Systemic Antibiotic Therapy for Chronic Osteomyelitis in Adults

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The standard recommendation for treating chronic osteomyelitis is 6 weeks of parenteral antibiotic therapy. However, oral antibiotics are available that achieve adequate levels in bone, and there are now more published studies of oral than parenteral antibiotic therapy for patients with chronic osteomyelitis. Oral and parenteral therapies achieve similar cure rates; however, oral therapy avoids risks associated with intravenous catheters and is generally less expensive, making it a reasonable choice for osteomyelitis caused by susceptible organisms. Addition of adjunctive rifampin to other antibiotics may improve cure rates. The optimal duration of therapy for chronic osteomyelitis remains uncertain. There is no evidence that antibiotic therapy for >4–6 weeks improves outcomes compared with shorter regimens. In view of concerns about encouraging antibiotic resistance to unnecessarily prolonged treatment, defining the optimal route and duration of antibiotic therapy and the role of surgical debridement in treating chronic osteomyelitis are important, unmet needs.

Chronic osteomyelitis is an infection of bone that does not result from acute hematogenous seeding or penetrating injury and usually occurs by contiguous spread and has been present for several weeks. Perhaps the earliest known case of chronic osteomyelitis dates to the Permian era, in an unfortunate dimetrodon that developed infection in a fractured spinal shaft [1]. This 250 million–year-old case highlights 3 of the problems that remain common when managing chronic osteomyelitis: (1) the diagnosis was established only after bone (or rather fossil) biopsy; (2) no cultures were performed to define the etiologic organism; and (3) treatment (if any) was probably delayed and certainly ineffective.

In the antibiotic era, chronic osteomyelitis remains difficult to treat and has a high rate of relapse after apparently successful treatment [2–4]. Indeed, case reports have described relapses of osteomyelitis up to 80 years after the initial presentation [5–8]. These relapses are probably due to bacterial evasion of host defenses by hiding intracellularly and as nonreplicating persisters within biofilm [9]. Because of these concerns, clinicians often treat chronic osteomyelitis with antibiotic therapy that is parenteral, high dose, and prolonged. This standard recommendation derives largely from the belief that it takes 3–4 weeks for infected bone to revascularize as well as from experience treating children with acute osteomyelitis. It was codified by a seminal case series by Waldvogel et al [10–12] in 1970. The authors stated that "osteomyelitis is rarely controlled without the combination of careful, complete surgical debridement and prolonged (4–6 weeks) parenteral antibiotic therapy at high dosage." However, this case series was retrospective and uncontrolled, and it included a heterogeneous patient population, and parenteral penicillin was the predominant antibiotic administered.

What have we learned about treating chronic osteomyelitis in the past few decades? Previous reviews of this topic have concluded that available literature is inadequate to determine the best agent, route, or duration

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Table 1. Bone Penetration of Parenteral Antibiotics: Data From Clinical Studies

Drug (Dose)	Patients, No.	Serum Level, Mean, μg/mL	Bone Level, Mean, μg/g	Ratio of Bone/Serum Levels, %	Reference
Agents Predominantly Used to Treat Gram-Positive Infections					
Oxacillin (2 g)	NA	NA	NA	10[a]	[16]
Ampicillin (2 g)	20	NA	12	17[b]	[17]
Sulbactam (1 g)			7	12[b]	
Ampicillin (1 g)	40	NA	20	33[b]	
Sulbactam (0.5 g)			5	17[b]	[18]
Cefazolin (1 g)	35	80	10 (knee), 30 (hip)	13 (knee), 37 (hip)	[19]
Cefazolin (1 g)	20	45	8	18	[20]
Cefazolin (1 g)	17	52	6	11.5	[21]
Cefazolin (2 g)	6	98	15	15	
Cefazolin (1 g)	48	NA	6	7.5[b]	[22]
Cefazolin (1–2 g)	16	25–216	3–10	<10	[23]
Vancomycin (1 g)	14	22 (medullary)	2.3 (medullary)	10	[24]
		22 (cortical)	1.1 (cortical)	5	
		16.8 (infected)	3.6 (infected)	21	
Daptomycin (6 mg/kg)	4	73	5	7	[25]
Agents Predominantly Used to Treat Gram-Negative Infections					
Ceftriaxone (1 g)	13	104	20 ± 6	19	[26]
Ceftriaxone (2 g)	40	130	19 ± 7 (medullary)	15	[27]
			6.5 ± 1.6 (cortical)	5	
Ceftriaxone (2 g)	42	NA	17 ± 9 (medullary)	NA	[28]
			3 ± 0.7 (cortical)	NA	
Ceftazidime (2 g)	10	150	5 (ischemic legs)	3	[29]
Ceftazidime (1 g)	43	NA	20	27[c]	[30]
Imipenem (500 mg)	6	NA	6 (infected)	48[c]	[31]
Cefepime (2 g)	10	73 ± 24	74 ± 16 (cancellous)	100	[32]
			68 ± 12 (cortical)	87	
Imipenem (1 g)	16	NA	4	16[c]	[33]
Imipenem (500 mg)	10	13	2.6 (infected)	20	[34]
Meropenem (500 mg)	15	30	5.75	17	[35]
Piperacillin (3 g)/tazobactam (0.375 g)	10	NA	NA	20/25[d]	[36]
Piperacillin (4 g)	NA	200	15	7.5	[37]
Piperacillin (2 g)	18	95	5	5	[38]

Abbreviation: NA, not applicable.

[a] Full article not available in English; the abstract reported a 10% ratio.

[b] Assuming peak ampicillin serum levels of 120 and 60 μg/mL at doses of 2 and 1 g, respectively [39, 40], peak sulbactam levels of 60 and 30 μg/mL at doses of 1 and 0.5 g [39, 40], and a peak cefazolin level of 80 μg/mL at a dose of 1 g [41].

[c] Assuming peak serum levels of 75 μg/mL for ceftazidime [42] and 12.5 μg/mL and 25 μg/mL for imipenem at doses of 500 and 1000 mg, respectively [43, 44, 45].

[d] As specified in the study abstract.

of antibiotic therapy [13–15]. Undeterred, we set out to review studies published since 1970 in an attempt to address 4 fundamental questions regarding treatment of chronic osteomyelitis in adults: (1) Are certain antibiotic agents preferred choices? (2) Are oral regimens acceptable for selected cases? (3) For how long should antibiotic therapy be given? and (4) Is surgical debridement always necessary for cure? We searched PubMed and ScienceDirect for the term ''osteomyelitis'' from 1970 to 2011, and EBSCO, Web of Science, and Google Scholar for any types of studies on treatment of chronic osteomyelitis in adults. We reviewed all articles if they, or at least their abstracts, were in English.

PHARMACOLOGY OF OSTEOMYELITIS THERAPY

Parenteral Antibiotic Agents

β-Lactam antibiotics (penicillins, cephalosporins, and carbapenems) penetrate bone at levels ranging from ~5% to 20% of those in serum (Table 1). Nevertheless, because serum levels of

parenterally delivered β-lactam antibiotics are so high, absolute bone levels likely exceed target minimum inhibitory concentrations (MICs) of etiologic bacteria in most cases. In contrast, because serum levels of oral β-lactam agents are <10% of those of parenteral agents, oral dosing is unlikely to achieve adequate bone levels. β-lactam penetration is higher in infected than in uninfected bone [31, 33, 34], but it is markedly decreased in patients with peripheral vascular disease [29, 46] and is probably low in sequestra.

Similar to β-lactam antibiotics, vancomycin penetrates bone poorly [24] (Table 1). However, when serum levels of vancomycin were >35 μg/mL, its penetration of sternal bone (~30% of serum concentrations) was better than in axial skeletal bone [47, 48]. Daptomycin also penetrates bone relatively poorly (Table 1), but levels are probably high enough to exceed the target MICs for bacteria in bone [25, 49].

Oral Antibiotic Agents

Recent studies demonstrate that oral antibiotics can achieve levels in bone that exceed MICs of targeted organisms (Table 2). In particular, fluoroquinolones, linezolid, and trimethoprim have been found to achieve bone concentrations at ~50% of serum [52, 53, 55] (Table 2). Although the sulfamethoxazole component of trimethoprim-sulfamethoxazole (TMP-SMX) has poorer penetration (10%–20%), its serum concentrations are 20-fold higher than those of trimethoprim, so its bone concentrations generally exceed the MICs of susceptible organisms. Because TMP-SMX exhibits concentration-dependent killing [88–90], higher doses (ie, 7–10 mg/kg trimethoprim, or 2 double-strength tablets twice per day) may result in greater efficacy when treating chronic osteomyelitis. The lack of a fixed 1:5 ratio of concentrations of trimethoprim and sulfamethoxazole at the site of infection does not hinder their synergy [91].

Other orally available agents to which many community-associated strains of methicillin-resistant *Staphylococcus aureus* (MRSA) are susceptible are doxycycline and clindamycin [92–95]. Doxycycline penetrates, and discolors, teeth [96] and bone, but concentrations range from as low as 2% in axial skeletal bone [62, 63] to as high as 86% in mandibular bone [61] (Table 2). Clindamycin reliably penetrates bone at levels of approximately 40%–70% of serum [64–66] (Table 2), and its achievable bone levels should exceed the MICs of susceptible MRSA isolates.

An oral antibiotic option for treatment of anaerobic osteomyelitis is metronidazole, which penetrates bone at concentrations approximating those in serum [67, 68] (Table 2). In case reports, metronidazole has been found to cure anaerobic osteomyelitis, including as salvage therapy after failure of clindamycin or cephalosporin therapy [97–100]. Rifampin also achieves concentrations in bone near, or exceeding, those in serum [69, 82, 83, 101] (Table 2). Because serum concentrations of rifampin increase dramatically at doses >450 mg/d [102, 103], prescribing 600 mg once daily should suffice. Finally, both fusidic acid [70, 71, 104] and fosfomycin [72] penetrate bone extremely well, at concentrations in excess of target MICs (Table 2).

In summary, oral options for the treatment of chronic osteomyelitis based on pharmacokinetic considerations include fluoroquinolones, TMP-SMX, or fosfomycin for susceptible gram-negative bacilli, and TMP-SMX, clindamycin, and linezolid for susceptible gram-positive infections. Rifampin and fusidic acid are reasonable adjunctive agents for combination therapy.

ANIMAL MODELS OF CHRONIC OSTEOMYELITIS

Standard models of chronic staphylococcal osteomyelitis include those in which infection is induced in long bones of rabbits and rats [2]. In such models, in vitro kill curves do not reliably predict in vivo efficacy. For example, in both models, rifampin was more active in vivo than clindamycin, azithromycin, vancomycin, trimethoprim, and ciprofloxacin, and it was synergistic in vivo with each of these agents as well as with cephalothin, despite being either indifferent or antagonistic to all of them in vitro [82, 101, 105]. In addition, ciprofloxacin monotherapy had minimal in vivo effect when treating infection caused by *S. aureus* strains susceptible to ciprofloxacin in vitro [82]. Thus, rifampin exhibits synergistic activity in vivo with myriad antibiotics, and clinicians should be cautious about using ciprofloxacin monotherapy to treat osteomyelitis caused by *S. aureus*, regardless of the MIC of the isolate.

NONRANDOMIZED CLINICAL TRIALS

Parenteral Therapy

In nonrandomized studies of adults with chronic osteomyelitis, 4–6 weeks of parenteral β-lactam antibiotic therapy has cured 60%–90% of cases (Table 3). The varying cure rates may be related to variable diagnostic criteria, use of concomitant surgical debridement (specifically reported in only 2 studies [107, 108]), or duration of follow-up. In multiple studies, the cure rates of infections caused by *Pseudomonas* were lower than those for other pathogens [108, 109, 112].

Vancomycin achieves low cure rates for chronic osteomyelitis [117, 121, 122]. In patients receiving outpatient parenteral antibiotic therapy of osteomyelitis, treatment of *S. aureus* infection with vancomycin (compared with β-lactam agents) had an odds ratio (OR) for recurrence of 2.5 by multivariate analysis [121, 122]. Other independent risk factors for recurrence included the presence of diabetes mellitus (OR, 1.9), peripheral vascular disease (OR, 7.9), and infection with *Pseudomonas* (OR, 2.2).

In a salvage study of patients with MRSA osteomyelitis that had failed to respond to previous therapy, all 9 patients who were treated with daptomycin had clinical resolution of their

Table 2. Bone Penetration of Antibiotics With High Oral Bioavailability: Data From Clinical Studies

Drug	Patients, No.	Dose	Route	Serum Level, Mean (Range), μg/mL	Bone Level, Mean (Range), μg/g	Serum-Bone Ratio, %	Reference
Ciprofloxacin	7	500 mg	Oral	1.4 (0.4–2)	0.4 (0.2–0.9)	30	[50]
	7	750 mg	Oral	2.6 (0.9–4)	0.7 (0.2–1.4)	27	
	6	500 mg	Oral	2.0 (0.9–3)	0.7 (0.2–1.4)[a]	35	
	4	750 mg	Oral	2.9 (1–6)	1.4 (0.6–2.7)[a]	48	
Ciprofloxacin	20	200 mg	Intravenous	NA	2 (medullary)	66	[51]
					1.4 (cortical)	47[b]	
Ciprofloxacin	15	200 mg	Intravenous	NA	0.1–0.9	3–30[b]	[52]
Levofloxacin	9	500 mg	Intravenous	8	6 (medullary)	75	[53]
					3 (cortical)	38	
Levofloxacin	12	500 mg	Intravenous	7.5	7.4 (medullary)	99	[54]
					3.9 (cortical)	50	
Enoxacin	24	400 mg	Oral or	2.4	0.9	37.5	[55]
	7		Intravenous		1.3[b]	55	
Moxifloxacin	10	400 mg	Intravenous	4.9	1.9 (medullary)	39	[56]
					1.3 (cortical)	27	
	10	400 mg	Oral	3.7	1.8 (medullary)	49	
					1.6 (cortical)	43	
Linezolid	13	600 mg	Oral	NA	4	40[c]	[57]
Linezolid	12	600 mg	Oral	NA	9	51[c]	[58]
Linezolid	10	600 mg	Oral	23	8.5	37	[59]
TMP-SMX	14	1 DS tablet twice daily for 2 d	Oral	7.4/143	3.7/19	50/15	[60]
Doxycycline	6	200 mg	Intravenous	NA	2.6	86[a]	[61]
Doxycycline	25	200 mg	Intravenous	NA	0.2	6[a]	[62]
Doxycycline	34	200 mg	Intravenous	6	0.13	2	[63]
Clindamycin	13	600 mg	Intravenous or intramuscular	NA	5	67[a]	[64]
Clindamycin	27	300 mg	Intramuscular	7.33	2.63	40	[65]
Clindamycin	23	600 mg	Intravenous	8.5	3.8	45	[66]
Metronidazole	16	500 mg	Intravenous	NA	14	100[a]	[67]
Metronidazole	17	1500 mg	Intravenous	34	27	79	[68]
Rifampin	32	300 mg	Intravenous	2	5 (1.4–8.8)	>100[c]	[69]
Fusidic acid in infected bone[d]	15	500 mg 3 times daily	Oral	NA	7.3 (1.7–14.9)		[70]
	14	1 g 3 times daily	Oral	NA	9.8 (3.4–14.8)		
Fusidic acid in uninfected bone	9	500 mg 3 times daily for 5 d	Oral	27 (2–109)	12 (1–40)	44	[70]
	15	500 mg 3 times daily for 6–10 d	Oral	45 (5–166)	21 (2–75)	47	
	14	500 mg 3 times daily for >10 d	Oral	27 (3–59)	25 (3–79)	93	
Fusidic acid	30	2 or 3 g/d	Oral	15–210	1.5–54	NA	[71]
Fosfomycin	19	10 g once, then 5 g 3 times daily	Intravenous	NA	13.5 (uninfected)	NA	[72]
					42.1 (infected)[d]		
Fosfomycin	9	100 mg/kg	Intravenous	377 ± 73	96 ± 15	25	[73]

Abbreviations: NA, not applicable; TMP-SMX, trimethoprim-sulfamethoxazole.

[a] Levels in infected (osteomyelitic) bone after debridement.

[b] Assuming peak serum levels of 3 μg/mL for ciprofloxacin [74], 20 μg/mL for linezolid [75, 76], 3 μg/mL for doxycycline [77], 8 μg/mL for clindamycin [66, 78, 79], and ~14 μg/mL for metronidazole [80, 81].

[c] Concordant animal data [79, 82, 83, 84, 85, 86, 87].

[d] Infected bone refers to levels measured in osteomyelitic bone that was debrided.

Table 3. Cure Rates in Nonrandomized Clinical Trials of Parenteral Agents for Chronic Osteomyelitis With or Without Infected Prosthesis in Adults

Drug	Dose (Duration)	Follow-up	Cure,[a] No. of Patients (%)	Comment	Reference
Cefazolin	2–4 g/d (mean, 35 d)	Mean, 34 mo	15/16 (94)	4/5 diabetic foot infections cured, all with debridement	[23]
Cefotaxime	1 g/8 h (duration unclear)	0–17 mo	24/27 (89)	Cure defined as disease ''arrested''	[106]
Cefotaxime	2–16 g/d (mean, 23 d)	?	25/32 (78)	Cure with surgery in 21/24, without surgery in 4/8	[107]
Imipenem	0.1–1 g/6 h (mean, 5 wk)	Mean, 11 mo	20/34 (59)	*Pseudomonas* main cause of failure: 10/14 cured	[108]
Ceftazidime	2 g/12 h (2–16 wk)	>12 mo	9/15 (60)	12 cases caused by *Pseudomonas*	[109]
Cefotaxime	2 g/6 h (mean, 40 d)	6 mo	40/55 (73)	…	[110]
Aztreonam	2 g/6 h (14–55 d)	4–18 mo	11/11 (100)	All infections due to gram-negative rods	[111]
Aztreonam	2 g/8 h (mean, 40 d)	Mean, 6 mo	13/18 (72)	All due to *Pseudomonas*	[112]
(Cefsulodin or piperacillin or imipenem) + (ofloxacin or pefloxacin or ciprofloxacin)	Varying doses (≥4 mo)	Mean, 3 y	11/15 (73)	All due to *Pseudomonas*	[113]
Ampicillin-sulbactam	1.5 g/6 h (mean, 41 d)	?	42/49 (86)	All patients diabetic; 14 patients had amputations	[114]
Ticarcillin-clavulanate	9–12 g/d (mean, 6 wk)	?	39/50 (78)	…	[115]
Cefepime + (ofloxacin or ciprofloxacin)	Cefepime: 2 g twice daily (4 wk); ofloxacin: 200 mg 3 times daily (3–9 mo); ciprofloxacin: 500–750 mg twice daily (3–9 mo)	?	22/28 (79)	Mixture of chronic osteomyelitis and prosthetic implant infections; quinolones given intravenously at first and then by mouth	[116]
Vancomycin	Variable dosing (mean, 6 wk)	?	44/81 (54)	62 patients underwent debridement; 30 had infected prostheses, 27 had removal	[117]
β-Lactam or vancomycin	Variable for β-lactam; vancomycin: 1 g/12 h (mean, 66 d for MRSA, 55 d for MSSA)	>12 mo	30/35 (86)	Relapses: 0/15 patients treated with rifampin vs 5/20 treated without rifampin; all started with intravenous therapy; many received subsequent oral therapy with various agents	[118]
Daptomycin	6 mg/kg/d	?	8/9 (89)	Infection resolved in all patients, relapse in 1 patient; salvage therapy	[119]
Daptomycin	6 mg/kg/d (median, 38 d)	Mean, 9 wk	16/25 (64)	16 resolved, 8 improved	[49]
Daptomycin	Variable dosing (mean, 35 d)	Mean, 76 d	42/67 (63)	Failures more likely with no debridement (24% vs 5%) and with doses <4 mg/kg/d (35% vs 12%)	[120]

Abbreviations: MRSA, methicillin-resistant *Staphylococcus aureus*; MSSA, methicillin-sensitive *S. aureus*.

[a] Definitions of cure varied among the trials.

infection by the end of therapy, but 1 patient subsequently relapsed [119]. Larger retrospective studies of daptomycin treatment of chronic osteomyelitis have reported cure rates of 65%–75% [49, 120]. Case reports suggest the potential for quinupristin-dalfopristin and tigecycline to cure chronic osteomyelitis, but clinical data are limited [123–126].

Oral Therapy: Fluoroquinolones

There are more studies of fluoroquinolones for treating chronic osteomyelitis than of all other antibiotic classes (Table 4). Cross-study comparisons are difficult because of the varied criteria for enrollment, utilization of debridement, antibiotic dosing regimens, duration of follow-up, and definitions of cure. Nevertheless, we draw several general inferences from these studies.

1. Most studies reported cure rates of 60%–80% [129, 138, 139].
2. Cure rates were similar to debridement rates (when reported), but because none of the studies specifically reported cure rates of patients who did and did not undergo debridement, the benefit of debridement can only be inferred.
3. The majority of failures occurred in patients infected with *Pseudomonas*, and to a lesser extent, patients infected with *S. aureus*.
4. Therapy was typically given for 12–16 weeks, and at doses higher than those used for most other infections (eg, ciprofloxacin at ≥1500 mg/d), but it is not possible from the available data to conclude that this high-dose and prolonged treatment is necessary.

Oral Therapy: Other Agents

Although it should never be used alone for treating osteomyelitis, several reports have shown that rifampin improves treatment outcomes when used in combination with other antibiotics (Table 4). Norden et al [101] added rifampin to therapy with a β-lactam, doxycycline, or an aminoglycoside in 14 patients, most of whom had had osteomyelitis for >15 years and in whom multiple prior treatment attempts had failed. Overall, 50% were cured, and patients in whom treatment failed were all infected with gram-negative bacilli resistant to the non-rifampin agent. In another study of patients with *S. aureus* osteomyelitis, there were no relapses among 15 patients in whom rifampin was added to treatment with various other antibiotic agents compared with 5 relapses among 20 patients who did not receive adjunctive rifampin [118]. Finally, adjunctive rifampin improved cure rates of prosthetic joint infections in 2 recent studies [143, 144].

A large compassionate-use data set demonstrated that linezolid treatment cured 60% of the 89 patients with chronic osteomyelitis [145]. In several case reports, clindamycin therapy successfully eradicated anaerobic osteomyelitis [153–155]. Likewise, among 12 patients with chronic (primarily staphylococcal) osteomyelitis treated with clindamycin at very low doses (75–150 mg/6 h), 5 patients were cured and another 5 showed substantial improvement [146].

TMP-SMX is second only to ciprofloxacin in the number of published studies of its effectiveness for treatment of chronic osteomyelitis. Saengnipanthkul et al [148] reported a 45% cure rate using standard dose TMP-SMX (1 double-strength tablet twice daily) to treat 66 patients with chronic osteomyelitis, only 55% of whom underwent surgical debridement. Cure rates based on surgical debridement were not separately reported. In contrast, Sanchez et al [149] treated 27 patients with staphylococcal osteomyelitis (25 *S. aureus*) with a higher –than-usual dose of TMP-SMX (7 mg/kg/d of trimethoprim divided into 2 or 3 daily doses) along with rifampin for a mean of 5 weeks, in addition to surgical debridement. After follow-up of 6 months to 5 years, all of the patients were cured.

Javaloyas de Morlius et al [78] reported their results with treating 37 patients with 44 episodes of osteomyelitis, 34 of which were associated with an orthopedic implant. After a week of parenteral antibiotic therapy, the patients received a median of 10 weeks of oral treatment with TMP-SMX plus rifampin (23 patients), TMP-SMX alone (5 patients), or rifampin plus ciprofloxacin (7 patients). At 2 years of follow-up, all 10 patients who had their hardware removed were cured, compared with 18 of 24 patients (75%) in whom hardware was left in place.

Stein et al [150] prescribed TMP-SMX for 6–9 months to treat 39 patients with prosthetic devices infected with MRSA. The overall success rate was 67% in the intention-to-treat population and 87% in the per-protocol population (after exclusion of 9 patients who were unable to tolerate completing the treatment). Significantly more patients who had their infected prosthetics removed were cured compared with those who did not. Likewise, de Barros et al [84] treated 60 patients with chronic osteomyelitis with TMP-SMX for 6 months, along with appropriate surgical debridement; 59 (98%) were cured after 12–60 months of follow-up. Finally, Nguyen et al [151] reported that either TMP-SMX (8 mg/kg/d) or linezolid combined with rifampin cured 79%–89% of patients with infected orthopedic implants or chronic osteomyelitis. Taken together, these data support the efficacy of high-dose TMP-SMX, the importance of concurrent surgical debridement, and the possible benefit of adjunctive rifampin therapy and prolonged therapy when treating chronic osteomyelitis, especially in patients with an associated infected implant.

Consistent with their excellent bone penetration, both fosfomycin [72, 152] and fusidic acid [156, 157], the latter preferably in combination with another anti-staphylococcal agent, have also demonstrated efficacy in treating chronic osteomyelitis. Others have summarized results of the numerous published case series describing fusidic acid combination therapy for osteomyelitis [156].

Table 4. Cure Rates in Nonrandomized Clinical Trials for Oral Treatment of Chronic Osteomyelitis With or Without Infected Prosthesis in Adults

Drug	Dose (Duration)[a]	Follow-up	Cure,[b] % (No. of Patients)	Comment	Reference
Fluoroquinolones					
Ciprofloxacin	500–750 mg twice daily (3–4 mo)	1 y	33 (12/36)	All cured patients had foreign material removed; 1/3 underwent debridement	[127]
Ciprofloxacin	750 mg twice daily (3–4 mo)	6 mo	91 (21/23)	Cure defined as resolution or improvement	[128]
Ciprofloxacin	750 mg twice daily (3 mo)	7–21 mo	65 (13/20)	Only 7/13 *Pseudomonas* infections cured; all debrided	[129]
Ciprofloxacin	750 mg twice daily (2–4 mo)	1–17 mo	77 (17/22)	4 patients who failed therapy with *Pseudomonas*; 20 debrided	[130]
Ciprofloxacin	750 mg twice daily (1–6 mo)	0–22 mo	48 (14/29)	7/12 *Pseudomonas* and 4/9 *Staphylococcus aureus* infections cured	[131]
Ciprofloxacin or nafcillin, clindamycin, or gentamicin	750 mg by mouth twice daily (12–64 d) (ciprofloxacin); or varying doses and durations	25–39 mo	79 (11/14) for ciprofloxacin vs 83 (10/12) for intravenous therapy	Not randomized; patients were sequentially enrolled in the 2 arms	[132]
Ciprofloxacin	200 mg intravenous twice daily, then 750 mg by mouth twice daily	?	67 (6/9)	Unknown duration of treatment; 5/7 *Pseudomonas* infections cured	[133]
Ciprofloxacin	200 mg intravenous twice daily, then 750 mg by mouth twice daily	?	83 (10/12)	Unknown duration of treatment	[134]
Ciprofloxacin	500–1500 mg twice daily (0.5–18 mo)	?	68 (30/44)	*Pseudomonas* eradicated microbiologically in 20/28	[135]
Levofloxacin	500 mg/d	?	60 (9/15)	Failure of cure in 6 patients with *S. aureus* and 1 with *Pseudomonas* infection	[136]
Pefloxacin	400 mg/12 h intravenous for 4 doses, then 400 mg/12 h by mouth (3–6 mo)	?	76 (29/38)	All cured patients had foreign material removed; 1/3 underwent debridement	[137]
Ofloxacin	200 mg/8–12 h (3–6 mo)				
Ciprofloxacin	500–750 mg/12 h (3–6 mo)				
Ofloxacin	200 mg 3 times daily (4–6 wk)	>6 mo	85 (98/115)	Failure of cure in 3/15 patients with *Pseudomonas* and 5/74 with *S. aureus* infection; debridement in 113	[138]
Ciprofloxacin	750–1000 mg twice daily (3 mo)	12 mo	61 (19/31)	No benefit from higher dose; all had soft tissue, but not bone, debrided	[139] [c]
Ofloxacin + rifampin	Ofloxacin: 200 mg 3 times daily; rifampin: 300 mg 3 times daily (both, 6–9 mo)	>6 mo	71 (35/49)	All infections of prostheses	[140]
Levofloxacin + rifampin	Levofloxacin: 500 mg/d; rifampin: 600 mg/d (both, >6 wk)	>6 mo	72 (18/25)	All had prosthetic bone implants; mean duration of therapy, 5 mo for those cured and 2.6 mo for those without cure	[141]
Rifampin + (ofloxacin or fusidic acid)	Rifampin: 900 mg/d; ofloxacin: 200 mg 3 times daily; fusidic acid: 500 mg 3 times daily for 5 d, then twice daily (both, >6 mo)	Mean, 24 mo (range, 12–36 mo)	55 (11/20)	All patients had orthopedic implants, only 14 of which were removed; patients were assigned to treatment arm by year of birth (ofloxacin for even years, fusidic acid for odd years)	[142]

Table 4 continued.

Drug	Dose (Duration)[a]	Follow-up	Cure,[b] % (No. of Patients)	Comment	Reference
			50 (11/22)		
Other Agents					
Rifampin + various other antibiotics	600 mg/d (6 mo)	Variable	50 (7/14)	All cases refractory to prior therapy	[101]
Rifampin + quinolone vs other antibiotics	When used, rifampin at 20 mg/kg, divided into 2 daily doses (not to exceed 1800 mg/d)	Mean, 44 ± 32 mo	98 (37/39) vs 68 (40/59)	All patients had *S. aureus* prosthetic joint infections; 29 received rifampin in combination with nonquinolone antibiotics; in multivariate analysis, rifampin-quinolone combination had an odds ratio of 0.4 (95%, CI 0.17–0.97) for failure	[143]
Rifampin + levofloxacin (prospective) vs historical cohort with variable antibiotics, without or with rifampin	When used, rifampin at 900 mg/d (3–6 mo)	?	93 (13/14) (prospective) vs 63 (34/56) (historical without rifampin) vs 68 (21/31) (historical with rifampin)	All had retained prosthetic joints; by multivariate analysis, hazard ratio for treatment failure was 1.0 for historical cohort without rifampin, 0.55 (95%, CI 0.25–1.26) for historical cohort with rifampin, 0.11 (95%, CI 0.01–0.84) for prospective rifampin cohort ($P = .03$)	[144]
Linezolid	600 mg/12 h	?	60 (45/89)	Compassionate use program	[145]
Clindamycin	50–150 mg/6 h (mean, 16 wk)	Variable	42 (5/12)	…	[146]
TMP-SMX	1–2 DS tablet twice daily	?	83 (5/6)	No patients had debridement	[147]
TMP-SMX	1 DS tablet twice daily (4–8 wk)	11–70 mo	45 (30/66)	55% of patients had debridement	[148]
TMP-SMX + rifampin	TMP: 3.5 mg/kg twice daily; rifampin: 600–1200 mg/d (mean, 5 wk for both)	6 mo to 5 y	100 (27/27)	All patients had debridement	[149]
TMP-SMX with or without rifampin	DS tablet twice daily; rifampin: 300–450 mg twice daily (median, 10 wk for both)	2 y	82 (28/34)	10 patients had debridement, all of whom were cured	[78]
TMP-SMX	TMP: 5 mg/kg twice daily (6–9 mo)	24–75 mo	67 (26/39)	11 patients had device removed	[150]
TMP-SMX	Dose unclear (6 mo)	12–60 mo	98 (59/60)	All patients had debridement	[84]

Table 4 continued.

Drug	Dose (Duration)[a]	Follow-up	Cure,[b] % (No. of Patients)	Comment	Reference
(TMP-SMX or linezolid) + rifampin	TMP: 8 mg/kg; linezolid: 600 mg twice daily; rifampin: 10 mg/kg twice daily (all given intravenously for 1 wk and then by mouth)	≥12 mo	89 (37/41)	20 patients with chronic osteomyelitis and 56 with orthopedic implant infections; mean treatment durations were 15 wk (range, 1–53 wk) for TMP-SMX–based therapy and 18 wk (8–36 wk) for linezolid-based therapy; adverse event rates were similar (46% vs 43%), as were discontinuation rates (14% vs 21%)	[151]
			79 (29/38)		
Fosfomycin	10 g once, then 5 g 3 times daily	5–28 d	47 (29/60)	Outcome defined as "very good"; mean follow-up, 37 mo	[72]
Fosfomycin	4–8 g/d intravenous or by mouth		78 (29/37)	23 patients had debridement	[152]

Abbreviations: CI, confidence interval; DS, double-strength; TMP-SMX, trimethoprim-sulfamethoxazole.

[a] Drugs were administered orally unless otherwise specified.

[b] Definitions of cure varied among the studies.

[c] This was a randomized study of ciprofloxacin at 750 vs 1000 mg twice daily. Because no comparator therapy was used, it is included in the nonrandomized study category.

Randomized Clinical Trials

There have been few randomized trials of systemic therapy for osteomyelitis in adults. A systematic review published in 2009 found only 8 small trials, with a total of 228 evaluable subjects [158]. A composite analysis of the 5 trials that compared oral with parenteral treatment found no significant difference in remission rate at ≥12 months of follow-up, but the rate of moderate or severe adverse events was significantly higher with parenteral than with oral agents (15.5% vs 4.8%, respectively).

Adjunctive rifampin therapy has been studied in 2 randomized clinical trials of patients with chronic osteomyelitis caused by *S. aureus* [159, 160] (Table 5). Summarizing their results, more patients who received rifampin in addition to other antibiotics were cured compared with those who did not (17 of 20 [85%] vs 12 of 21 [57%]; $P = .05$ by Fisher's exact test), and no patient terminated therapy due to rifampin-related adverse effects. In another trial, Zimmerli et al [163] randomized patients with prosthetic devices infected with *Staphylococcus* spp. to receive either rifampin or placebo, plus ciprofloxacin, for 3–6 months. In the per-protocol population, cure rates were 100% for rifampin-treated versus 58% for placebo-treated patients ($P < .02$). Of note, the causative pathogen in 4 of the 5 patients whose infection failed to respond to ciprofloxacin monotherapy developed resistance to ciprofloxacin.

Six studies randomized patients with chronic osteomyelitis to receive either an oral fluoroquinolone (ciprofloxacin in 3 [164–166], ofloxacin in 3 [167–169]) or standard intravenous therapy (Table 5). In all, cure rates were similar for those treated with oral and intravenous therapy. Finally, Euba et al [170] randomized 50 patients with chronic osteomyelitis caused by methicillin-sensitive *S. aureus* to treatment with intravenous cloxacillin or oral TMP-SMX plus rifampin for 8 weeks. All patients underwent surgical debridement, and 20 (40%) patients had prosthetic implants. At the end of therapy, cure rates were nearly identical for the 2 regimens (91% and 89%, respectively), as were the rates of antibiotic-related adverse events (3 in each arm). Furthermore, at median follow-up of 10 years (interquartile range, 4–13 years), the relapse rate was similarly low (10% and 11%, respectively). Among the 3 patients who relapsed on oral therapy, 2 had retained prosthetic material.

CONCLUSIONS

Assessing treatments of chronic osteomyelitis is confounded by several factors, including the difficulty in diagnosing the condition or establishing a microbiological etiology, the presence of necrotic bone in most (and prosthetic implants in many) patients, and the lack of a consensus definition of cure. Nevertheless, we draw several conclusions from available published studies.

Table 5. Cure Rates in Randomized Clinical Trials of Antibiotics for Chronic Osteomyelitis With or Without Infected Prosthesis in Adults

Drug	Dose (Duration)	Follow-up	Cure,[a] % (No. of Patients)	Comment	Reference
Ceftazidime vs ticarcillin + tobramycin	Ceftazidime: 2 g/12 h intravenous; ticarcillin: 3 g/4 h intravenous; tobramycin: 1.5 mg/kg/8 h intravenous (mean, 35 d; range, 26–63 d)	2–31 mo	67 (6/9) vs 100 (9/9)	Open label; all patients had debridement	[161]
(Vancomycin or oxacillin) + (rifampin vs pyridium placebo)	Vancomycin: 1 g/12 h intravenous; oxacillin: 3 g/6 h intravenous; rifampin: 600 mg/d by mouth	?	90 (9/10) vs 62 (8/13)	Double-blind study	[159]
Nafcillin vs (nafcillin + rifampin)	Nafcillin: 20 mg/kg/4 h intravenous; rifampin: 600 mg/12 h by mouth (mean, 6 wk)	9–36 mo	80 (8/10) vs 50 (4/8)	Open label; 16 patients had debridement	[160]
Linezolid vs (ampicillin-sulbactam or amoxicillin-clavulonate)	Linezolid: 600 mg twice daily, by mouth or intravenous; ampicillin-sulbactam: 1.5–3 g/6 h intravenous; amoxicillin-clavulonate: 500–875 mg by mouth 2 or 3 times daily	?	61 (27/44) vs 69 (11/16)	Open label; part of larger trial of diabetic patients with soft-tissue infections; patients requiring >4 wk of therapy were excluded	[162]
Ciprofloxacin + (rifampin vs placebo)	Ciprofloxacin: 750 mg by mouth twice daily; rifampin: 450 mg by mouth twice daily (3–6 mo)	Median, 3 y	100 (12/12) vs 58 (7/12)	Double-blind study	[163]
Ciprofloxacin vs ''appropriate antimicrobial therapy''	750 mg by mouth twice daily (treatment for ≥6 wk)	?	50 (7/14) vs 69 (11/16)	For patients infected with *Pseudomonas*, cure rate were 3/8 for ciprofloxacin vs 7/9 for comparator antibiotics	[164]
Ciprofloxacin vs ceftazidime	Ciprofloxacin: 200 mg intravenous twice daily, then 500 mg by mouth twice daily; ceftazidime: 2 g/12 h intravenous	?	67 (2/3) vs 100 (3/3)	Part of larger study of serious gram-negative infections; open label	[165]
Ciprofloxacin vs (ceftazidime or nafcillin + amikacin)	Ciprofloxacin: 750 mg by mouth twice daily; other antibiotics: ? doses (mean, 8 wk)	1 y	77 (24/31) vs 79 (22/28)	Open label; all patients had debridement	[166]
Ciprofloxacin vs lomefloxacin	Ciprofloxacin: 750 mg by mouth twice daily; lomefloxacin: 800 mg by mouth twice daily	Median, 8 mo (range, 0–36 mo)	40 (2/5)	Open label; 5 failures with ofloxacin were due to infections with *Pseudomonas* (n = 2) or *Staphylococcus aureus* (n = 3)	
			71 (5/7)		
Ofloxacin vs (ceftazidime or cefazolin)	Ofloxacin: 400 mg by mouth twice daily (mean, 8 wk); ceftazidime: 2 g/12 h intravenous (mean, 4 wk); cefazolin: 1 g/8 h intravenous (mean, 4 wk)	Mean, 1.5 y	74 (14/19) vs 86 (12/14)	Open label; part of larger study of soft-tissue foot infections in diabetic patients	[167]
Ofloxacin vs ampicillin-sulbactam followed by amoxicillin-clavulonate	Ofloxacin: 400 mg by mouth twice daily; ampicillin-sulbactam: 1–2 g/6 h intravenous; amoxicillin-clavulonate: 500 mg by mouth 3 times daily	3–4 wk	39 (6/16) vs 20 (1/5)	Open label	[168]
Ofloxacin vs imipenem	Ofloxacin: 400 mg by mouth twice daily; imipenem:	?	69 (11/16) vs 50 (8/16)	All patients had debridement	[169]
	500 mg/6 h intravenous				
Cloxacillin vs (TMP-SMX + rifampin)	Cloxacillin: 2 g/4 h intravenous; TMP: 7–8 mg/kg by mouth twice daily; rifampin: 600 mg/d by mouth (8 wk)	Mean, 10 y	90 (19/21) vs 89 (24/27)	Open label; all patients had debridement	[170]

Abbreviation: TMP-SMX, trimethoprim-sulfamethoxazole.

[a] Definitions of cure varied by study.

First, oral antibiotic therapy with highly bioavailable agents is an acceptable alternative to parenteral therapy. The widely held preference for parenteral therapy for chronic osteomyelitis is based more on custom than evidence. There are actually fewer published studies of parenteral than oral therapy for osteomyelitis, and success rates are consistently similar for both routes. Furthermore, oral therapy is generally simpler for the patient, avoids risks associated with intravenous catheters, and is less expensive. Preferred oral agents, based on both pharmacokinetic and clinical data, include fluoroquinolones or TMP-SMX, which achieve high cure rates when administered for 8–16 weeks, particularly in the context of concomitant surgical debridement. We would like to see studies of shorter durations of treatment (eg, 4–6 weeks) to determine whether they produce similar results. It may be advisable to use higher-than-usual doses (eg, ciprofloxacin at 750 mg twice daily and TMP-SMX at 7–10 mg/kg/d of trimethoprim) when treating chronic osteomyelitis. Because gram-positive cocci have a high propensity to develop resistance during fluoroquinolone therapy [171], the reported relapses of staphylococcal osteomyelitis after ciprofloxacin or ofloxacin treatment are not surprising. Therefore, TMP-SMX and probably clindamycin are preferable for treating osteomyelitis caused by gram-positive cocci. Other options for selected cases could include linezolid or doxycycline, although toxicity with prolonged treatment limits use of the former agent, and no clinical data are available for the latter. For anaerobic osteomyelitis, oral metronidazole is the agent of choice, given its outstanding bone penetration and efficacy in case reports. Although the theory is still being debated, there is no evidence that bactericidal agents are superior to bacteriostatic in the treatment of osteomyelitis [172].

Second, adding rifampin to a variety of antibiotic regimens has been shown to improve the cure rates in: (1) animal models, (2) retrospective studies in humans, and (3) randomized clinical trials of chronic osteomyelitis and orthopedic implant infections. Hence, clinicians should consider adjunctive rifampin therapy (ie, combined with another active agent) for patients who are able to tolerate it and who do not require concomitant treatment with drugs with which it is likely to interact.

Third, clinicians must individualize the duration of antibiotic therapy based on the patient's clinical and radiographic response, with continued monitoring after cessation of therapy. No strong evidence supports the standard recommendation of 4–6 weeks of therapy after surgical debridement [4], nor is there evidence that more prolonged therapy further improves cure rates. Unfortunately, there are no well established markers of successful treatment and relapse rates remain substantial, even after prolonged antibiotic therapy. Defining the optimal duration of therapy for chronic osteomyelitis is an area of urgent need.

Fourth, surgical resection of necrotic and infected bone, in conjunction with antibiotic therapy, appears to increase the cure rate of chronic osteomyelitis. However, not all cases of chronic osteomyelitis require surgical debridement for cure, and we need studies to clarify which may and which may not. We need comparative effectiveness studies to answer these and a number of other questions regarding therapy of chronic osteomyelitis.

Note

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