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Original Article

Acute Community-acquired Osteoarticular Infections in Children: High Incidence of Concomitant Bone and Joint Involvement

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BACKGROUND/PURPOSE: Pediatric acute osteoarticular infections remain a challenging clinical issue for physicians. This paper provides recent clinical experiences on acute community-acquired osteoarticular infections in children in Taiwan.

METHODS: Children with acute community-acquired osteoarticular infections admitted to hospital were retrospectively reviewed and the findings compared with related infections in Taiwan published during the past 10 years.

RESULTS: We enrolled 27 children in our study, and reviewed 692 patients reported from six major studies in Taiwan. Of the 27 patients, 15 (55.6%) had concomitant bone and joint involvement. Blood cultures were positive in 44.4% of the children in this study and 48–52% in the other studies. Pathogens could be identified in 66.7% of our children and 63–76% in the other studies, when surgical specimens were available for culture. *Staphylococcus aureus* was consistently the most common pathogen found in all studies. Of the *S. aureus* isolates, methicillin-resistant *S. aureus* accounted for 13.3% in our study and 22–24% in the others.

CONCLUSION: Concomitant osteomyelitis and septic arthritis occurred in over half of our patients. The long-term effect of combined bone and joint infection on bone growth remains to be determined. Surgical intervention remains an important component of management of osteoarticular infections.

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Our findings are consistent with current recommendations of aggressive microbiology diagnosis and initiation of empirical monotherapy with oxacillin or oxacillin plus an agent effective against Gram-negative bacteria in most cases of community-acquired osteoarticular infections.

KEYWORDS: antibiotics, children, osteoarticular infection, osteomyelitis, septi arthritis

Introduction

Acute osteoarticular infections are relatively common in pediatrics, occurring at a rate of 5.5–12/100,000 children.[1] While osteoarticular infections may cause growth changes or pathologic fractures,[2] they often represent a diagnostic and therapeutic challenge for clinicians. Moreover, the initial laboratory data may be within normal limits,[3] and bone destruction due to osteomyelitis is not apparent on plain radiographs until 7–10 days after infection, and the roentgenogram of septic arthritis may be difficult to interpret, or unhelpful, as the joint structures are radiolucent in young children.[4,5] The recent application of new diagnostic tools [e.g. magnetic resonance imaging (MRI), computed tomography (CT), bone scans] along with more aggressive diagnostic approaches (e.g. surgical intervention and microbiological studies) has increased our ability to make an accurate diagnosis. In this report, we present our experiences on the clinical and laboratory features of community-acquired acute osteoarticular infections in children, and review six recently published papers on this subject from Taiwan, with the aim of providing updated information on pediatric osteoarticular infections.

Methods

Pediatric patients aged less than 18 years with acute community-acquired osteoarticular infections admitted to the Veterans General Hospital-Kaohsiung from January 1, 1999 to December 31, 2008 were retrospectively reviewed. The inclusion criteria were based on the characteristic signs and symptoms of osteoarticular infections (fever, redness, swelling, warmth, pain or functional impairment) and one of the following: (1) a positive microbiology result from bone and/or joint fluid cultures; (2) MRI or CT findings consistent with osteoarticular infection; and (3) positive bone scan if bone and/or joint fluid cultures, MRI, and CT were not done. Image studies (MRI, CT or bone scan) were arranged by physicians according to the individual clinical indications. Patients with concomitant fractures, malignancies, infections more than 14 days prior to admission, and infections acquired 7 days after hospitalization were excluded.

After enrollment, septic arthritis, osteomyelitis or concomitant septic arthritis and osteomyelitis were defined according to the involvement based on the evidence from microbiology and radiological or bone scan studies. The medical record of each patient was retrospectively reviewed with focus on relevant history, clinical manifestations, blood parameters, microbiologic features, surgical intervention and treatment. The blood parameters were recorded according to the results of initial blood samples drawn within 3 days of admission; white blood cell count (WBC) $\geq 11 \times 10^9$/L, C-reactive protein (CRP) ≥ 1 mg/dL, or erythrocyte sedimentation rate (ESR) ≥ 20 mm/hr were defined as abnormal.

Surgical interventions were carried out for hip joint infections and in patients with a poor response to antibiotics.[5–7] Additionally, joint fluids or surrounding pus were collected through needle aspiration. Periosteal pus aspiration, joint aspiration, arthroscopic irrigation, bone biopsy, and local debridement or curettage were all regarded as surgical interventions.

Also, we reviewed six articles published during the past 10 years and compared the clinical features, blood parameters, cultures results from blood and surgical specimens, microbiology results and resistance characteristics of pediatric osteoarticular infections in Taiwan.[5,7–11]

Statistical analyses

Clinical and laboratory data on admission were summarized and categorical variables were analyzed by Fisher's test. The χ^2 test, Kruskal-Wallis test and Mann–Whitney *U* test were used to analyze continuous variables. A *p* value of < 0.05 was considered statistically significant.

Results

Concomitant bone and joint infections

The findings of 27 children with osteoarticular infections in our study and those from 692 children from six major studies in Taiwan are summarized in Table 1.[5,7–11]

In our study, there were eight girls and 19 boys. The age on admission ranged from 9 months to 14.8 years, with an average of 7.6 years. Fourteen children received MRI, five received CT and 14 received bone scan studies. Seven children had septic arthritis, five had osteomyelitis and 15 had concomitant septic arthritis and osteomyelitis. The locations of the infections are listed in Table 2. Twenty infections were in the lower limbs, four in the trunk, and three in the upper limb. The most frequently involved sites were the bones around the knees ($n = 11$). As shown in Table 1, all studies showed a consistent trend of male/lower limb predominance.

Clinical features and focus of entry

In our study, 25 (92.6%) children had fever on admission. Classical manifestations, e.g. redness, swelling, warmth, pain and functional impairment were present in 40.7%, 74.1%, 48.1%, 85.2% and 63.0% of children, respectively. As shown in Table 1, the most common symptoms found in the other studies were either fever (57–90%) or pain.

In our study, 15/27 (55.6%) patients had no apparent focus for the entry point of infection, 10 (37.0%) had history of skin trauma, one (3.7%) had acute gastroenteritis (caused by *Salmonella* spp.), and one (3.7%) had pneumonia (caused by *Streptococcus pneumoniae*). Six of the 10 children with a history of prior trauma were proven to have *S. aureus* infection. The rate of *S. aureus* infections was similar between children with or without prior history of trauma ($p = 1.0$).

Laboratory features

In our study, initial WBC and CRP were abnormal in 44.4% and 88.9% of patients, respectively. ESR was elevated in all cases where data was available ($n = 23$), with an average of 68.2 mm/hr (range, 20–121 mm/hr). As shown in Table 1, blood parameters had a wide range of values in the other studies. On admission WBC, CRP and ESR were elevated in 37.8–85.0%, 58.1–100% and 57.9–91.0%, respectively. The averages of the data collected every 3 days for the individual parameters in our children throughout the course of treatment are shown in the Figure. The average WBC count over the first 3 days was 12.89×10^9/L and did not change significantly during the course of the infection or after treatment. The average CRP level in the first 3 days was 29 mg/dL, which then dropped rapidly over the first 7 days, and returned to normal (< 1 mg/dL) after 14–20 days. The average of ESR in the first 3 days was 66.8 mm/hr, which changed slowly and took 36 days to return to normal (< 20 mm/hr).

Microbiological features

In our study, blood cultures were performed in all patients and 20 (73.3%) children received surgical intervention. Pathogens were cultured from blood in 12 (44.4%) children and from surgical specimens in 11 (40.7%). For the other studies, the rates of surgical intervention, blood cultures, surgical specimen cultures and the overall culture rates are listed in Table 1. The overall culture-positive rates were between 63% and 76% when the results from blood cultures and cultures from surgical specimens were combined.

As shown in Table 1, *S. aureus* was the most common pathogen found in all the studies. Methicillin-resistant *S. aureus* (MRSA) accounted for 13.3–24.0% of all *S. aureus* isolates. In our study, pathogens were identified in 18 (66.7%) children, including 13 methicillin-sensitive *S. aureus* (MSSA), two MRSA, two *Salmonella* spp., and one *S. pneumoniae*. The two children infected by MRSA had no predisposing risk factors (i.e. prior hospitalization, residence in nursing homes or other long-term-care facilities within the past 6 months, presence of in-dwelling vascular or urinary catheters, or underlying chronic diseases). Both of the MRSA strains were sensitive to trimethoprim–sulfamethoxazole (TMP–SMX), ciprofloxacin, levofloxacin, rifampin and vancomycin.

Management and outcome

In our study, all children received intravenous antibiotics, followed by oral administration. Beta-lactamase-resistant penicillin, or oxacillin, was given intravenously to 25 patients [with 3 receiving it in combination with other antimicrobials (i.e. gentamicin, clindamycin, or TMP–SMX)]. Glycopeptides (vancomycin or teicoplanin) were administered to two patients who were later identified as MRSA-positive and to one patient with negative culture results.

Table 1. Clinical features of the severe major osteoarticular infections studies reported between 1999 and 2008 in Taiwan

Report	Study period	Number of cases (M:F)	Concomitant septic and arthritis and osteomyelitis (%)	Most common presentation	Fever (%)	Abnormal WBC rate (definition)	Abnormal CRP rate (definition)	Abnormal ESR rate (definition)	Most commonly involved joint	Surgical intervention rate (%)	Overall culture rate (%)	Blood culture rate (%)	Surgical specimens culture rate (%)	Most common pathogen	MRSA rate[a] (%)	Reference
1	1999–2008	27 (19:8)	55.5	Fever (92.6%)	92.6	44.4% ($\geq 11\times10^9$/L)	88.9% (≥1 mg/dL)	100% (≥20 mm/hr)	Knee	74	66.7	44.4	40.7	S. aureus (83.3%)	13.3	Present study
2	1971–2004	60 (36:24)	15.0	Pain (93.3%)	90.0	–	58.1% (>10 mg/dL)	89% (>20 mm/hr)	Knee	80.1	71.7	–	63.3	S. aureus (60.5%)	–	Yuan et al, 2006
3	1998–2002	209 (118:91)	–	Pain (79%)	57.0	–	71% (≥0.8 mg/dL)	80% (>20 mm/hr)	Femur	49	73	25	47.4	S. aureus (34.0%)	22.2	Yeh et al, 2005
4	1984–2003	209 (117:92)	35.9	Fever (66%)	66.0	37.8% ($>15\times10^9$/L)	80% (>0.9 mg/dL)	57.9% (>30 mm/hr)	Hip	29.7	69.4	–	–	S. aureus (45.5%)	–	Chang et al, 2005
5	1988–2000	58 (32:26)	33.0	Pain (81%)	74.0	40% ($>15\times10^9$/L)	–	89% (≥20 mm/hr)	Hip	74	74	27	63	S. aureus (58.2%)	24	Wang et al, 2003
6	1990–2000	123 (68:55)	4.9	–	–	–	88%	91%	Hip	76	63	33	45	S. aureus (71.8%)	22	Kao et al, 2003
7	1986–1997	33 (23:10)	12.0	Limitation of ROM (100%)	66.7	85%	100%	82%	Hip study only	100	76	52	63	S. aureus (44.0%)	–	Chen et al, 2001
8		719 (413:306)	4.9–55.5	Fever, pain or limitation of ROM	57–92.6	37.8–85.0%	58.1–100%	57.9–100%	Lower limbs	29.7–100	63–76	25–52	40.7–63.3	S. aureus (34.0–83.3%)	13.3–24.0	Overall

[a]Number of MRSA/Number of *S. aureus*. CRP=C-reactive protein; ESR=erythrocyte sedimentation rate; F=female; M=male; ROM=range of movement; NA=not available; WBC=white blood cell; MRSA=methicillin-resistant *Staphylococcus aureus*.

Table 2. Involved localization in 27 pediatric patients with acute community-acquired osteoarticular infections

Type and location of infection	Number of cases
Septic arthritis	7
Hip	4
Knee	2
Elbow	1
Osteomyelitis	5
Tibia	1
Femur	1
Calcaneus	1
Interphalangeal joint	1
Vertebra	1
Concomitant septic arthritis and osteomyelitis	15
Femur, tibia and knee	3
Femur and knee	3
Sacrum, ilium and sacroiliac	3
Hip and femur	2
Humerus and shoulder	1
Tibia and knee	1
Calcaneus and ankle	1
Multiple infection sites at the right femur, right ankle, and bilateral tibia	1

In our study, 25/27 children were symptom-free and without fever at the time of discharge from hospital. One child with underlying hypogammaglobulinemia and infected by MSSA died from septic shock on the 5th day of hospitalization despite intravenous oxacillin administration initiated on the first day of admission. One child had joint stiffness due to immobilization. This child fully recovered after 4 months of rehabilitation.

Discussion

In our study, we excluded children with fractures, with disease duration more than 14 days before admission, or patients with infections acquired 7 days after hospitalization. Our focus was on acute community-acquired infections and not subacute, chronic or nosocomial infections. As shown in Table 1, concomitant septic arthritis and osteomyelitis occurred in 4.9–55.5% of the reported cases. The reason for the high rate of concomitant bone and joint infections (55.5%) seen in our study is not known. It is likely that some of the other studies focused only on either osteomyelitis or septic arthritis. In addition, consideration of newer diagnostic tools (MRI, CT and bone scans) in our inclusion criteria might have led to a better definition of bone and joint pathology. High rates (33.0–35.9%) of bone and

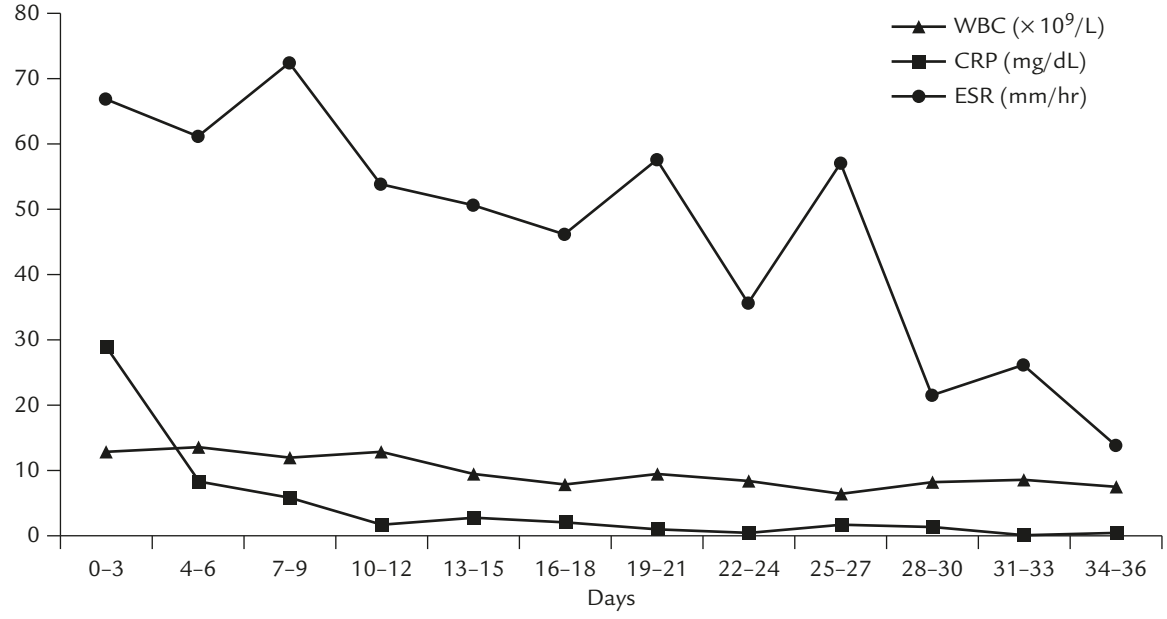

Figure. Average data for individual parameters collected throughout the treatment course of 27 pediatric patients with acute community-acquired osteoarticular infections. CRP=C-reactive protein; ESR=erythrocyte sedimentation rate; WBC=white blood cell.

joint infections have also been reported by others.[7,10] The long-term effects of the potential damage to growth plates on bone growth remain to be defined in this population.

Elevated ESR was observed in all patients in our study. As shown in Table 1, five of the seven studies showed that ESR was the most sensitive blood parameter in osteoarticular infections.[8,10–12] As shown in the Figure, WBC was not a sensitive indicator of infection and did not change before or after treatment. However, CRP was a very sensitive marker, declining rapidly within the first week. Thus CRP was a useful marker for the response to therapy during the acute phase of the disease. In contrast, ESR changed slowly and took 36 days to return to normal. ESR has been generally used as a marker for inflammation and for the duration of antibiotic therapy (generally 4–6 weeks).

The port of entry, such as skin trauma, gastroenteritis and pneumonia, may be helpful when the pathogen cannot be isolated. In our study, 17/27 (63.0%) children had no prior history of trauma and *S. aureus* was isolated from nine of 17 children. This finding is consistent with the suggestion that infections in children are often seeded hematogenously and usually without a history of trauma. This is in contrast to infections observed in adults or adolescents, which often associated with an open injury to the osteoarticular structures and surrounding soft tissues.[9,13]

In our study, 20 (74.1%) children had surgical interventions and the positive culture rates were comparable with those of other reports.[7,9–11,14,15] Blood cultures were positive in 12/27 (44.4%) children. These results were also comparable with those of other reports,[5,14] but higher than some other studies in Taiwan and a population-based study in Norway.[9–11,15,16] Microbiological studies and surgical interventions together identified pathogens in 20 (74.1%) of the children in our study. Clearly the culture of surgical specimens has increased the microbiological yield and promoted the clearing of pus and necrotic tissues.[5,7–11,17,18] In our study, although not statistically significant, the positive culture rate for surgical specimens was higher in children whose cultures were obtained before antimicrobial administration compared with those obtained after (75.0% *vs.* 66.7%; $p = 1.0$).

MRSA infections have continued to rise. In a recent study, MRSA was identified in 58–83% of all clinical *S. aureus* isolates (including nosocomial origin) from 12 major hospitals in Taiwan.[19] Huang et al[20] reported that the prevalence of MRSA nasal colonization among Taiwanese children was 31% in 2005–2006. The proportion of patients with community-acquired MRSA infections in Taiwan increased from 6% in 1997–1999 to 16% in 1999–2001.[21] Community-acquired MSSA results in a significantly lower proportion of osteomyelitis cases than community-acquired MRSA (3% *vs.* 24%, $p = 0.002$), and is three times less likely to be associated with deep-seated infections.[21] As shown in Table 1, MRSA accounted for 22–24% of *S. aureus* infections isolated from acute community-acquired osteoarticular infections in the other studies.[9–11] We encountered 13.3% MRSA. It is important to be aware of the recent increase in the incidence of MRSA infections in patients without apparent risk factors worldwide as well as in Taiwan.[10,20–25] The two strains of MRSA in our study were sensitive to TMP–SMX, similar to previous reports indicating that the community-acquired MRSA in Taiwan was 93–100% susceptible to TMP–SMX.[20,21,23–25] However, it is important to recognize that this sensitivity rate is constantly changing.

Based on our study and data from recently published articles, the risk of MRSA in community-acquired osteoarticular infections was 13–24%. At a time when MRSA was not prevalent, it seemed reasonable to initiate monotherapy with oxacillin, or a combination of oxacillin with an agent against Gram-negative bacteria (e.g. TMP/SMX or a third-generation cephalosporin). Some clinicians have used glycopeptides in severely ill children, patients suspected of MRSA infection, or infections with a poor response to other antibiotics in spite of adequate surgical intervention. From our literature review and clinical experience, it is generally agreed that aggressive microbiological diagnosis using cultures, as well as surgical intervention, are essential in the management of community-acquired osteoarticular infections in children. The major limitation of our study is that this is a retrospective review and lacks long-term follow-up data, specifically regarding the effect of bone and joint damage on bone growth. Clearly, it is important to continue efforts in finding appropriate approaches to the evolving issues related to bone and joint infections in children.

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