

ORIGINAL ARTICLE

Epidemiology and Antibacterial Treatment of Acute Hematogenous Osteomyelitis in Patients Hospitalized at Children's Clinical University Hospital in Riga, Latvia

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Summary

Introduction. Acute hematogenous osteomyelitis (AHO) is one of the most serious bacterial infections in children that may result in severe complications, such as sepsis, septic shock, bone and joint destruction, disruption of longitudinal bone growth, and even death. Early recognition and evaluation of severity of AHO, awareness of the local prevalence of different microorganisms, as well as timely initiated adequate treatment are crucial for prevention of serious complications.

Aim of the Study. To identify the main causative agents of AHO and their antibacterial susceptibility, and to evaluate the applied treatment strategies of AHO in pediatric patients in Clinical Children's University Hospital (CCUH) in Riga, Latvia.

Material and methods. All patients diagnosed with AHO and treated at CCUH were included in retrospective, descriptive study conducted between 1st of January 2014 and 31st of December 2017.

Results. The main causative agent for AHO in the study patients was methicillin-sensitive *Staphylococcus aureus* (MSSA), which was isolated from blood cultures of 40% (n=24) of patients and from 79% (n=57) of intraoperative cultures. The prevalence of methicillin-resistant *Staphylococcus aureus* (MRSA) was low (found only in one patient, or 1.4%). Thirteen different antibiotics were applied for treatment of AHO, of which Oxacillin was the most common (received by 89.4% of patients). In 57% of cases (n=54) the patients received monotherapy, and 43% of patients (n=40) received a combination of two or more antimicrobials. The most commonly used combination of antibiotics was Oxacillin plus Clindamycin, which was applied in 25.5% of cases (n=24). In 77% of cases (n=72), a transition from one antibiotic to another was observed. On discharge, oral treatment with Cefuroxime or Clindamycin was most commonly prescribed (in 52.5% and 36% of cases, respectively). The total duration of treatment varied between 5 and 20 days, with a median of 25 days.

Conclusions. The main causative agent of acute hematogenous osteomyelitis in children treated at Children's Clinical University Hospital was Methicillin-sensitive *Staphylococcus aureus* (MSSA). The prevalence of MRSA at CCUH was very low, which must be considered when prescribing empirical antibacterial treatment, giving preference to narrow spectrum antibiotics. Establishment of local guidelines for management of AHO in children at CCUH, including necessary investigations, treatment algorithm for inpatient and outpatient use with defined duration of treatment and time of conversion to oral antibiotics, follow-up and clinical endpoint criteria, and information for parents or carers.

Key words: acute hematogenous osteomyelitis, children, antibacterial treatment, causative agents

INTRODUCTION

Osteomyelitis is an inflammatory process of the bone leading to bone destruction, and it is mostly caused by a bacterial infection (6, 7). Acute hematogenous osteomyelitis (AHO), the most common type of osteomyelitis in paediatric population, is one of the most serious bacterial infections in children that may result in severe complications, such as sepsis, septic shock, bone and joint destruction, disruption of longitudinal bone growth, and even the death of the patient (6, 18).

The incidence of AHO in developed countries varies between 2 to 13 per 100 000 children per year (6) and is higher in boys (22). About 50% of cases occur in children below 5 years of age (12). An increase in incidence of musculoskeletal infections in children has been observed in recent studies (8), with emergence of resistant strains of bacteria (10, 15).

Varying prevalence of pathogens and growing resistance of microorganisms are the main factors determining the choice and duration of antibacterial treatment in case of AHO. The predominant causative agent of AHO in all age groups is *Staphylococcus aureus*, which is raising concern due to increasing isolation of Methicillin-resistant *Staph. aureus* (MRSA), and the possible acquisition of Panton-Valentine leukocidin (PVL) gene, a virulence factor associated with increased speed of propagation, severity of inflammation, and higher complication rate (6, 13). According to latest studies, the prevalence of MRSA amongst invasive infections caused by *Staphylococcus aureus* is approximately 8% in Europe (9), whereas in USA it is the causative agent of AHO in up to 40% to 50% of cases (7). Another microorganism with a significant role in pathogenesis of AHO is *Kingella*

kingae, a species of Gram-negative aerobic coccobacilli. In some European countries such as United Kingdom, Spain, France, also in Israel *K. kingae* is reportedly the second most common causative agent of AHO in children younger than 5 years (3, 4).

Early recognition and evaluation of severity of AHO, awareness of the local prevalence of different microorganisms, as well as creation of an adequate and timely plan for investigations and treatment are crucial for prevention of serious complications. The choice of empirical antibacterial treatment depends on the age and immunization status of the patient, most likely causative agents, gram stain, and other clinical and epidemiological aspects including the regional prevalence of MRSA (20). An adequate duration of prescribed antibacterial treatment, and establishment of criteria for transitioning from intravenous to oral administration are equally important, especially in paediatric population for both emotional and economic reasons.

AIM OF THE STUDY

The aim of this study was to detect the main causative agents of AHO and their antibacterial susceptibility, as well as to evaluate the applied treatment strategies of AHO in pediatric patients in Clinical Children's University Hospital (CCUH) in Riga, Latvia.

MATERIAL AND METHODS

This is a retrospective descriptive study which includes all patients with acute hematogenous osteomyelitis aged below 18 years who were treated in CCUH within the study period from 1st of January 2014 until 31st of December 2017. The data were extracted from the medical records available in the CCUH archive, which included patients treated in both surgical and acute paediatric wards. The patient case files with the following diagnose codes according to the 10th revision of International Statistical Classification of Diseases and Related Health Problems (ICD-10) were selected for the study:

M86.0 Acute haematogenous osteomyelitis;

M86.1 Other acute osteomyelitis;

M86.5 Other haematogenous osteomyelitis*.

*Latvian version of ICD-10 of this code does not apply to chronic osteomyelitis alone

Exclusion criteria:

1. Age above 18 years or below 7 days
2. Presence of comorbidities that may increase infection risk: acquired or congenital immunodeficiency (including use of immunosuppressants), patients undergoing chemotherapy, chronic illnesses (including cystic fibrosis, diabetes mellitus, malignancies, myopathies), chronic kidney or liver insufficiency, multiple genetic abnormalities.
3. Secondary osteomyelitis after open fractures or surgeries.

The study included demographic data of the patients, and the following data were analyzed:

- 1) Scope of investigations and their results;
- 2) Causative agents and their antibacterial susceptibility;
- 3) Antibacterial treatment applied in the hospital and after discharge;
- 4) Outcomes of treatment.

The data were processed using data analysis software *Microsoft Excel*.

RESULTS

1. Study population, clinical data, and site of inflammation

In total, medical records of 102 patients were eligible according to the selected diagnoses within the study period. Eight patients were excluded due to presence of one of the exclusion criteria (three children had chronic illnesses, two were receiving immunosuppressants, two children had secondary osteomyelitis after open fractures, one child had secondary osteomyelitis after surgery). In total, 94 cases of AHO patients were analysed, 64% (n=60) of whom were boys.

In 2014 there were 20 cases (11 boys and 9 girls), in 2015 – 25 cases (14 boys and 11 girls), in 2016 – 22 cases (17 boys and 5 girls), and 27 patients were diagnosed with AHO in 2017 (18 boys and 9 girls). The male to female ratio was 1.7 : 1. The number of cases increased with age, as the majority of cases (66% or 62 patients) consisted of patients aged 5 to 18 years, 25.5% of patients (n=24) were aged between 3 months to 5 years, and only 8.5% of patients (n=8) were younger than 3 months.

Most of the patients were self-referred to the hospital, only 13% of patients (n=12) were referred by a family doctor or an outpatient surgeon. 31% of patients (n=29) were transferred from another hospital.

The mean duration of symptoms before hospital admission was 3 to 4 days, more than half of the patients (n=52) were hospitalized up to 5 days after the onset of symptoms.

The predominant clinical symptoms noted on admission was pain (in 93% of cases, n=88) and limited range of motion (in 83% of cases, n=78). Localized swelling was present in 67% of cases (n=63), localized hyperaemia was noted in 38% of patients (n=36). Fever was documented in 72.5% of patients (n=67). Tachycardia was noted in nine patients, while tachypnoea was observed in 45% (n=42). Other symptoms listed on admission were drowsiness, fatigue, irritability, loss of appetite, poor overall condition, poor weight gain in infants, grunting.

The bones of the lower extremities (femur, tibia, pelvis), and the joints of the lower extremities (hips and knees) were more frequently affected. The site of infection is reflected in tables 1 and 2.

Table 1. Localization of inflammation of AHO patients in CCUH: the affected bones

Femur	27 (28.7%)
Tibia	19 (20.2%)
Metatarsal bones, wrist bones, ulna, metacarpal bones, spine	13 (13.8%)
Pelvis	12 (12.7%)
Humerus	9 (9.6%)
Calcaneus	7 (7.4%)
Mandibula, sternum, ribs, skull, maxilla, scapula, patella, talus	6 (6.4%)
Fibula	5 (5.3%)
Clavicle	3 (3.2%)
Radius	1 (1.1%)

Table 2. Localization of inflammation of AHO patients in CCUH: the affected joints

Hip joint	11 (11.7%)
Knee joint	3 (3.2%)
Foot joints	3 (3.2%)
Shoulder joint	2 (2.1%)
Elbow joint	0 (0%)

2. Investigations

All patients underwent routine laboratory investigations on admission and during hospitalization, the most common investigations were full blood count, CRP, IL-6, etc. The leukocyte count on admission was within normal range for 51.5% of patients (n=48). CRO and IL-6 were elevated in 72% of cases (n=68), and 86% of cases (38 out of 46 where requested), respectively. Erythrocyte sedimentation rate was elevated in all 4 cases where it was measured.

The diagnosis of AHO in most of the study patients was established clinically, and in most cases antibacterial treatment was initiated within the first day of hospitalization, even though the diagnosis was confirmed radiologically only later. Imaging diagnostics confirmed the diagnosis starting from the 3rd day of hospitalization, with the most sensitive investigations confirming AHO being ultrasound scan and MRI).

All patients had an X-ray of the affected region performed at least once during hospitalization, in 53% of cases (n=50) it was done at the emergency department on the day of admission.

3. Microbiological investigations and their results

Blood cultures were performed in 63.8% of cases (n=60), and 55% of them (n=33) were negative. The microorganisms isolated from the blood cultures are reflected in table No. 3. In two cases the blood culture was positive for multiple bacteria.

Table 3. Blood culture results in AHO patients

<i>Staphylococcus aureus</i>	24 (40%)
<i>Staphylococcus hominis</i>	2 (3.3%)
<i>Staphylococcus pyogenes</i>	1 (1.6%)
<i>Streptococcus pyogenes</i>	1 (1.6%)
<i>Haemophilus parainfluenzae</i> , beta-lactamase negative	1 (1.6%)
Negative	33 (55%)

Intraoperative cultures (pus, tampons, synovial fluid) were performed in 76.6% of cases (n=72), in 15% (n=11) of these cases it was negative. 79% of intraoperative cultures (n=57) methicillin-sensitive *Staphylococcus aureus* was isolated (see table No. 4). The prevalence of MRSA was low (it was isolated in only one of the cases, or 1.4%).

Table 4. Intraoperative culture results in AHO patients

<i>Staphylococcus aureus</i> (MSSA)	57 (79%)
<i>Streptococcus pyogenes</i>	2 (2.8%)
<i>Streptococcus viridans</i>	1 (1.4%)
Gram-negative cocci	1 (1.4%)
<i>Staphylococcus aureus</i> (MRSA)	1 (1.4%)
Negative	11 (15%)

The antibacterial susceptibility of the most prevalent microorganism, *Staphylococcus aureus*, is shown in table 5.

Table 5. Antibacterial susceptibility of *Staphylococcus aureus* in CCUH

	2013	2014	2015
Penicillin	18% (n=168)	20% (n=332)	20% (n=317)
Oxacillin	98% (n=304)	99% (n=389)	97% (n=408)
Erythromycin	77% (n=246)	88% (n=330)	88% (n=317)
Clindamycin	77% (n=246)	88% (n=330)	88% (n=317)
Gentamycin	98% (n=246)	99% (n=331)	97% (n=319)
Trimethoprim-Sulfamethoxazole	99% (n=168)	100% (n=291)	99% (n=318)
Ciprofloxacin	94% (n=246)	95% (n=331)	94% (n=312)
Rifampicin	100% (n=245)	99% (n=325)	98% (n=316)
Vancomycin		100% (n=41)	100% (n=61)

Management of AHO in the study patients

All the study patients received antibacterial treatment, which was most commonly initiated within the first day of admission (in 70%, or 66 cases), in 11.7% (n=11) cases it was started on day 2, three patients received it

from the day 3, and in five cases was delayed until the 5th day of hospitalization.

57% of patients (n=54) received monotherapy of a single antibacterial agent, and 43% of patients (n=40) received a combination of two or more antibiotics. The most frequently used combination of antimicrobials was Oxacillin with Clindamycin, which was applied in 24 cases (25.5%).

The most commonly applied antibiotic in the AHO patients in CCUH within the study was Oxacillin, which was received by 84 patients (89.4%). The choice of antimicrobial agents in the study population is displayed in Figure No. 1. In 77% of cases (n=72), switch to another antimicrobial agent was observed, which is largely due to the unavailability of oral form of Oxacillin.

During hospitalization, the majority of patients received intravenous antibacterial treatment, and the conversion to oral antibiotics was carried out after discharge. In only a quarter of patients (n=23) oral antibiotics were initiated during their stay at the hospital.

The duration of antibacterial treatment in the AHO patients administered during hospitalization varied between 5 to 35 days, with a median of 15 days.

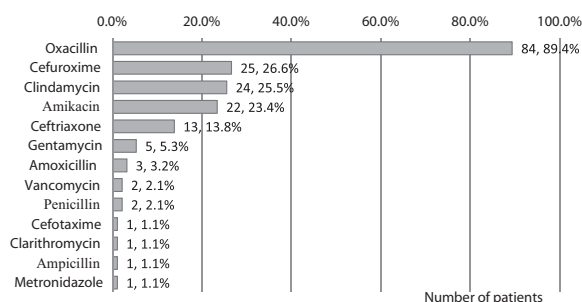


Fig. 1. Applied antimicrobial agents in AHO patients during hospitalization

On discharge, most frequently a 14-day course of oral antibiotics was prescribed (n=49, or 52%). The most common antibiotic administered after discharge was cefuroxime, which was received by 52.5% of patients (n=42) in whom the data were available. The antimicrobial agents prescribed for ambulatory treatment are shown in Figure No. 2. In nine cases antibacterial treatment was discontinued after discharge. The medical records of nine patients did not provide clear information on the duration or chosen medication of antibacterial treatment to be received after discharge.

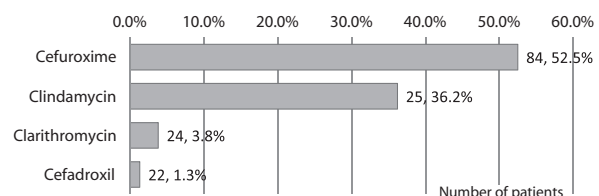


Fig. 2. Prescribed antibacterial treatment on discharge

The total duration of antibacterial treatment of AHO patients described in this study varied between 5 and 50 days, with a median duration of 25 days.

Within the study period, 70 of the AHO patients (75%) were treated surgically. The mean duration of hospitalization was 13 days, ranging from 4 to 35 days.

5. Outcomes

Complications were observed in 47% of patients (n=44). The most common complication was sepsis, which was observed in 19% of patients (n=18). Nine patients developed chronic infection. Other complications included septic arthritis (14 patients), pneumonia (7 patients) synovitis (5 patients), phlegmon (2 patients), pathological fractures, paresis of the foot, deep vein thrombosis, bursitis, abscess, and necrotizing fasciitis (1 patient each).

DISCUSSION

Despite continuing progress in development of new medical technologies, the diagnosis and treatment of acute hematogenous osteomyelitis remains a challenge for health care professionals. Diagnostic imaging may be ineffective in diagnosing AHO at the onset of first symptoms, therefore early clinical recognition of AHO and administration of empirical antibiotics is very important, as delayed treatment is associated with poorer prognosis (6). Microbiological examinations are time-consuming, thus knowledge of the predominant causative agents according to patient age, as well as regional antibacterial susceptibility is essential in prescribing adequate treatment.

In our study population, most of the AHO patients were older than 5 years (66%, or 62 patients), which is contrary to the findings of other studies (12, 14). However, there was marked male prevalence among the AHO patients, which matches the epidemiology elsewhere (11, 22).

Despite strong recommendations for performing etiologic diagnosis in all cases (19, 20), blood cultures were obtained for just 63.8% of the AHO patients, and culturing of other samples (pus, tampons used during surgery, synovial fluid) was performed in only 76.6% of patients. Similar to global trends, blood cultures yielded positive results in less than 50% of patients (20, 21).

According to microbiological investigations in patients diagnosed with AHO hospitalized in CCUH within the study period, the predominant causative agent was methicillin-sensitive *Staphylococcus aureus* (MSSA), which was isolated in 40% of the obtained blood cultures (n=24), and in 79% of the materials obtained during surgeries (n=57). *S. aureus* is one of the most common causative microorganisms for purulent infections, and is known to be the most prevalent causative agent for AHO in children (6). The data on the prevalence of Panton-Valentine leukocidin (PVL) in *S. aureus* isolated from cultures were not available for the study population, but a study of patients with at *S. aureus* infections treated at CCUH conducted between 2006 and 2008 reported a 75% prevalence of PVL

positive isolates (5). PVL is a bicomponent cytotoxin that destroys leukocytes by pore-forming activity and enables the microorganism to penetrate deeper into tissue, and is associated with abscess formation, skin and tissue necrosis, disseminated infection, prosthetic material infections, and other complications including mortality (2, 13, 16). More studies are necessary to investigate the role of PVL toxin in the outcome of AHO at our study site. Similarly to other European countries, the prevalence of MRSA bacteraemia amongst those of *S. aureus* origin has decreased from 26.6% in 2004 to 9% in 2009 (9). The prevalence of MRSA in AHO patients from our study sample was even lower, 1.4%, which must be considered when prescribing antibacterial treatment.

All AHO patients described in this study received antibacterial treatment, and in most cases (70%) it was applied on day one of hospitalization. It was delayed until the 5th day after admission in only five patients. Even though treatment was initiated early, broad differences were observed in choice of prescribed antibiotics and duration of treatment.

In our study, thirteen different antimicrobials were used for treatment of AHO, of which the predominant medication was Oxacillin (received by 89.4% of patients). In 47% patients, a combination of two or more antibiotics was applied, the most common combination was Oxacillin plus Clindamycin. According to guidelines for diagnosis and management of bone and joint infections by European Society for Pediatric Infectious Diseases (ESPID), monotherapy of first or second generation cephalosporins, or anti-staphylococcal penicillins is recommended for uncomplicated osteomyelitis in children older than 3 months at settings with low MRSA prevalence, and Clindamycin should be used at sites with the prevalence of MRSA exceeds 10 to 15%. However, combining cephalosporins or anti-staphylococcal penicillins with clindamycin might be suitable in case of PVL positive MSSA infections (20), and, although for the study patients the information was unavailable, earlier reports have shown a high prevalence of PVL positivity in *S. aureus* infections at CCUH (5).

The high rate of transition from one antibiotic to another (in 77% of cases) was likely not due to inefficacy of treatment but rather because of unavailability of oral forms of Oxacillin. On discharge, continuing the antibacterial treatment with oral Cefuroxime and Clindamycin, which were received by 52.5% and 36% of patients, respectively. The total duration of antibacterial varied between 5 and 50 days, with a median of 25 days. Although the duration of antibacterial treatment is still debatable and different strategies are used worldwide (6), ESPID guidelines suggest on average three to four week course. The wide variance of duration of treatment and choice of antimicrobials in CCUH demonstrate lack of locally established guidelines, and the scientific basis for use of different management strategies remains unclear.

The preferred route of initial antibacterial treatment for AHO is intravenous (6, 20). According to latest studies, transition from intravenous to oral antibiotics should be applied when the fever has been absent for 24–48 hours, inflammation markers have normalized, and when there has been marked clinical improvement with disappearance of most symptoms, also when the repeated blood cultures are negative and MRSA or PVL-positive *S. aureus* infections have been ruled out (17). These criteria have also been adopted by the ESPID guidelines for treatment and management bone and joint infections in children (20). In our study, most of the AHO patients received intravenous antibacterial treatment during hospitalization, and continuation of oral antibiotics was prescribed on discharge. Conversion to oral antibiotics during their hospital stay was carried out only in a quarter of patients (n=23). This may indicate that more frequent evaluation for possible conversion to oral treatment should be performed, thus decreasing the rate of complications associated with intravenous access, and increase comfort for the little patients.

Although the number of cases of acute hematogenous osteomyelitis described in this study is not small for the population of Latvia, studies involving larger number of patients could provide more reliable results.

CONCLUSIONS

1. The main causative agent of acute hematogenous osteomyelitis in children treated at Children's Clinical University Hospital was Methicillin-sensitive *Staphylococcus aureus* (MSSA). The prevalence of MRSA at CCUH was very low, which must be considered when prescribing empirical antibacterial treatment, giving preference to narrow spectrum antibiotics.
2. There is a lack of clearly established guidelines for management of AHO at CCUH: the choice of antibiotics, duration of treatment and time of conversion to oral antibiotics are not clearly defined.
3. Construction and acceptance of local guidelines for management of AHO in children at CCUH, including necessary investigations, treatment algorithm for inpatient and outpatient use, follow-up and clinical endpoint criteria, and information for parents or carers.

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Conflict of interest: None

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