

Success of Short-Course Parenteral Antibiotic Therapy for Acute Osteomyelitis of Childhood

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The outcome of acute osteomyelitis treated with sequential therapy consisting of a short course of parenteral antibiotics, followed by oral antibiotics, was studied. To be considered acute osteomyelitis, related symptoms must have been present for less than 2 weeks before diagnosis. Short-course parenteral antibiotics (therapy for 7 days or less) and then oral antibiotics were used to treat 29 patients (median age, 6.3 years). Pathogens were identified from blood cultures and bone aspirates. *Staphylococcus aureus* was isolated in 59%. Median duration of parenteral antibiotics and oral antibiotics was 4 days

(range, 0-7 days) and 28 days (range, 14-42 days), respectively. Median duration of combined (parenteral and oral) therapy was 32 days (range, 20-49 days). No failures or complications were noted at the 6-month follow-up, which was available for 27 patients. Short-course parenteral antibiotic therapy followed by oral therapy appears to be effective for treatment of acute, uncomplicated osteomyelitis.

Keywords: osteomyelitis; parenteral antibiotic therapy; *Staphylococcus aureus*

Introduction

Osteomyelitis is an uncommon but potentially debilitating disease in children. The reported incidence is 0.02% in children younger than 13 years old.¹ The diagnosis of osteomyelitis involves a combination of clinical findings, laboratory data, bacteriologic tests, and radiologic studies.²⁻⁴ The standard textbook recommendation for treatment of osteomyelitis consists of 3 to 6 weeks of antibiotic therapy, with varied recommendations for the duration of parenteral therapy.⁵⁻⁸ The minimum duration of parenteral antibiotic treatment has been recently reconsidered.⁹⁻¹¹ The variation reported in treatment regimens is presumably based on historical treatment failures with shorter courses of therapy and the lack of distinguishing acute versus chronic osteomyelitis. We have summarized our experience with short-course parenteral antibiotic therapy for acute osteomyelitis to add insight into the efficacy and safety of such treatment.

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Methods

We reviewed the medical records of all children with the discharged diagnosis of osteomyelitis for 5 consecutive years from 1995 to 2000. Charts were reviewed for the accuracy of diagnosis. Osteomyelitis was defined as a combination of (1) clinical suspicion based on fever, bone pain, or decreased usage of a limb, and (2) an abnormal bone scan or magnetic resonance image (MRI). We defined acute osteomyelitis as those patients with symptoms present for less than 14 days before diagnosis. Patients were excluded from the study for osteomyelitis symptoms exceeding 14 days (or recurrent), a chronic underlying medical condition, immunodeficiency, associated fracture, septic arthritis, chronic arthritis, multifocal osteomyelitis, or concomitant bone abscess (as defined by the need for surgical débridement or drainage).

Parenteral antibiotic therapy for 7 days or less (intramuscular or intravenous administration) was considered short-course therapy. Patients with acute osteomyelitis who were treated with short-course antibiotic therapy constituted the study group. Follow-up was obtained from the hospital record or from the primary care office record. Cure was defined by the absence of symptoms for 1 year after discontinuing

Table 1. Sites of Osteomyelitis

Long Bones		Others	
Distal femur	7	Talus	2
Proximal femur	3	Pubis	2
Distal tibia	7	Ilium	1
Proximal tibia	2	Clavicle	1
Proximal fibula	1		
Distal fibula	1		
Distal humerus	1		
Distal radius	1		

antibiotics. Failures were defined by the need to switch from oral antibiotics back to parenteral antibiotics or restarting antibiotics after being discontinued.

Statistical analyses were conducted using SPSS 12 (SPSS, Chicago, Ill). Medians and interquartile ranges (IQR, 25th-75th percentile) were provided for non-normal data. Confidence intervals for proportions were calculated using Stata 6 (StataCorp, College Station, Texas). The institutional review board of the hospital approved the study.

Results

Study Group

Our hospital discharged 138 patients with the principal diagnosis of osteomyelitis. A review of their records found that 100 (72%) fulfilled criteria for acute osteomyelitis. Sixty-one were excluded from the study because of chronic underlying disease (9), immunodeficiency (10), associated fracture (10), septic arthritis (5), multifocal osteomyelitis (14), and concomitant bone abscess (13). Of the remaining 39 patients, a short-course regimen of parenteral antibiotics was used to treat 29 (74%). Median age of the 29 study patients was 6.3 years (IQR, 2.9-9.0 years), and 19 (70%) patients were boys. Distribution of the sites of osteomyelitis is shown in Table 1.

Clinical Presentation

Median duration of symptoms before admission was 4 days (range, 0-12 days). Decreased limb use (93%), pain (90%), and fever (83%) were the most common presenting symptoms. Point tenderness of the involved bone was the most common sign on physical examination, occurring in 72% of the patients. Other signs included decreased range of motion in the adjacent joint (52%), erythema (38%), and pain (31%).

Laboratory Data

All the patients had a complete blood count and erythrocyte sedimentation rate (ESR, Westergren) on admission. The median white blood cell count (WBC) was 11 800/mm³ (IQR, 7700-15 400/mm³), and median absolute neutrophil count was 7400/mm³ (IQR, 4600-10 600/mm³). The median ESR was 42 mm/h (IQR, 27-60 mm/h).

Bacteriology

Etiologic agents were identified in 20 (69%) of 29 patients. One or more blood cultures were obtained from all 29 patients. *S aureus* was the only pathogen identified in 10 (34%) of the blood cultures. Bone aspirate was performed in 14 (48%) patients, and 9 (64%) of these cultures were positive: *S aureus* was isolated in 6 patients and *Streptococcus pyogenes* in 3 patients. Two patients had both a positive blood culture and bone culture. In 1 patient, *S aureus* was isolated from soft tissue overlying the infected bone. None of the *S aureus* isolates were methicillin resistant.

Radiology

Plain radiographs were obtained in 28 patients (96%). Findings from radiographs at the time of admission were normal in 15 (54%), soft tissue changes were noted in 7 (25%), and 6 (21%) had decreased bone density and abnormality of the bone cortex or marrow. Technetium-labeled bone scans were performed in 24 (83%) of 29 patients, and all demonstrated focal, increased uptake. Nine patients (31%) had an MRI, including the 5 patients who did not have a bone scan; all had findings consistent with osteomyelitis.

Management

The median duration of parenteral antibiotic therapy was 4 days (range, 0-7 days). The median duration of subsequent oral antibiotic therapy was 28 days (range, 14-42 days). The median duration of total combined antibiotic therapy was 32 days (range, 20-49). For patients with bacteremia, the median duration of parenteral therapy was 6 days (range, 4-7 days) (Figure 1).

Cefazolin was the most frequently used parenteral antibiotic (93%), with a median daily dosage

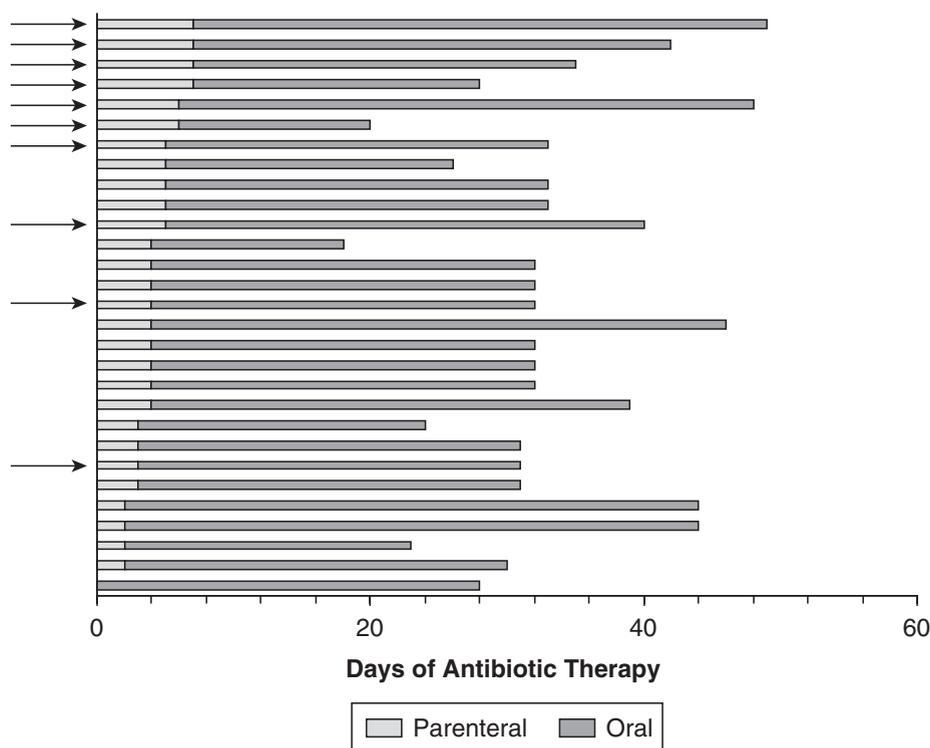


Figure 1. Parenteral and oral antibiotic therapy for each study patient. Patients with bacteremia are indicated by an arrow.

of 150 mg/kg (IQR, 140-150 mg/kg), and cephalexin was the most frequently used oral antibiotic (90%) with a median daily dosage of 100 mg/kg (IQR, 95-100 mg/kg). Median duration of hospitalization was 4 days (range, 2-7 days).

Follow-up for at least 6 months was available for 27 (93%) patients. Median duration of follow-up was 1.2 years (IQR, 0.8-2.8 years). No failures and no other complications have been noted (95% CI, 0%-12%).

Acute Uncomplicated Osteomyelitis Treated With Long-Course Therapy

Ten patients with acute uncomplicated osteomyelitis were eligible for the short course of parenteral antibiotics but received longer courses of therapy. Their median age was 6.0 years (IQR, 2.0-12.3 years), the median duration of parenteral therapy was 15 days (range, 10-28 days), the median hospitalization was 10 days (range, 1-28 days), and the median total antibiotic therapy was 32 days (range 28-46 days). No failures or complications were noted among this group of patients over a median follow-up of 1.5 years.

Discussion

Osteomyelitis is a relatively rare disease of childhood and is therefore difficult to study prospectively. Additionally, even among the rare cases of osteomyelitis, several patient subgroups must be considered and managed differently, including acute versus chronic osteomyelitis, transcutaneous inoculation versus hematogenous osteomyelitis, bony abscess versus uncomplicated osteomyelitis, and immunocompromised versus immunocompetent hosts. Most of the medical literature regarding treatment of osteomyelitis has been derived from historical reviews. During the last 2 decades, increasing evidence shows that acute hematogenous osteomyelitis can be treated with a short course of parenteral antibiotics and then a more prolonged course of oral antibiotics. We undertook this study to review our experience with such therapy for acute osteomyelitis.

In defining our patients, we used a standard definition of acute, uncomplicated osteomyelitis as symptoms of less than 2 weeks and no associated open wounds, fractures, or joint infection. Accordingly, the presentation of patients with acute osteomyelitis in our study group was similar to previous reports.^{12,13}

Clinical features of our study group matched previous study patients with regard to sites of infection,¹⁴⁻¹⁶ results of the WBC count and ESR,¹⁶⁻¹⁸ frequency of bacteremia,^{9,16,19} predominance of *S aureus* as the etiologic agent,^{9,14,16} and the lack of plain radiographic changes at the time of diagnosis.^{7,8} From a diagnostic standpoint, all patients had abnormal findings on the bone scan or MRI, and bone aspiration was superior to blood cultures for determining the pathogen, as previously noted.^{13,15,20}

Currently, most acute osteomyelitis is treated with sequential intravenous and then oral antibiotics.^{5,9,17,21-24} This approach to treatment has become more common only in the last decade; before that time, therapy was entirely intravenous and lasted from 4 to 8 weeks.^{13,25,26} Shorter intravenous antibiotic treatment and a greater reliance on oral antibiotic therapy has been supported in retrospective¹⁰ and prospective studies,^{24,27-29} but textbook recommendations and common practice continue to vary for duration of parenteral therapy and criteria for switching to oral antibiotic therapy.⁶⁻⁸ The reasons for such variation between the medical literature and current practice are many.

First, study populations reported in the osteomyelitis literature are often different because of variables of age, duration symptoms, pathogens, presence of joint involvement or bone abscess, and immune status; therefore, general recommendations for treating all cases will tend to suggest more conservative (longer) courses of parenteral antibiotics.

Second, the size of the study groups has been limited,^{24,27-29} and the duration of follow-up has been relatively short,^{27,29} which raises uncertainty about the long-term outcome for patients treated with short courses of parenteral antibiotics. For some, the prolonged use of oral antibiotics has raised concern about compliance.^{22,23,30} Additionally, there is no consensus on a minimum duration of parenteral antibiotic treatment and no accepted recommendation on when to transition to oral therapy. Proposals for when to switch to oral therapy have included improved clinical condition (including the absence of fever) plus either falling ESR,²² improved plain radiographs,²⁹ and more recently, a decreasing level of C-reactive protein.³¹ The recent availability and confidence in home intravenous therapy with percutaneously placed central venous catheters has led to many patients getting prolonged parenteral therapy even beyond stages of clinical improvement, and the risk of these catheters must be weighed against the

risk of treatment failure with oral therapy.³² Finally, treatment failures using short-course parenteral therapy have been reported^{27,29,33}; however, the study groups in those studies include complex cases of osteomyelitis.

In review of the prior related studies, two prospective studies by Cole et al,^{34,35} were among the first studies to establish the efficacy of short-course parenteral therapy in acute osteomyelitis. The authors defined "acute osteomyelitis" based on history and symptoms of less than 14 days' duration. Diagnosis was made on history and physical exam and not necessarily confirmed by radiograph. In the first study of 55 patients published in 1982, the authors reported their median parenteral therapy duration of 3 days (range, 2 to 5 days) and a total duration of antibiotic therapy of 6 weeks. Antibiotic levels were not monitored, follow-up was for 4 years after discharge from the hospital, and no failures were noted. In 1987, the same group reported excellent results with an additional 50 patients enrolled in a similar prospective study. The authors further shortened the duration of antibiotic therapy to a total of 3 weeks (with the same initial parenteral therapy as previously described) and showed similar outcomes.

Most recently, Peltola et al^{11,12} reported a prospective study of 50 pediatric cases of acute *S aureus* osteomyelitis. Their definition of "acute osteomyelitis" was identical to previous definition by Cole. Their patients received an average of 4 days of intravenous cephadrine or clindamycin, followed by oral antibiotics for a total duration of treatment of 3 to 4 weeks. Peak antimicrobial serum inhibitory values or serum bactericidal levels were not monitored. The authors had excellent results with no complications or failures over an average follow-up of 27 months. They also concluded that the treatment of acute staphylococcal osteomyelitis could be simplified and made easier for patients.

A corresponding editorial by Nelson³⁶ addressed the importance of monitoring of serum bactericidal activity of the oral antibiotics. Nelson agreed with the concept of an early switch to oral therapy, but he strongly argued that antibiotic levels need to be monitored for successful therapy.³⁶ This argument stemmed from his own studies conducted in 1978 and 1982, in which treatment failures were attributed to low serum bactericidal levels.^{30,37}

The most recent retrospective analysis on acute osteomyelitis is one by Karwowska et al.¹⁹ Their study presents the outcomes of 128 cases of acute

osteomyelitis treated between 1984 and 1996. Their median duration of intravenous therapy was 11 days, and the median duration of the total antibiotic course was 38 days. The median duration of follow-up was 1.2 months (range, 0.1-22.2 months), and complications occurred in 6.6% of patients. Antibiotic levels were monitored in a few patients, and the only defined risk factor for complications was the higher incidence of polymicrobial infections, and not the duration of antibiotic therapy.

Our study results agree with the prospective studies by Peltola et al¹¹ and Cole et al^{34, 35} and retrospective studies from Nelson et al³⁰ and Karwowska et al.¹⁹ Our median duration of parenteral therapy was only 4 days, and our median total antibiotic therapy was 32 days. Our median duration of hospital stay was 4 days, and our median duration of follow-up was 1 year. We did not identify any failures or complications within a limited follow-up.

In our institution, general pediatricians alone care for some patients, and others are managed by the specialty services of infectious disease or orthopedic surgery; therefore, the decisions regarding antibiotic course, transition to oral therapy, and follow-up are not standardized. In general, the criteria for switching from intravenous to oral therapy often requires clinical improvement that includes a return to normal body temperature, improvement in local symptoms, and an ability to be compliant with an oral antibiotic comparable to the intravenous drug. In practice, patients often remain in the hospital pending results of cultures, antibiotic sensitivities of any isolates, and clearance of associated bacteremia. Furthermore, serum bactericidal levels (as an estimate of compliance and adequacy of oral therapy) have not been recommended routinely, but we use high doses of oral antibiotics and maintain close clinical follow-up.

Although not an issue for our patients in this study, increasing rates of methicillin-resistant *S aureus*³⁸ may require prolonged courses of intravenous vancomycin in the future; this highlights the increasing importance for an accurate microbiologic diagnosis.

Our data have several limitations. The confidence interval for our observed absence of complications or failures could still be as high as 12%. Although no complications of short-course parenteral therapy were noted, patients who were excluded for bony abscess may represent patients who were initially considered for short-course parenteral therapy

before the need for surgical intervention was recognized. Additionally, with a relatively short duration of follow-up, long-term consequences of our management may not be appreciated. Finally, it is impossible to retrospectively determine why some patients who were eligible for short-course parenteral therapy received longer courses of antibiotic therapy.

Conclusion

Our results are adding to the accumulating data that short-course parenteral therapy for acute, uncomplicated osteomyelitis is safe and successful. As a corollary, failure to respond to initial parenteral antibiotic treatment should prompt further intravenous therapy and investigation for a bone sequestrum, subperiosteal abscess, or an atypical or resistant pathogen.

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