Fig 2B). It is also the best modality for evaluation of the surrounding anatomy. Contrast can be used to help delineate solid masses (eg, tumors) from fluid-filled spaces (eg, abscesses). However, MRI is not 100% sensitive, and it cannot always establish noninfectious from infectious causes of edema. MRI is also limited by cost and, for some patients, the need for sedation.

Computed tomography (CT) may be useful, especially in evaluating the bone architecture. It has a particular niche in children with implanted metal devices in whom MRI is contraindicated or in whom the quality of the MRIs is compromised by the implant. CT or MRI can be used in the evaluation of late manifestations of disease, such as sequestra and involucra. CT is faster, is less expensive, and less often requires sedation than MRI but results in significant exposure to radiation.

Combined positron emission tomography/CT is emerging as a technology that is useful in the diagnosis of osteomyelitis. It has the advantage of identifying foci of infection very early in the process, and it easily scans the entire body in a very short amount of time. (22) At this time, however, cost and radiation exposure prohibit its widespread acceptance. Nevertheless, it does have a particular role in diagnosing infections adjacent to metallic implants that preclude evaluation by MRI.

Ultrasonography is often used to detect effusions of joints (especially in the hips), which may indicate the

presence of septic arthritis. Ultrasonography is of limited utility in the diagnosis of osteomyelitis but is useful in the detection of associated venous thrombi.

DIAGNOSIS

A definitive diagnosis of osteomyelitis is made with biopsy or aspirate of the affected site. The biopsy can be performed percutaneously with a needle or in an open manner. The method of the biopsy is dictated by the site to be biopsied and the provider performing the biopsy. It is desirable to send bone and bone aspirate samples for histologic evaluation and cytologic analysis, respectively, and both for culture. By including specimens for histology and cytology, neoplastic processes can be evaluated for presence. During the biopsy, it is important to avoid passing through areas of cellulitis or myositis to avoid contamination to the sample. If unusual or noninfectious causes are suspected (based on exposures and history), synovial tissue should also be sent for pathology and appropriate cultures (Table 1). Without microbiology and pathology, the diagnosis of OAI is based on clinical reasoning and radiology. (23)

CAUSATIVE PATHOGENS AND THEIR IDENTIFICATION

The causative pathogens of acute OAIs are listed in Table 2. Most are caused by *S aureus* in every age group. The proportion of methicillin-resistant *S aureus* (MRSA) versus methicillin-susceptible *S aureus* (MSSA) varies by region, although notably hospital-wide antibiograms may overestimate the percentage of OAIs caused by MRSA. (13) Clindamycin resistance, which reaches 25% to 50% in some

regions (for MSSA and MRSA), is also important when considering *S aureus*. Other pathogens are more age dependent than *S aureus*. In neonates, group B streptococci and *Salmonella* species are important pathogens that often have comparatively indolent clinical presentations. In toddlers and preschoolers, *Kingella kingae* is well described, and in some areas of the world it causes more disease than *S aureus* in this age group. (24) This pathogen also tends to be more indolent and is described in association with mouth ulcers. Other regularly observed pathogens are *Streptococcus pyogenes*, *Neisseria meningitidis*, *Neisseria gonorrhoea*, *Salmonella* species, and *Streptococcus pneumoniae*. A full list of additional pathogens with some common associations is given in Table 1.

Identification of the causative pathogen relies on blood and source cultures of infected material and is the first step in ensuring the most effective therapy. Optimally, blood cultures should be obtained before antibiotic drug therapy and be of adequate volume and number (preferably 2 aerobic cultures). A consistent 2–blood culture policy for all patients with suspected OAI may increase positivity by 10% (to 49%). (13) Overall, positive blood cultures can be expected in 30% to 50% of patients. Source culture is extremely valuable and should be sent for aerobic incubation, with anaerobic, fungal, and mycobacterial culture reserved for select patients (Table 1). When infected material is sent for culture, aerobic yield is improved if both broth culture (in the form of a blood culture bottle) and traditional plates (blood, chocolate, and MacConkey) are used as media. Although traditional microbiologic methods continue to be

valuable, particularly for susceptibility testing, methods to identify pathogens from culture more rapidly are becoming standard. These include polymerase chain reaction for panels of pathogens and mass spectrometry for protein signatures. Although most of these new methods require growth in traditional media first, panels for use directly on specimens are also in development. (25) Concern for unusual pathogens (eg, *B burgdorferi*, *Coccidioides immitis*, or *Mycobacterium tuberculosis* in immunocompromised patients) can require special media, and consultation with the receiving laboratory is advised.

INPATIENT MEDICAL AND SURGICAL MANAGEMENT

Once the diagnosis of acute hematogenous OAI is likely, a provider is faced with various decisions regarding optimal management. Should the patient have surgery (for therapeutic or microbial diagnostic reasons)? Should antibiotic agents be initiated immediately or only after source culture? Which microbes should be targeted, and what are the advantages and disadvantages of one regimen over the other? The answers will depend on the clinical status of the child, the availability of surgical staff, the location of the infection, the microbial differential diagnosis, and local susceptibility patterns.

Surgical interventions are clearly indicated for osteomyelitis, including decompression of subperiosteal abscesses, drainage of associated soft tissue abscesses, and drilling/decompression of intraosseous abscesses. These interventions are aimed at debulking infection, restoring adequate blood flow (thus limiting cell death), increasing antibiotic drug penetration, and preventing further spread of infection into contiguous spaces. In the case of suspected septic arthritis, a joint aspiration should be performed for both diagnostic and therapeutic purposes. If the joint aspirate is indicative of infection, the joint should be surgically drained and irrigated. Serial aspiration or percutaneous irrigation through catheters or cannulae has also been described. (26)(27) In areas where resources for surgery are limited, priority is given to the hip and shoulder joints and joints with large amounts of loculation and debris. Delay in diagnosis and treatment of a septic joint can lead to devastating long-term sequelae, including avascular necrosis, degenerative arthritis (due to death of cartilage), and chronic pain.

The procedures to obtain and process a source sample for pathology, cytology, and culture are described previously herein. This is not routine at all centers and is considered a controversial topic. Some arguments against making sampling a priority are that the clinical diagnosis is relatively

TABLE 2. Common Organisms by Age

AGE	ORGANISMS
Neonate	<i>Staphylococcus aureus</i> , <i>Streptococcus agalactiae</i> , <i>Salmonella</i> species, viridans group streptococci, <i>Streptococcus pneumoniae</i> , <i>Streptococcus pyogenes</i> , <i>Escherichia coli</i> , <i>Neisseria gonorrhoeae</i> , <i>Treponema pallidum</i>
3 mo to <5 y	<i>S aureus</i> , <i>Kingella kingae</i> , <i>S pyogenes</i> , <i>S pneumoniae</i> , <i>Haemophilus influenzae</i> , <i>Neisseria meningitidis</i>
≥5 y	<i>S aureus</i> , <i>S pyogenes</i> , <i>S pneumoniae</i> , <i>N meningitidis</i>
Adolescent	<i>S aureus</i> , <i>S pyogenes</i> , <i>N gonorrhoeae</i> , <i>N meningitidis</i> , <i>Fusobacterium</i> species

The most common organisms are shown in bold.

straightforward, the microbiology is reasonably predictable, procedures involve some risk, and some hospitals may not have the support needed to obtain a sample. However, prioritizing source sampling has multiple benefits provided that a child is clinically stable enough, there are surgical staff available, and the location of infection is accessible. (13) Microbial yield with operative source cultures is 86%. (28) Although 50% of blood cultures (+/- source culture) are positive, in another 30% of cases only the source culture is positive. (13) The benefits of knowing the pathogen include decreased broad spectrum antibiotic drug exposure (including toxic agents such as vancomycin), decreased days of therapy, (13)(23) potentially decreased use of invasive and costly interventions (such as central venous catheters and MRIs), and the possibility of better outcomes resulting from optimal drug choices and simplified management decisions. (23) Care of children with an unknown pathogen becomes challenging if they do not improve as expected or they develop an adverse reaction to their selected antibiotic agents. In these scenarios, the provider must choose alternatives without knowledge of the organism or its susceptibilities. Studies demonstrate that when the pathogen is known, patients are more likely to be discharged taking a single antibiotic drug. (23) In addition, source sampling can provide an opportunity for pathology that on occasion leads to alternate diagnoses as well as an opportunity to decrease bacterial load (source control) that may aid recovery (Table 1).

One study advocates obtaining a source sample before antibiotic drug therapy if the patient is stable and the delay is not expected to be greater than 12 hours; however, this is another area of controversy. (13) Other literature suggests that previous antibiotic drug use does not influence culture results, at least for *S aureus*. (28) Performing a culture before administering antibiotic drugs remains relevant because it is unclear what effect antibiotic agents might have on the recovery of other pathogens. Moreover, there is a concern that these studies did not assess possible effects on antimicrobial drug therapy and central line use in children who remain culture negative. Conversely, if antibiotic agents have been started, it should not dissuade source sampling because there is ongoing utility in differentiating MSSA from MRSA.

MANAGEMENT OF ANTIMICROBIAL DRUG THERAPY

Initially, children are usually treated intravenously, and then transitioned to oral therapy. An agent should be chosen that is effective against the most likely bacteria based on age, exposures, and local susceptibility patterns (Table 3). The

broadness of the regimen should be dictated by the severity of global illness and involvement of other organ systems. Empirically, *S aureus* should be targeted in children of all ages. The choice to cover MRSA depends on severity of illness, prevalence of that pathogen in the community, and whether one has a source culture as an end point for narrowing antimicrobial drug choices. In children younger than 3 years it is prudent to target *K kingae*, and this bacterium should also be considered for children 3 to 5 years of age. (24) Most choices that target *S aureus* will provide coverage for less common pathogens (such as *S pyogenes*), so expanding coverage to these less common pathogens should be based on culture results, exposures, age, or other risk factors (Table 1). Two comprehensive reviews of therapies were recently published. (29)(30) For children 1 to 3 years of age, some clinicians prefer cefazolin because it is effective against both MSSA and *K kingae*. (35) For those stable patients with risk factors for MRSA, clindamycin may be used instead of cefazolin. (35)(36) In the case of an unstable patient, vancomycin should be added to cefazolin due to studies demonstrating improved outcomes for patients with MSSA treated with beta-lactam antibiotic drugs compared with vancomycin alone. (37) If a patient has signs and symptoms related to toxin-mediated disease or has an undrained abscess, the addition of clindamycin is considered appropriate by some experts. (38) Some institutions also prefer nafcillin to cefazolin, particularly if a child has a positive blood culture for MSSA; although given the comparative adverse effects and cost, it is not clear whether this is justified outside of central nervous system infection. (39)(40) Parenteral therapies for OAIs with MRSA include vancomycin, clindamycin (although resistance is high in some locations), linezolid, daptomycin, and ceftaroline. (29)(30)

Length of intravenous treatment is a point of some controversy, and recommendations have fluctuated over time. Recently, data endorse the safety of switching to oral therapy early, with resulting similar clinical outcomes, earlier discharge events, and decreased adverse events (such as central line complications). (13)(41) Before transitioning to oral therapy, the patient should be afebrile for at least 24 hours, have significantly improved clinical examination findings, exhibit a falling CRP level, have cleared bacteremia (if present at the start of therapy), and be able to tolerate oral therapy. Also, ideally the organism and its susceptibilities are known. These previously mentioned conditions are consistent with the new recommendations from the European Society for Pediatric Infectious Diseases. (5) Some institutions use a discrete CRP value (ie, <20 mg/L [<190 nmol/L]) before transitioning to oral therapy. (42) Other

TABLE 3. Common Antibiotic Drugs and Monitoring for Patients with OAI^s (5)(29)(30)(31)(32)(33)

	CEFAZOLIN (IV)	CEFALEXIN (PO)	CEFADROXIL (PO)	NAFCILLIN (IV)	CEFTRIAXONE (IV)	VANCOMYCIN (IV) (4)	CLINDAMYCIN (IV OR PO) (3)	AMPCILLIN (IV)	AMOXICILLIN (PO)	SULFAMETHOXAZOLE (PO)	DAPTOMYCIN (IV)	CEFTAROLINE (IV)	LINEZOLID (IV OR PO)
Routine daily dosing for OAI	100-150 mg/kg per day divided Q8H	100-150 mg/kg per day divided QID (TID also may be effective)	100-150 mg/kg per day divided TID (BID may be effective)	200 mg/kg per day divided Q8H	100 mg/kg per day divided Q12-24H	60-80 mg/kg per day divided Q8H	30-40 mg/kg per day; IV divided Q8H; PO divided TID	200 mg/kg per day divided Q8H	90-100 mg/kg per day divided TID	6-12 mg/kg per day divided BID	8-12 mg/kg per day Q24H	45 mg/kg per day divided Q8H	Age <11 y: 30 mg/kg per day divided Q8H; age ≥12 y: 600 mg Q12H
Maximum daily dose for moderate OAI	6,000 mg/d divided Q8H	4,000 mg divided QID	3,000 mg/d divided TID	8,000 mg/d divided Q8H	2,000 mg/d Q24H	6,000 mg/d divided Q6-8H, based on trough serum concentrations	1,800 mg/d IV/PO divided Q8H	8,000 mg/d divided Q8H	3,000 mg/d divided TID	640 mg/d divided BID	No established maximum dose	1,800 mg/d divided Q8H	1,800 mg/d divided Q8H
Maximum daily dose for severe OAI	8,000 mg/divided Q8H	4,000 mg/d divided QID	4,000 mg/d divided QID	12,000 mg/d divided Q4H	4,000 mg/d divided Q12H	6,000 mg/d divided Q6-8H, based on trough serum concentrations	3,600 mg/dIV divided Q8H; 1,800 mg/dPO divided TID	12,000 mg/d divided Q4H	4,000 mg/d divided QID	640 mg/d divided BID	No established maximum dose	1,800 mg/d divided Q8H	1,800 mg/d divided Q8H
Single-dose maximum for OAI	2,000 mg	1,000 mg	1,000 mg	2,000 mg	2,000 mg	2,000 mg (adjust dose with levels, can use continuous, consult ID)	900 mg IV, 600 mg PO	2,000 mg	1,000 mg	320 mg	No established maximum dose	600 mg	600 mg
Notable advantages	Inexpensive Not caustic to veins Q8H administration	Inexpensive Easy to find Reliably covered Palatable Clinically studied	TID dosing	Penetrates CNS/CSF Studied for intravascular infection	Penetrates CNS/CSF	Covers MRSA reliably	High penetration Highly bioavailable Eagle effect/toxin inhibition	Penetrates CNS/CSF	TID dosing well tolerated and well absorbed	High penetration Highly bioavailable	Once daily dosing covers MRSA reliably	Covers MRSA reliably	Covers MRSA reliably
Notable disadvantages	Poor CNS/CSF penetration	QID or TID dosing	Not clinically well studied Hard to find, often not covered Expensive	Caustic to veins (best to use central line) Extravasations grade 3 Expensive Adverse effects common Q6H administration	Controversial for MSSA coverage	Less effective for MSSA vs beta-lactams Toxicity Need for levels	Unpalatable Expensive MSSA/MRSA susceptibilities variable	More frequent dosing Not active against MSSA	Not active against MSSA	May not be as effective in initial therapy or with abscess formation	Higher doses may result in CPK elevation	Lacking clinical and PK data in pediatrics for OAI ^s	Hematologic adverse effects with longer treatment durations
Organism ^a													
MSSA	+	+	+	+	+/-	+	+	0	0	+	+	+	+
MRSA	0	0	0	0	0	+	+/-	0	0	+	+	+	+
<i>Streptococcus pyogenes</i> (group A strep)	+	+	+	+	+	+	+	+	+	+/-	+	+	+
<i>Streptococcus pneumoniae</i>	+	+	+	+	+	+	+	+	+	+/-	+/-	+	+
<i>Kingella kingae</i>	+	+	+	+/-	+	0	ND	+/-	+/-	+	ND	+	ND
Adverse effects ^b (1)													

Continued

TABLE 3. (Continued)

	CEFZOLIN (IV)	CEPHALEXIN (PO)	CEFADROXIL (PO)	NAFACILLIN (IV)	CEFTRIAZONE (IV)	VANCOMYCIN (IV) (4)	CLINDAMYCIN (IV OR PO) (3)	AMPICILLIN (IV)	AMOXICILLIN (PO)	TRIMETHOPRIM-SULFAMETHOXAZOLE (PO)	DAPTOMYCIN (IV)	CEFTAROLINE (IV)	LINEZOLID (IV OR PO)
Bone marrow suppression	+	+	+	+	+	+	+	+	+	+	+	+	+
Drug fever	+/-	+/-	+/-	+/-	+/-	+/-	+/-	+	+/-	+/-	+/-	+/-	+/-
Nephrotoxicity	+/-	+/-	+/-	+	+	+	+/-	+/-	+/-	+	+/-	+	+/-
Elevated transaminases	+/-	+/-	+/-	+/-	+	ND	+	+	+/-	+	+/-	+/-	+
Laboratory tests to monitor for infection resolution and adverse effects (34)	CBC with diff, CRP or ESR, BMP	CBC with diff, CRP or ESR, BMP	CBC with diff, CRP or ESR, BMP	CBC with diff, CRP or ESR, BMP, LFTs	CBC with diff, CRP or ESR, BMP, LFTs	CBC with diff, CRP or ESR, BMP, vancomycin trough	CBC with diff, CRP or ESR, BMP, LFTs	CBC with diff, CRP or ESR, BMP, LFTs	CBC with diff, CRP or ESR, BMP	CBC with diff, CRP or ESR, BMP, LFTs	CPK, CBC with diff, CRP or ESR, BMP	CBC with diff, CRP or ESR, BMP	CBC with diff, CRP or ESR, LFTs

Other antibiotics may be indicated based on culture results. Generally, laboratory examinations are followed weekly but the interval depends on patient factors, antibiotic drug therapy, and route of administration. (34)
 All antibiotic drugs may cause Clostridium difficile colitis, rash, anaphylaxis, drug fever, drug-induced hypersensitivity syndrome, antibiotic drug-associated diarrhea, Stevens-Johnson syndrome, hives, and other reactions (see drug package details). Clinically, patients should be followed for signs of reactions as listed and for compliance and other complaints. Patients with central venous catheters should, in addition, be monitored for line infections, line patency and disruption, and skin reactions and infection at the insertion site. Adverse effects listed are the most common but do not represent all adverse effects.
 BID=twice daily, BMP=basic metabolic panel (blood urea nitrogen, creatinine, potassium, chloride, glucose, calcium), CBC=complete blood cell count, CNS/CSF=central nervous system/cerebrospinal fluid, CPK=creatinine phosphokinase, CRP=C-reactive protein, diff=differential count, ESR=erythrocyte sedimentation rate, ID=infectious diseases, IV=intravenous, LFT=liver function test (alanine aminotransferase, albumin, alkaline phosphatase, aspartate aminotransferase, direct bilirubin, total bilirubin, total protein), MIC=minimum inhibitory concentration, MRSA=methicillin-resistant Staphylococcus aureus, MSSA=methicillin-susceptible Staphylococcus aureus, OAI=osteoarticular infection, PK=pharmacokinetic, PO=oral, QID=four times per day, Q4H/Q6H/Q8H/Q12H/Q12-24H/Q24H=every 4/6/6-8/8/12/12-24/24 hours, TID=3 times daily.

^aFor organisms, + indicates active; +/-, variable; 0, not recommended; and ND, no data.

^bFor adverse effects, + indicates documented that it has been associated; +/-, few case reports, occurrence uncommon; and ND, no data.

experts treat children with documented bacteremia differently, requiring a set duration of intravenous therapy (usually 7–14 days). Patients with acute OAIs and transient bacteremia should not be treated differently than those without bacteremia because, by definition, all patients with acute hematogenous OAIs were at some point bacteremic. If bacteremia is prolonged (repeatedly positive culture after 24 hours of effective antimicrobial drug therapy), investigation for a significant undrained or necrotic source (large abscess), and/or an intravascular source (venous clot, endocarditis) should be considered, and a longer duration of intravenous therapy is justifiable. Patients with positive blood cultures should have cultures repeated every 24 hours until negative to ensure clearance of bacteremia, which is an indicator of control of the infection. For routine cases without persistent bacteremia, some institutions continue to treat intravenously for the entire course of therapy; this is no longer justifiable in most cases. (43)(44) A possible exception for prolonging intravenous therapy is when MRSA is the pathogen, although prolonging intravenous therapy often has more to do with associated complications and susceptibility patterns.

Unlike adults, children's bones are much more vascular, which simultaneously predisposes them to OAIs but also allows for successful oral therapy. The choice of oral therapy is driven by culture results and local susceptibility patterns (Table 3). (29)(30) Each oral regimen has notable drawbacks and advantages. Of particular mention is dosing of cephalalexin and cefadroxil because this is also an area of some controversy. All oral cephalosporins (and beta-lactam antibiotic drugs, for that matter) provide more killing time (time > minimum inhibitory concentration) if given in the maximum number of daily doses (eg, every 8 hours instead of every 12 hours). (45) However, clinicians must balance this greater bacterial killing time against concerns about patient compliance with more doses per day. For example, cephalalexin should be dosed at 100 to 150 mg/kg per day (maximum, 4,000 mg daily), optimally divided 4 times daily. This provides optimal killing time, an advantage particularly in treating bone infections. Depending on the minimum inhibitory concentration of the organism, it may be reasonable to administer cephalalexin divided 3 times daily for families who find 4 doses daily to be difficult to do. Cefadroxil, an alternative to cephalalexin, is used at some pediatric centers as a twice- or thrice-daily alternative. Compared with cephalalexin, there is less published clinical experience with cefadroxil, although the pharmacokinetic studies suggest a similar killing time compared with cephalalexin. For standard 500-mg oral doses, peak serum concentrations are 16 µg/mL for cefadroxil and 18 µg/mL for cephalalexin. Cefadroxil

has a longer half-life compared with cephalalexin (1.5 hours vs 1 hour) but higher protein binding (20% vs 10%). Thus, this drug may be considered for the oral phase of treatment of pediatric OAI with the caveats that it is less studied, has less accumulated clinical experience, and may be difficult to obtain. Dosing is also not well standardized, although recent guidelines and reviews suggest 120 to 150 mg/kg per day divided 3 times daily. (29)(46) The other oral cephalosporins are significantly inferior for MSSA and should not be chosen over cephalalexin or cefadroxil for oral therapy. Oral options for MRSA potentially include clindamycin, doxycycline, linezolid, and trimethoprim-sulfamethoxazole, but choice must be confirmed with susceptibilities.

In addition to coverage of *S aureus*, empirical *K kingae* coverage should be considered in children younger than 3 to 5 years. Because it is often diagnosed empirically, or by polymerase chain reaction, susceptibilities are often not available. Most *K kingae* strains are susceptible to penicillins, but 25% produce a narrow spectrum beta-lactamase. Cefazolin, cephalalexin, and cefadroxil all cover *K kingae* as well as MSSA. There is significant resistance to trimethoprim-sulfamethoxazole (25%), so empirically covering MRSA and *K kingae* with a single drug is difficult. (35)(36)(47) The fluoroquinolones are active against *K kingae* and some strains of MRSA but are not studied in pediatric OAIs and may be difficult to administer in pediatrics due to the associated dietary restrictions (eg, milk products), among other concerns. (48)(49)

Total length of therapy (intravenous plus oral) is another controversial topic. All children should be treated until they are clinically well and, preferably, until their acute-phase reactant levels have normalized. The CRP level is generally normal in 7 to 10 days, and ESR in approximately 3 weeks, except in more severe cases. (50)(51)(52) If the acute-phase reactant levels have not normalized in those time frames or begin to rise again after falling, complications should be considered. With future studies, these criteria alone may determine duration, but at this time the following minimum durations are recommended: 2 to 3 weeks for septic arthritis, 3 to 6 weeks for osteomyelitis, and 6 weeks for spinal osteomyelitis and neonatal infections. (5)(53) Shorter courses are described in reports from Finland (10 days for septic arthritis, 3 weeks for uncomplicated osteomyelitis), but these patients had uncomplicated disease and normalized acute-phase reactant levels, and none had MRSA. (54)(55) Some experts recommend longer durations for complicated cases (those with infection of >1 space) or for those with MRSA.

During therapy with antibiotic drugs, patients are at risk for related adverse drug events (ADEs). (41)(56)(57)(58)

These ADEs are most common in those treated intravenously and in the first few weeks of therapy. (57)(58) For those receiving intravenous therapy, monitoring for ADEs is advisable weekly, and for those taking oral antimicrobial drugs, it is advisable weekly for the first few weeks of treatment, then less frequently thereafter. (59) Monitoring should be tailored to the antimicrobial agent but may include a complete blood cell count for myelosuppression, a creatinine level for kidney injury, liver function testing for hepatitis, and acute-phase reactant levels for relapse or ADE-related inflammation. A clinical review should always be performed for diarrhea, nausea, rash, lymphadenopathy, mucous membrane changes, generalized joint swelling, new fevers, or clinical relapse of presenting symptoms. If a central line is present, line obstruction, accidental line removal, and line infections are additional risks. Over the course of therapy, up to 30% of patients with central lines will have a complication. (57)

OUTCOMES, SEQUELAE, AND FOLLOW-UP IMAGING

With appropriate treatment, most children will recover from acute hematogenous osteomyelitis without any long-term sequelae. However, multiple long-term problems may develop. Osteomyelitis that abuts or crosses the physis can cause physeal arrest, which may lead to growth disturbance with length discrepancy or angular deformity (Figs 2 and 3). With extensive involvement of the bone, pathologic fracture may occur and can mimic relapsed infection. Fractures can result in angular deformity of the bone, malunion, or nonunion. Septic arthritis can result in severe damage to the articular cartilage and, in rare cases, avascular necrosis of the involved bone. Both of these conditions may lead to early degenerative joint disease and the need for total joint arthroplasty early in life.

Although no consensus recommendations exist, it is common orthopedic practice to monitor OAI similarly to monitoring physeal or intra-articular traumatic fractures, with follow-up imaging to observe for potential sequelae. If not dictated otherwise by a particular surgery, monitoring should include radiographs of the involved bone at intervals of 3 and 6 months after the end of treatment for osteomyelitis. For infections that involve the physis, there should also be a repeated radiograph performed 1 year after treatment. For septic arthritis, these intervals also apply, but additionally there should be a radiograph obtained 2 years after treatment. For patients who develop angular deformity, the radiographs should include the entire extremity so that alignment is assessed. The goal of follow-up is to identify issues that can be corrected easily (eg, angular deformity,

leg-length discrepancy) while the patient is still growing. Once skeletal maturity is reached, the options available to correct these problems are limited and have a much higher degree of complexity and potential morbidity.

COMPLICATED OAIs

OAIs are considered complicated if there is infection in multiple locations, if infection is extensive and not amenable to source control, or if they involve more than 1 space in the infected area (eg, osteomyelitis and septic arthritis extending into the surrounding soft tissues or vasculature). In the United States, approximately 50% of patients have infection localized to a single space. (13) Infections of more than 1 space do not need to be treated differently provided source control is felt to be adequate and perfusion is not unusually impaired. Multispace infections do have slower decreases in the ESR, even with adequate treatment, which may indicate a need for slightly prolonged therapy.

Complex OAIs can lead to toxic shock syndrome, and if caused by *S aureus* (rather than *S pyogenes*), drainage of each source must be seriously considered for therapeutic purposes. Adolescents with staphylococcal sepsis can have a multifocal infection with no identified intravascular source of bacteremia. (60)(61) Lemierre syndrome (septic thrombophlebitis usually of the internal jugular vein) is another multifocal infection that often involves the musculoskeletal system and requires anaerobic coverage. (62)

SPECIAL SCENARIOS IN OAI

The diagnosis of acute hematogenous OAI is straightforward in most cases, and the causative organisms are somewhat predictable. However, unusual presentations may lead to the misdiagnosis of noninfectious etiologies as an acute OAI, or an unusual pathogen may erroneously be treated as a usual pathogen (Table 1).

Key history elements to obtain include travel, pets, certain foods, underlying illness, and sexual practices. For example, a child presenting with a swollen, red knee in an area where *B burgdorferi* is uncommon may be presumed to have culture-negative septic arthritis with a common pathogen, particularly if antibiotic agents are given before source sampling, instead of Lyme arthritis. A similarly presenting child may own a pet rat, implicating *Streptobacillus moniliformis*, or have a sexual history, implicating *Neisseria gonorrhoea*. Or they may have a history of rash, red eyes, and red lips, elevating the possibility of Kawasaki syndrome in the differential diagnosis. Exposures are also important clues in the diagnosis of endemic fungi, *M tuberculosis*, and *Brucella*

species, or certain viruses. Children initially diagnosed as having rheumatologic disease have turned out to have these pathogens, a scenario where synovial tissue for pathology and culture is particularly important, and serologies may be revealing. Underlying illness, such as sickle cell hemoglobinopathy or agammaglobulinemia, also necessitates the consideration of alternative pathogens.

Neonatal OAIs have 2 unique clinical presentations. The first is a mild presentation with pseudoparalysis that is easily mistaken as a brachial plexus palsy, resulting in a missed diagnosis. The second is a very ill picture in which the focal OAI may go unnoticed, and because the usual antibiotic drugs for “rule out sepsis” do not cover *S aureus*, there is a risk of delay in appropriate treatment.

OAI in unusual anatomical locations or with referred pain may also cause diagnostic difficulty. Symptoms in the pelvis, psoas, spine, feet, sternum, clavicle, ribs, and scapulae tend to present with vaguely localized or referred pain. For example, infection of the hip may refer pain to the knee, or infection of the sacroiliac joint may refer pain to the groin. Similarly, inflammation in a space, such as in synovial fluid, may be a sympathetic reaction to infection in a contiguous site (eg, pelvic osteomyelitis with a hip effusion). At its initial presentation, CRMO is not yet chronic, recurrent, or multifocal and, therefore, may be difficult to recognize. CRMO more often involves the pelvis and clavicle and is sometimes symmetrical. On radiographs, soft tissue edema is less frequent. Biopsy before antimicrobial drug therapy is extremely helpful in this situation because, by definition, CRMO will be culture negative, and the histology is typically one of chronic infection with a plasmacytic infiltrate and marrow fibrosis. The diagnosis of CRMO remains one of exclusion, but because it is often easily treatable, it is important to make with as much supporting information as possible.

Children with a diagnosis of OAI continue to be regularly admitted to the hospital for diagnosis and management, including initiation of prolonged antimicrobial drug therapy.

Although most of the clinical research is retrospective, we have nonetheless gained insight into improved methods of care during the past decade. Further research is needed to further define optimal diagnostics, antibiotic drug management, and length of therapy.

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Summary

- On the basis of strong evidence, children can safely be switched to oral therapy for the duration of treatment once discharge criteria are met, including afebrility, falling acute-phase reactant levels, clinical improvement, ability to tolerate oral medications, and existence of a reasonable oral option for therapy. There is usually not a need for placement of a central venous catheter for prolonged therapy.
- On the basis of strong evidence, source sampling will increase the percentage of children with a known bacterial cause of OAI by approximately 30%.
- On the basis of strong evidence, *Kingella kingae* and methicillin-resistant *Staphylococcus aureus* are extremely common pathogens for OAIs in some geographic areas.
- On the basis of moderate evidence, pathogen identification in osteomyelitis may reduce time on broad-coverage antibiotic agents and lead to shorter intravenous treatment durations.

References for this article are at <http://pedsinreview.aappublications.org/content/41/3/120>.

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1. Which of the following is more likely to be seen in a neonate with hematogenous osteomyelitis than in an 11-year-old with hematogenous osteomyelitis?
 - A. Involucrum.
 - B. Subperiosteal abscess.
 - C. Septic arthritis.
 - D. Sequestrum.
 - E. Unifocal osteomyelitis.
2. A previously healthy 20-month-old girl who lives in Kansas presents to the emergency department in February with a 2-day history of limp, and today she will not bear any weight on her right leg. Her mother states that her temperature last evening was 101.3°F (38.5°C). She had a viral upper respiratory infection a week ago. On examination she is somewhat fussy but consolable. Her temperature is 102.1°F (38.9°C). She cries with any movement of her right hip. There is no apparent swelling or erythema. She holds the right leg with her hip and knee flexed and her hip externally rotated. The remainder of her examination findings are normal. A complete blood cell count notes a normal hemoglobin level and platelet count, and her white blood cell count is 14,100/ μ L (14.1×10^9 /L). Her erythrocyte sedimentation rate is 55 mm/hr. Which of the following is the most likely diagnosis?
 - A. Lyme disease.
 - B. Osteoid osteoma.
 - C. Transient synovitis.
 - D. Septic arthritis.
 - E. Vertebral osteomyelitis.
3. A previously healthy 10-year-old boy is admitted to the hospital after being seen in the emergency department with a 2-day history of increasing left ankle pain and a 1-day history of fever. Today he will not bear any weight on his left leg. His brother has a history of recurrent methicillin-resistant *Staphylococcus aureus* skin infections that have been clindamycin resistant. The patient had a pustule on his chest that drained 5 days ago. A radiograph of his left ankle showed no abnormalities. He is alert and answers questions. His temperature is 103.2°F (39.6°C). His left ankle has moderate swelling and is tender to palpation primarily on the superior and medial aspects. The remainder of his examination findings are normal. Two blood cultures are pending. His C-reactive protein level is 190 mg/L (1,809 nmol/L). Orders are written for intravenous (IV) vancomycin and cefazolin. Which of the following is the most appropriate next step in management?
 - A. Add IV clindamycin.
 - B. Bone scan.
 - C. Combined positron emission tomography/computed tomography.
 - D. Computed tomography.
 - E. Magnetic resonance imaging (MRI).

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4. A fully immunized previously healthy 20-month-old boy who attends child care presents to the office with his mother due to concern of right shoulder pain and fever. Three days ago, his mother picked him up from under his arms when he awakened from a nap and he cried. His mother thought he had “slept on it funny” but then noted that he was not using his right arm as much. Yesterday he felt warm and his temperature was 100.5°F (38.1°C). He has continued to eat well. He was seen in the office 5 days ago with nasal congestion, and 2 oral ulcers were seen on examination. The family has no pets. He is afebrile in the office. On examination he cries with movement of the right shoulder. Ultrasonography of the right shoulder shows a mild to moderate joint effusion. He is admitted to the hospital. His C-reactive protein level is 24 mg/L (228 nmol/L), and his complete blood cell count is normal. Which of the following is the most likely pathogen?
- A. *Bartonella henselae*.
 - B. *Fusobacterium necrophorum*.
 - C. *Haemophilus influenzae*.
 - D. *Kingella kingae*.
 - E. *Streptococcus agalactiae*.
5. A 7-year-old girl was admitted to the hospital 7 days ago for right knee pain and fever. MRI on admission revealed proximal right tibial bone marrow edema and enhancement consistent with osteomyelitis but no apparent abscess. Admission blood cultures times 2 grew methicillin-susceptible *Staphylococcus aureus* (MSSA) that was resistant to clindamycin and susceptible to cefazolin, oxacillin, doxycycline, linezolid, and trimethoprim/sulfamethoxazole. A follow-up blood culture the day after admission also grew MSSA, but blood cultures 2 and 3 days after admission showed no growth. Due to persistent fever and knee pain with swelling on day 4 of hospitalization, a repeated MRI was performed and there was a subperiosteal abscess. She was taken to the operating room that day for open drainage of the abscess, and culture also grew MSSA. She has been afebrile the past 2 days, and her pain is markedly improved. Her C-reactive protein level was 83 mg/L (790 nmol/L) on admission and today it is 18 mg/L (171 nmol/L). She is eating well and tolerating a regular diet. On admission she was started on clindamycin and was changed to IV nafcillin the following day based on the blood culture polymerase chain reaction result noting MSSA, and she has continued receiving IV nafcillin. She has no drug allergies. Which of the following is the most appropriate next step in management?
- A. Change to IV ceftriaxone with home IV therapy to complete 8 weeks of treatment.
 - B. Change to oral cephalexin to complete 6 weeks of treatment as an outpatient.
 - C. Change to oral doxycycline to complete 6 weeks of treatment as an outpatient.
 - D. Continue IV nafcillin with home IV therapy to complete 8 weeks of treatment.
 - E. Continue IV nafcillin in the hospital to complete 2 weeks of treatment.

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