

Pediatric acute hematogenous osteomyelitis: analysis of patients assisted in a university hospital

Osteomielite hematogênica aguda em Pediatria: análise de casos atendidos em hospital universitário

Osteomielitis hematogénica aguda en Pediatria: análisis de casos atendidos en hospital universitario

Pedro Fiorini Puccini¹, Maria Aparecida G. Ferrarini², Antônio Vlado Iazzetti³

ABSTRACT

Objective: To describe occurrence, evolution, and outcome of acute hematogenous osteomyelitis in children and adolescents.

Methods: A descriptive study of 21 cases with patients aged zero to 14 years-old, diagnosed with acute hematogenous osteomyelitis assisted at the Pediatric Infectious Disease Follow-Up Clinic of Escola Paulista de Medicina, between 2005 and 2009. The medical records were reviewed. Descriptive analysis and Spearman's rank correlation were performed, with a 95% confidence interval.

Results: The incidence in males was higher than in females, and children over five years of age were the most affected ones. Fever and pain were the main symptoms, and the long bones were the most often affected. The most commonly recovered pathogen was *Staphylococcus aureus*. The time interval between the onset of symptoms and the diagnosis was 9.7 days, the length of hospital stay was 24.7 days, and the duration of treatment was 71.7 days. Complete resolution occurred in 71.4% of the cases and complications appeared in 28.6% of them, being chronic osteomyelitis the main one.

Conclusions: Data regarding gender, age, etiology, and evolution were in accordance with literature reports. The duration of the treatment was ten weeks, which is longer than usual reports. There were no significant correlations between duration of symptoms before the diagnosis, dura-

tion of hospital stay, and duration of treatment, considering the small sample size.

Key-words: osteomyelitis; children; /etiology; clinical evolution; treatment.

RESUMO

Objetivo: Descrever a ocorrência, a evolução e o desfecho de pacientes com osteomielite hematogênica aguda na faixa etária pediátrica.

Métodos: Estudo descritivo de 21 casos de pacientes de zero a 14 anos com diagnóstico de osteomielite hematogênica aguda, em acompanhamento no Ambulatório de Infectologia Pediátrica da Escola Paulista de Medicina entre 2005 e 2009. A coleta de dados ocorreu pelo levantamento de prontuários. Realizaram-se a análise descritiva e o teste de correlação de Spearman, com intervalo de confiança de 95%.

Resultados: Foi identificada maior incidência no sexo masculino e em crianças maiores de cinco anos. Febre e dor foram os sintomas mais frequentes. Os ossos longos foram os mais acometidos. O principal agente etiológico identificado foi o *Staphylococcus aureus*. Em média, o tempo de sintomatologia até o diagnóstico foi de 9,7 dias, o de internação, 24,7 dias, e o total de antibioticoterapia foi de 71,7 dias. A resolução completa do quadro ocorreu em 71,4% dos casos, com permanência de sequelas em 28,6% deles, sendo a evolução para osteomielite crônica a principal delas.

Instituição: Escola Paulista de Medicina da Universidade Federal de São Paulo (Unifesp), São Paulo, SP, Brasil

¹Graduação em Medicina pela Escola Paulista de Medicina da Unifesp, São Paulo, SP, Brasil

²Mestre em Pediatria pela Escola Paulista de Medicina da Unifesp, São Paulo, SP, Brasil

³Doutor em Pediatria; Professor Adjunto na Escola Paulista de Medicina da Unifesp, São Paulo, SP, Brasil

Endereço para correspondência:

Pedro Fiorini Puccini

Avenida Piassanguaba, 1.923 – Planalto Paulista

CEP 04060-003 – São Paulo/SP

E-mail: puccinipetro@gmail.com

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Conclusões: As características dos pacientes e da doença referentes a sexo, idade, etiologia e evolução mostram-se concordantes com o descrito na literatura. O tempo de tratamento foi de aproximadamente dez semanas, valor acima do habitualmente encontrado nos diferentes estudos. Não foram encontradas correlações significantes entre o tempo de sintomatologia até o diagnóstico, o tempo de internação e o tempo total de antibioticoterapia, havendo a limitação do tamanho da amostra.

Palavras-chave: osteomielite; crianças; etiologia; evolução clínica; tratamento.

RESUMEN

Objetivo: Describir la ocurrencia, la evolución y el desenlace de pacientes con osteomielitis hematogénica aguda en la franja de edad pediátrica.

Métodos: Estudio descriptivo de 21 casos de pacientes de cero a 14 años con diagnóstico de osteomielitis hematogénica aguda, en seguimiento en el Ambulatorio de Infectología Pediátrica de la Escola Paulista de Medicina, entre 2005 y 2009. La recolección de datos ocurrió por el inventario de prontuarios. Se realizaron análisis descriptivo y la prueba de correlación de Spearman, con intervalo de confianza de 95%.

Resultados: Se identificó mayor incidencia en el sexo masculino y en niños con más de cinco años. Fiebre y dolor fueron los síntomas más frecuentes, y los huesos largos fueron los más atingidos. El principal agente etiológico identificado fue el *Staphylococcus aureus*. En promedio, el tiempo de sintomatología hasta el diagnóstico fue de 9,7 días; el de internación, 24,7 días y el total de antibioticoterapia fue de 71,7 días. La resolución completa del cuadro ocurrió en 71,4% de los casos, habiendo permanencia de secuelas en 28,6% de ellos, siendo la evolución para osteomielitis crónica la principal de ellas.

Conclusiones: Las características de los pacientes y de la enfermedad referentes a sexo, edad, etiología y evolución se mostraron concordantes con lo descrito por la literatura. El tiempo de tratamiento fue de aproximadamente diez semanas, valor superior al habitualmente encontrado en los distintos estudios. No se encontraron correlaciones significantes entre el tiempo de sintomatología hasta el diagnóstico, el tiempo de internación y el tiempo total de antibioticoterapia, habiendo la limitación del tamaño de la muestra.

Palabras clave: osteomielitis; niños; etiología; evolución clínica; tratamiento.

Introduction

Hematogenous osteomyelitis is an invasive bacterial disease currently classified as an important cause of morbidity in childhood. Its annual incidence, unchanged in the last decades, ranges from 1:5,000 to 1:10,000 children and is two times higher among boys^(1,2).

Signs and symptoms of osteomyelitis, although well known, are not specific and vary according to age due to the dissemination of local infection, which may reach even the adjacent joint in newborns. Its diagnosis depends on clinical suspicions primarily and, when made at an appropriate time and followed by the initiation of adequate treatment, leads to good outcomes for most patients, with complication rates of about 5% and mortality close to zero^(3,4).

Surgery is not always necessary in cases of hematogenous osteomyelitis. Treatment is basically defined as general patient care, such as hydration, analgesia and treatment of anemia, when necessary, as well as the administration of antibiotics to fight the probable pathogen and to avoid progressive tissue necrosis and complications. Such complications may include the progression to chronic osteomyelitis, pathological fracture, joint instability and changes in the epiphyseal plate⁽⁵⁾.

In all age groups, empirical treatment with antibiotics is initiated according to the most probable pathogen and should include *Staphylococcus aureus*. For newborns, additional coverage should be provided against Gram-negative bacteria⁽⁶⁾. The duration of IV antibiotic administration should be defined by the fever curve and clinical progression, and it is usually about two weeks. In cases there are signs of uncontrolled infection one week after the initiation of adequate antibiotics, the chance of complications should be evaluated^(6,7). Total antibiotic treatment time is usually long and ranges from four to eight weeks for acute osteomyelitis in different studies⁽¹⁻⁴⁾. Its discontinuation should be decided based on the improvement of the lesion and the general condition of the patient, as well as on inflammation markers, particularly erythrocyte sedimentation rate (ESR). Studies in the literature suggest that good progression is primarily associated with use of adequate antibiotics, absence of comorbidities and early diagnosis⁽⁵⁾.

Recent studies compared different diagnostic methods, focusing on whether an early diagnosis may be established⁽⁸⁻¹²⁾. Moreover, different patient groups have been studied to define the disease characteristics, its progression and changes along time, particularly in determinant factors of better or

worse prognoses, such as etiology and the patterns of pathogen resistance to antimicrobial drugs⁽¹³⁻¹⁷⁾.

Therefore, this study discusses the characteristics of a group of patients to provide a better understanding of clinical presentations, treatment strategies and disease progression. For that purpose, it describes the occurrence, progression and outcome of acute hematogenous osteomyelitis in patients seen in the Pediatric Infectious Disease Outpatient Clinic of Escola Paulista de Medicina, Universidade Federal de São Paulo (Unifesp), São Paulo, Brazil.

Methods

This descriptive case series included patients aged zero to 14 years with a diagnosis of hematogenous osteomyelitis followed up in the Pediatric Infectious Disease Outpatient Service of Escola Paulista de Medicina, Unifesp, from February 2005 to October 2009.

The variables under study were those that describe the disease, such as sex, age, site affected, isolated pathogen and type of treatment, as well as time to diagnosis, hospital stay and duration of antibiotic treatment.

Medical charts were reviewed after identifying the patients with osteomyelitis according to outpatient visit records. Sixty-six cases of osteomyelitis were found, and their medical charts in the Medical and Statistical Filing Service of Hospital São Paulo were reviewed. Sixty charts were retrieved and analyzed, and 21 were cases of acute hematogenous osteomyelitis. Of the cases excluded, 17 were not hematogenous, 12 were chronic osteomyelitis, seven had an unspecific diagnosis.

Excel 2000 for Windows 7 Home Premium was used to build the database and analyze data descriptively. The Statistical Package for the Social Sciences (SPSS) 10.0 was used for statistical analysis (Spearman rank correlation) with 95% confidence intervals ($\alpha=0.05$).

This study was approved by the Ethics in Research Committee of Unifesp and Hospital São Paulo.

Results

The 21 cases of acute hematogenous osteomyelitis were analyzed according to two age groups: 0 to less than 5, and 5 to 14 years. The first group had 38.1% of the cases, and the second, 61.9%. In both groups, there were more boys, at a rate of 76.2% of all patients in the two age groups.

The analysis of trauma in clinical history and use of antibiotics before the diagnosis of osteomyelitis were analyzed revealed that trauma was denied in 76.2% of the cases, but prior use of antibiotics was recorded for 47.6%.

The most frequent symptoms were fever and pain, found in over 70% of the cases. The analysis of site of infection revealed that osteomyelitis of the femur was the most frequent and accounted for one third of the cases (Table 1).

The analysis of underlying or previous pathologies revealed that three patients had a history of septic arthritis and

Table 1 - Characteristics of acute hematogenous osteomyelitis cases seen in the Pediatric Infectious Disease Outpatient Clinic of Escola Paulista de Medicina from 2005 to 2009

Characteristic	Yes	%	No	%	Total
Symptoms – clinical conditions					
Fever	15	71.4	6	28.6	21
Pain	15	71.4	6	28.6	21
Edema	11	52.4	10	47.6	21
Functional disability	11	52.4	10	47.6	21
Hyperemia	5	23.8	16	76.2	21
High temperature	5	23.8	16	76.2	21
Affected site					
Femur	7	33.3	14	66.7	21
Tibia	6	28.6	15	71.4	21
Humerus	3	14.3	18	85.7	21
Iliac	2	9.5	19	90.5	21
Fibula	1	4.8	20	95.2	21
Foot	1	4.8	20	95.2	21
Finger	1	4.8	20	95.2	21

Table 2 - Isolated pathogen* in culture and susceptibility tests of acute hematogenous osteomyelitis cases seen in the Pediatric Infectious Disease Outpatient Clinic of Escola Paulista de Medicina from 2005 to 2009

Pathogen	n	%
Oxacillin-susceptible <i>Staphylococcus aureus</i>	7	33.3
Oxacillin-resistant <i>Staphylococcus aureus</i>	2	9.5
Oxacillin-resistant <i>coagulase-negative Staphylococcus</i>	1	4.8
<i>Streptococcus agalactiae</i>	1	4.8
<i>Streptococcus pyogenes</i>	1	4.8
<i>Acinetobacter baumannii</i> susceptible to several antimicrobials	1	4.8
<i>Enterobacter spp</i>	1	4.8
Not identified	7	33.3
Total	21	100.0

*Isolated in blood, bone fragment or secretion culture.

two had hemoglobinopathies. The following comorbidities were found in one case each: juvenile idiopathic arthritis, systemic hypertension, cellulitis and genetic syndrome.

Pathogens were identified in 14 of the 21 cases (66.7%) in blood culture (six cases), bone fragment culture (four cases), or secretion culture (eight cases). Table 2 shows that *Staphylococcus* was responsible for 71.4% of the cases for which the pathogen was isolated. Infection by coagulase-negative *Staphylococcus* was recorded for one case in which the same pathogen was isolated in bone fragment and secretion cultures. Although not usual, that patient was at school age and had no immunodeficiency.

The initial empirical antibiotic regimens were based on the most frequent pathogens of osteomyelitis. In eight cases (38.1%), initial treatment used oxacillin and ceftriaxone; in six (28.6%), oxacillin; and in two (9.5%), cephalothin. Vancomycin was introduced as the initial empirical treatment in two cases (9.5%) with a history of previous hospitalizations due to septic arthritis. The associations of oxacillin and amikacin, cephalothin and amikacin, and ampicillin and gentamicin were administered in one case each (4.8%) for newborns.

In addition to treatment with antibiotics, 14 patients (66.7%) also underwent at least one surgical debridement procedure. Treatment in hyperbaric chamber, however, was not used in any case in this study.

Treatment had to be changed during the progression of the cases due to different reasons. Hospital discharge, when IV antibiotics have to be replaced with oral equivalents, was the main reason and accounted for 35% of the changes. The results of antimicrobial susceptibility tests and the fact that oxacillin was not available in the hospital accounted for 20% of the changes each. Clinical factors were responsible for 15% of the changes, and laboratory findings, for 10%.

During outpatient follow-up, six patients (28.6%) had sequelae, such as progression to chronic osteomyelitis, seen in three cases. Deformities and limitation of movement range were found in one case each and were associated in another case. The two patients that had movement range limitations had osteomyelitis in the neonatal period.

ESR was the main test for inflammation during the clinical and laboratory follow-up of these cases of osteomyelitis. Graph 1 compares the dispersion of ESR values at admission, discharge and discontinuation of antibiotic treatment. ESR values at admission varied greatly and lied within the normal range in some cases. In contrast, at the time of antibiotic discontinuation, they were clearly more homogeneous.

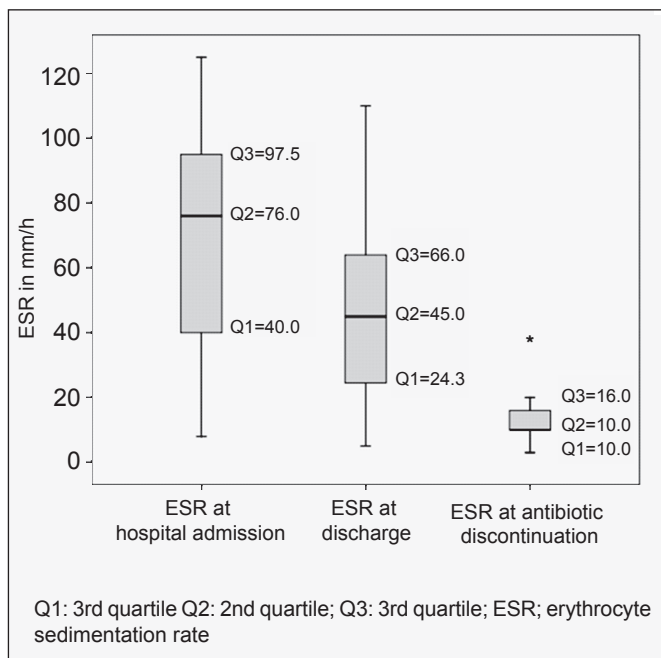
Time to diagnosis, duration of hospital stay and duration of antibiotic treatment are shown in Table 3. Mean values for each time were 9.7, 24.7 and 71.7 days.

The correlation between progression time for the cases under study was analyzed to investigate whether a shorter time to diagnosis would result in shorter of hospitalization and antibiotic treatment duration. However, there were no statistically significant correlations between these variables (Spearman rank correlation, $p > 0.05$).

Discussion

In this descriptive study of 21 cases of acute hematogenous osteomyelitis in a pediatric population, the male-to-female ratio was 3.2:1. Although Riise *et al*⁽¹⁶⁾ did not find any difference between sexes in the incidence of osteomyelitis, most studies^(1,13-15) effectively demonstrated a predominance of male sex. Zaoutis *et al*⁽¹⁷⁾, for example, found that boys were affected in 62% of the cases.

The analysis of distribution according to age group in our study showed that the incidence in children younger than five years and in those five years or older was 38.1% and 61.9%. This result is in agreement with that reported by Zaoutis *et al*⁽¹⁷⁾, who studied children aged 2 months to 17 years and found an incidence of 42% and 58% for the same age groups.



Graph 1 - Comparison of ESR values at three time points in the progression of acute hematogenous osteomyelitis cases

Table 3 - Time in days between events in the progression of acute hematogenous osteomyelitis cases seen in the Pediatric Infectious Disease Outpatient Clinic of Escola Paulista de Medicina from 2005 to 2009

Ethnicity	Difference between time points		n	Time in days			
	Initial time point	→ Final time point		Mean	Median	Q25	Q75
Time to diagnosis	Onset of clinical signs and symptoms	Initiation of empirical antibiotic treatment for osteomyelitis	21	9.7	8.0	5.5	14.0
Hospitalization time	Initiation of empirical antibiotic treatment for osteomyelitis	Hospital discharge	21	24.7	18.0	13.0	41.5
Total antibiotic treatment duration	Initiation of empirical antibiotic treatment for osteomyelitis	Discontinuation of antibiotic treatment	19	71.7	64.0	54.0	81.0

Q: quartile.

In agreement with other studies in the literature, the most frequently affected sites were the long bones, with the femur in 34% of the cases, the tibia in 28% and the humerus in 14%. According to Weichert *et al*⁽¹¹⁾, the femur is affected in 36% of the cases, the tibia in 33%, and the humerus in 10%.

In our study, pathogens were detected in 67% of the 21 cases, most often in secretion cultures. Arnold *et al*⁽¹⁴⁾ identified pathogens in 48% of their cases of osteomyelitis, and Goergens *et al*⁽¹⁸⁾, in 45%, whereas Moumile *et al*⁽¹³⁾ collected data for 186 cases of bone infection and identified pathogens in 19%.

Staphylococcus aureus was isolated in 64% of the cases for which the pathogen was identified. *Streptococcus pyogenes* and *Streptococcus agalactiae* were isolated in one case each (0.7%). Moumile *et al*⁽¹³⁾ found *Staphylococcus aureus* in 60% of the cases with isolates, whereas *Streptococcus pyogenes* and *Streptococcus agalactiae* were responsible for 0.8% of the cases each. *Streptococcus pneumoniae* was isolated in 13% of the cases for which the pathogen was known in the study conducted by Moumile *et al*⁽¹³⁾, but was not found in our study.

Of the nine bacteria of the *Staphylococcus aureus* isolated in our study, two (28%) were resistant to oxacillin. Arnold *et al*⁽¹⁴⁾ identified *Staphylococcus aureus* in 34 cases of osteomyelitis, 23 (67%) of which were caused by oxacillin-resistant pathogens.

In the service where our study was conducted, there are no routine methods to identify *Kingella kingae*, a pathogen that has been shown to play an important role in bone and joint infections in children, particularly those younger than 2 years^(14,19).

The median ESR value at admission was 76.0mm/h (Q1=40.0 and Q3=97.5). For the same time point, Riise *et al*⁽¹⁶⁾ found lower and more homogeneous values, at 41mm/h (Q1=27 and Q3=52). The same authors also found that median duration of symptoms until admission was 8 days, the same value found in our study.

Mean duration of antibiotic treatment in our study was about 10 weeks (71.7 days). As mentioned before, treatment duration is long and variable in different studies. Weichert *et al*⁽¹¹⁾ reviewed publications about the duration of acute osteomyelitis treatment in children and found that mean antibiotic treatment lasted up to 12 weeks according to Blockey and Watson⁽²⁰⁾; from six to nine weeks in the study by Kolyvas *et al*⁽²¹⁾; six weeks, according to Kulhanjian *et al*⁽²²⁾; two weeks according to Jacobs *et al*⁽²³⁾; and in the study by Peltola *et al*⁽²⁴⁾, three weeks.

Although an early diagnosis is extremely important in hematogenous osteomyelitis, there are no data in the literature to estimate statistically significant values for time of diagnosis after first symptom and case progression. Because of the size of our study sample, no correlation was established between time to diagnosis and duration of hospitalization and antibiotic treatment (Spearman rank correlation, $p > 0.05$).

This study showed that acute hematogenous osteomyelitis is an important infection among children, particularly those in pre-school or school. The disease should be classified as a severe bacterial infection that requires hospitalization and antibiotic treatment for a long time, and whose progression results in permanent sequelae for a substantial number of patients.

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