Ceftriaxone Therapy for Staphylococcal Osteomyelitis: A Review

B. Joseph Guglielmo,[1] Andrew D. Luber,[1,a] Domenic Paletta, Jr.,[1,a] and Richard A. Jacobs[2]

[1]Department of Clinical Pharmacy, School of Pharmacy, and [2]Division of Infectious Diseases, School of Medicine, University of California San Francisco, San Francisco, California

Ceftriaxone, although less active than standard antistaphylococcal agents, is potentially useful in the treatment of osteomyelitis. Thirty-one patients with osteomyelitis due to *Staphylococcus aureus* were identified, 22 of whom were treated with ceftriaxone and 9 with other agents. Of those patients treated with ceftriaxone, 17 were cured; all treatment failures were associated with chronic osteomyelitis and continued presence of necrotic bone or infected hardware. It is concluded that ceftriaxone is effective in the ambulatory treatment of *S. aureus* osteomyelitis.

Intravenous antimicrobial treatment of staphylococcal osteomyelitis increasingly takes place in the ambulatory care setting [1]. Ceftriaxone, which has long pharmacological half-life [2], may have utility as once-daily treatment for osteomyelitis. However, it is less potent than established antimicrobials such as cefazolin [3]. Furthermore, its high level of protein binding [4] can result in subtherapeutic, free, microbiologically active serum levels. We investigated the efficacy of ceftriaxone as home-care therapy for *Staphylococcus aureus* osteomyelitis.

Patients and Methods

We screened all patients hospitalized during 1991–1996 with an International Classification of Disease (9th revision)–coded diagnosis of *S. aureus* osteomyelitis (figure 1). Excluding those patients with infections due to methicillin-resistant *S. aureus* or other organisms, we identified a cohort of 31 patients at the Medical Center at the University of California San Francisco. All received iv therapy for a minimum of 6 weeks, which included 1–2 weeks of nafcillin, cefazolin, or vancomycin prior to discharge from the hospital. Twenty-two patients were treated with ceftriaxone, 2 g once daily, and 9 with other agents (all doses are currently provided in table 2). MICs for cefazolin and nafcillin were ≤ 0.5 μg/mL, and MIC for vancomycin was ≤ 1.0 μg/mL. The mean duration of therapy $\pm$ SD was 49 ± 7 days. All patients were followed up for a minimum of 6 months.

Definitions. Clinical cure was defined as complete resolution of all signs and symptoms confirmed by microbiological examination. Indeterminate outcome was defined as resolution of signs and symptoms with continuation of suppressive antimicrobial therapy. Treatment failure was defined as continued inflammation with persistent infection or superinfection requiring further surgical and/or antibiotic therapy. Acute osteomyelitis was defined as newly recognized bone infection; chronic disease was defined as a relapse of a previous treated or untreated infection [5].

Statistical analyses. Patients who received ceftriaxone were compared with those who received standard antistaphylococcal therapy (cefazolin, vancomycin). No patient received long-term nafcillin. All patients received 1–2 weeks of nafcillin or cefazolin or vancomycin prior to discharge from the hospital. Categorical variables were evaluated with the Fisher's exact test; continuous variables were compared by use of the Student's t test. $P < .05$ was considered significant.

Results

Tables 1 and 2 show the treatment outcomes for those patients who received ceftriaxone or other standard antistaphylococcal therapies. Of the 22 patients who received ceftriaxone, 17 were considered cured. All of them had native bone osteomyelitis or had had infected prostheses removed at the initiation of antimicrobial therapy. The outcomes for 2 patients were considered indeterminate; in these instances, infected hardware could not be removed and oral antimicrobials were administered. The 3 patients for whom ceftriaxone treatment failed had necrotic bone that could not be surgically excised.

Received 4 June 1999; revised 24 September 1999; electronically published 6 January 2000.

This study was approved by the Committee on Human Research at the University of California San Francisco.

Financial support: Roche Pharmaceuticals, Nutley, NJ.

Present affiliation: Western University College of Pharmacy, Pomona, California (A.D.L.); Parke-Davis, San Francisco, California (D.P.).

Reprints or correspondence: Dr. B. Joseph Guglielmo, Department of Clinical Pharmacy, School of Pharmacy, University of California San Francisco, San Francisco, CA 94143–0622 (bjg@itsa.ucsf.edu).

Clinical Infectious Diseases 2000; 30:205–7

1058-4838/2000/3001-0037$03.00

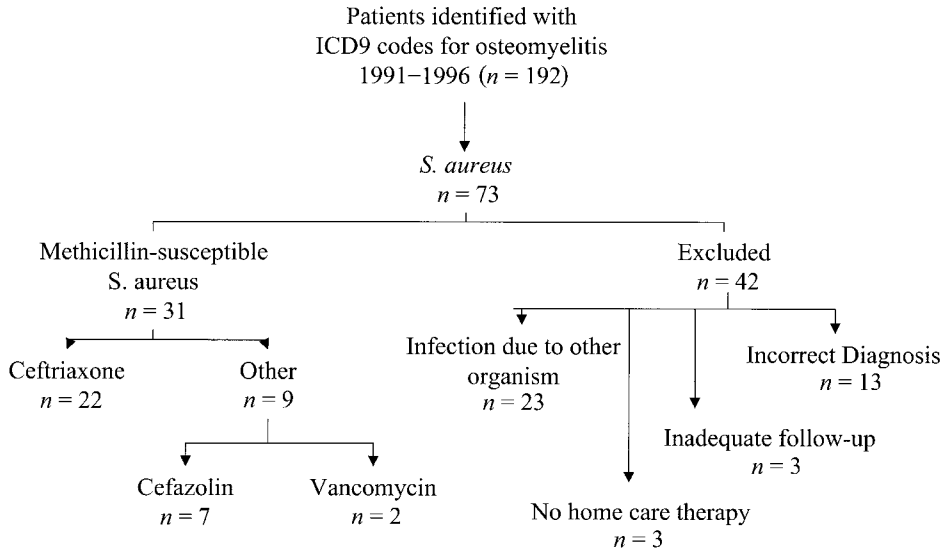

Figure 1. Breakdown of diagnosis and therapy for 73 patients diagnosed with osteomyelitis due to *Staphylococcus aureus*

Although diarrhea and biliary tract symptoms have been described as common adverse effects associated with ceftriaxone therapy [6], they were not documented for any of the patients.

Of those patients who received cefazolin or vancomycin, 7 were considered cured, 1 had an indeterminate outcome, and the treatment for 1 failed. The 1 patient for whom treatment (vancomycin) failed had spinal osteomyelitis and infected hardware that could not be removed.

Table 1. Characteristics of and outcome for 22 patients who received ceftriaxone therapy for *Staphylococcus aureus* osteomyelitis.

	Infection				
Age, y	Site	Type	Hardware (removed)	Duration of therapy, w[a]	Outcome
67	Sternum	A	N	6	Cured
53	Sternum	A	N	7	Cured
46	Sternum	C	N	6	Cured
41	Spine	C	N	6	Cured
75	Spine	A	N	7[b]	Cured
28	Spine	A	Y (Y)	7	Cured
35	Bone flap	A	N	6	Cured
40	Bone flap	C	N	6	Cured
56	Bone flap	A	N	7	Cured
45	Bone flap	A	N	6	Cured
56	Bone flap	A	N	7	Cured
36	Bone flap	C	N	7	Cured
63	Knee	C	Y (Y)	6	Cured
46	Knee	C	Y (Y)	8	Cured
38	Knee	C	Y (Y)	9	Cured
44	Foot	C	N	6	Cured
27	Humerus	C	Y (Y)	8	Cured
46	Maxilla	C	N	6	F[c]
70	Bone flap	C	N	6	F[c]
56	Bone flap	C	N	10	F[c]
75	Spine	A	Y (N)	7	I[d]
52	Spine	A	Y (N)	6	I[d]

NOTE. A, acute; C, chronic; F, failed treatment; I, indeterminate outcome; N, no; Y, yes.

[a] All patients received 2 g of ceftriaxone q24h except as noted.

[b] This patient received 1 g of ceftriaxone q24h.

[c] Infected necrotic bone could not be surgically removed.

[d] Infected hardware (wires, plates, screws, and rods) could not be removed; the patient received long-term oral therapy.

Discussion

Although ceftriaxone has been suggested as a possible therapy for *S. aureus* osteomyelitis, clinicians have been reluctant to use it. It is less potent against *S. aureus* than are other agents; for example, the MIC_{90} for ceftriaxone is 2 μg/mL, whereas it is 0.5 μg/mL for cefazolin. An additional concern is ceftriaxone's moderate-to-high level of protein binding (85%–95%) [4]. It is a free antimicrobial that is microbiologically active [7], and free levels of β-lactams should remain above the MIC for most of the dosing interval [8]. Previously published reports suggest that treatment of serious staphylococcal infection with highly protein-bound cephalosporins is associated with clinical failure [9]. Normal-sized patients who received ceftriaxone, 2 g daily, have documented trough levels of 10–50 μg/mL [2], assuming unbound ceftriaxone to be ~10% of the total results in estimated free trough levels at 1–5 μg/mL [4]. Consequently, free microbiologically active levels remain above the MIC for most if not all of the dosing interval.

In summary, we report the largest series of cases of *S. aureus* osteomyelitis treated with once-a-day ceftriaxone therapy. Our findings suggest that ceftriaxone, similar to other more established antistaphylococcal regimens, is effective in the treatment of this serious infection. However, the documented treatment failures reinforce the importance of surgical excision of infected

Table 2. Characteristics of and outcome for 9 patients who received cefazolin and vancomycin therapy for *Staphylococcus aureus* osteomyelitis.

	Infection		Hardware	Therapy		
Age, y	Site	Type	(removed)	Regimen	Duration, w[a]	Outcome
31	Spine	A	Y (Y)	Cfaz, 1 g q8h	6	Cured
40	Spine	C	N	Cfaz, 2 g q8h	6	Cured
81	Spine	A	N	Cfaz, 2 g q12h	6	Cured
81	Spine	C	Y (Y)	Cfaz, 1 g q8h	6	Cured
52	Knee	C	Y (Y)	Cfaz, 1 g q8h	7	Cured
55	Tibia	C	N	Cfaz, 1 g q8h	7	Cured
40	Hip	C	Y (Y)	Vm, 1 g q12h	6	Cured
64	Spine	C	Y (N)	Vm, 1 g q12h	6	F[a]
75	Knee	C	Y (N)	Cfaz, 1 g q12h	6	I[b]

NOTE. A, acute; C, chronic; Cfaz, cefazolin; F, failed treatment; I, indeterminate outcome; N, no; VM, vancomycin; Y, yes.

[a] Infected hardware.

[b] Infected hardware (prosthesis) could not be removed; the patient received long-term oral therapy.

hardware or necrotic bone. The documented efficacy and safety of ceftriaxone, coupled with the convenience of its once-daily administration, suggest that it could be useful as therapy for *S. aureus* osteomyelitis.

References

1. Williams DN, Rehm SJ, Tice AD, Bradley JS, Kind AC, Craig WA. Practice guidelines for community-based parenteral anti-infective therapy. Clin Infect Dis **1997**;25:787–801.
2. Yuk JH, Nightingale CH, Quintiliani RH. Clinical pharmacokinetics of ceftriaxone. Clin Pharmacokinet **1989**;17:223–35.
3. Kucers A, Crowe SM, Grayson ML, Hoy JF, eds. The use of antibiotics: a clinical review of antibacterial, antifungal and antiviral drugs. Oxford: Butterworth Heinemann, **1997**:282–90, 352–68.
4. Hamilton RA, Kowalsky SF, McCormick EM, Echols RM. Protein binding of ceftriaxone, cefoperazone, and ceftizoxime. Clin Pharm **1987**; 6:567–9.
5. Lew DP, Waldvogel FA. Osteomyelitis. N Engl J Med **1997**;336: 999–1007.
6. Ko CW, Sekijima JH, Lee SP. Biliary sludge. Ann Intern Med **1999**;130: 301–11.
7. Drusano GL. Role of pharmacokinetics in the outcome of infections. Antimicrob Agents Chemother **1988**;32:289–97.
8. Craig WA. Pharmacokinetic/pharmacodynamic parameters: rationale for antibacterial dosing of mice and men. Clin Infect Dis **1998**;26:1–12.
9. Chambers HF, Mills J, Drake TA, Sande MA. Failure of a once-daily regimen of cefonicid for treatment of endocarditis due to *Staphylococcus aureus.* Rev Infect Dis **1984**;6(Suppl 4):S870–4.