# Acute Hematogenous Osteomyelitis in Children

## Pathogenesis, Diagnosis, and Treatment

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**KEYWORDS**

• Acute hematogenous osteomyelitis • Children • Pathogenesis • Diagnosis • Treatment

**KEY POINTS**

- Proper care for children with AHO is inherently a multidisciplinary and collaborative process that should be guideline driven and evidence based.
- AHO is the most difficult condition to understand in the realm of pediatric musculoskeletal infection and continues to present a significant clinical challenge due to the evolving epidemiology and complex pathogenesis.
- A lack of institutional consensus as to the most effective evaluation and management strategies may lead to variation in care, which in turn may have an adverse impact on clinical outcomes. Such variability, which may easily occur in large pediatric medical centers, can make coordination of care extremely difficult.
- Despite these challenges, a guideline-driven, multidisciplinary approach has been introduced and shown to effectively reduce hospital stay, improve the timing and selection of empirical antibiotic administration, reduce delay to initial MRI, reduce the rate of readmission, and shorten antibiotic duration.
- Carefully monitoring regional trends in microbiologic epidemiology and applying a guideline-driven approach for evaluation and treatment will improve care for children with AHO and, inevitably, those with other forms of musculoskeletal infection as well.

## INTRODUCTION

Musculoskeletal infection in children is a broad topic covering an array of conditions that may occur in isolation or in combination, including complex or systemic forms. These conditions include osteomyelitis (acute, subacute, and chronic), discitis, septic arthritis, pyomyositis, abscess (superficial or deep), cellulitis, fasciitis (including necrotizing fasciitis), lymphangitis, and lymphadenitis. Children with musculoskeletal infection may have additional involvement of other systems, including deep vein thrombosis (DVT), septic pulmonary embolism, pneumonia, empyema, endocarditis, bacteremia, and septic shock. The clinical presentation of children with any of these conditions may have sufficiently similar features to create an initial diagnostic dilemma until thorough history, physical examination, laboratory tests, plain radiographs, and advanced imaging can be performed. A variety of disciplines and hospital services are usually involved in the evaluation process, including emergency medicine,

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pediatrics, infectious disease, orthopedic surgery, intensive care, radiology, anesthesiology, laboratory, nursing, and pharmacy. Because of this, the care of children with musculoskeletal infection inevitably requires an organized, interdisciplinary approach to reach timely, comprehensive, and accurate diagnoses. From that point forward, effective treatment may be carefully planned and enacted with subsequent monitoring of the child until clinical resolution is achieved. Ideally, clinical practice guidelines should be established to help orchestrate the complex array of events that are necessary to reach the point of resolution with the best outcomes. Unfortunately, this is not a simple undertaking. There is a paucity of high-quality evidence to guide care. There are substantial regional variations in the incidence and severity of illness of children with these conditions. There is also moderate disagreement as to the categorical differentiation of the array of conditions that comprise musculoskeletal infection in children, which can confuse recommendations of evaluation and treatment at regional and institutional levels. Of even greater relevance, however, is the wide range of individual practice preferences, knowledge limitations, and institutional workflows that lead to variation in understanding and treating these conditions. To overcome these limitations, it is necessary to focus on foundational disorders and develop sound principles to guide awareness of pathophysiology, diagnosis, and treatment that serve to guide care for the wide array of disorders that comprise pediatric musculoskeletal infection. AHO is the principal disorder that enables establishing this foundation. Developing rational, evidence-based clinical practice guidelines for this one condition will effectively support the evaluation and management of the full spectrum of pediatric musculoskeletal infections because children with AHO represent the entire gamut of illness from mild to severe, simple to complex, and focal to systemic. For these reasons, this review is devoted exclusively to AHO in children, with the intent to provide an update on the current understanding of existing evidence and future directions, which should be explored to improve care for those with any form of musculoskeletal infection.

## EPIDEMIOLOGY

The incidence of AHO varies by region and time.[1] The authors reported a 600% increase in pediatric osteomyelitis over a 2-decade period within a community.[1] During that time, the local population had increased by 220%.[1] The relative virulence of the infections has seemingly increased, a concern attributed to the causative organism. The Agency for Healthcare Research and Quality provides national estimates on hospital discharges for children ages 0 to 17 years from the Healthcare Cost and Utilization Project (HCUP) Kids' Inpatient Database (KID). Trends between 1997 and 2012 suggest that the incidence of AHO has varied regionally, with the highest percentage currently reported the southern region (Fig. 1). Surveillance data from specific communities have reported varying incidence rates over time, with 1 report indicating a 600% increase in the incidence of osteomyelitis when comparison was made to the experience of the same organization 2 decades prior.[1] The incidence of AHO also varies according to the age and gender of the child due to processes of skeletal and vascular development.[2,3] The reported rate of AHO varies between 1:5000 and 1:10,000, with boys having a rate twice that of girls.[4–7]

## PATHOGENESIS

AHO is caused by bacterial seeding that is thought to develop due to transient bacteremia, which can result from otitis media, pharyngitis, and daily activities, such as brushing teeth.[8] A transient bacteremia alone is thought insufficient for the development of AHO due to the lack of available free iron in human blood to sustain the bacteria. Bacterial genetic up-regulation of virulence and iron metabolism genes or regional bone trauma are postulated to predispose to infection.[3] In rabbits, bacterial inoculation associated with bone trauma had a higher rate of osteomyelitis than those without injury.[9,10]

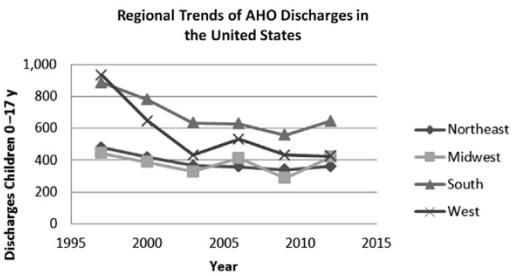


Fig. 1. HCUPnet KID data for hospital discharges of children 0 to 17 years by regions of the United States from 1997 to 2012. (*Data from* HCUP Kids' Inpatient Database (KID). Healthcare cost and utilization project (HCUP). Rockville (MD): Agency for Healthcare Research and Quality; 2015.)

Osteomyelitis typically develops in the metaphyseal region of long bones (or long bone equivalent areas, such as the calcaneal apophysis or inferior pubic ramus). It is surmised that the bacteria aggregate in these areas due to the tortuous blood flow, where the dilated capillaries make a sharp turn at the physis.[2,4,8] Once infection is established, it may expand and evolve to intraosseous, subperiosteal, or extraperiosteal abscesses or extend into an adjacent joint space, particularly if the metaphysis is intracapsular, resulting in contiguous septic arthritis.[2,8] The rate of adjacent septic arthritis and osteomyelitis is 33%.[6] Historically, the sequela-prone child was suspected of having contiguous osteomyelitis and septic arthritis due to persistent elevation of inflammatory markers after initial drainage of septic arthritis and considered to have a poor prognosis compared with those who had isolated septic arthritis.[7,11,12]

The microbiologic epidemiology of AHO has remained relatively consistent over time, with *Staphylococcus aureus* accounting for a majority of cases.[13] Regional variation of antibiotic resistance of *S aureus* has occurred in several communities within the United States. In south Texas, rates of methicillin-resistant *S aureus* (MRSA) (30.4%), methicillin-sensitive *S aureus* (28.6%), other organisms (19.6%), and no growth (21.4%) have been reported.[1,14] Identifying a causative organism may be a challenge, with rates of culture-negative osteomyelitis from 16% to 42%.[15] Supplemental techniques may enhance bacterial identification and include inoculation of blood or chocolate agar plates intraoperatively or the utilization of polymerase chain reaction (PCR) to identify *Kingella kingae* in children between the ages of 6 months and 4 years.[13,16] An organized approach to specimen acquisition and laboratory processing may improve utilization of resources (**Table 1**).[13] It is important to attempt to identify the causative organism whenever possible to effectively guide specific antibiotic therapy.[15,17,18]

Recent basic science research has explored the genome of *S aureus* and the virulence factors that may underlie the variability of illness severity seen among children with AHO.[13,19,20] A better understanding of the genetically encoded virulence capability of the bacteria may help to improve early recognition of children who are prone to develop severe illness and encourage a more aggressive initial treatment strategy in those cases.

## CLINICAL PRESENTATION

Children with AHO typically have symptoms 3 to 4 days prior to presentation.[5,21] Infection is more common in lower extremities than upper extremities, with the 3 most common sites the

**Table 1**
**Culture recommendations in the setting of acute hematogenous osteomyelitis in children**

| Source | Host Factors | Culture Recommendations |
|---|---|---|
| Blood | | Aerobic blood culture obtained prior to antibiotic administration. |
| | | If positive, repeat daily until 2 consecutive negative cultures. |
| | | If peripherally inserted central catheter or central line is placed, obtain surveillance cultures when febrile. |
| Bone | Healthy | Aerobic culture (only) obtained from the site of infection whenever possible. |
| | | Can be performed after antibiotic administration; do not withhold antibiotic if child is septic. |
| | Immunocompromise<br>Penetrating inoculation<br>Failed primary treatment | Aerobic, anaerobic, fungal, and acid-fast bacilli cultures; consider 16S or fungal PCR. |
| | Age 6 mo to 4 y | Consider *K kingae*; swab to blood or chocolate agar plate in operating room. |
| Joint fluid | | Assess for contiguous septic arthritis using cell count and aerobic culture. |
| Abscess | | Aerobic culture; consider *Bartonella* PCR if cat-scratch disease is suspected. |

femur (27%), tibia (22%), and humerus (12%).[7] Single-bone involvement is more common than multifocal infection.[4,5,7] More than 50% of cases occur in children under the age of 5 years.[7]

## Radiology

Evaluation of a child with concern for infection requires a thorough history and physical examination to be able to guide the appropriate selection of body area to be imaged and imaging modality.

## Conventional Radiography

Imaging always starts with conventional radiographs due to their low cost, availability, and ability suggest correct diagnosis and exclude other diagnoses.[22] High-quality plain radiographs demonstrate local bony changes, periosteal reaction, deep soft tissue involvement, and may identify concerning features suggestive of neoplasm or fracture which might have otherwise been overlooked. The first radiographic sign of AHO is deep soft tissue swelling with.[23,24] Lytic changes in the bone require 50% to -75% of the bone mineral density to be depleted before becoming evident on plain radiographs.[24] These more definitive signs of bone destruction and periosteal reaction may not occur until 1 to -2 weeks after the infection has been present.[23–25]

## Advanced Imaging

There are advantages and disadvantages with the use of advanced imaging modalities in the evaluation of children who present with signs and symptoms of possible deep infection (Table 2). Clinicians must carefully consider the issues of cost, diagnostic accuracy, timeliness of diagnosis, and potential delay in treatment with or without the use of these modalities. Additional imaging for osteomyelitis may include ultrasound (US), CT, and MRI. US is commonly used to evaluate hips for effusion and possible septic arthritis as well as screen for DVT in the setting of MRSA osteomyelitis. This imaging modality also is used to assess for psoas and subperiosteal abscesses.[26] US may demonstrate early changes of osteomyelitis with findings of deep soft tissue swelling.[26] Advantages include the noninvasive nature of the study and the ability to acquire the information without sedation.

CT is excellent for defining bony pathology.[23] This method has limited application, however, in the diagnosis and management of osteomyelitis in children due to radiation exposure and limited visualization of the anatomic and spatial extent of tissue inflammation. CT has demonstrated a sensitivity for osteomyelitis of 66% and specificity of 97%.[27] CT can provide detail about sequestration and large abscess formation, so

**Table 2**
**Imaging modalities for acute hematogenous osteomyelitis**

| | Advantages | Disadvantages |
|---|---|---|
| Radiograph | • Low cost<br>• No need for sedation<br>• Readily available<br>• High sensitivity, late | • Delayed appearance on radiograph<br>• Under-represents extent of disease |
| US | • Low cost<br>• Absence of radiation exposure<br>• No need for sedation<br>• Ability to detect and localize fluid collections for aspiration | • Technique dependent<br>• Depth of visualization<br>• Unable to penetrate bone |
| CT | • Higher cost<br>• Rare need for sedation<br>• Fast<br>• Excellent bony detail<br>• Ability to detect and localize fluid collections for aspiration | • Radiation exposure<br>• Uses CT resources<br>• Not great soft tissue visualization<br>• Does not distinguish inflammation in tissues<br>• Scatter from nearby metal |
| MRI | • No radiation exposure<br>• Uses MRI resources<br>• Excellent soft tissue visualization<br>• Distinguishes inflammation in tissues<br>• Ability to detect and localize fluid collections for aspiration | • Radiation exposure<br>• Uses CT resources<br>• Not great soft tissue visualization<br>• Does not distinguish inflammation in tissues<br>• Scatter from nearby metal |

it may play a role in monitoring disease progression after initial MRI acquisition. This may be a useful tool for the evaluation of AHO in resource constrained settings but the sensitivity is not nearly as high as that of MRI.[23,25,27]

MRI is excellent at soft tissue characterization at high resolution. It offers improved sensitivity and specificity over CT and the advantage of identifying marrow inflammation.[27,28] A multidisciplinary approach has been shown to decrease the time to MRI and surgery and demonstrated that continuation to the operating room from MRI can be safely performed as a single anesthetic event.[29,30] Earlier MRI and surgery leads to decreased hospital stay.[29,30] Interdisciplinary MRI protocols have been shown to reduce scan duration by limiting the number of body areas imaged and the number of MRI sequences performed.[30] MRI provides powerful information but the cost and resource utilization must be justified. In 1 study, only 16% of repeat MRIs demonstrated new findings and did not necessarily result in a change in intervention.[31] MRI has great utility as an initial screening test and has been recommended in cases of septic arthritis to identify adjacent bone infection prior to arthrotomy.[32] A particularly challenging area for which MRI has proved useful is the assessment of deep musculoskeletal infection in the pelvis.[33–35]

## Laboratory Studies

In the acquisition of blood and local tissue cultures for microbiology processing, additional laboratory studies can guide efficient and appropriate treatment of children with AHO. Multiple acute-phase reactants have been described and evaluated for their utility diagnosing infection, including C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), white blood cell count (WBC), interleukin 6, and D-dimer.[11,36–38] CRP and ESR have been demonstrated the most useful in evaluating AHO. CRP rises rapidly and is useful in monitoring disease resolution during the acute hospitalization phase, because it normalizes 7 days after the initiation of effective treatment.[11] ESR rises more slowly and gradually declines over 2 weeks to 3 weeks. This marker often helps ensure that the standard treatment duration is appropriate to resolve the infection. Initial blood cultures are positive in approximately 30% of children with AHO.[13] This rate may have an adverse impact from prior administrative of antibiotics.[13] It is, therefore, essential to obtain blood cultures from all children in whom there is legitimate concern of possible bone infection.

## Prognosis

Prognosis of osteomyelitis has yet to be carefully studied through longitudinal, prospective clinical outcomes research. Risks for poor outcome, however, generally include delay in diagnosis and contiguous involvement of bone and joint in areas of tenuous blood supply, such as the proximal hip or femur. A multidisciplinary approach to the evaluation and treatment of AHO, involving orthopedic surgeons, pediatricians, infectious disease specialists, and ancillary services, has resulted in a trend to decrease hospital length of stay and decrease delay to initial MRI.[29] Evidence-based algorithms for treatment may be used to guide decision making.[7,29] Although these improvements in process measures and intermediate outcomes have been demonstrated, it is still unclear whether these initiatives will ultimately improve the long-term clinical outcomes of children with AHO.

## Classification

To discuss and treat any disease, a classification system can help improve communication with other practitioners. Classification systems are only of utility, however, if they are reproducible and predict prognosis or guide treatment. Cierny and colleagues[39] developed a classification system for osteomyelitis and proposed treatment strategies based on this system. This classification was developed, however, for adults who often have underlying comorbidities.[39] The utility of Cierny's classification has not been validated for children who are typically healthy, with normal immune function at the time of infection. Pediatric AHO has traditionally been classified by age of onset and circumstance that are relevant to the most likely causative organisms. From this classification scheme, a proposal of empirical antibiotic therapy has been established (**Table 3**).[7,8]

More recently, a classification system has been proposed to assess the relative severity of illness of children with AHO as a guide to prognosis and risk of complications. A simple system to score illness severity using clinical, radiologic, and laboratory parameters, which are available during the first 4 days to 5 days of hospitalization, has been used to guide decisions for early hospital discharge in children with low severity scores.[14] This scoring system is heavily tied to the laboratory trending of the CRP, which has often been used to monitor recovery in children with AHO.[11,36]

Using a classification to guide decision making in the scheme of a clinical practice guideline, as seen in **Table 4**, can guide treatment,

**Table 3**
**Classification of acute hematogenous osteomyelitis by age and factors of onset (nosocomial vs community acquired)**

| Patient Characteristics | Causative Organisms | Empirical Antibiotics |
|---|---|---|
| Nosocomial infection | *S aureus*, Streptococci species, Enterobacteriaceae, Candida species | Nafcillin or oxacillin plus gentamicin or cefotaxime (or cetriaxone) plus gentamicin |
| Community-acquired infection | *S aureus*, group B Streptococcus, *Escherichia coli*, Klebsiella species | Nafcillin or oxacillin plus gentamicin or cefotaxime (or cetriaxone) plus gentamicin |
| Infantile (2–18 mo) | *S aureus*, *K kingae*, *Streptococcus pneumoniae*, *Neisseria meningitidis*, *Haemophilus influenzae* type b (nonimmunized) | Immunized: nafcillin, oxacillin, or cefazolin<br>Nonimmunized: nafcillin, oxacillin plus cefotaxime, or cefuroxime |
| Early childhood (18 mo to 3 y) | *S aureus*, *K kingae*, *Streptococcus pneumoniae*, *Neisseria meningitidis*, *Haemophilus influenzae* type b (nonimmunized) | Immunized: nafcillin, oxacillin, or cefazolin<br>Nonimmunized: nafcillin, oxacillin plus cefotaxime, or cefuroxime |
| Childhood (3–12 y) | *S aureus*, group A β-hemolytic streptococcus | Nafcillin, oxacillin, or cefazolin |
| Adolescent (12–18 y) | *S aureus*, group A β-hemolytic streptococcus, *Neisseria gonorrhoeae* | Nafcillin, oxacillin, or cefazolin; ceftriaxone and doxycycline for disseminated gonococcal infection |

**Table 4**
**Modified severity of illness scoring system for acute hematogenous osteomyelitis**

| Scoring Parameter | Criteria | Points | Total |
|---|---|---|---|
| Initial CRP mg/dL) | >15 | 2 | 0–2 |
| | 10–15 | 1 | |
| | <10 | 0 | |
| CRP hospital day 4–5 (mg/dL) | >10 | 2 | 0–2 |
| | 5–10 | 1 | |
| | <5 | 0 | |
| CRP hospital day 2–3 (mg/dL) | >10 | 2 | 0–2 |
| | 5–10 | 1 | |
| | <5 | 0 | |
| Band percentage of WBC | ≥1.5% | 1 | 0–1 |
| | <1.5% | 0 | |
| Febrile days on antibiotic | ≥2 | 1 | 0–1 |
| | <2 | 0 | |
| Intensive care unit admission | Yes | 1 | 0–1 |
| | No | 0 | |
| Disseminated disease[a] | Yes | 1 | 0–1 |
| | No | 0 | |
| Total | | | 0–10 |

[a] Examples of disseminated disease include: deep venous thrombosis, septic pulmonary embolism, pneumonia, endocarditis, and multifocal osteomyelitis.

reduce variability of care, and result in more effective treatment.[29] The severity of illness score for AHO can be determined within the first 4 days to 5 days of hospitalization. In general, children with mild (0–3) or moderate (4–7) scores can be considered for early discharge, whereas children with severe scores (8–10) typically require ongoing intensive evaluation and may require multiple surgical procedures or additional advanced imaging. This essentially enables a provider to objectively stratify a disease with a wide spectrum of clinical presentation. Using a guideline improves communication and decreases delay of necessary therapy.[29]

## TREATMENT

### Antibiotic Therapy

Management of AHO requires appropriate antimicrobial treatment to eradicate the infection. This typically begins with intravenous (IV) antibiotics to cover the most likely causative organism until culture or sensitivity data are available. Many cases of AHO are treated empirically either due to not obtaining a culture or a culture negative sample. In these cases, antibiotic selection is made from regional data about most common causative organism and rate of community-associated (CA)-MRSA, often with recommendations from pediatric infectious disease specialists.[18] Antibiotic selection is

essentially a community-based endeavor that requires knowledge of the local microbiologic epidemiology and antibiotic resistance patterns within each institution to guide effective empirical antibiotic selection. Culture-negative AHO has been successfully treated using clindamycin in communities with high rates of CA-MRSA.[15,17,18]

There has not been a consensus on antibiotic duration or route. A historical routine treatment, however, often consisted of 6 weeks of IV antibiotics. Better classification and monitoring of AHO have ultimately led to a reduction of the practice of prolonged IV antibiotic treatment, which has been shown to have a high complication rate of 25% to 38% and a 19% to 27% rehospitalization rate.[40]

Currently, the treatment of AHO involves sequential parenteral to oral antibiotic therapy for 4 weeks with a demonstrated efficacy similar to that of prolonged IV antibiotics.[41,42] Oral antibiotics offer an attractive alternative due to the reduction of cost and complications and should be considered in all appropriate cases.[43,44]

### Surgical Treatment

Surgical indications and specific guidance as to the specific technique or extent of surgery for AHO have not been studied extensively or clearly defined.[45] Surgical intervention and drainage have been reported as a necessity to avoid progression of disease.[46] Timely initiation of antibiotics may prevent progression, however, to the development of subperiosteal or intraosseous abscess formation that might otherwise require surgical intervention.[47] Imaging and laboratory data can help guide decisions regarding surgery. The specific surgical procedure performed may range in extent from simple (eg, 11-gauge needle biopsy of bone accompanied by aspiration of a subperiosteal abscess) to complex (eg, creation of a corical window with extensive débridement of metaphyseal cancellous bone). Children with moderately large abscesses or those who fail to respond to antibiotic therapy after 48 hours to 72 hours should be considered candidates for surgery.[45] When surgical intervention is performed, appropriate cultures should be sent and a bone biopsy should always be obtained to assess for infiltrative or malignant processes that may mimic infection. Some children may require more than 1 surgical procedure to help decrease the local burden of infection and improve their response to ongoing antibiotic administration. This decision is typically guided by the trends in a child's temperature (fever curve) and CRP. In general, if the CRP is static or rising and the child remains febrile, a surgeon is called on to determine if additional surgical débridement may be beneficial. This is typically a decision that must be made on a case-by-case basis (Fig. 2).

### Complications

Complications of AHO are reported in approximately 6% of children and include chronic infection, avascular necrosis, growth disturbance, pathologic fractures, DVT, and sepsis.[8,45,48,49] The rate of chronic osteomyelitis have been estimated to be 1.7% overall and the rate of recurrent infection has been reported as high as 6.8%.[45,50] Clinically significant DVT occurs between 0.4% and 6%, with a higher rate in children with MRSA.[45,49] Higher rates of DVT have been reported with routine DVT-US screening.[51] Growth disturbance occurs in 1.8% of children and presents a challenging problem that may not be evident for years after resolution of infection.[45,52] Pathologic fracture occurs in 1.7% of patients, typically occurring in those with who had more severe infections and who underwent surgical débridement.[45,53]

## DISCUSSION

AHO in children is an ideal condition to study due to its representation of a wide spectrum of disorders that comprise pediatric musculoskeletal infection. Proper care for children with AHO is inherently a multidisciplinary and collaborative process that should be guideline driven and evidence based. AHO is the most difficult condition to understand in the realm of pediatric musculoskeletal infection and continues to present a significant clinical challenge due to the evolving epidemiology and complex pathogenesis. A lack of institutional consensus as to the most effective evaluation and management strategies may lead to variation in care, which, in turn, may have an adverse impact on clinical outcomes. Such variability, which may easily occur in large pediatric medical centers, can make coordination of care extremely difficult. Despite these challenges, a guideline-driven, multidisciplinary approach has been introduced and shown to effectively reduce hospital stay, improve the timing and selection of empirical antibiotic administration, reduce delay to initial MRI, reduce the rate of readmission, and shorten antibiotic duration.[21] Carefully monitoring regional trends in microbiologic epidemiology and applying a guideline-driven approach for evaluation and treatment improve care for children with AHO

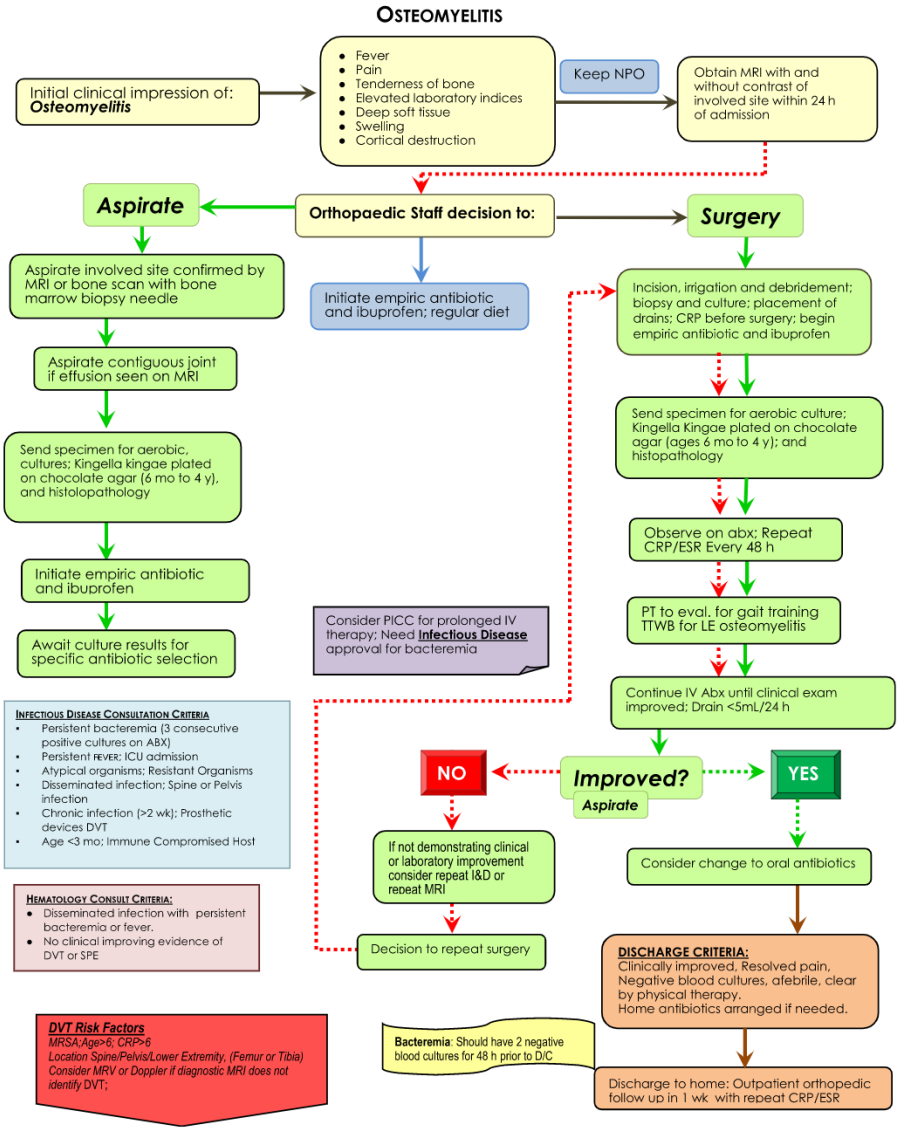


**Fig. 2.** Osteomyelitis treatment diagram. Abx, Antibiotic; D/C, discharge; DVT, deep venous thrombosis; eval., evaluation; I&D, irrigation and debridement; ICU, intensive care unit; LE, lower extremity; PICC, peripherally inserted central catheter; PT, physical therapy; SPE, septic pulmonary emboli; TTWB – toe touch weight bearing. (*Courtesy of* Children's Medical Center of Dallas, Dallas, TX; with permission.)

and, inevitably, those with other forms of musculoskeletal infection as well.

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