

ORIGINAL**Osteoarticular infections at a pediatric emergency core hospital in Japan**

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Abstract : Objectives : Osteomyelitis (OM) and septic arthritis (SA) in childhood might cause complications, sequelae, or even death if diagnosis and treatment are delayed. Here, we examined the outcomes of OM/SA at a pediatric emergency core hospital in Japan. **Methods :** This was a single-center, retrospective, observational cohort study at a pediatric emergency core hospital in Japan. Pediatric outpatients who underwent magnetic resonance imaging at the hospital in the period 2012–2020 were recruited. Primary outcomes were sequelae, recurrent symptoms, chronicity, and death. **Results :** Fifteen OM/SA patients (9 OM, 4 SA, 2 OM+SA) were recruited. The identified major pathogens included methicillin-susceptible *Staphylococcus aureus* (40.0 %, n = 6) and methicillin-resistant *S. aureus* (13.3 %, n = 2). Mean time from onset to first hospital visit, hospitalization, and initiation of effective antibiotics was 2 days, 3.9 ± 1.8 days, and 4.9 ± 2.2 days, respectively. All OM/SA patients recovered without complications or sequelae. **Conclusions :** In this study, all patients with OM/SA showed a good prognosis. Despite the small sample size, this pilot study suggests that the pediatric emergency core system in Japan provides early treatment and a good prognosis for patients diagnosed with OM/SA. *J. Med. Invest.* 70 : 236-240, February, 2023

Keywords : osteomyelitis, pediatric emergency system, retrospective cohort study, septic arthritis

INTRODUCTION

In Japan, most pediatric medical expenses are covered by the national health insurance system with co-payment by local governments (1). In addition, primary pediatric emergency medical centers and pediatric emergency core hospitals have been set up in each medical area (2-4). These areas are divided according to the population and ease to access. First, patients go to local clinics or primary pediatric emergency medical centers. Severely ill patients are transferred to pediatric emergency core hospitals. A duty doctor takes initial treatment. Thus, pediatric healthcare utilization in Japan is largely unaffected by income or residential location (5), and pediatric emergency patients have relatively easy access to medical care. According to estimations based on a population-weighted random sample from a nationally representative panel of households, Japanese children had 2.5 times more physician visits and 11 times more hospital-based outpatient clinic visits than children in the United States (5). However, although Japan has high medical access for the entire population, data on the quality of the pediatric emergency system remain lacking (6, 7).

Pediatric osteomyelitis (OM) and septic arthritis (SA) are urgent disorders that can result in sequelae such as joint deformities and leg-length discrepancies if treatment is delayed. However, OM and SA are difficult to diagnose due to unclear signs and the rarity of these pathologies (8, 9). Risk factors for a worse prognosis of OM and/or SA in the pediatric population

are younger age and delay in treatment greater than 5 days from symptom onset (10). Early diagnosis of OM/SA requires a hospital that readily accepts referrals even when the signs are unclear or the diagnosis tentative, as well as careful interviews and medical examinations conducted by a multidisciplinary clinical team comprising pediatricians, radiologists, and orthopedic surgeons (11). The outcome of OM/SA may be reflected by the quality of the pediatric emergency care system.

Here, we investigated the prognosis of OM/SA at a pediatric emergency core hospital in a city in Japan. We also examined the factors that affect the prognosis of OM/SA, such as time from onset, time to treatment, and multidisciplinary team collaboration.

METHODS

This was a single-center, retrospective, observational study conducted at Tokushima Prefectural Central Hospital, a pediatric emergency medical service core hospital that has accepted pediatric emergency patients 24 hours a day, 365 days a year since 2012. The hospital is located in Tokushima Prefecture in the southern part of Japan. The prefecture has a geographic area of 4146 km² and a population of 728,633 (as of October 1, 2019) (12). The Ethics Committee of Tokushima Prefectural Central Hospital approved the study (approval no. 20-14). Participants and their guardians were given the opportunity to refuse to participate in the study through the information disclosure documents published on the Tokushima Prefectural Central Hospital website (<https://tph.pref.tokushima.lg.jp/central/ourHospital/ourActivities/ethicsReviewBoard/7207663/>).

Criteria for inclusion in the study were : age < 16 years old, admitted to Tokushima Prefectural Central Hospital from the outpatient setting in the period 2012–2020, and osteoarticular

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lesions observed on magnetic resonance imaging (MRI) during that hospitalization. We suspected of having OM or SA because of the symptoms (fever, pain, limited range of motion, and so on). These complaints were less likely to be noticed by others in younger children, who cannot complain directly, and were reminiscent of juvenile idiopathic arthritis, and reactive arthritis in addition to OM and SA. We underwent MRI examination to determine the presence of osteoarticular lesions and confirm the diagnosis. No patients were diagnosed with OM or SA without MRI because we conducted MRI to all patients who were suspected OM or SA. Patients who developed OM/SA during hospitalization or lost to follow-up were excluded from this study. In our hospital, OM and SA are diagnosed based on MRI findings (bone marrow swelling, low intensity in T1-weighted images and increased signals in short-tau inversion recovery, joint effusion, and surrounding skin and soft tissue changes) and the result of microbiological culture. We started the treatment according to the following algorithm : patients who have apparent symptoms were administered the antibiotics as soon as possible. We first chose cefazolin in assumption to common pathogens, methicillin-susceptible *Staphylococcus aureus* and group A streptococcus of OM and SA. In the case of difficult to diagnose, if not serious condition, we sometimes waited start of treatment until appearance of apparent symptoms or MRI studies. The timing of switching from intravenous antibiotics to oral antibiotics is determined based on clinical symptoms and the causative pathogen. In the present study, the primary outcomes were sequelae, recurrent symptoms, chronicity, and death. The following data were also obtained : time from onset to hospital visit, time from onset to diagnosis, time from onset to initiation of effective antibiotics, and time from onset to consultation with an orthopedic surgeon or radiologist. All items for assessment were extracted from the medical records. Time from onset to initiation of effective antibiotics was determined based on clinical improvement and results of antibiotic susceptibility testing.

RESULTS

A total of 9230 pediatric patients were admitted to Tokushima Prefectural Central Hospital in the period 2012-2020 (Figure 1). 41 patients were suspected of having OM or SA. We underwent MRI examination to determine the presence of osteoarticular lesions and confirm the diagnosis. No patients were diagnosed with OM or SA without MRI because we conducted MRI to all patients who were suspected OM or SA. The images were negative for the presence of osteoarticular lesions in 24 patients and these patients were classified as non-OM/SA. The images were positive in the remaining 17 patients (0.18 % of hospitalizations) and these patients were diagnosed with OM/SA. However, 1 patient was lost to follow-up and 1 patient was found to have developed SA during hospitalization and so these 2 patients were excluded from the study. Thus, 15 patients diagnosed with OM/SA patients were enrolled in the present study (OM alone, 9 patients ; SA alone, 4 patients ; OM+SA, 2 patients ; Table 1 and Table 2). The enrolled OM/SA patients showed male dominance (with 11 males, 73.3 % ; Table 1). The lower limbs and pelvic areas were affected in 13 (86.7 %) of the 15 patients. Fever (> 37.5°C) was present in all (15/15) patients, pain in 14 patients (93.3 %), and limited range of motion in 11 patients (73.3 %) (Table 1).

The causative pathogen was identified in 11 of 15 patients (73.3 %) by blood culture, local puncture culture or polymerase chain reaction (Table 1) : methicillin-susceptible *Staphylococcus aureus* and methicillin-resistant *Staphylococcus aureus* were the most frequently identified pathogens, with 6 and 2 cases, respectively.

Median time from onset to first hospital visit was 2 days (IQR 1–3) (Table 3). Mean time from onset to admission was 3.9 ± 1.8 days. Mean time from onset to initiation of effective antibiotics in consideration of clinical improvement and antibiotic susceptibility was 4.9 ± 2.2 days. Effective therapy was initiated within

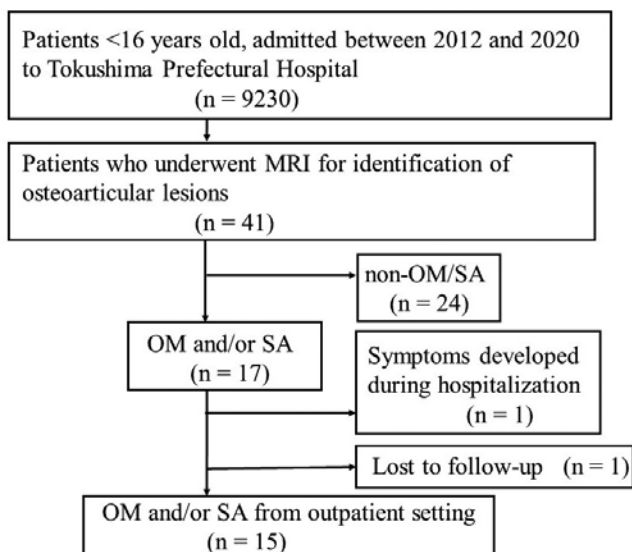


Figure 1. Flow chart of enrollment in the present study. OM, osteomyelitis ; SA, septic arthritis.

Table 1. Characteristics in OM/SA patients

		OM / SA n = 15
Age at onset (y.o) (median and IQR)		9 (5–12)
Male		73.3 % (n = 11)
Causative agent	MSSA	40.0 % (n = 6)
	MRSA	13.3 % (n = 2)
	<i>Kingella kingae</i>	6.7 % (n = 1)
	<i>E. coli</i>	6.7 % (n = 1)
	<i>S. pyogenes</i>	6.7 % (n = 1)
	Unknown	26.7 % (n = 4)
Symptom	Fever	100 % (n = 15)
	Swelling	40.0 % (n = 6)
	Pain	93.3 % (n = 14)
	Limited range of motion	73.3 % (n = 11)
	Reluctance to feed	46.7 % (n = 7)
Department first visited	Pediatrics	60.0 % (n = 9)
	Orthopedics	13.3 % (n = 2)
	Internal medicine	13.3 % (n = 2)
	Dermatology	6.7 % (n = 1)
	Others	6.7 % (n = 1)

OM, osteomyelitis ; SA, septic arthritis ; MSSA, methicillin-susceptible *Staphylococcus aureus* ; MRSA, methicillin-resistant *Staphylococcus aureus* ; *E. coli*, *Escherichia coli* ; *S. pyogenes*, *Streptococcus pyogenes*.

Table 2. Demographic data and symptoms of patients diagnosed with osteomyelitis and/or septic arthritis

Patient	Diagnosis	Sex	Age (y.o.)	Past history	Location	Fever	Swelling	Pain
1	OM	M	12	–	Left femur	+	+	+
2		M	8	Chronic eczema	Left calcaneus	+	–	+
3		F	9	–	Bilateral fibula Right calcaneus	+	–	+
4		F	8	–	Right calcaneus	+	+	+
5		M	12	–	Lower anterior iliac spine	+	–	+
6		M	10	–	Sacrum	+	–	+
7		M	12	Gorham–Stout syndrome	Atlas, axis	+	–	+
8		F	13	Hereditary spherocytosis	Right ilium	+	–	+
9		M	4	Trisomy 21	Right radius	+	+	–
10	SA	M	7	–	Left hip	+	–	+
11		M	2	–	Left knee	+	+	+
12		M	12	–	Right sacroiliac joint	+	+	+
13		M	2	–	Left hip	+	–	+
14	SA+OM	M	12	–	Right hip	+	–	+
15		F	5	–	Right knee	+	+	+

OM, osteomyelitis ; SA, septic arthritis ; M, male ; F, female

Table 3. Time course and prognosis of osteomyelitis and/or septic arthritis

	OM / SA n = 15	
Time from onset to first visit (days)	2 (1–3)	
Time from onset to admission (days)	3.9 ± 1.8 (1–8)	
Time from onset to initiation of effective antibiotics (days)	4.9 ± 2.2 (2–9)	
Delay until initiation of effective therapy > 5 days	33.3 % (n = 5)	
Time from onset to radiologists consultation (days)	5 (3–8)	
Time from onset to orthopedics consultation (days)	3.9 ± 1.8 (1–8)	
Hospitalization (days)	23.9 ± 5.6 (15–36)	
Open surgery	0	
Puncture and lavage	2	
IV antibiotics	CEZ	80.0 % (n = 12)
	VCM	20.0 % (n = 3)
Oral antibiotics	CEX	46.7 % (n = 7)
	ST	26.7 % (n = 4)
	MINO	6.7 % (n = 1)
	AMPC	6.7 % (n = 1)
	TFLX	6.7 % (n = 1)
Duration of IV antibiotics (days)	18.8 ± 4.9 (11–30)	
Duration of oral antibiotics (days)	26.6 ± 18.6 (0–68)	
Complications and sequelae	0	

IV, intravenous injection ; OM, osteomyelitis ; SA, septic arthritis ; CEZ, cefazolin ; VCM, vancomycin ; CEX, cephalexin ; ST, sulfamethoxazole-trimethoprim ; MINO, minocycline ; AMPC, amoxicillin ; TFLX, tosylflouxacin.

Parametric data was presented as mean ± standard deviation (range) and non-parametric data was presented as median (interquartile range (IQR)).

5 days from onset in 66.7 % of patients (n = 10). 53.3% of patients (n = 8) were started effective therapy on the day of admission and all patients were started within 3 days from admission. Mean time from onset to orthopedics consultation was 3.9 ± 1.8 days, and median time from onset to radiologist consultation was 5 days. All patients recovered without sequelae, chronicity, recurrence, or death (Table 3).

MRI studies were conducted at a median of 5 days after onset (IQR 3–8). Two of the 15 patients (13.3 %) showed no abnormalities on the first MRI (on days 3 and 5 from symptom onset, respectively), but abnormalities on a second MRI (on days 9 and 14 from symptom onset, respectively). All patients with SA or OM+SA showed joint effusions. Among the OM patients, none showed subperiosteal abscess formation. All of the OM/SA patients showed skin and soft tissue changes. In bone marrow, 7 patients showed low intensity on T1-weighted images and 10 patients showed increased signals on short-tau inversion recovery images. Five of the 9 patients with OM and 1 of the 2 patients with OM+SA showed edematous bone marrow swelling. Ultrasonography was performed in 11 of 15 patients (5 of 9 patients with OM, all patients with SA or OM+SA), revealing joint effusion in 2 patients with SA and 2 patients with OM+SA.

In the OM/SA patients, cefazolin was the most commonly administered intravenous agent (12 patients ; 80 %), followed by vancomycin (3 patients ; 20 %) (Table 3). No patients required conversion to open surgery, but 2 patients with SA underwent puncture and lavage, 1 of whom (patient 14) required subsequent arthroscopic surgery.

DISCUSSION

The present analysis revealed that OM/SA patients admitted to a pediatric emergency medical core hospital in a city in Japan showed a good outcome. Yamagishi *et al.* similarly reported that 16 of 20 patients (80 %) with community-acquired OM/SA recovered with no complications or sequelae at a pediatric emergency

medical core hospital in Osaka, a major city in Japan (a geographic area of 1905 km² and a population of 8,823,358 (as of July 1, 2019)) (13, 14). A previous report from the United Kingdom showed that none of 70 children with OM/SA showed complications or sequelae (15). Jagodzinski *et al.* (15) described that the success of treatment was predicated community awareness, early referral, and rapid access to high-quality care. However, these previous studies were single-center investigations, and no nationwide surveillance of OM/SA outcomes has been conducted, except for surveillance related to disease burden (16-18).

One third of the patients still failed to receive the optimal treatment within 5 days in this cohort. OM/SA are uncommon disorders that occur in 1.3–8/100,000 children (19). The difficulties in diagnosing pediatric OM/SA involve the ambiguous nature of the associated sign as well as the rarity of these pathologies. For example, patient 9, who had trisomy 21 (Down syndrome), did not complain of any pain, which likely can be attributed to hypo-responsivity to pain or to intellectual disability (20, 21). OM is also difficult to distinguish from bone destruction accompanying Gorham–Stout syndrome (patient 7)(22, 23). Four of the 15 patients (27 %) had already been treated with oral antibiotics at a private clinic based on a provisional diagnosis of OM/SA prior to our visit. It is possible that the undetected blood culture on admission may have made subsequent drug selection and diagnosis of osteomyelitis difficult. On the other hand, we cannot rule out the possibility that the prior oral antibiotics were effective for OM/SA in this cohort.

Despite such difficulties in recognizing OM/SA, most patients in the present study had visited local clinics or emergency centers for children within 2 days after symptom onset, and about 70% of cases received appropriate treatment within 5 days after symptom onset. A previous report from Malawi showed a mean delay from onset to first presentation at hospital of 6.6 days (24). A delay in diagnosis of >5 days from onset is seen in about 60 % of patients even in Spain (25). One reason for the relatively early diagnosis of OM/SA found in this study may be that Japan has an established pediatric emergency transport and referral system (4). Even at this time, the system makes it easy for patients to visit private clinics and primary emergency centers even at night, and primary care physicians can easily refer patients to secondary and tertiary hospitals even when the diagnosis is not confirmed. To this end, it is important that private clinics, primary emergency centers, and secondary and tertiary hospitals collaborate regularly, specifically by carefully exchanging medical information documents and holding study sessions. It is also necessary to inform parents of the risks of OM and SA and the guidelines for consultation.

However, this study has several limitations. First, the study population was relatively small. For example, only 2 patients with methicillin-resistant *S. aureus* were included, and such patients showed a poor prognosis in a previous report (13). The generalizability of whether pediatric emergency systems impact the prognosis of OM/SA is limited, and multicenter surveillance of a large cohort is required to confirm the outcomes of OM/SA patients in the whole Japanese pediatric population. Second, the retrospective cohort design may have resulted in selection bias. Because the objective of the study was to investigate outcomes of OM/SA in the pediatric emergency care system, we excluded inpatients with OM/SA. However, the 1 case excluded based on this criterion was a preterm neonate with OM who showed a good outcome after early and appropriate treatment. We attempted to reduce observational biases, and primary outcomes were judged by senior orthopedic surgeons or pediatricians who were not involved in the study.

In conclusion, this retrospective pilot study showed good outcomes for pediatric OM/SA patients at a pediatric emergency

core hospital in Japan. Multicenter surveillance is required to investigate the outcomes of OM/SA in the pediatric population, which we consider will reflect the quality of the healthcare system as a whole, and the pediatric emergency system in particular.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The study conformed to the Declaration of Helsinki and was approved by the Ethics Committee of Tokushima Prefectural Central Hospital (IRB number. 20-14). In order to access the medical record used in the study, the administrative permission is required, and the authority is granted by the institutional review board of Tokushima Prefectural Central Hospital. The authors notified information concerning the research, including the purpose of utilization of information utilized in the research, and opportunities to refuse that the research is implemented shall be ensured for the research subjects to participants and their guardians on Tokushima Prefectural Central Hospital website (<http://www.tph.gr.jp/department/section/ethics/>) in accordance with the “Ethical Guidelines for Medical and Biological Research Involving Human Subjects”. The Review Board of the Ethics committee of Tokushima University Hospital approved these opt-out consent option for this retrospective study.

CONSENT FOR PUBLICATION

Not applicable.

AVAILABILITY OF DATA AND MATERIALS

Data are available upon reasonable request. The authors are not authorized to share unauthorized data with a third party. However, data for statistical analysis are available from the corresponding author on reasonable request.

COMPETING INTERESTS

The authors have no conflicts of interest relevant to this article to disclose.

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AUTHORS' CONTRIBUTIONS

M.T., K.Suga., and S.K. designed the study; M.T. and K.Suga. collected and analyzed data; M.T. and K.Suga. wrote the manuscript; K.Suga. performed statistical analysis; S.T., T.T., K.F., A.O., M.S., K.Shichijo., H.K., N.K., and S.K. provided critical review and gave conceptual advice. All authors read and approved the final manuscript.

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