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Comparison of the characteristics of culture-negative versus culture-positive septic arthritis in children

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Septic arthritis in children can be difficult to diagnose and may be associated with severe morbidity. A majority of apparent septic arthritis cases may have negative culture, thereby creating a dilemma regarding treatment. The medical charts of 209 children with the diagnosis of septic arthritis were retrospectively reviewed to evaluate the differences between culture-negative (n = 64) and culture-positive (n = 145) cases. Demographic data, clinical manifestations, treatment, and outcome were analyzed. Laboratory data recorded included white blood cell count, erythrocyte sedimentation rate, C-reactive protein, imaging studies, and culture results. Patients with culture-negative arthritis had a significantly lower incidence of fever (56.3% vs 70.3%, p=0.047), local pain or tenderness (42.2% vs 69.7%, p=0.0001), changes in the overlying skin (45.3% vs 62.1%, p=0.024), motion limitation (25.0% vs 42.8%, p=0.014), and osteomyelitis (25.0% vs 40.7%, p=0.029). Culture-negative patients had a longer duration of symptoms or signs before diagnosis (10.1 ± 8.9 days vs 6.5 ± 5.7 days, p=0.046) and a shorter antimicrobial course (24.5 ± 5.1 days vs 35.7 ± 8.1 days, p=0.001). Children with culture-negative septic arthritis had a lower prevalence of residual joint dysfunction at 6 months after treatment (3.1% vs 11.7%, p=0.046). In conclusion, children with culture-negative septic arthritis have milder clinical manifestations, earlier response to treatment, and a better outcome than those with culture-positive disease.

Key words: Bacterial infection, clinical outcome, risk factors, septic arthritis

Septic arthritis is an infection for which long-term antibiotic therapy is recommended [1,2]. Successful treatment of septic arthritis in children depends on early recognition and prompt institution of therapy, including appropriate antibiotic choice and length of therapy [3]. Thus, identification of the causative pathogen is important for selecting an appropriate antibiotic in patients with septic arthritis. When a pathogen cannot be demonstrated, however, empiric therapy is needed.

An etiologic diagnosis is sought by culturing joint fluid obtained by aspiration or surgical drainage, although blood cultures sometimes yield the pathogen [4]. However, the pathogen cannot be identified in around 20-40% of cases of septic arthritis [1,5-7]. The purpose of this study was to compare the natural history, clinical presentation, laboratory results, treatment course and outcome of children with culture-negative and culture-positive septic arthritis.

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Materials and Methods

The medical records of children younger than 15 years of age with a diagnosis of septic arthritis who were hospitalized from January 1984 to December 2003 were reviewed. Septic arthritis was diagnosed based on the finding of purulent material in the joint space or the isolation of a bacterial pathogen from joint fluid. Osteomyelitis was defined by positive culture from aspiration of the involved bone or evidence on radiograph or bone scan. Radiography may demonstrate early changes including joint effusion, soft tissue swelling, periarticular osteoporosis, and joint space loss. The latter include periosteal reaction, marginal and central erosions, destruction of subchondral bone, subluxation or dislocation, and intra-articular bony ankylosis [8].

Patients meeting any of the following criteria were excluded from the study: 1) arthritis associated with an open fracture, postsurgical puncture wound, or other obvious trauma; 2) known history of autoimmune disease; 3) treatment with systemic steroids in the previous 2 months; 4) congenital osteoarticular anomaly;

5) no culture from the involved joints; 6) treatment with antibiotics for less than 2 weeks; 7) subsequent diagnosis of juvenile rheumatoid arthritis; or 8) lost to follow-up within 6 months.

According to the results of cultures of joint fluid and blood, the patients were divided into the culture-positive or culture-negative group. The demographic features, involved joints, clinical manifestations, laboratory results, treatment, and outcomes were recorded and compared between the 2 groups. Outcome was evaluated both at the end of treatment and 6 months later.

Student's *t* test, Fisher's exact test, and Pearson chi-squared association test were used to analyze the results. Differences were considered to be statistically significant when the *p* value was <0.05.

Results

A total of 209 children were included in this study, of whom 145 (69.4%) had culture-positive and 64 (30.6%) culture-negative arthritis. The characteristics of the children are summarized in Table 1. There were no significant differences in age, gender, or the involved joint between the 2 groups. The mean age was similar in the culture-positive group (4.9 ± 4.6 years) and the culture-negative group (4.0 ± 4.2 years). Joints in the lower extremity were most commonly involved in both groups. The most commonly involved joint was the hip, followed by the knee.

Fever, pain and tenderness, changes in the overlying skin, limitation of range of motion, and associated osteomyelitis were more common in children with culture-positive arthritis (Table 2). The duration of symptoms before diagnosis, such as pain, discomfort, or refusal to walk, was significantly longer in patients with culture-negative arthritis.

There were no significant differences in the incidence of an elevated initial total leukocyte and absolute neutrophil count or erythrocyte sedimentation rate (ESR) between the 2 groups (Table 3). The culture-positive group had a higher initial level of C-reactive protein (CRP). Characteristic features of septic arthritis were found with similar frequency on plain radiographs and bone scan in the 2 groups. Among the 145 children with culture-positive arthritis, 98 (67.6%) had pathogens isolated from the joint fluid while in 69 (47.6%) these were isolated from blood. *Staphylococcus aureus* was the most common isolate (45.5%), followed by *Streptococcus pyogenes* (7.9%), *Salmonella* spp. (10.3%), *Haemophilus influenzae* (4.8%), and *S. pneumonia*e (4.8%).

Patients with culture-positive disease received intravenous antibiotics for a longer duration (mean, 22.9 ± 7.8 days; range, 6 to 36 days) than patients with culture-negative arthritis (mean, 13.1 ± 5.2 days; range, 7 to 23 days) [Table 4]. However, the duration of subsequent oral antibiotic therapy was similar in the culture-positive group (12.8 ± 4.7 days) and the culture-negative group (11.4 ± 5.1 days). All patients underwent needle aspiration of a joint, and the number undergoing arthrotomy in both groups did not differ significantly (29.7% overall, 27.6% in the culture-positive and 33.4% in the culture-negative group).

Residual joint dysfunction after completing treatment was noted in 26 patients (17.9%) in the culture-positive group (14 with limp, 12 with limited range of motion) and 8 (12.5%) in the culture-negative group (5 with limp, 3 with limited range of motion). At 6 months after discharge, 17 patients in the culture-positive group had residual dysfunction (9 with a limp, 6 with limited range of motion, and 2 with limb length discrepancy), and only 2 patients in the culture-negative group had residual dysfunction (both with limp) [$p<0.05$].

Table 1. Characteristics of 204 pediatric patients with septic arthritis

	All (n = 209) No. (%)	Culture-positive group (n = 145) No. (%)	Culture-negative group (n = 64) No. (%)	*p*
Age				
Mean ± SD	4.3 ± 4.5	4.9 ± 4.6	4.0 ± 4.2	>0.05
<2 years	106 (50.7)	77 (53.1)	29 (45.3)	>0.05
2-5 years	42 (20.1)	25 (17.2)	17 (26.6)	>0.05
6-10 years	34 (16.3)	22 (15.2)	12 (18.8)	>0.05
>10 years	27 (12.9)	21 (14.5)	6 (9.3)	>0.05
Range	NB-15 years	NB-15 years	24 days-5 years	
Gender				
Male	117 (55.9)	81 (55.2)	36 (56.3)	>0.05
Female	92 (44.1)	64 (44.8)	28 (43.7)	>0.05

Abbreviations: SD = standard deviation; NB = newborn

Table 2. Clinical features of 204 pediatric patients with septic arthritis

	All (n = 209) No. (%)	Culture-positive group (n = 145) No. (%)	Culture-negative group (n = 64) No. (%)	*p*
Fever	138 (66.0)	102 (70.3)	36 (56.3)	0.047
Pain/tenderness	128 (61.2)	101 (69.7)	27 (42.2)	0.0001
Overlying skin changes	119 (56.9)	90 (62.1)	29 (45.3)	0.024
Limited ROM	78 (37.3)	62 (42.8)	16 (25.0)	0.014
Limp	52 (24.9)	36 (24.8)	16 (25.0)	>0.05
With osteomyelitis	75 (35.9)	59 (40.7)	16 (25.0)	0.029
Duration of symptoms/signs before diagnosis (mean ± SD) [days]	7.6 ± 7.2	6.5 ± 5.7	10.1 ± 8.9	0.046
Joint involved				
Hip	79 (37.8)	57 (39.3)	22 (34.3)	>0.05
Knee	53 (25.4)	33 (22.8)	20 (31.3)	>0.05
Ankle	22 (10.5)	17 (11.7)	5 (7.8)	>0.05
Shoulder	22 (10.5)	17 (11.7)	5 (7.8)	>0.05
Elbow	5 (2.4)	2 (1.4)	3 (4.7)	>0.05
Sacroiliac	7 (3.3)	3 (2.1)	4 (6.3)	>0.05
Others	3 (1.4)	3 (2.1)	0 (0)	>0.05
Multiple	18 (8.7)	13 (8.9)	5 (7.8)	>0.05

Abbreviations: ROM = range of motion; SD = standard deviation

Discussion

We found that children with culture-negative septic arthritis had a milder presentation and a better outcome than those with culture-positive septic arthritis. Studies on childhood septic arthritis have reported a wide range of rates for the isolation of pathogens (52-82%) [1,5-7], which depended on the selection criteria used. Commonly used inclusion criteria in most previous investigations of septic arthritis in children included aspiration of purulent material or a bacterial isolate from the joint space together with a typical clinical presentation, including localized tenderness and pain, swelling, redness, and reduced mobility of the joint. Radiologic or radionuclide scan findings have also been used as inclusion criteria [4,7,9,10]. Strict exclusion criteria have been adopted to avoid selection of patients with other conditions associated with milder disease or patients without bacterial infection. This may have resulted in the exclusion of some patients with bacterial infections who had negative cultures. However, we still found that patients with negative cultures had a milder clinical presentation.

The demographic features of our patients were similar to those in previous studies. Septic arthritis is more common in young children, and half of our patients were less than 2 years of age. The hip joint was most commonly involved, followed by the knee, ankle, and shoulder joints. Involvement of more than 1 joint was noted in 8.7% of our patients.

The subjective symptoms of infants are hard to determine. Objective signs, such as fever, changes in the overlying skin, limited range of motion, and associated osteomyelitis, were found more frequently in

Table 3. Laboratory data and characteristic findings on imaging for 204 pediatric patients with septic arthritis

	All No.[a] (%)	Culture-positive group No.[a] (%)	Culture-negative group No.[a] (%)	*p*
WBC count >15,000/mm^3	79/209 (37.8)	54/145 (37.2)	25/64 (39.1)	>0.05
PMN >10,000/mm^3	79/209 (37.8)	56/145 (38.6)	23/64 (35.9)	>0.05
Initial CRP >0.9 mg/dL	128/160 (80.0)	105/121 (86.8)	23/39 (59.0)	0.0004
Initial ESR >30 mm/h	70/121 (57.9)	53/88 (60.2)	17/33 (51.5)	>0.05
X-ray findings	97/204 (47.5)	65/141 (46.1)	32/63 (50.8)	>0.05
Bone scan findings	94/103 (91.3)	61/68 (89.4)	33/35 (94.1)	>0.05

Abbreviations: WBC = white blood cell; PMN = polymorphonuclear neutrophils; CRP = C-reactive protein; ESR = erythrocyte sedimentation rate

[a]Number of patients with the finding/number of patients examined.

Table 4. Treatment and joint dysfunction in 204 pediatric patients with septic arthritis

Variable	All (n = 209) No. (%)	Culture-positive group (n = 145) No. (%)	Culture-negative group (n = 64) No. (%)	*p*
Mean duration of antibiotic therapy ± SD (days)				
Intravenous	19.8 ± 8.3	22.9 ± 7.8	13.1 ± 5.2	0.0001
Oral	12.4 ± 5.0	12.8 ± 4.7	11.4 ± 5.1	>0.05
Total	32.2 ± 7.4	35.7 ± 8.1	24.5 ± 5.1	0.001
Arthrotomy (n)	62 (29.7)	40 (27.6)	22 (33.4)	>0.05
Joint dysfunction (n)				
End of treatment	34 (16.3)	26 (17.9)	8 (12.5)	>0.05
Six months after discharge	19 (9.1)	17 (11.7)	2 (3.1)	0.046

Abbreviation: SD = standard deviation

the culture-positive group. Pain is a subjective complaint, although tenderness may be easier to observe on examination. Pain or tenderness was significantly more common in the culture-positive group. About one-fourth of patients in each group had a limp. Many patients were not yet walking or had just started to walk, so that it was difficult for the parents to note any gait abnormality. The duration from the onset of first symptoms or signs to diagnosis was longer in the culture-negative group.

S. aureus was the most common pathogen isolated in patients with positive culture result. Except for *S. pyogenes*, the other isolates, including *Salmonella* spp., *H. influenzae*, and *S. pneumoniae*, were all common pathogens similar to those isolated in previous reports from Taiwan [1,2,11-13]. The finding that *S. aureus* was the most common pathogen isolated in our series may explain why most of those culture-negative patients who were treated empirically with anti-staphylococcal antibiotics had a good response. It is thus very likely that *S. aureus* was also the main pathogen in the culture-negative group. A similar assumption was made in previous studies of children with culture-negative osteomyelitis [3,14]. In a previous study of staphylococcal arthritis, polymerase chain reaction demonstrated persistent expression of *S. aureus* DNA in the synovial fluid for 10 weeks despite adequate antibiotic treatment and sterile synovial fluid [15].

In this study, total leukocytes, absolute neutrophil counts, and ESR were similar in both groups, but patients with culture-positive arthritis were significantly more likely to have an elevated CRP. Lyon and Evanich [3] found that the average CRP in children with culture-positive septic arthritis was 10.2 mg/dL, compared with 3.6 mg/dL in those with culture-negative arthritis. Measurement of CRP is thought to be more helpful in diagnosis than the ESR or leukocyte count [16].

Plain-film radiographs do not reveal destructive joint lesions in the early stage of septic arthritis, but may provide useful diagnostic information in patients with suspected hip joint arthritis. Swelling of the joint capsule with displacement of the fat line is an early sign of hip joint destruction. As capsular swelling progresses, the femoral head is displaced laterally and upward. Radionuclide bone scan is useful, especially when the exact site of infection is not certain or when multiple joints might be involved [8]. Bone scans showed evidence in about 90% of our patients, with no significant differences between the 2 groups. By contrast, X-ray showed findings characteristic of septic arthritis in only about 50% of patients in both groups.

The empiric choice of antibiotics is generally based on the most common pathogen suspected. A diagnostic procedure is highly recommended before initiating antimicrobial therapy. The duration of antibiotic therapy is still a matter of controversy. A previous study recommended a minimum duration of 3 weeks [17], although shorter courses have been suggested [18,19]. The total duration of antibiotic therapy was shorter in the culture-negative than in the culture-positive group in this study, mainly because of a shorter period of parenteral treatment, but the culture-negative patients still had a better outcome.

Surgical intervention is indicated in hip joint infections and in patients with poor response to antibiotics [13]. In this study, there was no significant difference between the number of patients with hip joint infection and the number receiving arthrotomy.

Residual dysfunction was found in 10-25% of children with septic arthritis [7,20]. Better results have been reported in children receiving early dexamethasone treatment [21]. Sequelae are more common in those with *Enterobacteriaceae* infection and with hip joint involvement. In this study, the incidence of joint dysfunction was not significantly different between the 2 groups immediately after stopping antibiotics;

however, significantly more dysfunction was found at 6 months in the culture-positive than in the culture-negative group.

If the patient with septic arthritis is stable without signs of sepsis, antibiotics should be withheld until a culture is performed. This may reduce the incidence of negative culture [16]. Because pus exerts a bacteriostatic effect, diluting the exudate before culturing it may also increase the yield [16,22].

In conclusion, compared with the culture-positive group, children with culture-negative septic arthritis had milder disease, received a shorter course of antibiotics, and had a better outcome. However, the need for each patient's response to treatment to be monitored carefully, with modification of therapy as indicated, should be emphasized.

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