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GUIDELINES

# Clinical Practice Guideline by the Pediatric Infectious Diseases Society and the Infectious Diseases Society of America: 2021 Guideline on Diagnosis and Management of Acute Hematogenous Osteomyelitis in Pediatrics

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This clinical practice guideline for the diagnosis and treatment of acute hematogenous osteomyelitis (AHO) in children was developed by a multidisciplinary panel representing Pediatric Infectious Diseases Society (PIDS) and the Infectious Diseases Society of America (IDSA). This guideline is intended for use by healthcare professionals who care for children with AHO, including specialists in pediatric infectious diseases, orthopedics, emergency care physicians, hospitalists, and any clinicians and healthcare providers caring for these patients. The panel's recommendations for the diagnosis and treatment of AHO are based upon evidence derived from topic-specific systematic literature reviews. Summarized below are the recommendations for the diagnosis and treatment of AHO in children. The panel followed a systematic process used in the development of other IDSA and PIDS clinical practice guidelines, which included a standardized methodology for rating the certainty of the evidence and strength of recommendation using the GRADE (Grading of Recommendations Assessment, Development and Evaluation) approach. A detailed description of background, methods, evidence summary and rationale that support each recommendation, and knowledge gaps can be found online in the full text.

**Key words.** acute hematogenous osteomyelitis; Guideline; pediatrics; *Staphylococcus aureus*.

## DIAGNOSIS AND MANAGEMENT OF ACUTE HEMATOGENOUS OSTEOMYELITIS IN PEDIATRICS

I. **What noninvasive diagnostic laboratory tests should be performed in children with suspected acute hematogenous osteomyelitis (AHO)?**

**Recommendations:**

1. In children with suspected AHO, we recommend performing blood culture prior to the administration of antimicrobial therapy (strong recommendation and moderate certainty of evidence).
2. In children with suspected AHO, we suggest performing a serum C-reactive protein (CRP) on initial evaluation (conditional recommendation and very low certainty of evidence). **Comment:** Serum CRP has a low accuracy to establish the diagnosis of AHO, but in situations where AHO is confirmed, the serum CRP performed on initial evaluation can serve as the baseline value for sequential monitoring.
3. In children with suspected AHO, we suggest against using serum procalcitonin (PCT) (conditional recommendation and low certainty of evidence).

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## II. What imaging studies should be performed in children with suspected AHO?

**Recommendations:**

1. In children with suspected AHO, we recommend obtaining plain radiography of the potentially infected bone(s) rather than not performing plain radiographs (*strong recommendation* and *moderate certainty of evidence*). **Comment:** Despite the low sensitivity of plain radiography for detecting AHO on initial presentation, other important diagnoses may be ruled out by this simple, quick, safe, and relatively inexpensive imaging test.
2. In children with suspected AHO requiring further imaging studies to confirm the diagnosis, we suggest magnetic resonance imaging (MRI) rather than scintigraphy (bone scan), computerized tomographic (CT) scan, or ultrasound (US) (*conditional recommendation* and *very low certainty of evidence*). **Comment:** For children suspected to have uncomplicated AHO, imaging may not be required to establish or confirm the diagnosis. However, if a child does not respond to medical therapy within 24 to 48 hours or signs and symptoms suggest a potential role for surgical debridement, MRI may be performed to better define the location and extent of infection or to evaluate for an alternative diagnosis such as a malignancy. In children with suspected AHO who have associated joint effusion or other concern for the spread of infection into an adjacent joint (or soft tissues), US evaluation may provide valuable diagnostic guidance for further management. See IDSA/PIDS guideline for the management of bacterial arthritis in children (IN PRESS).

## III. What is the role of invasive procedures in the diagnosis of children with suspected AHO?

**Recommendation:**

1. In children with suspected AHO, we suggest performing invasive diagnostic procedures to collect aspirates and/or biopsy specimens of bone and/or associated purulent fluid collections for routine microbiological studies (aerobic bacteriologic culture and Gram stain) rather than only performing noninvasive diagnostic tests (*conditional recommendation* and *moderate certainty of evidence*). **Comment:** This recommendation places a high value on confirming the microbiological diagnosis to allow optimization of the spectrum and duration of antimicrobial therapy. The decision to implement this recommendation and its timing may be influenced by factors such as local feasibility of obtaining invasive diagnostic procedures (by interventional radiology [IR] or in the operating room), individual clinical situations (eg, need for therapeutic surgical intervention and concerns regarding procedural risks or sedation), positive results of prior noninvasive diagnostic tests (eg, blood culture), and duration of any prior antimicrobial therapy.

## IV. For children who require empiric antimicrobial therapy for AHO, should antibiotics be initiated before invasive diagnostic procedures or can they be withheld until after these procedures are performed?

**Recommendations:**

1. In children with presumed AHO who are ill-appearing or have rapidly progressive infection, we recommend starting empiric antimicrobial therapy immediately rather than withholding antibiotics until invasive diagnostic procedures are performed (*strong recommendation* and *moderate certainty of evidence*). **Comment:** The yield of positive cultures from specimens collected by invasive diagnostic procedures (bone biopsy and aspirate), when obtained within 24 to 48 hours after initiation of antibiotic therapy, is similar to the yield when these cultures are obtained prior to the administration of antibiotics.
2. In children with presumed AHO who are not clinically ill and for whom an aspirate or biopsy by invasive diagnostic procedure is being planned prior to initiating antibiotics, we suggest withholding antibiotics for no more than 48 to 72 hours (*conditional recommendation* and *very low certainty of evidence*). **Comment:** The decision to implement this recommendation incorporating a reasonable delay may be influenced by local accessibility to experts and resources to perform invasive diagnostic procedures or the time required for transport to a higher level of care if appropriate. For children likely to have AHO, it is advisable that children remain hospitalized for observation while withholding antibiotics until cultures can be obtained.

## V. In children with suspected AHO, how should empiric antimicrobial therapy be selected?

**Recommendation:**

1. In children with suspected AHO, we recommend using empiric antimicrobial therapy active against *Staphylococcus aureus* (*strong recommendation* and *moderate certainty of evidence*). **Comment:** Antimicrobials with activity against community-acquired methicillin-resistant *S. aureus* (CA-MRSA) should be considered based on local susceptibility data and patient history with regard to previous CA-MRSA infections and/or colonization. In the presence of a clinical presentation, physical examination, exposure history, or other risk factors that either are inconsistent with *S. aureus* infection or suggest need for coverage for other organisms, additional empiric antimicrobial coverage for pathogens other than *S. aureus* may be warranted (such as younger age for *Kingella kingae* or children with underlying hemoglobinopathies who have increased risk for *Salmonella* spp. infection).

**VI. In children with AHO, in whom should invasive therapeutic procedures be performed at the time of diagnosis?**

**Recommendations:**

1. In children with AHO who present with sepsis or have a rapidly progressive infection, we recommend debridement of the infected bone and any associated abscesses as soon as possible after diagnosis, rather than treating with medical therapy alone (*strong recommendation* and *moderate certainty of evidence*).
2. In a child with AHO who is clinically stable but is documented to have a substantial abscess (greater than 2 cm), we suggest debridement rather than treating with medical therapy alone (*conditional recommendation* and *very low certainty of evidence*).

**VII. In children with AHO, should surgical-site antimicrobial agents be added to systemic antimicrobial therapy?**

**Recommendation:**

1. In children with AHO requiring a surgical procedure, we recommend against routine use of surgical-site (ie, instilled or implanted) antimicrobial agents (*strong recommendation* and *very low certainty of evidence*). **Comment:** This recommendation places a high value on avoiding unnecessary harm and cost associated with this intervention.

**VIII. In children with suspected or confirmed AHO who responds to initial *empiric* therapy, how should *definitive* parenteral and oral therapy be selected?**

**Recommendations:**

1. In children with confirmed AHO, selection of a definitive antibiotic regimen should be based on the principles of selecting an effective agent against the identified pathogen, with the narrowest spectrum, lowest adverse effect profile, and most favorable host tolerance (*Good Practice Statement*).
2. In children with *suspected* AHO without an identified bacterial cause, selection of a definitive antibiotic regimen should be based on the principles of selecting an effective agent based on the most likely causative organism(s), with a spectrum comparable to that on which the patient demonstrated clinical and laboratory improvement, and with the lowest adverse effect profile and most favorable host tolerance (*Good Practice Statement*).

**IX. In children with suspected or confirmed AHO, what clinical and laboratory criteria should be used to assess the response to treatment?**

**Recommendation:**

1. In children with suspected or confirmed AHO receiving antimicrobial therapy, we suggest performing sequential monitoring of CRP in addition to serial clinical evaluation to assess response to therapy, rather than relying solely on clinical evaluation (*conditional recommendation* and *low certainty of evidence*). **Comment:** Serial clinical examinations that assess the febrile response, pain, and musculoskeletal function are important clinical parameters to monitor response to treatment.

**X. In hospitalized children with suspected or documented AHO responding well to initial intravenous therapy and deemed ready for hospital discharge, should they be (1) be transitioned to oral therapy or (2) outpatient parenteral antibiotic therapy (OPAT)?**

**Recommendations:**

1. For children with suspected or documented AHO who respond to initial intravenous antibiotic therapy, we recommend transition to an oral antibiotic regimen rather than OPAT when an appropriate (active against the confirmed or presumed pathogen(s)) and well-tolerated oral antibiotic option is available (*strong recommendation* and *low certainty of evidence*). **Comment:** This recommendation places a high value on avoidance of harms and costs as well as on the improvement of acceptability, feasibility, and equity.
2. For children with suspected or documented AHO who respond to initial parenteral antibiotic therapy but for whom oral antimicrobial therapy is not feasible, we suggest transition to OPAT, rather than remaining in an acute-care hospital for the total duration of therapy (*conditional recommendation* and *very low certainty of evidence*). **Comment:** This recommendation places a high value on avoiding harms and costs associated with unnecessary and prolonged hospital stay. The decision to implement this recommendation and the selection of the type of OPAT (home, intermediate care facility, and clinic) may be influenced by the availability of local resources.

**XI. In children with AHO presumed or proven to be caused by *S. aureus* who have had an uncomplicated course and responded to initial therapy, is a 3- to 4-week total duration of antibiotics (parenteral plus oral) recommended over a longer course?**

**Recommendation:**

1. In children with AHO presumed or proven to be caused by *S. aureus* who have had an uncomplicated course and

responded to initial therapy, we suggest a 3- to 4-week duration of antibiotics rather than a longer course (*conditional recommendation* and *very low certainty of evidence*). **Comment:** Although the optimal duration of therapy is best described for uncomplicated courses of AHO due to methicillin-susceptible *S. aureus* (MSSA), longer duration may be necessary for other pathogens, including more virulent strains of *S. aureus* (such as USA 300 and Panton Valentine leucocidin + [PVL+], whether CA-MRSA or MSSA), and for complicated courses.

**XII. In children with AHO, should end-of-therapy imaging studies be routinely obtained?**

**Recommendations:**

1. In children with uncomplicated AHO that does not involve the physis, we recommend against obtaining end-of-therapy MRI (*strong recommendation* and *low certainty of evidence*) and suggest against routine end-of-therapy plain radiographs (*conditional recommendation* and *very low certainty of evidence*).
2. In children with complicated AHO or with involvement of the physis, we suggest end-of-therapy imaging studies (plain radiographs and/or MRI) (*conditional recommendation* and *very low certainty of evidence*).

**XIII. For children who do not respond to therapy, or relapse following completion of therapy, which interventions are appropriate to optimize outcomes?**

**Recommendations:**

1. For children either experiencing primary treatment failure or early or late recurrence of AHO:
    a. Clinicians should assess the adequacy of the antimicrobial regimen (spectrum of activity, dosage and penetration to the site of infection, and adherence) before deciding on the need to broaden the spectrum or to restart antimicrobials (*Good practice statement*).
    b. Clinicians should reassess the need for surgical intervention for therapeutic and/or diagnostic purposes (*Good practice statement*). **Comment:** The accuracy of the diagnosis of AHO may need to be reconsidered, especially in culture-negative cases.

**XIV. For children who have successfully completed antimicrobial therapy for documented or suspected AHO, in what situations is long-term follow-up required to address potential sequelae?**

**Recommendation:**

1. In children with AHO who are determined to be at risk of long-term adverse outcomes, we suggest a follow-up period of at least 1 year by specialists with experience treating children with AHO (*conditional recommendation* and *low certainty of evidence*).

## INTRODUCTION

Acute hematogenous osteomyelitis (AHO) occurs when bacteria enter and proliferate within the cellular and extracellular matrix of bone, generally accompanied by a host inflammatory response. Bacteria may reach bone matrices via hematogenous spread (primary bacteremia), direct inoculation (traumatic or procedural), or contiguous spread from infection of adjacent soft tissues or synovial fluid. Infection in bones may spread to adjacent joints or soft tissues and into the bloodstream, which can lead to secondary bacteremia with or without additional metastatic foci of infection [1, 2].

The incidence of AHO in children ranges from 1.2 to 13 cases per 100 000 children per year [3–8] and may vary as virulent pathogen strains emerge [8–10] and then wane over time [11]. In children, AHO occurs most frequently in the long bones (eg, femur, tibia, and humerus), but 10% to 25% of cases involve short or non-tubular bones, including the pelvis, vertebrae, clavicle, calcaneus, skull, ribs, and scapula [3, 12–15]. Most of the cases involve a single bone, but about 5% involve multiple bones [12, 14, 16].

The presentation of AHO varies from well-localized infection over a single metaphysis with a minimal associated systemic inflammatory response to multifocal infection with septic shock. Fever and pain are the most common manifestations of bone infection. For infants, pain may be expressed only as a failure to bear weight or reduced use of an extremity [3, 12, 13, 16–19] (the so-called "pseudoparalysis"). Most of the children with AHO present within 1 week of the onset of symptoms, but some cases are more indolent [12, 13, 18]. Edema, warmth, erythema, and tenderness over the infected bone are common but may not always be visible or palpable, depending on the location of infection [13, 17]. Pain or tenderness out of proportion to soft tissue findings should raise suspicion of osteomyelitis rather than merely presumed soft tissue infection [13]. AHO of pelvic bones can present with non-localizing pain, limp, groin pain, or inability to bear weight, which can result in delay in diagnosis [20]. Limp and refusal to walk, along with back pain, may be associated with vertebral osteomyelitis. Bacterial arthritis can occur as an extension of bone infection at any age [21–24].

Many conditions create clinical signs and symptoms that are similar to AHO. Infection of adjacent soft tissues (myositis and pyomyositis) or noninfectious inflammatory conditions such as transient (or toxic) synovitis, discitis, rheumatic fever, polymyositis, juvenile idiopathic arthritis, and post-infectious arthralgias or arthritis may mimic osteomyelitis. Congenital syphilis can involve bones and mimic other etiologies of osteomyelitis

in young infants. Bone tumors such as osteosarcoma, Ewing sarcoma, metastases from neuroblastoma, Langerhans cell histiocytosis, and benign osteochondromas or osteoid osteomas may have clinical presentations that overlap with osteomyelitis [25]. Bone pain may occur from leukemia, bone infarction associated with sickle cell disease, or metabolic defects such as Gaucher disease. Legg-Calve-Perthes disease and slipped capital femoral epiphysis can mimic AHO of the proximal femur. Complex regional pain syndromes and bacterial sepsis may also cause limb pain suggestive of bone infection [1, 26, 27]. Bone fractures sometimes cause fever and, when nondisplaced, may mimic osteomyelitis [28]. Chronic nonbacterial osteomyelitis, an auto-inflammatory disease, is often indistinguishable during the initial presentation from culture-negative AHO.

#### Guideline Focus

This clinical practice guideline focuses on AHO in otherwise healthy children 1 month to <18 years old in North America. Neonates are excluded due to important differences in pathogenesis, management, and outcomes compared with older infants and children. These include differences in bacterial pathogens, sites and progression of infection, immunologic immaturity inherent in the neonate, lack of robust antimicrobial pharmacokinetic data for neonates of various gestational and postnatal ages, and increased risk of poor long-term outcomes based on neonatal bone anatomy. It is reasonable to apply this guideline to infants beyond the neonatal period (4 to 8 weeks of age), including preterm infants who are older than 44 to 48 weeks corrected age at the onset of infection.

The clinical presentations of osteomyelitis and bacterial arthritis can overlap substantially in children and these entities may occur concomitantly [1]. Discitis may be associated with vertebral osteomyelitis in some cases. These entities are not addressed in this guideline and additional information on the diagnosis and management of bacterial arthritis in children is provided in a separate guideline (IN PRESS). Though osteomyelitis can be caused by fungi and mycobacteria, these etiologies and associated clinical circumstances are not common and will not be further discussed. Treatment guidelines or guidance for these entities may be found in organism-specific publications. Bone infections due to loss of integumentary barriers (eg, decubitus ulcers and open fractures), vascular insufficiency from diseases such as diabetes (rare risk factor for pediatric osteomyelitis), or associated with various devices can occur in children but will not be addressed in the current document.

#### Key Definitions

Osteomyelitis traditionally has been divided into acute and chronic infections. Cases also may be classified as having an uncomplicated or complicated course.

The guideline panel has used the following clinical definitions that correspond with treatment recommendations in the guideline:

- *Acute* osteomyelitis is defined as the diagnosis of bone infection within 4 weeks after the onset of clinical manifestations (symptoms or signs) in a previously uninfected bone.
- *Chronic* osteomyelitis is defined as a more protracted, often indolent disease process with (1) presence of a *sequestrum* and/or (2) *relapse* of infection in the same site (bone) weeks to years after apparently successful treatment of the initial infection in that site. Sequestra may arise as a complication of treated or untreated AHO. Relapse can be characterized by intermittent periods of quiescence and recurrent pain, swelling, and/or sinus tract drainage.

*Acute osteomyelitis* includes presentations that may be relatively mild, or "subacute," particularly when the infection is well-localized as well as moderate and severe. These clinical diagnoses can be associated with tissue histopathology that encompass the presence of acute or chronic host inflammatory responses (eg, neutrophilic, mononuclear, and/or eosinophilic infiltrates) that do not per se indicate the presence of acute or chronic osteomyelitis. *Chronic osteomyelitis*, while rare in childhood and adolescence in North America, can occur as an initial clinical presentation or arise as a complication of AHO.

The panel recognizes that some presentations of bacterial osteomyelitis will not fit cleanly into this acute vs chronic dichotomy. Examples include (1) the presence, at the time of initial diagnosis, of a lytic lesion in a metaphysis of a long bone (*Brodie abscess*), which may represent acute or chronic osteomyelitis, or (2) indolent presentations with the onset of symptoms or signs >4 weeks before diagnosis but without clear evidence of chronic osteomyelitis. Management of such presentations should be determined on a case-by-case basis and is influenced by feasibility and success of debridement of sequestra, the pace of healing as evidenced by serial imaging studies during the first several weeks of therapy, and clinical response to antimicrobial therapy.

*Uncomplicated* vs *complicated* course designations are based on features of the clinical presentation and course of treatment. Complicated infections are more likely to require additional diagnostic and therapeutic interventions and a longer duration of therapy (Table 1).

A nuanced approach is important in defining a course as uncomplicated or complicated when this distinction is used to guide management decisions. For example, one or more positive blood cultures alone do not require the designation of a course as complicated. Local extension of infection into adjacent soft tissues that responds rapidly to therapy with or without surgical intervention may also be considered uncomplicated. Although often associated with other clinical features or courses that are reasonably considered complicated, a child with initial sepsis or septic shock who readily responds to treatment may be considered uncomplicated. Growth plate injury or pathologic fracture also may occur when the clinical course

**Table 1. Characteristics of Uncomplicated vs Complicated Osteomyelitis[a]**

| Characteristic | Uncomplicated | Complicated |
|---|---|---|
| Sites of infection | Single bone | • 2 or more bones involved<br>• Additional soft tissue sites of infection beyond the bone (eg, muscle [myositis or pyomyositis], pneumonia, and liver abscess) |
| Clinical response to medical and surgical treatment | Rapid (within 3-5 d), including signs of sepsis or septic shock | • Slow, prolonged response, or lack of clinical response<br>• Need for more than 1 surgery for source control |
| Course of bacteremia when present | Rapid resolution of bacteremia (serial blood cultures become negative when obtained within 1-2 d after the initiation of therapy and source control) | • Prolonged bacteremia (3 or more days), suggestive of uncontrolled infection/distant site(s) of infection |
| Acute sequelae of infection | None | • Venous thrombosis or septic thrombophlebitis<br>• Endocarditis |
| Late sequelae of infection | No findings that suggest risk of physis injury or other short- or long-term osteoarticular sequelae of infection | • Findings concerning for physeal injury with potential impacts on bone growth with long-term sequelae<br>• Presence of or concern for pathologic fracture |

[a]This set of criteria is consensus based with primary focus on clinical findings and course. It may be reasonable to include additional laboratory tests such as the serum C-reactive protein (CRP) in making a determination of an uncomplicated vs complicated course. Concepts such as (1) rapid fall of the CRP concentration within 48 h of initiation of treatment or (2) a 50% or more decline from peak CRP concentration within 3 to 5 d of admission or first surgical debridement may considered. Further research into the various components and functionality of this definition, and any added utility of the CRP or other laboratory markers, will have value and is encouraged.

initially appeared uncomplicated. The infecting strain alone (eg, USA 300 *S. aureus*) also is not a sole determinant of a complicated vs uncomplicated course.

## METHODOLOGY

### Clinical Practice Guidelines

Clinical Practice Guidelines are statements that include recommendations intended to optimize patient care by assisting practitioners and patients in making shared decisions about appropriate health care for specific clinical circumstances. These are informed by a systematic review of evidence and an assessment of the benefits and harms of alternative care options [29]. The "IDSA Handbook on Clinical Practice Guideline Development" provides more detailed information on the processes followed throughout the development of this guideline [30].

### Guideline Panel Composition

The Chair of the guideline panel was selected by the leadership of the Pediatric Infectious Diseases Society (PIDS) in conjunction with IDSA leadership (C. W.). Two co-chairs were selected by the chair to assist in leading the panel (A. C. and J. B.). A total of 20 panelists comprised the full panel. The panel included physicians with expertise in pediatric infectious diseases, pediatric hospital medicine, general pediatrics, pediatric emergency medicine, pediatric orthopedic surgery, and epidemiology. Panelists also were diverse in gender, geographic distribution, and years of clinical experience. A guideline methodologist (V. L.) oversaw all methodological aspects of the guideline development and identified and summarized the scientific evidence using the "PICO" format (Patient/Population [P]; Intervention/Indicator [I]; Comparator/Control [C]; Outcome [O]) questions. IDSA staff (G. D.) oversaw all administrative and logistic issues related to the guideline panel.

### Disclosure and Management of Potential Conflict of Interest

All members of the expert panel complied with the IDSA policy on conflict of interest (COI), which requires disclosure of any financial, intellectual, or other interest that might be construed as constituting an actual, potential, or apparent conflict. Evaluation of such relationships as potential conflicts of interest was determined by a review process which included assessment by the Standards and Practice Guideline Committee (SPGC) Chair, the SPGC liaison to the Guideline panel and the Board of Directors liaison to the SPGC, and if necessary, the Conflicts of Interests Task Force of the Board. This assessment of disclosed relationships for possible COI was based on the relative weight of the financial relationship (ie, monetary amount) and the relevance of the relationship (ie, the degree to which an independent observer might reasonably interpret an association as related to the topic or recommendation of consideration). The reader of these guidelines should be mindful of this when the list of disclosures is reviewed. See the Notes section at the end of this guideline for the disclosures reported to IDSA.

### Clinical Questions and Evidence Review

The clinical practice guideline development started in 2011. A first iteration was nearly completed by 2017 at which point a decision was made to revisit the methodology to fulfill the National Academy of Medicine standards on trustworthy guidelines [29]. In line with these standards, the GRADE (Grading of Recommendations Assessment, Development and Evaluation) approach for the assessment of the certainty of evidence and strength of recommendation was integrated into the process.

Consequently, the initial list of relevant clinical questions for this guideline created by the whole panel was reviewed, restructured, and discussed with co-chairs. The final set of clinical questions was approved by the entire panel. All outcomes of interest were identified a priori and explicitly rated for their relative importance for decision-making. Each clinical question was assigned to a subgroup of panelists.

The Health Sciences Library System at the University of Pittsburgh designed the literature searches and MeSH terms for Ovid Medline, and the William H. Welch Medical Library of Johns Hopkins University—designed the literature searches and MeSH terms for EMBASE and Cochrane Reviews. Searches were limited to studies published in English and restricted to year of publication (from 2005 to 2019). The initial formal literature search was performed in August 2017 and an update of the review of the literature was conducted again in May 2019. To supplement the electronic searches, the panelists had the option of manually searching journals, conference proceedings' reference lists, and regulatory agency websites for relevant articles through 2020.

A subgroup of panelists (A. C. A., M. C. M., S. F., C. J. H., M. P. K., and J. R.) screened titles and abstracts of all identified citations. All potentially relevant citations were subjected to a full-text review, using predefined inclusion and exclusion criteria that were tailored to meet the specific population, intervention, and comparator of each clinical question. Abstracts and conference proceedings, letters to the editor, editorials, review articles, and unpublished data were excluded. The results of the literature search were supervised and thoroughly reviewed by the guideline methodologist for the final selection of the relevant articles. Panel members reviewed the final set of included articles for accuracy. Once the articles were selected, the guideline methodologist in conjunction with panelists extracted the data for surrogates and pre-determined patient-important outcomes. Where applicable, data were pooled using random-effects model (fixed effects model for pooling of rates) using RevMan [31].

The guideline methodologist prepared the evidence summaries for each question and assessed the risk of bias and the certainty of evidence. The risk of bias was assessed by using the Cochrane risk of bias tool for randomized controlled trials [32], the Newcastle-Ottawa scale (NOS) for non-randomized studies [33], and the QUADAS-2 tool for diagnostic test accuracy studies [34]. The certainty in the evidence was determined for each critical and important outcome and then for each recommendation using the GRADE approach for rating the confidence in the evidence [35, 36] (see Figure 1). The summaries of evidence were developed in the GRADEpro Guideline Development Tool [37] and reviewed by panel members responsible for each PICO and edited as appropriate. The final evidence summaries were presented to the whole panel for deliberation and drafting of recommendations. Literature search strategies, Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow-diagram detailing the search results, and evidence profiles tables, and additional data, such as meta-analysis results when appropriate, can be found in the Supplementary Material.

Ranking of the outcomes by importance for decision-making was determined by consensus for each PICO question. In situations where a PICO question compared the use of one specific antibiotic regimen to another (eg, comparing spectrum of activity, route of administration, or duration of therapy) and the beneficial effects of the 2 regimens were similar, then the undesirable outcomes could be ranked as critical for decision-making, but several other considerations might have also been taken into account, such as antimicrobial stewardship issues for appropriate use, as well as costs.

#### Development of Clinical Recommendations

All recommendations were labeled as either "strong" or "conditional" according to the GRADE approach [30]. The words "we recommend" indicate strong recommendations and "we suggest" indicate conditional recommendations. Figure 1 provides the suggested interpretation of strong and conditional recommendations for patients, clinicians, and healthcare policymakers. For recommendations where the comparator treatment or tests are not formally stated, the comparison of interest is implicitly referred to as "not using the intervention" (either not using a specific treatment or a diagnostic test).

High-quality evidence was lacking for many recommendations. According to GRADE guidance on discordant recommendations, strong recommendations in the setting of lower-quality evidence were only assigned when the panelists believed they conformed to 1 of the 5 accepted paradigmatic conditions [38]. For recommendations pertaining to good practice statements, appropriate identification and wording choices were followed according to the GRADE working group [39]. A good practice statement represents a message perceived by the guideline panel as necessary in regard to actual current healthcare practice, is supported by a large body of indirect evidence difficult to summarize, and indicates that implementing this recommendation would clearly result in large net positive consequences. "Research Needs" were noted for recommendations as deemed appropriate by the panel.

The final presentation of evidence summaries and the development of the recommendations was performed by a face-to-face meeting of the whole expert panel in San Francisco, CA, in October 2018, which was followed by a series of conferences (from November 2018 to September 2019). All members of the panel participated in the preparation of the draft guideline and approved the recommendations.

#### Revision Process

Feedback was obtained from 3 external individual peer expert reviewers. The guideline was reviewed and approved by the Pediatric Orthopaedic Society of North America (POSNA). The IDSA Standards and Practice Guidelines Committee (SPGC) and Board of Directors and PIDS Board of Directors reviewed and approved the guideline prior to publication. The guideline was also reviewed by appropriate sections and committees of the American Academy of Pediatrics.

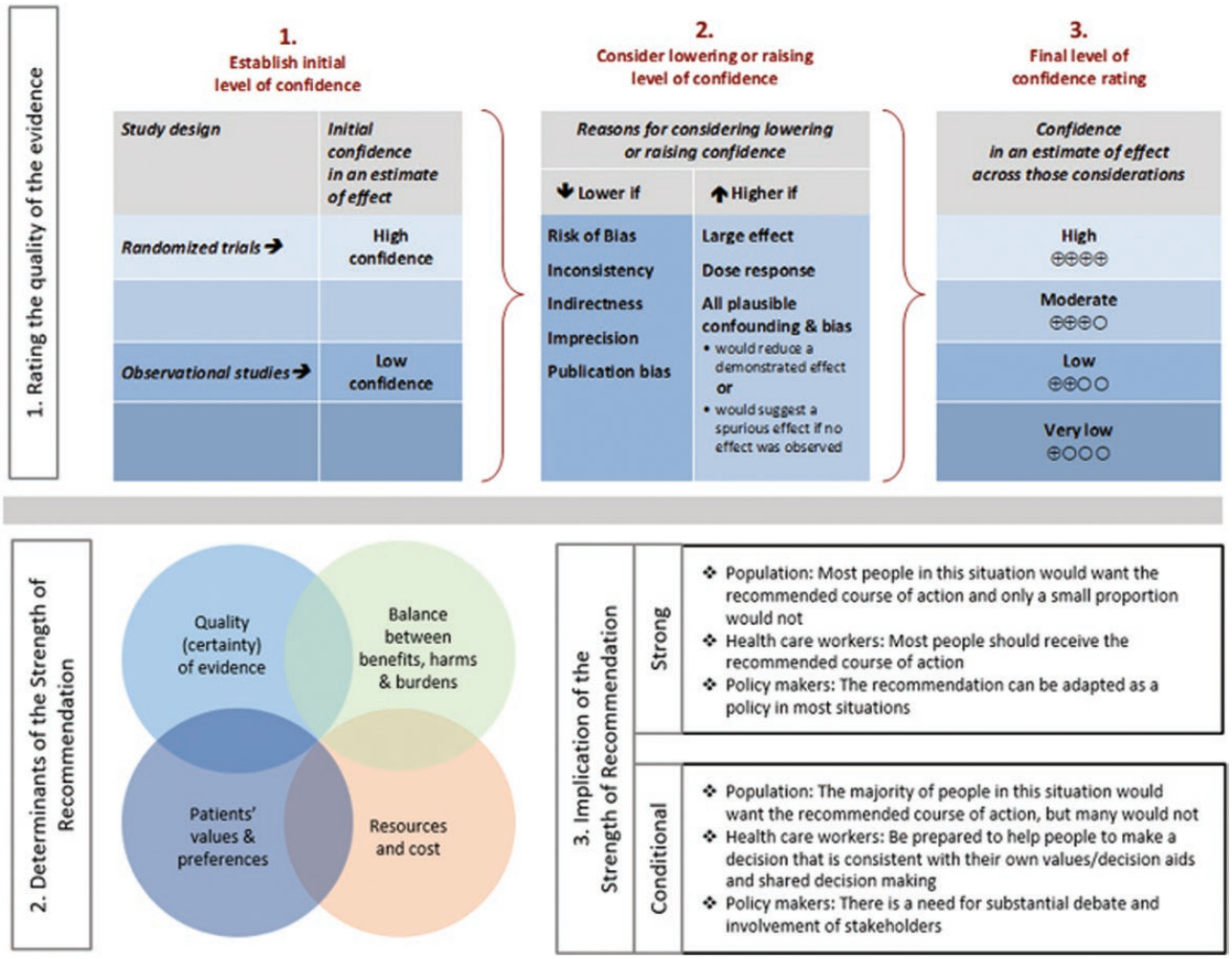


**Figure 1.** Approach and implications to rating the quality of evidence and strength of recommendations using the GRADE (Grading of Recommendations Assessment, Development and Evaluation) methodology.

#### Revision for Currency Schedule

Approximately, every 2 years and more frequently if needed, IDSA and PIDS will determine the need for revisions to the guideline by an examination of the current literature and the likelihood that any new data will have an impact on the recommendations. Any revision to the guideline will be submitted for review and approval to the appropriate Committees and Boards of IDSA and PIDS.

## DIAGNOSIS AND MANAGEMENT OF AHO IN PEDIATRICS

### I. What noninvasive diagnostic laboratory tests should be performed in children with suspected AHO?

**Recommendations:**

1. In children with suspected AHO, we recommend performing blood culture prior to the administration of antimicrobial therapy (*strong recommendation* and *moderate certainty of evidence*).
2. In children with suspected AHO, we suggest performing a serum C-reactive protein (CRP) on initial evaluation (*conditional recommendation* and *very low certainty of evidence*). **Comment**: Serum CRP has a low accuracy to establish the diagnosis of AHO, but in situations where AHO is confirmed, the serum CRP performed on initial evaluation can serve as the baseline value for sequential monitoring.
3. In children with suspected AHO, we suggest against using serum PCT (*conditional recommendation* and *low certainty of evidence*).

#### Complete Blood Count

***Background***

As for many other infectious diseases, a complete blood count (CBC) with differential is generally performed on initial evaluation of children with suspected AHO to assess the severity of infectious processes (eg, anemia and thrombocytopenia) as well as to provide useful information regarding

alternative diagnoses (eg, leukemia). The peripheral white blood cell (WBC) count can be elevated (leukocytosis) but is in the normal range in most of the children with AHO [3, 5, 10, 40–45]. The accuracy of the WBC count for the diagnosis of AHO is less than that of CRP [4, 46]. WBC count may be higher on average when (MRSA is the etiology compared with MSSA, other pathogens, or with culture-negative status [47], and in complicated compared with uncomplicated cases [42]. WBC counts overlap considerably among these etiologies and scenarios and do not provide discriminatory value. Although the WBC count has a very low accuracy for the diagnosis and stratification of AHO, the information provided by a CBC can provide important adjunctive information for decision-making for children with suspected or confirmed AHO. Anemia and reactive thrombocytosis may be seen in some children with AHO at presentation [48, 49].

### Blood Culture

#### *Summary of Evidence*

Blood cultures are routinely performed to identify the specific etiologic agent in AHO. Our systematic review of the literature identified 2 meta-analyses plus 17 recent case series that provided data on the yield of blood culture in pediatric AHO [3, 49]. Dartnell et al [3] reviewed the literature up to 2010 and reported the trend of blood culture positivity in AHO during different time frames from pre-1990 to post 2000. Throughout the studied period, the blood culture positivity rate was similar across time periods, ranging from 41% (pre-1990) to 44% (1990–2000) [3, 49–62]. Russell et al [49] reviewed the literature up to 2014 and reported a pooled analysis of blood culture positivity rate in children with AHO of 21.5% (95% confidence interval [CI]: 10.9 to 34.5) from 4 European studies.

Our systematic review of the literature included 17 studies reporting the positivity rate of blood culture in pediatric AHO from 2005 to 2019 (see Supplementary Material) [4, 20, 45, 49–62]. These studies collectively included 1422 patients with confirmed osteomyelitis (ranging from 10 to 303 patients per study). Individual studies indicated that approximately one-third of blood cultures from children with AHO will yield the causative organism (median of 34.2%, range from 11.0% to 48.5%). The pooled positivity rate of blood culture from these studies is 31.2% (95% CI: 26.3 to 36.0) (see Figure 2). Additionally, in one series that included 286 children with osteoarticular infections exclusively due to *S. aureus*, 155 (54.2%) had a positive blood culture [63].

Blood culture contamination (false-positive results) occurs at a low frequency, generally fewer than 5% of cultures. Microbes such as coagulase-negative staphylococcal species, alpha-streptococci (other than *S. pneumoniae* or *S. anginosus* group), *Bacillus* species, Corynebacteria (diphtheroids), and Cutibacteria (formerly Propionibacteria) are typical causes of false-positive blood culture results [50, 52, 56]. It is often

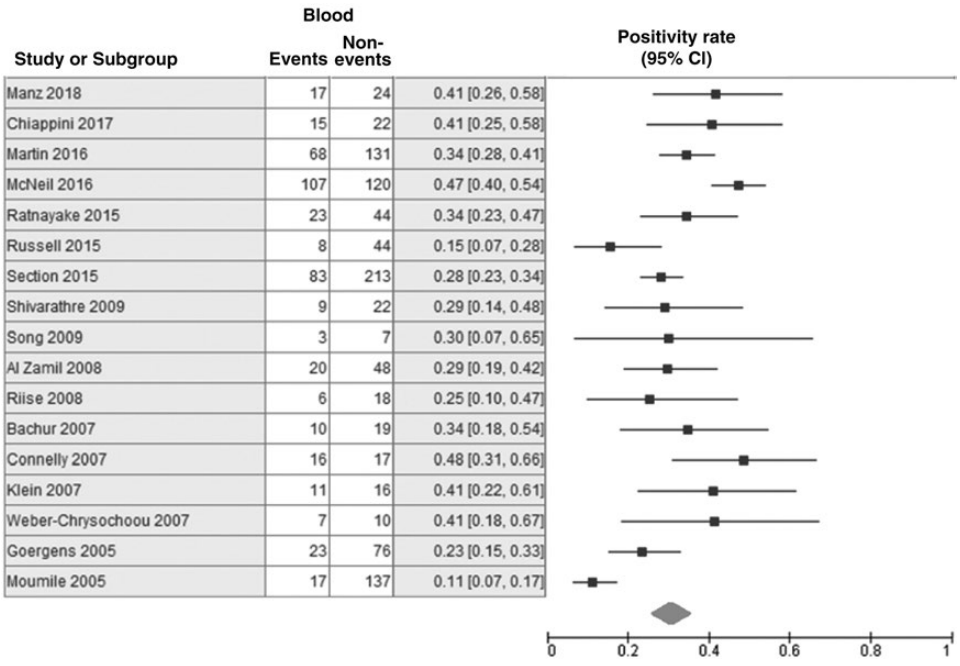


**Figure 2.** Forest plot of positivity rate of blood culture (BC) on admission (prior to the administration of antimicrobial therapy) in children with acute hematogenous osteomyelitis (AHO). Pooled positivity rate of blood culture (n = 1,422 patients, 17 studies) = 31.2% (95% CI: 26.3 to 36.0). Studies that reported osteoarticular infections without stratifying patients for their underlying type of infections were excluded. If stratification was performed and relevant information on patients with AHO was available, then this study was included in the meta-analysis, and only patients diagnosed with at least an AHO were included in the pooled results presented here. Characteristics of included studies are shown at the end of the Diagnosis Section of Supplementary Material. Abbreviation: CI, confidence interval.

relatively easy to classify such organisms as contaminants, but consultation with pediatric infectious diseases experts and the clinical microbiology laboratory may be needed for final interpretation.

Although the proportion of cases of AHO with confirmed microbial etiology is usually improved when specimens from bone or adjacent sites of infection are obtained for culture and/or Polymerase Chain Reaction (PCR)-based testing in addition to blood culture (see III) [3, 49–51, 54, 60, 64–66], blood cultures sometimes provide the only positive microbiological result even when bone specimens are obtained. Identification of the causative pathogen from blood cultures may also obviate the need for subsequent bone aspiration that would otherwise be pursued only for microbiological diagnostic purposes [67].

Persistently positive blood cultures can also help identify patients with associated deep venous thrombosis (DVT) (or need for source control—see VI and XIII). In a series of 466 children with AHO, of whom 28 (6%) had DVT, the rate of positive blood culture was significantly higher in those with DVT (82%) than in those without (38%) [68]. All 28 with DVT had *S. aureus* infection (10% of the 274 *S. aureus* cases). The presence of DVT was also associated with more frequent persistence of bacteremia and greater severity of illness, in the form of more intensive care unit (ICU) admissions and surgical interventions.

***Rationale for Recommendation***

Blood cultures performed prior to the administration of antimicrobial therapy in a child with suspected AHO currently identify the microbial etiology of AHO in about a third of cases, usually within 12 to 24 hours. In some cases, blood cultures provide the only positive result, even when invasive/intraoperative cultures also are obtained. Positive blood cultures may obviate the need for invasive diagnostic specimens. The yield of blood cultures obtained after the initiation of effective antibiotics generally declines rapidly over a few hours of exposure, best described with *S. aureus*, but likely to occur with all susceptible pathogens. Blood cultures have low cost and the primary undesirable effects are those associated with venipuncture. False-positive results due to contamination generally are readily discernible and do not generate undesirable consequences once the organism is speciated. The panel made a strong recommendation for the use of blood cultures as part of the initial evaluation for potential AHO based on the benefits that clearly outweigh risks.

### C-Reactive Protein

***Summary of the Evidence***

AHO remains a diagnosis primarily pursued based on clinical suspicion from the history and physical examination. CRP is a nonspecific, acute-phase inflammatory reactant that is elevated in most of the children with AHO. Despite widespread adoption, high-quality data regarding the utility of elevated CRP values as a useful diagnostic test for AHO in children are limited. One systematic review of AHO in children reported a pooled sensitivity of CRP of 80.5% (ranging from 75.9% in one cohort, which included culture-negative osteomyelitis, and up to 100% in patients presenting with concomitant septic arthritis) [3]. Another systematic review noted a range of sensitivity of 72% to 89% [46], with a lower sensitivity of 47% in a series of children with AHO of the calcaneus [69].

Our systematic review of the literature identified 6 published studies from 2005 to 2019 assessing the diagnostic test accuracy of CRP in children suspected of AHO. Characteristics of the studies as well as diagnostic test accuracy data are shown in Supplementary Material [4, 5, 41, 70–72]. Collectively, these studies indicate very limited value for CRP as a diagnostic test for AHO in children. Numeric cutoffs varied between studies and none established a definitive CRP value above which the diagnosis of osteomyelitis should be suspected. One study provided area under the curve (AUC) data for CRP, which also showed low accuracy [4]. All 6 studies have significant methodological limitations. One prospective cohort study compared CRP with compatible clinical manifestations, cultures, and imaging but was limited by small sample size [41]. One evaluated 259 patients with both CRP and ESR, retrospectively, and determined CRP aided in the diagnosis but lacked a well-defined reference standard [71]. Two studies prospectively evaluated patients with clinical suspicion of limp and/or osteomyelitis, but enrollment was based on the presence of elevated inflammatory markers [4, 72]. Two case-control studies selected control groups that may bias toward the overestimation of the accuracy of CRP for AHO [5, 70]. One retrospective study evaluated patients presenting to an emergency department (ED) with atraumatic limb pain that included 17 children with orthopedic infection and 242 with other etiologies (prevalence of infection of 6.6%). Deriving the optimal cutoff from the dataset (cutoff presumed at 7 mg/dL or 70 mg/L), they reported a negative predictive value of 97% [71]. This result suggests that serum CRP performed in a similar context might be helpful to rule out osteoarticular infections, but the value of this strategy has yet to be confirmed by prospective studies.

Several case series have suggested that 62% to 98% of children with culture-positive osteomyelitis will have an elevated CRP on admission [42, 44, 49]. CRP values in general are higher in cases with increased disease severity [47, 73]. Two studies suggest that CRP values are higher on average in children with bacteremia compared with those without bacteremia [49, 74]. The AUC for CRP in prediction of bacteremia in these 2 studies were 0.59 [74] and 0.75 (CRP cutoff of 4.25 mg/dL or 42.5 mg/L) [49], respectively. Mean CRP values were reported to be higher in children with osteomyelitis plus bacterial arthritis than in children with osteomyelitis alone (and CRP values in children with bacterial arthritis alone are higher than both osteomyelitis groups) [3, 42, 45]. The considerable overlap

in values precludes the use of CRP to distinguish the presence or absence of bacterial arthritis in children with suspected osteomyelitis or vice versa [43].

Initial CRP results can vary by causative organism. CRP values appear to be higher on average for AHO caused by *S. aureus*, and particularly CA-MRSA strains, than for other microbes or culture-negative cases [3, 6, 10, 47, 48, 60, 64, 75, 76]. Some [10, 47] but not all [9] studies have described higher mean CRP concentrations in cases due to MRSA than MSSA. CRP was normal in 9 (39%) of a series of 23 children with osteoarticular infections due to *K. kingae* [64].

CRP values appear to be higher when complications such as subperiosteal abscess, pyomyositis, and deep vein thrombosis (DVT) are present, though specific thresholds for reasonably ruling these in or out are not established [68, 77–81]. Initial CRP values did not differ between *S. aureus*-related cases with and without orthopedic complications in one study [63].

The differential diagnosis of CRP elevation is broad. In general, bacterial infections elicit higher CRP concentrations than viral infections, but there can be considerable overlap. Interpretation may be difficult in patients with a concomitant viral illness. CRP can be elevated due to inflammation associated with autoimmune or autoinflammatory conditions, and some malignancies, as well as tissue trauma, including surgery [82–85].

#### *Rationale for Recommendation*

The existing literature regarding CRP as a diagnostic test for AHO is limited by small sample sizes, poor methodology, varied populations of interests (ie, wide range of pretest probabilities) and control groups, varied reference standards, use of different numeric cutoffs, and verification bias. Results suggest limited accuracy in discriminating AHO from other infectious or noninfectious processes. Despite these issues, in a child with suspected osteomyelitis, we suggest performing a CRP on initial evaluation. CRP is offered in most of the hospital settings, requires a blood draw, is relatively inexpensive, and produces results that usually are quickly available. When taken in the context of the clinical presentation and other testing modalities, CRP may add benefit for multidisciplinary clinical decision-making for children with clinically suspected AHO. The primary utility of CRP on admission is as a baseline for serial measurements during the treatment course (see VIII). Normal or minimally elevated concentrations of serum CRP do not exclude AHO but may raise the need to explore potential noninfectious etiologies of the clinical presentation.

### Erythrocyte Sedimentation Rate

#### *Background*

The erythrocyte sedimentation rate (ESR) became a common test used in the management of AHO in children in the 1970s, primarily as a serial measurement used to guide the duration of therapy [18, 86]. Its use in children with AHO in North America appears to have declined as CRP use increased starting in the mid-1990s. Historically, case series have described ESR elevation in 90% to 100% of children with AHO [3, 18, 41, 70, 87], but rates as low as 70% to 87% also have been reported [57, 61]. The ESR functions similarly to the CRP in terms of diagnostic utility for AHO in children, with predictive values that vary based on the various cutoffs that were used [4, 5, 41, 70, 71]. ESR combined with CRP may slightly improve sensitivity and negative predictive value for the diagnosis of AHO [40, 70–72], but specific thresholds and the overall clinical utility of using both CRP and ESR for diagnostic purposes remain uncertain. The ESR tends to rise more slowly than CRP in acute infection and to decrease more slowly than CRP in an appropriately treated infection; the ESR is no longer used routinely to diagnose AHO in children.

### Procalcitonin

#### *Summary of Evidence*

PCT is an acute-phase reactant that increasingly is being used to support clinical decision-making around initiation and discontinuation of antibiotics in a variety of clinical scenarios [88–91]. Higher serum concentration of PCT is seen more commonly in severe bacterial infections than viral infections and inflammatory diseases [89, 92]. PCT is increasingly available in North American centers with clinically useful turn-around time for test results, similar to CRP.

Our systematic review of the literature identified 3 studies that have evaluated the diagnostic accuracy of serum PCT concentration in children suspected to have AHO [41, 93, 94]. Two of these reports consisted of prospective cross-sectional studies evaluating consecutive patients suspected to have AHO and/or bacterial arthritis to assess the accuracy of PCT on admission. Both studies used a prespecified cutoff value $\geq$ 0.5 ng/mL [41, 93], and a total of 383 patients were included, but the reported prevalence of osteoarticular infections varied widely between the 2 studies (14.2% and 52.2%). PCT diagnostic test accuracy ranged as follows: sensitivity from 13% to 43%, specificity from 97% to 100%, positive predictive value from 40% to 100%, and negative predictive value from 62% to 87% (see Supplementary Material). These wide variations in accuracy might be explained by the different populations included in each study (eg, Butbul-Aviel only included limping children with fever), by the different reference standards used to confirm the final diagnosis of osteoarticular infections (Faesch included a "presumed infection" group, which were culture-negative infections) as well as the small sample size (especially in the Butbul-Aviel study, which only included 44 patients).

The third cross-sectional study assessed the accuracy of PCT in 187 patients suspected to have osteomyelitis (further diagnosed as having acute osteomyelitis or non-acute osteomyelitis) as compared with 80 healthy volunteers [94]. The reported

sensitivity and specificity for the diagnosis of acute osteomyelitis were 77.2% and 69.5% with a cutoff of 3.56 ng/mL (cutoff being driven by the dataset rather than prespecified). Due to the methodological limitations, the reported accuracy of PCT may be overestimated.

***Rationale for Recommendation***

The available studies of PCT as a diagnostic test for AHO in children exhibited multiple methodological limitations, leading the panel to judge that PCT is likely not accurate enough to be used for the diagnosis of osteoarticular infections. The evidence available at this time does not show any advantage of PCT over CRP or ESR as a diagnostic test for AHO in children. Obtaining a serum PCT is similar from a patient perspective to serum CRP (ie, discomfort from phlebotomy and costs of testing). There is no published experience to date regarding the utility of serial measures of PCT in children with AHO. Thus, the panel suggests against obtaining a serum PCT as part of the evaluation of children with suspected or confirmed AHO.

***Research Needs***

Future prospective studies to determine a particular serum CRP threshold that is reasonably predictive of the diagnosis of AHO would be helpful. Use of an appropriate reference standard such as a positive culture or molecular test from bone, tissue, or blood in association with compatible imaging results will be essential. Similar prospective evaluation of CRP utility in AHO caused by various organisms (eg, *S. aureus, S. pyogenes, Kingella,* and *Salmonella*) or when AHO is culture-negative also would be helpful. The roles of PCT and ESR also may merit further evaluation for clinical utility, primarily as baseline tests to assist in subsequent management decisions. Identification of better inflammatory markers to assist in the diagnosis of AHO is needed. Studies evaluating the utility of emerging molecular diagnostic technologies on blood specimens will be important, as these may increase the yield of blood specimens for microbial etiologies in AHO.

## II .What imaging studies should be performed in children with suspected AHO?

**Recommendations:**

1. In children with suspected AHO, we recommend obtaining plain radiography of the potentially infected bone(s) rather than not performing plain radiographs (*strong recommendation* and *moderate certainty of evidence*). **Comment:** Despite the low sensitivity of plain radiography for detecting AHO on initial presentation, other important diagnoses may be ruled out by this simple, quick, safe, and relatively inexpensive imaging test.
2. In children with suspected AHO requiring further imaging studies to confirm the diagnosis, we suggest MRI rather than scintigraphy (bone scan), CT scan, or US (*conditional recommendation* and *very low certainty of evidence*). **Comment:** For children suspected to have *uncomplicated* AHO, imaging may not be required to establish or confirm the diagnosis. However, if a child does not respond to medical therapy within 24 to 48 hours or signs and symptoms suggest a potential role for surgical debridement, MRI may be performed to better define the location and extent of infection or to evaluate for an alternative diagnosis such as a malignancy. In children with suspected AHO who have associated joint effusion or other concern for the spread of infection into an adjacent joint (or soft tissues), US evaluation may provide valuable diagnostic guidance for further management. See IDSA/PIDS guideline for the management of bacterial arthritis in children (IN PRESS).

### Plain Radiographs

***Summary of the Evidence***

Plain radiographs have been a mainstay of the initial management of AHO in children for decades. The primary and important value of plain films at the time of initial presentation is to identify or exclude other pathologic conditions such as bone tumors or fractures [3, 95].

A systematic review of 3 studies published in 2012 reported that sensitivity of plain films for the detection of AHO ranged from 16% to 20%, whereas specificity ranged from 80% to 100% [3, 77, 96, 97]. Our systematic review of the literature from 2005 to 2019 identified only 1 study reporting all 4 accuracy measures (sensitivity, specificity, and negative predictive and positive predictive values) [96]. This study of 183 patients with suspected AHO showed low sensitivity (16%) at initial presentation, but the reported specificity and positive predictive value were each 96% [96]. In 4 other studies that provided only sensitivity data, sensitivity ranged from 20% to 37% [7, 44, 45, 77].

Plain films are more likely to show abnormal bone findings in children with prolonged duration of symptoms prior to presentation. Soft tissue swelling and loss of fat planes around bones may be evident within 3–10 days of the symptom onset. Adjacent joint space widening suggests effusion from a concurrent bacterial arthritis. Periosteal thickening or elevation, focal osteopenia, or osteolytic lesions, which require >30% to 50% bone loss to be detectable on plain radiographs, usually are not evident until 10–20 days after the onset of symptoms. Sclerosis is a relatively late finding (>21 days after onset). The sensitivity of plain films for the presence of AHO thus increases over time [87, 96]. Plain radiographs, therefore, may also provide information on chronicity or duration of bone infection [1].

Plain radiographs are readily available, have low radiation dosage and relatively low costs, and do not require sedation [95]. Normal findings in plain radiographs at presentation do not exclude the presence of AHO, and any abnormalities seen on subsequent plain radiographs generally represent the natural

history of the infectious process rather than evidence of deterioration if the child is clinically improving.

#### *Rationale for Recommendation*

Although the sensitivity of plain radiographs for the diagnosis of AHO is low, their value both in narrowing the differential diagnosis and as potential baseline studies outweighs the concern around the high false-negative rate for AHO. Because the overall benefits exceed risks, the panel thus makes a strong recommendation that plain radiographs remain a routine part of the evaluation of children with suspected AHO.

### Advanced Imaging: MRI, Scintigraphy, CT, and US

Advanced imaging is often necessary to more definitively establish the presence of AHO or more precisely define the extent of infection in and around the infected bone as well as rule out other noninfectious processes. MRI, bone scintigraphy, CT, and US have all been used for these purposes and have varying potential roles in the diagnosis and management of AHO (see also XII).

### Diagnostic Test Accuracy for the Diagnosis of AHO

#### *Summary of the Evidence*

Our systematic review of the literature identified a total of 12 studies published between 2005 and 2019 reporting on the diagnostic test accuracy of one or more advanced imaging studies for the diagnosis of AHO [4, 7, 44, 45, 57, 77, 96, 98–102]. Sensitivity of MRI for the diagnosis of AHO ranged from 81% to 100% in 8 studies [4, 44, 45, 77, 96, 98–100] and specificity ranged from 67% to 94% in 5 studies [4, 96, 98–100]. MRI with gadolinium contrast administration has slightly better sensitivity than MRI without contrast [98, 99, 102]. Positive predictive values ranged from 80% to 93% [4, 96, 99] but may be somewhat lower in children with sickle cell disease (76% in a single study) [100]. Sensitivity of bone scintigraphy ranged from 30% to 91% in 6 studies [4, 7, 44, 57, 77, 96], whereas specificity was reported to be 47% and 84% in 2 of these studies [4, 96]. Data regarding the accuracy of CT and US for the diagnosis of AHO in children are more limited in terms of sample size and number of studies. The diagnostic test accuracy of CT was reported in only 2 studies: sensitivity was 67% to 100% [44, 96] and specificity was 50% in 1 of the 2 studies [96]. Lastly, sensitivity of US varied from 17% to 76% in 4 studies [44, 45, 96, 101], and specificity was reported to be 47% and 91% in 2 studies [96, 101]. The wide variation observed in diagnostic test accuracy of the different imaging modalities may have resulted from differences in population selection (suspected vs confirmed AHO and AHO caused by various bacteria vs restricted to *S. aureus* only), in the timing of each imaging study, in the reference standard (MRI only vs extended reference standard including multiple tests), and from potential verification bias (not all patients received the same tests in all studies).

Of these 13 studies initially identified through our systematic review of the literature, 5 studies directly comparing the diagnostic accuracy of MRI with other imaging modalities in the same cohort of patients suspected of AHO (see Table 2). Among 4 recent studies evaluating MRI and technetium-99 3-phase scintigraphy (bone scan), the comparative sensitivity ranged from 81% to 100% for MRI and from 53 to 91% for scintigraphy [4, 44, 77, 96], and the comparative specificity was 67% to 94% for MRI and 47% to 84% for scintigraphy [4, 96]. Similar results were seen in 2 older studies [103, 104]. Based on these reviewed studies, the committee concluded that MRI has better overall diagnostic test accuracy than bone scintigraphy for the diagnosis of AHO.

Similarly, among 2 studies evaluating the accuracy of MRI and CT, comparative sensitivity ranged from 81% to 100% for MRI and from 67% to 100% for CT [44, 96]; comparative specificity was 67% for MRI and 50% for CT [96]. These 2 studies were judged imprecise due to the small sample size. However, an older study of a slightly larger patient cohort showed similar

**Table 2. Comparative Diagnostic Accuracy of Different Imaging Modalities vs Magnetic Resonance Imaging (MRI) in Children With Suspected Acute Hematogenous Osteomyelitis (AHO)[a]**

| | N | Sensitivity (95% CI) | Specificity (95% CI) |
|---|---|---|---|
| MRI vs bone scintigraphy | | | |
| MRI | 343 | 81% (64-93) to 100% (90-100) [4, 44, 77, 96] | 67% (22-96) to 94% (86-98) [4, 96] |
| Bone scintigraphy | 236 | 53% (38-67) to 91% (80-97) [4, 44, 77, 96] | 47% (31-64) to 84% (60-97) [4, 96] |
| MRI vs CT scan | | | |
| MRI | 57 | 81% (64-93) to 100% (82-100) [44, 96] | 67% (22-96)[96] |
| CT scan | 25 | 67% (38-88) to 100% (63-100) [44, 96] | 50% (1-98)[96] |
| MRI vs ultrasonography | | | |
| MRI | 95 | 81% (64-93) to 100% (91-100) [44, 45, 96] | 67% (22-96)[96] |
| Ultrasonography | 177 | 17% (9-28) to 60% (41-77) [44, 45, 96] | 47% (24-70)[96] |

Abbreviations: CI, confidence interval; CT, computerized tomographic; MRI, magnetic resonance imaging.

[a]Ranges of diagnostic test accuracy results were presented due to the small number of studies included in the analysis. Furthermore, missing information on absolute number of patients receiving the index tests according to the final diagnosis in the Malcius study precluded pooling of sensitivity and specificity. Various sources of heterogeneity between studies (eg, presence of verification bias, ie, not all tests were performed in all patients, or significant difference of timing between tests) and variation in reference standard (based on MRI or other criteria) further impeded any meaningful interpretation of pooled results [4, 44, 45, 77, 96].

results (sensitivity of 86% for MRI vs 62% for CT and specificity of 100% for MRI and 75% for CT) [103]. The panel concluded that MRI has better diagnostic accuracy than CT for the diagnosis of AHO.

Lastly, 3 studies directly compared the accuracy of MRI and US: sensitivity ranged from 81% to 100% for MRI and 17% to 60% for US [44, 45, 96], whereas specificity was 67% for MRI and 47% for US in 1 study [96]. Again, the panel concluded that MRI was more accurate than US for the diagnosis of AHO.

#### Additional Considerations

##### *Magnetic Resonance Imaging*

MRI has supplanted skeletal bone scans as the advanced imaging modality of choice when information regarding the presence or extent of infection is needed beyond that provided by physical findings and plain radiography results [45, 59, 105, 106].

MRI can detect subperiosteal and adjacent soft tissue abscesses plus sinus tracts and high-signal periarticular changes suggestive of concomitant septic arthritis. MRI provides more anatomic information than radiographs, scintigraphy, or CT; MRI does not use ionizing radiation [95]. MRI also offers an advantage over scintigraphy in the detection of deep vein thromboses associated with AHO mostly caused by some virulent *S. aureus* strains (often MRSA) [107]. MRI interpretation in AHO at presentation is not significantly affected by prior surgical interventions [108]. However, false-positive MRI results can be due to noninfectious inflammatory diseases, fractures, or bone stress reactions [100].

MRI has potential negative aspects. The time and lack of body motion required to perform MRI often require sedation in young children. Arranging MRI studies with sedation can lead to imaging delays that may also lead to an undesirable delay in needed clinical decision-making including surgical intervention. To mitigate delays, limited or rapid sequence MRI and whole-body MRI procedures are being evaluated but are not yet validated or routinely available [109, 110].

MRI is a valuable modality in many cases of suspected AHO, especially when there is concern for soft tissue extension or need for localization of infection to guide surgical procedures to obtain specimens or achieve source control. However, MRI is not necessary for appropriate management in all cases. In presentations where the clinical and/or plain radiograph findings are sufficiently suggestive of AHO and surgical intervention is deemed unnecessary, the need for further imaging can be based on the subsequent clinical course (see XII).

##### *Bone Scintigraphy*

Bone scan has been the most commonly used nuclear medicine approach for the diagnosis of AHO in children and was the preferred advanced imaging modality in many centers prior to the early 2000s. Nevertheless, fractures, malignancy, osteoid osteoma, soft tissue cellulitis, and pyogenic arthritis also can result in positive scan results [97, 103, 111, 112]. Positive bone scans do not always effectively delineate the disease process and may require follow-up with more definitive imaging such as MRI. Bone scans may be falsely negative in the first 48 hours of infection or in the presence of large subperiosteal abscess that limits blood flow (and in neonates) [113].

Sedation is not routinely required for bone scan but may be required for young children [111]. Radiation dosages of bone scans are low [114]. Given the greater sensitivity of MRI for diagnosis of AHO and its lack of radiation exposure, the primary utility for bone scans in this era is in selected presentations where suspected AHO is not clinically localizable or is potentially multifocal [3, 106], more definitive imaging such as MRI is not readily available, or sedation risks are deemed to outweigh potential benefits of more definitive imaging.

Gallium imaging, indium or technetium tagged-WBC scans, and other nuclear medicine approaches have been used as diagnostic tests for AHO, but there is far less experience with these than bone scans in children with suspected AHO. Gallium and indium scans have higher radiation doses than technetium scans and require a 24-hour wait time for final imaging post injection. Indium scans require 20–40 mL of patient blood as a source for WBC [44, 95, 112]. These types of scans may have utility in highly selected circumstances, in consultation with experts in pediatric nuclear medicine and radiology.

##### *Computed Tomography*

CT requires significant radiation exposure, though study times are short (usually obviating the need for sedation) and access is usually readily available. CT may be an appropriate alternative to MRI in circumstances in which CT imaging can be obtained in a more timely manner than MRI and/or avoidance of sedation is an important clinical consideration. Similar to plain radiographs that may not show changes for 1–2 weeks, the sensitivity of CT early in AHO is not well defined but is likely to be less than MRI which can identify bone marrow edema early in the course of infection. CT imaging may demonstrate cortical bone destruction, gas in bone, or presence of bony sequestra better than MRI, but these findings are not common in AHO in children [115].

##### *Ultrasound*

US can detect subperiosteal and soft tissue fluid collections when these are associated with AHO but cannot provide the evaluation of bone or bone marrow per se. Cortical erosion (irregularity) may be detectable when symptoms have been present for more than 1 week [116–119]. US is not routinely recommended for the diagnosis of AHO but may have a greater role in resource-poor practice settings to detect subperiosteal or soft tissue abscess where the availability of MRI is limited.

US can be useful for guiding aspiration of fluid collections, including joint effusions of associated bacterial arthritis, in suspected AHO [95, 119]. It also may have a role in children with sickle cell disease when there is a need to distinguish between AHO and vaso-occlusive crisis: the presence or absence of subperiosteal fluid collections had PPV of 85% and NPV of 85%, respectively, for AHO in children with sickle cell disease in one study [101]. US (Doppler) also may be useful in detecting DVT associated with AHO [107]. US is increasingly available at the bedside, is relatively inexpensive, and does not require sedation.

***Rationale for Recommendation***

MRI is superior in diagnostic test characteristics and ability to identify associated complications in children with AHO compared with bone scan, CT, and US. The lack of radiation exposure with MRI is an advantage over bone scan and CT, though the latter modalities seldom have the sedation requirement that is frequent with MRI in young children. MRI costs (without sedation) are typically similar to CT but greater than bone scan. MRI may not be able to be performed within the needed time frame in many centers, especially when personnel required for safe pediatric sedation are not readily available.

Considering all of these factors, MRI is suggested as the preferred imaging modality if imaging data beyond plain films are needed to support diagnostic efforts (and management—see XII) in children with suspected AHO. CT, bone scan, or US may be appropriate alternatives in some cases depending on the specific clinical and logistical circumstances. US may be especially useful in evaluating joint effusions and subperiosteal abscesses associated with suspected AHO.

***Research Needs***

Ongoing development and validation of limited sequence/rapid MRI techniques or other approaches, including nuclear medicine imaging techniques such as fluorodeoxyglucose-positron emission tomography, for the diagnosis of AHO in children are needed. Reductions in time required (and thus sedation need) for MRI and radiation exposure for other methods would provide major advances in care for children with suspected AHO [120]. Additional evaluation of the utility of bedside US in various types of clinical presentations of AHO also may be beneficial.

## III. What is the role of invasive procedures in the diagnosis in children with suspected AHO?

**Recommendation:**

1. In children with suspected AHO, we suggest performing invasive diagnostic procedures to collect aspirates and/or biopsy specimens of bone and/or associated purulent fluid collections for routine microbiological studies (aerobic bacteriologic culture and Gram stain) rather than only performing noninvasive diagnostic tests (*conditional recommendation* and *moderate certainty of evidence*). **Comment:** This recommendation places a high value on confirming the microbiological diagnosis to allow the optimization of the spectrum and duration of antimicrobial therapy. The decision to implement this recommendation and its timing may be influenced by factors such as local feasibility of obtaining invasive diagnostic procedures (by IR or in the operating room), individual clinical situations (eg, need for therapeutic surgical intervention and concerns regarding procedural risks or sedation), positive results of prior noninvasive diagnostic tests (eg, blood culture), and duration of any prior antimicrobial therapy.

***Summary of Evidence***

Cultures of bone and soft tissue collected by invasive procedures have historically been performed to identify the specific etiologic agent in AHO. The standard practice remains performing routine aerobic bacterial culture and Gram stain on these specimens. Our systematic review of the literature identified 12 studies published between 2005 and 2019 reporting on the added value of cultures of bone and soft tissue from the affected area to blood cultures on the yield of pathogens identification in pediatric AHO [45, 49–51, 54–58, 60, 61, 65]. These 12 studies collectively included 1240 children with confirmed AHO (ranging from 10 to 244 patients per study). Blood cultures identified a pathogen in 32.9% of cases, while the combination of bone and tissue cultures with blood cultures identified the causative pathogen in 55.4%. In other words, this pooled analysis showed a 24% increase in the yield of pathogen identification when adding bone/tissue cultures to blood cultures (Risk Difference [RD]: 23.6%; 95% CI: 17.9 to 29.2) (see Figure 3). This analysis may underestimate the added value of bone and tissue cultures since not all patients were tested with both blood cultures and bone/tissue cultures. Most of the studies on bacteriologic yield for deep tissue cultures report on aspiration procedures rather than bone biopsy. If no fluid is aspirated, a bone biopsy is usually performed to obtain material for culture [50, 121, 122].

Our systematic review of the literature (including a total of 17 studies, 962 children with confirmed AHO) showed that the yield of standard cultures averaged 65.4% (95% CI: 55.5 to 75.3) [7, 20, 44, 45, 49–56, 58–62] (see Figure 4). Cultures for anaerobes, mycobacteria, and fungi were not necessary unless risk factors are identified by patient history or physical examination [52]. Placement of a portion of specimens into aerobic blood culture bottles (in addition to standard culture plating) may improve the detection of fastidious microbes such as *K. kingae* [44, 123].

PCR-based testing using 16S ribosomal ribonucleic acid (16S rRNA) gene amplification and sequencing was increasingly used

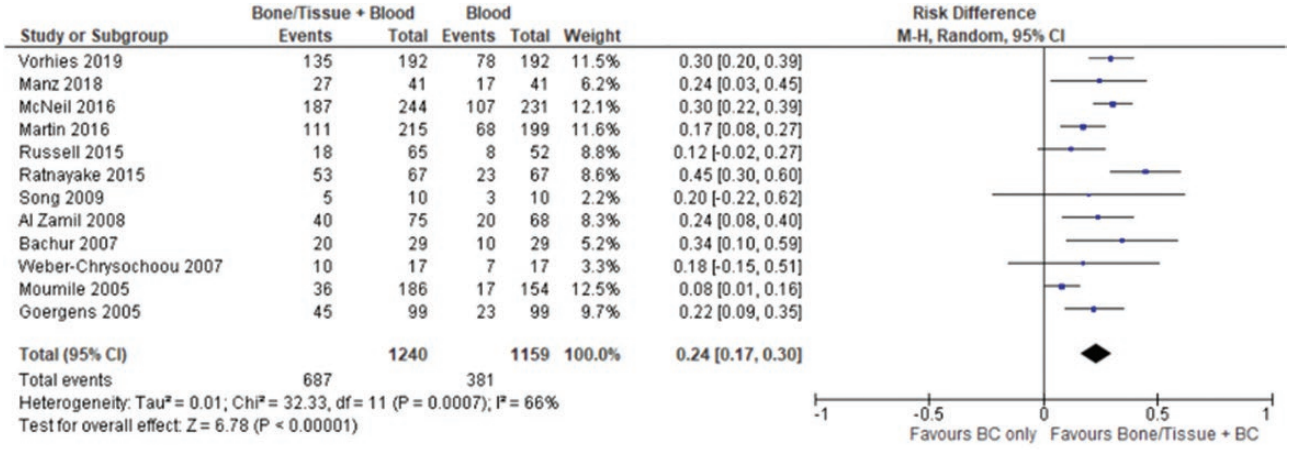


**Figure 3.** Forest plot of positivity rate of bone/tissue cultures in addition to blood cultures vs culture positivity of blood cultures alone in children with acute hematogenous osteomyelitis (AHO). Studies that reported osteoarticular infections without stratifying patients for their underlying type of infections were excluded. If stratification was performed and relevant information on patients with AHO was available, then this study was included in the meta-analysis, and only patients diagnosed with at least an AHO were included in the pooled results presented here. Characteristics of included studies are shown at the end of the Diagnosis Section of Supplementary Material. **[45, 49–51, 54–58, 60, 61, 66].**

in the past decade, especially in culture-negative cases [6, 44, 45, 51, 123, 125]. The use of PCR primers for specific genes of *S. aureus*, *K. kingae*, and other microbes also has been described [44, 126]. Utility of a target-enriched multiplex PCR approach to detect multiple pathogens and genes conferring methicillin and clindamycin resistance has been evaluated in a sample of 25 children with musculoskeletal infection. PCR had 100% concordance with culture results (17 of 17) and detected pathogens in 3 of the 8 culture-negative cases [127]. Current PCR testing methods appear to provide modest incremental yield in

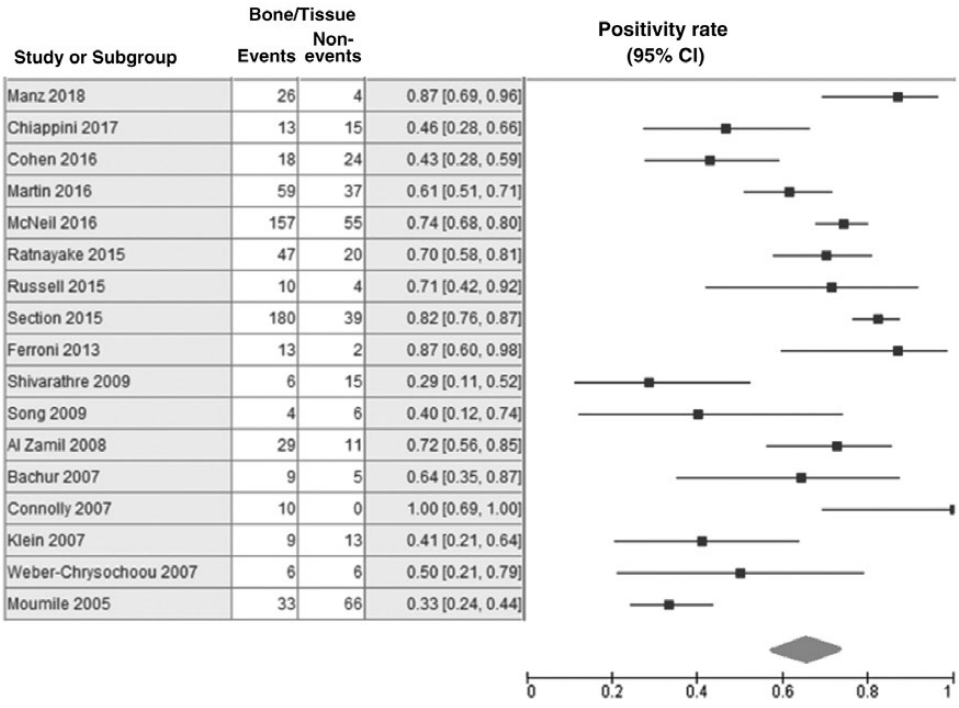


**Figure 4.** Forest plot of positivity rate of bone/tissue cultures in children with acute hematogenous osteomyelitis (AHO). Pooled positivity rate of bone/tissue culture (n = 962 patients, 17 studies) = 65.4% (95% CI: 55.5 to 75.3). Studies that reported osteoarticular infections without stratifying patients for their underlying type of infections were excluded. If stratification was performed and relevant information on patients with AHO was available, then this study was included in the meta-analysis, and only patients diagnosed with at least an AHO were included in the pooled results presented here. Characteristics of included studies are shown at the end of the Diagnosis Section of Supplementary Material.
**[7, 20, 44, 45, 49–55, 58–62, 124].**

detection/identification of pathogens in AHO when standard cultures are negative. PCR test results can be negative when culture results are positive [51]. These tests remain adjunctive to and not replacements for standard cultures at this time.

Additional evidence to support or refute a bacterial etiology in biopsy specimens that are either culture-positive or culture-negative may come from tissue histopathology that describes both the cellular content of infected bone as well as document the presence or absence of bacteria on special stains. Histopathologic evaluation is routinely performed on any tissue specimen obtained from a child with suspected AHO, but no recent prospective evaluation of the diagnostic yield of histopathology compared with standard culture or molecular diagnostic techniques has been published.

Indirect evidence shows that the added value of cultures of bone and soft tissue collected by invasive diagnostic procedures likely leads to improved patient-important outcomes. A systematic review by Dartnell et al [3] noted an increasing trend toward medical management of AHO without drainage and/or debridement procedures. In a large propensity-matched cohort study, outcomes among children with no or negative cultures were excellent in both those receiving outpatient parenteral antimicrobial therapy (OPAT) and oral therapy [128], suggesting, indirectly, that management without culture results rarely leads to treatment failure, regardless of route of therapy. However, these investigators did not specifically assess failure in culture-positive vs culture-negative children. A prospective study of 345 children showed no difference in outcomes between the 265 children who had an identified pathogen and the remaining 80 who did not, though this study was conducted in a population with a very low incidence of MRSA and may not be generalizable to the current epidemiology in the North America [129].

Other evidence favors the performance of an operative or IR procedure to obtain material for culture in addition to blood cultures. A retrospective study designed specifically to address the impact of cultures of the infected sites on management showed that these were the only means by which a pathogen was identified in 80 of the 216 cases (37%). A positive bone or adjacent soft tissue culture result led to a more defined, focused therapy in 85% of these cases, 19% of whom had been on ineffective empiric therapy [50]. A smaller retrospective study from 2012 reported that children who had an identified pathogen or were started on a single antibiotic were more likely to be discharged on a single agent when compared with those with no pathogen identified (90% vs 52%, $P < .01$), although this study also noted an unexpected finding that those with positive cultures were less likely to be sent home on oral therapy (44% vs 76%, $P = .02$), possibly reflecting local standards of care [130].

A retrospective study from Nashville, TN, found that children with culture-negative osteomyelitis in the era of CA-MRSA (typically USA300) were treated longer than during the pre-CA-MRSA era, both for parenteral therapy (median of 16.0 vs 9.0 days, $P < .05$) and total days of therapy (median of 38.0 vs 28.0 days, $P < .05$). The children with culture-negative AHO did not have more severe illness than those who were culture positive [131]. Hospital length of stay (LOS) was less for those children who were culture negative compared with those who were culture positive: 5.0 days (interquartile range [IQR] 4.0 to 7.0) vs 6.0 days (IQR 5.0 to 9.0), $P < .05$). The authors presumed that negative cultures prompted prolonged treatment as CA-MRSA could not be ruled out as a pathogen.

No studies addressed costs or harms in children who underwent invasive diagnostic procedures.

***Rationale for Recommendation***

The panel concludes that knowledge of the pathogen and its susceptibility pattern often simplifies treatment decisions by allowing more confidence in narrowing the spectrum of antimicrobial therapy and transitioning to a pathogen-specific oral agent for completion of the course of antimicrobial therapy. Susceptibility testing may be more critical in some geographical regions than others, given the evolving prevalence of CA-MRSA and clindamycin resistance among *S. aureus* strains of all types. Obtaining specimens for culture, and possible molecular-based tests, from bone aspiration, bone biopsy, or other sites of infection (eg, soft tissues) improves the likelihood of (1) microbiologic confirmation of the causative organism and (2) knowledge of the susceptibility data for the microbe, depending on the test. Despite the potential harms and costs associated with these invasive procedures, the benefits of this information may outweigh any undesirable effects. Ultimately, the decision to perform an aspiration or biopsy procedure for diagnostic purposes and its timing should be considered on a case-by-case basis and is often influenced by other factors, especially the local feasibility of performing the procedure in a timely manner.

***Future Research***

Prospective studies that (1) evaluate the utility of bone and/or soft tissue specimens for culture and antibiotic susceptibility for optimal clinical and other patient-focused outcomes and (2) assess (a) the sensitivity and specificity of advanced molecular testing, including next-generation sequencing for bacterial genomes to identify microbial etiology and (b) ability of such testing to provide adequately predictive susceptibility data.

## IV. For children who require empiric antimicrobial therapy for AHO, should antibiotics be initiated before invasive diagnostic procedures or can they be withheld until after these procedures are performed?

**Recommendations:**

1. In children with presumed AHO who are ill-appearing or have a rapidly progressive infection, we recommend starting empiric antimicrobial therapy immediately rather than withholding antibiotics until invasive diagnostic

procedures are performed (*strong recommendation* and *moderate certainty of evidence*). **Comment:** The yield of positive cultures from specimens collected by invasive diagnostic procedures (bone biopsy and aspirate), when obtained within 24 to 48 hours after initiation of antibiotic therapy, is similar to the yield when these cultures are obtained prior to the administration of antibiotics.

2. In children with presumed AHO who are not clinically ill and for whom an aspirate or biopsy by invasive diagnostic procedure is being planned prior to initiating antibiotics, we suggest withholding antibiotics for no more than 48 to 72 hours (*conditional recommendation* and *very low certainty of evidence*). **Comment:** The decision to implement this recommendation incorporating a reasonable delay may be influenced by local accessibility to experts and resources to perform invasive diagnostic procedures or the time required for transport to a higher level of care if appropriate. For children likely to have AHO, it is advisable that children remain hospitalized for observation while withholding antibiotics until cultures can be obtained.

***Summary of the Evidence***

In efforts to maximize the opportunity to identify the causative microbe, a guiding principle has been to obtain all cultures prior to the administration of antibiotics. The clinical status of the child with suspected AHO determines the timing of initiation of antibiotics relative to any logistical delays in obtaining these cultures. Children who are relatively well or stable sometimes have been carefully observed without initiation of therapy for a few hours to days while the experts and resources required to obtain invasive cultures are assembled. There are no data that specifically address the risks and benefits of planned delays in the initiation of antibiotics for the purpose of obtaining cultures in children with AHO of any severity.

For children with AHO accompanied by sepsis, data from the studies on sepsis in children have relevance. Initiation of appropriate antimicrobial agents >3 hours after the presentation in a retrospective, multicenter study of 130 children with sepsis (21%) or septic shock (79%) was associated with a 4.92-fold increased risk of mortality (95% CI: 1.3 to 18.6) [132]. In a study of 1179 children with sepsis at 54 hospitals, completion of a sepsis bundle within 1 hour that included administration of broad-spectrum antibiotics was associated with a lower risk of in-hospital mortality (odds ratio [OR]: 0.59; 95% CI: 0.38 to 0.93, $P = .02$) [133].

Indirect data from adults with sepsis also show the advantages of immediate therapy (rather than delayed therapy) [135]. For adults with septic shock, a large retrospective cohort study demonstrated that appropriate therapy within 1 hour from documentation of hypotension yielded a survival rate of 80%, but each hour of delay during the first 6 hours of shock was associated with a 7.6% decrease in survival [135]. Results from a more recent, large retrospective review of 18 000 adults with sepsis from 165 ICUs in Europe, the United States, and South America confirmed increasing mortality rate with each additional hour of time to first administration of antimicrobials during the first 6 hours following the diagnosis of sepsis [136]. Beyond mortality, improved outcomes in post-infection ICU LOS and post-infection hospital LOS have also been identified with earlier antimicrobial therapy [137]. These data further support the recommendation for early administration of antibiotics with rapidly progressive AHO infection in the child who is ill-appearing and has characteristics of sepsis.

A related issue is whether the rate of pathogen detection from bacterial cultures from invasive procedures is different between cultures obtained before vs after antimicrobial therapy. We did not find prospective data, but retrospective data from 4 single-center studies with a collective total of 615 patients were found [50, 52, 54, 138]. The positivity rate of bone or soft tissue cultures collected from invasive procedures after the patients received antibiotics was reportedly higher than in patients not receiving antibiotics prior to such procedure (81.8% among 374 children and 69.7% in 241 others, respectively). Indeed, our meta-analysis showed that this difference was statistically significant (risk ratio [RR]: 1.14; 95% CI: 1.01 to 1.28) (RD: 9.8%; 95% CI: 0.7 to 19.5) (see Supplementary Material for more details). Nevertheless, given the retrospective nature of these publications, the populations of children receiving antibiotic therapy before culture may not be comparable to those for whom cultures were obtained prior to antibiotics, especially since 3 of the studies did not adjust for potential confounders. Furthermore, the observed estimate might have been further biased by the probable presence of confounding by indication (ie, children presenting with severe disease are more likely not only to receive antibiotics prior to sample collection but also to have positive bone due to a higher inoculum).

The total duration of antibiotics prior to obtaining cultures impacts the yield of positive cultures. One analysis noted a longer mean duration of antibiotics in those with negative bone cultures after receipt of antibiotics than those with positive results after receipt (79 hours vs 40 hours, $P = .039$) [139]. Another found that children who received antibiotics for 24 to 48 hours prior to IR-obtained cultures had a lower rate of positive cultures compared with those receiving ≤ 24 hours of antibiotic treatment (90% vs 50%, $P = .04$) [50]. These 2 analyses were from studies that had partially overlapping patient samples from the same center.

The impact of prior antimicrobial therapy on the positivity rates of molecular-based pathogen tests has not been evaluated to date. The window of positivity after starting antibiotics may be longer for molecular tests than for standard culture.

For a child who is not systemically ill appearing or has a clinical course that has developed more slowly over several days to

weeks, delaying the administration of antimicrobial agents for up to 48 to 72 hours may be reasonable if this allows desired cultures of bone or other tissues to be obtained. Such delays can be necessary due to (1) variations in the availability of physicians and support staff and/or timeframe required to mobilize the team required to obtain invasive cultures among the diverse institutions providing care to children across North America or (2) a need to arrange transfer of the child to a different facility where the required care can be provided.

A delay in starting antimicrobial therapy while arranging diagnostic surgical intervention can be associated with a risk of harm from ongoing significant local injury by both pathogen and host inflammatory response. Such risks may be low in slowly progressive or well-localized infection, particularly those infections caused by less virulent pathogens. It can be difficult to ascertain clinically when an apparently low-grade infection may progress to sepsis or significant tissue injury that could lead to long-term sequelae. It is thus important that the child remains under close observation while waiting to start antibiotics.

Based on the above data on the yield of invasive cultures obtained within 24 to 48 hours after initiation of therapy, the need to delay therapy until desired cultures are obtained may be less important than generally thought. Still, limited time delay may maximize the opportunity to identify the causative pathogen, at least in some cases, which may positively impact definitive antibiotic therapy in terms of options and toxicities that are important to patients. If the blood culture becomes positive for a likely pathogen while waiting for the diagnostic procedure to be performed, antibiotics can be started without further delay.

***Rationale for Recommendation***

The evidence for the benefits of immediate antimicrobial therapy for AHO in the ill-appearing child with signs/symptoms of sepsis is indirect, derived from pediatric data on the benefits of early antibiotic therapy for sepsis without AHO. The benefits (decreased mortality and other patient-oriented outcomes) from early antibiotic therapy clearly are greater than the potential loss of benefits from knowledge of the specific pathogen and its antibiotic susceptibility profile, should invasive diagnostic cultures of bone or other tissues be negative due to starting antibiotics before samples are obtained. Substantial observational data also now suggest that obtaining invasive cultures up to 24 to 48 hours after the initiation of antibiotics does not appear to impact the rate of positive bone culture results. As noted in the Surviving Sepsis Campaign Guidelines [134], blood cultures can usually be obtained prior to the administration of antibiotic therapy and offer a modest chance (see I) of establishing a microbiologic diagnosis.

While no prospective data exist for suspected AHO in children who are not systemically ill appearing, the panel consensus was that an intentional, but cautious, delay in initiating antibiotic therapy, in order to obtain cultures that could provide a definitive microbiologic diagnosis, may be particularly helpful in situations where the clinical presentation is either indolent (eg, symptoms present for 7 to 14 days with no or minimal progression) or not characteristic of AHO caused by *S. aureus*, or when suspicion exists for uncommon microbial etiologies. Identifying the specific pathogen may allow the selection of effective antibiotic therapies that have less toxicity and/or facilitate better adherence.

When the decision is made to delay the initiation of antibiotics to obtain a culture(s), the child should be observed for signs of potential local or systemic progression of the infection. The location (inpatient or outpatient) and frequency of assessment are determined on a case-by-case basis, taking into account the clinical course up to the time this decision is made as well as patient/family preference and informed risk tolerance. A delay of greater than 48 to 72 hours is more difficult to justify, given the potential risks of progression and recent observational data that culture yield from invasive specimens 24 to 48 hours into antibiotic therapy are similar to those obtained prior to therapy. Case-by-case determinations remain appropriate.

## V. In children with suspected AHO, how should empiric antimicrobial therapy be selected?

**Recommendations:**

1. In children with suspected AHO, we recommend using empiric antimicrobial therapy active against *S. aureus* (*strong recommendation,* and *moderate certainty of evidence*). **Comment:** Antimicrobials with activity against CA-MRSA should be considered based on local susceptibility data and patient history with regard to previous CA-MRSA infections and/or colonization. In the presence of a clinical presentation, physical examination, exposure history, or other risk factors that either are inconsistent with *S. aureus* infection or suggest need for coverage for other organisms, additional empiric antimicrobial coverage for pathogens other than *S. aureus* may be warranted (such as younger age for *K. kingae* or children with underlying hemoglobinopathies who have increased risk for *Salmonella* spp. infection).

***Summary of Evidence***

Given that *S. aureus* is the most common pathogen causing AHO in all age groups in North America [10, 15, 47, 140–150], it is understandable that over the past 50 years there has been no publication of prospective, controlled data comparing the efficacy and safety of empiric regimens for pediatric osteomyelitis that contain anti-staphylococcal agents vs those that do not. Similarly, since the emergence of CA-MRSA infections, no prospective controlled studies have evaluated the efficacy and safety of empiric regimens that compare anti-MRSA regimens with those that only provide the activity against MSSA in children with AHO.

While the use of combination antimicrobial therapy is a common practice for severe CA-MRSA infections, no controlled data are available on which to base recommendations for combination therapy. Agents active against CA-MRSA or MSSA typically provide adequate coverage for less common Gram-positive pathogens causing AHO, including *S. pyogenes*.

Our systematic review of the literature found 15 studies of confirmed AHO (published between 2015 and 2019) including 806 children in whom a microbiologic etiology was determined by positive culture of tissue and/or blood. The pooled rate of *S. aureus* infections was 78.2% (95% CI: 71.7 to 84.6) [7, 44, 49–61]. From these reports, the proportion of methicillin resistance in *S. aureus* was approximately 33% but varied widely geographically and over time, from 0% in earlier studies in various locations to more than 30% after 2015 in the United States. While nearly all *S. aureus* strains are penicillin-resistant, most still remain susceptible to anti-staphylococcal penicillins (ASP), such as methicillin, oxacillin, and nafcillin, as well as to first-generation cephalosporins, such as cefazolin and cephalexin. Cefazolin and nafcillin/oxacillin are considered therapeutically equivalent in pediatric AHO, based on in vitro data and retrospective studies in children; however, no comparative data are available that assess differences in efficacy or safety.

Decisions on empiric therapy are best informed by review of the most recent data on the susceptibility of *S. aureus* isolates from children at the clinician's institution. In regions with low rates of CA-MRSA osteomyelitis (less than ~10%), some experts begin therapy with oxacillin/nafcillin or cefazolin in the absence of bone cultures for children with mild to moderate illness, closely watching for a response to treatment. In regions where resistance to methicillin is estimated to be less than 10% to 20% or greater, panel consensus is that empiric therapy should include agents active against CA-MRSA, usually clindamycin or vancomycin. Vancomycin is a common initial choice for children who are critically ill at presentation, regardless of regional MRSA prevalence.

No controlled data exist to suggest superiority of one drug over the other for efficacy; however, clindamycin is preferred over vancomycin when the strain is susceptible to both, due to renal safety concerns that accompany the high vancomycin exposures often required to achieve pharmacodynamically targeted serum concentrations that may be needed for cure of some invasive CA-MRSA infections. Clindamycin, if active against the isolate, also provides the opportunity for a seamless transition to oral therapy.

Resistance to clindamycin occurs among both MSSA and MRSA and varies geographically from 5% to 40% within the United States. Clindamycin resistance is primarily due to the expression of a methylase gene (*erm*) that leads to methylation of the clindamycin ribosomal-binding site. Expression of *erm* may be inducible upon exposure to macrolides or be constitutive (with methylase always being produced) [151]. Many clinical microbiology laboratories test for this distinction via the "D-test" or its microbroth dilution equivalent but may report both categories of inducible or constitutive resistance simply as resistant. A small subset among an overall population of organisms that the laboratory reports to be macrolide-susceptible, but carry inducible methylase resistance, is in fact completely resistant with methylase expression being continuous. This subpopulation then has the potential to emerge during clindamycin therapy with resultant treatment failure. Such cases have been described in children (none with AHO) but appear to be uncommon [152–154]. Expert opinion varies and uncertainty remains around the question regarding the use of clindamycin for the treatment of AHO when the resistance mechanism is macrolide-inducible.

Trimethoprim/sulfamethoxazole (TMP/SMX) demonstrates in vitro activity against most strains of CA-MRSA and has been shown effective in the treatment of skin infections caused by CA-MRSA. No controlled data exist on the use of TMP/SMX for osteomyelitis, with only limited published retrospective data in 11 children [155]. There is a theoretical concern that thymidine released from damaged host tissues with any severe infection may allow the microbe to overcome the folate antagonism of TMP/SMX [156].

For children suspected to have *S. aureus* infections for whom beta-lactams, vancomycin, or clindamycin cannot be used due to concerns for antibiotic resistance, allergy, or poor tolerability, parenteral daptomycin and parenteral/oral linezolid provide additional options, although no prospectively collected data in osteomyelitis are currently available for linezolid. A multicenter, randomized, double-blinded controlled study has recently been completed with daptomycin for pediatric osteomyelitis [157], with 73 daptomycin-treated children compared with 73 children treated with standard-of-care antibiotics (vancomycin 51%, nafcillin/oxacillin 33%, cephalosporin 18%, and clindamycin 1%). Outcomes were statistically similar (at the predetermined "early" clinical improvement time point of day 5 into treatment), with 78% response in the daptomycin arm vs 83% response in the comparator arm; pathogens were isolated from 62 children, primarily *S. aureus*, with only 4 children documented to be infected by CA-MRSA in each group. Treatment-emergent adverse events were noted in 46% of children in the daptomycin arm vs 63% in the comparator arm [157].

In a single-center, retrospective study of children with osteomyelitis treated with linezolid, cure was described in 11 of the 13 subjects [158]. The use of linezolid for more than 2 weeks, regardless of route of administration (parenteral or oral), is associated with an increased risk of bone marrow suppression and peripheral neuropathy. These adverse effects usually resolve over many weeks once linezolid is discontinued. A single-center, randomized, open-label, controlled study of ceftaroline for pediatric osteomyelitis [159] is ongoing, with results pending.

Doxycycline, often active against *S. aureus* including MRSA, has not been prospectively studied in AHO. Theoretical concerns exist for lack of active antibiotic in infected bone tissue, based on the knowledge of the formation of stable tetracycline-calcium complexes in these tissues. While short treatment courses of doxycycline are not felt to be associated with staining of teeth and bones in children 8 years of age and younger, the longer courses required for AHO may be associated with these tetracycline-class adverse events.

For children with severe disease, particularly those with osteomyelitis accompanied by severe sepsis, some prefer the use of vancomycin with or without a protein synthesis-inhibiting antibiotic (eg, clindamycin). Others prefer a combination of oxacillin/nafcillin and an MRSA-active antibiotic in an effort to provide optimal empiric therapy to cover CA-MRSA, MSSA, and *S. pyogenes* [160, 161]. Toxin-mediated disease can be a concern in severe cases, and cell-wall active agents may have decreased effectiveness in high inoculum disease (Eagle effect) [162]. The addition of a protein synthesis-inhibiting antibiotic such as clindamycin may be helpful in these circumstances, but there are no data that compare treatment regimens for children with known toxin-mediated staphylococcal infections. The presence and role of toxin production in disease severity remain uncertain.

For preschool-aged children or others for whom infection caused by *K. kingae* is a consideration (eg, epiphyseal osteomyelitis) [163], the addition of ampicillin, a beta-lactam/beta-lactamase inhibitor combination (for beta-lactamase positive strains), or a cephalosporin to empiric anti-MRSA therapy can be considered. The clinician may also observe for 48–72 hours for a clinical response to MRSA-active agents such as clindamycin or vancomycin that have no activity against *Kingella*, and for those with an inadequate response, consider the addition of agents active against *Kingella*.

*Streptococcus pneumoniae* remains an occasional cause of osteomyelitis [164, 165]. Antibiotics with activity against CA-MRSA and MSSA are often but not always active against pneumococci.

Atypical aspects of the clinical presentation, presence of underlying conditions such as hemoglobinopathies, and history of specific exposures (eg, pet reptiles [166] or incomplete immunization) may indicate the need for antibiotic coverage for pathogens in addition to *S. aureus* (and *S. pyogenes*). Such organisms include *Salmonella*, *Brucella*, *and Haemophilus influenzae* type b.

***Rationale for Recommendation***

The benefits of empiric therapy active against *S. aureus* are substantial given its high frequency as a pathogen in pediatric AHO. Based on the correlation between susceptibility testing and clinical effectiveness of antibiotics that demonstrate in vitro activity against *S. aureus* for a wide range of infections in adults and children, and the substantial retrospective data published on AHO, we believe that empiric therapy with an anti-staphylococcal antibiotic is essential.

Regarding the choice of anti-staphylococcal therapies, in regions where the prevalence of CA-MRSA causing pediatric AHO is low, cefazolin or oxacillin/nafcillin is preferred for empiric therapy of presumed MSSA infection based on greater safety and tolerability, compared with vancomycin or clindamycin, and greater efficacy compared with vancomycin; for regions with CA-MRSA prevalence 10% to 20% or greater, clindamycin or vancomycin is preferred; although for the clinically stable child, cefazolin is reasonable empiric therapy pending cultures, or for those whom close observation with medical management is felt to be appropriate. In regions where clindamycin resistance in MRSA is substantial (approximately 10% to 20% or greater), vancomycin is preferred for empiric therapy for CA-MRSA. Other antibacterial agents with activity against CA-MRSA exist, but high-quality published data are insufficient to suggest routine therapy with these agents (see Table 3).

Appropriate choice of empiric therapy should be guided by local antibiotic resistance patterns and/or hospital antibiogram as well as disease severity. Many antibiotics may show activity in vitro against bacterial pathogens that cause AHO, but the lack of published data on doses that provide adequate antibiotic exposure for AHO, treatment outcomes, and safety does not permit recommendations for their routine use at this time.

***Research Needs***

Newer parenterally administered antimicrobial agents with activity against *S. aureus*, particularly those targeting CA-MRSA (such as ceftaroline, daptomycin, linezolid, oritavancin, and

**Table 3. Empiric Parenteral Therapy for Children With Acute Hematogenous Osteomyelitis (AHO) Based on Local Epidemiology of Resistance in Bone Isolates of *S. aureus* to Methicillin and Clindamycin[a]**

| | | Clindamycin Resistance Rate | | |
|---|---|---|---|---|
| | | <10% to 20% | >10% to 20% | |
| MRSA Rate | <10% to 20% | Cefazolin or oxacillin/nafcillin | Cefazolin or oxacillin/nafcillin | |
| | >10% to 20% | Clindamycin | *Options for clinically stable, nontoxic patient*: vancomycin, cefazolin, or oxacillin/nafcillin | *Options for clinically moderate to severely ill patient*: vancomycin, daptomycin, ceftaroline, or linezolid |

[a]This guidance represents consensus of the Guideline Panel. There are no studies that specifically address the relationship of initial therapies based on this or other frameworks with patient outcomes.

dalbavancin), should be compared with standard-of-care antimicrobial therapy for osteomyelitis. Orally administered agents with activity against *S. aureus*, particularly those active against CA-MRSA (clindamycin, linezolid, tedizolid, and TMP-SMX), should be compared for transitioning to oral therapy for AHO. Newer agents with increased activity against *S. aureus*, particularly those with excellent absorption, tolerability, and high bone antibiotic exposure, are needed. Combination therapy for severe disease, including scenarios where toxin-mediated impacts are a concern, requires prospective evaluation. Investigations of optimal regimens for other pathogens such as *Salmonella*, in various types of hosts, also would be useful.

## VI. In children with AHO, in whom should invasive therapeutic procedures be performed at the time of diagnosis?

**Recommendations:**

1. In children with AHO who present with sepsis or have a rapidly progressive infection, we recommend debridement of the infected bone and any associated abscesses as soon as possible after diagnosis, rather than treating with medical therapy alone (*strong recommendation* and *moderate certainty of evidence*).
2. In a child with AHO who is clinically stable but is documented to have a substantial abscess (greater than 2 cm), we suggest debridement rather than treating with medical therapy alone (*conditional recommendation* and *very low certainty of evidence*).

***Summary of Evidence***

Determination of the need for surgical intervention as part of source control of the infectious process for children with osteomyelitis is made on the basis of clinical, laboratory, and imaging data. This need may be evident at the time of diagnosis (see III) or become evident a few days or more into the course of therapy (see XIII). Many experts agree that early surgical intervention is indicated for children with osteomyelitis who present with sepsis or have a rapidly progressive infection, worsening clinical status, or imaging findings that show abscess or fluid collections judged unlikely to improve or resolve with medical therapy alone [67, 167, 168]. Persistent bacteremia in the face of effective antibiotic therapy also can merit surgical intervention for source control.

The need for source control to ensure clinical improvement (defervescence and/or clearance of ongoing bacteremia) appears intuitive and is largely founded on expert experience [169]. Pediatric-focused literature on this topic in general, and for AHO in particular, is sparse. Optimal management of AHO amenable to surgery in children is thought to be generally similar to management in adults [170]. It has been stated as a general principle that every established source of infection should be controlled as soon as possible [170], but ultimately the urgency and timing of surgical intervention are determined by the rapidity of progression of clinical findings and response (or lack thereof) to medical therapy.

Data collected from studies on source control in adults with sepsis associated with drainable infections provides indirect evidence to support source control efforts in pediatric AHO. In a Spanish national multicenter prospective observational trial in adults, crude ICU mortality was lower (21.2% vs 25.1%; $P = .010$) in patients with sepsis who underwent source control compared with those who did not. Adjusted hospital mortality was also lower in those with source control procedures (OR: 0.81; 95% CI: 0.66 to 0.99) but delay in source control beyond 12 hours was not associated with increased mortality [171].

When surgery is undertaken, the goal is to debride all dead and devitalized tissue with the creation of optimal soft tissue conditions around the infected area [170, 172]. This usually involves incision of the bone cortex with irrigation and debridement of the infected or necrotic bone. This is accomplished by making a bone window in the metaphyseal region of infected long bones or in the cortex of long bone equivalents such as the calcaneus. Care is taken to avoid injury to the growth plate or peri-chondral physeal ring.

The safest and most direct route to address all suspected foci of infection is taken, while permitting a more extensive exposure should it become necessary during the initial procedure or during subsequent surgical procedures. The bone cortex may be incised with a curette or drill and expanded to achieve an opening sufficient to debride grossly infected bone while small enough to avoid destabilization of the architecture (generally $1 \times 3$ cm in dimension in the most commonly infected long bones). Drain placement after debridement allows continued evacuation of the infection during the days that follow the procedure.

The biomechanical ability of the bone to withstand force is limited after exposure to infection and surgery. Pathologic fractures can occur under these circumstances and merit the additional safeguards of limited weight bearing with assistive devices and physical therapy guidance. Activity restrictions need to be emphasized during the period of bone healing and regeneration.

Data regarding abscess or fluid collection size that mandates surgical drainage are very limited, whether within the bone, subperiosteal space, or adjacent soft tissues. Drainage of abscesses 2 cm or more in diameter has been suggested [59, 173, 174]. Resolution of infection with medical management alone has been described in small numbers of children with abscesses <1 cm diameter [59, 173].

Bacterial arthritis can be associated with AHO. The involved joint(s) is usually drained at presentation when clinically apparent. If joint involvement becomes apparent during the clinical course, this can be managed at that time.

The need for anticoagulation therapy for associated DVT is determined on a case-by-case basis, usually in consultation with a hematologist. The presence of DVT in association with AHO can be a factor when deciding to pursue surgical drainage of bone and/or abscesses vs medical therapy alone. Associated soft tissue foci of infection, adjacent or remote to the primary site of infection, at times, may be a primary source of persisting infection that requires control.

***Rationale for Recommendation***

For AHO patients who present with sepsis or have rapidly progressing infection, potential benefits of surgery on patient-important outcomes include (1) faster improvement in hemodynamic status and decreased need for intensive care, (2) faster clinical recovery (due to better perfusion and drug targeted antibiotic delivery); (3) reduction in local and metastatic spread of infection; (4) decreased PICU and/or hospital LOS; and (5) possible lower overall costs of care (indirect potential benefit secondary to 4). Potential harms of surgery include risks of anesthesia, bleeding, secondary infection, and other procedure-related complications. The panel consensus is that the potential benefits of surgical intervention clearly outweigh the risks in patients with AHO-associated severe systemic illness or rapidly progressing infection.

In those with non-severe presentations, the presence of drainable abscesses or fluid collections (eg, >2 cm diameter) may allow more rapid recovery and potentially shorten hospital LOS and total course of therapy. Risks of surgical intervention are similar to those for more severely ill children with AHO. Types of intervention to be undertaken (eg, operative or IR; under general anesthesia or sedation) and other clinical factors can be considered in clinical decision-making. The panel consensus is that the potential benefits of surgical intervention for these larger abscesses/fluid collections often outweigh the risks in these children.

***Research Needs***

Prospective studies are needed in children with non-severe presentations of AHO to compare surgical intervention (and its timing) with medical therapy alone. The size and location of abscesses should be clearly delineated, both in bones and surrounding soft tissues. Multicenter collaborations will be essential.

## VII. In children with AHO, should surgical-site antimicrobial agents be added to systemic antimicrobial therapy?

**Recommendation**:

1. In children with AHO requiring a surgical procedure, we recommend against routine use of surgical-site (ie, instilled or implanted) antimicrobial agents (*strong recommendation* and *very low certainty of evidence*). **Comment:** This recommendation places a high value on avoiding unnecessary harm and cost associated with this intervention.

***Summary of Evidence***

The outcome of AHO in children treated with systemic antibiotics plus surgical debridement when needed is generally excellent (see XIV) and appears to preclude the need for routine instillation or implantation of antibiotic solutions or materials into bone or adjacent sites of infection. Surgical intervention is often limited to aspiration or biopsy of the infected bone, making local placement of antibiotics impractical in most of the cases. For children with AHO that has not improved or has recurred with standard therapy and for whom further surgical debridement/intervention is planned, intraoperative delivery of antibiotics to the local site of infection may sometimes be used, but there are limited data to support this practice. High cure rates have been described even in chronic osteomyelitis without such therapy [174].

Two retrospective studies in children have described the use of implanted antibiotic materials in children with chronic osteomyelitis. Antibiotic-impregnated cement rods or beads were used in 4 children along with surgical debridement and systemic antibiotics with fully functional outcomes at 36 to 46 months of follow-up [175]. Good long-term outcomes also have been described in 12 children who had calcium sulfate-tobramycin pellets implanted as adjunctive therapy [176]. A few case series have reported good outcomes in adult patients with chronic osteomyelitis managed by single-stage surgery using biodegradable aminoglycoside-impregnated calcium sulfate-based materials in association with systemic antibiotic therapy [177–179].

The use of any implantable antibiotic delivery materials that are not biodegradable requires a second surgery to remove the materials [180]. Potential toxicity associated with the use of locally instilled or implanted antibiotics has been minimally studied. A study of 20 neonates with AHO and bacterial arthritis documented systemic concentrations of gentamicin just below the lower end of the therapeutic range after local implantation of gentamicin-containing materials [181]. There were concerns for subclinical renal injury but no evidence of ototoxicity. These data may not be able to be extrapolated beyond the neonatal period. In a case series of 21 adults with chronic osteomyelitis of the tibia treated with systemic antibiotics, surgical debridement, and implanted biodegradable calcium sulfate-tobramycin pellets, wound complications were noted in 52%, though causation is not clear [178].

***Rationale for Recommendation***

The primary rationale for the recommendation against routine use of implanted or instilled antibiotics in pediatric AHO is that in general, the outcome of AHO treated without such agents

is good and there is no evidence that outcomes are improved with the use of these agents compared with systemic antibiotics alone. Potential harmful outcomes include the need for additional surgery if nonbiodegradable materials are used, potential surgical complications regardless of the type of material used, possible antibiotic-related toxicity if large dosages are implanted in small patients, and additional costs of these materials [177, 178, 180, 182, 183]. A discordant strong recommendation despite very low certainty of evidence is made due to uncertain benefit, with greater certainty around potential harm and increased costs.

#### *Research Needs*

Clinical trials of effectiveness and safety of biodegradable surgical-site antimicrobial therapy in children with AHO unresponsive to standard systemic antibiotic therapy and surgical debridement could be useful [184]. Ongoing advances in polymeric carriers (eg, microspheres) and scaffolds that may improve antibiotic delivery and bone healing, respectively, may allow new approaches that could improve outcomes and reduce risks of pathologic fractures and other complications of AHO [180]. These technologies can be evaluated in children.

## VIII. In children with suspected or confirmed AHO who responds to initial *empiric* therapy, how should *definitive* parenteral and oral therapy be selected?

**Recommendations:**

1. In children with confirmed AHO, selection of a definitive antibiotic regimen should be based on the principles of selecting an effective agent against the identified pathogen, with the narrowest spectrum, lowest adverse effect profile, and most favorable host tolerance (*Good Practice Statement*).
2. In children with *suspected* AHO without an identified bacterial cause, selection of a definitive antibiotic regimen should be based on the principles of selecting an effective agent based on the most likely causative organism(s), with a spectrum comparable to that on which the patient demonstrated clinical and laboratory improvement, and with the lowest adverse effect profile and most favorable host tolerance (*Good Practice Statement*).

#### *Summary of the Evidence*

Clinicians should treat AHO with an antimicrobial agent directed specifically toward the causative organism at a dose, route, frequency of administration, and duration that are sufficient to eradicate the pathogen. The choice should be based on in vitro susceptibility and published clinical trial data (see Tables 4 and 5). In general, the narrowest spectrum antibiotic should be prescribed for both intravenous and subsequent oral therapy. Narrow spectrum therapy provides a number of benefits for both inpatients and outpatients, as outlined by policy statements from professional societies and by the Centers for Disease Control and Prevention. These potential benefits include reduction of antimicrobial resistance in the individual patient, reduced antimicrobial pressure for the environment, reduced toxicity, and often reduced cost [185–187].

This section discusses effective oral therapy options in the context of narrowed parenteral therapy for culture-positive cases and response to initial empiric therapy in culture-negative cases. The criteria for switching from parenteral to oral therapy are reviewed in section X.

#### *Antimicrobial Management in Cases Where the Microbial Etiology Is Identified*

The initial clinical studies for antibiotic treatment of pediatric AHO, primarily for the treatment of MSSA, were performed over 30 years ago [189]. Many of these studies did not use randomized, controlled, double-blinded study designs, nor did they adequately evaluate clinical or safety treatment endpoints at specific time points in a systematic fashion. As they were not well-standardized, we cannot compare specific outcome measures at specific time points in order to assess how well each antibiotic performed relative to the others or compared with untreated children (historical "control" populations) [3, 189, 190, 193, 194, 198].

In general, for MSSA isolates, first-generation cephalosporins (eg, cefazolin) or ASP (eg, nafcillin and oxacillin) are the preferred parenteral agents. For MSSA infections, the safety and tolerability benefits of beta-lactam therapy are likely to be greater than glycopeptides (vancomycin), lincosamides (clindamycin), and oxazolidinones (linezolid), but no controlled data comparing efficacy, tolerability, and adverse event profiles between agents have been collected specifically in children with AHO. Excellent outcomes with the transition to oral therapy with high-dose cephalexin or clindamycin are well documented [87, 128, 189, 190, 193, 194, 199, 200].

For CA-MRSA isolates that are susceptible, clindamycin is the preferred agent. For CA-MRSA infections, the tolerability and safety benefits of clindamycin are greater than vancomycin; in addition, clindamycin therapy may be readily converted from parenteral to oral therapy due to its good enteral bioavailability. Adding flavoring to the liquid formulation of clindamycin may increase adherence.

Vancomycin remains the preferred initial antimicrobial agent for clindamycin-resistant CA-MRSA infections. Other MRSA-active agents may be considered as alternatives (eg, ceftaroline, daptomycin, linezolid, and TMP-SMX) but have been used less often than vancomycin for the treatment of AHO. Few published data exist for treatment outcomes, safety, tolerability, or standardized dosing of antimicrobial agents (including vancomycin)

**Table 4. Antibiotic Choice and Duration of Therapy for *Uncomplicated* Pediatric Acute Hematogenous Osteomyelitis (AHO) Caused by *Staphylococcus aureus*[a,b]**

| Pathogen | Parenteral Therapy | Oral Convalescent Therapy | Duration[c] |
|---|---|---|---|
| *Staphylococcus aureus*, methicillin susceptible | Preferred[d]:<br>Cefazolin<br>Semi-synthetic penicillin[e], eg, oxacillin and nafcillin | Preferred: Cephalexin | 3 to 4 weeks if uncomplicated |
| | Alternatives[d]:<br>Clindamycin<br>Vancomycin<br>Ceftaroline | Alternative: Clindamycin | 3 to 4 weeks if uncomplicated |
| *S. aureus*, methicillin-resistant, susceptible to clindamycin | Preferred: Clindamycin | Preferred: Clindamycin | 3 to 4 weeks if uncomplicated |
| | Alternatives:<br>Vancomycin<br>Daptomycin<br>Ceftaroline<br>Linezolid | Alternatives[f]: Linezolid | No data |
| *S. aureus*, methicillin-resistant, resistant to clindamycin | Preferred: Vancomycin | Preferred: Linezolid | No data |
| | Alternatives:<br>Daptomycin<br>Ceftaroline<br>Linezolid | Alternatives: Insufficient clinical data for the treatment of AHO to recommend other oral antibiotics with in vitro activity against *S. aureus* | No data |

[a]Uncomplicated AHO is defined as the presence of infection in a single site with rapid clinical response to antimicrobial therapy (ie, resolution of fever and marked improvement in clinical signs within 3 to 5 d), with no more than a single early surgical procedure required as source control for the infection (see Introduction text). Complicated infections may require a longer duration of treatment than uncomplicated infections, particularly if multiple surgeries are needed to establish source control. See text.

[b]Not all antibiotics listed have been prospectively evaluated in clinical trials of acute bacterial osteomyelitis. Prospective studies to evaluate the effectiveness of a range of antibiotic doses in various degrees of severity of uncomplicated and complicated osteomyelitis, with or without surgery, have not been performed, although retrospective data have been reported for many antibiotics in the treatment of pediatric osteomyelitis.

[c]The suggested duration of therapy should be based on clinical course (pace of resolution of fever and clinical signs and symptoms, noting the need for surgical intervention(s) required, if any), supported by decline of inflammatory markers.

[d]Preferred and alternative agents are selected based on published data regarding in vitro activity, clinical efficacy, and safety. Agents are generally listed in order of preference.

[e]Many of the beta-lactamase-stable penicillins cause significant phlebitis in peripheral veins with infusion; administration through a central venous catheter is preferred.

[f]Alternative antibiotics that may display in vitro activity against *S. aureus* have not been evaluated prospectively in AHO. However, linezolid has been evaluated in prospective, controlled clinical trials for invasive methicillin-resistant *S. aureus* nosocomial pneumonia in adults ([207]) and is more likely to provide adequate therapy of invasive *S. aureus* AHO, compared with trimethoprim/sulfamethoxazole, which is not recommended for children with AHO by the Infectious Diseases Society of America (IDSA) Clinical Practice Guidelines for Treatment of Methicillin-Resistant *Staphylococcus aureus* Infections in Adults and Children (ref [192]).

in CA-MRSA osteomyelitis on which to base recommendations. Initial guidelines by IDSA for vancomycin dosing in severe CA-MRSA infection suggested the pursuit of serum trough levels > 15 μg/mL, though not specifically in children with AHO. However, achieving this high degree of vancomycin exposure was not associated with better outcomes when used initially in the treatment of AHO in children but was associated with increased risk for acute kidney injury [186]. Subsequent American Society of Health-System Pharmacists Guidelines on vancomycin dosing in severe CA-MRSA infection suggests achieving an exposure that incorporates both vancomycin exposure over an entire dosing interval (the "area under the time vs vancomycin serum concentration curve" [AUC]), and the minimum inhibitory concentration (MIC) of *S. aureus*, to achieve an AUC/MIC of 400 [201].

Data for oral therapy in the treatment of clindamycin-resistant MRSA isolates are also limited. Case series support the use of linezolid or TMP-SMX for clindamycin-resistant MRSA isolates that are susceptible to these agents, although the safety and tolerability, as well as the optimal dose and duration of therapy needed for AHO, are not well established [154, 158, 202].

For penicillin-susceptible *S. pneumoniae* isolates and *S. pyogenes*, penicillin or ampicillin is the preferred beta-lactam agents. For *S. pneumoniae* isolates that are penicillin-non-susceptible, ceftriaxone should be effective if reported as susceptible by the laboratory. Although no prospective data on the treatment of AHO caused by penicillin- or ceftriaxone non-susceptible isolates of pneumococcus are available, in vitro testing may offer additional treatment options, including linezolid, ceftaroline, levofloxacin, or daptomycin.

Septic arthritis is the most prominent musculoskeletal infection caused by *K. kingae*, although bone involvement may also occur. *K. kingae* is typically susceptible to cephalosporins and resistant to clindamycin and vancomycin; *K. kingae* infections are discussed in greater detail in the companion IDSA/PIDS guideline for acute bacterial arthritis.

For children with severe, life-threatening disease or disseminated staphylococcal infection, combination therapy may be considered, although no controlled or uncontrolled data have been published to document the superiority of combination therapy over monotherapy for AHO [192,203,204]. Retrospective data from patients with staphylococcal or streptococcal toxic shock syndrome support the addition of clindamycin as a ribosome-targeting antibiotic to decrease toxin production to improve survival [205, 206] and in vitro data suggest that both clindamycin and linezolid reduce exotoxin gene expression and protein synthesis [162]. Table 4 outlines the preferred and alternative antibiotics for infections caused by *S. aureus*.

**Table 5. Antibiotic Dosages for Pediatric Acute Hematogenous Osteomyelitis (AHO)[a] (Dose Adjustment May Be Needed in Children With Renal or Hepatic Failure)**

| Antibiotic | Dosage | Maximum Daily Adult Dosage | Comments |
|---|---|---|---|
| **Parenterally Administered Antibiotics** | | | |
| Cefazolin | 100-150 mg/kg/d in divided doses every 8 h | 12 g/d | Higher end of dosing range for more serious, invasive infection. |
| Ceftaroline [188] | 45 mg/kg/d in divided doses every 8 h, each dose infused over 1-2 h, max 600 mg/dose | 1.8 g/d | Dose designed for the phase 2 treatment of pediatric acute osteomyelitis, including MRSA (ClinicalTrials.gov Identifier: NCT02335905), and also designed for the phase 3 treatment of complicated pneumonia caused by MRSA (ClinicalTrials.gov Identifier: NCT01669980). |
| Clindamycin [189, 190] | 30-40 mg/kg/day in divided doses every 6 to 8 h | 2.7 g/d | |
| Daptomycin [157] | Age-adjusted doses:<br>12-17 y: 7 mg/kg<br>7-11 y: 9 mg/kg<br>1-6 y: 12 mg/kg | | Not recommended for children under 1 year of age based on safety concerns in animal models of infection. |
| Linezolid[b] [191] | 30 mg/kg/d in divided doses every 8 h for children < 12 y and 20 mg/kg/d in divided doses every 12 h for children ≥12 y | daily dose 1200 mg | Doses provided were studied prospectively for pneumococcal pneumonia, and uncomplicated skin infections, including MRSA. |
| Nafcillin | 100-200 mg/kg/d in divided doses every 6 h | 12 g/d | Doses as high as 200 mg/kg/d have been used for meningitis. |
| Oxacillin | 100-200 mg/kg/d in divided doses every 6 h | 12 g/d | Doses as high as 200 mg/kg/d have been used for meningitis. |
| Vancomycin[89, 192] | 40-60 mg/kg/d in divided doses every 6 to 8 h | No mg/kg maximum but follow for renal toxicity | For MRSA: dosing to achieve an AUC/MIC of >400; associated with less renal toxicity than trough concentrations of 15-20 mcg/mL.<br>Monitor serum concentrations. |
| Telavancin, Dalbavancin, and Oritavancin | | | Insufficient data exist for these agents for the treatment of bone infections caused by MRSA in adults to make recommendations for children. |
| Combination therapy for serious invasive *S. aureus* infections with multiple antibiotics, including gentamicin +/– rifampin, has not been evaluated prospectively. Please consult an infectious diseases specialist. | | | |
| **Orally Administered Antibiotics [193–195]** | | | |
| Amoxicillin | 50-100 mg/kg/d in divided doses every 8 h | 4 g/d | Not studied for AHO caused by pneumococcus or group A *Streptococcus* in children; doses in the higher end of the range may be needed to achieve adequate exposure in necrotic bone or abscesses, even for fully susceptible organisms. |
| Cephalexin | 75-100 mg/kg/d in divided doses three or four times per day | 4 g/d | Some experts recommend up to 6 g/d in divided doses four times per day |
| Clindamycin | 30-40 mg/kg/d in divided doses three or four times per day | 1.8 g/d | Some experts recommend up to 2.7 g/d in divided doses three times per day |
| Levofloxacin [192, 196], if susceptible | 16-20 mg/kg/d in divided doses two times per day for children 6 mo to 5 y and 8-10 mg/kg/d once daily for children 5 to 16 y | 750 mg/d | Use if no other active oral antibiotic therapy available |
| Linezolid[b] | 30 mg/kg/d in divided doses three times per day for children < 12 y and 20 mg/kg/d in divided doses two times per day for children ≥12 y | 1200 mg/d | |
| Trimethoprim-sulfamethoxazole | Only evaluated prospectively for uncomplicated skin infections, with very limited retrospective data for osteomyelitis; therefore, no recommendation for osteomyelitis can be made at this time. | | |

For children infected by *S. aureus*, but allergic to beta-lactams and intolerant of vancomycin, clindamycin, and linezolid, levofloxacin is a potential treatment option.
References: [87, 89, 188–197].
Abbreviations: AUC, area under the curve; MRSA, methicillin-resistant *Staphylococcus aureus*.
[a]Not all antibiotics listed and all doses recommended have been prospectively evaluated in clinical trials of AHO. The dose required to achieve the desired exposure within infected bone is dependent on the blood flow to infected bone and resulting concentrations of antibiotic achieved in bone (some bone may be necrotic) and within abscesses that may be present in infected bone. Prospective studies to evaluate the effectiveness of a range of antibiotic doses in various degrees of severity of uncomplicated and complicated osteomyelitis, with or without surgery, have not been performed, although retrospective data have been reported for many antibiotics in the treatment of pediatric osteomyelitis.
[b]For children receiving linezolid for more than 2 wk, weekly screening for thrombocytopenia and neutropenia is recommended.

***Antimicrobial Management in Cases Where The Microbial Etiology Is Not Identified.***

Often, clinicians must treat AHO without positive cultures. This scenario occurred in 40 (47%) of the 85 children [208] in a 2003 report, in 46 (35%) of the 131 children [129] in Finland, and in 877 (42.6%) of the 2060 children in 36 hospitals in the United States [128]. Initial empiric therapy is selected on the basis of the local epidemiology and resistance patterns of AHO pathogens. A favorable clinical and laboratory response to empiric therapy suggests that the antimicrobials in use are active against the responsible pathogen if infection is present. Some reports suggest that many children who respond empirically to CA-MRSA regimens may be more likely to be infected by MSSA, and switch to MSSA-active agents may be considered for definitive therapy with close observation [131]. For children with culture-negative AHO, the optimal oral agent should have a comparable spectrum of coverage to the parenteral agent to which the child demonstrated clinical and laboratory improvement. Local microbiologic or epidemiologic data may also be useful in selecting the optimal oral agent. The likelihood of treatment success in situations where the spectrum of antimicrobial activity for the selected oral agent differs from the spectrum of activity for the empiric parenteral antibiotic has not been defined.

If vancomycin was started empirically, the options include completing a full course with parenteral vancomycin or switching to oral therapy with another agent. Vancomycin can be considered for the entire treatment course if CA-MRSA infection is likely, and the benefits of parenteral therapy are judged to be greater than the risks of (1) adverse events associated with vancomycin and the administration of parenteral therapy and (2) the risk of inadvertently selecting an inadequate oral agent. Clindamycin is a common option as equivalent oral therapy if vancomycin was selected initially. However, the local or regional prevalence of clindamycin-resistance among MRSA and MSSA should be considered before clindamycin is considered adequate oral therapy, as the frequency of resistance in specific communities in the USA varies widely, ranging from 5% to 40%. Less well-studied options for CA-MRSA oral therapy exist (eg, linezolid and TMP-SMX).

***Antimicrobial Management When Associated DVT Is Present.***

Data are limited that specifically address antibiotic treatment regimens for AHO with associated DVT. The presence of DVT is concerning for if not indicative of endovascular infection. Use of bactericidal agents as per endocarditis for the entire treatment course for AHO with associated DVT is considered prudent by many at this time. However, some experts have clinical experience with good outcomes when using clindamycin for AHO with associated DVT.

***Antimicrobial Management With Respect to Adverse Event Profile.***

Given the relatively long duration of therapy, attention to safety is important. Antimicrobial agents that have the potential for renal toxicity (eg, vancomycin and gentamicin) require laboratory monitoring for serum creatinine and serum antibiotic concentrations typically on a weekly basis once the child's status is stable on an effective dose of the drug.

Beta-lactam agents may suppress the bone marrow at high doses given over a prolonged period of time; weekly or biweekly (every 2 weeks) assessments of marrow function (eg, a CBC with differential) may be helpful, perhaps when prolonged courses are deemed necessary in complicated cases. There are no prospective data on this issue. The possible benefit of such monitoring can be weighed against the burdens of pain and travel for the child and family.

Many antibiotics may be associated with diarrhea. Probiotics may have a modest protective effect [209]. Clindamycin is notably associated with *Clostridioides difficile*-associated colitis, requiring education of care providers regarding symptoms of colitis and the need to notify healthcare practitioners if such symptoms develop.

In prospective, pediatric, pre-licensure evaluations of linezolid, hematologic abnormalities were no more frequent in those treated with linezolid compared with children treated with other antibiotics [210]. Long-term adverse events, such as optic and peripheral neuropathies, have been described in both adults and children receiving more than 4 weeks of linezolid [198]. Linezolid is a reversible, nonselective inhibitor of monoamine oxidase and should be used with caution in patients who are on an selective serotonin reuptake inhibitor medication [211]. Other antibiotics, such as clindamycin, do not require routine serum monitoring for toxicity in the child who is otherwise clinically well [189, 190, 212].Fluoroquinolones are prescribed in adults for parenteral or oral therapy of osteomyelitis caused by enteric bacilli (including *Escherichia coli*, *Klebsiella* spp., and *Enterobacter* spp.) or *Pseudomonas aeruginosa*; for children, based on concerns for cartilage/tendon injury noted in animal toxicity studies, non-fluoroquinolone oral antimicrobial agents (beta-lactams, aminoglycosides, and TMP-SMX) are preferred if appropriate for the clinical scenario. For children receiving long-term therapy with fluoroquinolones, attention is required for the development of arthritis/arthralgia, primarily in weight-bearing joints. This potential adverse event should be discussed with families, with instructions for the family to return for evaluation should symptoms consistent with a persistent arthropathy or tendinopathy occur for more than 2–3 days during therapy [213].

Trimethoprim-sulfamethoxazole may cause mucocutaneous and other inflammatory reactions, including Stevens-Johnson syndrome, and drug rash with eosinophilia and system symptoms (DRESS), as well as leukopenia and thrombocytopenia [214].

***Rationale for Recommendation***

Treatment of children with suspected or documented bacterial AHO that is responding to empiric antibiotic therapy is best

managed by selecting a definitive antimicrobial regimen with either parenteral or oral agents based on principles of selecting an effective agent with the narrowest spectrum agent with the lowest adverse event profile and the best host tolerance. The benefits of selecting an agent based on these principles are expected to be large and unequivocal in all circumstances. However, the final selection of a definitive antimicrobial regimen needs to be contextualized for those with positive or negative cultures (and those from whom cultures were not obtained).

***Research Needs.***

Data assessing outcomes for children with severe infections treated with monotherapy compared with combination therapy are needed, particularly for critically ill children. Studies of currently available parenteral and oral agents, particularly those with activity against CA-MRSA (eg, ceftaroline, linezolid, and TMP-SMX), are needed, including comparative effectiveness studies. Additional prospectively collected data on the adverse drug events associated with long-term antibiotic therapy are important to provide evidence for recommendations on the tests and frequency of testing that should be suggested for children receiving therapy for AHO. Studies that address optimal therapy for AHO with associated DVT also would be helpful.

## IX. In children with suspected or confirmed AHO, what clinical and laboratory criteria should be used to assess the response to treatment?

**Recommendation:**

1. In children with suspected or confirmed AHO receiving antimicrobial therapy, we suggest performing sequential monitoring of CRP in addition to serial clinical evaluation to assess response to therapy, rather than relying solely on clinical evaluation (*conditional recommendation* and *low certainty of evidence*). **Comment:** Serial clinical examinations that assess the febrile response, pain, and musculoskeletal function are important clinical parameters to monitor response to treatment.

***Summary of the Evidence***

AHO is monitored with both clinical and laboratory evaluations to ensure appropriate response to treatment and optimal outcomes. Clinical improvement (eg, resolution of fever and local signs of inflammation, increased mobility or movement of the affected region) plus laboratory evidence of resolving inflammation (declining CRP concentration) are expected when medical and surgical interventions are effectively controlling the infection. Clinical response rates with appropriate interventions can vary due to factors that include the specific pathogen, site(s) involved, severity and extent of infection, need for surgical intervention(s), need for restriction of weight bearing, and patient motivation to resume activities. Fever, when present, usually resolves within 3 to 5 days in uncomplicated courses [47]. Fever is more prolonged in children with AHO who have disseminated infection rather than with local infection only [215]. AHO caused by strains of *S. aureus* (eg, USA 300/CA-MRSA) that cause more extensive disease have been associated with more prolonged febrile courses than AHO caused by non-USA 300 MSSA strains [10, 47, 48], other microbes, and culture-negative cases [10]. One recent study did not find a difference in febrile course between children with AHO caused by CA-MRSA vs MSSA, though the former required more surgical interventions [216].

Serial measurement of serum CRP has been widely used as a means of assessing response to therapy and the potential need for additional interventions in children with AHO since the mid-1990s [43, 81, 87]. CRP elevation is present in many but not all children with AHO at presentation (see I).

In uncomplicated courses of AHO, the CRP typically peaks between days 2 and 4 of treatment and returns to the normal range in about 9 to 12 days [65, 87]. In a series of 26 children with AHO, 92% experienced a decline in CRP of at least 50% within 4 days of therapy [217]. These data have been used to support shorter courses of therapy in children with uncomplicated courses [43] and early transition to oral therapy [87, 217]. Successful transition to oral therapy after good clinical response plus CRP decline to 2 to 3 mg/dL (20 to 30 mg/L) was described in another study [42].

Higher peak concentrations and slower declines toward the normal range have been associated with the presence of subperiosteal abscess or pyomyositis [77], bacteremia [74], and with a variety of complications [42, 60, 66, 215, 218]. Such complications have included the presence of multifocal disease, need for more than one surgical intervention, or readmission for ongoing signs of infection within 6 months [60, 81]. CRP concentrations ≥8 mg/dL (≥80 mg/L) on the fifth day of treatment were associated with clinical signs that led to repeat surgical drainage procedures in 10 of 11 children [218]. High peaks of CRP also have been associated with the presence of DVT [80] and concomitant septic arthritis [42].

In one comparative analysis based on microbial etiology alone (without adjusting for complicated courses) CRP normalization occurred in a median of 25 days (range 14 to 52; n = 36) for children with AHO caused by CA-MRSA strains, vs 8 days (range 5 to 14; n = 72) for MSSA, 11 days (range 6 to 16; n = 57) for other microbes, and 6 days (range 3 to 11; n = 125) for culture-negative cases [10]. In a study of 299 children with AHO, of whom 58 (19%) had complicated courses, the mean time for CRP normalization (<2 mg/dL or <20 mg/L) was 6.9 ± 13.2 days for uncomplicated courses vs 15.4 ± 11.9 days for complicated cases [60].

CRP concentration at baseline, 48, and 96 hours comprise 3 of 7 components of a severity of illness score used to stratify

disease severity and predict the risk of long-term sequelae (see XIV) [66, 69]. CRP elevation was also a key variable in another model predictive of severity of musculoskeletal infection in children, with risk of disseminated disease increasing steadily across a continuum of increasing CRP concentrations [215], but without clear cutoffs for specific risks being identified in terms of sensitivity, specificity, and predictive values.

CRP elevation is not specific to AHO and its complications. Initial and persistent elevation sometimes may be seen in other disease processes, including malignancy and autoimmune and autoinflammatory disorders [82, 83]. Persistent elevation during the course of documented AHO also can be the result of concurrent or intercurrent viral infections or intercurrent bacterial infections, such as intravascular catheter-related phlebitis or bacteremia, or *C. difficile* infection. Postsurgical increases in CRP after orthopedic procedures, on the order of 3 to 15 mg/dL (30 to 150 mg/L), may be seen, usually peaking on the second to third postoperative day [84, 85, 219].

ESR normalization over time also has been used as a guide to the duration of antimicrobial therapy for optimal outcomes [86]. The ESR peaks similarly to CRP but normalizes more slowly [43, 65, 87, 220]. ESR normalization in uncomplicated cases usually occurs within 3 to 4 weeks [18, 65]. Time to normalization for ESR is longer for complicated vs uncomplicated clinical courses of AHO [18, 42, 220]. Like the CRP, normalization of the ESR is typically slower in children with AHO with concurrent septic arthritis than with AHO alone [13, 65]. Intercurrent infections or diseases during the course of treatment for AHO may lead to increases in ESR or more prolonged time to normalization, especially with longer courses of therapy for complicated cases. The utility of ESR normalization as a guide to the duration of therapy in complicated courses remains uncertain.

***Rationale for Recommendation***

Physical examination has limited potential for harm and generally provides the necessary information for clinical decision-making. Measurement of serum CRP concentration is widely available in a timely manner, is relatively inexpensive, and is an objective, adjunctive data point that supports clinical decision-making. Pain and discomfort can occur from venipuncture that may not otherwise be required, but these are usually mild.

The relatively rapid normalization of CRP has been interpreted as providing useful clinical guidance for both early switch to oral therapy and avoidance of prolonged antibiotic therapy for uncomplicated disease. Although higher CRP peaks and prolonged time to normalization correlate in general with various aspects of the extent and severity of infection in children with AHO, no specific thresholds of CRP concentration have been well validated for specific clinical interventions or decisions regarding the duration of therapy.

As fever abates and local signs of inflammation begin to resolve, there usually is a concurrent fall in serum CRP concentration. Persistent elevation of CRP from what is expected in a typical uncomplicated course, especially when associated with slower than expected clinical improvement, can raise concerns that lead to (1) additional imaging to better define the extent of the infection (eg, persisting abscess) and its complications (eg, associated DVT) or (2) surgical intervention(s) that may optimize short- and long-term outcomes, and (3) reconsideration of the differential diagnosis (eg, infection vs cancer). The interpretation of persistent elevation of the CRP in the face of apparent clinical improvement is uncertain. This discordance can raise concerns about the need for more evaluation or intervention but acting on such data reflexively could lead to unnecessary actions and associated risks. Such discordance can be caused by intercurrent infection or other issues unrelated to the underlying musculoskeletal infection.

Within the limitations outlined above, the panel suggests sequential monitoring of CRP as an adjunctive measure in children with AHO that can be taken into account with other clinical factors in management decision-making. There are no data to support a particular frequency of CRP monitoring during the course of AHO in children. Measurement every 2 to 3 days during the early therapeutic course, rather than daily, followed by weekly or other periodic measurement until normalization (or a clear trend toward normalization is evident) is an acceptable approach.

***Research Needs***

More detailed analyses of the clinical utility of serial serum CRP concentrations or other markers of systemic inflammation, including PCT, the ESR, or various biosignatures, especially when elevation persists in the context of apparent clinical improvement, would be useful. Identification of specific CRP or other biomarker cutoff values would be helpful for specific clinical situations, such as the need for additional surgery vs observation for persisting small abscesses or fluid collections or as a guide to the duration of thrombolytic therapy for DVT associated with AHO. Multicenter studies using iterative protocols may be a way forward to gain insight into some of these questions.

## X. In hospitalized children with suspected or documented AHO responding well to initial intravenous therapy and deemed ready for hospital discharge, should they be (1) be transitioned to oral therapy or (2) OPAT?

**Recommendations:**

1. For children with suspected or documented AHO who respond to initial intravenous antibiotic therapy, we recommend transition to an oral antibiotic regimen rather than OPAT when an appropriate (active against the confirmed

or presumed pathogen(s)) and well-tolerated oral antibiotic option is available (*strong recommendation* and *low certainty of evidence*). **Comment:** This recommendation places a high value on avoidance of harms and costs as well as on the improvement of acceptability, feasibility, and equity.

2. For children with suspected or documented AHO who respond to initial parenteral antibiotic therapy but for whom oral antimicrobial therapy is not feasible, we suggest transition to OPAT, rather than remaining in an acute-care hospital for the total duration of therapy (*conditional recommendation* and *very low certainty of evidence*). **Comment:** This recommendation places a high value on avoiding harms and costs associated with unnecessary and prolonged hospital stay. The decision to implement this recommendation and the selection of the type of OPAT (home, intermediate care facility, and clinic) may be influenced by the availability of local resources.

***Summary of Evidence***

Our systematic review of the literature sought studies that compared the efficacy and tolerability of transition to oral vs completion of treatment with parenteral therapy among children with AHO who had improved after initial inpatient intravenous antibiotic treatment. Four retrospective cohort studies were identified [128, 186, 221, 222] including 4226 subjects, 47% of whom were treated by the oral route (see Table 6). Two were large multicenter studies with propensity score-based matching that accounted for the majority of subjects [128, 222]. The other 2 were smaller studies [186, 221] with a high risk for bias secondary to lack of adjustment for confounders, but these accounted for less than 5% of the measured effect of our findings. One of the latter was a single-site study that only described the outcomes of bacteremic AHO patients [186].

Important outcomes for decision-making included treatment failure at follow-up (ranging from 6 to 37 months) between subjects transitioned to oral when compared with patients continued on OPAT. Treatment failure in the oral treatment group was comparable to the OPAT group and was relatively uncommon in both groups (4.6% in 1989 children on oral vs 6.2% in 2237 on OPAT). Minimal residual confounding despite the propensity score-based matching in the 2 larger studies could potentially explain the observed lower but not significant difference in treatment failure among those transitioned to oral therapy (RR: 0.79; 95% CI: 0.60 to 1.02) (RD: −1.3%; 95% CI: −2.5 to 0.1). Treatment failure definitions are listed in Table 6 and were not limited to recurrence of infection or long-term orthopedic complications.

Other outcomes important to patients that were assessed included: unscheduled visits and rehospitalization rates of all causes, catheter-related complications, and adverse drug reactions. Unscheduled visits and re-hospitalization rates were assessed using data from 2 large studies that included 4049 subjects [128, 222]. The rate of these treatment-related complications was significantly less common for children who transitioned to oral therapy (6.5%, n = 1953) when compared with children on OPAT (16.2%, n = 2076) (RR: 0.43; 95% CI: 0.23 to 0.79), mainly due to the frequency of intravascular catheter-related complications in the latter group. Indeed, catheter-related complications reported for 3 [128, 221, 222] of the 4 studies in our analysis were fairly common for children on OPAT, occurring in 9.7% of the cases (n = 2161). Lastly, adverse drug reactions reported in the 2 large studies [128, 222] were uncommonly reported for either route of administration but significantly less common in children transitioned to oral therapy (1.3 vs 2.6%) (RR:0.49; 95% CI: 0.27 to 0.88).

The timing of switch to oral therapy should be based primarily on the clinical course as outlined in section IX. Various studies have described the transition to oral therapy based on criteria such as after 2 to 4 days of IV therapy [223], after 7 days or less [58], or when ready for hospital discharge [42, 217]. Median LOS for children discharged to OPAT vs home on oral therapy in the 2 large multicenter studies was 6.9 days [80, 128] and 4 days (interquartile range 3 to 6 days) [222].

In children who have blood cultures that are positive for *S. aureus* but for whom there are no concerns of endovascular infection or endocarditis, switch to oral therapy also may be based on the clinical course and response to therapy. In a summary of studies in Finland that included 265 children with osteoarticular infections, of whom 131 had AHO with or without septic arthritis and 134 with septic arthritis alone, 83% of those with bacteremia had MSSA as an etiology. Among the subset of 131 with AHO, 66% had bacteremia. There was no difference in long-term outcomes in the overall study sample based on shorter vs longer courses of intravenous (IV) antibiotic therapy [224]. In another study that included MRSA and MSSA etiologies of pediatric osteoarticular infections, prolonged courses of vancomycin were not associated with improved outcomes, though 22 of the 26 children discharged on oral regimens had MSSA [183]. Use of agents considered to be bactericidal probably is not required in these cases. Beyond widespread clinical experiences, including those captured in the practice variation summarized in the 2 large propensity score-based multicenter studies [122,218], there are modest data that support this approach, especially for MSSA strains.

Selection of the oral regimen is based on susceptibility data when available in culture-positive cases or reasonably inferable from PCR-based pathogen identification (see VIII). In culture-negative cases, the selection of an oral agent can be challenging. Factors to be considered include the similarity of antimicrobial spectrum of the oral agent to that of the empiric regimen that led to a good clinical response, documented local or regional

**Table 6. Evidence Profile Table on Transitioning Regimen to Oral Therapy vs Continuing Parenteral Therapy in Children With Suspected or Documented Acute Hematogenous Osteomyelitis (AHO) Responding Well to Initial Intravenous Therapy and Deemed Ready for Hospital Discharge[a]**

| | Certainty Assessment | | | | | | No. of Patients | | Effect | | Certainty | Importance |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| No. of Studies | Study Design[b] | Risk of Bias | Inconsistency | Indirectness | Imprecision | Other Considerations | Transitioning to Oral Antibiotics | Continuing IV Antibiotics | Relative 95% CI | Absolute 95% CI | | |
| Treatment failure (follow-up: range from 6 to 37 mo)[c] | | | | | | | | | | | | |
| 4 | Observational studies [128, 186, 221, 222] | Not serious[d] | Not serious | Not serious | Not serious[e] | None | 91/1989 (4.6%) | 139/2237 (6.2%) | RR 0.79 (0.60 to 1.02) | 13 fewer per 1000 (from 25 fewer to 1 more) | ⨁⨁◯◯ LOW | CRITICAL |
| Catheter-related complications | | | | | | | | | | | | |
| 3 | Observational studies [128, 221, 222] | Not serious[f] | Not serious[g] | Not serious | Not serious | Large magnitude of effect[h] | 0/1963 (0.0%) | 210/2161 (9.7%) | NA[i] | 97 fewer per 1000 (from 110 fewer to 85 fewer) | ⨁⨁⨁◯ MODERATE | CRITICAL |
| Rehospitalisation (all causes) (follow-up: median 6 mo) | | | | | | | | | | | | |
| 2 | Observational studies [128, 222] | Not serious | Not serious[g] | Not serious | Not serious | Large magnitude of effect[i] | 127/1953 (6.5%) | 336/2076 (16.2%) | RR 0.43 (0.23 to 0.79) | 92 fewer per 1000 (from 125 fewer to 34 fewer) | ⨁⨁⨁◯ MODERATE | CRITICAL |
| Adverse drugs reaction | | | | | | | | | | | | |
| 2 | Observational studies [128, 222] | Not serious | Not serious | Not serious | Not serious | Large magnitude of effect[i] | 26/1953 (1.3%) | 55/2076 (2.6%) | RR 0.49 0.27 to 0.88) | 14 fewer per 1000 (from 19 fewer to 3 fewer) | ⨁⨁⨁◯ MODERATE | CRITICAL |

Abbreviations: CI, confidence interval; RR, risk ratio.

[a]Population: In children with suspected or documented AHO responding well to initial intravenous therapy and deemed ready for hospital discharge; Intervention: transitioning regimen to oral therapy; Comparator: continuing parenteral therapy.

[b]Studies that reported osteoarticular infections without stratifying patients for their underlying type of infections were excluded. If stratification was performed and relevant information on patients with AHO with or without septic arthritis was available, then this study was included. Patients diagnosed with septic arthritis in the absence of osteomyelitis were excluded from the pooled results presented in our analysis.

[c]Treatment failure was defined as: (1) in Keren et al [128] study: revisit to the ED or a rehospitalization for a change in the antibiotic prescribed or its dosage, prolongation of antibiotic therapy, conversion from the oral to the peripherally inserted central catheter route, bone abscess drainage, debridement of necrotic bone, bone biopsy, drainage of an abscess of the skin or muscle, arthrocentesis, or diagnosis of a pathologic fracture; (2) in Zaoutis et al. [222] study: re-hospitalization within 6 mo with assigned diagnosis or procedure codes consistent with acute osteomyelitis as the sole diagnosis, chronic osteomyelitis, a potential complication of acute osteomyelitis (eg, myositis, arthritis, etc.), or a surgical procedure related to the musculoskeletal system; (3) in Liu et al [221] study: recurrence needing a repeat course of antibiotics therapy, with or without a repeat surgical debridement; (4) in McNeil et al [186] study: long-term orthopedic complications included chronic osteomyelitis, limb-length discrepancy/growth arrest, angular deformity, chronic dislocation, avascular necrosis, or pathologic fracture.

[d]Liu et al [221] and McNeil et al [186] were considered at high risk of bias due to the presence of residual confounding, whereas Keren et al [128] and Zaoutis et al [222] used a propensity score-based full matching to adjust for important known confounders (Keren et al [128] study included age (≤5 vs >5 y), race (white vs nonwhite), insurance (government vs commercial/self-pay), length of stay (in days), location of the infection (shoulder, arm, and hand; pelvis and thigh; lower leg and foot; multiple sites; and unspecified), 4 indicators for a surgical procedure (arthrocentesis, osteotomy, soft tissue incision and drainage, and arthrotomy), and isolation of the causative pathogens in the cultures of blood, bone, and joint aspiration fluid (findings negative or positive for methicillin-resistant *Staphylococcus aureus* [MRSA], methicillin-sensitive *S. aureus* [MSSA], or other organisms). Since the later studies contributed to more than 90% of the studied population, this domain was not rated down for risk of bias.

[e]Based on an inferiority margin of 15%, not further rated down for imprecision.

[f]Liu et al [221] were considered at high risk of bias due to the presence of residual confounding, whereas Keren et al [128] and Zaoutis et al [222] used a propensity score-based full matching to adjust for important known confounders (see above). Since the later studies contributed to more than 90% of the studied population, this domain was not rated down for risk of bias.

[g]Not rated down for inconsistency since the substantial measured heterogeneity regarding the magnitude of effect was not considered to reduce our certainty in the presence of an effect.

[h]Patients in the group transitioning to oral antibiotics are not expected to receive an IV catheter, thus the events in this group should remain close to zero; therefore, the magnitude of effect is at least expected to be large, which increases the confidence in the estimate of effect.

[i]Large magnitude of effect measured (ie, RR < 0.5 without evidence of residual confounders), which increases the confidence in the estimate of effect.

[j]Due to zero events, unable to estimate relative risk.

susceptibility data for *S. aureus*, and any clinical or laboratory circumstances that may predict a pathogen other than *S. aureus*.

If an empiric antistaphylococcal beta-lactam regimen active against MSSA (eg, cefazolin, nafcillin, and oxacillin) is associated with a clinical and laboratory response in a child with no proven pathogen, then oral therapy with comparable spectrum agents such as cephalexin is a good option. When the effective empiric regimen consisted of vancomycin, with or without other agents effective against various types of *S. aureus*, a switch to oral cephalexin as therapy for presumed MSSA may be considered if the benefits of a narrower spectrum, better-tolerated antibiotic are deemed greater than the risk of relapse of potential CA-MRSA infection (ie, the frequency of CA-MRSA in the community is less than 10% to 20% and the child is not known to be colonized with CA-MRSA). Oral clindamycin also may be considered in this scenario. Other agents (eg, linezolid or TMP-SMX) may be considered on a case-by-case basis.

Our systematic review did not identify any comparative studies regarding the benefits and harms of continuation of parenteral antibiotics as an inpatient vs as an outpatient in the specific setting for children treated for AHO. However, a 2018 systematic review [225] including 1 RCT and 18 observational studies compared inpatient vs OPAT (at home) for many different pediatric infectious diseases. Despite no pooled analysis provided in this systematic review, there were no differences in treatment failure rates, readmission rates, or adverse events for the great majority of the studies included. Children treated at home received longer total courses of treatment in half of the studies included in the analysis. Costs associated with home-based OPAT were substantially lower in most of the studies, and OPAT was deemed satisfactory by patients and their families.

***Rationale for Recommendation***

Our systematic review found that comparably good treatment outcomes occur for children transitioned to oral therapy as well as for children who continued on OPAT after improving on initial inpatient intravenous therapy. However, patient-important outcomes favor oral antibiotics over OPAT, especially considering catheter complication rates with their resulting need for unscheduled revisits and rehospitalizations. In the context that the 2 alternatives are potentially equivalent regarding treatment failures and that transitioning to oral therapy clearly results in fewer harms, and considering increased acceptability to patients and their families, the panel agreed to make a strong recommendation despite low certainty of evidence.

With regard to the issue of *S. aureus* bacteremia, the panel considered that such bacteremia in children does not carry the same risk of occult endovascular infection (including endocarditis) that may be seen in adults, and that similar outcomes are expected whether these children are treated with short or longer courses of IV therapy. The decision regarding oral switch should be based more on the clinical course than the presence or absence of bacteremia, unless there is clear evidence of endovascular infection or bacteremia that is prolonged beyond the point of adequate source control.

If oral antimicrobial therapy is not feasible, transitioning from an acute care hospital to OPAT rather than remaining in the hospital to complete the needed course of therapy may reduce harms and costs associated with unnecessary and prolonged hospital stay. Availability of local resources will influence the decision to implement this recommendation and the selection of the type of OPAT.

***Research Needs***

Although having data from randomized controlled trials comparing short- and long-term outcomes of initial parenteral therapy followed by either oral or OPAT for children with AHO would be ideal, such studies are unlikely to be done in this era, given the costs, plus the substantial observational data that support early oral switch therapy. Additional large comparative effectiveness studies with more specific outcomes data would be useful. Well-designed studies that address when bacteremia may be an appropriate factor in decision-making around the timing of the transition to oral therapy would have value.

## XI. In children with AHO presumed or proven to be caused by *S. aureus* who have had an uncomplicated course and responded to initial therapy, is a 3- to 4-week total duration of antibiotics (parenteral plus oral) recommended over a longer course?

**Recommendation:**

1. In children with AHO presumed or proven to be caused by *S aureus* who have had an uncomplicated course and responded to initial therapy, we suggest a 3- to 4-week duration of antibiotics rather than a longer course (*conditional recommendation* and *very low certainty of evidence*).
   **Comment:** Although the optimal duration of therapy is best described for uncomplicated courses of AHO due to MSSA, longer duration may be necessary for other pathogens, including more virulent strains of *S. aureus* (such as USA 300 and PVL+, whether CA-MRSA or MSSA), and for complicated courses.

***Summary of the Evidence***

Duration of therapy for AHO in children traditionally has ranged from 3 to 6 weeks, and sometimes longer, depending on the severity of the infection, its complications, and its etiology [86]. This practice was based on clinical experience and a seminal study of 163 cases in Dallas reported in 1975, where

children treated for <22 days of antibiotic therapy had a 19% failure rate [18].

There are no comparative studies from any era comparing a 3- to 4-week course of antibiotics to a longer course and no studies with a treatment course of shorter than 3 weeks. Therefore, observational studies with a 3- to 4-week course were reviewed and indirectly compared with those with a longer course (ie, 6 weeks or more). We identified 5 one-arm studies published since 2005 that provided data on outcomes based on the duration of therapy, each with at least 6 months of follow-up. Treatment failure was defined as persistent or relapsing infections, excluding noninfectious complications or elevated CRP without clinical correlation.

Three studies evaluating treatment failure after a course of 3 to 4 weeks of antibiotics were pooled for this arm [226, 229, 230]. The largest study described 131 children in Finland with complicated or uncomplicated culture-positive osteomyelitis (89% due to MSSA, no CA-MRSA) who were part of a long-term study from 1983 to 2005. These children were treated with a short course of IV antibiotics followed by oral therapy until most symptoms and signs of AHO subsided and the CRP had fallen below 2 mg/dL (20 mg/L) [87, 223]. The children were divided into short-term (n = 67) and long-term therapy groups (n = 64), but the criteria for this group assignment were not specified. Children received a median of 3.7 and 4.1 days of IV therapy in the short- and long-term groups, respectively. The median total days of IV plus oral therapy combined were 20 days in the short-term group (with 90% treated for 10 to 21 days) and 30 days in the long-term group (with 90% treated for 30 to 43 days). None in either group experienced a recurrence and one in each group had minor sequelae at 1 year of follow-up [223]. The authors noted that this study was primarily a description of good outcomes with shorter courses (about 3 weeks) of antimicrobial therapy in children who demonstrated rapid clinical and laboratory improvement.

In another study, 30 of the 37 Australian children with uncomplicated AHO were cured with 21 days of antibiotics. The other 7 received longer courses, primarily due to concerns about their clinical course or laboratory parameters [226]. Twelve were culture-positive, all for *S. aureus*, presumably all MSSA based on their treatment regimens. All 37 were normal clinically and radiologically at 1 year of follow-up. A third study described 42 Danish children with AHO who received a median of 6 days (IQR 4 to 9) of IV therapy followed by a median of 19 days (IQR 15 to 22) of oral therapy [227]. Twenty (48%) required surgical intervention and 25 (60%) were MSSA; no CA-MRSA was isolated. Two (5%) experienced recurrence, and both of these children had symptoms for >5 weeks prior to diagnosis.

A primary concern regarding the applicability of shorter courses (ie, 3 weeks) for AHO from the above studies to North American populations was the absence of more virulent USA 300/PVL-positive CA-MRSA in these studies [228]. Of note, in recent years, the attribution of potential virulence based on methicillin susceptibility or resistance among *S. aureus* strains has become less straightforward, as the USA 300 strain family now encompasses both CA-MRSA and MSSA lineages [229, 230].

Two studies provided data on treatment failure in children treated on average for approximately 6 weeks [63, 231]. Among 45 children in France with non-severe presentations of AHO who were treated for a median of 43 days (IQR 33 to 48), predominantly via the oral route, there were no long-term sequelae at 6 months of follow-up. No microbiological data were provided, so it is unclear if these results are generalizable [231]. In a series of 286 children with culture-confirmed *S. aureus* osteoarticular infections (44% USA300 and 28% MRSA) who were treated for a median of 42 days (IQR 29 to 55), 27 (9.4%) had orthopedic complications. From the 256 patients with AHO, 11 developed chronic osteomyelitis (4.3%). There was no difference in duration of total therapy or route of therapy between those with and without complications. Those with complications were more likely to have >1 surgical procedure [63].

A pooled summary of the above 3 one-arm studies reporting duration of 3 to 4 weeks vs the 2 studies on longer antibiotics course is presented in Supplementary Material. Based on the available data, no difference in treatment failure (defined as persistent or recurrence infection) was observed between the 2 compared groups, but this conclusion remains very uncertain.

There are very limited data for duration of therapy for AHO caused by pathogens other than MSSA. Children with AHO due to CA-MRSA strains may or may not require longer courses than MSSA, depending on disease severity and complications.

In a retrospective series of 21 children with AHO caused by *S. pneumoniae*, the mean total duration of antimicrobial therapy was 57.5 ± 48.6 days (SD), with a median of 38 (ranging from 23 to 196). This included 13 (62%) who received oral therapy for part of their courses (mean: 43 days, range: 12 to 147 days) [164]. In another series of 28 children with pneumococcal AHO, the mean total duration was 42.2 ± 10.5 (SD) days, of which a mean of 24.2 ± 14.6 was parenteral [232]. This study also included 29 children with AHO due to *S. pyogenes* who were treated with a mean total duration of 50 ± 19.7 days, of which a mean of 20.4 ± 11.4 was parenteral, and 45 children with AHO due to *S. aureus*, who received a mean total of 71 ± 44.7 days of therapy, of which a mean of 24.3 ± 16.5 was parenteral. Clinical courses did not differ among these 3 causative pathogens in terms of surgical interventions, days of fever, or sequelae [232, 233]. Whether the treatment durations associated with good outcomes for MSSA and CA-MRSA should be applied routinely to AHO due to *S. pneumoniae* or *S. pyogenes* is unclear.

The range of treatments administered in case reports and small series of AHO due to *K. kingae* have ranged from 3 weeks to 6 months [234]. Courses on the shorter side of this range likely are adequate. For osteomyelitis caused by *Brucella* spp.,

a minimum course of 6 weeks of therapy is a standard recommendation [161].

Children with prolonged duration of symptoms prior to diagnosis (ie, weeks) may be at increased risk of recurrence, but it is not known whether recurrences in these circumstances can be prevented by longer courses of antibiotics.

Adverse event data for prolonged courses of antibiotic therapy also are provided in Supplementary Material. These were derived from a large database study showing that antibiotic courses (predominantly oral) greater than 4 weeks for any indication were not associated with a higher incidence of serious adverse events than were shorter courses. This study focused on 3 agents not commonly used for the treatment of AHO in children—amoxicillin, ciprofloxacin, and doxycycline—but did evaluate outcomes for children in addition to adults. In a small study of 60 children with osteoarticular infections treated with a mean duration of parenteral therapy of 35.9 days, 17 were considered to have allergic or adverse reactions to their antibiotic regimen, with onset at a mean of 24.4 days of therapy [235].

#### *Rationale for Recommendation*

For children with uncomplicated courses of AHO due to *S. aureus* (whether MSSA or CA-MRSA), the failure rate following a 3- to 4-week course of appropriate antibiotics at adequate dosage is too low to justify routinely prescribing a longer course. It also is uncertain whether a longer course would prevent failures.

For *complicated* courses caused by any strain of *S. aureus*, longer courses remain appropriate, with total duration based case-by-case on the rate of improvement in clinical findings and laboratory markers of inflammation and any ongoing need for surgical intervention. This approach also may be reasonable for complicated courses due to other pathogens such as *S. pyogenes* and *S. pneumoniae*. Similarly, shorter courses (3 to 4 weeks) for uncomplicated courses caused by these and other pathogens such as *K. kingae* may be adequate.

Longer courses of therapy, even when predominantly oral in route, may be associated with an increased risk of clinical and laboratory adverse events compared with shorter courses. Impacts of prolonged therapy on the child's microbiome may have future health implications. Depending on the specific agent prescribed, costs of therapy also may become a consideration. When OPAT is required, shorter durations, when appropriate for the clinical scenario, may improve patient quality of life and lower the risk of adverse events.

#### *Research Needs*

Comparative studies that address the optimal duration of antibiotics for uncomplicated and complicated AHO due to *S. aureus,* taking into account microbial virulence factors in addition to methicillin-susceptibility status, are needed. Further evaluation of clinical responses, specific types of complications, and the role of inflammatory markers in cases where there is apparent discordance between pace of resolution of clinical findings and decline in inflammatory markers as drivers of the duration of therapy would be helpful. Multicenter efforts to iteratively evaluate management protocols for less common microbes such as *S. pyogenes*, *S. pneumoniae*, and others would have value. Studies of the short- and long-term impacts of various regimens on host microbiomes could provide important insights.

### XII. In children with AHO, should end-of-therapy imaging studies be routinely obtained?

**Recommendations:**

1. In children with uncomplicated AHO that does not involve the physis, we recommend against obtaining end-of-therapy MRI (*strong recommendation* and *low certainty of evidence*) and suggest against routine end-of-therapy plain radiographs (*conditional recommendation* and *very low certainty of evidence*).
2. In children with complicated AHO or with involvement of the physis, we suggest end-of-therapy imaging studies (plain radiographs and/or MRI) (*conditional recommendation* and *very low certainty of evidence*).

#### *Summary of the Evidence*

Findings on all imaging modalities for children with AHO, including MRI, can be slow to resolve and thus are not routinely useful to determine the duration of therapy or the risk of recurrence of infection. Imaging study data were not included in the one severity of illness scoring system designed to identify children with AHO courses that place them at higher risk of long-term sequelae [67].

Evidence from the literature regarding the utility of follow-up MRI is limited to 2 retrospective studies [236, 237]. In a series of 59 children with AHO, only 11 (11%) of the 104 follow-up MRI imaging studies prompted a change in management [236]. Ten (21%) of the 47 follow-up MRIs ordered for persisting or worsening symptoms, and 7 (88%) of the 8 ordered for CRP concentrations that were increasing or not decreasing resulted in a treatment change. None of 43 ordered as routine follow-up resulted in a treatment change. In a smaller study of 27 children with AHO, only 1 of the 20 (5%) follow-up MRI studies ordered routinely, vs 4 of the 8 (50%) ordered for clinical concerns, resulted in a change in treatment [240].

The utility of end-of-therapy plain radiographs has not been well studied. Follow-up plain radiographs during the course of therapy are more likely to show abnormal findings than early plain radiographs. In 2 studies that provided data on plain radiographs taken 15 to 19 days after presentation, abnormalities consistent with AHO were present in 82% [96] and 68% [87], respectively. Most such changes did not correlate with the

clinical status of the child, and such abnormalities may persist at least a year in a small minority of children [87].

***Rationale for Recommendation***

In children with *uncomplicated* courses, with no concern for growth plate involvement, routine follow-up imaging studies do not appear to add value to clinical care over time. Routine plain radiographs involve minimal radiation and have limited potential for harm, but such studies seem unnecessary in children with *uncomplicated courses*. Additional considerations are important for MRI imaging. The risk from sedation required for young children undergoing MRI studies is not trivial. In developed countries, the risk of death in children from general anesthesia is about 1 in 10 000, whereas the risk of a serious adverse event is about 1.4 in 1000 [238]. Risks from pediatric sedation procedures outside the operating room are on the order of 5.6 per 10 000 [239]. Given the potential for harm and the lack of evidence for benefit, the panel made a strong recommendation against routine repeat MRI in *uncomplicated* courses despite only low certainty of evidence. Repeat MRI during the course of therapy should be reserved for children who are not responding clinically to therapy, for whom such imaging may guide appropriate interventions, or who develop symptoms compatible with recurrent or chronic osteomyelitis (during the initial treatment course or subsequent to it).

End-of-therapy radiographs are appropriate in cases of *complicated* osteomyelitis and when there is a concern for the involvement of the physis. Plain radiographs toward the end of therapy in complicated courses may show evidence of sequestra, with risk for chronic osteomyelitis, or risks for other complications such as pathologic fracture. The number needed to image, given the relatively small percentage of children with AHO who develop long-term complications (see XIV), is uncertain, but the panel consensus is that end-of-therapy radiographs for children with *complicated* osteomyelitis may provide meaningful baseline data for interpreting subsequent imaging studies if abnormalities of bone growth become evident over time or symptoms of infection recur. In *complicated* courses deemed at high risk for long-term sequelae, MRI and/or plain radiographs at the end of therapy may provide guidance regarding the need for and intensity of long-term follow-up (see XIV). Evaluation of risks vs benefits of MRI during the course of therapy or at the end of therapy should be undertaken on a case-by-case basis.

***Research Needs***

Additional studies regarding the utility of plain films and MRI during the course and at the end of therapy in children with AHO, especially for complicated courses, with regard to medical decision-making, reassurance of patients and families, and guidance for long-term follow-up, would be helpful.

## XIII. For children who do not respond to therapy, or relapse following completion of therapy, which interventions are appropriate to optimize outcomes?

**Recommendations:**

1. For children experiencing either primary treatment failure or early or late recurrence of AHO:
   a. Clinicians should assess the adequacy of the antimicrobial regimen (spectrum of activity, dosage and penetration to the site of infection, and adherence) before deciding on the need to broaden the spectrum or to restart antimicrobials (*Good practice statement*)
   b. Clinicians should reassess the need for surgical intervention for therapeutic and/or diagnostic purposes (*Good practice statement*). **Comment:** The accuracy of the diagnosis of AHO may need to be reconsidered, especially in culture-negative cases.

***Summary of Evidence***

Failure to ultimately achieve clinical and microbiologic cure is rare as reported in most case series of AHO in children. However, a few children will (1) fail to respond to initial therapy (primary failure), (2) have a good clinical response to initial therapy but experience recrudescence during therapy (secondary failure), or (3) have later relapse/recurrence of infection weeks to months to years after completion of therapy. This aspect of management has not been systematically studied, likely due to its relative infrequency over time at any given center.

*Primary treatment failure* in a child with apparent AHO may be indicated by lack of improvement of local (ie, overlying erythema or edema, tenderness, and limitation of range of motion) and/or systemic signs of infection (ie, persisting fever that is not trending downward and ongoing clinical signs of sepsis) 2 to 4 days after the initiation of presumed adequate antimicrobial therapy, with or without definitive surgical/procedural intervention. Lack of expected improvement of inflammatory markers (eg, reduction in serum CRP concentration, particularly in the context of lack of clinical improvement, may indicate treatment failure. *Secondary treatment failure* may occur early in the course after a few days of apparent clinical improvement or after hospital discharge on the selected outpatient regimen.

Primary and secondary failure can have multiple causes, including:

- The dosage (and resulting antibiotic exposure) of the prescribed antimicrobial regimen is inadequate for the infection being treated

- The prescribed antimicrobial regimen is not being administered appropriately (eg, administration errors and non-adherence)
- The causative microbe is not susceptible to the current antibiotic regimen
- Emergence of resistant organisms during therapy
- The primary site(s) of infection (eg, sequestrum, subperiosteal abscess) requires surgical intervention (eg, drainage or debridement)
- One or more concurrent but adjacent (eg, pyomyositis) or metastatic foci of infection exist that require surgical intervention
- There is a new, unrelated infection, or a noninfectious etiology (eg, chronic multifocal recurrent osteomyelitis [141] and nondisplaced fracture of a long bone [28])

For children with primary or secondary treatment failure, the first step generally is reassessment of the antibiotic regimen. If the microbial etiology and its antibiotic susceptibilities are known, and the regimen and its administration are deemed appropriate, then additional imaging (eg, MRI) of the primary site(s) or other suspected sites of infection is often the next step to determine the need for surgical intervention for adequate source control for the infection. Inappropriate antibiotic selection or dosage should be corrected. This may include increasing the antibacterial spectrum of therapy while awaiting susceptibility data.

If no pathogen has been identified, obtaining additional cultures from the site(s) of infection should be strongly considered, whether previously obtained and negative or not previously obtained. Antibiotic pretreatment should not preclude a decision to drain or aspirate a focus of infection, especially in situations of apparent treatment failure without a proven etiology (see V). Obtaining such cultures prior to changing the antibiotic regimen is suggested when clinically feasible.

For children with secondary failure as outpatients, assessment of adherence is necessary, whether the route of administration of the prescribed regimen is oral or intravenous. Repeat imaging studies often will be necessary in these cases to assess for persisting foci of infection that may require debridement or drainage.

Persistent bacteremia is a category of primary treatment failure that may lead to hematogenous complications and metastatic spread of infection [55]. There are no comparative data regarding surgical intervention vs medical therapy alone with particular durations of ongoing bacteremia despite adequate antibiotic therapy. In a child with a documented focal infection that can be drained, who is receiving medical therapy only but has bacteremia that persists 48 to 72 hours (particularly in the child with little clinical response), the panel suggests the need for surgical intervention (see VI). Shorter duration of bacteremia without other evidence of clinical worsening may be observed while on an antibiotic regimen that is deemed effective against the documented microbe. Persistent bacteremia also may suggest the presence of occult secondary foci of infection or an associated DVT. The presence of DVT may impact antibiotic regimen options as well as route and duration of therapy.

Late relapse following appropriate antibiotic and surgical therapy for AHO is uncommon, generally <1% to 2% [42, 53, 66, 74, 128, 223]. In a child who presents with apparent late relapse, the first step is to determine whether the symptoms or signs are due to bacterial osteomyelitis (ie, chronic osteomyelitis in these scenarios) vs another etiology (eg, chronic recurrent multifocal osteomyelitis). An approach similar to that outlined for evaluation of poor response to initial therapy can be undertaken. Reassessment of the adequacy of the antibiotic regimen and adherence to the prescribed course is a starting point. Imaging studies (plain radiographs and/or MRI, depending on the presentation) should be obtained. Bone biopsy or other invasive techniques to examine and culture involved bone(s), including histopathologic evaluation, may be helpful to expand the diagnostic considerations, especially if the diagnosis is uncertain and the etiology of the initial infection was not confirmed. Surgical debridement of sequestrum and involucrum, when present, may be needed. Of note, antibiotic treatment of chronic osteomyelitis arising as a relapse of AHO is typically prolonged and will not be addressed in this guideline.

***Rationale for Recommendation***

A clinician may be challenged by a child who is not responding to what is believed to be the best antimicrobial and surgical therapy, regardless of the timing of onset of the new signs, symptoms, and laboratory values that may signal apparent treatment failure. This situation may even occur in cases for which a presumptive or definitive pathogen has been detected. Potential causes that may be responsible for failure to respond include both errors in diagnosis of a bacterial etiology of osteomyelitis and inadequate medical/surgical therapy. Complete reevaluation of the child should be considered, rather than empirically broadening antibacterial coverage or restarting antibiotics, which could place the child at unnecessary risk of additional antibiotic exposure and missed opportunities for appropriate management. The benefits of such reassessment are believed to be large and unequivocal.

***Research Needs***

Prospective studies that assess response to medical and surgical therapies, with stratification of outcomes by pathogen (including virulence factors and antibiotic susceptibilities), antibiotic dosing exposure, sites of osteomyelitis, severity of infection at presentation, and complications during the clinical course need to be performed to provide insights into rates of failure attributable to each facet of management. Standardization of antibiotic therapy and approach to surgical management will be necessary to compare outcomes across the multiple institutions that will likely be needed for these studies.

## XIV. For children who have successfully completed antimicrobial therapy for documented or suspected AHO, in what situations is long-term follow-up required to address potential sequelae?

**Recommendation:**

1. In children with AHO who are determined to be at risk of long-term adverse outcomes, we suggest a follow-up period of at least 1 year by specialists with experience treating children with AHO (*conditional recommendation* and *low certainty of evidence*).

***Summary of Evidence***

Long-term adverse outcomes include the presence of osteonecrosis, cartilaginous degeneration of joint surface(s), chronic/recurrent osteomyelitis, avascular necrosis of bone(s), pathological fractures, malunion, contracture, limb length discrepancy, deformity, and restriction of range of motion. A systematic review of the literature from 2005 to June 2019 did not yield any articles that compared the outcome of AHO with or without follow-up beyond the end of therapy. Six recent studies provide insights into frequencies of particular outcomes [53, 74, 82, 128, 222]. Five studies were found that explored clinical predictors of long-term outcomes in children with AHO [42, 63, 66, 240–242]. Most of the children with long-term sequelae had identifiable risk factors early in the course of their illness.

In a multicenter analysis of 1969 children with AHO diagnosed from 2000 to 2005 in the United States, 21 (1.1%) developed suspected chronic osteomyelitis and 33 (1.7%) required a musculoskeletal surgical procedure within 6 months after hospital discharge [222]. In another multicenter study of 2060 children with AHO diagnosed from 2009 to 2012, 9 (0.4%) had pathologic fracture and 29 (1.4%) required debridement of necrotic bone within 6 months after hospital discharge [128]. Four studies with sample sizes ranging from 121 to 195 identified rates of long-term sequelae of 2.0% to 7.9% [53, 74, 81, 241]. These were primarily angular deformity or limb length discrepancy resulting from physeal injury.

A 7-element, 10-point severity of illness score, based on initial presentation (see Supplementary Material), was used to stratify 139 children as having mild (n = 78 [56.1%]; score 0 to 2), moderate (n = 35 [25.2%]; 3 to 6), or severe AHO (n = 25 [17.9%]; >6) [67, 168]. These elements were: CRP values at presentation and 48 and 96 hours into treatment, WBC band percentage, ICU admission, duration of fever, and presence of disseminated infection. Long-term adverse outcomes occurred in 1.3% of children with mild, 5.9% with moderate, and 32.0% with severe AHO. Eight (72.7%) of the 11 children with long-term adverse outcomes were classified as having severe illness by the scoring system.

A retrospective series of 286 children in Houston from 2011 to 2017 with acute AHO and/or septic arthritis (of whom 30 had isolated septic arthritis) with cultures positive for *S. aureus* identified 27 (9.4%) with osteoarticular sequelae, including chronic osteomyelitis in 14, pathologic fracture in 8, growth arrest in 4, and avascular necrosis in 2 (one had fracture and arrest) [63]. Fever (>38°C) more than 4 days after admission (OR: 1.9; 95% CI: 1.8 to 5.5) and need for surgical intervention after hospital day 3 (delayed source control: OR: 5.9; 95% CI: 2.0 to 17.9) were associated with orthopedic complications in multivariable analysis. Infection with an *agr* III *S. aureus* strain also was associated with these complications (OR 5.1; 95% CI: 1.6 to 16.3) but ICU admission and bacteremia were not. Laboratory markers of inflammation were not evaluated in this study.

A retrospective study of 129 children in Thailand with AHO and/or septic arthritis from 1996 to 2006 reported outcomes for 79 (61.2%) at 2 or more years of follow-up [242]. Of the initial 129, 37 (28.7%) were neonates. Osteoarticular sequelae including one or more avascular necrosis of an epiphysis, limb length discrepancy, and pathologic fracture were present in 23; 14 of whom (60.9%) were neonates. Osteoarticular sequelae were associated in univariate analyses with duration of symptoms at presentation > 1 week, delay in receipt of appropriate antibiotics of >3 days, involvement of the hip joint, infection due to CA-MRSA, and neonatal infection.

Among 83 children with AHO in Costa Rica from 1992 to 1994, 11 (14.3%) of the 77 who had ≥6 months of follow-up had limitations of mobility, 5 of whom had bone growth arrests [152]. Factors associated with these sequelae were marked initial and persisting elevations of serum CRP concentration, axillary temperature >37.4 0°C for >7 days, marked local swelling or warmth for >10 days, marked local pain or limited motility for >10 days, need for >1 surgical drainage procedure, and >1 focus of AHO or septic shock.

Pathologic fracture is a well-recognized but uncommon complication of AHO. In a series of 17 children from Houston with a pathologic fracture associated with *S. aureus AHO* (15 were MRSA), mean time to fracture from the onset of symptoms was 72 days (range 20 to 150 days) [241]. During a mean of 22.4 months of follow-up, 2 of the 17 required surgical procedures for nonunion at the fracture site; 7 had varying degrees of angular deformity, at least 1 of whom required surgical intervention; 1 had evidence of physeal arrest; and 2 required resection of sequestrum. Compared with 49 matched controls without fracture followed for a mean of 10 months, those with fracture had more complicated courses with regard to number of surgical procedures, hospital LOS, and duration of antimicrobial therapy. Initial MRI findings present in at least 14 of the children with pathologic fracture were the presence of a subperiosteal abscess with size ≥50% of the bone circumference and a sharp zone of diminished bone marrow enhancement. These findings were less common in those without fracture. An associated intramuscular abscess also was more common in those with vs without fracture.

Three studies found associations between microbial factors and severity of AHO and its outcomes: *S. aureus* strains that

express Panton-Valentine leucocidin [240, 243] or the type III allele of the *S. aureus* accessory gene regulator (*agr* III) [63]. However, the clinician typically does not have access to these details about the pathogen.

In summary, children who have persistent findings on physical examination (eg, edema and limitations of mobility) or radiographic studies at the end of antimicrobial therapy, or who demonstrate the following or similar clinical scenarios, may benefit from long term follow-up:

1. Prolonged duration of symptoms prior to treatment
2. Fever that persists 4 or more days after initiation of effective therapy and debridement
3. Persisting elevation of CRP after 4 or more days after initiation of effective therapy (in the absence of additional surgeries), as associated with complicated infection
4. Disseminated or multifocal infection
5. Surgery required for source control beyond the third day of effective therapy and initial debridement
6. Involvement of the hip joint
7. Imaging studies that suggest increased risk for pathologic fracture (eg, areas of decreased marrow enhancement)
8. Children with scores of 6 or more on the Modified Osteomyelitis Severity of Illness Score [67, 168] (see Supplementary Material)

#### *Rationale for Recommendation*

Most of the children with AHO have a favorable outcome and will not need specific follow-up, beyond a heightened awareness within their medical home regarding the child's history of AHO and its potential risks. For the approximately 5% to 10% who will have osteoarticular sequelae from AHO, the great majority of these children can be identified on the basis of clinical and laboratory aspects at time of presentation and early clinical course and can be followed closely to optimize their functional outcomes.

Children who have uncomplicated courses are at low but not negligible risk for long-term complications that may become evident during skeletal growth and maturation. This risk merits informing parents/guardians (and the child when developmentally appropriate) about the need to bring clinical concerns that may be related to their prior bone infection to the attention of the child's medical home.

#### *Research Needs*

Additional prospective studies on predictors of long-term outcomes to better guide long-term follow-up would be helpful. The creation and evaluation of long-term follow-up criteria are needed for use by primary care providers responsible for children who are at risk of sequelae. These criteria should document the need for referrals to pediatric orthopedic and physical therapy specialists for additional surgical intervention or physical therapy when appropriate.

## Supplementary Data

Supplementary materials are available at the *Journal of the Pediatric Infectious Diseases Society* online.

## Notes



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