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Position Statement

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Diagnosis and management of acute osteoarticular infections in children

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Abstract

Acute hematogenous osteomyelitis and septic arthritis are not uncommon infections in children and should be considered as part of the differential diagnosis of limb pain and pseudoparalysis. Most bone infections in children arise secondary to hematogenous seeding of bacteria into bone. The most common pathogens are *Staphylococcus aureus* and *Kingella kingae*. Children with septic arthritis should be evaluated promptly by orthopedic specialists for aspiration and possible debridement of concomitant osteomyelitis. Optimal empiric therapy after appropriate cultures continues to be intravenous cefazolin. In most cases, conversion to oral antimicrobials should occur when the patient has clinically improved and has decreasing inflammatory markers. For most uncomplicated cases of osteomyelitis, current recommendations are 3 to 4 weeks of antimicrobial therapy compared with the 6 weeks previously recommended.

Keywords: *Acute osteomyelitis; C-reactive protein test; Methicillin-resistant* Staphylococcus aureus*; Methicillin-susceptible* Staphylococcus aureus*; Septic arthritis*

Hematogenous osteomyelitis presents frequently in physician offices and emergency departments. The incidence in developed countries ranges from 1 to 13/100,000 children (or 2.38 cases per 1000 admissions), and is more frequent in young children (1–3).

This position statement focuses on acute osteomyelitis (AO) and acute septic arthritis (SA) resulting from hematogenous seeding of bacteria into bone and joints in previously healthy children. It excludes infections of the head and neck, infections associated with prostheses and those caused by direct or contiguous spread (e.g., secondary to trauma, surgery or fractures). Nor does it address infections with symptoms present for more than one month or SA resulting from disseminated gonococcal infection.

PATHOGENESIS AND DEFINITIONS

The pathologic definition of osteomyelitis is an inflammation of the bone and bone marrow due to infection with a microbial pathogen. Traditionally, AO was defined with symptoms for less than 2 weeks, although micro-organisms and outcomes appear to be similar in patients who have symptoms for up to 4 weeks. By contrast, chronic osteomyelitis is defined with symptoms for more than 1 month in cases where avascular bone (sequestrum) alone or surrounded by new bone (involucrum) is present (Brodies' abscess).

The source of the bacteremia leading to AO or SA usually is not clinically evident, suggesting that colonization in the mucous membranes of the respiratory tract or through skin is the most likely portal of entry. Bacteria causing AO are common colonizers of the upper respiratory tract, including *Staphylococcus aureus, Kingella kingae, Streptococcus pneumoniae* and *Streptococcus pyogenes* (4–6). *K kingae* has particularly high colonization rates in infants (at 12%) with progressively lower colonization rates in older children (6%) (7).

AO can occur in any bone but the most common site is the metaphysis in long tubular bones, such as the femur, tibia or

humerus (8,9). At the metaphysis, the nutrient artery ends in small arterial loops that empty into venous sinusoids. It is hypothesized that bacteria can translocate from the vessels into pooled blood at this site (possibly as a result of minor trauma), resulting in replication and suppuration. Bacterial toxins, inflammatory cytokines, ischemia and possibly the leukocytes themselves promote local bony destruction. When suppuration occurs in the metaphysis of bones, infection can extend to adjacent sub-periosteal areas and, later, to overlying soft tissues.

SA may occur concurrently with AO, particularly in children younger than 2 years of age whose transphyseal vessels may be instrumental in spreading infection. Also, the joint capsule extends beyond the epiphyseal plate in younger infants, permitting easier spread from the metaphysis. Use of sensitive magnetic resonance imaging (MRI) techniques has suggested that the incidence of AO associated with SA is higher in younger children, occurring in 37% under 2 years compared with only 17% over 10 years (10).

CLINICAL MANIFESTATIONS

Clinical suspicion for AO or SA should be entertained when a patient presents acutely with pseudoparalysis (decreased movement or use) in an affected area or limping. Often pain is the only symptom. The presence of fever may not be a dominant feature at presentation but makes AO or SA even more likely. Infants or newborns may experience nonspecific signs that can be misinterpreted as trauma.

When metaphyseal infection has progressed to cause an adjacent abscess at the periosteum and the bone site is superficial, localized swelling or fluctuance and erythema may be evident at the site. When the presenting symptoms are predominantly skin and soft tissue pain, swelling and erythema, an acute cellulitis or fasciitis must be considered in the differential diagnosis.

The clinical signs and symptoms of AO and SA often overlap, especially when the hip joint is involved. In such cases, it is difficult to determine whether the child has pain in the femoral metaphysis or the femoro-acetabular joint. Features of SA alone include specific swelling of the joint, joint effusion and pain on movement of the isolated joint. Infection of pelvic bones can be difficult to diagnose because the pain is difficult to localize, signs of inflammation are less evident and presentation may be mistaken for an intra-abdominal process. AO should always be considered in *S aureus* bacteremia with no apparent source.

The clinical course of AO and SA due to methicillin-resistant *S aureus* (MRSA) appears to be more severe and complicated compared with methicillin-susceptible *S aureus* (MSSA) (11–14). Typically, AO and SA due to *K kingae* are milder and more subacute compared with infections by *S aureus*, although there are also reports of severe disease due to *K kingae* (15–17).

DIFFERENTIAL DIAGNOSIS

Conditions that should be considered in the differential diagnosis of children presenting with possible AO or SA are presented in Table 1 (18–25). Some authors have suggested that if C-reactive protein (CRP) is normal or low within the first few days of an acute presentation, the probability of AO or SA is low (26–28). Other systemic medical conditions to consider include acute presentations of juvenile idiopathic arthritis, reactive arthritis secondary to a prior infection or lupus erythematosus. Congenital syphilis can also present with pseudoparalysis due to painful unilateral or bilateral periostitis, osteitis or lytic lesions located in the metaphysis of long bones.

DIAGNOSTIC IMAGING AND LABORATORY INVESTIGATIONS

Pathological assessment of a bone specimen is the gold standard for the diagnosis of AO, but there are also key laboratory investigations supporting a clinical diagnosis. Most children with a high suspicion of AO or SA will need to be seen at a hospital and should be assessed by an orthopedic surgeon or paediatrician to complete investigations.

White blood cell count is generally, but not always elevated. A CRP test should be done at presentation. CRP is an acute phase protein produced by the liver that has a short half-life of 8 hours. Testing CRP is preferred to an erythrocyte sedimentation rate (ESR) because it is more sensitive and decreases faster with appropriate therapy (27–29). Both ESR and CRP can be abnormal in other infectious, rheumatologic and neoplastic processes, however. In a study of culture-positive AO and SA, the reported sensitivity of CRP at diagnosis was 95% (95% CI 91% to 97%). ESR and CRP both peaked on day 2 of presentation, with the level of CRP normalizing in 10 ± 0.5 days. In this cohort of 265 children with confirmed osteoarticular infections, all had an elevated CRP and/or ESR within 3 days of admission (26). Procalcitonin may be more specific in differentiating between infection and other inflammatory musculoskeletal lesions but this test is not widely available for diagnostic purposes in Canada, nor has it been validated for specific diagnosis of AO or SA (30).

The classic bone lesions of AO, as seen using conventional radiography, are lytic lesions and localized periosteal lifting. However, such findings are only evident 7 to 21 days after onset of infection. Therefore, when symptoms are more recent, the sensitivity of plain radiography is low. Although plain films usually appear normal, they are required to exclude other important pathologic lesions, such as benign or malignant neoplasms and fractures (31). However, joint effusions are often apparent on a plain radiograph in SA. The major use of ultrasound (US) in the management of AO or SA is to detect fluid collection in subperiosteal areas and soft tissues, or excess fluid in the joint space in the case of SA, especially when physical examination has not been revealing. In some cases, US is able to characterize fluid as potentially reactive (or not).

MRI with gadolinium enhancement is the most sensitive and specific noninvasive test for diagnosing AO, because it provides

Table 1. Selected differential diagnosis for acute limp pain or pseudoparalysis

Differential diagnosis of acute focal pain in limb or near bone	Predominant symptoms	Other differentiating features
Acute bacterial osteoarticular infection (AO)	Acute onset of new limp, reluctance to use a limb or pseudoparalysis in a preverbal child. With spinal infection, reluctance to sit or stand or an impaired ability to bend due to pain may be present. Possible fever or rigours in the days before presentation.	Localized pain to palpation or point tenderness with pressure, overwhelmingly at the distal or proximal ends of bones. May be unable to move joint actively with adjacent SA. Usually accompanied by mild, localized swelling and (sometimes) by erythema. Localized fluctuance may be present if there is a periosteal abscess. Usually, child has had fever but may not be prominent at time of presentation.
Transient synovitis of hip	Usual age is 4–10 years. Hip pain and new limping, fever generally low-grade. Child can usually weight-bear but also may not. History of upper respiratory tract infection in the preceding 2 weeks.	Nontoxic appearance, usually < 38.5°C fever. CRP is usually < 20 mg/L. Gradually improves over several days, which may be hastened by nonsteroidal anti-inflammatory agents.
Fracture or trauma (e.g., Toddler's fracture)	Acute onset of pain while active or after a recognizable traumatic event.	Localized pain to palpation. Hematoma or bruising, with localized swelling if trauma is local. No history of fever.
Lyme disease arthritis	Living in or travel to a Lyme-endemic area 2 to 12 months before symptom-onset. Usually monoarthritis, with swelling of a knee (occasionally hip or other large joints) without major constitutional symptoms on history.	Much less painful than SA. Usually, child does not have recent fever. Baker's cyst may be present. Often still willing to weight-bear. CRP is < 40 mg/L.
Cellulitis	Rapid development of swelling, redness and pain over hours or a day. Erythema has usually preceded the development of pain.	Area of erythema, warmth, swelling and tenderness of the skin. Usually is more extensive than one focal area. Skin is edematous and tender to touch. Can have lymphangitis. Child may be able to weight-bear and move an underlying joint.
Chronic recurrent multifocal osteomyelitis (CRMO) (first presentation)	Insidious onset of bone pain. Lesions often affect the metaphysis and the epiphysis. Child may have low-grade fever and malaise. Pain is often worse at night. Diagnosis is based on a relapsing disease course. Lesions often involve unusual sites, such as the clavicle, jaw or scapula. There may be intense sclerosis with healing on radiographs.	Local tenderness with some warmth and swelling but sometimes no objective signs. One-third of cases have low-grade fever, malaise and weight loss. May have palmoplantar pustulosis, psoriasis or other dermatologic conditions.
Hematologic malignancy	Prominent associated systemic complaints, such as fever, fatigue, anorexia, weight loss and arthralgia, limb or muscle pain. Child may be reluctant to walk or have metaphyseal lucencies and periosteal reactions, as with acute osteomyelitis.	No localized pain to palpation but may have joint swelling and evidence of mild synovitis on joint exam. May have fever.
Bone neoplastic lesion (benign or malignant, including histiocytosis)	Typically occurs in the diaphysis or in flat bones. Typically gradual onset (over weeks). Pain is often worse at night and associated with refusal to weight-bear.	In addition to pain, may have a palpable soft tissue or bony mass.

Table 1. *Continued*

Differential diagnosis of acute focal pain in limb or near bone	Predominant symptoms	Other differentiating features
Juvenile idiopathic arthritis	Typically gradual onset (over weeks). May be oligoarthritic (<4 joints) or polyarthritic. More likely to be symmetric, often with extra-articular symptoms.	Often, symptoms are less severe compared with bacterial SA. May have contracture if more subacute. May need synovial fluid analysis to exclude SA when presenting with monoarthritis. Usually, fewer white blood cells in joint fluid compared with SA.
Systemic lupus erythematosus	Often constitutional symptoms (fever, weight loss, fatigue, anorexia, diffuse lymphadenopathy) predominate. Cutaneous symptoms (e.g., rash, ulcers) at presentation are also common.	Arthritis is usually milder than with SA. Child may also have hematologic (leukopenia, anemia) abnormalities and abnormal urinalysis.
Reactive arthritis	Oligoarthritis of larger joints, usually 2 to 3 weeks after a preceeding infection of the gastrointestinal or urogenital tract. May also have ocular and urinary symptoms.	Arthritis is more subacute and less severe compared with bacterial SA.
Poststreptococcal reactive arthritis	Acute onset of symmetrical or asymmetrical arthritis. Usually polyarticular, nonmigratory and can be persistent or recurrent. Usually 3–14 days after preceding streptococcal infection.	May have extra-articular manifestations, (e.g., vasculitis, glomerulonephritis). In acute rheumatic fever, the joints are tender and swollen with a characteristic migratory feature and exquisite response to non-steroidal anti-inflammatory drugs or salicylates.

AO Acute osteomyelitis; CRP C-reactive protein; SA Septic arthritis.

information on associated soft tissues and growth plate (epiphysis) involvement in addition to quantifying supraphysiologic fluid in the joint space. MRI does not entail radiation exposure but may require a general anaesthetic. The earliest finding of AO on MRI is bone marrow edema (32). MRI is also useful for differentiating benign or malignant bone lesions from osteomyelitis (33). MRI is not required when a solid clinical diagnosis is made with supporting laboratory parameters and positive clinical response to empiric therapy.

Radionucleotide bone scans may be useful when radiographs appear normal and MRI is unavailable. Even in young children, bone scans do not require general anaesthesia. The overall sensitivity of nuclear imaging is estimated to be at least 80%, but very early presentations of small foci can lead to a false-negative test result. Bone infarction associated with osteomyelitis may also result in a false-negative scan. Other conditions, such as fractures or tumours, can lead to false-positive scans. Therefore, specificity for nuclear images is lower than for MRI. Location of uptake may also be important. Uptake in the metaphysis is only supportive of osteomyelitis, whereas uptake at other sites, such as the diaphysis, is more suggestive of other etiologies. When multifocal sites of infection are suspected, nuclear imaging may be a useful initial test.

Computed tomography, though generally less sensitive than MRI for detecting bone marrow edema, may be useful in settings where MRI and bone scans are unavailable or not possible, or for image-guided interventions.

The optimal method of SA diagnosis is aspiration of the joint. If this procedure is not possible, US can confirm the presence of joint fluid, while MRI can help determine whether fluid is inflammatory. A radiologist should be consulted to optimize imaging.

IDENTIFYING A PATHOGEN

Before the widespread use of Hib-conjugated vaccine, *Haemophilus influenzae* type b was a common cause of osteoarticular infections (34,35). Currently, *S aureus* is the most common organism cultured in fully immunized persons with AO or SA beyond the neonatal period. In the USA, an increase in the incidence of osteoarticular infections has been attributed to MRSA (11,13,36).

Blood, bone and joint fluid cultures commonly test negative (an estimated 30% to 90% of the time) (37–41). *K kingae* is now identified as an important causative pathogen, based on joint fluid from young children. These bacteria do not grow

well when plated from swabs, but yield increases significantly when fluid samples are inoculated into blood culture bottles (42). Subjecting culture-negative specimens to further molecular testing has also increased the diagnostic yield for *K kingae* (6,43,44). Current data support both the probability that *K kingae* is the dominant pathogen in children younger than 4 years old presenting with SA (with or without OA) and that *S aureus* is the more common pathogen in older children.

Less common causes of AO include streptococcus species, such as *S pneumoniae*, *S pyogenes* and *S agalactiae*, with rare cases being due to other bacteria. Enterobacteriaceae or fungi are uncommon causes of AO, but they do occur in special populations (e.g., neonates, immunocompromised individuals or in cases with exposure to unique environments). Persons with sickle cell disease are prone to infections with Salmonella species in addition to *S aureus*.

Because AO and SA are of hematogenous origin, every effort should be made to obtain an adequate volume of blood for culture before initiating antibiotics, to increase the probability of detecting an associated transient bacteremia, especially during a febrile episode. Higher blood volumes are more likely to yield a positive blood culture. Therefore, it is recommended that a total of 2 mL to 4 mL be drawn in children weighing 1 kg to 2 kg, 6 mL in children 2 kg to ≤12 kg, 10 mL to 20 mL in children 13 kg to 40 kg, and 40 mL in children > 40 kg (45). Blood cultures that test positive should be repeated after 48 hours of antimicrobial therapy to ensure clearance. *S aureus* in a blood culture should never be considered a contaminant.

In cases of SA, aspiration of joint fluid by a radiologist or surgeon should be attempted—if practical—before antibiotics. Such testing would determine whether the joint is infected, with clear therapeutic benefit. If this test is not available at the primary care site, be sure to consult with an orthopedic surgeon. In cases of AO, surgery should also be strongly considered when there is suspected subperiosteal fluid or abscess at presentation. When the patient fails to improve clinically within the first few days on antibiotics, repeat imaging to identify bone or joint fluid collections or soft tissue abscesses and reconsider debridement surgery if either of these signs are identified. Obtaining a specimen for bacteriological and pathological diagnosis is important because it may yield a pathogen not covered by empiric therapies (e.g., MRSA or another bacterial or fungal pathogen).

When surgery is performed, all samples of bone, tissue or joint fluid should be placed in sterile containers. Swabs are strongly discouraged due to low yield. Any fluid should be inoculated into blood culture bottles and tissues should be cultured as per routine protocols (41). Clinical protocols should also recommend saving an aliquot for possible molecular testing in the event that the child is not improving on empiric therapy and other pathogens are suspected.

EMPIRIC MANAGEMENT AND TARGETED THERAPY

Children with suspected SA should be evaluated promptly by an orthopedic surgeon for consideration of urgent irrigation. The role of surgery in AO will depend on the location, acuity, presence of associated abscess, size of lesion and response to empiric therapy.

In Canada, complete response occurs in the vast majority of fully immunized children with AO or SA who are treated with a first-generation cephalosporin. In the absence of a positive blood, synovial fluid or bone culture, it can be assumed that most cases are due to MSSA or *K kingae*, both of which respond adequately to this antibiotic. Therefore, cefazolin at a dose of 100 mg/kg/day to 150 mg/kg/day divided every 6 hours or 8 hours should be the empiric intravenous (IV) antimicrobial choice for suspected AO and SA. *K kingae* is predictably resistant to clindamycin, vancomycin and cloxacillin (7).

Some consultants recommend broadening empiric therapy coverage to cover *H influenzae,* with cefuroxime 150 mg/kg/day IV divided every 8 hours for children less than 4 years old who are unimmunized or living in an area where cases of invasive *H influenzae* are more common than usual. MRSA should be considered if there is a high prevalence in the community or the child is a known carrier. In cases where cultures will ultimately become available because bone has been biopsied and/or the joint aspirated, vancomycin can be added empirically to cefazolin, if clinically indicated.

When a pathogen is detected, antibiotics should be modified, if appropriate. The most common isolate is MSSA. In such cases, continue cefazolin or narrow therapy to cloxacillin (150 mg/kg/day to 200 mg/kg/day IV divided every 6 hours), always recognizing that cloxacillin can cause vein irritation, especially in younger children.

TRANSITION FROM INTRAVENOUS TO ORAL THERAPY AND DURATION OF TREATMENT

Traditionally, acute osteoarticular infections in children were treated with at least 6 weeks of antimicrobial therapy, with variable lengths of IV therapy. Recently, studies using two large comparative databases have addressed the issue of length of IV therapy more rigorously (46,47). One study used a retrospective cohort approach to compare outcomes in 1969 children more than 6 months of age with AO, approximately one-half of whom were discharged on oral antibiotics and one-half on IV antibiotics following a median hospitalization of 4 to 5 days. The primary treatment failure rate was similar in both groups (4% in the oral group and 5% in the IV group [OR 0.77 (95% CI 0.49 to 1.22)]) (46). A subsequent study carried out in 38 hospitals in the USA used a retrospective observational study design that

matched patients by age group, length of stay, location of infection, surgical procedure and isolation of bacterial pathogens (including MRSA). This study included data from 2060 children aged 2 months to 18 years, 80% of whom had infection in a lower extremity. At discharge, about one-half received oral antibiotics while the rest received IV antibiotics. The median length of stay in hospital was 6 days. Excluding patients with MRSA, the most common antimicrobials prescribed were cephalexin or cefazolin. The failure rate was 5% in the oral group and 6% in the IV group (47). Complications related to IV catheter use in outpatients increased emergency room visits significantly (to rates between 4% and 41%) (46–48). The data suggest cumulatively and strongly that oral antimicrobials are usually appropriate at discharge, even for patients who were bacteremic, provided that a negative blood culture has been documented (49). Contraindications to oral therapy include expected poor medication compliance or follow-up, malabsorption or slow clinical resolution of infection.

Transitioning to oral therapy is based on clinical improvement and decrease in CRP. Patients with uncomplicated AO are expected to be afebrile, with significant clinical improvement after 3 to 7 days of appropriate IV therapy. When a lower extremity is infected, the ability to weight-bear should be evident; with upper extremity infection there should be only mild pain with routine use. The CRP should be demonstrably lower before converting to oral therapy, but the exact level to be attained is unclear: the clinical course is probably a more important indicator. Other studies have used either a decrease in CRP level by 50% over a 4-day period or a level between 20 mg/L and 30 mg/L and good clinical response for transitioning to oral therapy (50,51).

One Canadian study showed that median doses of 40 mg/kg of oral cephalexin administered every 8 hours resulted in pharmacokinetic parameters predicted to be bactericidal in osteoarticular infections caused by MSSA (52). Most clinicians recommend administering 120 mg/kg/day to 150 mg/kg/day orally, if the dosing interval is three times per day (to a maximum dose of 6 g per day). Some clinicians, however, recommend a lower dose: 100 mg/kg/day to 120 mg/kg/day divided four times, because the half-life of cephalexin is short (approximately 1 hour). Cloxacillin can also be prescribed for susceptible *S aureus*, bearing in mind the poor taste of oral suspension. Most clinicians recommend a dose of 100 mg/kg/day to a maximum of 1 g four times daily.

For AO due to MRSA, the time required to meet clinical and laboratory criteria before switching to oral therapy is usually longer than for other pathogens or for culture-negative cases. When local susceptibilities are known and the patient meets all clinical and laboratory criteria for oral therapy, treatment with clindamycin, trimethoprim-sulfamethoxazole or linezolid can be considered in consultation with an infectious diseases physician. All patients need to be monitored closely.

One recent review summarizing data from six studies published between 2002 and 2009 indicated that while duration of therapy varied, most patients with uncomplicated AO could be treated adequately with initial parenteral therapy followed by oral therapy, for a total duration between 21 and 28 days (37,38,50,53–59). For most uncomplicated cases of AO—which respond rapidly to empiric therapy and continue to improve on oral antimicrobials—current recommended treatment length is for a total of 3 to 4 weeks of antimicrobial therapy compared with the 6 weeks recommended previously. For SA, the usual duration is 3 to 4 weeks, but most clinicians still recommend a total duration of 4 to 6 weeks of therapy if the hip is involved. These recommendations for duration of therapy apply regardless of whether blood cultures were positive and always assume a positive clinical response.

Discontinuing antimicrobial therapy should be based on the clinical resolution of initial symptoms and normalization of CRP. Some children who resume full physical activities soon after treatment experience temporary, intermittent mild pain that need not cause concern.

FOLLOW-UP

Clinical evaluation is necessary before discontinuing antimicrobial treatment. A normal CRP should be documented unless it has normalized previously.

Although baseline radiographs at diagnosis should always be obtained, routine radiographs at the end of therapy are only clearly indicated when the growth plate is involved and/or a large lytic lesion presents initially. A radiograph at the end of therapy typically shows sclerosis and changes consistent with healing, with the lytic lesion usually still evident. In cases where the infection involved the growth plate or an immediately adjacent epiphyseal or metaphyseal region, orthopedic follow-up is required. Because there is poor correlation between clinical resolution and changes on MRI or computed tomography, follow-up tests should be reserved for patients who develop complications or who are not improving clinically.

RECOMMENDATIONS

1. Acute osteomyelitis (AO) and acute septic arthritis (SA) should be considered in all children who present with pain involving a bone or joint and/or pseudo paralysis. While fever supports the diagnosis, this symptom may be absent.
2. In previously healthy children, the most common pathogens causing AO and SA are *S aureus* and *K kingae*. Given the current epidemiology, recommended empiric therapy is IV cefazolin, started after obtaining blood cultures. Children with suspected SA or with AO complicated by an abscess should be evaluated promptly by an orthopaedic surgeon.
3. MRI using gadolinium enhancement is the most sensitive and specific noninvasive test for AO. Radionucleotide

bone scans may be useful when MRI is not available, but it is important to note that they have a lower sensitivity and specificity compared with MRI.

4. Conversion from IV to oral therapy should occur when a patient has clinically improved, inflammatory markers have started to normalize and compliance and follow-up is assured. C-reactive protein testing is recommended to monitor response to therapy and should be normal before stopping therapy.
5. For uncomplicated cases of AO and SA, duration of antimicrobial therapy is generally 3 to 4 weeks (4 to 6 weeks for hip SA) rather than the 6 weeks previously recommended.

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