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Emergency Department Management Of Acute Hematogenous Osteomyelitis In Children

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Abstract

Acute hematogenous osteomyelitis has an annual incidence of approximately 2 to 13 cases per 100,000 persons in developed countries. It can be difficult to diagnose in pediatric patients due to the condition's often vague presentation. However, it is critical for the emergency clinician to be able to properly identify osteomyelitis, as it can have devastating consequences if left untreated. Because this is a relatively rare condition, there is limited evidence to guide the management, and there is a lack of standardized guidelines. In this issue, a systematic approach to the workup and treatment of a child who presents with possible acute hematogenous osteomyelitis is discussed. The most critical components of the history and physical examination, diagnostic studies, and treatment options are reviewed, including algorithms to guide management. Special populations are given consideration throughout the discussion, and management algorithms are provided.

Case Presentations

An 8-year-old boy with a history of sickle cell disease presents to the ED on a weekday afternoon because he could no longer keep up with his teammates during soccer practice. His mother is very worried and tells you that he is "not walking right." She had taken him to his pediatrician earlier in the week because of right leg pain and was told to give him ibuprofen as needed. As the week progressed, he has complained of increasing right leg pain, and later developed a limp. Today, he could not run with his teammates because the pain had worsened. His mother tells you that he felt warm on the way to the ED. The boy denies any trauma. He has not had any chest pain or pain elsewhere in his body, and the rest of his review of systems is negative. His physical examination is notable for a low-grade temperature and mild tachycardia. As he climbs onto the examination bed, you notice that he favors his left leg. He is tender to palpation over the distal aspect of his right femur with some swelling noted, and he begins crying as you palpate. He has full range of motion of his hips, knees, and ankles without any joint swelling or tenderness, and he has normal sensation and reflexes. The rest of his physical examination is normal, as well. You inform the patient and his mother that the differential diagnosis for this presentation is broad and further workup is needed. You tell her you will start with pain medication, x-rays, and blood work. As you think about all of the children you have seen with a limp, you narrow your differential diagnosis, considering the acute onset of this patient's symptoms and the focal nature of his pain. Aside from plain films and blood work, you consider what else will be helpful for his workup. What specific lab tests might help you to make a diagnosis? In addition to the x-ray, should you order a CT scan, bone scan, or an MRI? If this is an infectious process, what antibiotics should you choose? Is the fact that he has sickle cell disease related to this presentation?

A previously healthy 2-month-old girl is brought to the ED for "crying all the time" for the past 3 days. Initially, her mother was unsure why her daughter was crying so much, but now she thinks it happens every time she changes her diaper. She feels that the crying is due to some kind of pain. She checked a rectal temperature at home prior to presenting to the ED, and she recalled that it was 38.6°C. On taking further history, you learn that the infant was born vaginally, full-term, and that her mother had no complications during pregnancy or delivery. Of note, her mother is a nurse at your hospital. On physical examination, the patient's vital signs are notable for a fever to 38.9°C rectally. As you observe her lying on the examining table, you note that she is not moving her left leg. There is minimal swelling over her left calf, and she cries if you try to flex or extend her left knee. She has normal pedal pulses with good capillary refill. Her skin is intact, and the rest of her physical examination is normal. You inform her mother that you would like to perform some x-rays and order laboratory tests. As you think about her constellation of symptoms, you begin to form a differential diagnosis, likely with an infectious cause. What pathogens are likely to have caused this presentation? Is this related to her knee, and should you perform ultrasound on the knee joint? What are some other diagnoses you need to assess and rule out?

Introduction

Unrecognized osteomyelitis can have devastating consequences, such as sepsis, disruption of bone growth, and deformity.[1] To further complicate matters, presenting symptoms (including fever, irritability, or pseudoparalysis) can be nonspecific and difficult to localize.[2,3] These factors make it critical for every emergency clinician to be aware of when to suspect osteomyelitis and to know how to work up suspected osteomyelitis in children.

Acute hematogenous osteomyelitis (AHO) is defined as an infectious process in the bone lasting < 14 days. Chronic osteomyelitis, which occurs less commonly in children, is a process that lasts > 14 days, and is more often associated with trauma, foreign bodies, and neurologic disorders.[4] In a recent systematic review of 132 published articles, the incidence of osteomyelitis in developed countries was found to be 1.94 to 13 per 100,000.[1] The incidence has been reported to be higher in developing countries and in special populations. The highest reported incidence is among the Aboriginal peoples of Western Australia.[5] In the largest prospective population-based multicenter study in Norway, Riise et al followed 429 patients referred to the hospital for signs and symptoms consistent with osteomyelitis.[6] They found that the total annual incidence rate for acute osteomyelitis was 8 per 100,000 and that the incidence was higher for patients aged < 3 years. A review of multiple retrospective studies found the mean age to be 6.6 years old with a male-to-female ratio of 1.82:1.[7] The same review found that most cases of osteomyelitis had an unknown cause, though blunt trauma and recent systemic illness were noted to be significant risk factors in 29.4% and 37.4% of cases, respectively. It should also be noted that there is controversy regarding the incidence of osteomyelitis over time; some studies have reported a decrease, while others have reported an increase. Gillespie et al examined hospital data over a 17-year period (from 1965 to 1982) in 4 different countries (Australia, New Zealand, England, and Scotland) and found a significant decline in 4 of the 6 populations studied and no trend in the other 2 populations.[5] Blythe et al reported a decline in the incidence of acute and subacute osteomyelitis of 44% from 1990 to 1997 in children aged < 13 years.[7] In contrast, Malcius et al examined data over a 21-year period (from 1982 to 2003) and found an increase in the incidence of AHO among children in Lithuania.[8]

Osteomyelitis in children usually involves long bones, and the femur and tibia are the most commonly involved.[1] This condition can also occur in the pelvis[9] and vertebrae. Vertebral osteomyelitis should be considered as a differential diagnosis for any patient presenting with back pain. Certain populations, such as those with sickle cell disease, are at higher risk for osteomyelitis. All patients with sickle cell disease are at higher risk of various types of infection due to increased bone marrow turnover, poor perfusion, and functional asplenia.[10] Additionally, these patients tend to have prolonged and more severe osteomyelitis, partly due to microvascular disease and bone infarction.[11] They frequently have different causative pathogens and more commonly present with multifocal disease.[11,12] *Salmonella* species are the most common etiology of AHO in this population, but *Staphylococus aureus* and other enteric gram-negative bacilli are also important pathogens.

Evidence-based clinical practice guidelines for osteomyelitis are not only helpful to the emergency clinician, but also to every provider taking care of a child with osteomyelitis. This was recently highlighted in an article by Copley et al. This group developed and implemented clinical practice guidelines with input from several departments and services (including pediatrics, orthopedics, infectious disease, and social work). After implementation of the practice guidelines, patients had fewer antibiotic changes, a shorter hospital stay, and a lower readmission rate.[13]

Critical Appraisal Of The Literature

A systematic search of published literature from 1970 to June 2013 was undertaken using PubMed. The search was performed using the search terms *osteomyelitis, pediatric, bone infection, joint infection, hematogenous, sickle cell disease, imaging,* and *antibiotics.* Additional papers were identified through bibliographies of key studies. Over 100 articles were reviewed. Searching the Cochrane Database of Systematic Reviews using the key term *osteomyelitis* identified 1 relevant review.[14] The authors of this review attempted to determine whether an empiric antibiotic treatment approach was effective and safe compared to pathogen-directed treatment in this group of patients. The authors, were, however, unable to locate any trials on efficacy and safety, and we recommend that a randomized controlled trial should be undertaken to establish optimum antibiotic treatment. The Infectious Diseases Society of America has not published any clinical guidelines specifically for osteomyelitis; however, there is a guideline on treating prosthetic joint infections complicated by osteomyelitis.[15] The Infectious Diseases Society of America is currently developing a new practice guideline on vertebral osteomyelitis, which is projected to be published in the spring of 2014. The American Academy of Pediatrics has not published any guidelines for the diagnosis or treatment of osteomyelitis in children.

The most notable study relevant to an emergency clinician's perspective is the 2008 study by Riise et al.[6] This multicenter prospective trial followed 429 children and investigated important questions related to incidence, laboratory values, imaging, and other diagnoses for children referred to the hospital with suspected osteomyelitis. This study found that the incidence of osteomyelitis was highest in patients aged < 3 years, erythrocyte sedimentation rate (ESR) ≥ 40 mm/h was the laboratory marker with the highest positive predictive value, magnetic resonance imaging (MRI) had a positive predictive value of 85%, and blood culture was only positive in 26% of patients with AHO. One comprehensive systematic review published in 2012 is a meta-analysis that included 132 articles incorporating more than 12,000 pediatric patients.[1] This review yielded comprehensive information on symptoms, location, laboratory markers, imaging, etiology, and treatment. Forty percent of children were afebrile on presentation, the femur and tibia are the most commonly infected bones, *S aureus* is the most common pathogen detected, and ESR is the most common abnormal laboratory value in children with AHO. Other than this systematic review, the majority of clinical evidence for pediatric AHO falls into Classes III and IV, based on the National Institutes of Health classifications, as osteomyelitis is rare and often difficult to study. When available, recommendations in this issue are evidence-based. Accepted practice and expert consensus are explicitly noted.

Etiology And Pathophysiology

AHO is the most common type of osteomyelitis that occurs in children, while osteomyelitis caused by contiguous spread of infection or vascular insufficiency is more rare.[3,16] In cases of AHO, once the bacteria are in the bloodstream, they most often seed the metaphysis of a particular bone because of the rich blood supply. Bacteria are then able to adhere to the cartilaginous matrix of bone, causing local inflammation.[16] Bacteria are able to express receptors for components of the bone matrix. The body's immune system utilizes phagocytes to contain the infection and, in the process, releases proteolytic enzymes that lyse the surrounding tissue. Once the pus spreads into vascular channels, it can impair blood flow and cause ischemic necrosis of bone.[17] The pus may also separate the diaphysis from the periosteum, causing an abscess within the periosteal space.[3] **(See Figure 1, page 4.)**

In their comprehensive review of 132 articles, Dartnell et al found that the femur and tibia were

the most common sites of infection, with an incidence of 26.9% and 26.0%, respectively.[1] They also determined that the most commonly affected bone in the upper extremity is the humerus.[1,3] In 2005, Gonzalez et al examined records of patients admitted to the PICU with community-acquired *S aureus* over an 18-month period. Of the 14 patients requiring admission for severe sepsis, 10 patients had ≥ 2 bones or joints infected.[18] Blood cultures are positive in < 50% of cases, and pus or tissue cultures are positive in 65% to 75% of the cases.[1]

The most frequent cause of AHO is *S aureus*.[1,3,17] In a 2008 retrospective study of 290 children admitted with AHO, Saavedra-Lozano et al isolated bacteria in 55% of cases and found that methicillin-sensitive *Staphylococcus aureus* (MSSA) accounted for 45% of the bacteria and methicillin-resistant *Staphylococcus aureus* (MRSA) accounted for 23% of the isolated bacteria.[19] Furthermore, when the study was broken down into 2 different time periods, the authors found that the incidence of MRSA had increased from 6% to 31%, while the incidence of MSSA had decreased from 57% to 40%. It is important to note that some forms of MSSA and MRSA also secrete a necrotizing toxin called Panton-Valentine leukocidin (PVL).[20] PVL-positive bone and joint infections are associated with more-severe infections requiring prolonged treatment and often repeat surgical therapy.[21]

According to post-1996 data, after *S aureus*, the next most common causes of AHO are *Streptococcus spp, Kingella kingae,* and *Staphylococcus epidermidis*.[1] In a prospective study of children aged < 4 years, Ceroni et al followed 43 patients with osteoarticular infections over a 2-year period. Bacteria were isolated in 28 patients, and 23 of these (82.1%) were found to be *K kingae*.[22]

There are certain populations for which the emergency clinician must consider the differential of pathogens that may be the cause of osteomyelitis. For example, although the *Haemophilus influenzae* type B (Hib) vaccine has made a dramatic impact in reducing osteomyelitis caused by Hib,[23] this is an important pathogen to consider in unvaccinated children and neonates. For a detailed list of the most important pathogens in each age group, see **Table 1.**

For patients with sickle cell disease, *Salmonella* species are the most commonly isolated pathogens, found more than twice as often as *S aureus*.[12] One hypothesis as to why these patients are at particu-

Figure 1. Hematogenous Osteomyelitis Of A Tubular Bone In A Child

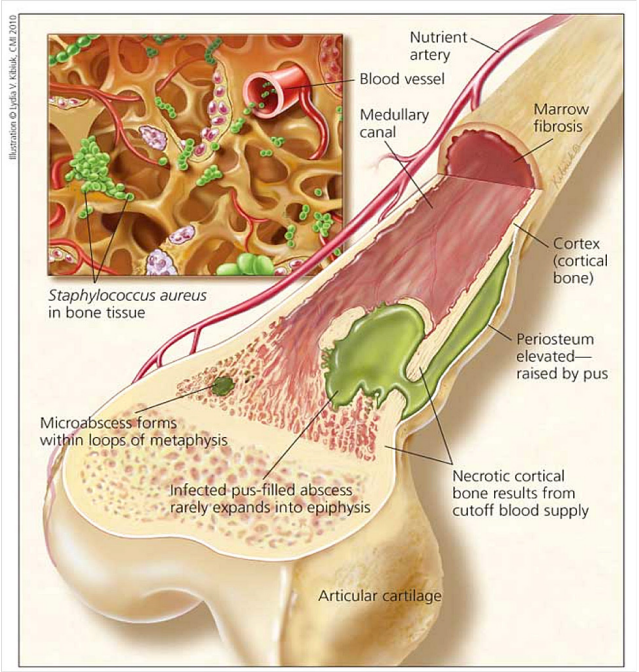

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Table 1. Most Common Etiologies Of Acute Hematogenous Osteomyelitis, By Age Group

Infectious Cause	Recommended Antibiotics
Neonates and Young Infants (Aged Birth to 3 Months)	
• *S aureus* • *Escherichia coli* and other gram-negative rods • Group B streptococci • *Haemophilus influenzae*§	MSSA* versus MRSA† coverage plus cefotaxime (Claforan®)
Young Children (Aged 3 Months to 5 Years)	
• *S aureus* • *Kingella kingae*‡ • *S pyogenes* (group A streptococci) • *Streptococcus pneumoniae* • *Haemophilus influenzae*§	MSSA* versus MRSA† coverage
Older Children and Adolescents (Aged > 5 years)	
• *S aureus* • *S pyogenes* (group A streptococci)	MSSA* versus MRSA† coverage

*MSSA coverage consists of any 1 of the following antibiotics: oxacillin (Bactocill®), nafcillin (Nallpen®), cefazolin (Kefzol®, Ancef®), ampicillin-sulbactam (Unasyn®), or clindamycin (Cleocin®).

†MRSA coverage consists of any 1 of the following antibiotics: clindamycin, vancomycin (Vancocin®), linezolid (Zyvox®), or daptomycin (Cubicin®), though local antibiotic susceptibility patterns should be taken into account.

‡Empiric coverage of *K kingae* is controversial and should be considered on a case-by-case basis. Choosing a second- or third-generation cephalosporin (such as cefuroxime [Ceftin®, Zinacet®], cefotaxime, or ceftriaxone [Rocephin®]) or ampicillin or ampicillin-sulbactam, however, provides MSSA coverage as well as coverage of *K kingae*.

§*Haemophilus influenzae* should especially be considered in unvaccinated children.

Abbreviations: MRSA, methicillin-resistant *Staphylococcus aureus*; MSSA, methicillin-sensitive *Staphylococcus aureus; S aureus, Staphylococcus aureus; S pyogenes, Streptococcus pyogenes.*

lar risk of contracting gram-negative enteric bacilli is that there may be intravascular sickling of the bowel vasculature leading to ischemia/infarction and mucosal barrier breakdown, predisposing these patients to bacteremia. A systematic review by Burnett et al examined 9 studies of the etiology of osteomyelitis in patients with sickle cell disease and found that the ratio of gram-negative bacilli to *S aureus* was 2.9:1.[12]

Fungal species are also known to cause AHO. *Coccidioides immitis* can affect immunologically normal hosts, and should be considered in patients who live in or have traveled to areas where the fungus is endemic (American southwest and northern Mexico).[24] *Histoplasma capsulatum* can also cause osteomyelitis, but is generally restricted to patients with a cell-mediated immunodeficiency.[3] Vertebral osteomyelitis due to *Pseudomonas aeruginosa* has been associated with intravenous drug abuse, and *Brucella spp* (contracted from consuming contaminated meat or dairy products) can result in bacteremia and vertebral osteomyelitis. Although uncommon, tuberculosis can also cause osteomyelitis.[25] Osteomyelitis has been confirmed in case reports of patients given the BCG vaccine.[26]

Differential Diagnosis

Since the presenting signs and symptoms of AHO are often vague and nonspecific, the emergency clinician must be aware of and consider a workup that includes the myriad of other etiologies of musculoskeletal pain in children. Trauma is one of the most common reasons for pediatric patients to present to the emergency department (ED),[27] with sprains, fractures, and dislocations high on the list of differential diagnoses. In the absence of known trauma, the acute presentation of musculoskeletal pain has a much broader differential.

In the largest prospective study to date, Riise et al examined pediatric patients referred to a hospital pediatric or rheumatology department with pain that was < 6 weeks in duration and not caused by trauma.[6] Other inclusion criteria were 1 or more of the following: (1) joint swelling; (2) limited range of motion or limp; (3) joint pain with an elevated ESR, C-reactive protein (CRP) level, or white blood cell (WBC) count. Of the 429 children included in the study, only 37 (8.6%) had osteomyelitis. The most common diagnoses were transient arthritis (25.4%), transient limp (9.8%), and juvenile idiopathic arthritis (9.3%). Of note, 4.4% of patients were found to have a skin infection, and 1.6% were found to have septic arthritis. Other "cannot miss" differential diagnoses include abscesses and malignancies. A more complete list is presented in **Table 2.**

Prehospital Care

Children may be transported by prehospital personnel to an ED after evaluation by primary care physicians or from other EDs and when additional resources are needed to diagnose the cause of the symptoms. The initial workup can be started prior to the patient's arrival at the hospital, and referring clinicians can note specific portions of the workup that were started in their clinic or hospital. The top priority is maintaining the patient's airway, bacteremia, sepsis, or with multiple sites of osteomyelitis and sepsis, or with multiple sites of osteomyelitis, can become very ill, hemodynamically unstable, and require admission to the pediatric intensive care unit (PICU), although this is rare.[28] In cases where there are signs of shock, intravenous access and fluid resuscitation should be initiated. If the patient has significant pain, but is stable, pain control should be administered en route to the ED.

Once these issues are addressed, it is important to expedite the patient's arrival to the ED, as they may need advanced imaging and antibiotics, which should be delivered in a timely manner.

Table 2. Differential Diagnosis Of Acute Osteomyelitis

Infectious	**Neoplasm**
• Cellulitis	***Benign***
• Septic arthritis	• Osteoid osteoma
• Subcutaneous abscess	• Eosinophilic granuloma
• Iliopsoas abscess	• Chondroblastoma
• Cat scratch disease	• Unicameral bone cyst
• Chronic nonbacterial osteomyelitis	• Aneurysmal bone cyst
• Discitis	***Malignant***
• Pyomyositis	• Osteosarcoma
• Reactive arthritis	• Ewing sarcoma
• Rheumatic fever	• Neuroblastoma
• Lyme disease	• Acute lymphoblastic leukemia
• Toxic synovitis	• Acute myeloblastic leukemia
Musculoskeletal	**Hematologic**
• Accidental trauma	• Bone infarction (patient with hemophilia or sickle cell disease)
• Nonaccidental trauma	
• Osgood-Schlatter disease	
• Fracture	**Neurologic**
• Soft-tissue injury	• Complex regional pain syndrome
• Joint hypermobility syndrome	• Neuromuscular pain
• Slipped capital femoral epiphysis	**Rheumatologic**
• Legg-Calvé-Perthes disease	• Myositis
Genetic	• Juvenile idiopathic arthritis
• Gaucher disease	• Polyarteritis nodosa
	• Systemic lupus erythematosus
	• Henoch-Schönlein purpura

Emergency Department Evaluation

History

Pediatric patients with AHO generally present with fever and localized pain, swelling, and loss of limb function though, across all age groups, no single sign or symptom is pathognomonic of the disease. Additionally, being unable to obtain a reliable history in preverbal pediatric patients increases the challenge of making this diagnosis. The age of the patient and the location of the infection are relevant for discovering signs and symptoms. Loss of function can present as refusal to move a limb (pseudoparalysis) in infants and neonates or as a limp in toddlers and older children. Fever is found in 40% to 66% of patients,[1,29-31] and Dartnell et al's meta-analysis of over 12,000 patients suggested a 61% sensitivity of fever. When present, fever is usually low-grade, but a small minority of patients may have fever > 39ºC.[31]

Localizing symptoms (including pain, decreased movement of an extremity, or limp when lower extremity bones are involved) are found in a majority of patients (between 56% and 94% in various observational studies).[1,29-31] The reliability of such symptoms depends on the patient's age. Localizing signs may also be completely absent in AHO. Patients may present only with malaise and fever of unknown origin, or, in infants, irritability and decreased oral intake. Vague and nonspecific complaints are especially common in pelvic osteomyelitis, resulting in delayed diagnosis and significant morbidity.[9,32] In a recent review of 146 cases of pelvic osteomyelitis reported since 1966, Zvulunov et al found that a delay in diagnosis resulted in permanent disability in 3.4% of cases.[32] The correct diagnosis, on average, was delayed 12 days.

If there is a history of trauma and a wound, the patient's vaccination records should be reviewed. It is especially important to focus on tetanus, as the patient may need a tetanus vaccine and/or administration of tetanus immune globulin. It is also important to confirm that the child is vaccinated against *Pneumococcus* and Hib, as these are known pathogens that can cause AHO. Since most vaccination records are kept with the primary care provider, remember to ask the provider to review the vaccination history if they are calling with a referral.

A focused history of the symptom time course typically reveals several days to 1 week of worsening symptoms, although some patients present up to 14 days after onset.[29,30,33] A more prolonged course of symptom development may suggest subacute or chronic osteomyelitis, such as that caused by fungi and mycobacteria. Recent travel or exposure to a person with tuberculosis is indicative of this etiology. Night sweats or weight loss may suggest malignancy. When coupled with a travel history or exposure to tuberculosis, this may suggest an etiology of tuberculosis.

Emergency clinicians should determine whether there is a history of trauma in patients, as fracture and soft-tissue injury are often on the differential diagnosis of AHO. A history of blunt trauma at the site of osteomyelitis, however, is surprisingly common, and has been seen in 17% to 29% of patients.[1,32] This suggests that blunt trauma of bone tissue predisposes bone to hematogenous infection. A study by Morrissy and Haynes introduced *S aureus* into the bloodstream of a group of rabbits that had undergone trauma designed to cause fracture of the epiphyseal plate of a leg bone and introduced the pathogen to another group of animals that had not undergone any trauma.[34] In the animals that underwent both trauma and induced bacteremia, 94% developed osteomyelitis that was often extensive, and 100% of the animals developed osteomyelitis when a higher dose of bacteria was injected intravenously. Those animals with introduced bacteremia but no antecedent trauma experienced a significantly lower incidence of osteomyelitis, and, when it did occur, histological analysis of the bone showed foci of osteomyelitis that were usually localized and confined by the inflammatory reaction. A study by Kabak et al showed similar results.[35] These studies suggest that trauma predisposes bone tissue to being seeded by hematogenous organisms and may explain why trauma is so commonly seen preceding osteomyelitis.

Other relevant historical points that may impact the choice of empiric antibiotics for treatment include a history of immunodeficiency, vaccination status, hemoglobinopathy (such as sickle cell disease), previous history of MRSA infections, or other risk factors of infection with MRSA.

Physical Examination

A careful physical examination should be performed. Vital signs often show fever as well as tachycardia caused by the fever and/or pain. The examination should focus on the musculoskeletal system in the area of symptoms. Palpate for localized tenderness and check the range of motion of all joints, especially above and below the area of perceived pain. Soft tissue overlying a bone infection will demonstrate signs of inflammation (including erythema, swelling, and focal tenderness) in roughly half of cases.[29-31] Examine the skin for puncture wounds or evidence of trauma and palpate for localized tenderness or bony deformities that may suggest contusion, sprain, or fracture. Pathologic fracture secondary to infection is uncommon; however, a case of AHO presenting with fracture has been documented.[36] Examine the joint immediately above and below the painful area, as osteomyelitis in children presents with adjacent septic arthritis in one-third of cases.[37] Spread of the infection into the

adjacent joint space is especially common in younger children. The physical examination may disclose a swollen, painful leg with a palpable cord, suggesting deep venous thrombosis of the lower extremity with or without septic pulmonary emboli.[38-40]

In neonates, emergency clinicians must rely more on examination and the history provided by caregivers to assess the patient. In this population, osteomyelitis is often multifocal; therefore, a full musculoskeletal examination should be performed.[16] Observe the extent to which the infant uses each limb and assess for lethargy and the infant's overall muscle tone. Assess the range of motion of all joints and palpate carefully along all long bones, ribs, pelvis, and spine to locate tenderness or warmth.

Point tenderness along the spinous processes of the neck or back suggests vertebral osteomyelitis. Pelvic osteomyelitis can present with vague and poorly localizing symptoms. Emergency clinicians should have a high level of clinical suspicion for pelvic AHO in patients with constitutional symptoms and complaints of hip or buttock pain.

Diagnostic Studies

The initial workup should include a WBC count with differential, ESR, CRP, and a blood culture. X-rays, if available, are often useful to exclude trauma. These diagnostic studies can be completed prior to the patient's arrival in the ED, if the equipment is available, as this may expedite care. Vascular access should be obtained, as the patient may need antibiotics and parenteral pain medication.

Peripheral Blood Investigations

There is no blood test that is completely sensitive or specific for osteomyelitis; however, investigation of peripheral blood markers of systemic inflammation is essential in the workup. These include WBC count with differential, ESR, and CRP. At least 1 blood culture should be sent, but preferably 2, in order to increase the yield. ESR and CRP are most useful, as these have been found to be elevated in 73% to 100% and 70% to 100% of patients, respectively.[1,16,28,30,32,33,41] CRP is generally more sensitive than ESR, as CRP rises more quickly with acute inflammation than ESR and can more reliably demonstrate early infection.[3,41] WBC count is the least helpful of the inflammatory markers, with a sensitivity of 34% to 43% in AHO.[1,29,31,41] It should be noted that a left-shifted WBC differential may be seen in osteomyelitis,[30] and, when present, a left shift should raise suspicion for infection.

Higher levels of inflammatory markers have been associated with concomitant septic arthritis,[1] abscess formation, and pyomyositis,[42,43] as well as a more complicated disease course.[44] Once antibiotics are started, inpatient clinicians commonly follow ESR and CRP levels to monitor the response to therapy. CRP usually normalizes faster than ESR. One common strategy is to transition from intravenous to oral antibiotics when there is clinical improvement and normalization of CRP, and to stop oral antibiotics when ESR has normalized.[44] For this reason, it is important to draw these laboratory studies before initiation of therapy. A blood culture should also be drawn in patients with possible musculoskeletal infections, especially those with fever.

Other laboratory values can aid in narrowing the diagnosis. In patients presenting with localized inflammation and fever, it is often difficult to differentiate between arthritis, myositis, cellulitis, fasciitis, or osteomyelitis. An elevated creatinine kinase (CK) level (also known as creatinine phosphokinase [CPK]) suggests muscle inflammation or breakdown. If joint involvement is suspected, consider testing for sexually transmitted infections or Lyme antibodies (in endemic regions). Joint fluid should be sent for cell count with differential as well as Gram stain and culture. Consideration should be given to sending the joint fluid for polymerase chain reaction (PCR) testing for *K kingae* if PCR testing is available and the testing is warranted by clinical suspicion.

Imaging Studies

X-Ray

Plain radiographs are the initial imaging modality of choice in febrile patients with localized tenderness on examination. Radiographs can show nonspecific soft-tissue edema, with bone changes seen in 15% to 58% of patients with AHO.[1,2,30,45] It should be noted that radiographs have even lower sensitivity in pelvic osteomyelitis.[31,42] Bone changes on x-ray suggest substantial bone destruction, which typically occurs 1 or more weeks after the onset of infection.[3,16,46] An example of a positive radiograph is seen in **Figure 2 (page 8).** Bone changes shown by radiography can include periosteal elevation and new periosteal bone formation, with lytic lesions appearing later in infection.[30] Positive bone changes on x-ray are 80% to 100% specific for osteomyelitis and should prompt further workup and imaging.[1] Keep in mind that a negative study does not rule out the diagnosis of osteomyelitis. A study of x-rays performed on the 15th day of hospitalization for pediatric patients (ie, late in the course of disease) found them to be 82% sensitive and 92% specific.[45]

Ultrasound

Circumferential ultrasound of a painful long bone may be useful in the workup of AHO. Though ultrasound has low sensitivity and specificity for the diagnosis of osteomyelitis (55% and 47%, respec-

tively, in 1 study[45]), it is a safe, fast, and inexpensive imaging modality that may be able to detect soft-tissue and subperiosteal abscesses as well as adjacent joint effusions.[1,33,47,48] **(See Figure 3.)** It is also useful in guiding drainage, when indicated. Ultrasound can simultaneously diagnose deep vein thrombosis, a known (but uncommon) complication of severe osteomyelitis.[39] It has also been shown to assist with the diagnosis of pelvic osteomyelitis by demonstrating abscesses.[48]

Bone Scan

A technetium-labeled (99mTc) bone scan is 53% to 100% sensitive for AHO and can demonstrate infection early in the course of the disease.[1,29-31,45] One study found a specificity of 84%.[45] Bone scans are useful in localizing the source of infection in patients presenting with poorly localized symptoms.[43,49,50] This is especially useful in small children and in pelvic osteomyelitis, where pain is often referred to the hip or upper leg.[32] However, bone scans have poor resolution and cannot delineate fluid collections or other complications of AHO. Furthermore, false-positive results can occur with trauma, soft-tissue infection, malignancy, arthritis, and increased uptake in physeal cartilage, which can be a normal finding in younger children.[35,46]

Magnetic Resonance Imaging

MRI has become the gold standard of imaging for AHO, especially early in the disease course. Compared to bone scan, MRI has much better resolution of bone and soft tissue and can demonstrate cortical destruction, bone marrow edema, muscle edema, and abscesses.[51] MRI can demonstrate the extent of soft-tissue and bony involvement as well as the presence of nearby septic arthritis.[43,52] Dartnell et al reviewed 132 articles on AHO and found that MRI is 80% to 100% sensitive for osteomyelitis.[1] Several other studies found MRI to have a sensitivity of 81% to 100% and a specificity of 67% to 100%,[45,48,51] making MRI the best imaging modality for detecting and ruling out AHO.[53] The disadvantages of this modality, however, include its high cost and the potential need for sedation of the patient. There is no consensus in the literature on indications for using MRI to assess AHO in children.

Computed Tomography

Computed tomography (CT) scans have limited usefulness in assessing AHO.[2,9,36] CT can demonstrate bony destruction with high spatial resolution;[46] however, in a study by Kaiser et al, these findings were

Figure 2. Brodie Abscess

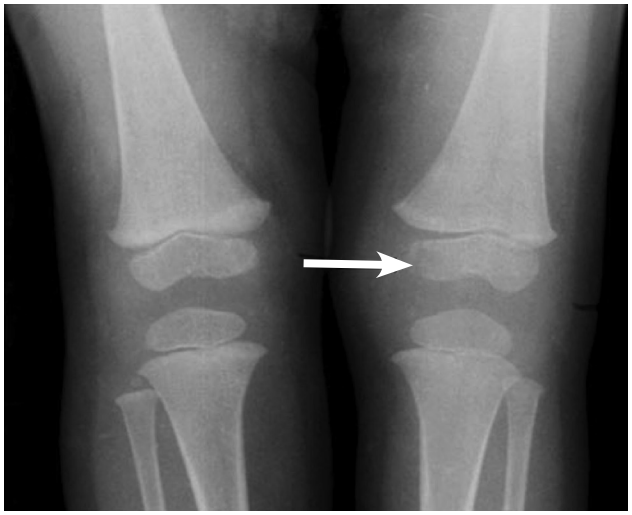


Image shows a Brodie abscess in an afebrile 20-month-old child with a history of a 3-week limp and normal erythrocyte sedimentation rate and C-reactive protein level. White arrow points to subtle lytic lesion of the medial aspect of the distal left femoral epiphysis.

Springer and *Pediatric Radiology,* Volume 43, 2012, page S196, Osteomyelitis and Beyond, R. Paul Guillerman, figure 6a, with kind permission from Springer Science and Business Media.

Figure 3. Ultrasound Scan Of Subperiosteal Abscess

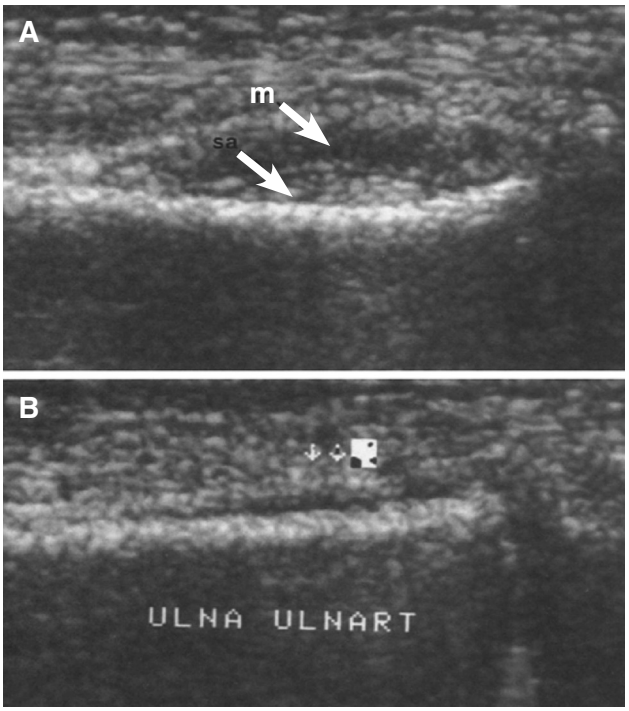


Image shows a subperiosteal abscess in the left distal ulna of a boy aged 2 years. A moderately highly echogenic area is visible in the posterior part (View A) and a small slightly echogenic fluid collection is visible in the medial part (View B). There is swelling of the adjacent muscle layer (m).

Springer and *Pediatric Radiology,* Volume 24, 1994, page 338, Early Detection of Subperiosteal Abscesses by Ultrasonography: A Means for Further Successful Treatment in Pediatric Osteomyelitis, S. Kaiser, figures 5a, 5b, with kind permission from Springer Science and Business Media.

seen on CT only in cases in which bone changes had been seen initially on conventional radiographs.[48] As mentioned, these bone changes are not common in early infection when most patients present to the ED. CT scans can also demonstrate deep soft-tissue edema as well as abscesses and bone sequestra and involucra, which may require surgery. This modality, however, is only 67% sensitive and 50% specific for AHO.[45] CT exposes children to significant radiation, and emergency clinicians should work with radiologists to use weight-based dosing so that exposure is as low as reasonably achievable. CT may be most useful when MRI and bone scan are not available.

Special Diagnostic Considerations

Emergency clinicians often face the dilemma of which imaging modality to utilize, after plain radiography, when osteomyelitis is on the differential. Bone scan, CT scan, and MRI all have benefits and drawbacks, and the decision must be based on the individual characteristics of the case. It is important to remember that no imaging modality is 100% sensitive for the diagnosis of osteomyelitis and both MRI and bone scan can lead to false negatives. For instance, while MRI is often noted in the literature to be more sensitive than bone scan, a recent case report demonstrated that a bone scan detected AHO in the distal tibia of a 9-year-old girl, while an MRI that was performed the same day was negative.[54]

While bone scans expose patients to ionizing radiation, they give emergency clinicians a very sensitive imaging modality that is cheaper and quicker than MRI and does not require sedation. Also, unlike MRI, bone scans can image the entire body, making them useful in finding multifocal or distant osteomyelitis, or those infections with referred symptoms. An algorithm for choosing imaging modalities is presented in **Clinical Pathway For Workup Of Suspected AHO (page 10).**

In a study by Connolly et al, the use of bone scan and MRI was evaluated in 213 children with possible osteomyelitis.[49] Bone scan provided adequate imaging to diagnose 92% of osteomyelitis cases, and, in all patients with uncertain diagnoses after bone scan, MRI did not alter management. Furthermore, a suspected diagnosis of AHO based on bone scan was refuted by MRI in only 1 case. Connolly et al recommended using bone scan for the initial imaging of suspected osteomyelitis, with MRI reserved for cases that are slow to respond to therapy. In certain situations, however, MRI should be used initially, including cases of suspected pelvic osteomyelitis, as these patients often present with nonspecific symptoms and frequently have abscesses in need of drainage.[9,29,32,49] A case can be made that MRI should be used initially in very ill children and in children with highly elevated inflammatory markers, as these have been associated with abscess and other complications. MRI is not necessary in all cases of osteomyelitis, even if it is readily available, as bone scan together with ultrasound may provide adequate information to initiate treatment. More research is needed to identify the optimal choice of imaging in acute osteomyelitis.

Microbiologic Studies

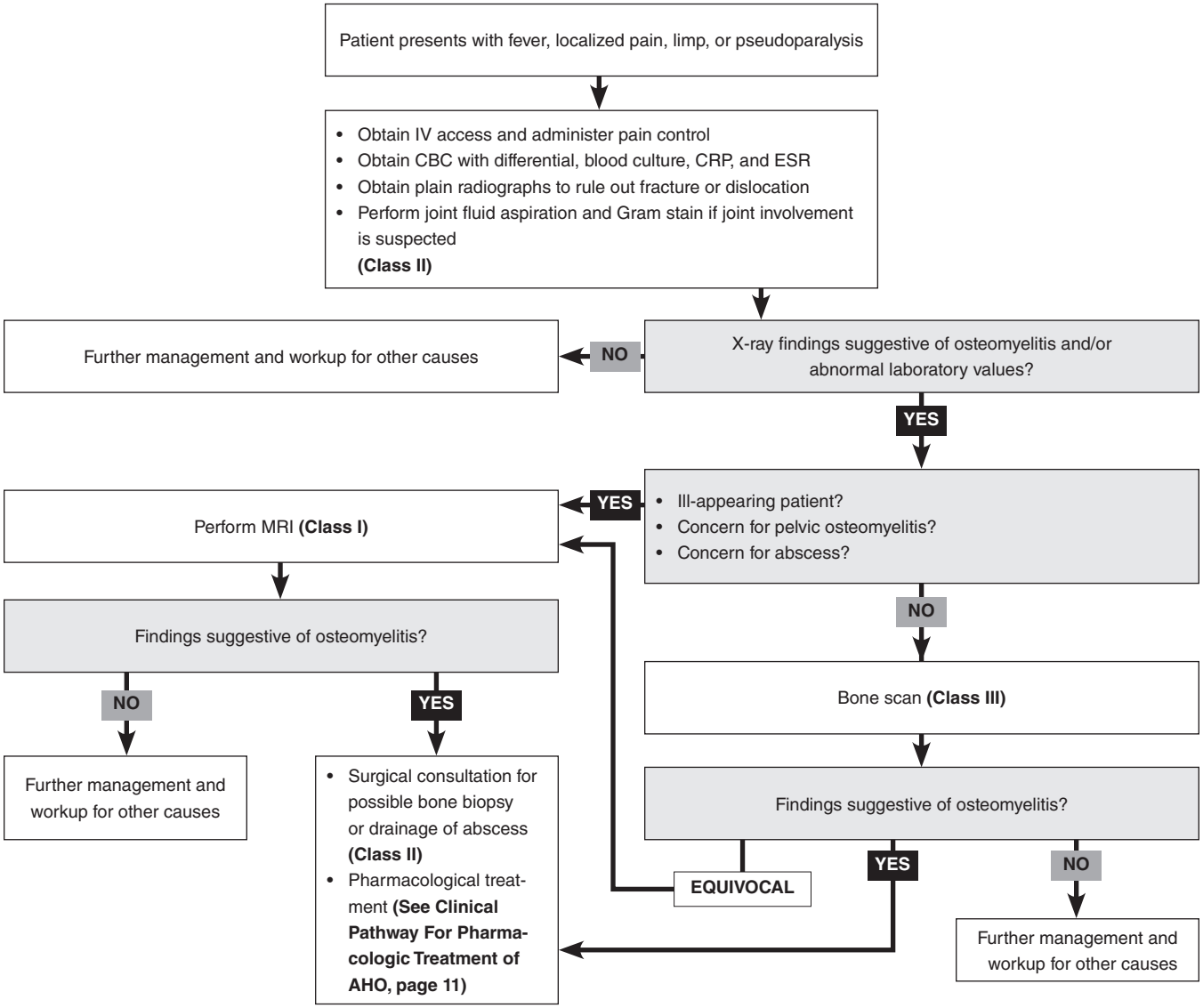
Microbiologic diagnosis in osteomyelitis is extremely useful for determining long-term antibiotic treatment choices, and every attempt should be made to obtain a tissue sample for culture before initiating empiric antibiotic treatment. A causative pathogen is discovered from blood culture in roughly one-quarter to one-half of patients,[1,29,30,32,33,55] and the yield may be higher from blood cultures drawn in febrile children. Bone tissue culture is the most helpful for microbiologic diagnosis, being positive in 82% to 100% of patients.[30,33] Obtaining a sample of infected bone is optimal before starting antibiotic therapy; however, in a child with signs of severe sepsis or septic shock, empiric antibiotics should be administered as rapidly as possible. If pus is obtained from collections or from the bone itself, the chances of a positive culture are higher. Timely consultation with orthopedic or general surgery services will facilitate tissue diagnosis and drainage or debridement, if necessary. Coordinating care between the ED, surgical services, and radiologists increases the number of patients who successfully have bone tissue sampled before initiation of antibiotics.[14]

In addition to peripheral blood samples, the etiologic microbe can, potentially, be cultured from any of the following sources: bone, drainage from soft tissue and periosteal collections, and/or joint aspiration if concomitant synovitis is found. In technically difficult areas of the body (such as the pelvis and the spine), it may be challenging to obtain a sample of bone prior to initiating antibiotics. Furthermore, interventional radiologists and surgeons may be reluctant to biopsy a vertebral body in a young pediatric patient. PCR testing of a bone sample may be useful for diagnosing infections caused by *K kingae*, a common etiology of septic arthritis and a less common cause of osteomyelitis.

Treatment

The choice of empiric antibiotics should be made based on the most common etiologic organisms given the patient's demographics, medical history, and risk factors, as well as local antibiotic resistance patterns. Familiarity with an individual hospital's antibiogram is useful. Gram stain from drained and sampled material can be useful, providing prompt information regarding possible etiologies and choice of antibiotic therapy while awaiting culture results. After an adequate sample of bone tissue is acquired, intravenous antibiotics should be started. The most

Clinical Pathway For Workup Of Suspected Acute Hematogenous Osteomyelitis



Abbreviations: AHO, acute hematogenous osteomyelitis; CBC, complete blood count; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; IV, intravenous; MRI, magnetic resonance imaging.

Class Of Evidence Definitions

Each action in the clinical pathway section of *Pediatric Emergency Medicine Practice* receives a score based on the following definitions.

Class I
- Always acceptable, safe
- Definitely useful
- Proven in both efficacy and effectiveness

Level of Evidence:
- One or more large prospective studies are present (with rare exceptions)
- High-quality meta-analyses
- Study results consistently positive and compelling

Class II
- Safe, acceptable
- Probably useful

Level of Evidence:
- Generally higher levels of evidence
- Non-randomized or retrospective studies: historic, cohort, or case control studies
- Less robust randomized controlled trials
- Results consistently positive

Class III
- May be acceptable
- Possibly useful
- Considered optional or alternative treatments

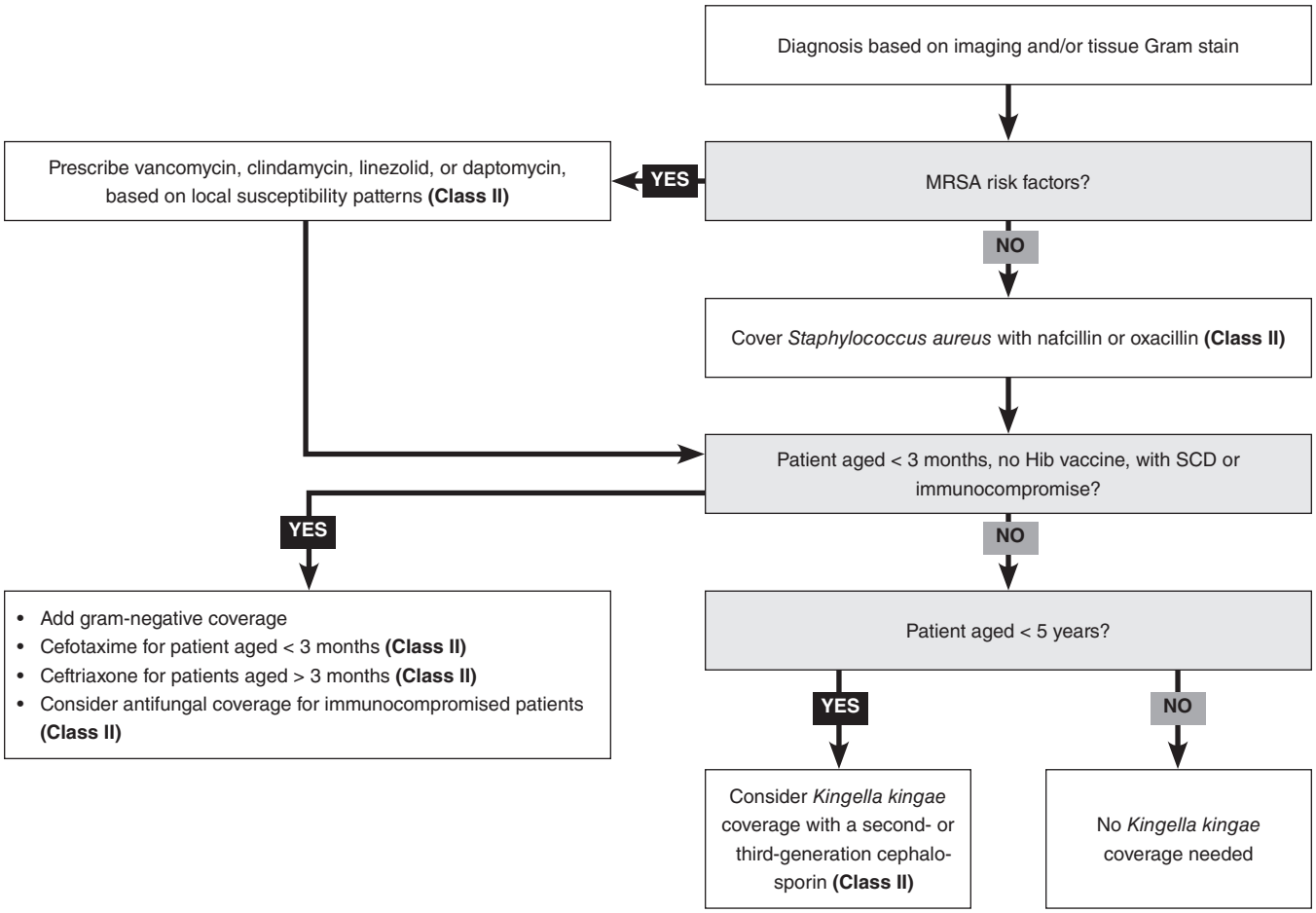
Level of Evidence:
- Generally lower or intermediate levels of evidence
- Case series, animal studies, consensus panels
- Occasionally positive results

Indeterminate
- Continuing area of research
- No recommendations until further research

Level of Evidence:
- Evidence not available
- Higher studies in progress
- Results inconsistent, contradictory
- Results not compelling

This clinical pathway is intended to supplement, rather than substitute for, professional judgment and may be changed depending upon a patient's individual needs. Failure to comply with this pathway does not represent a breach of the standard of care.

Clinical Pathway For Pharmacological Treatment Of Acute Hematogenous Osteomyelitis



Abbreviations: *K kingae, Kingella kingae;* MRSA, methicillin-resistant *Staphylococcus aureus;* SCD, sickle cell disease.
For class of evidence definitions, see page 10.

common bacteria causing osteomyelitis for various age groups as well as suggested antibiotic choices are noted in **Table 1. (See page 4.)** Treatment of osteomyelitis with systemic antibiotics reduces long-term complications of the disease (including growth plate damage, deformity, limb-length discrepancy, pathologic fracture, and loss of life or limb).

Despite decades of research, the optimal choice of antibiotics for pediatric patients with AHO has not been established.[56] Peltola et al conducted a quasi-randomized controlled trial examining the use of clindamycin versus first-generation cephalosporins for acute osteoarticular infections. The study included 82 patients with osteomyelitis and found that patients treated with either antibiotic reached the primary endpoint of full recovery (free of signs and symptoms of an osteoarticular infection and no antimicrobials being readministered for this indication during the 12-month follow-up period). Of note, this study found no clindamycin resistance in over 200 strains of *S aureus* isolated from children.[57]

It is common practice to transition from intravenous to oral antibiotics when treating children with AHO. In a prospective randomized trial investigating the use of short-term (10 days) versus long-term (21 days) intravenous antibiotics followed by oral antibiotics in 12 children with osteomyelitis after surgical drainage, Jaberi et al found similar outcomes with regard to infection, eradication, functional use of the limb, and improved radiographic appearance in both treatment groups.[58] In the oldest prospective randomized trial, Kaplan et al compared 25 children receiving a longer course of intravenous nafcillin/methicillin (mean treatment time of 27 days) versus another group receiving a shorter course of intravenous clindamycin (mean treatment time of 5.8 days) before transitioning to oral therapy and found excellent outcomes in each group.[59]

Cincinnati Children's Hospital Medical Center has published a Best Evidence Statement regarding the duration of intravenous therapy in AHO and recommended that the transition to oral antibiotics should be considered within the first 7 days.[60] This recommendation was drawn from a systematic review,[61] prospective randomized controlled trials,[58,59,62,63] a prospective study,[67] and retrospective reviews.[65-71]

Adequate coverage of *S aureus* is the foundation of empiric antibiotic therapy for AHO in patients of all ages. The need to cover MRSA should be balanced against the risk of breeding resistance as well as the cost and adverse effects of broad-spectrum antibiotics. If suspicion for infection with MRSA is low, an antistaphylococcal penicillin (such as nafcillin or oxacillin) or a first-generation cephalosporin (such as cefazolin) are good choices. If MRSA is prevalent in the community, or if the patient has risk factors for infection with MRSA, vancomycin is the antibiotic of choice. If the patient has an allergy to vancomycin or some other contraindication to its use, other possible choices are clindamycin, daptomycin, or linezolid. It should be noted that many strains of MRSA have the genetic ability to become resistant to clindamycin in the course of treatment.[72] The choice should be tailored to resistance patterns in the local community; however, if a patient is extremely ill or hemodynamically unstable, emergency clinicians should consider broader-spectrum antibiotics. In the near future, new PCR assays may be able to detect the presence of MRSA in a tissue sample within a few hours; however, until these assays become widespread, empiric coverage of MRSA is essential in those at risk.

In addition to coverage of *S aureus*, certain populations should also receive empiric antibiotic therapy to cover gram-negative bacilli. Neonates and younger infants are at risk for infection with *Escherichia coli* and other gram-negative organisms. For neonates, cefotaxime is preferable to ceftriaxone due to concerns over alteration in bilirubin metabolism. Group B streptococci cause various infections, including osteomyelitis, in newborns and will be covered by the antibiotic chosen for *S aureus*. Patients not vaccinated against Hib should be covered for this organism. In addition to *S aureus,* patients with sickle cell disease should be covered for *Salmonella spp* and other gram-negative organisms with a third- or fourth-generation cephalosporin.[12] Immunocompromised patients should be covered broadly, including gram-positive and gram-negative organisms. Gram stain of tissue suggesting infection with gram-negative bacilli should also prompt appropriate coverage. Good antibiotic choices for this category of pathogen include third- or fourth-generation cephalosporins, depending on local sensitivity patterns. In children aged < 5 years, a second- or third-generation cephalosporin (such as ceftriaxone) will also cover *K kingae*, an emerging etiology of osteomyelitis in this age group. In patients who have developed osteomyelitis after being bitten by animals, cover anaerobes with antibiotics such as ampicillin-sulbactam. An algorithm for choosing treatment is seen in **Clinical Pathway For Pharmacologic Treatment Of AHO (page 11).** Specific dosing recommendations have not been provided in this article for 2 reasons: (1) many of the recommended medication doses would need to be adjusted based on the individual patient's renal function and creatinine clearance ability; and (2) many hospitals have their own recommendations on drug dosages for effective osteomyelitis treatment, based on local etiologies and drug resistance patterns. The emergency clinician should determine the appropriate dosing based on the needs of the individual being treated.

Once there is suspicion for osteomyelitis, early surgical consultation may expedite potential drainage of collections and procurement of a bone tissue

sample for microbiological analysis. Precise indications for surgical intervention are not clear; however, every attempt should be made to acquire a bone tissue sample. Depending on institutional culture and individual judgment, this is usually performed by either a surgeon or by an interventional radiologist.

Special Circumstances

Sickle Cell Disease

Pediatric patients with sickle cell disease presenting with musculoskeletal complaints deserve special mention. This medical history should be taken into account by emergency clinicians when considering the differential for such presentations and in choosing empiric antibiotic therapy.

Patients with sickle cell disease are at increased risk of musculoskeletal infection due to decreased splenic function as well as poor microvascular flow. *Salmonella* species are the most common etiology of AHO in this population. Other microbes that commonly cause osteomyelitis in this group of patients are *S aureus* and other enteric gram-negative bacilli.[12] Acute osteonecrosis due to avascular necrosis is a common complication in sickle cell disease, and differentiating this condition from AHO can be difficult. Devitalized bone tissue is at higher risk for hematogenous infection, and infected bone tissue is at risk of necrosis, so the two conditions may present together, thus complicating the differential in these patients even further. One method of differentiating avascular necrosis from AHO is based on aspiration of fluid collections. A purulent exudate suggests infection and requires antibiotics, while aspiration of blood suggests avascular necrosis, which requires only supportive measures.[46,50]

Mycobacteria And Fungi

Less common etiologies for osteomyelitis, such as fungi and tuberculous and nontuberculous mycobacteria, should be considered in patients with immunodeficiency or in those at risk for direct inoculation of the bone after surgery or penetrating trauma. These infections usually have a subacute or chronic clinical course. Fungal osteomyelitis is rare and often presents with slowly progressive pain at the site of infection.[73] Markers of systemic inflammation are often normal,[74,75] which can lead to delayed diagnosis.[74] Candidal osteomyelitis should be suspected in patients at risk for candidemia, including those with immunosuppression, use of broad-spectrum antibiotic therapy, indwelling catheters, intravenous nutrition, and recent surgery.[76-78] Other fungi that can cause osteomyelitis (although rarely) include *Aspergillus spp, Histoplasma spp,* and *Cryptococcus spp.* When fungal osteomyelitis is suspected, bone tissue should be sent for potassium hydroxide preparation and fungal culture. A diagnosis of fungal osteomyelitis should prompt aggressive antifungal therapy as well as a search for causes of immunodeficiency.[76,79]

Tuberculous osteomyelitis caused by *Mycobacterium tuberculosis* should be suspected with a subacute onset of symptoms and risk factors (eg, living in or traveling to an endemic country, HIV infection, and known tuberculosis contacts). Nontuberculous mycobacterial osteomyelitis can also occur in HIV patients as well as patients who have suffered penetrating trauma. A case of nontuberculous mycobacterial osteomyelitis of the femur has been described in an immunocompetent girl treated months earlier for cervical lymphadenitis with the same bacterium.[68]

Kingella kingae

Improved culturing techniques and improved access to PCR have suggested *K kingae* as among the most common causes of osteoarticular infections in children aged < 4 years.[80,81] *K kingae* is a gram-negative bacillus that commonly colonizes the oropharynx and respiratory tract of children. It occasionally causes invasive disease (such as endocarditis and bacteremia), but it can also cause musculoskeletal infections, with osteomyelitis being less common than septic arthritis. *K kingae* is difficult to culture on solid growth media, which is likely the reason that its importance in osteoarticular infection has been recognized only in recent decades. It is likely still underdiagnosed, and often emergency clinicians do not test for it. The microorganism is transmitted among children in close contact, and Kiang et al have documented an outbreak of *K kingae* osteomyelitis/septic arthritis in a day care center, with a total of 3 cases.[82]

Inoculation of joint fluid directly into blood culture bottles can increase recovery of this organism[83] and similar practice may also help with bone tissue biopsy and aspirated fluid from subperiosteal collections. PCR of joint fluid in septic arthritis or bone biopsy in osteomyelitis further improves detection of *K kingae*.[81] Swabs of the nasopharynx (the presumed source of hematogenous infections with this bacterium) may also prove useful. In a study of mixed osteoarticular infection (osteomyelitis and/or septic arthritis), PCR performed on oropharyngeal swabs proved to be 100% sensitive and 90.5% specific for infection with *K kingae*.[80] Other PCR techniques may be even more accurate.[81] Most of these infections are septic arthritis and more research is needed to better understand the significance of *K kingae* in osteomyelitis and the use of PCR to diagnose it as the infectious etiology.

Many emergency clinicians will not empirically cover *K kingae* with antibiotics, as infection with this organism is thought to be relatively mild. Furthermore, there is concern that initiation of several empiric antibiotics can complicate the transition to

Risk Management Pitfalls For Acute Hematogenous Osteomyelitis

1. **"The x-ray was normal, so I did not pursue a diagnosis of osteomyelitis."**
   X-rays are often normal in AHO, and non-specific changes are seen in only 15% to 58% of patients with AHO.[1,2,30,45] X-rays have even less sensitivity in pelvic osteomyelitis. It typically takes ≥ 7 days for changes associated with osteomyelitis to be seen on x-ray.[3,16,46]

2. **"The WBC count and differential were unremarkable, so it couldn't have been osteomyelitis."**
   WBC count is the least helpful of the inflammatory markers, with a sensitivity of 34% to 43% in AHO.[1,29,31,41] ESR and CRP are most useful, and are elevated in 73% to 100% and 70% to 100% of patients, respectively.[1,16,28,29,30,32,33,41]

3. **"I treated a 6-month-old who had no MRSA risk factors with nafcillin and heard that his condition worsened the next day."**
   Although *S aureus* is the most common cause of AHO, there are certain populations where gram-negative bacilli coverage is also indicated or should be considered. This includes children aged < 5 years, children who have not completed the Hib vaccine series, and children with sickle cell disease.

4. **"A young boy with abdominal pain, who had a negative CT scan 3 days ago, was discharged, and then returned to the ED and was diagnosed with pelvic osteomyelitis."**
   Pelvic osteomyelitis may present as hip, thigh, or abdominal pain, which frequently leads to delayed diagnosis and misdiagnosis. Keep pelvic osteomyelitis on your differential for any patient presenting with abdominal pain, as a misdiagnosis of pelvic osteomyelitis has been shown to cause significant permanent disability.

5. **"An adolescent patient who had a renal transplant 1 year ago presented with pain over her femur. Her blood work was completely normal, so I discharged her. When she came back to the ED, I found I had missed osteomyelitis."**
   Immunosuppressed patients are at risk for less common etiologies of osteomyelitis, such as fungal osteomyelitis. It is important to remember that markers of systemic inflammation are often normal in fungal osteomyelitis.

6. **"I suspected osteomyelitis, but the CRP was normal, so I decided AHO was ruled out."**
   No marker of inflammation, including CRP, is 100% sensitive for AHO. Clinical suspicion should prompt further testing even if all blood work is normal.

7. **"A patient presented with findings of cellulitis. I did not do any blood work and treated with cephalexin. The symptoms returned after the antibiotic course was finished, and an MRI showed osteomyelitis."**
   Osteomyelitis can present with an overlying cellulitis with or without an abscess. These conditions can often be difficult to differentiate from one another. If there is any suspicion for deeper infection of the muscle or bone, emergency clinicians should get an initial plain radiograph and send a blood sample for measurement of CRP, ESR, and a WBC count with differential. Also consider obtaining CPK levels to rule out muscle involvement.

8. **"A pediatric patient had a history of trauma at the site of leg pain, but the x-ray was negative. I sent him home with recommendations for ice, rest, and anti-inflammatory medicines. He returned later with worsening symptoms and was diagnosed with osteomyelitis."**
   A significant proportion of children with AHO have a history of trauma at the site of infection. Trauma to bone tissue may predispose it to hematogenous infection. A history of trauma should not deter emergency clinicians from further workup for osteomyelitis.

9. **"My facility does not have MRI capability, so I referred a child with suspected osteomyelitis to a larger academic center."**
   Bone scan, ultrasound, or CT can aid in workup for osteomyelitis when MRI is not available. In most cases, clinical suspicion and a positive bone scan is sufficient evidence to support obtaining a bone sample for culture and to effectively treat AHO.

10. **"I diagnosed osteomyelitis, recovered a microbe in blood and bone culture, and treated it with an effective antibiotic for 6 weeks. The patient returned several weeks after completion of the antibiotics with recurrence at the same site."**
    Treatment failure is common in osteomyelitis, occurring in 4.7% of children in 1 study.[71] Even in the absence of sequestra or abscess, appropriate treatment can fail for reasons that are poorly understood.

oral therapy. A study by Yagupsky looked at the antibiotic susceptibility of 85 strains of *K kingae* recovered from children with osteoarticular infection.[84] All strains were highly sensitive to penicillin, and minimal inhibitory concentrations to cefuroxime and linezolid were low, suggesting susceptibility, while a significant portion of strains were resistant to oxacillin and clindamycin. The author of that study recommended the use of cephalosporins as the empiric agents of choice when there is suspicion for infection with *K kingae*. Empiric coverage of suspected osteomyelitis in pre-school-aged children with a second- or third-generation cephalosporin (as long as MRSA is not suspected)will cover all of the most common etiologies, including *K kingae*.

Disposition

All pediatric patients with suspected AHO should be admitted to an inpatient ward or pediatric intensive care unit, as appropriate, for intravenous antibiotic therapy and monitoring. Antibiotics will likely be switched from intravenous to oral after several days of clinical improvement and decreasing inflammatory markers. The total antibiotic course is typically several weeks, or until ESR has normalized, and will be completed at home. Every effort should be made to obtain a bone sample before initiation of antibiotics. This decision should be multidisciplinary and should involve specialists from surgery and infectious disease, if available. Ill patients and those with surgical indications (specifically, abscesses or sequestra) may also be transferred to the operating room for drainage and debridement. Patients with hemodynamic instability or signs of sepsis should be admitted to a PICU for management.

Early physical therapy, as tolerated, is important in children with AHO to prevent deconditioning and muscle atrophy. Children with osteomyelitis are at risk of fracture at the site of infection, so they should refrain from full physical activity while gradually increasing weight-bearing activities. Optimal care of a child with AHO requires coordination among multiple hospital services, including the ED, inpatient pediatrics, surgical services, radiologists, nursing, and social work.[14]

Cost-Effective Strategies For Osteomyelitis

- **When osteomyelitis is suspected and plain films are negative, consider a bone scan for the next step in the workup prior to MRI. Bone scans are much less costly than an MRI.**
  Risk Management Caveat: If a patient is very ill or has severely elevated inflammatory markers, MRI should be strongly considered. In cases of suspected pelvic osteomyelitis, it is also reasonable to follow skeletal scintigraphy with MRI, or to perform MRI alone, given the high incidence of abscesses associated with pelvic osteomyelitis. If your center does not have MRI capability, it is important to transfer the patient to a center that can perform MRI after the patient has been stabilized.
- **If suspicion for MRSA is low, then an anti-staphylococcal penicillin (such as nafcillin or oxacillin) is a good choice for empiric antibiotic coverage in patients of all ages.**
  Risk Management Caveat: The need to cover MRSA should be balanced against the risk of breeding resistance as well as the cost and adverse effects of broad-spectrum antibiotics. If MRSA is prevalent in the community, or if the patient has risk factors for infection with MRSA, vancomycin is the antibiotic of choice.

Summary

AHO may be a challenge to diagnose, given the variety of presenting signs and symptoms that patients can demonstrate on initial evaluation. However, given the devastating consequences of untreated osteomyelitis, emergency clinicians must keep osteomyelitis in the differential for patients with nonspecific limb pain, limp, and/or fever, and they must know how to work up patients and how best to treat based on age and other risk factors. Important points to note in the history include fever, pseudoparalysis in infants, limp, tenderness over a bone, and a history of trauma. On physical examination, the emergency clinician should look for point tenderness, signs of trauma, erythema, and swelling, and check the range of motion of all joints (especially above and below the area of perceived pain). The initial workup includes CRP, ESR, complete blood count (CBC) with differential, and blood culture. CRP is the most sensitive measure of acute inflammation. Plain x-rays should be taken for any patient with point tenderness, a history of trauma, joint effusion, concern for malignancy, and/or abnormal laboratory values. The emergency clinician must be aware that plain x-rays typically do not show signs of osteomyelitis until the infection has been present ≥ 7 days. Advanced imaging (such as bone scan and MRI) is more useful in diagnosing osteomyelitis, and some evidence suggests a bone scan can be done prior to MRI. Once the diagnosis of AHO is made based on careful history, physical examination, laboratory testing, and imaging, patients must be treated appropriately. In order to best tailor antibiotic therapy, every effort should be made to obtain a Gram stain and culture of tissue from the infection site (although this is not always possible). An associated abscess or extensive

bony destruction leading to sequestra or involucra will require surgical management. Antibiotic choice depends on common pathogens within a specific age group as well as other risk factors (such as MRSA risk or sickle cell disease).

Case Conclusions

You treated the 8-year-old boy with sickle cell disease, with ibuprofen, and he stopped crying. You ordered an ESR and CRP (which were both elevated), and a CBC with differential (which came back normal). A blood culture was sent to the laboratory. Given his point tenderness, you ordered plain films of his right femur and knee joint, which were normal. Remembering that plain films do not usually show signs of AHO in the first week, you considered other imaging modalities. Because of the amount of time it would have taken to obtain a bone scan, the radiation exposure, and the fact that you were confident this was localized disease, you decided to order an MRI. The MRI demonstrated findings consistent with AHO of the distal femur, with a subperiosteal abscess. You called the surgery team and the boy was taken to the OR to drain the abscess and get a bone biopsy. As you thought about what antibiotics this patient would need, you remembered that in patients with sickle cell disease, Salmonella is the most common pathogen. You discussed this with the surgeon and decided to cover the patient postoperatively with oxacillin for S aureus and ceftriaxone for Salmonella species.

As you managed the young boy, you were also caring for the infant girl who presented with fever and pseudoparalysis. Thinking that her pseudoparalysis might be due to pain, you placed an IV and gave her pain medication. After about 30 minutes, she began to move her left leg. You ordered the same laboratory studies that you did for the previous patient, and found that her CRP was elevated to 40 mg/L. X-rays were normal, and there were no other findings that caused concern for nonaccidental trauma. You ordered an MRI, which demonstrated findings consistent with AHO of the proximal tibia. You called the surgery team to ask about a bone biopsy, but this could not be completed in a timely fashion. Although it would have been ideal to obtain Gram stain and culture data prior to administering antibiotics, you decided that the antibiotics were more important at this time to prevent the complications of osteomyelitis. Remembering that gram-negative organisms are common in infants, you started her on cefotaxime. In addition, you noted her mother was a nurse, and upon further questioning, she told you that she has had several MRSA skin infections over the years. With this history, you decided to also cover the infant with vancomycin for MRSA and then you admitted her to the pediatrics floor. At the end of your shift, you reflected on how different presentations, age groups, and past medical history were important when considering the pathogens that cause osteomyelitis and the treatments you recommended.

References

Evidence-based medicine requires a critical appraisal of the literature based upon study methodology and number of subjects. Not all references are equally robust. The findings of a large, prospective, randomized, and blinded trial should carry more weight than a case report.

To help the reader judge the strength of each reference, pertinent information about the study, such as the type of study and the number of patients in the study, will be included in bold type following the reference, where available. In addition, the most informative references cited in this paper, as determined by the authors, will be noted by an asterisk (*) next to the number of the reference.

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1. The following are common pathogens for AHO in otherwise-healthy infants (aged < 1 year) except:
a. Group B streptococci
b. *S aureus*
c. *Pseudomonas aeruginosa*
d. *Escherichia coli*

2. Which of the following is the most sensitive laboratory value in the diagnosis of AHO?
a. CPK
b. ESR
c. CRP
d. WBC with differential

3. In children presenting with pain localized to a limb, which serum test can aid in determining deeper tissue involvement?
a. Creatinine
b. CPK
c. Troponin
d. Blood culture

4. How long does it typically take for bony changes due to AHO to appear on x-ray?
a. 1 to 3 days
b. 3 to 4 days
c. 4 to 6 days
d. ≥ 7 days

5. Ultrasound of suspected osteomyelitis is useful because it can demonstrate or rule out all of the following EXCEPT:
a. Bone infection
b. Subperiosteal abscess
c. Joint effusion
d. Deep vein thrombosis

6. Bone scans (skeletal scintigraphy) are not useful in detecting:
a. Abscess
b. Trauma
c. Malignancy
d. Osteomyelitis

7. In suspected pelvic osteomyelitis, use of the following imaging modality is indicated:
a. Plain radiograph
b. MRI
c. Bone scan
d. CT scan

8. For a patient with confirmed osteomyelitis, MRSA risk factors, and an allergy to vancomycin, all of the following antibiotics would be reasonable EXCEPT:
a. Clindamycin
b. Linezolid
c. Daptomycin
d. Ceftriaxone

9. In addition to *Staphylococcus* coverage, antibiotic therapy to cover gram-negative bacilli should be considered in all of the following patients EXCEPT:
a. Children aged < 5 years
b. Patients who have not received the pneumococcal vaccine
c. Patients who have not received the Hib vaccine
d. Patients with sickle cell disease

10. All of the following will increase detection of *K kingae* EXCEPT:
a. Injecting synovial fluid into blood culture bottles
b. Oropharyngeal swabs
c. Three blood cultures drawn from separate venipuncture sites
d. PCR

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