DATE: July 2016

TEXAS CHILDREN'S HOSPITAL
EVIDENCE-BASED OUTCOMES CENTER
Acute Hematogenous Osteomyelitis (AHO)
Evidence-Based Guideline

Definition: Acute hematogenous osteomyelitis (AHO) is inflammation of bone and bone marrow caused by an infectious organism that reaches the bone through the bloodstream. Osteomyelitis is considered acute if a diagnosis is made within 2 weeks of the onset of symptoms.

Pathophysiology: AHO is the most common form of osteomyelitis found in children; it occurs as the result of an infection that spread through the bloodstream. Although any bone can be affected, AHO occurs primarily in the long bones, most commonly the femur or tibia. [1] The pathophysiology and epidemiology of osteomyelitis are greatly influenced by the anatomy of the bone in pediatric patients. [1-3] The blood supply to the bone (nutrient artery) divides into a tortuous capillary bed that joins sinusoidal veins before entering the bone marrow of the metaphysis. The slow movement of blood and lack of a reticuloendothelial lining make it easy for bacteria to seed the bone and grow rapidly. [2,3] The bacterial growth leads to cellulitis in the bone marrow which then causes an inflammatory response. [3] The inflammatory response leads to the accumulation of leukocytes which produces an exudate that causes pressure and necrosis of the bone.
The most common causative organisms are *Staphylococcus aureus* and *group A streptococcus.* However, unusual causes may include *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Salmonella*, and *Kingella kingae*. [1-4]

Inclusion Criteria
- Age ≥60 days
- Healthy children without underlying conditions (e.g., spina bifida, sickle cell disease, immunodeficency)
- Clinical findings of AHO

Exclusion Criteria
- Toxic appearance
- Contiguous osteomyelitis (next to a decubitus ulcer)
- Penetrating trauma
- Postoperative
- Chronic osteomyelitis

Differential Diagnosis
Fracture
Myositis
Discitis
Cellulitis
Toxic synovitis
Slipped capital femoral epiphysis (SCFE)
Legg calve perthes (LCP)
Juvenile idiopathic arthritis (JIA)
Reactive arthritis
Septic arthritis
Post-infectious arthritis
Bone tumor (e.g., Ewing's sarcoma, osteosarcoma)
Leukemia (e.g., acute lymphoblastic, acute myeloid)
Hemearthrosis (e.g., bleeding disorder)
Spondylolisthesis
Spondylolysis

Diagnostic Evaluation: Children with acute hematogenous osteomyelitis have a risk of progressing to septic shock. Clinicians should immediately refer to the Septic Shock guideline and intervene rapidly if patient has toxic appearance, ill appearance, altered mental status, and/or compromised perfusion with abnormal vital signs.

Vital Sign Changes of Sepsis [5]

Age	Heart Rate	Resp Rate	Systolic BP	Temp (°C)
0d - 1m	>205	>60	<60	<36 or >38
>1m - 3m	>205	>60	<70	<36 or >38
>3m - 1y	>190	>60	<70	<36 or >38.5
>1y - 2y	>190	>40	<70 + (age in yr x 2)	<36 or >38.5
>2y - 4y	>140	>40	<70 + (age in yr x 2)	<36 or >38.5
>4y - 6y	>140	>34	<70 + (age in yr x 2)	<36 or >38.5
>6y - 10y	>140	>30	<70 + (age in yr x 2)	<36 or >38.5
>10y - 13y	>100	>30	<90	<36 or >38.5
>13y	>100	>16	<90	<36 or >38.5

Signs and Symptoms of Shock [5]

Exam Abnormalities			
	Cold Shock	**Warm Shock**	**Non-Specific**
Peripheral Pulses	Decreased or weak	Bounding	
Capillary Refill (central vs. peripheral)	≥3 sec	Flash (<1 sec)	
Skin	Mottled, cool	Flushed, ruddy, erythroderma (other than face)	Petechiae below the nipple, any purpura
Mental Status			Decreased, irritability, confusion, inappropriate crying or drowsiness, poor interaction with parents, lethargy, diminished arousability, obtunded

History: Assess for
- Favoring an extremity/Limp
- Limp deformity
- Patient/Family skin and soft tissue infection (SSTI)
- Fever (current or recent)
- Trauma
- Bone pain
- Cellulitis
- Duration of symptoms
- Pain with diaper changes (non-toilet trained children)

Physical Examination

A complete physical exam should be performed assessing for:

- Erythema
- Warmth
- Swelling
- Point tenderness
- Gait refusal
- Restricted movement
- Failure to bear weight
- Metaphyseal pain

Laboratory Tests

Obtain a blood culture, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and complete blood cell count (CBC). [6-16]

Consider obtaining a BUN/Creatinine for antibiotic monitoring parameters. (See Antibiotic Table, pp. 4-5)

Diagnostic Imaging Studies:

Obtain a plain radiograph to rule out fracture or malignancy.

Obtain magnetic resonance imaging (MRI) for diagnostic and surgical interventions. [14,17-21]

Critical Points of Evidence*

Evidence Supports

- Obtain a blood culture in patients with suspected acute hematogenous osteomyelitis. [6,7,10,11,14-16] – Strong recommendation, low quality evidence
- Obtain an IR-performed bone biopsy with culture in patients not requiring surgery when the blood culture is negative at 24 hours. [6,11,15,16,22] – Strong recommendation, low quality evidence
- Utilize MRI for diagnostic imaging and surgical interventions. [14,17-21] – Strong recommendation, low quality evidence
- Initiate antibiotic treatment after drawing a blood culture and within 24 hours of bone biopsy (if required). [7,11,15,16] – Strong recommendation, low quality evidence
- Administer short-term parenteral antibiotics followed by oral therapy for uncomplicated, confirmed AHO. Criteria for transition to oral therapy include: defervescence, clinical improvement, source control, negative blood culture, ability to take oral antibiotics, and improving CRP. [22-36] – Strong recommendation, low quality evidence
- Consider utilizing a PICC if prolonged IV therapy is required. [22-35] – Weak recommendation, low quality evidence
- Use IV ketorolac perioperatively (≤5 days duration) in patients with AHO and pain scores >4. [37-43] – Strong recommendation, low quality evidence
- Use scheduled acetaminophen or ibuprofen for patients with AHO and mild pain (pain scores ≤4). [44-47] – Strong recommendation, low quality evidence
- Use ibuprofen, acetaminophen, or oxycodone for patients with AHO and moderate pain (pain scores >4). [44-47] – Strong recommendation, low quality evidence

Evidence Against

- Do not routinely obtain a post-surgical MRI. Consider a post-surgical MRI if persistent, worsening, or new clinical findings. [48,49] – Weak recommendation, very low quality evidence

Evidence Lacking/Inconclusive

- Utilize ESR, CRP, and CBC, in conjunction with other diagnostic studies, to establish a diagnosis of acute hematogenous osteomyelitis. [8,9,12-14] – Strong recommendation, very low quality evidence
- Consider additional analgesia for patients with AHO and moderate pain (pain scores >4) who are receiving ibuprofen, acetaminophen, or oxycodone. [44-46] – Weak recommendation, very low quality evidence
- Use IV morphine in conjunction with acetaminophen or ibuprofen for patients with AHO and severe pain (pain scores >7). [50,51] – Strong recommendation, very low quality evidence
- No evidence found regarding the use of procalcitonin as a diagnostic adjunct for children with suspected AHO.

*NOTE: The references cited represent the entire body of evidence reviewed to make each recommendation.

Condition-Specific Elements of Clinical Management

General: [2,52] Localized bone pain and fever should raise clinical suspicion of AHO with the pain being reported as constant, and the level of pain increasing gradually. It's important to note that the classic signs of inflammation (e.g., redness, warmth and swelling) do not appear unless the infection has progressed through the metaphyseal cortex into the subperiosteal space.

AHO may be further divided into ***uncomplicated osteomyelitis*** and ***complicated osteomyelitis***. This distinction is made by reviewing images obtained on MRI. Patients with complicated osteomyelitis may have a subperiosteal abscess, myositis, contiguous septic arthritis, associated venous thrombosis, or skin and soft tissue infection. These patients may require surgical intervention one or more times during the course of their disease.

Treatment requires antimicrobial therapy in all cases and may require surgical incision and drainage.

Treatment Recommendations

Antibiotic Recommendations

In Houston, children with suspected AHO should be empirically treated to cover *S. aureus. S. aureus* is responsible for the overwhelming majority of skin and soft tissue infections seen at TCH. About 30-50% of *S. aureus* osteomyelitis infections at TCH are MRSA and the remaining are MSSA. Local surveillance data from the Infectious Disease laboratory

reports that for community *S. aureus* isolates at TCH, 12-13% are clindamycin-resistant.

Empiric/First Line Treatment

Well-appearing children with AHO should be treated with clindamycin as the disease process is monitored and cultures are pending.

Well-appearing children with AHO who have a history of staphylococcal infections or significant healthcare exposure may require vancomycin as first-line treatment.

See Antibiotic Table for additional recommendations (pp. 4-5).

Bone Biopsy/Initiation of Antibiotics

Antibiotics should be initiated after drawing a blood culture and within 24 hours of bone biopsy (if required).

Intravenous (IV) Access

Reliable intravenous access is very important in the treatment of osteomyelitis. If blood cultures are reported as negative, the clinician may decide to establish long-term IV access through the placement of a PICC, or have the patient remain with peripheral IV access.

Duration of Antibiotic Therapy

The duration of treatment for osteomyelitis can range from 3 to 12 weeks with most patients requiring treatment for 4 to 6 weeks. Treatment duration is dependent on the extent of the disease, causative organism, and inflammatory markers.

Admission Criteria

- Suspected AHO

Discharge Criteria

- Improved range of movement
- Pain controlled
- Appropriate mental status for age
- Tolerating PO
- Appropriate support system (e.g., PMD, caregivers)
- Defervescence
- Decreasing CRP
- Home Health orders for PICC placed, if needed
- If initial blood culture positive, subsequent blood cultures are negative
- Baseline “monitoring labs” obtained
- Follow-up visits scheduled (e.g., PMD, Infectious Disease, PT)

Consults/Referrals

Consult Orthopedic Surgery for patients with complicated osteomyelitis requiring drainage or debridement.

Consult Interventional Radiology for bone biopsy or PICC line placement

Consult Infectious Disease once a diagnosis of AHO has been confirmed.

Consult Physical Therapy for concern regarding range of motion and gait training, following surgical intervention.

Consult Care Management upon admission for AHO.

Request to see Child Life for coping techniques, procedural teaching, and psychosocial support

Follow-Up Care

Follow-up care is recommended for all children hospitalized with AHO.

For a child who is not following the expected clinical course, consider complications, such as an alternative or ineffective antibiotic treatment due to lack of antibiotic coverage or resistance patterns.

Measures

Structure

- Cost of pain medications

Process

- Proportion of Orthopedic Surgery consults
- Proportion of Infectious Disease consults
- Proportion of Child Life Requests to See
- Proportion of Physical Therapy consults
- Proportion of Interventional Radiology consults
- Length of time to transition from IV to PO

Outcome

- Failure to respond to antibiotic treatment
  - Unplanned readmission within 30 days and type of antibiotic
- Time to MRI
- Proportion of PICCs placed
- Proportion of PICC complications (e.g., infection, line breaking, movement of catheter)
- Overall proportion of positive blood cultures
- Proportion of positive blood cultures on antibiotics
- Proportion of positive blood cultures off antibiotics
- Proportion of contaminated or insufficient blood culture samples
- Proportion of blood cultures that identified a pathogen
- Proportion of bone biopsies that identified a pathogen
- Proportion of surgical cultures that identified a pathogen
- Proportion of changes to antibiotics
- Proportion of adverse events
- Proportion of adverse events for prolonged IV antibiotics
- Proportion of adverse events for prolonged oral antibiotics
- Proportion of positive, negative, and complicated MRIs
- Proportion of positive, negative radiographs
- Proportion of children diagnosed with DVT
- Need for subsequent surgical intervention following debridement and drainage
- Length of stay (e.g., inpatient, observation)
- Pain scores for patient in first 24 hours (stratified by those who underwent surgical procedure and those who did not)
- Documentation of pain score every 4 hours
- Time to first pain medication
- # of days patient in moderate or severe pain

Treatment of Acute Hematogenous Osteomyelitis (AHO) in Children† [53]									
Antibiotic	**Infant/Child Dose** **Adolescent/Adult Dose** ***MAX Dose***	**Frequency**	**Potential Adverse Effects**	**Monitoring Parameters**[Ω]	**MSSA**	**MRSA**	***Streptococcus pneumoniae***	***Streptococcus* Group A**	**Gram (-) bacteria**
Intravenous Medications – First Line Treatment									
CeFAZolin[‡,£] **(Ancef®)**	100 mg/kg/DAY 500 mg-2 grams ***MAX*** *(Child): 2 grams/dose or 6 grams/DAY* ***MAX*** *(Adult): 2 grams/dose or 12 grams/DAY*	Q 6-8h Q 6-8h Q 6-8h Q 6-8h	• Myelosuppression • Renal toxicity • Rash • Diarrhea	• Penicillin allergy • CBC d/p • BUN/SCr** • UA**	+	-	+	+	±
Clindamycin **(Cleocin®)**	13 mg/kg 600-900 mg ***MAX:*** *900 mg/dose or 4.8 grams/DAY*	Q 8h Q 8h Q 8h	• Diarrhea • Colitis • Elevated transaminases	• CBC d/p** • LFTs**	+	+	+	+	-
Nafcillin[‡,£] **(Unipen®)**	50 mg/kg 500 mg-2 grams ***MAX:*** *2 grams/dose or 6 grams/DAY*	Q 6h Q 4-6h Q 4-6h	• Local injection site pain/phlebitis • Myelosuppression • Renal toxicity • Hepatotoxicty • Rash • Diarrhea	• Penicillin allergy • CBC d/p • BUN/SCr** • UA** • LFTs	+	-	-	+	-
Penicillin G[¥] **(Pfizerpen-G®)**	50,000 units/kg 3-4 million units ***MAX:*** *24 million units/DAY*	Q 4-6h Q 4-6h Q 4-6h	• Local injection site pain/phlebitis • Myelosuppression • Renal toxicity • Rash • Diarrhea	• Penicillin allergy • CBC d/p** • BUN/SCr** • UA**	-	-	+	+	-
Vancomycin[¥,£] **(Vancocin®)**	15 mg/kg 15 mg/kg ***MAX:*** *4 grams/day*	Q 6h Q 6-8h Q 6-8h	• Myelosuppression • Renal toxicity • Red Man Syndrome • Diarrhea	• CBC d/p • BUN/SCr	+	+	+	+	-
Intravenous Medications – Second Line Treatment									
CefTRIAXone **(Rocephin®)**	75 mg/kg 2 grams ***MAX:*** *2 grams/dose or 4 grams/DAY*	Q 24h Q24h Q 12-24h	• Myelosuppression • Rash • Elevated transaminases • Diarrhea	• Penicillin allergy • CBC d/p** • BUN/SCr** • LFTs**	+	-	+	+	+
CefOTAXime[‡,£,*] **(Claforan®)**	50-75 mg/kg 1-2 grams ***MAX:*** *2 grams/dose or 12 grams/DAY*	Q 8h Q 6-8h Q 6-8h	• Myelosuppression • Renal toxicity • Rash • Diarrhea	• Penicillin allergy • CBC d/p** • BUN/SCr** • UA**	+	-	+	+	+

Treatment of Acute Hematogenous Osteomyelitis (AHO) in Children† [53]									
Antibiotic	**Infant/Child Dose** **Adolescent/Adult Dose** ***MAX Dose***	**Frequency**	**Adverse Effects**	**Monitoring Parameters**Ω	**MSSA**	**MRSA**	***Streptococcus pneumoniae***	***Streptococcus* Group A**	**Gram (-) bacteria**
Oral Medications									
Amoxicillin¥ **(numerous)**	100 mg/kg/DAY 250-1000 mg ***MAX:*** *1 gram/dose; 4 grams/DAY*	Q 6-8h Q 6-8h Q 6-8h	• Myelosuppression • Renal toxicity • Rash • Diarrhea	• Penicillin allergy • CBC d/p** • BUN/SCr** • UA**	-	-	+	+	-
Cephalexin‡,¥ **(Keflex®)**	100 mg/kg/DAY 250-1000 mg ***MAX:*** *1 gram/dose*	Q 6-8h Q 6-8h Q 6-8h	• Myelosuppression • Renal toxicity • Rash • Diarrhea	• Penicillin allergy • CBC d/p • BUN/SCr** • UA**	+	-	-	+	±
Clindamycin (Cleocin®)	13 mg/kg 600-900 mg ***MAX:*** *900 mg/dose*	Q 8h Q 8h Q 8h	• Gastrointestinal upset • Diarrhea • Colitis • Elevated transaminases	• CBC d/p** • LFTs**	+	+	+	+	-
Penicillin VK (numerous)	25-50 mg/kg/DAY 125-500 mg ***MAX:*** *2 grams/DAY*	Q 6-8h Q 6-8h Q 6-8h	• Myelosuppression • Renal toxicity • Rash • Diarrhea	• Penicillin allergy • CBC d/p** • BUN/SCr** • UA**	-	-	+	+	-
SMX/TMP¥ **(Bactrim®)**	10-12 mg (TMP)/kg/DAY 160 mg-320 mg (TMP)/DAY ***MAX:*** *320 mg (TMP)/DAY*	Q 12-24h Q 12-24h Q 12-24h	• Myelosuppression • Renal toxicity • Hepatotoxicity • Rash • Diarrhea	• CBC/Diff • BUN/SCr** • UA** • LFTs**	+	+	+	-	+

NOTE: Consider insurance/Medicaid formulary restrictions.

†Susceptibilities based on "Sanford Guide to Antimicrobial Therapy: 2015" (**red** indicates testing done by TCH Clinical Pathology Department – refer to antibiogram for exact % susceptibility); antibiotic choice should always be streamlined based on cultures and susceptibilities [54]

‡Caution in patients with severe penicillin allergy; cross-reactivity ~10%

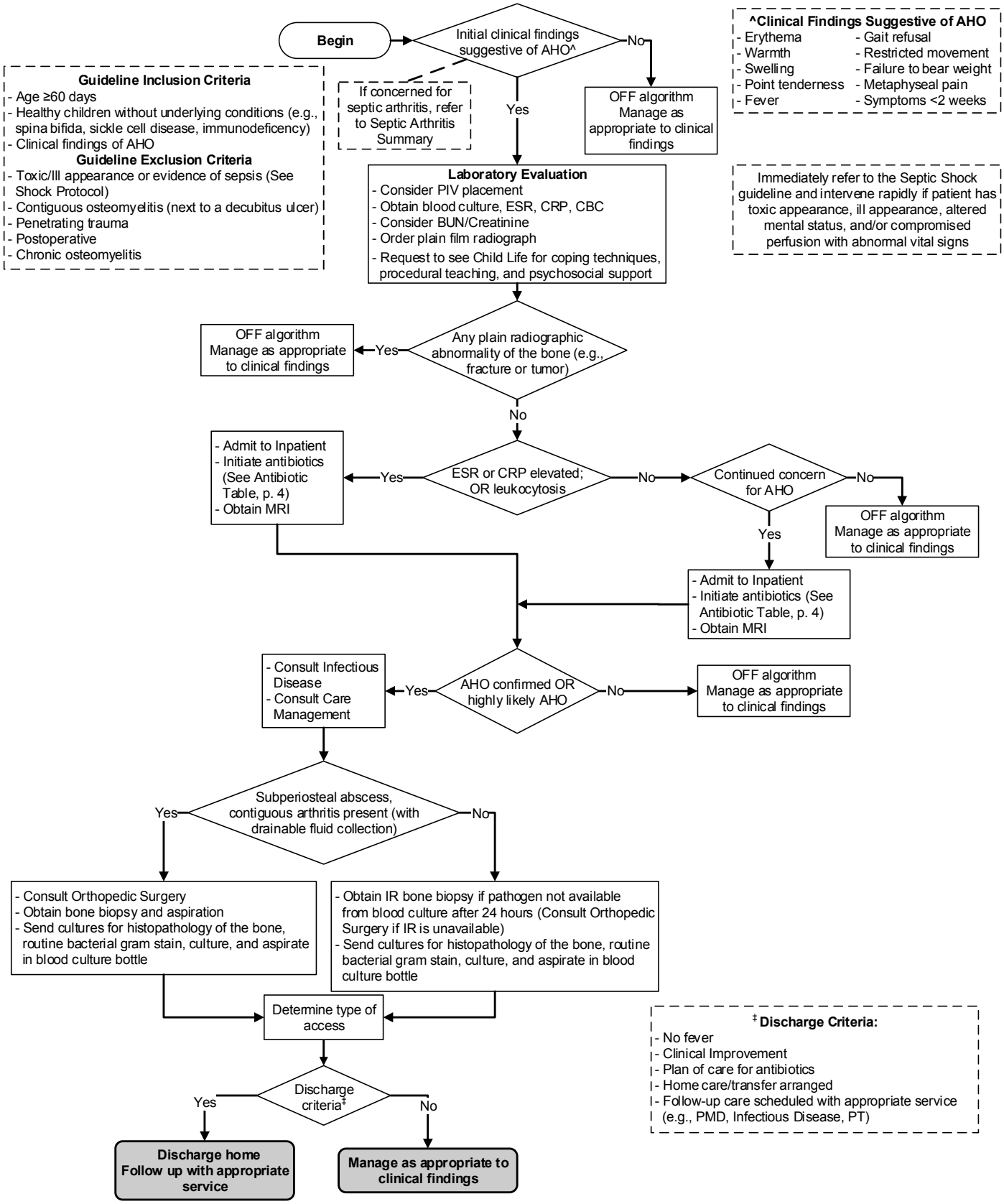
¥Requires dose adjustment in renal impairment

ΩMay obtain pertinent labs once/twice weekly during long-term therapy upon discretion of appropriate service

**Consider

*Restrictions for cefOTAXime use: 1) Neonatal patients (defined as: ≤44 weeks postmenstrual age OR neonates <1 month of age), 2) Patients receiving calcium-containing IV fluids with a single lumen or single IV site.

TCH Evidence-Based Outcomes Center
Clinical Algorithm for Acute Hematogenous Osteomyelitis (AHO)



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Clinical Standards Preparation

This clinical standard was prepared by the Evidence-Based Outcomes Center (EBOC) team in collaboration with content experts at Texas Children's Hospital. Development of this clinical standard supports the TCH Quality and Patient Safety Program initiative to promote clinical standards and outcomes that build a culture of quality and safety within the organization.

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Development Process

This clinical standard was developed using the process outlined in the EBOC Manual. The literature appraisal documents the following steps:

1. Review Preparation
   - PICO questions established
   - Evidence search confirmed with content experts
2. Review of Existing External Guidelines
   - Cincinnati BESt (Best Evidence Statement)
3. Literature Review of Relevant Evidence
   - Searched: PubMed, Cochrane Library, National Guideline Clearinghouse, Google
4. Critically Analyze the Evidence
   - 9 randomized controlled trials and 36 non-randomized studies
5. Summarize the Evidence
   - Materials used in the development of the clinical standard, literature appraisal, and any order sets are maintained in an Acute Hematogenous Osteomyelitis (AHO) evidence-based review manual within EBOC.

Evaluating the Quality of the Evidence

Published clinical guidelines were evaluated for this review using the **AGREE II** criteria. The summary of these guidelines are included in the literature appraisal. AGREE II criteria evaluate Guideline Scope and Purpose, Stakeholder Involvement, Rigor of Development, Clarity and Presentation, Applicability, and Editorial Independence using a 4-point Likert scale. The higher the score, the more comprehensive the guideline.

This clinical standard specifically summarizes the evidence *in support of* or *against* specific interventions and identifies where evidence is *lacking/inconclusive*. The following categories describe how research findings provide support for treatment interventions.
"Evidence Supports" provides evidence to support an intervention
"Evidence Against" provides evidence against an intervention.
"Evidence Lacking/Inconclusive" indicates there is insufficient evidence to support or refute an intervention and no conclusion can be drawn *from the evidence*.

The **GRADE** criteria were utilized to evaluate the body of evidence used to make practice recommendations. The table below defines how the quality of the evidence is rated and how a strong versus weak recommendation is established. The literature appraisal reflects the critical points of evidence.

Recommendation	
STRONG	Desirable effects clearly outweigh undesirable effects or vice versa
WEAK	Desirable effects closely balanced with undesirable effects
Quality	**Type of Evidence**
High	Consistent evidence from well-performed RCTs or exceptionally strong evidence from unbiased observational studies
Moderate	Evidence from RCTs with important limitations (e.g., inconsistent results, methodological flaws, indirect evidence, or imprecise results) or unusually strong evidence from unbiased observational studies
Low	Evidence for at least 1 critical outcome from observational studies, RCTs with serious flaws or indirect evidence
Very Low	Evidence for at least 1 critical outcome from unsystematic clinical observations or very indirect evidence

Recommendations

Practice recommendations were directed by the existing evidence and consensus amongst the content experts. Patient and family preferences were included when possible. The Content Expert Team and EBOC team remain aware of the controversies in the diagnosis/management of Acute Hematogenous Osteomyelitis (AHO) in children. When evidence is lacking, options in care are provided in the clinical standard and the accompanying order sets (if applicable).

Approval Process

Clinical standards are reviewed and approved by hospital committees as deemed appropriate for its intended use. Clinical standards are reviewed as necessary within EBOC at Texas Children's Hospital. Content Expert Teams are involved with every review and update.

Disclaimer

Practice recommendations are based upon the evidence available at the time the clinical standard was developed. Clinical standards (guidelines, summaries, or pathways) do not set out the standard of care and are not intended to be used to dictate a course of care. Each physician/practitioner must use his or her independent judgment in the management of any specific patient and is responsible, in consultation with the patient and/or the patient's family, to make the ultimate judgment regarding care.

Version History

Date	Action	Comments
Mar 2012	Originally completed	