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# PIDS/IDSA 2023 Guidelines for Diagnosing and Managing Acute Bacterial Arthritis in Pediatrics

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Published December 13, 2023

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**Published:** 06 November 2023

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A correction has been published: *Journal of the Pediatric Infectious Diseases Society*, piae 065, <https://doi.org/10.1093/jpids/piae065>

**Published:** 13 July 2024

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## Abstract

This clinical practice guideline for the diagnosis and treatment of acute bacterial arthritis (ABA) in children was developed by a multidisciplinary panel representing the 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 ABA, including specialists in pediatric infectious diseases and orthopedics. The panel's recommendations for the diagnosis and treatment of ABA are based upon evidence derived from topic-specific systematic literature reviews.

Summarized below are the recommendations for the diagnosis and treatment of ABA 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 approach (Grading of Recommendations Assessment, Development and Evaluation) (see [Figure 1](#)). 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.

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## Executive Summary

### I. What non-invasive diagnostic laboratory tests should be performed in children with suspected ABA?

## **Recommendations:**

1. In children with suspected ABA, we recommend performing blood culture prior to administration of antimicrobial therapy (*strong recommendation, moderate certainty of evidence*).
2. In children with suspected ABA, we suggest measuring serum C-reactive protein (CRP) on initial evaluation (*conditional recommendation, very low certainty of evidence*). **Comment:** Serum CRP has a low accuracy to establish the diagnosis of ABA given the variability between pathogens, but in situations where the initial CRP is elevated, this result can serve as the baseline value for sequential monitoring that may guide decision-making regarding duration of antimicrobial therapy.
3. In children with suspected ABA, we suggest against measuring serum procalcitonin (*conditional recommendation, low certainty of evidence*).

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

### **Recommendations:**

1. In children with suspected ABA, we recommend obtaining plain radiography of the affected joint and adjacent bones rather than not performing plain radiographs (*strong recommendation, moderate certainty of evidence*). **Comment:** Despite the low sensitivity of plain radiography for detecting presence of joint effusion or adjacent osteomyelitis on initial presentation, other important etiologies of acute musculoskeletal pain may be identified.
2. In children with suspected ABA in whom further imaging studies are required to detect the presence of joint effusion, particularly of the hip or the shoulder, we recommend performing ultrasonography of the affected joint before performing more complex and less widely available imaging tests (*strong recommendation, moderate certainty of evidence*). **Comment:** Ultrasonography documenting the absence of joint effusion suggests that ABA is not present.
3. In children with suspected ABA in whom further imaging studies are required to assess the extent of inflammation and infection, including adjacent osteomyelitis and pyomyositis, we suggest performing a magnetic resonance imaging (MRI) study rather than other imaging modalities (e.g., computerized tomography (CT) or bone scintigraphy) (*conditional recommendation, very low certainty of evidence*). **Comment:** Children with ABA at high risk of adjacent osteomyelitis include those with more than 3 or 4 days of symptoms prior to presentation, *S. aureus* infection, and marked elevation of CRP, but these risk factors require further validation.

## **III. For children with suspected ABA, when should diagnostic invasive procedures be performed to collect synovial fluid from affected joint(s) and which diagnostic tests should be performed on the collected joint fluid?**

### **Recommendations:**

1. In children with suspected ABA, we suggest collecting synovial fluid from the affected joint by arthrocentesis prior to starting empiric antimicrobial therapy (*conditional recommendation, moderate certainty of evidence*).

2. On joint fluid obtained by arthrocentesis, we recommend performing white blood cell count and differential and routine microbiological cultures (aerobic bacterial culture and Gram stain) (strong recommendation, *moderate certainty of evidence*). **Comment:** Further diagnostic testing may be beneficial in certain situations: 1) molecular testing for specimens from which no pathogen has been identified by Gram stain and aerobic bacterial culture, (particularly in preschool-aged children at higher risk of *K. kingae* infection); and 2) more extensive scope of microbial testing, beyond aerobic bacterial culture (e.g., anaerobic, fungal, and/or mycobacterial cultures and stains; molecular testing, which may include metagenomic next-generation sequencing), in children who are immunocompromised or who have a history of penetrating injury. Additional molecular tests may be performed on synovial samples held in the laboratory, or for additional cultures, a repeat arthrocentesis may be required.

#### **IV. At the time of presentation, can parenteral antimicrobial agent administration be delayed until joint specimens have been obtained?**

##### **Recommendations:**

1. In children with presumed ABA who are ill-appearing or have rapidly progressive infection, we recommend immediately starting empiric antimicrobial therapy (after blood cultures are obtained if possible) rather than withholding antibiotics until invasive diagnostic procedures are performed (strong recommendation, *moderate certainty of evidence*). **Comment:** Invasive diagnostic procedures should occur as soon as feasible, even if antibiotics have already been administered.
2. In children with presumed ABA who do not appear clinically ill, we suggest withholding antimicrobial therapy, while under careful observation, until an *initial* joint aspirate is collected for diagnostic purposes (conditional recommendation, *very low certainty of evidence*).  
**Comment:** The decision to initiate antimicrobials prior to invasive diagnostic procedures depends on the severity of the clinical presentation, local accessibility to experts and resources or, if appropriate, the time required for transport to a higher level of care for additional diagnostic or debridement procedures. The ability to diagnose pathogens by molecular diagnostic techniques suggests that critical information on pathogen identity is now less dependent on obtaining bacterial cultures prior to starting antimicrobial therapy.

#### **V. Which empiric antimicrobial agent(s) should be provided for children with suspected ABA?**

##### **Recommendations:**

1. In children with suspected ABA, we recommend using empiric antimicrobial therapy active against *S. aureus* (strong recommendation, *moderate certainty of evidence*). **Comment:** Antimicrobials with activity against community-acquired MRSA (CA-MRSA) should be considered based on local susceptibility data and severity of disease. Adding empiric antimicrobial coverage for pathogens in addition to coverage for *S. aureus* may be warranted when other pathogens are suspected based on relevant aspects of immunization, exposure history, clinical presentation, or physical examination.
2. In infants and preschool aged children (6 to 48 months of age) with suspected ABA, we suggest selecting empiric therapy to include activity against *K. kingae* rather than only targeting *S.*

*aureus* (conditional recommendation, *very low certainty of evidence*). **Comment:** With *K. kingae* reported as the most frequent pathogen in this age group in recent studies, additional therapy is suggested if empiric therapy used for *S. aureus* is not active against *K. kingae*.

## **VI. When should advanced imaging be performed and/or invasive procedures be repeated in the management of presumed or confirmed bacterial arthritis in children?**

### **Recommendations:**

1. In children with presumed or confirmed ABA who demonstrate a poor clinical and laboratory response within 48–96 hours (continued fever, persistent bacteremia and/or rising CRP) after initial invasive procedures (open or arthroscopic) and initiation of appropriate antimicrobial therapy, we suggest performing MRI if not previously obtained (conditional recommendation, *very low certainty of evidence*). **Comment:** MRI is performed to evaluate for adjacent AHO, pyomyositis, or abscess as potential indications of ineffective source control to provide a basis to determine whether additional invasive procedures should be considered.
2. In children with presumed or confirmed primary ABA who demonstrate a poor clinical and laboratory response within 48–96 hours (continued fever, persistent bacteremia and/or rising CRP) after initial invasive procedures, and evidence to suggest persisting foci of infection (ineffective source control), we suggest additional invasive procedures to ensure adequate source control (conditional recommendation, *very low certainty of evidence*). **Comment:** When ABA is associated with adjacent osteomyelitis, management should follow the osteomyelitis guideline.

## **VII. In children with presumed or confirmed ABA who require a surgical procedure, should surgically administered (intra-articular) antimicrobial agents be routinely used in addition to systemic antimicrobial therapy?**

### **Recommendation:**

In children with presumed or confirmed ABA who require a surgical procedure, we recommend against the routine use of intra-articular antimicrobial agents (strong recommendation, *very low certainty of evidence*). Comment: This recommendation places a high value on avoiding unnecessary harms and costs associated with this intervention.

## **VIII. What is the role for adjuvant corticosteroids in children with presumed or confirmed ABA?**

### **Recommendation:**

In children with presumed or confirmed ABA, we suggest against using adjunctive corticosteroid therapy (conditional recommendation, *very low certainty of evidence*). **Comment:** This recommendation places a high value on avoiding potential serious harms despite providing potential minimal beneficial effects.

## **IX. In children with presumed or confirmed ABA who respond to initial empiric therapy, how should selection of agents be made for definitive parenteral and oral therapy? (See Section XI for discussion of oral versus parenteral therapy.)**

## **Recommendations:**

1. In children with confirmed ABA, selection of a definitive antimicrobial 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 patient tolerability (*Good Practice Statement*).
2. In children with presumed ABA with no pathogen identified, selection of a definitive antimicrobial regimen should be based on the principles of selecting an effective agent based on the most likely causative organism(s), with an antimicrobial spectrum comparable to that of empiric therapy to which the patient initially responded, with the lowest adverse effect profile and most favorable patient tolerability (*Good Practice Statement*).

## **X. In children with presumed or confirmed ABA, what clinical and laboratory criteria should be used to assess the response to therapy?**

### **Recommendation:**

In children with presumed or confirmed ABA receiving antimicrobial therapy with or without surgical intervention, in addition to serial clinical evaluation, we suggest performing CRP at initial evaluation followed by sequential monitoring of CRP to assess response to therapy, rather than relying solely on clinical evaluation (conditional recommendation, *low certainty of evidence*). **Comment:** Serial clinical examinations that assess the febrile response, pain and musculoskeletal function remain the primary means of monitoring response to treatment.

## **XI. Should hospitalized children with presumed or confirmed ABA who are responding well to initial intravenous therapy, no longer requiring skilled nursing care and deemed ready for hospital discharge be transitioned to a) oral therapy or b) outpatient parenteral antibiotic therapy (OPAT)?**

### **Recommendations:**

1. For children with presumed or confirmed ABA who respond to initial intravenous antibiotic therapy, we recommend transition to an oral antibiotic regimen rather than OPAT when an appropriate, well-tolerated oral antibiotic option is available, and that antibiotic is active against the confirmed or presumed pathogen(s) (strong recommendation; *low certainty of evidence*).  
**Comment:** This recommendation places a high value on avoidance of harms and costs, as well as on considerations of patient's values and preferences, feasibility, acceptability, and equity.
2. For children with presumed or confirmed ABA who respond to initial parenteral antibiotic therapy but for whom oral antimicrobial therapy is not feasible, we suggest transition from the acute-care hospital to OPAT, rather than remaining in the hospital for the total duration of therapy (conditional recommendation, *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, clinic) may be influenced by availability of local resources.

## XII. For children with presumed or confirmed ABA, what duration of therapy with antimicrobial agents is recommended?

### Recommendations:

1. In children with confirmed primary ABA without adjacent osteomyelitis with rapid clinical improvement and consistent, progressive decrease in CRP by the end of the first week of treatment, we suggest treating for a total duration of antimicrobial therapy (parenteral plus oral) as short as 10 to 14 days for common pathogens (*S. aureus*, *S. pyogenes*, *S. pneumoniae*, and *H. influenzae* type b), rather than for longer courses of 21 to 28 days (conditional recommendation, *low certainty of evidence*). **Comment:** For children with slower clinical response, inadequate source control, or persistently elevated CRP, courses of therapy of 21 to 28 days may be preferred. Such longer durations may be more commonly required when infection is caused by pathogens with relatively less antibiotic susceptibility or greater virulence, particularly enteric or non-fermenting Gram-negative bacilli and some *S. aureus* strains (e.g., USA300 or similarly virulent strains, whether MSSA or MRSA). Children with ABA with adjacent osteomyelitis should be treated according to the osteomyelitis guideline.
2. In children with presumed primary ABA without adjacent osteomyelitis with rapid clinical improvement and consistent, progressive decrease in CRP by the end of the first week of treatment, we suggest treating for a total duration of antimicrobial therapy (parenteral plus oral) as short as 10 to 14 days rather than for longer courses (conditional recommendation, *very low certainty of evidence*). **Comment:** For children with slower clinical and laboratory responses, longer courses of therapy may be preferred, as noted above.

## XIII. Are follow-up imaging studies needed to assess the response to and duration of therapy for primary ABA?

### Recommendation:

In children with primary ABA with expected improvement during medical management with or without surgical intervention, associated with full clinical recovery, we suggest against routine follow-up imaging (conditional recommendation, *very low certainty of evidence*). **Comment:** In situations where there is any clinical concern for previously undetected adjacent osteomyelitis, a plain film may be considered just prior to cessation of antimicrobial therapy if osteomyelitis was not reasonably excluded by advanced imaging studies (e.g., MRI) earlier in the course.

## XIV. For children with presumed or confirmed ABA who do not respond to therapy, or relapse following completion of therapy, which interventions are appropriate to optimize outcomes?

### Recommendation:

For children with presumed or confirmed ABA either experiencing primary treatment failure, or early or late recurrence:

- a. Clinicians should assess adequacy of the antimicrobial regimen (spectrum of activity, dosage, and antibiotic exposure at the site of infection, adherence) and of joint debridement and irrigation before

deciding on the need to broaden the spectrum or to restart antimicrobials (*Good Practice Statement*).

b. Clinicians should assess the need for additional diagnostic evaluation for possible adjacent osteomyelitis, along with any need for surgical intervention for therapeutic and/or diagnostic purposes (*Good Practice Statement*). **Comment:** The initial diagnosis of primary ABA may need to be reconsidered.

## XV. How long do children with primary ABA require follow-up examinations to address sequelae (e.g., joint contractures, potential growth arrest) due to the infection?

### Recommendation:

In children with primary ABA, we suggest close follow-up by providers with expertise in management of musculoskeletal infections until the completion of antibiotic therapy and return of function in the infected joint (conditional recommendation, *very low certainty of evidence*).

**Comment:** For primary ABA that responds promptly to treatment, follow-up is not routinely required beyond 2-3 weeks from the start of treatment. For children with ABA with adjacent osteomyelitis, see 2021 PIDS/IDSA Guideline on Diagnosis and Management of Acute Hematogenous Osteomyelitis in Pediatrics.

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## Introduction

Acute bacterial arthritis (ABA) is the result of bacterial pathogens entering a joint in the developing infant or child, most often in the context of bacteremia. Many terms have been used to describe this infection including "suppurative" [1-3], "purulent" [4-6], and "pyogenic" [7-9] arthritis. The panel elected to use ABA to be more precise regarding the scope of diagnosis and management outlined in this guideline (see [Table 1](#) for definitions). These guidelines use the term "suspected" ABA for patients prior to the confirmation of the diagnosis by traditional microbiologic methods and/or molecular studies, after which the term "confirmed" is used. The term "presumed" is employed when all testing to identify a bacterial etiology has been negative, but the patient is treated as though they have ABA. Finally, the term "excluded" is used when this diagnosis is considered unlikely.

There are over 200 joints in the human body, with a great diversity in structure and function [10]. The reported incidence of ABA in children from resource-rich Western countries is approximately 2-10/100,000 children annually, but varies by pathogen, age, immunization status, joint involved, sex, and race/ethnicity [11-13]. Some differences in the epidemiology of pediatric ABA have been documented in resource-rich countries in Asia, with no clear basis for observed differences [14, 15]. ABA in children most often involves the highly flexible diarthrodial joints that contain synovial fluid, typically the hip (in approximately 25-40% of reported arthritis), knee (13- 56%), ankle (9-23%),

elbow (5-20%), and shoulder (4-10%) [11, 16-18]. Fibrocartilaginous joints that do not contain synovial fluid are less commonly infected and often are more difficult to diagnose clinically (intervertebral joints [e.g., discitis], pubic symphysis joints and the sacroiliac joints) [19-22].

Pathogens identified in ABA are often age-specific, reflecting maturation of host immunity and exposures to microorganisms from individuals, pets, animals, and the environment. Most commonly, bacteremia in an otherwise healthy child leads to translocation of a pathogen into the joint synovial fluid, despite the lack of a recognized preceding risk factor ("primary arthritis"). Less commonly, organisms gain access to the joint space by direct inoculation from trauma (accidental or iatrogenic). Recent data suggest changes in the pathogens detected over the past several decades, particularly with decreases in vaccine-preventable infections caused by *Streptococcus pneumoniae* and *Haemophilus influenzae* type b (*Hib*) and increases in methicillin-resistant *Staphylococcus aureus* (MRSA) [9, 17, 23]. *S. aureus* is the most commonly identified pathogen among highly immunized populations of children in reports that relied on traditional bacterial culture-based diagnostic techniques [16, 17, 24]. Of note, the reported incidence of certain pathogens has increased substantially over the past decade. This is likely the result of enhanced methods used to detect pathogens, including molecular techniques, that have demonstrated a higher yield of *Kingella kingae* [25-29]. *S. pyogenes* continues to cause a small portion of ABA cases, similar to *S. pneumoniae* [16, 23, 25, 28, 29]. Although *K. kingae* is reported as the most common pathogen detected in recent studies of young children, *S. aureus* appears to be associated with the greatest risk of long-term complications of infection [30, 31].

The clinical presentation is dependent on the pathogen, the age of the child, and the joint involved. Many pathogens incite a brisk inflammatory response following infection of the joint space. This response can include prominent local signs (e.g., pain, swelling, erythema) and symptoms of infection in the involved joint, often accompanied by systemic signs/symptoms and laboratory markers of inflammation that are characteristic of serious invasive bacterial infection. Tenderness of the joint and associated tissues usually increases with movement of the joint (or in the case of fibrocartilaginous non-mobile joints, particularly in infants with sacroiliitis, pain with weight-bearing or sitting). Due to the deeper anatomic location of some infected joints, swelling and erythema may not be clinically detected. However, for less virulent bacterial pathogens, the diagnosis of ABA can be difficult, as the degree of inflammation in the joint may only be mild to moderate, with a corresponding lack of significant systemic symptoms, and perhaps evidenced by non-use of a limb or holding the involved joint in a position of comfort (i.e., pseudo-paralysis). Laboratory markers of inflammation may be minimally elevated in these cases of ABA, adding to the difficulty of making the correct diagnosis.

Although prospective, controlled studies reporting a consistent clinical and laboratory dataset collected from infected children have not been published, multiple retrospective reviews suggest differences in the clinical and laboratory presentation, clinical course, and outcomes between the two most common bacterial pathogens, *S. aureus* and *K. kingae* [16, 31, 32]. A history of relatively acute onset of symptoms and more rapid progression of joint pain over 24-48 hours is more characteristic of *S. aureus* infection and is consistent across all age groups. In contrast, the onset of symptoms for *K. kingae* infection in infants and preschool-aged children, the most common age groups for this pathogen, appears in many cases to be more indolent, less well-defined, with less

severe symptoms and often without the rapid progression to severe pain and systemic symptoms usually seen with *S. aureus*. In addition, most children with *K. kingae* infection are young (infants or preschool-aged), with limited ability to share specific localizing symptoms [32, 33].

ABA occurring with associated contiguous osteomyelitis, particularly with *S. aureus*, is common. Metastatic sites of infection (distal or contiguous), appearing simultaneously with ABA are uncommon despite a presumed or confirmed preceding bacteremia. Notably, there is a lack of association of *S. aureus* ABA with endocarditis. Rare complications of *K. kingae* infection beyond joint disease have been described, including endocarditis [32]. Multiple concurrently infected joints are uncommon in ABA caused by *S. aureus* or *K. kingae*. Less common ABA pathogens, also associated with bacteremia, such as *Streptobacillus moniliformis* (Rat Bite Fever), *Fusobacterium necrophorum* (Lemierre's syndrome) and *Neisseria gonorrhoeae* (gonorrhea) may be associated with concurrent infection of multiple joints as well as other distinct anatomic sites of infection.

Many conditions other than ABA (both infectious and non-infectious) may be associated with inflammation of joints, often accompanied by systemic symptoms. These include various nonpyogenic bacterial infection (e.g., Lyme arthritis, mycobacterial), non-bacterial infections (viral, fungal), as well as post-infectious, autoinflammatory, autoimmune (juvenile idiopathic arthritis [JIA]), hematologic, oncologic, chemical, and traumatic arthritis. Infection adjacent to a joint may also cause inflammation in the joint or a perception of inflammation in the joint [13, 24, 34, 35].

The term "culture-negative" ABA has been used for many years to label clinical presentations consistent with ABA for which bacterial cultures of synovial fluid and blood are negative. Molecular testing methods developed over the past 15 years now allow identification of causative microbes in a high proportion of cases where cultures are negative, and the frequency of pathogen identification in such cases is likely to increase over time. The panel suggests the use of "presumed ABA with no identified pathogen" for culture-negative cases with clinical signs of arthritis, elevated white blood cell count with neutrophil predominance in synovial fluid, and a clinical course consistent with ABA (i.e., temporal improvement and resolution after drainage and initiation of antimicrobial therapy).

## **Guideline Focus**

This clinical practice guideline focuses on ABA in otherwise healthy children 1 month to 17 years old in North America. Uncommon bacterial causes of ABA are not discussed in this document, as adequate, controlled data are not available to support recommendations. Treatment recommendations for these uncommon pathogens may be found in other organism-specific or disease-specific texts and publications. The clinical presentations of osteomyelitis and ABA can overlap substantially in children [36]; these entities may occur concurrently. For additional recommendations on acute hematogenous osteomyelitis, a companion guideline was recently published [37]. Neonates are excluded due to important differences in bacterial pathogens [38], complications of infection, immunologic immaturity, as well as lack of adequate antimicrobial pharmacokinetic data for neonates of various gestational and postnatal ages.

# 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. The "IDSA Handbook on Clinical Practice Guideline Development" provides more detailed information on the processes followed throughout the development of this guideline [39].

## 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 logistical issues related to the guideline panel. Panel members writing this Guideline also co-authored the Pediatric Osteomyelitis Guideline [37].

## 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 (i.e., monetary amount) and the relevance of the relationship (i.e., 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 [40]. In line with these standards, the GRADE approach for the assessment of the certainty of evidence and strength of recommendation was integrated in the process. Consequently, a new set of clinical questions was developed and approved. 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 January 2005 to January 2022). The initial formal literature search was performed in August 2017 and updates of the review of the literature were conducted again in May 2019, February 2021, and January 2022. 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 2022.

A subgroup of panelists (A.C.A., 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. A minimum of 10 reported confirmed ABA cases were required for published manuscripts to be included in the pooled analysis. 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 predetermined patient-important outcomes. Where applicable, data were pooled using random effects model (fixed effects model for pooling of rates) using RevMan [41].

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 [42], the ROBINS-I [43] for observational studies and the QUADAS-2 tool for diagnostic test accuracy studies [44]. 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 [45, 46]. The summaries of evidence were developed in the GRADEpro Guideline Development Tool [47] 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, PRISMA flow diagram detailing the search results, 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 (e.g., comparing spectrum of activity, route of administration, or duration of therapy) and the beneficial effects of the two 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, tolerability, as well as costs.

## Development of Clinical Recommendations

All recommendations were labeled as either "strong" or "conditional" according to the **GRADE approach** [39]. 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" (not using either a specific treatment or a diagnostic test).

High certainty of evidence was lacking for many recommendations. According to GRADE guidance on discordant recommendations, strong recommendations in the setting of lower certainty of evidence were only assigned when the panelists believed they conformed to one of the five accepted paradigmatic conditions [48]. For recommendations pertaining to good practice statements, appropriate identification and wording choices were followed according to the GRADE working group [49]. A good practice statement represents a message perceived by the guideline panel as necessary in regard to actual current health care 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.

Final presentation of evidence summaries and the development of the recommendations was partially 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 video teleconferences by the whole panel, or by specific members of the panel for completion (from November 2018 to May 2023). All members of the panel participated in the preparation of the draft guideline and approved the recommendations.

## Revision Process

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

## Revision for Currency Schedule

Approximately every two 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.

# Recommendations for the Diagnosis and Management of ABA in Pediatrics

## I. What non-invasive diagnostic laboratory tests should be performed in children with suspected ABA?

### Recommendations:

1. In children with suspected ABA, we recommend performing blood culture prior to administration of antimicrobial therapy (*strong recommendation, moderate certainty of evidence*).
2. In children with suspected ABA, we suggest measuring serum C-reactive protein (CRP) on initial evaluation (*conditional recommendation, very low certainty of evidence*) **Comment:** Serum CRP has a low accuracy to establish the diagnosis of ABA given the variability between pathogens, but in situations where the initial CRP is elevated, this result can serve as the baseline value for sequential monitoring that may guide decision-making regarding duration of antimicrobial therapy.
3. In children with suspected ABA, we suggest **against** measuring serum procalcitonin (*conditional recommendation, low certainty of evidence*).

### Blood Culture

#### Summary of Evidence

Blood culture is recommended for children with suspected ABA to aid in identification of the etiology of infection. Our systematic review of the literature identified one meta-analysis along with several recent case series that provided data on the yield of blood culture in pediatric ABA. This study reviewed the literature up to 2014 and reported a pooled rate of blood culture positivity in children with ABA of 23.9% (95% CI: 8.4 to 44.2%) from four European studies plus their local data [50].

Our updated systematic review included 22 studies reporting the positivity rate of blood culture in pediatric ABA from 2005 to 2022. These studies collectively included 2,172 children with presumed or confirmed ABA (ranging from 18 to 239 patients per study) [12, 24, 28, 50-68]. In our analysis, we addressed two cohorts of patients who were analyzed and reported separately. The first cohort included patients with presumed or confirmed primary ABA. The second cohort included patients from studies where it was impossible to separate those with primary ABA from those with adjacent osteomyelitis (see [Table 1](#) for definitions). Patients in these studies who could definitively be identified as having ABA with adjacent osteomyelitis were excluded from these analyses [37].

Our systematic review showed that for children with presumed or confirmed primary ABA, the pooled blood culture positivity rate among the 15 included studies [12, 24, 50-59, 66-68] was 20.0% (95%CI: 13.7 to 26.2%) and the median rate of blood culture positivity was 21.7% (ranging from 6.2% to 53.8%) (see Figure 2). The range of blood culture positivity rates varied greatly between studies, mainly due to heterogeneity of included patients (presumed vs confirmed ABA) and in diagnostic testing methods. For cohorts including both children with primary ABA and ABA with

adjacent osteomyelitis, the pooled blood culture positivity rate among the 7 studies [28, 60-65] was 27.0% (95%CI: 21.0 to 33.0%) and the median rate was 21.5% (ranging from 15.5 to 37.0%) (see **Supplementary Material Figure I** ).

Pathogen identification in ABA is optimized when cultures of multiple sites, including blood, synovial fluid, and bone (if adjacent osteomyelitis is present) are evaluated. A blood culture adds minimal cost to care in these patients and can often be collected during first venipuncture and/or placement of peripheral intravenous (IV) access. Patients with bacteremia and ABA frequently have positive synovial fluid cultures [62]; however, in case series of ABA there are a few patients with a positive blood culture but negative synovial fluid culture, particularly if antibiotics were given before synovial fluid collection [53-55, 57, 64, 69, 70]. Obtaining a blood culture does not eliminate the need for obtaining a synovial fluid sample as the latter is more likely to be positive than the blood culture. Synovial fluid specimens are usually collected early in hospitalization at the time of diagnostic and/or therapeutic joint aspiration or surgical debridement and irrigation. However, a blood culture may be positive earlier than cultures from other sites; susceptibilities may provide information for focusing antibiotic therapy. Utilization of rapid molecular assays for identification of MRSA for positive blood cultures or fluorescent *in situ* hybridization may expedite definitive antibiotic therapy.

Identification of a pathogen by blood culture can help confirm the diagnosis of ABA given that other conditions, including transient nonbacterial synovitis, reactive arthritis, and rheumatologic conditions can manifest similarly. Pathogen identification may reduce the need for multiple antibiotics in areas of high prevalence of resistance (MRSA) or patients with risk factors for pathogens other than typical Gram-positive etiologies (e.g., young children at risk for *K. kingae* infection or children with hemoglobinopathies who have increased risk for infection with *Salmonella* spp).

In otherwise healthy children being evaluated for ABA, false positive blood cultures due to contamination with skin or oral flora, occur, but with rates generally <5% [29, 51, 58, 70]. Coagulase negative staphylococci, diphtheroids, viridans group streptococci and *Cutibacterium acnes* are most often contaminants in the absence of prosthetic joint material. Consultation with a pediatric infectious disease specialist can assist in determination as to whether other culture results represent contamination.

In circumstances where obtaining blood for culture cannot readily be accomplished and there are concerns for possible associated sepsis or rapid progression of infection, initiation of antimicrobial therapy should not be delayed [71]. (See Question IV).

#### *Rationale for Recommendation*

Blood cultures performed before antibiotic administration in children with suspected ABA will identify the etiology of infection in about 20% of cases and may provide the only positive diagnostic result. A positive blood culture does not obviate the need for an invasive diagnostic procedure with additional cultures, as synovial fluid needle aspiration or joint irrigation is often therapeutic. Blood cultures have relatively low cost, and the primary undesirable effects are those associated with venipuncture. False positive results due to contamination are often 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 ABA based on benefits that clearly outweigh risks.

## C-reactive Protein (CRP)

### Summary of Evidence

ABA is suspected in children presenting with an acutely painful and/or swollen joint. Blood markers of systemic inflammation, such as CRP, can aid in distinguishing ABA (particularly caused by *S. aureus*) from transient nonbacterial synovitis, but not necessarily other inflammatory conditions such as reactive arthritis, acute rheumatic fever (ARF), or JIA, all of which may also be associated with an elevated CRP. The serum CRP is usually, but not always, elevated at the time of presentation of children with ABA [72-77].

CRP alone, or when used in combination with clinical history and examination (weight bearing status, fever, duration of symptoms) has insufficient specificity or sensitivity to confirm or rule-out the diagnosis of ABA. However, it is useful to obtain a CRP at the time of clinical presentation because, if elevated, it can be used to monitor appropriate response to management.

Our systematic review of the literature identified three prospective cohort studies and one retrospective case-control study assessing the diagnostic test accuracy of CRP in children presenting with various signs and symptoms (fever, limp, swelling, pseudo-paralysis, or failure to bear weight) suspicious for musculoskeletal infections from 2005 to 2022 [78-81]. Collectively, these studies suggested very limited value for CRP as a confirmatory diagnostic test for ABA in children. Numeric cut-off levels varied between studies and were often not set *a priori*, and none established a definitive CRP value above which the diagnosis of ABA should be suspected or below which it could be excluded. All four included studies had other significant methodological limitations ([Table 2](#)).

A recent prospective study evaluated the predictive value of CRP in patients presenting with suspected musculoskeletal infection, "ABA, osteomyelitis, and pyomyositis." This study identified, *a posteriori*, the optimal cut-off from the cohort of included patients and may have resulted in an overestimation of diagnostic test accuracy. This cut-off value of 23.8 mg/L (2.38 md/dL) has not subsequently been validated in a prospective study. The study was also limited by a small sample size and lack of any documented microbiology results [80]. Another prospective cohort study evaluated two CRP cutoff levels (100 and 500 mg/L [10 and 50 mg/dL]) in children with compatible clinical, culture, and imaging manifestations of bone and joint infections, but was limited by small sample size [78]. A third study prospectively evaluated patients presenting to the Emergency Department with non-traumatic limp or pseudo-paralysis, but inclusion required abnormal ESR or CRP (>10 mm/hr and >100 mg/L respectively) [79]. Thirteen of 64 (20%) of children in this study had confirmed infections caused by *S. aureus*; specific testing for *K. kingae* was not performed. No evaluation of the children without elevated markers was reported. An additional study reported on the accuracy of CRP in children with definite ABA. The study compared CRP values at three levels, defined as mild (> 4 mg/L), moderate (> 40 mg/L) and severe (> 100 mg/L), in children with three confirmed diagnoses: ABA, osteomyelitis and ARF [81]. At the mild level, sensitivity was 100% versus 74% and 41% at the higher cutoffs ([Table 2](#)).

In one other prospective study of 134 culture-positive ABA patients, a predetermined cutoff of 20 mg/L [73] had a sensitivity of 95.5% in this highly selected population. Specificity and positive predictive value could not be determined as they only included patients with culture positive ABA.

Our systematic review of the literature identified two published studies from 2005 to 2022 specifically evaluating the diagnostic testing accuracy of CRP in differentiating ABA and transient nonbacterial synovitis of the hip [74, 76]. These studies evaluated the diagnostic test accuracy of CRP at a pre-determined cut-off of >20 mg/L in a total of 359 children with hip joint effusion identified on ultrasound. The pooled sensitivity and specificity were 85.7% and 91.9% respectively, but prevalence of ABA greatly varied between studies due to differences in patient selection: 9.3% [76] of all children with a hip effusion on ultrasound had ABA, while 70.8% [74] of a selected group of patients with high suspicion for ABA undergoing hip aspiration had ABA.

A multivariable prediction model in one of these studies [76] showed that refusal to weight bear and CRP > 20 mg/L were independent determinants in differentiating ABA from transient nonbacterial synovitis of the hip, with increased CRP level being the strongest predictive factor (odds ratio 81.9, p-value < 0.001). Children with neither predictor had <1% probability of ABA, indicating excellent negative predictive value of their model. In a cohort of 32 children presenting with painful hip effusion referred for ultrasound-guided joint aspiration and a prevalence of confirmed or presumed ABA of 21.9% [82], a pre-determined CRP cut-off of >10 mg/L was predictive of ABA (OR 7.9, p-value=0.03).

In addition to these studies, a recent meta-analysis assessing the diagnostic test accuracy of CRP for bone and joint infections in children and adolescents suggested that at a threshold of 20 mg/L, the estimated pooled sensitivity of C-reactive protein was 86% (68%-96%) and the pooled specificity was 90% (83%-94%) [83]. Nevertheless, this meta-analysis only included 4 studies which were limited by heterogeneity of included population (and thus the pre-test probability of having ABA), methodological limitations and/or small sample size (e.g., only 2 of the 4 studies included at least 10 ABA cases).

In one study of ABA, CRP values appear to be higher when patients had bacteremia [50, 84]. Another study of ABA found that a markedly elevated CRP was associated with the need for more than one surgical procedure (OR = 1.1; 95 % CI = 1.03–1.18; p = 0.005); for every 10 mg/L of increase in CRP, the odds of undergoing a second surgery increased by 9.6% [52]. The authors concluded that a CRP of 150 mg/L was the level above which a second surgery would likely be needed.

The relationship between CRP level and adjacent osteomyelitis in ABA has been examined in multiple studies [24, 51, 67, 73, 85-87]. Generally, CRP was higher in cases of ABA with adjacent osteomyelitis compared with either site of infection on its own, but substantial overlap in ranges limits the utility of CRP alone in this determination. CRP has been used as one factor in an algorithm developed to guide performance of MRI to detect osteomyelitis associated with ABA, but the utility of this approach also remains uncertain (See Question II) [86, 88-90].

Initial CRP results may vary by causative pathogen. CRP values appear to be higher on average for osteoarticular infections caused by *S. aureus*, although none of these studies report CRP values for patients with ABA separately [23, 91], and many studies did not perform molecular diagnostic

studies on joint fluid to assess for the presence of *K. kingae*. Some, but not all, studies have described higher mean CRP concentrations for cases due to MRSA than methicillin-susceptible *S. aureus* (MSSA), either for all osteoarticular infections (site of infection not further defined in data presented) [23, 92, 93] or for ABA with or without concomitant osteomyelitis [62].

Several studies provided comparisons between suspected ABA with no identified pathogen [24, 53] or suspected ABA/osteomyelitis with no identified pathogen [51] versus those with an identified etiology (by culture, PCR, or both). These reported lower CRP concentrations in cases without an identified etiology, but most reporting institutions were not pursuing identification of *K. kingae* as a pathogen with routine performance of molecular studies on synovial fluid at the time. One study found no difference in CRP concentrations between cases with and without identified etiology [50]. Thus, CRP concentrations cannot be used to reliably distinguish ABA from causes of arthritis with no identified bacterial pathogen.

Identification of *K. kingae* as an important and common etiology of osteoarticular infections in young children has increased as more centers are performing PCR on bone and synovial fluid specimens. Two studies [30, 94] reported on a combined total of 54 children with ABA or osteomyelitis due to *K. kingae*; these patients are reported as having mild or no elevation in CRP but provide no comparison to other etiologies. Other studies provided comparisons of CRP levels in children with ABA due to *K. kingae* versus those with all other pathogens combined [25, 29], or versus those with *S. aureus* infections alone [28, 95]. These studies show lower CRP concentrations at admission for children with *K. kingae* infection than with other pathogens; however, they do not provide cut-off values that would definitively distinguish etiology using CRP.

Lower CRP levels are seen in Lyme arthritis compared with ABA. Lyme disease should be considered in afebrile, ambulatory children presenting with large joint arthritis (particularly the knee) who have low CRP and/or ESR and appropriate epidemiologic risks for Lyme disease [96-99].

#### *Rationale for Recommendation*

The primary utility of CRP on admission is as a baseline for serial measurements during the treatment course. The existing literature regarding CRP as a diagnostic test for ABA is limited by small sample sizes, suboptimal methodology, varied populations of interest (i.e., wide range of pretest probabilities) and control groups, varied reference standards, use of different numeric cut-offs, and verification bias. Results suggest limited accuracy in discriminating ABA caused by any bacterial pathogen from other infectious or non-infectious processes. Despite these limitations, in a child with suspected ABA, we suggest performing a CRP on initial evaluation. CRP is offered in most hospital settings, can be obtained simultaneously with blood being drawn for culture and other tests, is relatively inexpensive, and produces results that usually are quickly available. When taken in context of the clinical presentation and other testing modalities, CRP may add benefit for multidisciplinary clinical decision making for children with clinically suspected ABA. Although not specifically analyzed in published studies (particularly those prior to widespread routine use of molecular tests for diagnosis of ABA), children with a low initial CRP are likely to include many with *K. kingae* infections, for whom long-term outcomes are excellent [24, 94]. Normal or minimally

elevated concentrations of serum CRP do not exclude ABA but should prompt investigation of additional non-infectious etiologies.

## Procalcitonin

### Summary of Evidence

Procalcitonin (PCT) is an acute phase reactant that increases during infection. It is purported to rise more rapidly and be more specific for bacterial infection compared with other markers of inflammation. The diagnostic accuracy of procalcitonin for ABA has been evaluated in three prospective, cross-sectional studies [78, 80, 100] in which children with ABA or osteomyelitis were included. These studies used varying combinations of clinical, microbiological, and radiographic criteria to classify patients as having ABA or osteomyelitis. Clinicians were blinded to PCT results in two of the included studies [78, 100]. The studies had different disease prevalence as a result of differences in inclusion criteria. One included only patients with fever along with musculoskeletal complaints (ABA prevalence 52.2%) [78], whereas two included both febrile and afebrile patients (ABA prevalence 14.2% [100] and 21.1% [80], respectively). A PCT cut-off value  $\geq 0.5$  ng/mL was considered *a priori* as positive in two of these studies [78, 100], while the other derived the optimal cut-off value from their studied cohort [80].

At a PCT cut-off value of 0.5 ng/mL, the two included studies reported a high specificity (96.9% [100] and 100.0% [78]) of PCT when used to discriminate confirmed and presumed osteoarticular infections vs. non-infected patients, while reporting a very low sensitivity (12.5% [100] and 43.5%, [78]. In the third study, the optimal cut-off was determined to be 0.1 ng/mL, and the authors reported that patients with a PCT value over 0.1 ng/mL were 2.5 times more likely to have acute musculoskeletal infections than those with a PCT value below this cut-off [80]. Nevertheless, this same study showed that CRP performed better than PCT [80].

In addition to these studies, a recent meta-analysis assessing the diagnostic test accuracy of serum PCT for bone and joint infections in children and adolescents also confirmed the paucity of published data, precluding any formal conclusion [83]. Another meta-analysis [101] of 10 studies of PCT in osteoarticular infection not restricted to ABA, concluded superior positive and negative likelihood ratios and improved area under a receiver operating characteristic curve (AUC) for PCT compared with CRP; however, the results of this meta-analysis were primarily based on adult populations, thus not considered generalizable to the pediatric population.

### Rationale for Recommendation

PCT has utility in risk stratification among bacterial versus nonbacterial etiologies of some clinical scenarios. However, currently available data regarding accuracy of PCT in the diagnosis of children with ABA have limitations of relatively small sample sizes of children with ABA or osteomyelitis. Validity is uncertain and the sensitivity appears suboptimal. Also, no prospective evaluation of PCT to distinguish successful from unsuccessful antimicrobial/surgical therapy of ABA has not been conducted. In addition, PCT is not routinely available in many hospitals and is more expensive than CRP.

## **Complete Blood Count (CBC)**

### *Background*

A complete blood cell count (CBC) with differential generally should be performed on initial evaluation of children with suspected ABA (see Table 1 for definitions) to assess the severity of infectious processes as well as to provide useful information regarding alternative diagnoses (e.g., leukemia). The peripheral white blood cell (WBC) count is often but not always elevated in children with ABA [59, 72, 74, 80, 102-104].

The WBC is higher on average with adjacent osteomyelitis infection than without [86, 88] and may be higher when ABA is caused by *S. aureus* or streptococcal species than *K. kingae* [95, 105]; however, substantial overlap precludes the use of a specific diagnostic cut-off value. WBC does not differ on average, between confirmed and presumed ABA cases (see Table 1 for definitions) [24, 106]. WBC on admission also is not useful in distinguishing ABA from Lyme arthritis [96].

The WBC is often higher in children with ABA than transient nonbacterial synovitis, a clinically defined syndrome traditionally often referred to as toxic synovitis (see Table 1 for definitions), but the substantial overlap precludes diagnostic value in distinguishing these entities [74-77, 107, 108]. There is also overlap in WBC values between ABA and acute rheumatic fever (ARF) [109].

Discriminatory value of the peripheral blood WBC is, thus, limited for the differential diagnosis of suspected ABA, but the information provided by a CBC can provide important adjunctive information for decision-making for children with these clinical presentations.

## **Erythrocyte Sedimentation Rate**

### *Background*

The Erythrocyte Sedimentation Rate (ESR) is usually, but not always, elevated in children with ABA at the time of presentation. [59, 72, 74, 102, 103]. Like CRP, the ESR is usually higher in ABA than in transient nonbacterial synovitis [74, 75, 77, 108] or ARF [109]. ESR is also typically higher in children who have ABA with an adjacent musculoskeletal infection than without [88], lower in Lyme arthritis than ABA caused by pyogenic bacteria [96], and lower in ABA caused by *K. kingae* compared with other bacterial pathogens (*S. aureus*, beta-hemolytic streptococci, and pneumococci) [105]. However, the overlap of ESR ranges in each of these situations precludes discriminatory utility. The ESR often does not normalize until the fourth week after initiation of therapy for ABA, well after antimicrobial therapy has usually been discontinued (see Question X).

Therefore, the Guideline Panel does not see value in the routine inclusion of ESR testing in children being evaluated for suspected ABA as a diagnostic test to differentiate bacterial from nonbacterial causes of joint inflammation. In addition, the ESR does not substantially assist in the assessment of the pathogen. It has also not been found helpful for the assessment of adjacent musculoskeletal infection to determine the need for a more extended duration of antimicrobial therapy.

## **Lyme Serology**

## Background

Children living in Lyme disease-endemic areas in North America and Europe may develop arthritis as the result of *Borrelia burgdorferi* infection which may be difficult to distinguish, clinically, from ABA. Synovial fluid WBC counts in Lyme arthritis overlap with those in ABA [110]. Clinicians need to make initial management decisions based on clinical factors without waiting for the results of bacteriologic studies and Lyme disease serologies to avoid joint irrigation or arthrotomy that are unnecessary for Lyme arthritis. Lyme arthritis typically involves the large joints, particularly the knee, which is affected in 90% of cases [96, 97]. The hip, elbow, and shoulder may also be involved, usually one joint at a time. The hallmark of Lyme arthritis is a large joint effusion. However, patients usually do not experience the severe pain and systemic toxicity more often seen in ABA caused by many other bacterial etiologies. Children with Lyme arthritis are more likely to be weight bearing at presentation, lack fever, and have lower inflammatory markers. A peripheral WBC <10,000 cells/microliter and ESR <40 mm/hr in a weight bearing child with arthritis of the knee indicates a very low risk for ABA [96-99]. We endorse the recently updated IDSA Lyme Disease guideline in its strong recommendations regarding the diagnostic testing in suspected Lyme arthritis; namely, in children with known prior exposure and in those living in areas with high background seroprevalence, we support the recommendation to use serum antibody testing (ELISA with confirmatory Western blot and interpretation of bands) over PCR or culture of blood or synovial fluid. To improve diagnostic specificity for the seropositive child in whom a definitive diagnosis is required, PCR of synovial fluid or synovial tissue is preferred over culture of *B. burgdorferi* [111].

## Research Needs

Future prospective studies to determine whether a particular serum CRP threshold is reasonably predictive of the diagnosis of ABA would be helpful. Use of an appropriate reference standard such as a positive culture or molecular test from joint fluid or blood will be essential. Similar prospective evaluation of CRP utility in ABA caused by various organisms (e.g., *S. aureus*, *K. kingae*, *S. pyogenes*, *S. pneumoniae*) would be important.

The roles of PCT or other inflammatory markers or new, more accurate and precise biosignatures also may merit further evaluation of clinical utility for diagnostic purposes and for serial assessment in support of management decisions regarding the course of therapy. Studies evaluating the utility of emerging molecular diagnostic technologies, including nucleic acid amplification techniques and metagenomic next generation sequencing tests on blood and tissue specimens will be important, as these may increase the portion of ABA cases for which the microbial etiology is identified [112].

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

### Recommendations:

1. In children with suspected ABA, we recommend obtaining plain radiography of the affected joint and adjacent bones rather than not performing plain radiographs (*strong recommendation, moderate certainty of evidence*). **Comment:** Despite the low sensitivity of plain radiography for detecting presence of joint effusion or adjacent osteomyelitis on initial presentation, other important etiologies of acute musculoskeletal pain may be identified.

2. In children with suspected ABA in whom further imaging studies are required to detect the presence of joint effusion, particularly of the hip or the shoulder, we recommend performing ultrasonography of the affected joint before performing more complex and less widely available imaging tests (*strong recommendation, moderate certainty of evidence*). **Comment:** Ultrasonography documenting the absence of joint effusion suggests that ABA is not present.
3. In children with suspected ABA in whom further imaging studies are required to assess the extent of inflammation and infection, including adjacent osteomyelitis and pyomyositis, we suggest performing a magnetic resonance imaging (MRI) study rather than other imaging modalities (e.g., computerized tomography (CT) or bone scintigraphy) (*conditional recommendation, very low certainty of evidence*). **Comment:** Children with ABA at high risk of adjacent osteomyelitis include those with more than 3 or 4 days of symptoms prior to presentation, *S. aureus* infection, and marked elevation of CRP, but these risk factors require further validation.

## Background

In a child presenting with musculoskeletal pain and joint swelling, synovial thickening, and effusion in joints visible or palpable on physical examination, such as the knee, ankle, or elbow, imaging is not always required prior to aspirating the affected joint by an experienced provider. When joint swelling is not clinically apparent, as with the hip or shoulder, or when it is unclear if swelling is due to effusion or other intra-articular abnormalities such as synovitis, imaging can be performed to aid in determining presence of effusion, osteomyelitis, foreign bodies, or other nonABA disorders that cause joint inflammation. Advanced imaging with MRI may provide anatomic detail needed to define the extent of infection in and around the infected joint including identification of adjacent osteomyelitis and soft tissue abscesses.

## Plain Radiographs

### Summary of Evidence

Plain radiographs may be helpful in providing evidence consistent with infection or other etiologies of acute musculoskeletal pain. Early in ABA, there may be soft tissue swelling, blurring of fat planes, and joint widening with effusion. These radiographic findings progress to joint space narrowing from cartilage destruction and subchondral bone loss in later stages of infection. Adjacent osteomyelitis may be visible on plain radiographs if bone disease has been present for more than 10- 20 days. Normal plain radiographs do not rule out ABA or acute osteomyelitis. Plain radiographs are most useful to identify alternative etiologies of acute musculoskeletal pain including fractures, tumors, slipped capital femoral epiphysis, or Legg-Calve-Perthes disease.

Our systematic review of the literature identified a total of 9 studies published 2005 through 2022, including 736 patients with ABA, and reporting on sensitivity of plain radiography for the diagnosis of ABA with or without adjacent osteomyelitis (see **Supplementary Material Figures IIa** [2] [12, 25, 51, 54, 57, 63-65, 113]). The overall sensitivity of plain radiography for the presence of osteoarticular infections was 25.1% (95%CI: 15.7 to 34.6%), but abnormalities reported on plain radiography varied among studies (from swelling of soft tissue to joint effusion, or signs of osteomyelitis). Other sources of heterogeneity between studies such as presence of verification bias (i.e., not all tests

were performed in all patients) and variation in the reference standard (final diagnosis based on various sets of criteria) impeded further meaningful interpretation of the pooled results.

### Rationale for Recommendation

Although the sensitivity of plain radiographs for diagnosis of ABA is low, their value for confirming presence of effusion and providing evidence of alternative diagnoses outweighs the concern around the high false negative rate for ABA with or without adjacent osteomyelitis. Plain radiographs are readily available, have low radiation dosage and relatively low costs, and do not require sedation. Importantly, normal findings in plain radiographs at presentation do not exclude the presence of ABA or osteomyelitis. Abnormalities seen on subsequent plain radiographs in the appropriately managed child may represent the natural history of the infectious process rather than evidence of deterioration if the child is clinically improving. Because the overall benefits exceed risks, the panel makes a strong recommendation that plain radiographs remain a routine part of initial evaluation of children with ABA.

## Ultrasound

### Summary of Evidence

Ultrasound is a relatively low cost and noninvasive imaging study that can be used to characterize intra-articular and extra-articular abnormalities identified in children presenting with swelling or pain in or near a joint. It is especially helpful in determining a further course of action in a child with limitations in weight bearing and movement at the hip joint where direct visualization of the joint is impossible. Findings on ultrasound compatible with ABA include joint effusion and capsular thickening. Transient nonbacterial synovitis, the most common cause of an acute painful hip in children, is defined by the presence of only mild inflammation in synovial fluid and negative culture plus negative results of any molecular pathogen tests that are performed. This condition is most often self-limited. Advanced imaging may be required to distinguish transient nonbacterial synovitis from ABA to avoid unnecessary, invasive interventions in children with this benign condition, as there is significant overlap in the clinical presentation of these two conditions. It is possible that an undefined proportion of children previously diagnosed with transient nonbacterial synovitis and whose synovial fluid did not undergo molecular testing had *K. kingae* infection with resultant mild inflammation, negative cultures, and spontaneous resolution of disease [24]. In addition to the presence of effusion and synovial thickening, the echogenicity of the joint fluid may be helpful in distinguishing ABA from other etiologies of inflammation causing effusion. Ultrasound may also visualize extra-articular abnormalities, depending on the extent of the image, such as subperiosteal or soft tissue abscess, indicative of osteomyelitis or soft tissue infection.

Our systematic review of the literature identified a total of 7 studies published 2005 through 2022, including 473 patients with ABA reporting on sensitivity of ultrasonography for the diagnosis of ABA (see **Supplementary Material Figures IIa**  ) [12, 25, 51, 57, 64, 69, 113]. In these studies, although ultrasonography was performed for suspected ABA of the hip [64, 69] they may have included examinations of other joints (knee, shoulder, ankle, elbow) [57], or the joints being assessed were not specified [12, 25, 51, 113]. The overall sensitivity of ultrasonography for the presence of findings compatible with ABA (joint effusion, synovial thickening) using a variety of reference standards was

81.0% (95%CI: 72.8 to 89.2%) when all cases of ABA were considered (including those with adjacent osteomyelitis) but increased to 90.8% (95%CI: 83.2 to 98.5%) in patients with primary ABA [12, 25, 51, 57, 64, 69, 113]. In fact, the sensitivity of ultrasonography to detect increased synovial fluid in the presence of adjacent osteomyelitis ranged from 24.6 to 65.2%, reflecting that most joint effusions adjacent to osteomyelitis are likely to represent an inflammatory reaction rather than true infection [12, 25]. Heterogeneity in reference standards used to determine the presence of ABA in these studies (varying combinations of criteria including clinical presentation, synovial fluid cell counts, cultures, molecular diagnostic testing, and imaging) might limit the interpretation of the pooled results.

Our systematic review of the literature identified 2 studies reporting on the diagnostic testing accuracy of ultrasound to distinguish transient nonbacterial synovitis from ABA in children presenting with acute, atraumatic limp or hip pain [76, 114]. In the largest study, [76] the presence of hip effusion (without additional criteria) was considered indicative of possible ABA, but other nonstandardized clinical features were used to determine need for arthrotomy by treating clinicians. Among 680 children, 369 had no effusion present, none required subsequent treatment for ABA, and all made a complete spontaneous recovery with no sequelae at three months' follow-up (i.e., NPV of 100%). Among the 311 with effusion, only 42 (13.5%) underwent arthrotomy and only 29 (9.3%) were confirmed to have ABA (i.e., PPV 9.3%) with the remaining patients having a benign course of illness. An additional study evaluated the diagnostic testing accuracy of ultrasound to differentiate hip ABA and transient nonbacterial synovitis in a total of 127 patients presenting with an acutely painful hip [114]. In this study, predominant capsular thickening relative to effusion was considered an indicator of ABA. The pre-test probability for ABA was 46.5% and the sensitivity, specificity, positive and negative predictive values for ultrasound in diagnosing hip ABA were 86.4%, 89.7%, 87.9% and 88.4%, respectively.

#### *Rationale for Recommendation*

Ultrasonography is readily available at many institutions, is relatively low cost, and does not require sedation. The expertise of sonographers and radiologists at institutions that routinely care for few cases of pediatric ABA may not equal that of individuals who practice at facilities where ABA in children is more commonly seen. The sensitivity of ultrasound for joint effusion is high (approximately 90%), exceeding the accuracy of the clinical examination, laboratory, and plain radiograph findings, particularly for the hip [114]; however, the absence of a joint effusion does not completely rule out ABA. Many of the false negative ultrasound examinations were performed in the first 24 hours of illness; thus, children with a negative ultrasound result for effusion should have a repeat ultrasound examination or MRI if clinical suspicion for ABA persists. Delay in appropriate therapy in children with falsely negative ultrasounds results in unfavorable outcomes for affected joints [114]. Because the overall benefits exceed risks, the panel makes a strong recommendation that ultrasonography of the affected joint be performed before performing more complex and less widely available imaging tests.

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

##### *Summary of Evidence*

When an ultrasound is negative, advanced imaging modalities such as MRI or CT can be used to aid in determining the need for joint aspiration or arthrotomy. Bone scintigraphy for the diagnosis of bone and joint infections is no longer routinely available in many pediatric centers and has been replaced by more anatomically detailed techniques that do not require radionuclide exposure. MRI is highly sensitive and is the preferred study to differentiate between bone, joint, and soft tissue involvement. Findings on MRI that have been reported in association with ABA include joint effusion, synovial thickening, and enhancement; associated enhancement/edema of soft tissues and bone marrow may also be present. CT may demonstrate joint effusion and synovial thickening as well as soft tissue abnormalities but requires significant ionizing radiation exposure. MRI is generally the modality of choice for the diagnosis of osteomyelitis [37], but risks (and availability of) sedation may influence this choice when sedation is required to accomplish the study.

Our systematic review of the literature identified a total of 5 studies [12, 25, 51, 113, 115] published 2005 through 2022 reporting on the diagnostic test accuracy of MRI for the diagnosis of ABA. Most studies were retrospective and not all study subjects had all imaging performed. Direct comparisons between the different advanced imaging modalities were not available. The reference standards for the final diagnoses in these subjects were various combinations of clinical examination findings, laboratory results (inflammatory markers, synovial fluid cell count, cultures), response to antibiotics (or to no treatment), and the imaging studies themselves. While most studies report a sensitivity of MRI for the diagnosis of ABA in the range of 90-100% [25, 51, 113, 115], the proportion of patients with ABA imaged with MRI varied greatly between studies (range 9% to 53%) except one study where only subjects with MRI were included [115]. One study reported a substantially lower sensitivity of 56% in children with primary ABA [12]. Since most patients in these studies did not undergo MRI for ABA, the cases that did may reflect a selection bias toward the most difficult to diagnose patients.

Only one retrospective study examined variations in MRI techniques to diagnose musculoskeletal infections in children. This study examined the accuracy of fluid sensitive MRI sequences in 88 consecutive children suspected of musculoskeletal infections of which 13 had ABA and demonstrated these abbreviated MRI studies could accurately diagnose ABA (13/13 abnormal) [115].

Two studies evaluated the accuracy of MRI to differentiate hip ABA from transient nonbacterial synovitis in a total of 132 patients [116, 117]. These studies had an overall pre-test probability for ABA of 28.0%. These studies did not include all the same diagnostic criteria; however, both studies did assess differences in the grade (magnitude) of joint effusion, presence of synovial thickening and enhancement, alterations in signal intensity in soft tissue and bone marrow, changes in femoral head perfusion, and contralateral joint changes (effusion, synovial thickening). The pooled analysis of the most predictive criteria from each study showed that MRI has a sensitivity ranging from 83.3 to 84.2% and a specificity ranging from 93.5 to 100% to differentiate ABA from transient nonbacterial synovitis. Contralateral effusion was found to be a significant predictor of transient nonbacterial synovitis, and alterations in signal intensity of soft tissue compared to contralateral hip was a significant predictor of ABA in two studies [116, 117].

A single study evaluated the accuracy of MRI to differentiate ABA from inflammatory arthritis (e.g., post-infectious arthritis such as ARF, transient nonbacterial synovitis, and JIA) in a cohort of 59

children presenting with recent-onset arthritis of various joints [118]. The multivariate analysis identified the presence of bone marrow edema and absence of low signal intensity of the synovial tissue as being independently associated with the presence of ABA.

Although bone scintigraphy is no longer routinely recommended, the sensitivity of this diagnostic test for the diagnosis of primary ABA was estimated at 81.9% (95% CI: 76.2 to 86.8%) in a total of 212 children in 5 studies (see **Supplementary Material Figures IIa** [12, 25, 59, 64, 65] but ranged widely from 52% to 91%. The wide variation observed in diagnostic test accuracy of this imaging modality may have resulted from differences in population selection (suspected vs confirmed ABA, ABA 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).

Data regarding the accuracy of CT for the diagnosis of ABA in children are too limited in terms of sample size and number of studies to be meaningfully estimable.

### Ajacent Musculoskeletal Infections in Children with ABA

Our systematic review identified a total of 14 studies published 2005 through 2022 including 1,429 children with ABA (ranging from 20 to 310 children) that reported on the prevalence of adjacent osteomyelitis (see Figure 3) [12, 25, 51, 57, 60, 62-65, 90, 113, 119-121]. Overall, 32.2% (95%CI: 22.4 to 42.0%) of children with ABA had adjacent osteomyelitis, ranging from 7.7% to 68.2% (highest rate being reported in a study evaluating ABA of the shoulder). Four studies reported on the risk factors or clinical features associated with adjacent osteomyelitis [60, 62, 113, 119]. The following were significantly associated with adjacent osteomyelitis on univariate analyses: newborn (up to 4 months) or adolescent age group (13-20 years), longer duration of symptoms and/or fever before admission, higher temperature at presentation, higher CRP at presentation, infection of the shoulder, presence of bacteremia, positive Gram stain of joint fluid, and *S. aureus* as causative pathogen. Multivariate analysis was performed in two studies. A recent study of 71 children with ABA who underwent MRI [60] identified positive joint fluid bacterial culture ( $p$ -value=0.02) and pain for more than 4 days before admission ( $p$ -value=0.004) as risk factors for adjacent osteomyelitis. Another study reported *S. aureus* as the causative pathogen ( $p$ -value  $P<0.0001$ ) and symptom duration of more than 3 days at presentation ( $p$ -value=0.005) as risk factors for adjacent osteomyelitis [62].

Our systematic review of studies published 2005 through 2022 identified two studies from a single center that described derivation [88] and then validation [89] of an algorithm to predict adjacent musculoskeletal infections (including adjacent osteomyelitis, subperiosteal abscess or intramuscular abscess) in children with ABA. The derivation study reviewed 144 children with ABA and identified adjacent infections in 87 (61%) [88]. Independent predictive factors of presence of adjacent infections on admission were older age (above 3.6 years), higher CRP ( $>13.8$  mg/L), longer duration of symptoms (more than 3 days), lower platelets ( $<314 \times 10^9$  cells/ $\mu$ L), and higher ANC ( $> 8.6 \times 10^9$  cells/ $\mu$ L) [88]. In the subsequent validation study, among 109 children surgically treated for suspected ABA, the positive predictive value of the algorithm was 91% (95% CI: 0.78-0.97), albeit using a slightly lower CRP cut-off of 8.9 mg/L [89].

Application of this algorithm to 120 children from a different center found a positive predictive value of only 55.9%, with a receiver operating curve showing poor discrimination based on an AUC of only 0.54 [86]. In a separate study, among 51 children with ABA of the hip managed according to this algorithm, both sensitivity and specificity were lower compared to subjects in the original studies [90]. MRI altered management in 5 (9%) but half of the MRIs performed were deemed unnecessary.

Two other recent studies identified the following associations of adjacent osteomyelitis with ABA: presence of bacteremia, persistent fever after initiation of therapy, high CRP, and *S. aureus* as etiology [67, 87]. One study also found thrombocytopenia and the need for intensive care as associations with adjacent osteomyelitis, with *K. kingae* etiology occurring much more commonly in children with primary ABA without adjacent osteomyelitis [87]. The other study noted return to normal range of motion of the affected joint by the time of discharge in 95% of those with ABA alone compared with 65% in those with adjacent osteomyelitis [67].

Our systematic review of the literature identified one study assessing the impact of the implementation of routine preoperative MRI in patients with ABA to identify adjacent infection (osteomyelitis, pyomyositis) on need for repeat surgery (planned or unplanned) and length of stay (LOS) in 83 children with osteoarticular infections (see **Supplementary Material Table II d**) [122]. This retrospective pre/post-implementation study shows that routine MRI in patients with ABA prior to arthrotomy reduced the need for repeat surgery (RR: 0.57, 95%CI: 0.33 to 0.96), but had no significant impact on reducing unplanned repeat surgery (RR: 0.71, 95%CI: 0.45 to 1.11) or LOS (3.2 days shorter, p-value=0.2). These estimates were judged uncertain due to very serious risk of bias (e.g., type of study design, misclassification bias of the intervention of interest, absence of stratification for the type of osteoarticular infections and unadjusted analysis) and imprecision (i.e., few events and small sample size).

#### *Rationale for Recommendation*

The presumptive diagnosis of ABA can usually be made by a combination of clinical examination, laboratory tests and ultrasound without advanced imaging by MRI. Obtaining an MRI routinely in all children presenting with suspected ABA does not appear necessary and may incur risk of unnecessary sedation, especially in younger children. However, if examination by plain radiographs and ultrasound have not provided sufficient information to determine need for joint aspiration or arthrotomy, then the advanced imaging modality of choice is MRI; it may be helpful in confirming the diagnosis, determining the extent of infection (involvement of soft tissue and bone), identifying abscesses requiring surgical intervention, and distinguishing transient nonbacterial synovitis or other inflammatory arthritis from ABA.

Multiple factors that consistently increase the likelihood of adjacent osteomyelitis in children with ABA have now been identified in a number of studies. These include, but may not be limited to, severity of illness, presence of bacteremia, marked elevation of CRP, slow clinical response (persistent fever and local signs; need for repeat surgical procedures), and identification of *S. aureus* as the pathogen. In such clinical scenarios, obtaining an MRI is appropriate when management decisions and clinical course may be impacted. An option is to obtain follow-up plain

films at 2 weeks into therapy when the likelihood of detecting changes indicative of adjacent osteomyelitis would be increased. Exclusion of adjacent osteomyelitis is important for determining the duration of needed antimicrobial therapy (See Questions XI, XII and XIII).

## Research Needs

Additional prospective, controlled studies that assess the comparative utility of ultrasonography and newer, limited sequence/rapid MRI techniques for diagnosis and prediction of complications of ABA by pathogen (particularly MRSA and MSSA) are needed. Additional prospective studies that evaluate the utility of MRI at presentation or early in the clinical course of children with ABA, stratified by clinical and laboratory findings on admission (and within the subsequent 48 to 72 hours), as well as by infected joint site and specific pathogen, would be helpful.

## **III. For children with suspected ABA, when should diagnostic invasive procedures be performed to collect synovial fluid from affected joint(s) and which diagnostic tests should be performed on the collected joint fluid?**

### **Recommendations:**

1. In children with suspected ABA, we suggest collecting synovial fluid from the affected joint by arthrocentesis prior to starting empiric antimicrobial therapy (conditional recommendation, *moderate certainty of evidence*).
2. On joint fluid obtained by arthrocentesis, we recommend performing white blood cell count and differential and routine microbiological cultures (aerobic bacterial culture and Gram stain) (strong recommendation, *moderate certainty of evidence*). **Comment:** Further diagnostic testing may be beneficial in certain situations: 1) molecular testing for specimens from which no pathogen has been identified by Gram stain and aerobic bacterial culture, (particularly in preschool-aged children at higher risk of *K. kingae* infection); and 2) more extensive scope of microbial testing, beyond aerobic bacterial culture (e.g., anaerobic, fungal, and/or mycobacterial cultures and stains; molecular testing, which may include metagenomic next-generation sequencing), in children who are immunocompromised or who have a history of penetrating injury. Additional molecular tests may be performed on synovial samples held in the laboratory, or for additional cultures, a repeat arthrocentesis may be required.

### **Summary of Evidence**

The collection of synovial fluid of the affected joint(s) is a critical aspect of management of suspected ABA for diagnostic and therapeutic purposes. The initial invasive procedure to collect synovial fluid can be performed by arthrocentesis, potentially to be immediately followed by surgical drainage (arthroscopy or arthrotomy) as needed.

The choice and timing of the initial procedure is influenced by:

- Therapeutic need for drainage
- Severity of infection (based on vital signs, physical findings including clinical toxicity, and inflammatory marker elevation)
- Location, size, and ease of accessibility of the affected joint

- The requirement for anesthesia or sedation to perform supplemental imaging and/or arthrocentesis with the possibility of subsequent arthrotomy
- Availability of local resources to support necessary interventions

Historically, there has been a sense of urgency regarding aspirating a joint suspected of being infected by bacteria. However, recent experience has demonstrated a very low complication rate (<1%) for children with primary ABA. In contrast, the complication rate for children with ABA with adjacent osteomyelitis has been reported to be 38% [87]. In this study, children with adjacent osteomyelitis were significantly older (7.6 vs 2.7 years), had higher inflammatory markers (initial CRP 16.2 vs 5.2 mg/dL) and had higher rates of bacteremia (71.7% vs 9.7%). To determine if osteomyelitis is present, which would influence further evaluation and management, it is important to systematically gather all relevant data (history, physical examination, laboratory tests, and imaging) prior to proceeding with arthrocentesis and surgery.

The most common initial step in directly evaluating a joint space for the presence of infection is to obtain a synovial fluid sample by arthrocentesis, if practical. An exception is when there is suspicion of infection of a hip or shoulder joint, where more invasive procedures often are the best initial approach, depending on the clinical circumstances [see below]. Arthrocentesis is quick and minimally invasive and may be done with the child under sedation, general anesthesia, or awake, depending on the age and the ability of the child to cooperate with the procedure. Arthrocentesis may be performed by orthopedic surgeons, rheumatologists, interventional radiologists, or other trained providers. When the initial procedure is performed by a non-orthopedist and the fluid appears purulent (or initial testing suggests bacterial infection), orthopedic consultation for possible additional procedures such as arthroscopy or arthrotomy should be considered. However, aspiration of the infected joint via arthrocentesis may not only serve to verify the diagnosis of ABA but may also decrease the urgency for initial surgical intervention [123]. Some children demonstrate rapid clinical and laboratory improvement following initial aspiration with or without lavage to the extent that subsequent surgical intervention may not be necessary [55, 102, 124]. A recent study of children in Spain with ABA of the knee found that age < 3 years and CRP < 20 mg/L were predictive of successful outcome with aspiration alone [125]. Success with percutaneous aspiration, irrigation and tube drainage has been described [126]. Repeated aspiration of infected hips rather than arthrotomy has also been used with success [127].

The clinician performing arthrocentesis needs to consider the possibility of osteomyelitis in bone(s) adjacent to the involved joint [89, 128]. A more complicated clinical course and worse outcomes are associated when ABA is associated with adjacent osteomyelitis [87, 129, 130]. A retrospective study of children with ABA of the hip showed that aspiration of the femoral neck demonstrated adjacent osteomyelitis in some cases when MRI did not show evidence of bone involvement [120]. For children with ABA with adjacent osteomyelitis, procedures to provide drainage of the joint may need to be accompanied by additional procedures to debride the adjacent bone and soft tissue. Specimens from affected tissues should be submitted for culture and histopathology.

Drainage and irrigation of the infected joint via arthroscopy or arthrotomy is commonly performed in North America when ABA is the presumed or confirmed diagnosis. The goals of drainage are to decompress the joint and remove inflammatory debris. Arthrotomy or arthroscopy may be

performed initially in lieu of or may be indicated after arthrocentesis. The decision to proceed to one of these procedures immediately after arthrocentesis may be based on the gross appearance of the joint fluid, or joint fluid WBC count and differential, in the context of the clinical presentation and the specific joint that is infected. If an open or arthroscopic procedure is deemed unnecessary, the child should be observed closely for the need for further drainage of the infected joint. However, if additional procedures are deemed important but cannot be performed due to lack of resources, transfer to a facility with appropriate resources should be considered [See Question VI]. No North American studies have prospectively compared differences in outcomes between repeated needle aspirations and formal arthrotomy with irrigation for various joints (e.g., hip or shoulder) affected by common ABA pathogens. One study in Malawi randomized 61 children to aspiration versus arthrotomy for ABA of the shoulder and found no difference in outcomes. Nontyphoidal *Salmonella* species accounted for 80% of the positive joint fluid cultures in this study, so these findings may not be generalizable to other populations [131].

Arthroscopic drainage is safe and effective in a wide variety of joints including the hip, knee, ankle, shoulder, elbow, and wrist when performed by qualified surgeons [132-137]. Minimal invasiveness, shorter hospitalization, and improved visualization of the joint space for prognostic evaluation of the articular surface are all reported as potential advantages of arthroscopy over open drainage. A recent Australian study comparing arthroscopic and open treatment of children with ABA of the knee demonstrated that arthroscopy was associated with fewer repeat irrigations and shorter time to achieving range of motion and weight bearing [138].

Historically, arthrotomy has been recommended for ABA of the hips and shoulders, due to the risk of avascular necrosis from increased intracapsular pressure. A South African study of children with ABA of the hip reported uncomplicated recovery when treatment with antibiotics and arthrotomy occurred within 5 days of the onset of symptoms (although many children from this small study did not present for medical attention early in their infection), but significant and permanent hip damage when arthrotomy was delayed [139]. In recent years, arthroscopic drainage of the hip and shoulder joint has resulted in good outcomes[133, 134, 140] and offers several advantages over open drainage as noted above.

Regardless of the initial means of obtaining joint fluid, an adequate volume of fluid should be submitted to the laboratory rather than simply submitting a culture swab. Synovial fluid WBC count and Gram stain should be performed and provide results that are rapidly available. The WBC count is an important tool for helping to distinguish infection from other pathologic processes [141] but it is only a rough guide that should be interpreted in the context of clinical and other laboratory data. In ABA, the joint fluid WBC count is usually greater than 50,000/ $\mu$ l and often exceeds 100,000/ $\mu$ l, with a neutrophil predominance [142], while in transient nonbacterial synovitis the WBC count is commonly 5000 to 15,000/ $\mu$ l, often with mononuclear predominance. In JIA it is typically < 50,000/ $\mu$ l.

The cellular profile of Lyme arthritis may mimic that of ABA with polymorphonuclear cell predominance [96, 143] with over half of pediatric cases exceeding 50,000 WBC/ $\mu$ l [97, 110]. In one study in a Lyme endemic area, children with intermediate (25,000 to 75,000 cells/mm<sup>3</sup>) WBC counts in hip joint fluid were most likely to have ABA, followed by Lyme arthritis and then transient

nonbacterial synovitis [144]. Two small recent studies suggest potential moderate utility of urine dipstick leukocyte esterase test results on synovial fluid as a rapid means of differentiating infection from other causes of arthritis [145, 146], but further validation is required.

In some cases of culture positive ABA, the Gram stain may be negative [147], likely due to a low concentration of organisms. However, when positive, the Gram stain can provide timely information to guide the initial selection of antimicrobials [148, 149]. In general, narrowing antimicrobial therapy based solely on the Gram stain is not advised; however, identification of unanticipated pathogens may provide an opportunity for rapid initiation of additional pathogendirected therapy.

Cultures for aerobic bacteria are routinely performed, and in addition, laboratories should use chocolate (lysed sheep's blood) agar to enhance recovery of *N. gonorrhoeae* and *Haemophilus influenzae* type b. For young children it is now common practice to inoculate a sample of joint fluid directly into an aerobic blood culture bottle in an effort to enhance recovery of fastidious microbes such as *K. kingae* [150, 151]. Recent studies have shown that this approach enhances the recovery of other pathogens as well [106, 152]. Anaerobic, fungal, and mycobacterial cultures should not be performed routinely in otherwise healthy children with primary ABA because of negligible yield, but should be performed for children who are immunocompromised, have penetrating injury to the joint, or have failed primary treatment [70]. Other studies on joint fluid (e.g., pH, protein, LDH, lactate) are no longer recommended for routine use in children with suspected ABA.

Identification of the microbial etiology for ABA enables appropriate antibiotic therapy to be provided and helps guide other management decisions. Our systematic review of the literature included a total of 19 studies reporting on the added diagnostic yield of culture of synovial fluid to results of blood cultures alone for pathogen identification in pediatric ABA 2005 through 2022 [12, 24, 50, 52-59, 61-68]. These studies collectively included 2,090 patients with presumed or confirmed ABA (ranging from 18 to 268 patients per study). In our analysis, we addressed two cohorts who were analyzed and reported separately: the first cohort with presumed or confirmed primary ABA [12, 24, 50, 52-59, 66-68] and the second cohort from studies where it was impossible to separate those with primary ABA from those with adjacent osteomyelitis [61-65]. Patients in these studies who could definitively be identified as having ABA with adjacent osteomyelitis were excluded from these analyses [37] (see **Table 1** for definitions). Both analyzed subgroups showed a similar increase in the yield of pathogen identification when synovial fluid was cultured in addition to cultures of blood: risk difference (RD) (increase in yield) was 26.8% (95% CI: 20.1 to 33.5%) among 14 studies that included 1,545 patients with primary ABA and was 28.3% (95% CI: 19.0 to 37.7%) among 5 studies with 545 patients with either primary ABA or ABA with adjacent osteomyelitis (see **Supplementary Material Figures IIIa**).

Our systematic review of the literature also included a total of 34 studies reporting on the positivity rate of synovial fluid culture in pediatric ABA 2005 through 2022 [12, 25, 28, 50-66, 68, 69, 76, 90, 112, 121, 147, 153-159]. These studies collectively included 2,936 patients with pediatric ABA (ranging from 14 to 302 patients per study). Cohorts of patients were similarly stratified according to the final diagnosis. The yield of routine aerobic bacterial culture averaged 40.1% (95% CI: 33.5 to 46.7%) in 25 studies [12, 50-59, 66, 68, 69, 76, 112, 121, 147, 153-159] including 2,001 patients with primary ABA, and 41.7% (95% CI: 32.8 to 50.7%) in 9 studies [25, 28, 60-65, 90] of 935 patients

with either ABA or ABA with adjacent osteomyelitis) (see **Supplementary Material Figures IIIb** ). These analyses may underestimate the value of synovial fluid cultures (or subsequent molecular testing) since many studies included suspected cases of ABA which 1) had cultures rendered negative due to prior administration of antibiotics, 2) did not perform molecular testing, or 3) had confirmation of an alternate diagnosis (e.g., inflammatory, or reactive arthritis) later in the course of disease.

PCR-based testing using either single or multiple pathogen-targeted PCR (e.g., to specifically detect *K. kingae*), and 16S ribosomal ribonucleic acid (16S rRNA) gene amplification and sequencing were increasingly used in the past decade, especially in cases with no identified pathogen. Our systematic review of the literature included a total of 11 studies [28, 53, 54, 61, 66, 68, 112, 153, 155, 157, 159] reporting on the added value of PCR-based testing on synovial fluid in addition to culture in pediatric ABA 2005 through 2022. All studies included 16s rRNA or DNA amplification and sequencing. These studies collectively included 762 patients with pediatric ABA (ranging from 14 to 268 patients per study). Patient data were analyzed in two strata: one cohort with primary ABA and the other with ABA with adjacent osteomyelitis. Both subgroups showed a significant increase in the yield of pathogen identification when PCR-based testing on synovial fluid was performed in addition to culture: a risk difference of 18.7% (95% CI: 12.1 to 25.3%) in 9 studies including 672 patients with primary ABA [53, 54, 66, 68, 112, 153, 155, 157, 159] and a risk difference of 17.5% (95% CI: 5.8 to 29.1%) in 2 studies including 176 patients included in cohorts not differentiating cases of primary ABA and ABA with adjacent osteomyelitis [28, 61] (see **Supplementary Material Figures IIIc** ). When synovial fluid is initially obtained, it is reasonable to hold fluid for PCR and other molecular testing that may be ordered later in situations where Gram stain and culture do not demonstrate a pathogen; this technology is particularly important for demonstration of *K. kingae*, which often fails to grow with conventional cultures [27, 29, 61] or when antimicrobial therapy has been given prior to obtaining the synovial fluid [153].

PCR technology has also been developed for detection of resistance markers for *S. aureus* (e.g., *mecA* and *erm* genes). Application of these molecular tests for pediatric musculoskeletal infections has been described [160, 161]. In these studies, there was excellent concordance for detection of methicillin and clindamycin resistance, compared with conventional microbiological methods. Target-enriched multiplex polymerase chain reaction (TEM-PCR) technology can detect multiple bone and joint pathogens as well as resistance genes (e.g., *mecA*, *ermA*, *ermC*) and the virulence marker Panton-Valentine leukocidin [161]. Even in culture positive musculoskeletal infections, rapid identification of resistance by PCR can support more focused antimicrobial use. One study predicted that a musculoskeletal diagnostic panel would have decreased the time to pathogen identification (by 7 hours), time to definitive antimicrobial therapy (by 22 hours) and hospital LOS (by 26 hours) [162].

Newer molecular techniques include metagenomic next-generation sequencing (mNGS), in which non-human nucleic acid sequences from microbial pathogens can be detected in plasma or in osteoarticular tissues and synovial fluid and matched with published whole genome sequences of pathogens in order to detect matching sequences. This technique provides the potential to identify virtually all infecting bacterial pathogens causing osteoarticular infections, in contrast to most PCR techniques that can only identify one specific pathogen per PCR primer. This technique was

recently studied prospectively in pediatric osteoarticular infections in otherwise healthy children, with 21 children enrolled with clinically diagnosed ABA [112]. Only 25% of synovial fluid bacterial cultures were positive, but mNGS identified a pathogen in 50%, similar to diagnosis rates in children analyzed by culture plus PCR for *K. kingae* and *B. burgdorferi*. Both molecular techniques (PCR and mNGS) were able to diagnose *K. kingae* infections in children whose cultures were negative.

#### *Rationale for Recommendation*

This recommendation places a high value on confirming the microbiological diagnosis to allow optimization of the spectrum and duration of antimicrobial therapy. Indirect evidence shows that identifying the causal pathogens is likely to lead to improved patient-important outcomes by allowing for focused therapy with the narrowest spectrum antibiotics with the least toxicity, given for the shortest microbiologically and clinically effective duration.

Obtaining specimens for culture and molecular tests from joint aspiration or other procedures improves the likelihood of identification of and antimicrobial susceptibility data for the pathogen. There is a wide range of pathogens that cause ABA. Knowledge of the pathogen and its susceptibility pattern often simplifies treatment decisions by allowing antimicrobial therapy to be focused on a specific organism that also allows for the transition to a pathogen-specific oral agent for completion of the course of antimicrobial therapy. Despite the potential harms and costs associated with these invasive procedures, the benefits of pathogen-related information are felt to outweigh undesirable effects of the procedures. The choice of the procedure(s) to obtain synovial fluid is based on patient- and institution-specific considerations, resources, and experience.

#### *Research Needs*

Prospective studies are needed on invasively collected joint tissue and synovial fluid that assess 1) the sensitivity and specificity of advanced molecular testing, including next generation sequencing for bacterial genomes to identify microbial etiology and 2) ability of such testing to provide susceptibility data. Studies of inflammatory markers or biomarkers in serum and synovial fluid as means of distinguishing between infectious from non-infectious etiologies of arthritis would be helpful.

### **IV. At the time of presentation, can parenteral antimicrobial agent administration be delayed until joint specimens have been obtained?**

#### **Recommendations:**

1. In children with presumed ABA who are ill-appearing or have rapidly progressive infection, we recommend immediately starting empiric antimicrobial therapy (after blood cultures are obtained if possible) rather than withholding antibiotics until invasive diagnostic procedures are performed (strong recommendation, *moderate certainty of evidence*). **Comment:** Invasive diagnostic procedures should occur as soon as feasible, even if antibiotics have already been administered.
2. In children with presumed ABA who do not appear clinically ill, we suggest withholding antimicrobial therapy, while under careful observation, until an *initial* joint aspirate is collected

for diagnostic purposes (conditional recommendation, *very low certainty of evidence*).

**Comment:** The decision to initiate antimicrobials prior to invasive diagnostic procedures depends on the severity of the clinical presentation, local accessibility to experts and resources or, if appropriate, the time required for transport to a higher level of care for additional diagnostic or debridement procedures. The ability to diagnose pathogens by molecular diagnostic techniques suggests that critical information on pathogen identity is now less dependent on obtaining bacterial cultures prior to starting antimicrobial therapy.

### *Summary of Evidence*

In an attempt to maximize the identification and susceptibility testing of bacterial pathogens by culture, the standard of care for all bacterial infections has been to obtain cultures prior to administration of antimicrobial therapy. However, the clinical status of the child also has an important impact on the timing of the first dose of empiric antimicrobial therapy. For children with ABA accompanied by sepsis, extrapolation of data on outcomes from sepsis (without arthritis) in children based on timing of the start of appropriate antimicrobial agents is reasonable, as data specific to sepsis with ABA have not been published. For the ill-appearing child with clinical sepsis and rapidly progressive disease, early antibiotic therapy is associated with improved outcomes. In a retrospective, multicenter study of 130 children with sepsis (21%) or septic shock (79%), antimicrobials given >3 hours after presentation were associated with a 4.92-fold increased risk of mortality (95% CI: 1.3 to 18.6) [163]. In a study of 1,179 children with sepsis at 54 hospitals, completion of a sepsis bundle, including empiric therapy with broad spectrum antimicrobials within 1 hour of presentation, was associated with a lower risk of in-hospital mortality (Odds ratio [OR]: 0.59; 95% CI: 0.38 to 0.93, p-value = 0.02) [164].

Published data from adults with sepsis demonstrates the advantages of immediate therapy (rather than delayed therapy) [71]. For adults with septic shock, a large, retrospective cohort study demonstrated that appropriate therapy within one 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 [165]. Results from a large retrospective review of 18,000 adults with sepsis from 165 ICUs in Europe, the US, and South America confirmed increasing mortality rate with each additional hour of time to first administration of antimicrobials during the first 6 hours following diagnosis of sepsis [166]. Improved metrics in other patient-important outcomes such as intensive care unit (ICU) LOS and overall hospital LOS, have also been identified with earlier antimicrobial therapy [167]. These data indirectly support the recommendation for early administration of antimicrobials to children with sepsis and suspected ABA if resources for invasive sampling of fluid from the infected joint are not immediately available at the time of presentation for medical care.

For children with more indolent infection, the question of whether there is a benefit to withholding antimicrobials until joint fluid can be obtained by those qualified to perform such procedures is important, particularly when considering the benefits of pathogen identification and susceptibility testing by culture. For children who require transfer to a higher level of care, a delay of several hours prior to sampling the infected joint may occur.

In our systematic review of the literature, we were unable to find prospectively collected data to address the risks and benefits of delays in the start of empiric antimicrobial therapy for children with presumed ABA. We did identify six retrospective observational studies that assessed the impact of empiric antibiotic administration prior to joint fluid collection in children with suspected ABA (see **Table 3** and **Supplementary Material Figures IV**) [54, 62, 66, 112, 154, 155]. All six studies had small sample sizes and reported only unadjusted analyses. These studies often did not provide critical information such as specifics of antibiotics that were administered, or their appropriateness, or duration of antibiotic pre-treatment.

All six studies reported the yield of positive culture with or without antibiotic pre-treatment, but only one reported the patient-important outcomes of complications, requirement for repeated joint debridement and time from symptom onset to initial joint debridement [154]. The pooled analysis of the six studies suggests a comparable yield of synovial fluid cultures with or without antibiotic pre-treatment (RD: 1.2% increased yield (95%CI: -12.0 to 14.5%)).

The analysis of these patient-important outcomes, mainly derived from retrospective data review, showed that delaying antibiotics until after joint fluid collection may or may not have reduced the incidence of complications (RD: -12.0%, 95%CI: -33.0 to 9.0%) and the requirement for repeated irrigation and debridement ("washouts") (RD: -4.0%, 95%CI: -25.3 to 17.3%). However, the certainty in the evidence was judged to be very low due to 1) very serious risk of bias (retrospective study design, missing critical information regarding appropriateness, and timing and clinical response to the empiric pretreatment antibiotics, all of which could have influenced the measured outcomes), 2) use of unadjusted analyses (clinical outcomes were not stratified or adjusted for critical variables such as age and pathogen) and 3) imprecision based on small number of events, small sample size and estimates not reaching statistical significance.

The yield of bacterial cultures of joint fluid may be suboptimal for the identification of a pathogen without the addition of molecular diagnostic tests. For example, of the 5 studies included in our analysis, *K. kingae* was identified in less than 1% of cases (3 reported cases out of 312 children evaluated for a pathogen). However, the frequency of isolation, by study site, varied from no reported *K. kingae*, to 12% of isolates identified as *K. kingae* from an institution in Seattle that used PCR in addition to culture for microbiologic diagnosis [54]. These data suggest that pretreatment of children with antibiotics is not likely to impact a pathogen diagnosis by molecular techniques, compared with standard microbiological techniques, although the impact of prior antimicrobial therapy on the positivity rates of molecular-based pathogen tests has not been prospectively evaluated. However, it is biologically plausible that the timeframe in which a pathogen's nucleic acids can be detected by PCR or next generation sequencing may be longer following exposure to antimicrobials compared with standard microbiological culture (see Question III).

Potential complications of delayed antimicrobial therapy include persisting/increasing inflammation in the joint due to lack of effective therapy, which could potentially increase risk for chondrolysis. Such chondrolysis may vary by age of the child, joint involved, and pathogenicity of the organism causing infection, but published data are not available to quantify this risk if it exists. It is also possible that early antimicrobial therapy prior to drainage of the infected joint could produce

increased inflammation in the joint from the lysis of pathogens in the joint fluid with risk of additional cartilage injury, but as noted above, data to quantify this risk have not been published.

The risk of complications from joint aspiration by those not experienced or qualified has not been prospectively evaluated, but likely depends on the joint involved, the age of the child, and the level of training of the person performing this procedure.

#### *Rationale for Recommendation*

The benefits of early antimicrobial therapy prior to surgical sampling of joint fluid in children with sepsis are likely to outweigh any potential harms from not knowing the pathogen or susceptibilities. Infants and children with suspected ABA may present to primary care practitioners, urgent care clinics or emergency departments in a wide range of settings (rural, suburban, or urban), and so may present at institutions without pediatric orthopedic expertise. Retrospective review of low-quality data did not document a decrease in the culture isolation rate with antimicrobial therapy prior to sampling the joint fluid, as noted above. Molecular testing may still be able to detect the pathogen when joint fluid is obtained after antimicrobial therapy if cultures are negative.

For children with no signs of sepsis, withholding antibiotic therapy until after sampling of joint fluid theoretically may allow for increased isolation of pathogens and susceptibility testing, particularly for more fastidious pathogens. In addition, children may possibly benefit from waiting for a person skilled in the procedures for sampling joint fluid to be available, even if this requires transfer to a higher level of care, when compared with having a person not as skilled in these procedures emergently perform the sampling, possibly leading to complications. However, no data have been published to support a specific number of hours of delay that can be considered risk-free prior to starting effective antibiotic therapy.

#### *Research Needs*

Prospectively collected data are important to answer the question of the impact of effective empiric antibiotic therapy on relevant outcomes for children with ABA. In future studies, the covariates that may impact outcomes in pediatric ABA (joint involved, the age of the infant or child, and the pathogen responsible for the infection) should be controlled in order to assess a positive or negative impact (and the magnitude of the impact) of antibiotics administered to a child prior to invasive sampling of joint fluid. Molecular diagnostic techniques, including PCR targeting pediatric ABA pathogens, mNGS, or pathogen-specific molecular antigen tests should be prospectively studied simultaneously with joint fluid cultures, to assess the ability to diagnose specific pathogens, particularly fastidious organisms.

### **V. Which empiric antimicrobial agent(s) should be provided for children with suspected ABA?**

#### **Recommendations:**

1. In children with suspected ABA, we recommend using empiric antimicrobial therapy active against *S. aureus* (strong recommendation, *moderate certainty of evidence*). **Comment:** Antimicrobials with activity against community-acquired MRSA (CA-MRSA) should be considered based on local susceptibility data and severity of disease. Adding empiric

antimicrobial coverage for pathogens in addition to coverage for *S. aureus* may be warranted when other pathogens are suspected based on relevant aspects of immunization, exposure history, clinical presentation, or physical examination.

2. In infants and preschool aged children (6 to 48 months of age) with suspected ABA, we suggest selecting empiric therapy to include activity against *K. kingae* rather than only targeting *S. aureus* (conditional recommendation, very low certainty of evidence). **Comment:** With *K. kingae* reported as the most frequent pathogen in this age group in recent studies, additional therapy is suggested if empiric therapy used for *S. aureus* is not active against *K. kingae*.

### *Summary of Evidence*

As with all infections, empiric therapy for suspected ABA is designed to provide effective therapy against the most prevalent pathogens that cause injury to the joint. *S. aureus* has historically been known to be a common pathogen causing ABA in all age groups [91, 168-177]. Our systematic review of the literature found 32 studies of confirmed primary ABA (published 2005 through 2022) including 1,729 children in whom a microbiologic etiology was determined by positive culture or PCR of tissue and/or blood (see **Supplementary Material Table V** ) [12, 23, 25, 50-59, 66-69, 76, 94, 112, 119, 121, 141, 147, 154, 157, 158, 168, 178-181]. Overall, *S. aureus* has historically been the most commonly detected organism to cause ABA secondary to hematogenous spread in all age groups. The pooled rate of *S. aureus* infections was 42.6% (95%CI: 35.1 to 47.2%) for those with ABA in absence of osteomyelitis, but significantly higher in those with associated osteomyelitis (n=211 from 6 studies, 69.9% (95%CI: 47.9 to 78.2%)) [12, 23, 119, 121, 178, 181]. In fact, our analysis showed that *S. aureus* was more than twice as likely to be the causative organism in patients with ABA and adjacent osteomyelitis, compared with those with primary ABA (OR: 2.44, 95%CI 1.81 to 3.27).

The proportion of CA-MRSA in ABA varied widely geographically and over time during the past few decades but was documented to be as high as 50-60% of all *S. aureus* isolates in some reports [70, 179]. Of importance, since 2018, the incidence of CA-MRSA causing bone and joint infections appears to be decreasing in reports from North America, which may impact decisions for empiric therapy if this trend continues [182, 183].

Also important in the selection of empiric therapy is knowledge of the proportion of bacterial pathogens other than *S. aureus* identified from infected joints in children (either by culture or by PCR), ranging in our analysis of the literature from 15.4% to 92.1% (see **Supplementary Material Table V** ). Data for this table were extracted from the published literature – primarily retrospective reviews. The isolation of pathogens depended on the frequency of sampling inflamed joints; sampling frequency was dependent on how each center approached children with inflammation (of various degrees) that was present in different involved joints (e.g., hips vs knees). The decision to sample and analyze the joint fluid was usually at the discretion of a surgeon. The surgical techniques (aspiration, arthroscopy, open procedure) to sample synovial fluid were not standardized. The techniques used for pathogen identification were largely based on standard microbiology culture in most publications prior to 2010. The decision to pursue molecular testing on synovial fluid for research or for clinical care has evolved over the past 2 decades; molecular techniques used for diagnosis in the literature have not been standardized between institutions. In reports from Europe and North America, *K. kingae* was demonstrated to be a common pathogen in

pediatric ABA in infants and preschool aged children and was the most commonly identified pathogen in some [25, 28, 29, 53, 58, 94]. It is likely that recently described high rates of *K. kingae* detection are based on increased use of sensitive molecular techniques that provide enhanced detection (See Question III). Group A *Streptococcus* is a relatively common pathogen for pediatric ABA, representing up to 14% of identified pathogens in some studies [70].

Prior to widespread immunization with conjugate vaccines against pneumococcus and *Hib*, these polysaccharide encapsulated pathogens were frequent causes of ABA in infants but are now unusual in highly immunized populations. Similarly, meningococcus can cause joint infection as part of invasive infection, although much less commonly than pneumococcus or *Hib*. Detection of pathogens against which vaccines are not effective may also be age-dependent (e.g., Group B streptococcus and *E. coli* in very young infants). History of exposures to the environment and potentially contaminated foods should be obtained, as infection by certain pathogens such as *Salmonella* spp and *Brucella* spp may occur under these circumstances; empiric therapy that provides additional activity against these pathogens may be appropriate. For adolescents, sexual exposure is a risk factor for *N. gonorrhoeae* septic arthritis/tenosynovitis. Overall, in our review of the recent literature, no pathogen other than *S. aureus*, *K. kingae*, and group A *Streptococcus*, occurred in greater than 5% of cases of ABA in any study (see **Supplementary Material Table V** ).

In general, the acute nature of ABA is distinct from that caused by mycobacteria (including *M. tuberculosis*) or fungi, that are not addressed in these Guidelines. Similarly, penetrating trauma to the joint or surrounding structures is associated with additional or unusual pathogens that require consideration in the selection of empiric therapy but will not be discussed in these Guidelines.

Decisions on empiric therapy are best informed by review of the most recent data on ABA pathogens identified in a clinician's region, particularly with respect to susceptibility of *S. aureus* isolates. Therapy for *S. aureus* was developed in the 1940's, initially with the discovery and use of penicillin and subsequently with creation of anti-staphylococcal penicillins and cephalosporins active against penicillin-resistant strains of *S. aureus*. It is understandable that clinicians used these antibiotics several decades ago to treat proven and suspected *S. aureus* infections in children without the conduct of randomized, placebo-controlled trials. Initially, efficacy was often assessed by comparing the outcomes of those treated with these antibiotics to the outcomes of historical controls from the pre-antibiotic era. Since the emergence of CA-MRSA infections, no prospective controlled studies in pediatric ABA have evaluated the efficacy and safety of empiric regimens that compare anti-MRSA regimens with those that only provide activity against MSSA. While currently isolated *S. aureus* strains are almost uniformly penicillin-resistant, many remain susceptible to antistaphylococcal penicillins (ASP) such as methicillin (no longer commercially available in the USA), 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 ABA as well as in osteomyelitis, based on retrospective, non-comparative studies in children; however, no comparative data are available for an ASP and cefazolin.

In regions with low rates of CA-MRSA arthritis (less than ~10%), some experts begin therapy with oxacillin/nafcillin or cefazolin for children with mild to moderate illness, watching closely for a response to treatment. In regions where resistance to methicillin is estimated to be 10-20% or

greater, consideration should be given for empiric therapy to include agents for which *in vitro* and prospective clinical data exist for antimicrobials with activity against invasive CA-MRSA infection. For these agents, adequate joint drug exposure is expected, even if specific studies of synovial fluid concentrations have not been performed. Effective empiric therapy for CA-MRSA ABA is expected with clindamycin (unless local clindamycin resistance rates are high), vancomycin, daptomycin, ceftaroline, and linezolid. Clindamycin resistance occurs in both MRSA and MSSA, and should be a factor in selecting empiric therapy, given substantial resistance documented in some regions (5% to 40% of all *S. aureus* isolates). For reasons of drug safety, when the infecting strain is suspected to be susceptible to both clindamycin and vancomycin, empiric use of clindamycin (which is available in both intravenous and oral formulations) is preferred over vancomycin.

For children suspected to have *S. aureus* ABA for whom ASPs, vancomycin, or clindamycin cannot be used due to concerns for suspected antibiotic resistance or poor tolerability, alternative therapy is available. Parenteral daptomycin, parenteral ceftaroline, and parenteral/oral linezolid have been studied in prospective pediatric trials for complicated staphylococcal skin infections, including MRSA, and provide additional options for treatment based on *in vitro* susceptibility testing. Daptomycin has also been prospectively studied in pediatric osteomyelitis [184]. Further, alternatives to vancomycin should be considered for MRSA infections caused by relatively vancomycin-non-susceptible strains ( $\text{MIC} \geq 2 \mu\text{g/mL}$ ), given the higher vancomycin doses that may be required to achieve pharmacodynamically targeted serum exposures [185].

Trimethoprim/sulfamethoxazole (TMP/SMX) demonstrates *in vitro* activity against most strains of *S. aureus*, including CA-MRSA, and has been shown to be effective in the treatment of uncomplicated skin infections caused by CA-MRSA, however no controlled, comparative data exist on the use of TMP/SMX for ABA caused by CA-MRSA, although some experts recommend use [186]. No controlled, comparative data exist to suggest superior efficacy or effectiveness of any one of the above agents versus the others in treating invasive MRSA infections in children, assuming that the isolate is susceptible.

While the use of combination antimicrobial therapy for potential synergistic effects is a common practice in the treatment of severe infection caused by CA-MRSA, no controlled data are available on which to base recommendations for such combination therapy to improve outcomes. However, use of multiple agents in combination to increase the antibacterial spectrum of empiric therapy is appropriate for severe infections, particularly when coverage of Gram-negative pathogens is needed in addition to *S. aureus*.

*S. pneumoniae* remains an occasional cause of ABA, particularly in children who have not received pneumococcal conjugate vaccine (PCV) [187]. Antibiotics with activity against *S. aureus* are usually active against pneumococci, although some beta-lactam antibiotics may not be effective against strains of pneumococcus with reduced susceptibility to parenteral penicillin ( $\text{MIC} > 2 \text{ mcg/ml}$ ). Clindamycin resistance in pneumococcus occurs in up to 10% of strains in some populations of children [188].

*S. pyogenes* is usually susceptible to agents active against CA-MRSA or MSSA, although resistance to clindamycin has been reported [189].

For *K. kingae* and other Gram-negative pathogens, many agents active against CA-MRSA do not provide adequate antimicrobial activity, including ASPs, vancomycin, clindamycin, daptomycin and linezolid, supporting a need for additional empiric antimicrobial coverage with ampicillin or a cephalosporin if these antibiotics are used [190]. Current global epidemiologic studies for *K. kingae* document beta-lactamase positivity (ampicillin-resistant) rates of approximately 25%, although most beta-lactamase positive strains are colonizing rather than invasive strains [32, 191-193].

No controlled data exist on the incidence of complications or outcomes in children with untreated *K. kingae* infections (including endocarditis). However, retrospective data reported for children with culture-negative ABA (believed by the authors to include children with unrecognized *K. kingae* infection) suggested that active antibiotic therapy may not always be required. Of 89 children with culture negative arthritis without osteomyelitis, 55 were less than 5 years of age; only 13% received empiric therapy active against *K. kingae*. At the time of discharge on oral therapy, only 18% received an antimicrobial active against *K. kingae*. No long-term disability was noted in any child at 6 months from hospital discharge [24]. Although antimicrobial therapy against *K. kingae* is likely to provide some benefit, no published data document the degree of benefit or the risk of adverse outcomes compared with those who receive no active antibiotic treatment.

For the clinically stable child who is treated empirically with clindamycin, vancomycin, daptomycin or linezolid, the addition of a cephalosporin (cefazolin, cefuroxime, or cefotaxime/ceftriaxone) or ampicillin may be considered if *K. kingae* is suspected based on lack of clinical response or detected by positive cultures or molecular tests. Ceftaroline also demonstrates *in vitro* activity against Gram-negative pathogens including *Hib*, *E. coli* and *K. kingae*, similar to cefotaxime/ceftriaxone, in addition to providing MRSA activity, and may be considered for empiric therapy if more broad-spectrum activity is needed [194].

Parenteral administration of empiric antimicrobial therapy is appropriate and necessary for the vast majority of ABA presentations. Occasional circumstances, with careful consideration, may permit use of an oral regimen from the outset. (See Question XI).

#### *Rationale for Recommendation*

The existing literature on antimicrobial therapy for pediatric ABA for *S. aureus*, *K. kingae*, and other pathogens is limited by the retrospective nature of published data, as well as inconsistent methodology, varied populations reported, non-standardized surgical management and limited patient datasets for clinical and laboratory assessment of disease at the time of treatment or at post-hospitalization follow up. All these limitations add some uncertainty to conclusions drawn from the published data. No high quality prospectively collected comparative data are available to estimate disease burden or outcomes caused by the different ABA pathogens, particularly in light of treatment with different antimicrobial agents.

Despite the lack of high-quality data, the clinical use of several antimicrobial agents with *in vitro* activity against *S. aureus* has been effective for treatment of pediatric ABA over the past 4 decades. Further, the benefits of providing active therapy for treatment of *S. aureus* (rather than not treating) to decrease joint destruction, are judged to be far greater than the potential harms of antimicrobial therapy. Based on this body of indirect evidence, the Guideline Panel agreed that the certainty in the

balance of the magnitude of benefit over any harms of using empiric antimicrobial therapy active against *S. aureus* is high, and that all other considerations clearly favor this course of action (such as the patient's values and preferences, the costs, and feasibility), and thus support a strong recommendation.

For *K. kingae*, no prospectively collected comparative data exist on the impact of one antimicrobial versus another, or the impact of antimicrobial treatment vs no antimicrobial treatment, assuming all children have surgical aspiration/debridement and irrigation of infected joints. The available indirect evidence, mainly consisting of a relatively limited number of retrospective reports, shows a possible but minimal clinical effect of empirically adding coverage for *K. kingae*. Thus, even if it is biologically plausible that effective antibiotic therapy will produce improved outcomes for pediatric ABA, the Guideline Panel agreed that the certainty in the balance of benefits versus harms was very low. This agreement is based on existing evidence concerning broadening the spectrum of empiric therapy to include activity against *K. kingae* for infants, toddlers, and preschool-aged children (6 to 48 months of age). Thus, only a conditional recommendation was made.

Appropriate choice of empiric therapy should be guided by local antibiotic resistance patterns (CA-MRSA) and/or hospital antibiogram as well as disease severity and immunization status. Although many antibiotics may show activity *in vitro* against bacterial pathogens that cause ABA, lack of published data for treatment of children with ABA using one of these alternative options does not permit recommendations for their routine use at this time. Similarly, for the child with relatively mild disease, no prospective data exist on the efficacy of oral therapy used at the start of treatment (rather than parenteral therapy). Therefore, our committee did not provide a recommendation for starting treatment by the oral route of administration.

### **Research Needs**

Newer parenterally administered antimicrobial agents with activity against *S. aureus*, including those targeting CA-MRSA (such as ceftaroline, daptomycin, linezolid, oritavancin, dalbavancin, telavancin) should be compared with standard-of-care antimicrobial therapy for MRSA infection (vancomycin and clindamycin). Orally administered agents with activity against *S. aureus*, particularly those active against CA-MRSA (clindamycin, linezolid, tedizolid, TMP/SMX), should be compared for efficacy and safety as convalescent oral therapy for ABA. Newer agents with increased activity against *S. aureus*, particularly those with excellent absorption, tolerability, and high joint antibiotic exposure are needed. Evaluation of combination antibiotic therapy for severe disease would provide useful information to determine if more rapid sterilization of the joint space to improve long-term outcomes might be achieved. The role of medical therapy alone vs open surgical drainage/aspiration/arthroscopic drainage with medical therapy should be investigated to assess the time course of sterilization of the joint, clinical response and long-term morbidity following ABA. Controlled data on the outcomes of preschool children with documented *K. kingae* ABA are needed, as are controlled data on the benefits of active anti-*Kingella* therapy, particularly in children with adequate source control.

## **VI. When should advanced imaging be performed and/or invasive procedures be repeated in the management of presumed or confirmed bacterial arthritis in children?**

## Recommendations:

1. In children with presumed or confirmed ABA who demonstrate a poor clinical and laboratory response within 48-96 hours (continued fever, persistent bacteremia and/or rising CRP) after initial invasive procedures (open or arthroscopic) and initiation of appropriate antimicrobial therapy, we suggest performing MRI if not previously obtained (conditional recommendation, *very low certainty of evidence*). **Comment:** MRI is performed to evaluate for adjacent AHO, pyomyositis, or abscess as potential indications of ineffective source control to provide a basis to determine whether additional invasive procedures should be considered.
2. In children with presumed or confirmed primary ABA who demonstrate a poor clinical and laboratory response within 48-96 hours (continued fever, persistent bacteremia and/or rising CRP) after initial invasive procedures, and evidence to suggest persisting foci of infection (ineffective source control), we suggest additional invasive procedures to ensure adequate source control (conditional recommendation, *very low certainty of evidence*). **Comment:** When ABA is associated with adjacent osteomyelitis, management should follow the osteomyelitis guideline [37].

### Summary of Evidence

For consideration about initial invasive procedure type and timing, please see Question III. Many children will re-accumulate fluid in the joint space despite the initial invasive procedure(s) to manage their ABA, even with placement of drains. Fluid re-accumulation is not a cause for undue concern among children who are clinically improving. Ongoing observation with clinical reassessment is generally appropriate. With effective antibiotic and surgical therapy, most children with primary ABA will improve quickly. Ongoing findings of systemic illness or persistent bacteremia should prompt an evaluation for localized disease both within and beyond the joint.

While there are no high-quality data to guide the decision for when repeated invasive surgical procedures (such as arthroscopy or arthrotomy after arthrocentesis) are required, surgeons should consider performing further procedures on the affected joint for children who are failing to improve or are worsening clinically [195]. Retrospective studies of children with ABA of the hip have identified higher preoperative temperature, initial misdiagnosis of ABA, longer time from initial symptoms to surgery, presenting CRP >100 mg/L (normal <10), presenting ESR >40 mm/hour, adjacent AHO, and intraoperative cultures positive for MRSA as risks for requiring a repeat procedure [196, 197]. These repeat procedures allow for better source control of the infection and may provide new data from joint fluid or biopsies to support an alternative, non-infectious diagnosis. Similarly, bone biopsy or curettage should be considered in those with concern for adjacent osteomyelitis.

The choice of method for repeat procedures (open, arthroscopic, repeated needle aspiration) is largely guided by the experience of the orthopedic surgeon. However, if an initial (or serial) needle aspiration is not successful, then a more extensive approach (arthrotomy or arthroscopy) is generally indicated. Approximately 10% of children randomized to aspiration in a study conducted in Malawi required a second aspiration but had clinical outcomes equivalent to their counterparts randomized to arthrotomy [131]. While no other studies have prospectively compared differences in

outcomes between repeated needle aspirations and formal arthrotomy with irrigation for various joints (e.g., hip or shoulder) affected by common ABA pathogens, several investigators have reported excellent ABA outcomes with serial aspirations, which were required in between 4% to 20% of patients [102, 126, 127, 198]. A small case series suggests that failure rate with repeated aspirations may be higher among children older than 10 years, compared those of younger children [199].

Serial arthroscopy may likewise be necessary to address joint fluid re-accumulation or ongoing symptoms for those managed with initial arthroscopy. In two small case series, including young children and those with hip ABA, serial arthroscopy was reported to be required in approximately 10-15% of patients [200, 201]. One small series found that no children with arthroscopy-managed ABA of the knee required repeat procedures, compared with 39% of children managed by open arthrotomy, and that the arthroscopy group improved more quickly as determined by joint range of motion and weight-bearing [138]. In general, however, most experts would favor formal arthrotomy with irrigation and drainage for children with ongoing symptoms during ABA of the hip.

Following initial irrigation and drainage of the infected joint, the surgeon may place a drain to allow continued evacuation of the joint during the early post-operative period while antibiotics are being administered. No well-conducted studies are available to guide the selection of drain type or the length of time the drain should remain in place. Typically, drains are removed at the bedside when their output volume becomes low, usually within a few days of surgery. Once the drain has been removed, the moderate amount of ongoing joint inflammation may produce joint fluid that outpaces its reabsorption, but as inflammation decreases for children improving on antibiotic therapy, reabsorption eventually reduces joint swelling in most cases.

#### *Rationale for Recommendation*

This conditional recommendation is based on very low certainty of evidence, and places high value on considerations of patient values and preferences, feasibility, acceptability, equity, and cost in recommending that children with primary ABA with worsening symptoms after an initial procedure have advanced imaging and a repeat procedure as necessary for source control.

#### *Research Needs*

Future research needs include comprehensive prospective studies to develop methods of stratifying severity of illness at the initial medical encounter for children with ABA, to predict which children are more likely to need repeat invasive procedures. Stratification by pathogen and involved joints will facilitate the clinical utility of such studies. Comparing outcomes from the various types of procedures to obtain source control (needle aspiration, arthrotomy, arthroscopy), by joint and by pathogen would be helpful, as well as determining the need and outcomes for repeated procedures.

### **VII. In children with presumed or confirmed ABA who require a surgical procedure, should surgically administered (intra-articular) antimicrobial agents be routinely used in addition to systemic antimicrobial therapy?**

#### **Recommendation:**

In children with presumed or confirmed ABA who require a surgical procedure, we recommend against the routine use of intra-articular antimicrobial agents (strong recommendation, very low certainty of evidence). **Comment:** This recommendation places a high value on avoiding unnecessary harms and costs associated with this intervention.

### *Summary of Evidence*

High cure rates are achieved with systemic antimicrobials and drainage of infected articular fluid in children, precluding the need for surgical site (i.e., intra-articular) antimicrobial administration. (See Question XV). One potential desirable effect of intraarticular administration includes high, local antibiotic concentrations with decreased systemic exposure and associated toxicity. However, most antibiotics achieve excellent concentrations in synovial fluid following parenteral or oral administration [202, 203]. Moreover, there is a theoretical concern (without identifiable formal evidence) that intra-articular administration of antibiotics could produce chemical irritation and inflammation. Since pediatric data regarding the practice of intra-articular antibiotics are lacking, information must be drawn primarily from adult data of chronic osteomyelitis and prosthetic joint infections.

A few case series have reported outcomes in adult patients with chronic osteomyelitis managed by single-stage surgery using biodegradable tobramycin-impregnated calcium sulfate pellets (OSTEOSET<sup>®</sup>-T) in association with systemic antibiotic therapy [204, 205]. In children, a few retrospective chronic osteomyelitis (not ABA) case series have reported preliminary results on a limited number of patients with relatively short periods of follow-up [206, 207]. The patient populations in these studies form a heterogeneous group in terms of age, bone localization site, and type of chronic infection. These uncontrolled studies suggest that single-stage surgery using surgically placed antibiotics at the local site in association with systemic antibiotic therapy yields satisfactory outcomes and could potentially reduce the risk of recurrence of chronic osteomyelitis [206, 207]. Prospective data on the use of locally placed antibiotics for osteomyelitis or ABA have not been published. A review article describes advances in the local and targeted delivery of antibiotics, including antibiotics in biodegradable materials, for the management of osteomyelitis in general, but is not specific to the pediatric population or to ABA [208].

Potential toxicity associated with the use of aminoglycosides or glycopeptides placed intraoperatively, the cost and other potential harms related to the need for a second surgical procedure (when non-biodegradable implants are used) including the risk of general anesthesia, bleeding, surgical site infection, etc. need to be considered. In a study of neonatal osteomyelitis, locally applied gentamicin produced serum concentrations close to the minimal therapeutic concentration over a prolonged period [209]. Although there was no clinical evidence of renal failure and serum urea and creatinine levels during treatment with gentamicin remained normal, subclinical injury to the renal tubules, based on urine biomarkers, was reported in this study. Notably, there was no impairment of auditory function in the participants. Data regarding toxicity in neonates may not be easily extrapolated to older children who have higher renal aminoglycoside clearance that may result in lower systemic exposure. In a case series, wound complications were encountered in 52% of 21 patients following placement of biodegradable calcium sulfate/tobramycin mixture as an adjuvant treatment of chronic osteomyelitis of the tibia following exogenous trauma [205].

Case series of prosthetic joint infections (PJI) are similarly limited to adults. A retrospective analysis of 51 adults with culture negative PJI who received vancomycin and imipenem placed directly into the joint space reported favorable cure rates. [210] The results suggest that the use of intra-articular antibiotics may allow for single stage revisions, even for culture negative PJI. However, it is important to note that the pathophysiology of PJI is distinct from ABA in children, based in part on biofilm production on the prosthesis and different bacterial pathogens.

#### *Rationale for Recommendation*

The primary rationale for this recommendation is that, in general, the outcome of ABA in children who are treated appropriately is not documented to be improved with the addition of intraparticularly placed antibiotics. The potential additional risks of therapy and costs preclude a recommendation for routine surgical placement of antibiotics. A strong recommendation against this practice, despite very low certainty evidence, is made due to uncertain benefit with certain harms and costs.

#### *Research Needs*

Better defining and investigating the ABA populations who may benefit from local antibiotic placement would be helpful. Such populations may include those with unusual infectious causes with the potential of inadequate anti-infective drug exposure (e.g., highly resistant gram-negative pathogens, those with fungal or mycobacterial pathogens, those with PJI, and those with sites of inadequate blood flow).

### **VIII. What is the role for adjuvant corticosteroids in children with presumed or confirmed ABA?**

#### **Recommendation:**

In children with presumed or confirmed ABA, we suggest against using adjunctive corticosteroid therapy (conditional recommendation, *very low certainty of evidence*). **Comment:** This recommendation places a high value on avoiding potential serious harms despite providing potential minimal beneficial effects.

#### *Summary of Evidence*

Our systematic review of the literature (2005 through 2022) identified one randomized controlled trial [211] and two non-randomized studies [212, 213] evaluating the efficacy of corticosteroids as an adjunct to standard of care antibiotics in children with ABA (see **Supplementary Material Table VIIIa** ). Furthermore, three meta-analyses [214-216] combined the estimates of the RCT that we found [211] with a previously published RCT (which predated our original year of publication criteria) [217]. Patient-important outcomes judged critical for decision-making included: recurrence of infection or functional sequelae (at 12 months), recurrence of symptoms (within the first week), time to normal joint function, and serious adverse events, while those judged important but not critical for decision-making included: time to defervescence, time to normalization of CRP, duration of antibiotics, and duration of hospitalization.

The best available evidence is an RCT with 49 children with ABA randomized to receiving a four-day course of parenteral dexamethasone (0.15 mg/kg every 6 hours) in addition to antimicrobials (n=24)

or placebo with antimicrobials (n=25) [211]. Patients' characteristics appeared comparable in both groups at baseline. Mean age was 33 months, and joints most frequently involved were the hip (42.9%) and knee (36.7%). The causative agent was isolated in only 35% of patients, *K. kingae* (n=7) and MSSA (n=3) being the most common. Results may not be generalizable given the small percentage of *S. aureus* infections. Invasive procedures consisted of percutaneous aspiration and surgical drainage of the hip. Sample size calculation was based on an expected reduction of 3 days of parenteral treatment. This yielded a very small sample size requirement which may have been the cause of imbalance between treatment groups for important covariates (causative pathogens, joints affected, types of invasive procedures). Additional serious methodological concerns included: loss to follow-up at one year was substantial with only 29 (59%) of 49 patients assessed by investigators at that time point; and missing data for duration of hospitalization despite this being one of the primary endpoints.

The two non-randomized studies provided complementary evidence for outcomes either not reported or incompletely reported in the above RCT, specifically recurrence of symptoms within one week and duration of hospitalization. One evaluated 60 patients, 30 of whom had surgery and received IV antibiotics for three weeks, along with saline placebo, and 30 who received the same care with the addition of methylprednisolone 0.15mg/kg/day for 4 days [213]. It is uncertain if the results of the study are generalizable, as no culture results were reported from the hospitals participating in the study, and no long-term follow-up outcome data were reported. In addition, patients with concomitant sepsis were excluded.

The second observational study retrospectively evaluated 116 children aged 2 months to 18 years with ABA: ninety received antibiotics alone and 26 also received a four-day course of dexamethasone at the discretion of the attending physician, which could contribute to indication bias [212]. Microbiological confirmation was available for only 22% of patients, with *K. kingae* and MSSA being most frequently identified. Patients were comparable at baseline aside from higher incidence of knee involvement in the dexamethasone group. Nineteen of the 90 patients in the control group and 1 of 26 patients in the corticosteroid group received NSAIDs, which potentially confounds the effect of corticosteroids.

The meta-analysis [214] which included the two RCTs [211, 217] also concluded that the addition of dexamethasone may increase the proportion of patients without pain and with normal joint function at 12 months, as well as reduce the number of days of antibiotic treatment, but was not able to draw robust conclusions due to the low certainty in the evidence. Therefore, the evidence suggests a possible minimal but not statistically significant reduction in time to normal joint function, time to defervescence, time to normalization of CRP, and duration of IV antibiotics in the group receiving corticosteroids compared to the group not receiving dexamethasone. Duration of hospitalization may be shorter with the addition of dexamethasone, but this effect was judged to be very uncertain due to unadjusted confounders and small sample sizes of the included studies. The microbiology of the reported patients may also not be generalizable, since *S. aureus*, which is a common cause of more severe infections, comprised a minority of detected pathogens in these reported studies. A higher incidence of symptom recurrence occurred within one week in the group receiving dexamethasone, but the evidence was again considered very uncertain due to serious concerns for risk of bias (as mentioned above) and imprecision (very small sample size) (see **Supplementary**

**Material Table VIIIa** ). No recurrence of infection or functional sequelae at 12 months was reported in either group.

Serious adverse events associated with the use of corticosteroids are critical for decisionmaking. Despite the absence of reported adverse events in the three studies included in our analysis, a systematic review of the literature evaluating the toxicity of short-course oral corticosteroids in children included thirty-eight studies [218] reporting a total of 3,200 children in whom 850 adverse drug reactions (ADRs) were reported. The three most frequent ADRs were vomiting (5.4%), behavioral changes (4.7%), and sleep disturbance (4.3%). Infection was a serious, albeit rare ADR: five RCTs reported a pooled prevalence of infection during treatment periods of 0.9%, but of 3 children infected with varicella zoster, one died and two were admitted to the ICU with severe complications. When measured, 144 of 369 patients showed increased blood pressure; 21 of 75 patients showed weight gain; and biochemical hypothalamic–pituitary–adrenal axis suppression was detected in 43 of 53 patients.

An additional concern of corticosteroid administration is alteration of the temperature curve (i.e., "masking of fever") and/or generation of temporary improvement in local signs of inflammation, giving the impression of clinical improvement while the infection itself continues to progress. Corticosteroids are also problematic if there is diagnostic uncertainty as they may ultimately delay a diagnosis such as leukemia. They may also empirically treat autoimmune conditions such as JIA or rheumatic fever-associated arthritis. Other known common side effects of steroids include delayed wound healing and/or impaired glucose levels.

#### *Rationale for Recommendation*

The standard of care of antimicrobial therapy without corticosteroids has historically achieved excellent outcomes in children with ABA. Given that the data at this time are limited in scope, include low patient numbers, and provided minimal benefits as considered by the Guidelines Panel in the context of the known harms with use of corticosteroids, there is not a role for routine use of these agents as part of the management of ABA in children at this time. The current literature may not be generalizable to the North American patient populations in which *S. aureus* (especially MRSA) represents a frequently identified pathogen.

#### *Research Needs*

Controlled studies of corticosteroids for specific pathogens and joints may allow for more definitive recommendations in the future regarding possible benefit and harm.

### **IX. In children with presumed or confirmed ABA who respond to initial empiric therapy, how should selection of agents be made for definitive parenteral and oral therapy? (See Section XI for discussion of oral versus parenteral therapy.)**

#### **Recommendations:**

1. In children with confirmed ABA, selection of a definitive antimicrobial 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 patient tolerability (*Good Practice Statement*).

2. In children with presumed ABA with no pathogen identified, selection of a definitive antimicrobial regimen should be based on the principles of selecting an effective agent based on the most likely causative organism(s), with an antimicrobial spectrum comparable to that of empiric therapy to which the patient initially responded, with the lowest adverse effect profile and most favorable patient tolerability (*Good Practice Statement*).

### *Summary of Evidence*

#### **Antimicrobial Management in Confirmed ABA**

Clinicians should treat ABA 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 of agent should be based on *in vitro* susceptibility and published clinical trial data, though the latter currently are very limited. 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 (CDC). These potential benefits include reduction of antimicrobial resistance in the individual patient, reduced antimicrobial pressure for the environment, reduced toxicity, and often reduced cost [219- 221]. Preferred and alternative antimicrobial agents for specific pathogens (plus recommended durations of therapy) are listed in [Table 4](#). Recommended dosages for specific agents are listed in [Table 5](#).

For children with ABA caused by MSSA, a beta-lactam agent is preferred for initial parenteral treatment (cefazolin, nafcillin or oxacillin) and for definitive oral treatment (cephalexin). "High dose" cephalexin (100 mg/kg/day in 4 divided doses) was first studied with measurement of synovial fluid concentrations and recommended for pediatric bacterial joint infections caused by MSSA in the late 1970s [3, 222, 223]. No prospective, randomized studies were performed at that time, but over the past 4 decades, no reports of failures for MSSA ABA treated with cephalexin confirm that this dose is adequate for convalescent therapy following initial parenteral therapy and surgical management. Recent computer modeling of cephalexin dosing in children, using a pharmacodynamic driver of 40% T>MIC that is assumed for beta-lactam treatment of acute infections in animal models with retrospective validation in adults, suggests that higher doses may be required [224], for strains with MICs of 2 and 4 mg/L. The MIC<sub>90</sub> for MSSA is 4-8 mg/L [225-227] suggesting that oral therapy should be used only after initial parenteral therapy, surgical debridement, and clinical response to treatment. The bacterial inoculum is generally dramatically reduced at the point of oral switch therapy, and both innate and adaptive immune responses should be significant in assisting the host to clear the infection. Thus, "convalescent" oral therapy is not likely to require 40% T>MIC to be necessary for microbial eradication. The higher doses (120 mg/kg/day divided every 8 hours) required to achieve this pharmacodynamic target in 100%, 90% and 80% of children for MSSA with MICs of 0.25, 2 and 4 mg/L, respectively [224], do not appear to be required for good patient outcomes following oral transition therapy. Using the same high pharmacodynamic target, additional modeling provided support for a proposed cephalexin dosage (administered Q8H) of 45 mg/kg/day

for MSSA with an MIC of 1 mg/L; 75 mg/kg/day for an MIC of 2 mg/L; and 135 mg/kg/day for an MIC of 4 mg/L. Those doses are proposed for children weighing 10-15 kg, with slightly lower doses proposed for older children with higher body weights [228]. These studies, as the authors note, are based on serum concentrations, not on concentrations in synovial fluid at the site of infection.

Clindamycin is an alternative for susceptible MSSA isolates when beta-lactam agents cannot be used. In a prospective, quasi-randomized trial conducted in the treatment of 252 children with osteoarticular infections in Finland [229], 130 (52%) had ABA without osteomyelitis. Those born on odd days received clindamycin, and those born on even days received a cephalosporin for their treatment. Clindamycin was given at 40 mg/kg/day divided into 4 doses and cephalosporins (cephradine, cephalexin, or cefadroxil) were given at 150 mg/kg/day divided into 4 doses, with treatment administered by the oral route after 2-4 days. Outcomes did not differ in terms of reinfection rates or permanent sequelae. The high doses of each antibiotic were surprisingly well tolerated, with loose stools reported in only 1% (95% CI: 0 to 4%) of those treated with clindamycin and 7% (95% CI: 4 to 14%) of those treated with cephalosporins [229]. In another retrospective study of oral clindamycin therapy in 215 children, readmission rates were similar among 190 treated with a dosage of 30 mg/kg/day divided every 8 hours compared with 25 who were treated with a dosage of 40 mg/kg/day, at 2.6% and 4%, respectively ( $p$ -value=0.4) [230].

Clindamycin and ceftaroline, are preferable to vancomycin for parenteral therapy for susceptible MRSA strains, given their better safety profiles in the treatment of MRSA infections in general [186, 231]. Clindamycin has an advantage of ready conversion from parenteral to oral therapy due to its good bioavailability. Ceftaroline, as a beta-lactam antibiotic with FDA approval for pediatric and neonatal age groups for acute bacterial skin and skin structure infections, including those caused by MRSA, can reasonably be considered for treatment over clindamycin, given the safety and efficacy of beta-lactams in general, particularly when there are any concerns for endovascular infection [186]. Both antibiotics have antibacterial coverage beyond MRSA: clindamycin is active against anaerobic bacteria, while ceftaroline has Gram-negative coverage similar to ceftriaxone, a third-generation cephalosporin.

Ceftaroline and vancomycin are the preferred antimicrobial agents for clindamycin-resistant CA-MRSA infections when initial parenteral therapy is required. Other MRSA-active agents such as daptomycin or linezolid may be considered as alternatives for ABA, although few published data exist for treatment outcomes, safety, tolerability, or dosing for ABA of these antimicrobial agents.

Initial guidelines by IDSA for vancomycin dosing in severe CA-MRSA infections recommended target serum trough levels  $> 15$  micrograms/ml [185]. The high doses required to achieve this goal were associated with acute kidney injury and were not associated with improved outcomes in children with osteomyelitis when compared with lower doses [220, 232]. ASHP/IDSA/PIDS/SIDP guidelines on vancomycin dosing in severe CA-MRSA infection recommend achieving an exposure that incorporates both vancomycin exposure over the dosing interval (the "area under the time vs vancomycin serum concentration curve" \*AUC+), and the MIC of the infecting strain of MRSA, to achieve an AUC/MIC of 400 [185, 233]. Linking vancomycin exposure (AUC) as a function of the mg/kg dose, to the MIC allows the recommended dose to increase as the MIC increases. If the MIC is 2 mcg/mL of greater, the required vancomycin dose to achieve an AUC/MIC exposure of 400 will

often lead to renal toxicity. However, at MICs of 1.0 mg/L or lower, an AUC/MIC > 400 is often achieved with a trough significantly less than 15 micrograms/mL.

For oral therapy of CA-MRSA ABA, as with parenteral therapy, clindamycin is the preferred agent for susceptible MRSA strains. Limited data exist for linezolid [234] and TMP/SMX, as well as for doxycycline or minocycline.

*K. kingae* is generally susceptible to penicillins (with the notable exception of antistaphylococcal penicillins) and cephalosporins, as well as fluoroquinolones, and TMP/SMX. *K. kingae* strains are resistant to vancomycin and often resistant to clindamycin and linezolid [32, 190].

For penicillin-susceptible *S. pneumoniae* isolates and *S. pyogenes*, penicillin or ampicillin are the preferred parenteral beta-lactam agents, with phenoxyethyl penicillin or amoxicillin for oral therapy. For pneumococcal isolates that are reported as penicillin-non-susceptible, high dose parenteral penicillin has been used for pneumococcal pneumonia with penicillin MICs as high as 8.0 mg/L, though data for penicillin treatment of ABA due to pneumococci with high MICs are not available. For oral treatment, in general, pneumococci with a penicillin or ampicillin MIC < 2 mg/L are considered susceptible for the treatment of ABA, using high dosage penicillin or amoxicillin for the more resistant strains. Cefotaxime/ceftriaxone should be effective if the pneumococcal isolate is reported as susceptible by the laboratory (MIC < 1 mcg/ml for infections other than meningitis) but is much broader spectrum than penicillin or amoxicillin. Although no prospective data on ABA treatment exist to support recommendations, *in vitro* testing may reveal additional options for both parenteral and oral therapy, including clindamycin, linezolid, ceftaroline, levofloxacin, or daptomycin. Of concern, five of 24 pneumococcal isolates (21%) from children with osteoarticular infections from 2010 through 2015 in a single center study were resistant to clindamycin [187].

*Hib* is now a rare etiology of ABA in countries where *Hib* conjugate vaccines are in routine use, but invasive disease continues with both unencapsulated strains as well as encapsulated strains of *Haemophilus influenzae*, particularly serogroup a, but also serogroups f and e. Beta-lactamase positivity (e.g. ampicillin-resistance) varies, but appears to be similar to serogroup b [235-237]. Parenteral ampicillin may be used for beta-lactamase negative strains. Parenteral second (cefuroxime) or third generation cephalosporins (cefotaxime/ceftriaxone/ceftazidime) may be used as alternatives or for beta-lactamase producing isolates. For oral convalescent therapy for betalactamase negative strains, amoxicillin should be used. Oral second (cefuroxime) and third generation cephalosporins (cefdinir, cefpodoxime, ceftibuten) or beta-lactam/beta-lactamase inhibitor combinations (e.g., amoxicillin-clavulanate) should provide effective therapy, although they have not been prospectively studied for pediatric ABA [235-237].

*N. meningitidis* may cause ABA alone or as part of a systemic invasive infection (e.g., sepsis, meningitis) [238-240]. Reactive arthritis also can be associated with invasive meningococcal disease [239]. Because the great majority of strains in North America have been susceptible to penicillins and third generation cephalosporins, both have routinely been used for parenteral therapy for suspected or proven meningococcal ABA. However, emerging resistance to penicillin (and other agents) in the U.S. reported recently by the CDC has supported a recommendation by some experts for the use of third generation cephalosporins as empiric therapy for suspected meningococcal ABA

until susceptibility results are available [241]. Although oral agents are commonly prescribed for convalescent therapy of meningococcal ABA, there are no prospective data regarding their use, compared with a complete course with parenteral therapy. When ceftriaxone is not used for treatment, an appropriate prophylaxis regimen to eradicate nasopharyngeal carriage should be provided to the patient.

*N. gonorrhoeae* is not an uncommon pathogen among adolescents with ABA [242]. Parenteral therapy with a third-generation cephalosporin, typically ceftriaxone, should be started. Oral therapy generally should be considered only after antibiotic susceptibility data are available. Due to increasing resistance to azithromycin, combination therapy of azithromycin with ceftriaxone is no longer routinely recommended [243]. Oral options may include high dose oral cefixime or a fluoroquinolone if susceptibility has been documented [244]. Although the routine use of fluoroquinolones is not usually recommended for treatment of infections in children < 18 years old because of concerns for potential toxicity, use in this circumstance is appropriate. When gonococcal infection is documented, evaluation for other sexually transmitted infections, including HIV and syphilis, is warranted [243, 244].

*Salmonella spp* are seen most commonly in children with splenic dysfunction usually associated with a hemoglobinopathy, but may also be documented in immunocompetent children, often associated with osteomyelitis [245-247]. Treatment duration among a series of 12 children with *Salmonella* musculoskeletal infections with successful outcomes did not differ from a comparator group of children with MSSA infections [247]. Limited data exist on treatment duration for ABA caused by *Salmonella spp*. Courses longer than 10 to 14 days may be required, depending on the clinical and laboratory response of an individual child, with treatment up to 4 to 6 weeks, particularly in those with associated osteomyelitis.

*Brucella spp* can cause ABA following exposures to unpasteurized dairy products or other fluids or tissues from infected animals. When brucellosis is confirmed by culture or serologic testing in a child with ABA, the treatment regimens recommended for *Brucella* infections in general apply, usually doxycycline with rifampin for children older than 7 years, and TMP/SMX with rifampin for children ≤ 7 years (see Tables 4 and 5), although the safety of doxycycline in children ≤ 7 years is currently being reassessed. Six-to-12-week minimum courses are recommended, often with the addition of gentamicin for the first 1-2 weeks of therapy [248].

Lyme arthritis is the most common form of bacterial arthritis in some endemic geographic regions. This should be treated according to the IDSA Guideline for Prevention and Treatment of Lyme Disease [111].

### **Antimicrobial Management in Presumed ABA With No Pathogen Identified**

In the absence of a positive culture, there is no "gold standard" for the treatment of pediatric ABA. As noted in Question III, a microbial etiology for a substantial portion of children with clinical presentations consistent with ABA will not be identified by culture or PCR tests. Furthermore, situations in which cultures were not obtained in a clinical scenario compatible with ABA are also considered to be presumed ABA for the purposes of this discussion. Clinical findings and apparent response to antimicrobial therapy, plus supporting laboratory test results are relied on to make the

determination to continue antimicrobial therapy for presumed ABA in children with negative culture and molecular microbiological testing.

Children with presumed ABA tend to have less systemic inflammation, shorter duration of fever, a shorter hospital LOS than those with confirmed pyogenic pathogens such as *S. aureus*, though overlap in findings is substantial [24, 29, 65, 179]. Of note, children with documented *K. kingae* arthritis tend to have clinical and laboratory findings more similar to those children with presumed ABA with no pathogen identified than those with other confirmed pathogens [29].

Reasons for negative results of cultures (and any molecular test results, if performed) in children with clinical findings typical of ABA include:

- Presence of fastidious, difficult to isolate organisms such as *K. kingae*, *N. gonorrhoeae* or *N. meningitidis*
- Receipt of antibiotics prior to joint aspiration
- Inhibition of bacterial growth by antimicrobial factors in purulent joint fluid
- Microbial density below the level of detection for culture or PCR testing
- Non-infectious causes of arthritis: sterile inflammation from a reactive process mimicking ABA such as transient nonbacterial synovitis or reactive arthritis (including poststreptococcal reactive arthritis, or other post-infectious or rheumatologic/autoimmune disease [141])

An unknown portion of children with presumed ABA have bacterial etiologies. In a case series that included 89 such children with joint inflammation without associated osteomyelitis, 8 (9%) did not improve clinically while receiving antimicrobial therapy, prompting care providers to change antimicrobials. None had long-term disability evident on evaluation six months after completion of therapy [24]. Negative results of PCR testing do not exclude the presence of bacterial infection. A small proportion of culture negative cases will be caused by uncommon bacterial pathogens such as *Borrelia* or by mycobacteria or fungal pathogens (i.e., *Histoplasma*, *Blastomyces* and *Coccidioides*).

In children with suspected ABA and negative results of cultures after 48-72 hours of incubation (and negative results of any molecular microbial tests obtained), reconsideration of the diagnosis with re-evaluation for historical and physical examination findings that may support alternative etiologies is warranted. However, in the absence of alternative diagnoses, it is common practice to continue antimicrobial agents targeting the most common bacterial etiologies based on the child's risk factors (e.g., age, geographic location, travel history, current local outbreaks of specific pathogens, comorbid conditions). The potential benefits of completing a treatment course (i.e., prevention of long-term sequelae or relapse) may outweigh the risks of unnecessary antibiotic therapy. For those children who are improving while receiving initial empiric parenteral therapy (see Question V), treatment may be continued on that regimen until ready for hospital discharge and then switched to appropriate oral agents (See also Question XI).

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

Treatment regimens for ABA are generally shorter than those used for osteomyelitis, such that adverse events due to antimicrobial therapy may be less frequent with ABA than osteomyelitis.

Antimicrobial agents used during hospitalization that have the potential for renal toxicity (e.g., vancomycin and gentamicin) require laboratory monitoring of serum creatinine and serum antibiotic concentrations [185].

Beta-lactam agents may suppress the bone marrow at high doses given over a prolonged period; weekly or biweekly (every 2 weeks) assessments of marrow function (e.g., a complete blood count with differential) have not been studied prospectively, but may be helpful, particularly for courses of therapy of more than three weeks. The possible benefit of such monitoring can be weighed against the burdens of pain, travel and cost for the child and family.

Many antibiotics are associated with diarrhea. Probiotics may have a modest protective effect [249]. Clindamycin is notably associated with *Clostridioides difficile*-associated colitis in adults, requiring education of care providers regarding symptoms of colitis and the need to notify healthcare practitioners if such symptoms develop. Prospective data on the risk of *C. difficile* colitis in otherwise healthy children receiving clindamycin therapy for 2 to 3 weeks for ABA do not exist, but the risk is likely lower than that documented in adults [250]. Colonization with *C. difficile* in children under the age of 2 years is common and its detection in young children with diarrhea does not necessarily indicate causation [251].

In prospective, pediatric, pre-licensure evaluations of linezolid, hematologic abnormalities occurred but were no more frequent in those treated with linezolid compared with those receiving other antibiotics [252]. 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 [253]; courses of such duration will be uncommon for children with primary ABA. Linezolid is a reversible, nonselective inhibitor of monoamine oxidase and should be used with caution in patients who are on an SSRI medication.

Fluoroquinolones are prescribed in adults for parenteral or oral therapy of osteoarticular infections caused by enteric bacilli (including *E. coli*, *Klebsiella spp*, *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, TMP/SMX) are preferred if appropriate for the clinical scenario. However, for convalescent therapy, oral therapy with a fluoroquinolone is preferred over parenteral therapy with a non-fluoroquinolone agent (e.g., oral ciprofloxacin rather than intravenous ceftazidime for a *Pseudomonas* infection) [254]. For children receiving therapy with fluoroquinolones for ABA, attention is required for the development of arthritis/arthritis, 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 [254].

TMP/SMX may cause drug-related rashes, including Stevens-Johnson syndrome, and drug rash with eosinophilia and systemic symptoms (DRESS), as well as leukopenia and thrombocytopenia [255].

#### *Rationale for Recommendation*

Treatment of children with presumed or documented ABA 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.

### Research Needs

Studies of currently available parenteral and oral agents, particularly those with activity against CA-MRSA (e.g., ceftaroline, linezolid, TMP/SMX) are needed to evaluate safety and efficacy for ABA, including real-world comparative effectiveness studies. Studies that focus on children with primary ABA, distinct from those with ABA with adjacent osteomyelitis, would be helpful. Prospectively collected data on the adverse drug events associated with the oral agents and treatment courses used for confirmed or presumed ABA would also be useful.

## **X. In children with presumed or confirmed ABA, what clinical and laboratory criteria should be used to assess the response to therapy?**

### **Recommendation:**

In children with presumed or confirmed ABA receiving antimicrobial therapy with or without surgical intervention, in addition to serial clinical evaluation, we suggest performing CRP at initial evaluation followed by sequential monitoring of CRP to assess response to therapy, rather than relying solely on clinical evaluation (conditional recommendation, *low certainty of evidence*). **Comment:** Serial clinical examinations that assess the febrile response, pain and musculoskeletal function remain the primary means of monitoring response to treatment.

### *Summary of Evidence*

Gradual clinical improvement (resolution of fever over 2 to 4 days, reduction in joint pain, swelling, and other inflammatory signs, and increased mobility/range of motion of the affected joint) generally is expected as a response to administration of effective antimicrobial therapy with or without drainage of the affected joint [256]. The clinical course may be influenced by the initial severity of illness, adjacent osteomyelitis, the bacterial pathogen, and extent of required surgical intervention(s). Fever may be prolonged in children with ABA who have disseminated infection rather than joint infection alone [257]. ABA caused by some strains of *S. aureus* (e.g., USA 300/CAMRSA) have been associated with more prolonged febrile courses than ABA caused by non-USA 300 MSSA strains [92]. However, one study did not find a difference in febrile course between children with ABA caused by CA-MRSA versus MSSA, though CA-MRSA ABA required more surgical interventions [258].

ABA is usually accompanied by a rapid rise in serum CRP concentration, typically with a peak on day 2-3 of treatment in uncomplicated infection [73, 259]. With appropriate therapy, this is followed by a progressive decline, and the CRP typically returns to the normal range in about 9 to 12 days [73, 141, 260]. In general, the fall in CRP parallels the resolution of fever and clinical improvement in local signs of inflammation and return to normal function of the patient [141, 259, 261-263]. However,

situations may arise where persistent elevation of CRP alone may signal persistent disease that warrants additional investigation and intervention. If serial CRPs fail to trend downward or resume an upward trend, particularly if patients have a recurrence of fever, pain or local symptoms, children should be carefully evaluated for persistent ABA or adjacent osteomyelitis and may require advanced imaging such as MRI [158]. Successful transition to oral therapy after good clinical response plus CRP decline by 50% or more has been described [178, 264].

There are no clear data as to how frequently inflammatory markers should be measured during treatment or how specific values should affect treatment. The consensus of the Guideline Panel is that CRP may be evaluated every 2 or 3 days until the concentration begins to drop consistently. A declining CRP concentration can be used to provide information supplementary to the clinical course (i.e., fever curve and physical examination) for determining when a child with confirmed or suspected ABA may be transitioned to oral antimicrobial therapy and/or discharged home.

Once the CRP concentration has decreased substantially in the context of ongoing clinical improvement, further measurement is not necessary. In one case series, CRP levels decreased consistently during antibiotic therapy and the authors concluded that patients in whom CRP values return to normal earlier have better clinical and radiological outcomes than those who do not [265]. Failure of the CRP to fall markedly during the first days of inpatient therapy could be due to 1) an unaddressed focus of infection; 2) inadequate antimicrobial regimen (e.g., inadequate dosing, nonadherence to the antibiotic regimen, or antimicrobial resistance to empiric therapy) or 3) a noninfectious arthritis (e.g., autoimmune/inflammatory arthritis or malignancy). (See Question XIV) With recurrence of clinical signs or symptoms, or a plateauing or rise in CRP, either failure to address a persisting focus, or an unrelated, intercurrent viral or bacterial illness may be present; for failure to respond after transition to oral outpatient therapy, also consider non-adherence to the antibiotic regimen.

The role of other inflammatory markers, such as serum PCT, in the assessment of response to therapy or as a guide to duration of therapy for ABA in children has not been established.

The ESR has limited utility as an adjunctive factor in medical decision-making for treatment of ABA. In contrast to the CRP, the ESR rises and declines more gradually and may continue to rise during the acute phase of treatment, even with appropriate therapy [259]. In a study from Finland of children primarily infected by MSSA, the ESR took a mean of 18 days to normalize [73]. Some physicians continue to follow the ESR until normalization as a marker of resolved inflammation in the joint, suggesting a good long-term outcome for the child [266].

Normalization or substantial decline in blood WBC count (and proportion of neutrophils) over the first few days of therapy is consistent with response to therapy but has not been prospectively evaluated adequately as a biomarker of recovery. Inflammation that may elevate the blood WBC during the hospital treatment course, may not be caused by active infection (e.g., surgical trauma, necrotic tissue) in children with ABA.

Imaging studies generally are not needed to confirm response to therapy but may be indicated when clinical findings and laboratory studies are not demonstrating the expected resolution or normalization [158].

## *Rationale for Recommendation*

Physical examination provides essential information for clinical decision making. Measurement of serum CRP concentration is widely available in a timely manner, is relatively inexpensive, and can be an objective data point that supports clinical decision making. Pain, discomfort, and additional costs can occur from venipuncture.

The relatively rapid normalization of CRP has been interpreted as providing useful clinical guidance for early switch to oral therapy, discharge from the hospital, 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 ABA, no specific thresholds of CRP concentration have been well validated for specific pathogens or the various infected joints, with respect to the need to perform specific clinical/surgical interventions or, for the purposes of making decisions on duration of therapy.

As the infection is appropriately treated, 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, may prompt changes in management, including: 1) additional imaging to better define the extent of the infection and its complications; or 2) surgical intervention(s) that may optimize short- and long-term outcomes; and 3) reconsideration of the etiology of arthritis (e.g., infection vs autoimmune disorder).

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 without regard to the clinical context of recovery could lead to unnecessary actions and procedures and their associated risks. Such discordance can be caused by intercurrent infection or other issues unrelated to ABA.

Within the limitations outlined above, the Guideline Panel suggests sequential monitoring of CRP as an adjunctive measure in children with ABA 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 ABA in children. Measurement every 2 to 3 days during the early therapeutic course, rather than daily, followed by weekly or other periodic measurement until a clear trend towards normalization is evident, is an acceptable approach [37].

## *Research Needs*

More detailed analyses of the clinical utility of serial serum CRP concentrations and other biomarkers of systemic inflammation, by pathogen and by joint involved would be useful. Identification of specific CRP or other biomarker cutoff values would be helpful for specific pathogens and for specific clinical situations, such as the need for additional surgery versus ongoing observation. It is likely that multicenter studies using iterative protocols will be required to gain insight into some of these questions [37].

## XI. Should hospitalized children with presumed or confirmed ABA who are responding well to initial intravenous therapy, no longer requiring skilled nursing care and deemed ready for hospital discharge be transitioned to a) oral therapy or b) outpatient parenteral antibiotic therapy (OPAT)?

### Recommendations:

1. For children with presumed or confirmed ABA who respond to initial intravenous antibiotic therapy, we recommend transition to an oral antibiotic regimen rather than OPAT when an appropriate, well-tolerated oral antibiotic option is available, and that antibiotic is active against the confirmed or presumed pathogen(s) (*strong recommendation; low certainty of evidence*).  
**Comment:** This recommendation places a high value on avoidance of harms and costs, as well as on considerations of patient's values and preferences, feasibility, acceptability, and equity.
2. For children with presumed or confirmed ABA who respond to initial parenteral antibiotic therapy but for whom oral antimicrobial therapy is not feasible, we suggest transition from the acute-care hospital to OPAT, rather than remaining in the hospital for the total duration of therapy (*conditional recommendation, 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, clinic) may be influenced by availability of local resources.

### Background

ABA in children was once thought to require antimicrobial therapy for 21 to 28 days with at least 14 to 21 days via the intravenous route [267, 268]. Variations in approach have occurred since the mid-1970s when publications began to appear describing use of oral regimens after shorter durations of initial IV therapy [3, 269-271]. Since the 1980s, practice in many centers has steadily evolved towards routine use of oral antimicrobial switch therapy and shorter overall courses [12, 272-274].

### Summary of Evidence

No prospective, randomized clinical trials of early transition to oral therapy versus later transition or full IV courses have been performed in children with ABA. Our systematic review of the literature 2005 through 2022 identified a single retrospective study on this question among children with ABA hospitalized 1985 through 1995 [180] performed at two large, tertiary care children's hospitals with known local variation in practice between the hospitals (see Table 6). Data from 83 patients undergoing early transition (median of 7.4 days) were compared to 103 patients transitioned later (median of 18.6 days). Patients' characteristics were similar at baseline, except for mean ESRs being significantly higher in the early vs. the late transition group (54.0 +/- 28.4 vs 45.4 +/- 30.1, p-value < 0.05), suggesting the early transition group may have included children with more extensive or prolonged infection. Resolution of clinical symptoms was significantly more rapid in the early vs. the late transition group (mean days until asymptomatic + S.D. (range) 11.8 +/- 8.4 (1-55) vs. 16.0 +/- 15.3 (1-73), respectively, p-value <0.05). It is possible this observation of 4.2 days faster resolution (95%CI: 0.5 to 7.9 days) may have reflected variations in surgical management strategy between the 2 hospitals rather than simply the early versus late oral transition. Open drainage was more frequent in

the early transition group than the late transition group (83% vs 68% respectively; p-value=0.03); in contrast both initial joint aspiration and multiple joint aspirations were more frequent in the late transition group (32% vs 17% and 17% vs 0%, respectively). Still, outcomes were not worse in the early transition group. The certainty of evidence was rated as very low due to the risk of bias (mainly due to analyses being unadjusted, and to differences in management strategy with possible confounding-by-indication) and due to imprecision being rated as serious (few events and small sample size) (see Table 6).

A prospective, randomized clinical trial conducted in Finland (1983 to 2005) evaluated shorter total courses (10 to 15 days) of antimicrobial therapy versus longer (30 days) after transition to oral therapy following 2 to 4 days of parenteral therapy. There were no relapses or long-term sequelae among 130 children followed for 12 months [55]. One child in the longer course group had a recurrence 17 months after initial infection. The hip was the most commonly infected joint (n=48, 37%) followed by the knee (n= 32, 25%) and ankle (n=30, 23%). MSSA was isolated from joints or blood in 76 (58%), H. *Influenzae* type b in 23 (18%), S. *pyogenes* in 16 (12%) and S. *pneumoniae* in 11 (8.5%). The primary focus of this study was total duration of therapy. Serum CRP concentrations were monitored serially (normal value considered < 20 mg/L). Based on the provided data, most of the 130 children had CRP values above 90 to 100 mg/L on days 3 or 4 after initiation of therapy (approximately the time of oral switch), actually higher than the values on presentation. CRP values were then observed to fall from their peak at 3 to 5 days. Almost all had CRP values fall below 20 mg/L by 10 to 14 days. Of note, two-weeks after initiation of treatment, 31 (24%) of the children had varying degrees of joint swelling, restricting mobility, and persisting pain. Three (2%) had minor residual joint symptoms at 3 months and none at 12 months [55]. A subsequent analysis did not find any difference in outcomes with this early oral transition approach between children with osteoarticular infections with and without bacteremia [275]. None of the children had infection due to MRSA strains. Therefore, it is unclear if these data are generalizable to infections caused by the virulent USA 300 pulsotypes that frequently characterize MRSA strains in the USA and are occasionally found in MSSA strains.

A retrospective study in France from 2009 to 2014 followed 95 children with confirmed or suspected ABA for at least 2 years [276]. Intravenous therapy was given for a median of 4.5 days (IQR: 4 to 7), with median total duration of 15 days (IQR: 15 to 17) and in 10 (11%) for >21 days. None had long term sequelae. Etiology was confirmed in 40 (42%), with K. *kingae* in 18, S. *aureus* in 11 and S. *pyogenes* in 5. Criteria for transition to oral therapy were receipt of 48 hours of IV therapy, 24 hours without fever, improvement of clinical findings, and significant decrease in inflammatory markers, which included CRP <20 mg/L.

A prospective, two-center study of acute pediatric bone and joint infections (N= 70, of which 33 had ABA) conducted in Australia from 2001 to 2007 evaluated criteria for transition to oral therapy as early as 3 days into IV therapy [56]. Transition criteria were clinical improvement (improved pain, range of movement, and weight-bearing status), normalization of temperature and stabilizing CRP. S. *aureus* was isolated in 27% of those with ABA and streptococcal spp in 50%. Oral transition occurred in <4 days for 18 (54%) and <6 days for 27 (82%). Among the full group of 70 children with osteoarticular infection, CRP >100 mg/L best predicted the use of IV antibiotics for > 5 days (p-value=0.03). There were no sequelae at 1 year of follow-up.

A group of US investigators retrospectively reported on using clinical improvement plus CRP values having fallen to 20 to 30 mg/L (normal ≤ 9 mg/L) as criteria for transition to oral therapy in 194 pediatric osteoarticular infections (32 had ABA alone and 49 had osteomyelitis + ABA) from 2000 to 2007 [178]. Among those with ABA alone, MSSA was documented as the etiology for 17 (53%) and *K. kingae* in 6 (19%), and none had MRSA. There were no microbiological failures or long-term sequelae among the children with ABA alone.

A group from Singapore reported retrospective data on 37 overall osteoarticular infections (11 with ABA alone) between 2007 and 2013 and used a 50% decline in CRP values plus clinical improvement to transition to oral therapy [264]. *S aureus* (not further identified as methicillin-susceptible or -resistant) was isolated in 59% of these children. Within 4 days of treatment, 34 (92%) had at least a 50% decline in CRP. One of these had subsequent complications but none required switching back to IV therapy. No long-term complications were reported among the 11 with ABA alone.

Three retrospective studies provide additional experience with oral therapy for ABA. Among 94 children with ABA alone and 61 with ABA and osteomyelitis who were transitioned to oral therapy after ≤7 days of IV therapy between 2009 and 2015 in Nashville, TN, no treatment failures were associated with oral therapy [67]. In a study of 47 children with ABA in Australia from 1998 to 2002, oral switch was based on unspecified clinical improvement [59]. Median hospital LOS was 9.6 days (range 3 to 26 days). No other clinical or outcome data relevant to oral therapy were provided. Among 42 children in Chile in 2003 and 2004, oral transition was provided for 35 (83%) after 7 days of IV therapy [277]. The other 7 (17%) had longer IV courses. None had complications on short term follow-up.

Indirect evidence from children with osteomyelitis also supports the effectiveness of early transition to oral therapy for ABA without associated osteomyelitis. The pooled results of four retrospective cohort studies comparing outcomes in children with osteomyelitis who were transitioned to oral therapy ( $n = 1,989$ ) compared with those discharged home on OPAT ( $n = 2,237$ ) found comparable rates of treatment failure among the two groups: 4.6% oral vs 6.2% OPAT (RR 0.79, 95% CI: 0.60 to 1.02; RD -1.3%, 95% CI: -2.5 to 0.1) [37, 220, 278-280]. Treatment failure definitions included need for surgical or other interventions during oral or outpatient treatment for ongoing aspects of acute or chronic osteomyelitis.

No studies have specifically compared the frequency of adverse events between children with ABA treated with prolonged courses of IV therapy versus early transition to oral therapy. Relevant indirect evidence is available from three retrospective cohort studies of children with osteomyelitis [278-280]. Two large studies with 4,049 subjects combined documented unscheduled medical visits and re-hospitalization in 6.5% of children ( $n = 1,953$ ) transitioned to oral therapy compared with 16.2% of those on OPAT ( $n = 2,076$ ) with RR of 0.43 (95% CI: 0.23 to 0.79) [279, 280].

Adverse drug reactions also were less common in children transitioned to oral therapy versus OPAT: 1.3% versus 2.6% (RR: 0.49; 95% CI: 0.27 to 0.88) [279, 280]. Catheter-related complications occurred in 9.7% of children on OPAT in three studies that reported these data for 2,161 children combined [278-280].

Parenteral therapy may occasionally be deemed clinically necessary for the full course for a child with ABA. Our systematic review of the literature 2005 through 2022 did not identify any comparative studies regarding the benefits and harms of continuation of parenteral antibiotics as an inpatient versus outpatient parenteral antibiotic therapy (OPAT) in the specific setting for children treated for ABA. A 2018 systematic review [281] of this question for a number of other pediatric infections included one randomized controlled trial (RCT) and 18 observational studies. Despite the lack of a pooled analysis in the 2018 systematic review, no differences were noted in treatment failure rates, readmission rates or adverse event rates for the great majority of the included studies. Children treated at home received longer total courses of treatment in half of the studies compared with those treated in the hospital. Costs associated with home-based OPAT were substantially lower in most studies, and OPAT was deemed satisfactory by patients and their families.

### **Transition to Oral Therapy for Presumed ABA**

Our systematic review of the literature identified only one study that focused on ABA with no identified pathogen in 89 children [24]. Eight (9%) had a change of antimicrobial therapy during the early hospital course due to lack of clinical improvement. This included 6 (11%) of 54 children who were less than age 5 years. Sixty of the 89 (67%) were discharged on oral therapy, most commonly (85%) a single agent active against MRSA, with only 18% (10 of 55) of younger children receiving a regimen including an agent active against *K. kingae*. None of these children had evidence of disability on follow-up at 6 months, and none had late evidence of osteomyelitis. Median hospital LOS was 4 days (IQR: 4 to 6) and total duration of antimicrobial therapy was 24 days (IQR: 22 to 26). Of the 29 discharged on OPAT, five (17%) had a complication requiring re-evaluation or readmission.

A recent study of pathogen-positive cases by age supports decisions on selecting antibiotic therapy in presumed ABA and confirms the need for coverage for *S. aureus* throughout childhood and adolescence when treating ABA [66]. *K. kingae* occurs predominantly but not exclusively in children < 4 years old. *S. pneumoniae* most often infects children <10 years old. *S. pyogenes* most often infects children between 4 and 10 years old but can occur in all age groups.

### *Rationale for Recommendation*

Most children with ABA show relatively rapid clinical improvement during appropriate initial inpatient antimicrobial IV therapy plus any necessary surgical intervention of the infected joint. Our systematic review demonstrated reasonable evidence that children transitioned to oral therapy after such responses have excellent outcomes comparable to those treated with longer parenteral antimicrobial courses. Indirect data from studies of children with AHO also document comparable microbiological and clinical outcomes with early transition to oral therapy and fewer adverse effects related to the antimicrobial regimen. Patient-important outcomes favor oral antibiotics over OPAT, especially considering rates of catheter-related complications with their resulting need for unscheduled revisits and rehospitalizations.

For situations in which two alternatives appear equivalent regarding treatment failures, that transitioning to oral therapy clearly results in fewer harms, and that acceptability of oral transition is higher for patients and their families, the Guideline Panel consensus is to make a strong

recommendation despite somewhat low certainty of evidence. This transition to oral therapy is preferred even when the microbial etiology is not confirmed by laboratory testing.

Assessment of clinical improvement is the most important component of decision-making as to when to transition to oral therapy. Clinical improvement is indicated by the following:

- Substantial improvement in fever if present (a clear downward trend in peak and frequency of fever spikes) over the first days of observation in hospital
- Substantial improvement in local inflammatory signs, with partial if not complete return of movement or function of the affected joint(s)
- Improvement of clinical signs and symptoms of sepsis (hypotension, tachycardia, poor perfusion, irritability in infants) if initially present

Improvement in systemic inflammation as assessed by the serum CRP may be used as an adjunct in decision-making. Definitive thresholds for the CRP in guiding the timing of transition to oral therapy for children with ABA have not been established. Many studies combine results of patients with ABA with those who have osteomyelitis. We suggest that substantial clinical improvement coupled with some degree of decline in CRP are appropriate criteria for transition to oral therapy for children with ABA.

Additional factors for oral transition beyond selecting therapy based on antimicrobial spectrum include 1) availability of an oral agent with good oral bioavailability, palatability, and tolerability; and 2) assessment of the ability of the caregivers to comply with the treatment plan and follow up visits. Demonstration of the child's ability to take the selected oral agent prior to hospital discharge is useful when feasible. Close outpatient follow-up is important to confirm adherence to and tolerance of the prescribed oral antibiotic regimen.

Specific oral agents are reviewed in Questions V and IX. Clinical follow-up and laboratory testing after transition to oral therapy and discharge to home are discussed in Question X. Total duration of antimicrobial therapy is addressed in Question XII.

If oral antimicrobial therapy is not feasible, transitioning from an acute care hospital to OPAT rather than the child remaining in the hospital to complete the needed course of therapy may reduce harms and costs associated with unnecessary and prolonged hospital stay.

Based on limited data and the broad experience of many panel members, the Guideline Panel consensus is that most children with presumed ABA, with no pathogen identified, and no alternative plausible etiology for arthritis, may successfully be transitioned to oral therapy using the same criteria as for those with a pathogen identified, choosing an oral regimen with equivalent coverage to the intravenous regimen that led to improvement.

## Research Needs

The consensus of the Guideline Panel is that the available pool of clinical data from comparative effectiveness and observational studies, inclusive of short term and long-term effectiveness and adverse events, is substantial and supports routine transition to oral regimens for completion of therapy for both osteomyelitis and ABA. Therefore, randomized controlled trials (RCTs) comparing a

full treatment course with parenteral therapy, compared with early switch to oral therapy, would not appear to meet current ethical standards concerning clinical equipoise (assumption that there is not one “better” intervention), or not exceeding minimal risk within a randomized group (longer IV therapy is likely to have a higher risk of adverse effects without added benefit), or justice (use of fair and equal medical treatment). However, data are needed to better understand whether and/or what precise quantitative change in cytokine/chemokine profiles, or various types of biomarker panels, could be useful as a reliable indicator for optimal timing of transition to oral therapy. Comparative studies for oral switch can be conducted, particularly with newer oral antimicrobial agents. Such studies would be most helpful if data are stratified by specific joints and by specific pathogens, addressing both short term and long-term outcomes. Multicenter collaboration with pre-specified management protocols and data collection would likely be necessary. Studies that address scenarios for which oral therapy may be appropriate for the full course of treatment also are needed.

## **XII. For children with presumed or confirmed ABA, what duration of therapy with antimicrobial agents is recommended?**

### **Recommendations:**

1. In children with confirmed primary ABA without adjacent osteomyelitis with rapid clinical improvement and consistent, progressive decrease in CRP by the end of the first week of treatment, we suggest treating for a total duration of antimicrobial therapy (parenteral plus oral) as short as 10 to 14 days for common pathogens (*S. aureus*, *S. pyogenes*, *S. pneumoniae*, and *H. influenzae* type b), rather than for longer courses of 21 to 28 days (conditional recommendation, *low certainty of evidence*). **Comment:** For children with slower clinical response, inadequate source control, or persistently elevated CRP, courses of therapy of 21 to 28 days may be preferred. Such longer durations may be more commonly required when infection is caused by pathogens with relatively less antibiotic susceptibility or greater virulence, particularly enteric or non-fermenting Gram-negative bacilli and some *S. aureus* strains (e.g., USA300 or similarly virulent strains, whether MSSA or MRSA). Children with ABA with adjacent osteomyelitis should be treated according to the osteomyelitis guideline [37].
2. In children with presumed primary ABA without adjacent osteomyelitis with rapid clinical improvement and consistent, progressive decrease in CRP by the end of the first week of treatment, we suggest treating for a total duration of antimicrobial therapy (parenteral plus oral) as short as 10 to 14 days rather than for longer courses (conditional recommendation, *very low certainty of evidence*). **Comment:** For children with slower clinical and laboratory responses, longer courses of therapy may be preferred, as noted above.

### *Summary of Evidence*

These treatment recommendations apply to children with ABA (presumed or confirmed) who do not have adjacent osteomyelitis. When osteomyelitis is present, treatment recommendations for it, which include longer treatment duration, supersede these recommendations [37].

Traditional durations of antibiotic therapy for ABA without adjacent osteomyelitis in children were at least 3 weeks for *S. aureus*, and 14 to 21 days for other common pathogens. Our literature review

revealed one prospective multicenter randomized controlled trial conducted in Finland 1983 through 2005 which compared the efficacy of short (10 to 15 days) versus long (30 days) course antimicrobial treatment of culture-positive ABA in children without evidence of osteomyelitis (see **Table 7** ). Both arms of this study included two to four days of parenteral antibiotics followed by high dose oral antibiotics for the rest of the assigned duration of treatment. Antibiotics were stopped in the short-term group when there was evidence of clinical recovery and the CRP had declined to < 20 mg/L (< 20 mg/L was considered normal). The outcomes of interest were full clinical recovery (having no signs or symptoms of ABA at the end of the follow up period, with no re-administration of antimicrobial therapy for an osteoarticular indication since treatment completion) and the absence of disease or sequelae after discontinuation of antibiotic treatment during follow up ranging from 2 weeks to 12 months [55]. A total of 200 children aged 3 months to 15 years old presenting with presumed ABA were randomized, and outcomes for 130 were analyzed (47 were excluded due to the lack of isolated organism and 23 due to adjacent osteomyelitis); 63 were assigned to the shortterm treatment group (median 10 days total, IQR 10-15 days) and 67 to the long-term treatment group (all treated 30 days total). Children in both groups received IV antimicrobial therapy for a mean of 3 days prior to switching to oral therapy. Baseline characteristics appeared comparable between the groups with overall median age being 6.2 years old. The joints most frequently affected were the hip (36.9%), knee (24.6%) and ankle (23.1%); the main causative agents were MSSA (58.5%; none were MRSA), *Hib* (17.7%), *S. pyogenes* (12.3%) and *S. pneumoniae* (8.5%). Invasive procedures consisted of percutaneous aspiration in most children (n=110), and needle lavage (n=7). Sixteen children underwent surgical procedures (arthrotomy (n=15) and arthroscopy (n=1)) [55].

After initial joint aspiration and antimicrobial therapy, the sequential CRP levels of both groups followed similar curves and time to normalization, but more children in the short-term group experienced full clinical recovery at 2 weeks compared with the long-term group (53/63 (84.1%) vs 46/67 (68.7%), p-value 0.04), which could indicate a degree of failure of randomization or differences in surgical management between the 2 groups. At subsequent follow-up visits (3 months and 12 months), all 130 children experienced full recovery without evidence of recurrence of infection or sequelae. One patient in the long-term group experienced 2 late recurrences, with the first at 17 months after the initial episode. Ten days of antimicrobial therapy with evidence of clinical recovery and CRP decline to <20 mcg/L resulted in equivalent outcomes (full recovery with no increase of recurrence of infection and sequelae), compared with those treated for 30 days. The certainty of evidence was rated as low due to the risk of bias (potential failure of randomization due to exclusion of 70 patients for culture-negative or adjacent osteomyelitis) and imprecision (very few adverse outcome events in either group and relatively small sample sizes) [55].

In a prospective observational study of a shortened antimicrobial regimen with 33 children with ABA alone, 27 children were switched to oral therapy within 6 days. Thirty (91%) received total antimicrobial courses of 3 weeks, with 3 receiving longer total courses. Microbial etiologies were identified in 26 (79%), of which 7 were *S. aureus* and 13 were streptococcal spp. None had sequelae evident one year after treatment [56].

Among 95 children with ABA alone in a retrospective observational study of transition to oral therapy, the median duration of antimicrobial therapy was 15 days [IQR: 15 to 17] [276]. Ten (11%) were given total courses >21 days. Oral transition criteria were a minimum of 2 days of IV therapy,

24 hours without fever, improvement in clinical findings, and CRP < 20 mg/L. A minimum total course of 15 days of antimicrobial therapy was specified, with longer durations at the discretion of the treating clinicians based on clinical findings. On follow-up for at least two years, one (1%) had residual pain from an arthrotomy scar with normal MRI results. No others had any sequelae.

Following serial ESR values appears to have little value for determination of duration of therapy for children with ABA as it often remains elevated for 3 to 4 weeks or longer, even in children with rapid clinical recovery [55, 56].

## Pathogen-Specific Information

ABA caused by *S. aureus*, *S. pyogenes*, *S. pneumoniae* or *Hib* may be treated for 10 to 14 days if rapid clinical improvement and CRP decline (e.g., <20 mcg/L) are evident, based on the data from Finland as described above [55, 195, 262]. Treatment duration does not need to be prolonged for those children with bacteremia at the time of diagnosis [275], when 1) bacteremia resolves quickly and is attributable to the infected joint as the source, and 2) there are no additional clinical findings that raise concern for associated endovascular infection (septic thrombophlebitis) or endocarditis.

These shorter-course data may not apply when primary ABA is caused by more virulent, clinically aggressive strains of *S. aureus* that may be associated with disseminated infection and poor response to surgical and antibiotic treatments. In the past two decades, such *S. aureus* strains have often been identified as belonging to the USA300 lineage (whether MRSA or MSSA) [282]; such strains were not circulating in Finland at the time of the reports of these longitudinal multicenter studies [55, 195, 275]. Determination of clonal designation of more virulent pathogens is primarily an epidemiologic and research endeavor and not part of routine clinical laboratory reporting available to treating clinicians. Ultimately, the clinical course (pace of response to interventions) plus supporting laboratory data are the primary guides to duration of therapy for primary ABA caused by *S. aureus* rather than a specific antimicrobial susceptibility phenotype.

Definitions of "uncomplicated" vs "complicated" cases of primary ABA have not been standardized. Therefore, no prospective controlled studies have been conducted to determine the appropriate duration of therapy in "complicated" cases caused by specific pathogens at specific joints. Without evidence for benefits and risks of short vs long duration of therapy in "complicated" ABA, longer treatment courses of at least 21 to 28 days are considered reasonable, particularly for those cases caused by more resistant pathogens with a slow clinical and laboratory response to surgical and medical therapy.

*K. kingae* has been increasingly reported as an etiology of ABA, most commonly in children 6 to 48 months of age [191, 283, 284]. These infections usually are not severe and are characterized by lower fever (even afebrile), with fewer local signs of inflammation, and lower peak CRP values [95, 105] than those caused by the other common ABA pathogens. Response to treatment tends to be rapid. Specific prospective studies have not been conducted to determine the appropriate duration of therapy with antibiotics that demonstrate *in vitro* efficacy for *K. kingae*, but antibiotic treatment courses reported for other common ABA pathogens (IV plus oral) appear to be effective based on lack of data on reports of antibiotic failure and the fact that resolution of disease may occur following surgical management, without specific antibiotic therapy [24]. Approximately 5% of strains

of *K. kingae* produce beta-lactamase and may not be susceptible to ampicillin or first generation cephalosporins, but we are not aware of reports of treatment-failure with these antibiotics [285].

Invasive *N. meningitidis* infections, including meningitis, have been successfully treated with short courses (4 days) of parenteral ceftriaxone [239, 286-288]. Data on the effectiveness of a specified treatment course of antibiotics for meningococcal ABA is complicated by the different clinical presentations (primary ABA vs a manifestation of disseminated meningococcal disease) and the occurrence of noninfectious inflammatory complications, e.g., reactive arthritis, which may complicate the decision regarding surgical and medical management of these infections [8].

Published data do not specifically address pediatric primary meningococcal ABA. Administration of a 4-day course of parenteral penicillin or ceftriaxone was successful for treatment of 8 patients (mostly adults) with primary meningococcal ABA without meningitis, out of 522 reported with invasive meningococcal infection. None of these patients required surgical drainage [239].

However, some studies have used 14-day courses [238, 240]. Some experts will transition children to oral antibiotics using clinical and laboratory parameters described for other pathogens, but limited published data exist.

Primary gonococcal arthritis is common in sexually active adolescents; it is typically monoarticular and associated with positive synovial cultures and negative blood cultures. When associated with bacteremia, there may be involvement of multiple small joints. Higher doses of ceftriaxone are now recommended for initial treatment until results of susceptibility testing are available [244]. For fully susceptible strains, treatment may be completed with oral antibiotics, usually cefixime or fluoroquinolones, for a total course of 7 to 10 days. More data are needed on the duration of therapy and feasibility of oral treatment of antibiotic resistant organisms [243, 244].

ABA due to non-typhoidal *Salmonella* spp, is seen primarily in developing countries and is typically food- or water-borne [131, 289]. Underlying hemoglobinopathy including sickle cell disease is also a risk factor. Reptile pet-associated *Salmonella* infections have also been reported in the United States [246]. These very limited data suggest these infections may need to be treated for 4 – 6 weeks. ABA can also be a manifestation of *Brucella* infections. Treatment for at least 45 days is recommended for pediatric brucellosis [248, 290].

## Presumed ABA

In a retrospective study of 89 children 2002 through 2014 in Philadelphia, PA, with presumed ABA but no identified pathogen, without adjacent osteomyelitis, various antimicrobial regimens were used with median duration of 24 days [IQR 22 to 26] [24]. Sixty (67%) were transitioned to oral therapy, with 51 (85%) receiving an agent active against MRSA. Younger children, recognized to be at risk for *K. kingae*, only received an agent active against this microbe 18% of the time. There were no relapses after hospital discharge or disability evident at 6-month follow-up.

## Rationale for Recommendation

The available data indicate that the outcome of previously healthy children older than 3 months of age with culture proven ABA due to common pathogens treated for a total duration of 10 days is not different to those treated for 30 days, if clinical and CRP improvement is documented. This is

typically accomplished by 2 to 4 days of initial parenteral antibiotic therapy followed by transition to oral therapy. Use of shorter course antibiotics is anticipated to be safer and result in less impact on antibiotic resistance and microbiome diversity. It is also likely to be less expensive, allow for care providers to return to work earlier and facilitate the child's return to school and other daily activities.

There are very limited data on the management of ABA caused by: 1) more virulent *S. aureus* strains, such as the USA 300 strain, whether MRSA or MSSA; for less common pathogens; and 2) pathogens with decreased susceptibility (higher minimum inhibitory concentrations, *in vitro*) to antibiotics (including Enterobacteriales, and oxidase-positive Gram-negative pathogens). For more severe infections (e.g., "complicated ABA") as determined based on initial clinical and laboratory parameters and on the clinical course on therapy, a total duration of at least 3 to 4 weeks, determined on a case-by-case basis, is reasonable until additional data are available.

There are no data specific to shorter versus longer courses of treatment of children with presumed ABA with no pathogen identified. The Guideline Panel consensus is that total duration of therapy may be based on the observed response from clinical and laboratory data, with treatment durations as short as 10 days.

#### *Research Needs*

There is an ongoing need for prospective studies of duration of therapy stratified by pathogen (including susceptibilities to particular antimicrobial agents) and involved joint. Multicenter collaborations with pre-specified management protocols and data collection will likely be necessary. Pathogens for which it may be more difficult to achieve microbiologic cure, such as *Salmonella* spp, should be investigated for the appropriate duration of therapy. Collaborative efforts to develop definitions of uncomplicated and complicated primary ABA may help guide future design of clinical trials that may better inform clinical decision-making about duration of therapy with specific parenteral and oral antibiotics.

### **XIII. Are follow-up imaging studies needed to assess the response to and duration of therapy for primary ABA?**

#### **Recommendation:**

In children with primary ABA with expected improvement during medical management with or without surgical intervention, associated with full clinical recovery, we suggest against routine follow-up imaging (conditional recommendation, *very low certainty of evidence*). **Comment:** In situations where there is any clinical concern for previously undetected adjacent osteomyelitis, a plain film may be considered just prior to cessation of antimicrobial therapy if osteomyelitis was not reasonably excluded by advanced imaging studies (e.g., MRI) earlier in the course.

#### *Summary of Evidence*

A small proportion of children initially diagnosed with primary ABA without signs suggestive of adjacent osteomyelitis may actually have adjacent osteomyelitis or subsequent development of osteomyelitis that may not be clinically apparent at the time of presentation [62, 88, 291]. Our review of the literature did not identify any prospective systematic studies evaluating the utility or

comparison of outcomes of routine end of therapy follow-up imaging, whether using plain films or advanced imaging studies, among children with primary ABA for whom adjacent osteomyelitis had not been identified earlier in the therapeutic course.

In a series of 96 children ages 1 month to 12 years old with ABA and follow-up plain films at two weeks and six weeks after presentation, 21 had radiographic changes in an adjacent bone at 2 weeks and 10 others developed changes by six weeks [291]. Among 91 who returned for a 12-week evaluation, none had new findings indicative of associated osteomyelitis. MRI was not available in this study and *Salmonella* spp were the dominant pathogens.

One study provided follow-up plain film data on 42 children identified as having confirmed ABA with adjacent osteomyelitis by clinical and imaging findings during initial evaluation [62]. Of these, 33 (79%) had follow-up plain films that showed evidence of osteomyelitis. Follow-up plain radiographs in one (11%) of 9 with confirmed ABA without evidence of adjacent osteomyelitis on initial evaluations showed features consistent with presence of osteomyelitis on follow-up radiograph.

MRI has high but imperfect sensitivity (81 to 100%) for the presence of osteomyelitis but is superior to CT scan for detection of changes suggestive of osteomyelitis. MRI results that are negative for osteomyelitis obtained early in the course of suspected ABA may not fully exclude the presence of adjacent osteomyelitis [37]. For review of imaging considerations for children with ABA when there are concerns for adjacent osteomyelitis, see Question II.

#### *Rationale for Recommendation*

In circumstances where an MRI was obtained early in the clinical course and demonstrated no evidence of osteomyelitis adjacent to the infected joint, with a clinical course demonstrating an expected, rapid improvement without complications, adjacent osteomyelitis is very unlikely.

In circumstances where an MRI was not obtained during the treatment course and initial plain radiographs showed no evidence of osteomyelitis, a low risk of osteomyelitis still exists, even in clinical courses with rapid responses to therapy. Plain radiographs of the bones adjacent to the infected joint for children with full recovery are not routinely necessary. However, the risks of adjacent osteomyelitis for ABA caused by certain pathogens (MRSA) in certain joints (hips, knees) have not been prospectively defined, and may be greater than expected for less virulent pathogens (*K. kingae*).

The collective clinical experience of the Guideline Panel supports this conditional recommendation against routine follow-up imaging, but the Guideline Panel recognizes that the evidence base for making a recommendation for or against obtaining plain radiographs at end of therapy is very weak.

Our literature review also did not find reports of cases of relapse of infection after standard treatment courses for primary ABA due to the inadequacy of these regimens for occult adjacent osteomyelitis. It is also possible that early osteomyelitis, not clinically suspected or detected by imaging, may have been treated adequately with the 3-week duration previously recommended for ABA.

On rare occasions MRI imaging is reasonable, based on considerations of underlying comorbid conditions, or concerning clinical or laboratory findings for a particular child.

### Research Needs

Additional controlled, prospective studies of factors are needed to assess and quantify the risk of adjacent osteomyelitis, by pathogen and by involved joint, when the initial presentation is consistent with primary ABA. Additional data on long term sequelae from primary ABA are needed, also stratified by pathogen, and involved joint. Multicenter collaborations likely will be required for such studies.

## XIV. For children with presumed or confirmed ABA who do not respond to therapy, or relapse following completion of therapy, which interventions are appropriate to optimize outcomes?

Recommendations:

1. For children with presumed or confirmed ABA either experiencing primary treatment failure, or early or late recurrence:
  - Clinicians should assess adequacy of the antimicrobial regimen (spectrum of activity, dosage, and antibiotic exposure at the site of infection, adherence) and of joint debridement and irrigation before deciding on the need to broaden the spectrum or to restart antimicrobials (*Good Practice Statement*)
  - Clinicians should assess the need for additional diagnostic evaluation for possible adjacent osteomyelitis, along with any need for surgical intervention for therapeutic and/or diagnostic purposes (*Good Practice Statement*). **Comment:** The initial diagnosis of primary ABA may need to be reconsidered

### Summary of Evidence

Failure to ultimately achieve clinical and microbiologic cure is rare among children with ABA, and especially primary ABA [55, 67, 87, 230, 292]. When failure does occur, clinical patterns include: 1) failure to respond to initial therapy (primary failure); 2) a good clinical response to initial therapy but recrudescence during therapy (secondary failure); or 3) relapse/recurrence of infection weeks to months after completion of therapy. This aspect of management has not been systematically studied, likely due to its relative infrequency at any given center.

Primary treatment failure in a child with confirmed or suspected ABA is defined by lack of improvement of local (i.e., overlying erythema or edema, tenderness, limitation of range of motion) and/or systemic signs of infection (i.e., persistent fever that is not trending downward, or ongoing clinical signs of sepsis) two to four days after initiation of presumed adequate antimicrobial therapy, with or without definitive surgical/procedural intervention. Lack of expected improvement of inflammatory markers (e.g., reduction in serum CRP concentration), particularly in the context of lack of clinical improvement, may also indicate primary treatment failure. Secondary treatment failure may occur early in the course after a few days of apparent clinical improvement or after hospital discharge while on the selected outpatient antimicrobial regimen.

The presence of unrecognized adjacent osteomyelitis may be an important risk factor for relapse of ABA after an apparently successful treatment course. This has been described for multiple joints and multiple microbial etiologies [293-295]. Data on other risk factors for treatment failure or relapse are very limited.

Among 89 children with culture negative arthritis of presumptive bacterial etiology, without adjacent osteomyelitis, 8 (9%) required a change in antimicrobial therapy for clinical worsening or failure to improve within 48 hours of starting the initial regimen. Two required a repeat drainage procedure. No risk factors for failure were identified. There were no relapses after hospital discharge and no disability evident at 6-month follow-up [24].

Risk of treatment failure in a series of 74 children with ABA of the knee treated with antibiotics and needle aspiration alone was higher in children >3 years old and in children of any age with serum CRP concentration >20 mg/L [125]. Nine (21%) in a series of 42 children with ABA of the hip treated with single or multiple needle aspirations required subsequent open procedures due to failure to improve. Increasing age, especially >10 years old, was a risk factor for failure of joint aspiration alone (with no other invasive procedures) [199].

Two uncommon bacterial etiologies are particularly prone to relapse or delayed recovery, *Brucella* and *Borrelia*. Relapse was observed in 12 (14%) of 87 children with brucellosis with osteoarticular involvement after various 6-week courses of therapy. Relapses sometimes occurred in different joints from the initial infection [296]. Lyme arthritis in children can be slow to resolve and may require more intensive anti-inflammatory treatments than nonsteroidal agents in a small minority of cases [111, 297].

Primary and secondary failure that is not due to unrecognized adjacent osteomyelitis can have multiple causes, including:

- 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 (e.g., administration errors, non-adherence)
- The pathogen is resistant to the current antibiotic regimen
- Emergence of resistant organisms during therapy
- The involved joint space has not been adequately drained
- There is an undrained soft tissue focus of infection (e.g., pyomyositis) adjacent to the joint
- There is a remote/metastatic focus of infection that requires surgical intervention
- There is a new, unrelated infection (e.g., intercurrent viral infection or new bacterial wound infection)
- The etiology of joint inflammation is non-infectious (e.g., reactive, auto immune)

Reconsideration of the spectrum of the empiric antibiotic regimen may be necessary for children with primary or secondary treatment failure. Once the microbial etiology and its antibiotic susceptibilities are known, inappropriate antibiotic selection or dosage should be corrected. If the regimen is deemed appropriate, then additional imaging (e.g., MRI) may be warranted, to diagnose possible adjacent osteomyelitis, or secondary sites of infection. [37].

If no pathogen has been initially identified, obtaining additional cultures and tissue for histopathology and molecular pathogen detection from the involved joint(s), should be strongly considered, particularly if imaging documents persisting collections of fluid within the joint. Obtaining specimens for testing prior to changing the antibiotic regimen is suggested when clinically feasible.

For children with secondary failure following hospital discharge, assessment of adherence is necessary, whether the route of administration of the prescribed regimen is oral or IV. For outpatients on oral therapy, other factors may impact absorption of antibiotics, such as viral gastroenteritis. Repeat imaging studies may be necessary in these cases as well.

Persistent bacteremia is often due to occult secondary foci of infection (e.g., pyomyositis, subperiosteal abscess) or an associated deep vein thrombosis. Persistent bacteremia can be the result of or lead to complications and metastatic spread of infection [298]. Evaluation for uncontrolled sources of infection (e.g., the involved joint(s), adjacent bones and soft tissues, potential remote sites) should be considered. When bacteremia persists 48 to 72 hours into the course of antimicrobial therapy (particularly in the child with poor clinical response), the panel suggests obtaining MRI of the site(s) of infection to detect any foci of infection that may be amenable to surgical drainage. Detection of deep vein thrombosis as a risk for bacterial thrombophlebitis may require specialized imaging and may impact choice of antibiotic regimens as well as route and duration of therapy.

Late relapse following appropriate antibiotic and surgical therapy for ABA is uncommon in the absence of adjacent osteomyelitis, and evidence to support recommendations are not available. The potential for chronic osteomyelitis or misdiagnosis of an underlying rheumatologic condition as ABA should be considered. Investigations similar to those outlined for primary and secondary failure as detailed above may also be helpful, including new infection, or alternative, non-infectious diagnoses.

#### *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. This situation may occur in cases for which a definitive pathogen has been detected. Potential causes that may be responsible for failure to respond include inadequate medical or surgical therapy, presence of adjacent osteomyelitis that has not been detected, and/or errors in diagnosis of a bacterial etiology of joint inflammation. Re-evaluation of the child should be considered, especially in scenarios of presumed ABA with no pathogen identified and without bone involvement, 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. 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, involved joints, 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 component of management. The rarity of such events requires multicenter collaborations, with efforts required for standardization of antibiotic therapy and approach to surgical management for both "uncomplicated" and "complicated" ABA. Better diagnostic methods for non-infectious causes of arthritis (e.g., JIA) may allow alternative diagnoses to be made, without a need for additional imaging or surgical procedures.

## **XV. How long do children with primary ABA require follow-up examinations to address sequelae (e.g., joint contractures, potential growth arrest) due to the infection?**

### **Recommendation:**

In children with primary ABA, we suggest close follow-up by providers with expertise in management of musculoskeletal infections until the completion of antibiotic therapy and return of function in the infected joint (conditional recommendation, *very low certainty of evidence*).

**Comment:** For primary ABA that responds promptly to treatment, follow-up is not routinely required beyond 2-3 weeks from the start of treatment. For children with ABA with adjacent osteomyelitis, see 2021 PIDS/IDSA Guideline on Diagnosis and Management of Acute Hematogenous Osteomyelitis in Pediatrics [37].

### *Summary of Evidence*

Children with primary ABA should be followed during their therapy by those experienced in the management of this disease. While direct consultation for follow-up needs with Pediatric Infectious Diseases and/or Pediatric Orthopedic specialists is preferred, indirect consultation with such experts or others with experience managing joint infections (including by telephone) is recommended when logistical and practical matters preclude direct consultation.

Several studies provide long term outcome data that can partially inform follow-up needs after pediatric ABA. The majority of children with ABA have excellent outcomes. Some have poor functional and/or radiologic outcomes but it is rare that these are severe [229, 230, 299]. Significant complications that can arise include joint contractures and dysfunction, as well as bone growth arrest. The rate of complications following ABA is approximately 10% overall [300, 301] among children with adjacent osteomyelitis [67, 87, 230, 292]. This may be due to more extensive tissue injury from infection spreading into a joint from an adjacent epiphyseal osteomyelitis or as a consequence of infection eroding through the physis into the joint from an initial metaphyseal site.

Long term sequelae are uncommon in children with primary ABA. In a recent study, only 1 (0.7%) of 134 children with primary ABA had an abnormality with a median of 36 days of follow-up after the end of therapy [87]. This child suffered physeal injury from hip infection caused by MSSA that led to separation of the femoral epiphysis from the metaphysis two years later. A retrospective cohort study documenting various outcomes at the end of therapy found that, among 109 children with primary ABA, 103 (95%) had full range of motion (FROM) and 93 (85%) had no pain at the end of

therapy (median of 25 days) [67]. Another retrospective study evaluating long term follow-up of 52 children with primary ABA (32 children with ABA of the hip and 19 of the knee, with a mean follow-up of 8.5 and 7.7 years respectively) showed that no children had sequelae considered to be severe, but 10 (31%) of those with hip infections and 9 (47%) with knee infections had findings considered to be of mild to moderate severity [299].

Among children with ABA with adjacent osteomyelitis, long-term sequelae were evident in 40 (38%) of 105 with a median of 139 days of follow-up [87].

Children with primary ABA who have had a careful physical examination documenting their substantial improvement at the end of acute treatment for uncomplicated ABA at 10-14 days (i.e., lacking pain, decreased swelling, substantially improved range of motion and function, and decreased laboratory markers of inflammation if obtained) are likely at very low risk of sequelae during childhood. Based on the limited literature and clinical experience, longer follow-up is not necessary as the efforts, costs, and risks associated with ongoing follow up (including clinic visits, laboratory investigations, and radiographs) appear to outweigh any potential benefits for detecting long term sequelae for this group of children.

Complications are more likely among certain subgroups with ABA and are usually clinically present and recognized at the end of antibiotic therapy. These include premature infants during the first months of life [302] and infants less than 6 months of age [303], as well as those with ABA of the hip or shoulder, and those with delay of diagnosis or definitive surgical management beyond 4 days into treatment [69, 139, 304-306] or other delays in antibiotic therapy or sterilization of synovial fluid. Infection caused by resistant organisms, such as CA-MRSA, have been associated with increased risk of growth arrest of the femur in some series. It is unclear whether this finding is related primarily to delay in receipt of effective antimicrobial therapy or the presence of a more virulent microbe (e.g., USA 300 *S. aureus*) in the hip joint [307]. Avascular necrosis of the femoral head as a consequence of ABA of the hip was recognized way before the global spread of USA 300 *S. aureus* during the past two decades.

Children with any limitation in joint function at the end of acute therapy (such as decreased joint range of motion) should be followed closely by orthopedic specialists for complications or the need for ongoing management. Growth arrest can be typically detected within months from the initial infection; monitoring for growth arrest may be performed as part of ongoing routine wellchildcare by primary care providers as well as by orthopedic specialists. There are no data describing what can be done to prevent growth arrest, but orthopedic procedures to manage growth arrest can be performed if needed.

#### *Rationale for Recommendation*

This conditional recommendation is based on very low certainty of evidence, and places high value on considerations of patient's values and preferences, feasibility, acceptability, equity, and cost in recommending that children with either presumed or confirmed primary ABA who have substantial recovery at the end of acute management will not routinely require either orthopedic or infectious diseases follow-up. The recommendation for ongoing orthopedic specialist follow-up for ABA in children who appear to have higher risk of long-term complications with joint or bone growth or

function as outlined above, places high value on identifying complications early to allow for early intervention.

### Research needs

Future research needs include comprehensive controlled prospective studies to identify which clinical and laboratory parameters will help identify children at risk of developing long-term sequelae of ABA, stratified by joint and causative pathogen.

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## Supplementary Data

Supplementary materials (e.g., tables and figures) are available at the **Journal of the Pediatric Infectious Diseases Society**  online.

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## Notes

**Acknowledgments:** The expert panel expressed its gratitude for thoughtful reviews of an earlier version by Drs. Sheldon Kaplan, Paul Krogstad, and Nicole Le Saux. The panel would also like to thank Drs. Theoklis Zaoutis and David Feldman for their contribution to the guideline. The panel thanks Genet Demisashi and Hannah Rehm for their continued support throughout the guideline process. The panel also expresses gratitude to librarian Elena Guadagno for her continued literature support throughout the development of the guideline.

**Financial Support:** This work was supported by the Infectious Diseases Society of America and the Pediatric Infectious Disease Society.

**Potential Conflicts of Interest:** To provide thorough transparency, IDSA requires full disclosure of all relationships, regardless of relevancy to the guideline topic. Evaluation of such relationships as potential conflicts of interest is determined by a review process, which includes assessment by the Standard and Practice Guidelines Committee (SPGC) Chair, and the Board of Directors liaison to the SPGC and, if necessary, the Conflict of Interest (COI) Ethics Committee. The assessment of disclosed relationships for possible COIs is based on the relative weight of the financial relationship (ie, monetary amount) and the relevance of the relationship (ie, the degree to which an association might reasonably be interpreted by an independent observer 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. C. H. A. serves as an advisory/consultant for Emergency Medicine and Halozyme; receives research funding from Merk and Co, AstraZeneca, and Theravance

Biopharma; served as speakers bureau for Halozyme and Sanofi; held ownership interests in Emergency Medicine; and received research funding from Baxter International. S. R. A. served as an advisory/consultant for Cubist Pharmaceuticals; received research funding from Pfizer, Enanta, Moderna, Regeneron and Contrafect, the Centers for Diseases Control and Prevention, Cubist Pharmaceuticals, Pfizer, and the Urban Child Institute. A. A. receives research funding from Astellas Pharmaceuticals, Melina Therapeutics, Merck and Co., Nabriva Therapeutics, Pfizer, and Rempex Pharmaceuticals Inc.; receives organizational benefit from the Lon V. Smith Foundation; and served as an advisory/consultant for Astellas Pharmaceuticals and AstraZeneca. J. S. B. employer receives research funding from Merck and Co.; received research funding from Bayer, Cerexa Inc., Cubist Pharmaceuticals, Astra-Zeneca, Pfizer, Allergan, and Trius; receives research funding from the National Institutes of Health (NIH); received organizational benefits from AstraZeneca, Cerexa Inc., Cubist Pharmaceuticals, and Trius; and served as a member on the HHS National Biodefence Science Board. M. A. C. M. served in an advisory/ consultant role for Karius, Inc. and Avalere Health; received research funding from BioCryst Pharmaceuticals, the Sanford Health Research Foundation, NIAID, Pfizer, Moderna, and ContraFect Corporation. A. C. served in an advisory/consultant role for Cerexa, Inc., Merck and Co., the Cochran and Heidman Law Firms, GlaxoSmithKline, Insmed, for Lamson, Dugan, and Murray Law Firm, Moderna Therapeutics, Seqirus, Inc., Novartis, and SanofiPasteur; served in a promotional role for AstraZeneca, Merck and Co., GlaxoSmithKline, Novartis, Sobi, Inc., and Medimmune; has given expert testimony to the Cochran and Heidman Law Firms; received research funding from GlaxoSmithKline, Sanofi Pasteur, Merck and Co., Novartis, Pfizer, and Hoffman and LaRoche, Inc.; and received organizational benefit from InterHealth Nutraceuticals, Inc. L. A. C. received research funding from the Texas Scottish Rite Hospital. C. B. C. serves in an advisory/consultant role for Astellas Pharmaceuticals, Karius Diagnostics, Altimmune, Nabriva, Horizon Therapeutics, and Premier Inc; served in an advisory/consultant role for Cerexa Inc., Cubist Pharmaceuticals, GlaxoSmithKline, and Novartis; receives honoraria from UpToDate; and receives or has received research funding from the Centers for Disease Control and Prevention, Merck and Co., the National Institutes of Health, Cerexa Inc., GlaxoSmithKline, and Pfizer. S. C. E. received research funding Pfizer and Roche. S. L. F. receives other remuneration from Shionogi; receives research funding from the National Institutes of Health (NIH); and received research funding from Cerexa Inc. and Roche. C. H. receives research funding from GlaxoSmithKline, Pfizer, and Merck and Co. and received research funding from Astellas Pharmaceuticals, GlaxoSmithKline, Johnson & Johnson, and Merck and Co. M. P. K. receives research funding from the National Institutes of Health; serves on the Pediatric Infectious Diseases Society on their Board of Directors and pediatric committee on antimicrobial stewardship; and received research funding from the Academic Pediatric Association, the Agency for Healthcare Research and Quality, and the National Institutes of Health. V. L. has received past research funding from the Fonds de recherche du Québec Research (FRQ-S). L. J. M. received research funding from the National Environmental Education Foundation. J. R. serves in an advisory/consultant role for Westat; receives or has received past research funding from the Canadian Institute for Health Research; received renumeration from Pfizer; and received research funding from Alberta Innovates and the Collaborative Antiviral Study Group. S. S. S. receives remuneration from McGraw-Hill Medical Lippincott Williams and Wilkins and Elsevier Publishing; receives or has received past research funding from Agency for Healthcare Research and Quality, the National Heart Lung Blood Institute, and the Children's Hospital Association (formerly known as the Child Health Corporation of

America); and received research funding from the National Institute of Allergy and Infectious Diseases, the Patients Center Outcomes Research Institute, and the Robert Wood Johnson Foundation. C. R. W. receives honoraria from Up To Date, Inc.; served in an advisory/consultant role for Cerexa, Inc., Wyeth, and Pfizer; received research funding from Pfizer and Wyeth; serves on the Committee on Guideline Development for the American Academy of Pediatrics (AAP); was a member of the editorial board for the AAP Grand Rounds; was Chair of the AAP Section on Epidemiology, Public Health and Evidence; served on the AAP Task Force on Policy Development Process Improvement; and served on Board of Directors and as Treasurer and was an Associate Editor on the editorial board for the Journal of the Pediatric Infectious Diseases Society (JPIDS) for the Pediatric Infectious Diseases Society (PIDS). All other no disclosures reported. All authors have submitted the ICMJE Form for Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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