Etiology and Clinical Characteristics of Acute Suppurative Osteomyelitis in Children a Single Center Study in China

Jingfang Xu
The children's Hospital ,Zhejiang University School of medcine
Chunzhen Hua
The Children's Hospital,Zhejiang University School of Medcine
Wensong Ye
The Children's Hospital,Zhejiang University School of Medcine
Shanshan Shi
The children's Hospital,Zhejiang University School of Medcine
Qiang Shu (shuqiang@zju.edu.cn)
The Children's Hospital,Zhejiang University School of Medcine

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Abstract

Background Acute suppurative osteomyelitis is a common disease in pediatric orthopedics, but there are few studies on the etiology and treatment of this disease in children.

Objective To investigate the etiology and clinical characteristics of acute suppurative osteomyelitis in children.

Methods A retrospective study was conducted of pediatric in-patients with acute suppurative osteomyelitis between January 2011 and December 2017. Subperiosteal or intramedullary specimens were collected from each patient for culture. Bacterial identification and antibiotic susceptibility test were performed with the Vitek system.

Results A total of 104 patients were included and 64 (61.5%) were male. Sixty-six isolates were obtained from 65 (62.5%) patients. The most common pathogen was *Staphylococcus aureus* (51.0%, 53/104), followed by *Escherichia coli* (2.9%, 3/104), *Pseudomonas aeruginosa* (1.9%, 2/104), *Streptococcus pneumoniae* (1.9%, 2/104), *Ochrobactrum anthropi* (1.9%, 2/104), and other bacteria (3.0%, 3/104). Two pathogens were isolated from one patient. The etiology was unknown based on culture in 39 (37.5%) patients. The age of the patients infected with *S. aureus* was 6.67 (1.7, 9.1) years, which was significantly higher than that of patients infected with non-*S. aureus*, whose age was 2.42 (0.7, 7.8) years ($Z = 2.20$, P=0.028). Results of the antibiotic susceptibility test in 53 *S. aureus* strains showed that the resistance rates to oxacillin, trimethoprim-sulfamethoxazole, clindamycin, and erythromycin *were* 43.4%, 11.3%, 67.9%, and 69.8%, respectively. All *S. aureus* strains were sensitive to linezolid and vancomycin. More patients with sequelae were found among those infected with oxacillin-resistant *S. aureus* (26.1%, 6/23) compared with oxacillin-sensitive *S. aureus* (3.3%, 1/30, χ^2 4.06, P 0.044) or other pathogens (2.5%, 2/81, χ^2 10.94, $P = 0.001$).

Conclusion *S. aureus* was the most common pathogen causing acute suppurative osteomyelitis in children and its resistance rate to oxacillin was high. Further study is needed to determine the etiology in the patients in whom the pathogen cannot be identified based on culture.

Background

Acute suppurative osteomyelitis is an inflammation of the periosteum, bone mass, and bone marrow caused by bacteria. It is common in orthopedic infections of children [1]. If it is not effectively treated at an early stage, severe sepsis, pyogenic meningitis, and infectious shock may occur secondarily [2–4], and severe cases are life-threatening. Some patients may progress to chronic infections, bone growth abnormalities, and growth retardation [3, 5]. Therefore, it is an infectious disease that seriously threatens child health. Early sensitive antibacterial treatment is the key to improve the prognosis of this disease, and the rational choice of antibiotics is based on the correct judgment of the pathogen. The clinical manifestations of osteomyelitis caused by different bacteria vary, and the preferred antibiotics for

treatment are also different. Therefore, understanding the clinical characteristics, common pathogens, and drug resistance patterns of suppurative osteomyelitis in children is very important for the empirical medication by clinicians. This study retrospectively analyzed the clinical characteristics, pathogen types, and drug resistance patterns of children with acute suppurative osteomyelitis treated in our hospital from January 2011 to December 2017, to provide a reference for clinical diagnosis and treatment.

1 Study Subjects And Methods

1.1 Study design

This was a retrospective study. All case information of patients with a discharge diagnosis of acute suppurative osteomyelitis from January 1, 2011 to December 31, 2017 was searched in the electronic case system of our hospital. Inclusion criteria were as follows: (1) Children with local redness, swelling, heat, and pain, or restricted local movement; (2) A disease course of less than 2 weeks [3]; (3) Local tenderness; (4) Imaging examinations suggesting inflammation of the periosteum, bone mass, and bone marrow; (5) Purulent specimens obtained by subperiosteal puncture or surgery. Exclusion criteria were as follows: failure of subperiosteal puncture or surgery to collect sufficient specimens for bacterial culture.

1.2 Bacterial identification and antibiotic resistance test

Bacterial identification and antibiotic resistance test were performed with Vitek compact (Mérieux, France). Repeated isolation from the same patient was considered as one *S. pyogenes* clone.

1.3 Statistical analysis

Comparison of the incidence data between groups was performed using the $\chi 2$ test. Data assumed to be normally distributed were presented as mean ± standard deviation. Comparison of means between groups was performed using the *t* test. Data not assumed to be normally distributed were presented using the median with interquartile range (IQR) in parentheses. The Mann-Whitney U test was used to compare medians between groups. $P < 0.05$ was considered to indicate statistical significance.

2 Results

2.1 Demographic information

A total of 104 patients with acute suppurative osteomyelitis and whose ages ranged from 6 days to 14 years (mean age was 5.5±4.2 years) were included in the study. Sixty-four (61.8%) patients were male, and 49.0% (51/104) were aged < 4 years. In 87 cases of osteomyelitis, the lesions were located in the long bones of the extremities (83.7%, 87/104). Among these cases, in 33 cases (31.7%), the lesions were located in the femur; in 23 cases (22.1%), the lesions were located in the tibia; in 14 cases (13.5%), the

lesions were located in the humerus; and in 61 cases, the lesions were located in the metaphysis of long bones.

2.2 Isolation of pathogens

A total of 104 children underwent subperiosteal puncture or surgical specimen culture. The positive rate was 62.5% (65/104). A total of 66 bacterial strains were isolated. Among them, 53 were *Staphylococcus aureus* strains, with an isolation rate of 51.0% and a composition rate of 81.5% (53/65) in pathogen-positive individuals. Other bacteria included 3 strains of *Escherichia coli*, 2 strains of *Pseudomonas aeruginosa*, 2 strains of *Streptococcus pneumoniae*, 2 strains of *Ochrobactrum anthropi*, 1 strain of *Streptococcus viridans*, 1 strain of *Streptococcus pyogenes*, 1 strain of *Salmonella dublin*, and 1 strain of *Enterobacter cloacae*. *S. aureus* and *O. anthropi* were successively isolated from one patient. A total of 37.5% (39/104) of the specimens did not show pathogenic bacteria. There was no significant difference in the proportion of patients who used antibiotics before sample collection between the pathogen-culture positive patients (90.8%, 59/65) and pathogen-culture negative patients (92.3%, 36/39) (χ^2 = 0.07, P = 0.79). There was no significant difference in the proportion of patients who used antibiotics before sample collection between the *S. aureus* group (94.3%, 50/53 cases) and other patients (88.2%, 45/51) (χ^2 = 0.58, P = 0.45).

2.3 *Staphylococcus aureus* drug sensitivity results

All 53 strains of *S. aureus* produced β-lactamase, and they were resistant to penicillin G. Methicillin-resistant *S. aureus* (MRSA) accounted for 43.4% (23/53) of all strains. The sensitivity of the 53 strains to commonly used antibiotics is shown in Table 1. The resistance rates of MRSA and methicillin-sensitive *S. aureus* (MSSA) to clindamycin (91.3%, 21/23 vs. 50.0%, 15/30) and erythromycin (87.0%, 26/30 vs. 56.7%, 17/30) were statistically significant (χ^2 = 10.19, P = 0.001; χ^2 = 5.67, P = 0.017, respectively). There was no significant difference in the resistance rates to the other two antibiotics between MRSA and MSSA.

Antimicrobial agents	n	S% (n)	I% (n)	R% (n)
Penicillin G	53	0 (0)	0 (0)	100 (53)
Oxacillin	53	56.6 (30)	0 (0)	43.4 (23)
Trimethoprim-sulfamethoxazole	53	88.7 (47)	0 (0)	11.3 (6)
Vancomycin	53	100 (53)	0 (0)	0 (0)
Linezolid	53	100 (53)	0 (0)	0 (0)
Erythromycin	53	30.2 (16)	0 (0)	69.8 (37)
Clindamycin	53	32.1 (17)	0 (0)	67.9 (36)
Quinuputin/dafuputin	48	100 (48)	0 (0)	0 (0)
Tigecycline	37	100 (37)	0 (0)	0 (0)
Levofloxacin	53	100 (53)	0 (0)	0 (0)
Moxifloxacin	53	100 (53)	0 (0)	0 (0)
Nitrofurantoin	48	95.8 (46)	4.2 (2)	0 (0)
Note: S—Sensitive; I—Intermediate; R—Resistant				

Table 1
Demography characteristics of HIV/MTB co-infection patients by treatment outcomes in Guangxi, Southern China

2.4 Combined drug resistance of *S. aureus*

A total of 36 strains (67.9%) of *S. aureus* were multi drug-resistant strains that were resistant to three or more different types of antibiotics, including 29 strains that were resistant to penicillin, clindamycin, and erythromycin; 4 strains that were resistant to penicillin, clindamycin, erythromycin, and compound sulfamethoxazole; 2 strains that were resistant to penicillin, clindamycin, erythromycin, and compound sulfamethoxazole; and 1 strain that was resistant to penicillin, clindamycin, and compound sulfamethoxazole. The multi drug resistance rate of MRSA (87.0%, 20/23) was significantly greater than that of MSSA (53.3%, 16/30, $\chi^2 = 6.76$, P = 0.009).

2.5 Clinical characteristics, treatment methods, and outcomes

A total of 77 cases among these 104 children had fever, 19 cases were trauma causes, and 9 cases had infections in adjacent tissues. A total of 84.6% (88/104) of the lesions occurred in long bones, and 67.3%

(70/104) of the lesions occurred in the femur, tibia, and humerus. The white blood cell count ranged from 4.07×10^9/L to 42.12×10^9/L, with an average count of $(16.5 \pm 9.3) \times 10^9$/L. The C-reactive protein(CRP) level ranged from 3 mg/L to 226 mg/L, with 87.5% (91/104) higher than the normal level (8 mg/L).

Of the 104 patients, 29 were treated with a single antibiotic. Among them, 17 patients were treated with β-lactams alone (7 patients with MSSA infection were cured by oxacillin) and 12 were treated with vancomycin alone. A total of 8 patients used 2 types of antibiotics sequentially; among them, 7 patients were initially treated with β-lactams and switched to vancomycin or linezolid when they were identified as MRSA infection, and 1 patient with *O. anthropi* infection was switched to β-lactam treatment (Imipenem) after determination of the pathogen. A total of 67 patients used two antibiotics at the same time; among them, 34 patients were treated with β-lactams combined with vancomycin or linezolid (2 patients with *Escherichia* coli infection were treated with β-lactams alone after pathogen determination) and 33 patients were treated with 2 kinds of β-lactams (penicillins and cephalosporins in combination). A total of 90 patients were treated by surgery. All patients improved after treatments. Sequelae occurred in 8 patients (7.7%); among them, 5 cases (MRSA infections) developed chronic osteomyelitis, 2 cases had pathological fractures (1 each of MRSA and MSSA infection), and 1 case had pathological dislocation of the hip joint (negative bacterial culture). The incidence of sequelae in patients with MRSA infection (26.1%, 6/23) was significantly higher than that in patients with non-MRSA infection (2.5%, 2/81, χ^2=10.94, P = 0.001), and it was also significantly higher than that in patients with MSSA infection (3.3%, 1/30, χ^2 = 4.062, P = 0.044). The clinical characteristics of 53 cases of acute suppurative osteomyelitis caused by *S. aureus* and 51 cases of acute suppurative osteomyelitis caused by non-*S. aureus* are shown in Table 2. The age, body weight, and number of patients with CRP > 100 mg/L were significantly lower in patients with non-*S. aureus* infection than in patients with *S. aureus* infection.

	S. aureus group (n=53)	Non-*S. aureus* group (n=51)		*P* values
Male (n)	35	29	χ^2=0.92	0.34
Age (y); median (IQR)	6.67 (1.7,9.1)	2.42 (0.7,7.8)	Z=2.20	0.028
Weight (kg)	20.6±12.6	16.0±10.0	t=2.08	0.040
WBC ($\times 10^9$/L)	16.8±8.9	16.4±9.5	t=0.19	0.852
Admission CRP >8 mg/L (n)	48	43	χ^2=0.93	0.335
Admission CRP >100 mg/L (n)	25	14	χ^2=4.31	0.038
≥ 3 surgeries (n)	14	1	χ^2=12.59	<0.001
Operative treatment (n)	49	41	χ^2=3.26	0.07
Treated with vancomycin/linezolid	15*	4	χ^2=5.98	0.014
Treated with β-lactams	4	14#	χ^2=5.87	0.015
Vancomycin or linezolid with β-lactams in combination	23	11	χ^2=5.63	0.018
Penicillins and cephalosporins in combination	11**	22	χ^2=6.01	0.014
Sequelae (n)	7	1	χ^2=3.18	0.074
Length of stay (days) Median (IQR)	23 (15, 29)	18 (12, 24)	Z=1.59	0.113
* 5 infected by MSSA. The initial treatment of the 8 patients was β-lactams, which was switched to vancomycin or linezolid after bacterial culture confirmed MRSA infection; # 1 case was initially treated with vancomycin, and it was switched to imipenem after bacterial culture confirmed *Ochrobactrum anthropi* infection; ** All cases were infected by MSSA.				

Table 2
Clinical aspects of acute suppurative osteomyelitis caused by Staphylococcus aureus or non-Staphylococcus aureus

3 Discussion

Acute suppurative osteomyelitis can be caused by local trauma, infections of adjacent sites, or blood-borne infections; and blood-borne infections are the most common route of infection in children [6]. Only 18.3% of the children in this study had suspicious causes of trauma and 73% of the patients had hematogenous osteomyelitis, which is consistent with the literature report [6]. The lesions in most of the

children were located in the metaphysis of long bones, and the most common locations were the femur, tibia, and humerus, which are also consistent with the results of previous studies [7].

Pathogen isolation by culture is the key for targeted antibiotic therapy. Most of the bacteria isolated in this study were *S. aureus*, which is consistent with the results of other studies [3, 6, 8–9]. The incidence of MRSA in our study was as high as 43.4%. While this value is consistent with the national resistance rate of 36.1% for Staphylococcus to methicillin in Chinese children [10], it is significantly higher than that reported in other countries [5, 9, 11–12], which suggests that *S. aureus* is seriously drug resistant in Chinese children. It is generally believed that a long time is required for the antibiotics to reach bone tissues and to achieve effective bactericidal concentrations [13]; therefore, short-term administration of antibiotics is thought to have little effect on bacterial culture results of bone tissue specimens [14]. Although 91.3% of the children in this study had been treated with antibiotics before collecting bone marrow cavity purulent samples for culture, 62.5% of the children were still found to have pathogenic bacteria. There was no difference in the antibiotic usage rate between the bacterial culture positive patients and negative patients, suggesting that the type of pathogen is also an important factor affecting the positive rate of bone marrow cavity purulent sample culture. At different age stages, the common pathogens that cause suppurative osteomyelitis differ. *S. aureus* is more common in children over 4–5 years, and *Streptococcus* or *Kingella kingae* is more common in children under 4 years [8, 9]. The age of children with *S. aureus* infection in this study was significantly higher than that of children with non-*S. aureus* infection, which is consistent with previous reports [8]; however, the proportion of children with Streptococcus infection was relatively low, which might be related to the use of sensitive antibiotics before sampling.

Oxacillin is an effective drug for the treatment of MSSA infection. Cephalosporin is safe and effective for the treatment of MSSA osteomyelitis in children. Combined treatment with vancomycin can significantly reduce the mortality of severe sepsis [15]. MRSA is resistant to cephalosporins; clindamycin is the preferred option if the patient is not critically ill and the MRSA isolates are sensitive to clindamycin. The drug has good tissue penetration and good effects against bacterial toxins and is recommended as an empirical treatment for bone and joint infections in regions where the drug resistance rate is lower than 10–15% [3, 16]. The drug is also recommended in combination with other sensitive drugs to enhance the efficacy and improve the prognosis [17]. Chinese strains are highly resistant to clindamycin and macrolides [10]. The resistance rate of *S. aureus* to clindamycin was as high as 67.9% in this study; therefore, all children were not treated with clindamycin. MRSA has an even higher resistance rate to clindamycin; therefore, many patients in this study were treated with or in combination with vancomycin/linezolid. In view of the drug resistance features of pathogens in this region, vancomycin or linezolid should be selected for the initial empirical treatment of severe suppurative osteomyelitis in children over 4 years old [8,18–19]. Trimethoprim-sulfamethoxazole has been successfully used for the treatment of pediatric osteomyelitis due to MRSA in a small retrospective study by Messina *et al*[20]. *S. aureus* in China is generally less resistant to sulfa drugs [10]. In this study, the resistance rate of *S. aureus* to Trimethoprim-sulfamethoxazole was only 11.3%, which can be considered as a combined treatment

drug for MRSA infection or as a candidate drug for patients in the recovery stage and in patients with mild conditions. Its exact treatment effect needs to be determined by performing clinical controlled studies with a large sample size in the future. Children with *S. aureus* osteomyelitis had more severe inflammatory reactions and clinical symptoms and had higher CRP levels. They also had significantly more surgical treatments and higher incidences of sequelae than patients with osteomyelitis caused by other pathogens or unknown pathogens, which is consistent with previous reports [15, 17].

Streptococcus is generally believed to be the second most common cause of suppurative osteomyelitis in children [15]. In this study the proportion of streptococcal infections in the non-*Staphylococcus* aureus group was small, which may be related to the administration of β-lactams in most of the patients before sample collection. Cases with unknown pathogens accounted for a large proportion, and most of the infections were cured after treatments, which are postulated to be caused by β-lactam sensitive bacterial infections. Recently, *K. kingae* has become an emerging pathogen in the etiology of pediatric acute osteoarticular infection[21]. *K. kingae* was reported as the most frequent etiologic agent for acute osteoarticular infections in children between 6 months and four years [21–22]. However, this study did not isolate *K. kingae*, which may be related to the difficulty with *in vitro* culture of the bacteria [21] and to the administration of β-lactams before sampling. A polymerase-chain-reaction (PCR) assay in the tissue sample may enhance the yield of *K. kingae* [21–2]. In the future, we will perform bacterial PCR detection or high-throughput sequencing in the bone marrow cavity or in subperiosteal purulent samples of acute suppurative osteomyelitis in children with negative culture results to improve the rate of pathogen diagnosis in children.

In summary, in this study, bacterial culture confirmed that the pathogens of suppurative osteomyelitis in children were mainly *S. aureus*, with a high proportion of MRSA. Most of them were multi-drug resistant bacteria, with significant inflammatory reaction of osteomyelitis and high incidence of sequelae. Empirical treatment of osteomyelitis in older children should include vancomycin or linezolid. Children with non-*S. aureus* infections are younger and are mostly infected with unknown pathogens; further study is needed to determine the etiology of this infection.

Abbreviations

MRSA: Methicillin-resistant S. aureus ; MSSA :methicillin-sensitive S. aureus CRP: C - reactive protein

Declarations

Ethics approval and consent to participate

This study was approved by the Ethics Committee and the Institutional Board of Privacy and Security at the hospital (2020-IRB-035), and was performed under the institutions' opt-out passive consent policy.

Conflicts of Interest

The authors have no conflicts of interest to declare.

Data Availability

The data used to support the findings of this study are available from the corresponding author upon request.

Competing of Interests

The authors declare that they have no competing of interests.

Authors' contributions

Xu conducted the study. Hua, Ye and Shu guided in grouping the patients, Shi in data analysis, Xu and Shu in the preparation of this manuscript. All authors have read and approved the final version of this manuscript.

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