Mohammed Jazaa Alanazi et al, 2023;7(8):1136–1142.
https://doi.org/10.24911/IJMDC.51-1672403806

REVIEW ARTICLE

Diagnosis, treatment approaches and modalities of acute hematogenous osteomyelitis in children: a literature review

Mohammed Jazaa Alanazi[1], Ibrahim Musaad Alzahrani[2*], Abdullatif Alfadhel Alshanqiti[2], Razan Mohammed Alotaibi[3], Abdulmalik Brahim Alrebdi[4]

ABSTRACT

Acute hematogenous osteomyelitis (AHO) in children is a serious condition that affects the bones and is caused by different organisms. Reliable history, physical examination, basic laboratory tests, and radiological imaging studies lead to early detection and a significant reduction in morbidity and mortality. In contrast, long-term complications and morbidity are mainly due to delays in diagnosis and inadequate management. This literature review aimed to provide an evidence-based, comprehensive summary of AHO in children regarding the definition, epidemiology, risk factors, causes, pathogenesis, clinical picture, and differential diagnosis, specifically focusing on diagnosis and management. Most updated knowledge from the current literature reviews, systematic reviews, and practical guidelines have been summarized by targeting literature search on PubMed and Google Scholar, including articles published until November 2021. Despite the morbidity and frequency of AHO in children, it was found that there are low numbers of high-quality, updated data in this regard, especially the diagnosis and management of AHO in children. For this reason, the authors have provided an updated comprehensive summary of AHO in children to contribute to filling the research gap on this important topic.

Keywords: Acute, antibiotic therapy, children, hematogenous, osteomyelitis.

Introduction

Acute Hematogenous Osteomyelitis (AHO) is defined as an inflammation of the bones caused by a pyogenic organism, and the duration of symptoms is less than 2 weeks. Osteomyelitis has devastating outcomes and is a great burden worldwide, especially in children. Early diagnosis and management could have a tremendous positive effect and result in a decrease in morbidity. With the advancement of modern medicine and the varieties of different management techniques, the incidence of Osteomyelitis has decreased over the last 30 years [1]. Osteomyelitis could be classified according to the source of infection into hematogenous (endogenous) and non-hematogenous (exogenous) osteomyelitis. Hematogenous osteomyelitis could be further classified as AHO, subacute hematogenous osteomyelitis, and chronic hematogenous osteomyelitis. The incidence rate of AHO varies from 1:5,000 to 1:10,000 and has a 2:1 male-to-female ratio [2], with *Staphylococcus aureus* being the most detected organism [3].

However, despite the prevalence and morbidity of AHO in children, there is rarely high-quality and up-to-date data regarding AHO in children, especially the diagnosis and management of AHO in children. Thus, it was important to provide a comprehensive overview of AHO, especially

Correspondence to: Ibrahim Musaad Alzahrani
*College of Medicine, Taibah University, Medina, Saudi Arabia.
Email: Ibrahimalzahrani1997@gmail.com
Full list of author information is available at the end of the article.
Received: 30 December 2022 | **Accepted:** 08 March 2023

OPEN ACCESS
This is an open access article distributed in accordance with the Creative Commons Attribution (CC BY 4.0) license: https://creativecommons.org/licenses/by/4.0/) which permits any use, Share — copy and redistribute the material in any medium or format, Adapt — remix, transform, and build upon the material for any purpose, as long as the authors and the original source are properly cited. © Copyright: Author(s)

diagnosis and management, for the benefit of others. Therefore, this article aimed to review the definition, epidemiology, risk factors, causes, pathogenesis, clinical presentation, diagnoses, and management of children with AHO.

Subjects and Methods

A targeted literature search was performed on PubMed and Google Scholar, including articles published until November 2021. The following keywords were used for the literature search: "AHO," "Pediatrics," "Osteomyelitis," "Pediatrics osteomyelitis," "AHO," "Complications," "Diagnosis," "Pathogenesis," "Causes," "Risk factors," "Treatment." The inclusion criteria were articles on AHO in pediatrics and articles published in English. The exclusion criteria were related to AHO in adults and non-English articles.

Discussion

Epidemiology

Even with the development of treatment of osteomyelitis, it is still a major burden and a challenge worldwide. Although AHO could affect any age group, school-aged children have the highest incidence, which is particularly common in the age group between 7 and 10 years. The ratio between males and females is 1.5:2. AHO more commonly affects the metaphyseal growth plate because of the high blood supply and slower blood flow [4, 5].

Risk factors and causes

The pediatric osteomyelitis risk factor in the literature varies from the unknown by 29% to 47% for direct, blunt trauma, and 37% for recent systemic infection [1]. There are various indeterminant variables of risk factors and causative organisms. For example, for neonates, the risk factors could be due to prematurity, complicated delivery, central venous catheter, urinary tract infection, or active maternal infection at the time of delivery. And for older children, the risk factors are sickle cell disease, sepsis, and minor trauma vascular catheterization, such as hemodialysis and immunodeficiency disorders [6].

Staphylococcus aureus is the most common causative organism accounting for more than 80% of positive cultures, followed by Group A *Streptococcus* (GAS) and third is Group B *Streptococcus*. *Staphylococcus aureus* and *Salmonella* spp. are common in children with sickle cell anemia (SCA). Simultaneously, *Escherichia coli* and *Salmonella enteritidis*, alongside *S. aureus* and *Staphylococcus pneumoniae,* are frequently found in HIV-infected patients. In some European countries, children younger than 5 years are found to have a Kingella Kingae infection. This is because the vaccination against Haemophilus influenza B is uncommon in developed countries, except in unvaccinated children. The situation is similar for *Streptococcus pneumoniae.*

While Saudi Arabia and Finland have a low incidence of community-associated methicillin-resistant *S. aureus*, the incidence is increasing in many countries like United States, Greece, and Romania [5,6].

Pathogenesis

AHO is the most common type of osteomyelitis in children because of the hematogenous spread of pathogens. It generally affects many bones, particularly the femur 26.9%, followed by the tibia 26%, the pelvis 9.2%, and the humerus 8.2% [1]. The pathophysiology of AHO in children is still unclear, but it is suggested that it's a result of the special anatomy of children. The stasis could explain it and the slow flow of blood supply, accompanied by the bacteremia entering the metaphysis vessels that lack the reticuloendothelial lining making it susceptible to bacterial growth, resulting in inflammation and further bone destruction and necrosis. Also, with blunt trauma resulting in micro-thrombus or micro-hematomas, bones might become vulnerable to infection [3].

Signs and symptoms

The clinical presentation of AHO varies considerably depending on the child's age and causative organism [7].

The initial documented symptoms of AHO in an early presentation could be nonspecific in children of all ages, such as malaise and low-grade fever without a known origin. Once the infection has been confirmed in a specific bone, the symptoms are more localized and severe. AHO in children usually presents acutely with high-grade fever plus constitutional symptoms. These include irritability, reduced appetite or activity, refusal to walk, bone foci that suggest symptoms of inflammation (warmth, swelling, and tenderness), and restriction in limb function, such as a limp, restricted use of an extremity, and absent or decreased spontaneous movement of the limb (pseudo paralysis) [6].

The local signs and symptoms are joint swelling and pain associated with the classic signs of inflammation, like symptoms of pain, effusion, functional limitation, tenderness, and focal warmth. These signs are more commonly present at the onset of the disease in older children [7].

Late presentation of the disease is commonly associated with systemic manifestations such as pyrexia, tachycardia, and a painful limp. Also, edema involving the entire lower limbs, cellulitis, or abscess formation was documented in patients with late presentation [7].

The most common clinical presentations of children diagnosed with AHO based on a systematic review from the year 2019 are pain (81%), a localized sign or symptom (70%), high fever (62%), restricted range of motion (50%), and reduced load-bearing (pseudo paralysis) (49%) [5].

It was also reported by Lindsay et al. [8], about the seasonal variation associated with the severity and onset of symptoms in children with AHO. They documented that symptoms occur more commonly during the summertime (73, 34.9%) or spring season (54, 25.8%) than in the autumn (45, 21.5%) and wintertime.

Complications

In children with hematogenous osteomyelitis, several serious complications have been documented, including chronic osteomyelitis, avascular necrosis, septic pulmonary emboli, disseminated infection with multiorgan failure, arrest in the growth, and pathologic fractures. The early course of infection might be complicated acutely by persistent bacteremia, prolonged fever, sepsis, thrombophlebitis, and abscess formation requiring surgical procedures, extended hospital stays, and parenteral antibiotics therapy [9].

Distribution of the infection to the growth plate could cause serious complications such as length discrepancy of the limbs due to arresting the appendicular growth. Also, it was documented that the pathogen's distribution to the growth plate increases the incidence of pathological fractures in that area [9].

In children with AHO caused by methicillin-resistant *S. aureus* (MRSA), there is a greater likelihood of experiencing these complications than in children with a similar condition caused by methicillin-susceptible *S. aureus* or organisms other than *S. aureus* [5].

Children should be followed closely within 2 weeks of discharge to identify and treat any complications [5].

Differential diagnosis

Many diseases generate clinical signs and symptoms that are remarkably equivalent to AHO and should be ruled out before diagnosing the disease. These are the surrounding soft-tissue infections (pyomyositis and myositis), septic arthritis, non-infectious inflammatory diseases like transient or toxic synovitis, juvenile idiopathic arthritis, polymyositis, rheumatic fever, post-infectious arthralgia, discitis, or arthritis that might mimic hematogenous osteomyelitis. Infants with congenital syphilis could develop osteomyelitis that mimics other causes of osteomyelitis. Primary bone tumors like Ewing sarcoma, osteosarcoma, or secondary tumors such as tumors that metastasize from Langerhans cell histiocytosis, neuroblastoma, and osteoid osteomas, or benign osteochondromas might have clinical manifestations that are similar to AHO. The bone pain can also be due to metabolic defects such as Gaucher disease, acute lymphoblastic leukemia, and bone infarction, which could result from sickle cell crisis or other hemoglobinopathies. Legg-Calve-Perthes disease or slipped capital femoral epiphysis could mimic AHO that affects the proximal part of the femur. Bacterial sepsis and complex regional pain syndromes could lead to limb pain which is suggestive of bone infection. Non-displaced bone fractures could sometimes lead to a fever that mimics hematogenous osteomyelitis. Chronic nonbacterial osteomyelitis is usually unrecognizable during the initial presentation from culture-negative AHO [10].

Avascular necrosis, vitamin A deficiency, or chronic recurrent multifocal osteomyelitis are also significant differential diagnoses [5].

Diagnosis

The first step toward diagnosing AHO is to conduct a thorough history, physical examination, laboratory tests, and imaging and to detect the pathogen in the bone, blood, or joint fluid [11,12].

Obtaining laboratory tests and cultures of all patients before antibiotics are crucial to increasing the probability of identifying the causative pathogen and initiating the appropriate treatment [7,13].

Laboratory tests include the inflammatory markers C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), white blood cells (WBC), procalcitonin, and pancreatic stone function. CRP and ESR are commonly used inflammatory markers that help to rule out an acute osteoarticular infection. However, CRP is superior in monitoring the disease because it has a half-life of fewer than 19 hours and normalizes faster (7-10 days) than ESR, which takes more than 2-3 weeks [5]. In addition, the WBC count is not significant in younger children, though a higher count is alarming for the severity of the disease [7].

New emerging biomarkers are procalcitonin and pancreatic stone protein (PSP), used to diagnose acute pediatric osteomyelitis. Procalcitonin is a peptide hormone released by non-neuroendocrine parenchymal cells in the body. High levels are seen in severe bacterial infections and osteomyelitis. It is discussed as a potential diagnostic aid in diagnosing acute pediatric osteomyelitis [14]. PSP regenerates protein, is secreted by pancreatic acinar cells and by subsets of intestinal and gastric cells [15], and is linked with inflammation and infection. Combining procalcitonin and PSP levels showed a sensitivity of 85.87% and specificity of 84.21% in diagnosing acute osteomyelitis. Thus, they have the potential to be used as diagnostic markers in the early stages of the disease [14].

Cultures confirm the causative pathogens since detecting the causative pathogen is the milestone in selecting the appropriate antibiotic, especially in antibiotic-resistant pathogens [5].

Blood cultures have a lower diagnostic yield (10%-40%) than bone and joint sample cultures (40%-50% positive) [5]. The higher the blood volume, the higher probability of detecting the causative pathogens. Hence, the recommended total blood volume drawn from children weighing 1 to 2 kg is 2 to 4 ml. In children weighing more than 2 kg and less than ≤12 kg, it is 6 ml.

For children weighing 13 to 40 kg, it is 10 to 20 ml, and for children weighing more than >40 kg, it is 40 ml [16]. A retrospective study done by Lansell et al. [11], demonstrates that the rate of the culture testing negative is up to 42% in pediatric musculoskeletal infection. The early initiation of antibiotics might not affect the culture positivity and pathogen identification. However, the study has some limitations because of a small sample size. Polymerase chain reaction and 16-second ribosomal RNA gene sequencing are new emerging diagnostic modalities for rapidly and more efficiently identifying pathogens [5, 13].

Regarding imaging, plain radiography is known to be the initial imaging modality in patients suspected of musculoskeletal infection. In the initial phases of infection, images are often normal. Deep soft-tissue swelling is the key finding of the disease early on [7]. It helps exclude other causes (e.g., fractures, neoplasm) and establish a baseline to detect any changes that might occur in advance. These include lytic lesions and periosteal new bone formation [5, 7, 13] that takes around 1-2 weeks to develop after the onset of symptoms after depleting more than two-thirds of the bone mineral density [2]. Ultrasonography is sensitive in identifying joint effusion, soft tissue swelling, and subperiosteal abscess and aid in joint aspiration [5, 13]. Magnetic Resonance Imaging (MRI) is the most accurate imaging modality in detecting AHO, with significantly higher sensitivity (97%-100%) and specificity (92%) compared to radiographs or bone scintigraphy [5]. MRI could detect early changes of osteomyelitis within 2-5 days of the onset of the disease, detect the extent of the bony and soft tissue involvement, and determine the size of any effusions or abscesses. Also, it helps in ruling out other concomitant pathology [7,13]. The cost, availability, and need for younger children to be under sedation or anesthesia are the common disadvantages [5,7]. The computed tomography scan in high-income countries is not recommended in diagnosing musculoskeletal infection because of the high radiation exposure and has demonstrated a low sensitivity of 66% compared to MRI [2,5]. Technetium radionuclide (99mTc) bone scintigraphy is used as an alternative for MRI cases with braces or indwelling devices. It has high false-negative results in infants [5].

Management

Pediatric AHO requires a multidisciplinary team that includes specialists in pediatric infectious diseases, pediatricians, radiologists, and orthopedic surgeons [5].

Upon early evaluation of a child with suspected AHO, the hemodynamic state must be stabilized with fluid resuscitation, antipyretics, and analgesics as needed [4]. After stabilization and taking all the necessary culture specimens, the treatment should be started on empirical antibiotics. Once the culture and sensitivity test results appear, the empirical antibiotics are changed according to the results. There is a consideration of surgical intervention, as indicated in special cases [1].

The management of pediatric AHO largely depends on non-surgical treatment. If the antibiotics are started before large necrosis occurs, the treatment would mostly be successful without surgical intervention [17].

Antibiotic therapy

The selection and duration of antibiotics depend on many factors, e.g., the site of infection, the causative pathogen, host defense factors, the disease severity, and the response to the treatment [5].

Selection of empirical antibiotics

The choice of empirical antibiotics would depend on the common pathogen in each age group, associated risk factors (e.g., HIV or SCA), the prevalence of antibiotic resistance, and the immunization status [5] (Table 1).

The age groups are classified into a group of ≤3 months old and a group of >3 months old. In all age groups, the most common pathogen is *Staphylococcus* I. So, in all age groups, empirical antibiotics that cover *S. aureus*, e.g., nafcillin/vancomycin must be used [6,17].

The antibiotic coverage of *S. aureus* could be changed according to the prevalence of MRSA in the geographic area. If the prevalence of MRSA isolates is >10%, clindamycin resistance in MRSA isolates is <10%, and the

Table 1. *The common pathogens and the preferred empirical antibiotics according to the age groups.*

Age group	Common organism	Examples of preferred Antibiotic regimens	Consideration
≤3 months old	- *S. aureus* - group B *Streptococci* - Gram negative bacilli	- Nafcillin Plus - Cefotaxime/Gentamycin	The antibiotic regimen can be changed if the child has associated risk (e.g., HIV/SCA), a high prevalence of antibiotic-resistant bacteria in the same area, or if the child is non-Hib immunized
>3 months old	- *S. aureus* - *Streptococcus pyogenes* - *S. pneumoniae*	- nafcillin Plus - Cefazolin/clindamycin	

HIV, human immunodeficiency virus. SCA. Hib, Haemophilus influenza type B.

patient is not in a severe condition, the preferred antibiotic is clindamycin. If the clindamycin resistance in MRSA isolates is > 10%, or if the patient is in a severe condition, the preferred antibiotic to manage *S. aureus* is vancomycin [5].

For the age group under 3 months, the antibiotic should cover *S. aureus,* Gram-negative bacilli, and group B streptococci, e.g., nafcillin/vancomycin plus gentamicin/cefotaxime. For older than 3 months, the antibiotic should cover *S. pyogenes, S. pneumoniae*, and *S. aureus,* e.g., nafcillin plus cefazolin/clindamycin [6,17].

For non-Hib immunized children less than 4 years old, the antibiotic should cover H-influenzae type B and *S. aureus*, e.g., Nafcillin plus cefotaxime [17]. Antibiotics should also cover *Salmonella* species, e.g., cefuroxime, for children with sickle cell disease [5]. Children with HIV need a broad-spectrum antibiotic because they are susceptible to being infected by many organisms [17].

Organism-specific antibiotics

Once the culture is positive and the sensitivity test result appears, the antibiotic should be changed according to the result [17].

If the culture is negative, which occurs in 50% of suspected AHO cases, continuing the empiric antibiotic depends on the response to the empiric treatment. Generally, most cases with negative culture could be managed with the same regimen used for the positive culture cases in the same geographical location while considering other differential diagnoses [6].

Route and duration of antibiotics

Recent studies have emphasized a parenteral-oral regimen of antibiotics [17]. The appropriate duration of treatment is still unclear. It depends on many factors, e.g., the causative pathogen, the host defense factor, the disease severity, the response to the treatment, and clinical improvement [5]. It is important to know that the duration of the antibiotic regimen is not related to the symptoms and signs at the initial presentation, the presence or absence of positive direction, blood culture, the presence of antibiotic resistance, or purulent material [17].

To achieve the best outcomes, the treatment of antibiotics should continue until there is clinical and lab improvement, including normal CRP [3]. In general, the total duration of uncomplicated AHO is 4 days of intravenous antibiotics, followed by oral therapy, with a total duration of 4 weeks [17]. The total duration is usually longer in complicated cases, when there is delayed clinical improvement, or when there is the need for surgical debridement or persistent CRP elevation [6,17].

The exact duration of IV therapy is not specific. Generally, it could be switch from IV to oral therapy once there is clinical and lab improvement. There are 2 reliable signs on admission that are usually indicating the need to prolong IV therapy. These 2 signs are fever >38.4°C over 3 days or CRP > 100 over 5 days [1,6].

Monitoring

The therapy response could be monitored by serial examinations (e.g., pain and fever), CRP, ESR, WBC levels, and plain radiographs. The frequency of evaluations depends on the patient's clinical status. The signs and symptoms of clinical improvement include the resolution of fever, pain, and erythema is decreased. The signs of lab improvement include a decrease in the WBC and CRP (reduction of >50%). After receiving the appropriate treatment, the expected time for clinical improvement is usually after 4 days. Clinically and lab improvement indicates that the diagnosis and the antibiotic regimen are correct [6].

Surgical intervention

The surgical intervention's role is to improve the local area, e.g., removing the devitalized infected soft tissue and bone or removing a large abscess [17]. Indication of surgery includes abscess in the periosteal or deep soft tissue, signs and symptoms of refractory to empirical therapy, necrotic bone, and the presence of associated septic arthritis [5]. Also, surgical intervention could collect the purulent material from isolating the causative organism for therapeutic benefits [7]. Interventional radiology-guided aspiration of the bone is a less invasive method for taking bone cultures and could be used safely to obtain bone cultures in children with AHO not requiring open surgical drainage. It could also be used to obtain cultures where access to an area is very difficult [18].

Follow-up

Children with osteomyelitis should be seen every 1-2 weeks. In each visit, they should checked for clinical improvement, ESR, CRP, CBC with differential, aminotransferase (if the child receives b-lactam antibiotic), and the antibiotic side effects. The radiographs of the affected area should be obtained before stopping antibiotic therapy. After resolving the signs and symptoms with a normal radiograph and lab tests, the follow-up is unnecessary, and the antibiotic therapy is stopped [6].

Conclusion

Osteomyelitis is a localized bone infection caused by bacteria or fungal pathogens that come through a hematogenous or exogenous route. Once the child is presented to the emergency department, the attention must be focused on stabilizing the patient and giving the child IV fluid, antipyretic, and analgesics, as needed. The diagnosis of AHO is achieved by a combination of history, examination, laboratory investigation, imaging tests, and taking the necessary culture specimens before starting the empirical antibiotics. The treatment of AHO depends largely on non-surgical management, which includes administering empirical antibiotics and then continuing or changing the antibiotics according to the result of the culture and sensitivity tests. The selection of antibiotic

regimens depends on the common pathogens in each age group and other factors like the association of SCA. The clinical status and the treatment response determine the antibiotic's duration. Generally, the duration of non-complicated cases of pediatric AHO is 4 days of IV antibiotic therapy followed by oral therapy with 4 weeks of parenteral-oral antibiotic therapy.

List of Abbreviations

AHO	Acute hematogenous osteomyelitis
CRP	C-reactive protein
ESR	Erythrocyte sedimentation rate
Hib	Haemophilus influenza type B
HIV	Human immunodeficiency virus
MRI	Magnetic resonance imaging
MRSA	Methicillin-resistant *Staphylococcus aureus*
PSP	Pancreatic stone protein
SCA	Sickle cell anemia
WBC	White blood cell

Conflict of interest

The authors declared that there is no conflict of interest regarding the publication of this article.

Funding

None.

Consent to participate

Not required.

Ethical approval

Not required.

Author details

Mohammed Jazaa Alanazi[1], Ibrahim Musaad Alzahrani[2], Abdullatif Alfadhel Alshanqiti[2], Razan Mohammed Alotaibi[3], Abdulmalik Brahim Alrebdi[4]

1. Consultant, Division of Orthopedics, Department of Surgery, King Abdullah Bin Abdulaziz University Hospital (KAAUH), Princess Nourah Bint Abdulrahman University (PNU), Riyadh, Saudi Arabia
2. College of Medicine, Taibah University, Medina, Saudi Arabia
3. Faculty of Medicine, Princess Noura Bin Abdulrahman University, Riyadh, Saudi Arabia
4. Faculty of Medicine, Qassim University, Qassim, Saudi Arabia

References

1. Dartnell J, Ramachandran M, Katchburian M. Haematogenous acute and subacute pediatric osteomyelitis: a systemic review of the literature. J Bone Joint Surg (Br). 2012;94:584–95. https://doi.org/10.1302/0301-620X.94B5.28523
2. Funk SS, Copley LAB. Acute hematogenous osteomyelitis in children: pathogenesis, diagnosis, and treatment. Orthop Clin North Am. 2017;48:199–208. https://doi.org/10.1016/j.ocl.2016.12.007
3. Texas Children's Hospital Evidence-Based Outcomes Center. Acute Hematogenous osteomyelitis (AHO) and septic arthritis evidence-based guideline. Available from: https://www.texaschildrens.org/sites/default/files/uploads/documents/outcomes/standards/MSK_Infections_Guideline_FINAL.pdf
4. McNeil J. Acute hematogenous osteomyelitis in children: clinical presentation and management. Infect Drug Resist. 2020;13:4459–73. https://doi.org/10.2147/IDR.S257517
5. Thakolkaran N, Shetty A. Acute hematogenous osteomyelitis in children. Ochsner J. 2019;19:116–22. https://doi.org/10.31486/toj.18.0138
6. Krogstad P. Hematogenous osteomyelitis in children: epidemiology, pathogenesis, and microbiology. 2014. Available from: http://www.update.com/contents/hematogenous-osteomyelitis-in-children-epidemiology-pathogenesis-and-microbiology.
7. Gigante A, Coppa V, Marinelli M, Giampaolini N, Falcioni D, Specchia N. Acute osteomyelitis and septic arthritis in children: a systematic review of systematic reviews. Eur Rev Med Pharmacol Sci. 2019;23(2):145–58.
8. Lindsay E, Tareen N, Jo C-H, Copley L. Seasonal variation and weather changes related to the occurrence and severity of acute hematogenous osteomyelitis in children. J Pediatric Infect Dis Soc. 2018;7:e16–23. https://doi.org/10.1093/jpids/pix085
9. Alhinai Z, Elahi M, Park S, Foo B, Lee B, Chapin K, et al. Prediction of adverse outcomes in pediatric acute hematogenous osteomyelitis. Clin Infect Dis. 2020;71:E454–64. https://doi.org/10.1093/cid/ciaa211
10. Woods C, Bradley J, Chatterjee A, Copley L, Robinson J, Kronman M, et al. Clinical practice guideline by the pediatric infectious diseases society and the infectious diseases society of America: 2021 guideline on diagnosis and management of acute hematogenous osteomyelitis in pediatrics. J Pediatric Infect Dis Soc. 2021;10:801–44. https://doi.org/10.1093/jpids/piab027
11. Lansell A, Vasili Y, Suchdev P, Figueroa J, Kirpalani A. Impact of antibiotic pretreatment on cultures in children with osteomyelitis and septic arthritis: a retrospective review. BMC Pediatr. 2021;21:342. https://doi.org/10.1186/s12887-021-02806-w
12. Donaldson N, Sanders J, Child J, Parker S. Acute Hematogenous bacterial osteoarticular infections in children practice gaps. Available from: http://pedsinreview.aappublications.org/
13. Arkader A, Brusalis C, Warner W, Conway J, Noonan K. Update in pediatric musculoskeletal infections: when it is, when it isn't, and what to do. J Am Acad Orthop Surg. 2016;24:e112–21. https://doi.org/10.5435/JAAOS-D-15-00714
14. Cui C, Fu M, Gao B. Procalcitonin and pancreatic stone protein function as biomarkers in early diagnosis of acute pediatric osteomyelitis. Med Sci Monit. 2017;23:5211–7. https://doi.org/10.12659/MSM.904276
15. Graf R, Schiesser M, Reding T, Appenzeller P, Sun L, Fortunato F, et al. Exocrine meets endocrine: pancreatic stone protein and regenerating protein-two sides of the same coin. J Surg Res. 2006;133:113–20. https://doi.org/10.1016/j.jss.2005.09.030

16. Saux N. Diagnosis and management of acute osteoarticular infections in children. Canadian Pediatr Soc. 2018;23:336–43. https://doi.org/10.1093/pch/pxy049

17. Song K, Sloboda J. Acute Hematogenous Osteomyelitis in Children. J Am Acad Orthop Surg. 2001;9:166–75. https://doi.org/10.5435/00124635-200105000-00003

18. Mcneil J, Vallejo J, Forbes A, Hulten K, Mason E, Kaplan S. The Utilization of Interventional Radiology Procedures in the Microbiologic Diagnosis of Pediatric Acute Hematogenous Osteomyelitis. Research Gate InOpen Forum Infect Dis. 2015;2:1–66. https://doi.org/10.1093/ofid/ofv131.13