Outcomes of Osteomyelitis among Patients Treated with Outpatient Parenteral Antimicrobial Therapy

Alan D. Tice, MD, Pamela A. Hoaglund, RN, MSN, David A. Shoultz, PhD

PURPOSE: To examine the effects of diabetes, vascular disease, age, and antimicrobial therapy on clinical outcomes, including amputation rates, in patients with osteomyelitis treated in the outpatient setting.

METHODS: We performed a retrospective chart review of patients treated with intravenous antimicrobial therapy for osteomyelitis at an outpatient infectious diseases practice. All patients were followed for at least 6 months.

RESULTS: Four hundred and fifty-four patients qualified for inclusion, with follow-up information available for up to 10 years. One hundred and thirty-nine patients (31%) had recurrences and 27 (6%) had amputations. Of the recurrences, 108 (78%) occurred within 6 months and 132 (95%) within 1 year. In univariate analyses, peripheral vascular disease, diabetes, and the combination were all associated with the risk of recurrence; age (>70 years) was not. For osteomyelitis due to *Staphylococcus aureus*, the relative risk of recurrence, using a Cox regression model, was 0.8 for ceftriaxone (95% confidence interval [CI]: 0.4 to 1.5; $P = 0.53$), 1.1 for cefazolin (95% CI: 0.5 to 2.2; $P = 0.80$), and 2.5 for vancomycin (95% CI: 1.1 to 5.6; $P = 0.04$), as compared with the use of a penicillinase-resistant penicillin.

CONCLUSION: Diabetes and peripheral vascular disease are important factors in determining the prognosis of patients with osteomyelitis, but age is not. Almost all recurrences of osteomyelitis occur within 1 year. Recurrence rates with osteomyelitis associated with *S. aureus* appear to be higher with the use of vancomycin, whereas ceftriaxone and cefazolin appear to be similar to penicillinase-resistant penicillins. **Am J Med. 2003; 114:723–728.**

Prolonged intravenous antimicrobial therapy is considered the standard therapy for osteomyelitis (1). However, studies of the outcomes of patients with osteomyelitis are uncommon for several reasons. First, osteomyelitis is a disease in transition (2). The advancing age of the general population has caused an increase in the prevalence of diabetes and peripheral vascular disease, both of which are predisposing and complicating factors for osteomyelitis. Bone infections related to joint replacements and complex surgical interventions continue to increase, whereas the frequency of hematogenous osteomyelitis is decreasing. In addition, there have been major changes in therapy, including new antimicrobial agents and surgical techniques, and the use of outpatient parenteral antimicrobial therapy (3–8), which have become routine for patients with osteomyelitis (4,7,9,10).

Another factor contributing to the difficulty of studying outcomes in patients with osteomyelitis is the heterogeneous nature of the infections. Although the Cierny-Mader system is helpful for long bone infections (11), the major classification system remains the one suggested in 1970 by Waldvogel, Medoff, and Swartz, who characterized osteomyelitis by pathogenesis and chronicity (12–14). These authors were also the first to examine outcomes in osteomyelitis. Using the lack of signs or symptoms of infection 6 months after cessation of therapy as the endpoint, they found that a 4-week regimen of high-dose intravenous antimicrobial agents was more likely to be successful in an initial episode of hematogenous osteomyelitis than were shorter regimens (12). This finding led to the now conventional use of lengthy courses of intravenous antimicrobial agents to treat osteomyelitis. More recently, studies have suggested that oral antimicrobial therapy may be able to replace at least part of the parenterally administered regime in children (15–19) and possibly adults (20). Oral fluoroquinolones may be able to replace parenteral therapy, but they are limited by lack of coverage of *Staphylococcus aureus* and anaerobes (21–27). Another factor impeding the performance of outcomes studies in patients with osteomyelitis is the belief that at least a year of follow-up is needed (28).

Osteomyelitis is the second most common infection treated with outpatient parenteral antimicrobial therapy (29) after skin and soft tissue infections, and the infection for which the greatest number of days of outpatient parenteral antimicrobial therapy are provided at Infections Limited, a private clinic with 7 infectious disease specialists who provide physician-directed outpatient services for approximately 450,000 people in the greater Tacoma area.

From Infections Limited, P.S. (ADT, PAH), Tacoma, Washington; Outpatient Parenteral Antimicrobial Therapy Outcomes Registry (ADT, PAH), Tacoma, Washington; PPD Development (DAS), Wilmington, North Carolina; and Department of Epidemiology (DAS), University of Washington, Seattle, Washington.

This study was supported by Infections Limited, Tacoma, Washington, and an unrestricted educational grant from Roche Laboratories Inc, Nutley, New Jersey.

Requests for reprints should be addressed to Alan D. Tice, MD, Outpatient Parenteral Antimicrobial Therapy Outcomes Registry, 6240 Tacoma Mall Boulevard, Suite 104, Tacoma, Washington 98409, or alantice@idlinks.com.

METHODS

Infections Limited has treated more than 4000 patients with outpatient parenteral antimicrobial therapy since the program's inception in 1981 (30–32). Common practices are described in a handbook for outpatient parenteral therapy for infectious diseases (33). The clinic follows the guidelines for community-based parenteral anti-infective therapy established by the Infectious Diseases Society of America (34) and is accredited as an ambulatory infusion center by the Joint Commission for the Accreditation of Healthcare Organizations. Microbiologic studies for clinic patients are performed by our laboratory, which is certified by the College of American Pathologists. The standard dosage regimens administered in adults with normal renal function are either 2 g of a penicillinase-resistant penicillin such as oxacillin, nafcillin, or methicillin every 6 hours; 2 g of cefazolin every 8 hours; 2 g of ceftriaxone every 24 hours; or 1 g of vancomycin every 12 or 24 hours (the longer dosage interval is used for patients with impaired renal clearance). Decisions about antimicrobial therapy were made by the treating physician.

The medical records of all patients treated for osteomyelitis through our outpatient parenteral antimicrobial therapy program from January 1982 through April 1998 were reviewed. Patients were included in this study only if a clear pathogen was identified by initial culture results, at least 14 continuous days of parenteral antimicrobial therapy was given through the clinic or in the hospital, no more than two different antimicrobial agents were given, and at least 6 months had elapsed since the end of outpatient parenteral antimicrobial therapy. There were no exclusion criteria.

The diagnosis of osteomyelitis was based on the assessment of the infectious disease specialist in the clinic and the decision to administer a course of intravenous antimicrobial therapy. This diagnosis was based on clinical and physical assessment along with wound or blood cultures and radiographic examinations. Wound cultures were often done with a probe to bone or aspiration; bone biopsies were not done routinely.

If a patient's records contained no information about recurrence, a postcard was sent to that patient's last known address asking if there had been a recurrence, surgery, or further antimicrobial therapy related to the earlier infection. If the postcard brought no response, an attempt was made to contact the patient by telephone.

Patients included in the analysis were classified as either a "cure" or a "recurrence." Recurrence was defined as infection manifesting at the same site from which it had apparently been eliminated. If microbiology reports were available, recurrences were classified either as a "relapse" (original pathogen) or a "reinfection" (pathogen different from the original) based on identification and susceptibility reports. A new organism was considered a pathogen only if the treating physician administered an antimicrobial agent for treatment.

Statistical Analysis

To determine the risk factors for recurrence, we compared patients whose infections were apparently cured with those for whom a recurrence was recorded. Host factors included diabetes, peripheral vascular disease, and advanced age. Because *S. aureus* was the dominant pathogen identified, the choice of antimicrobial agent was also examined. Only initial recurrences were included in the analyses. Proportions were compared using the Fisher exact test. Odds ratios were used to estimate the relative risk of recurrence, with 95% confidence intervals. Cox regression models were also used to study the effects of antimicrobial type on recurrence in patients with *S. aureus*; potential confounders (peripheral vascular disease, diabetes, age >70 years) were included in the model. Relative risks were estimated from the hazard ratios derived from these models. All statistical analyses were performed using SPSS 9.0 for Windows NT (SPSS, Inc, Chicago, Illinois).

RESULTS

Approximately 1300 patients were identified with a diagnosis of osteomyelitis; 454 patients met the criteria for the study (Table 1). All patients had standard radiographs. Bone scans were performed in 177 patients (39%), computerized tomography in 18 patients (4%), and magnetic resonance imaging in 9 patients (2%). Most (90%) patients had contiguous osteomyelitis with an associated wound. Seventy-seven patients (17%) had a foreign body, which was removed in 27 patients (35%). Slightly more than half of patients had infections associated with *S. aureus*; other common pathogens included coagulase-negative staphylococci, streptococcal species (non–group D), and *Pseudomonas aeruginosa* (Table 1).

A broad range of antimicrobial agents was used by the 7 infectious disease specialists in the clinic. The mean (± SD) duration of outpatient parenteral antimicrobial therapy was not significantly different for the primary antimicrobial agents used. For the penicillinase-resistant penicillins, it was 28 ± 15 days; for ceftriaxone, it was 25 ± 12 days; for cefazolin, it was 26 ± 10 days; and for vancomycin, it was 28 ± 13 days. Approximately 45% of patients (n = 204) were hospitalized briefly before outpatient parenteral antimicrobial therapy was given.

The mean duration of follow-up was 28 ± 27 months (range, 6 to 128 months). Of the 454 patients, 315 (69%) were apparently cured at the time outcomes were measured; 139 (31%) had a recurrence. Of the recurrences, 56% (n = 78) occurred within 3 months after outpatient parenteral antimicrobial therapy, 78% (n = 108) within 6

Table 1. Clinical Characteristics of 454 Patients with Osteomyelitis Treated with Outpatient Parenteral Antimicrobial Therapy

Characteristic	Number (%) or Mean ± SD (Range)
Age (years)	51 ± 18 (6–92)
>70 years	71 (16)
<13 years	4 (1)
Male sex	295 (65)
Type of osteomyelitis	
Contiguous*	409 (90)
Hematogenous	27 (6)
Vascular	9 (2)
Unclassified	9 (2)
Location of osteomyelitis	
Foot	236 (52)
Leg	86 (19)
Hand	45 (10)
Spine	27 (6)
Other	60 (13)
Comorbid conditions	
Diabetes only	129 (29)
Peripheral vascular disease only	10 (2)
Both diabetes and peripheral vascular disease	44 (10)
Neither	258 (59)
Bacterial etiology	
Staphylococcus aureus	246 (54)
Staphylococci (coagulase-negative)	63 (14)
Streptococci (non-group D)	62 (14)
Pseudomonas aeruginosa	20 (4)
Other	63 (14)

* Osteomyelitis was considered "contiguous" if there was an associated wound.

months, and 95% (n = 132) within 12 months. Of the recurrences, 22 were considered relapses and 23 were considered reinfections; whether the recurrence was a relapse or reinfection was unknown in 94 patients for whom repeat microbiology results could not be located. Relapses occurred earlier than the reinfections. Only 6 relapses (27%) occurred after 6 months and 2 (9%) after 12 months, whereas 8 reinfections (35%) occurred after 6 months and 3 (13%) after 12 months. There was a 6% reinfection rate among patients with diabetes (8 of 129) compared with a 2% reinfection rate among patients without diabetes (6 of 325).

There were 13 deaths and 27 amputations during follow-up. All 27 amputations occurred within the first year (Figure), including 18 (67%) within the first 3 months of the completion of therapy and 22 (82%) within 6 months. Twenty-five (93%) of the amputations involved the legs or feet; 24 (88%) were performed in patients with diabetes and 9 (33%) in patients with peripheral vascular disease. In patients with diabetes, amputations were not always performed for recurrent infection, as there was often also severe vascular disease and neuropathy.

Risk Factors for Recurrence

Diabetes, peripheral vascular disease, and the combination were associated with recurrence (Table 2). Patients aged >70 years had only a slightly and nonsignificantly increased risk of recurrence.

In a Cox regression model, the antimicrobial agent used to treat osteomyelitis due to *S. aureus* was related to the risk of recurrence, even after adjustment for age, diabetes, and peripheral vascular disease (Table 3). Success rates in patients treated initially with cefazolin or ceftriaxone were similar to the standard penicillinase-resistant penicillins. However, patients treated with vancomycin had about a twofold greater rate of recurrence than patients treated with a penicillinase-resistant penicillin.

DISCUSSION

Our results indicate that therapy of osteomyelitis with outpatient parenteral antimicrobial therapy is safe and effective, although diabetes and peripheral vascular disease worsened the prognosis for a successful outcome. The rates of recurrence and amputation that we observed were similar to those reported in other series (35). Recurrence rates of osteomyelitis due to *S. aureus* were similar for therapy with cephalosporins and penicillinase-resistant penicillins, but recurrences were more likely with vancomycin. Age was not associated with recurrence.

Several previous studies have reported that diabetes and peripheral vascular disease increase the risk of amputation (35–39). For example, lower extremity amputations have been reported to be 13 times more frequent among patients with diabetes (35). With a substantial risk of failure for a single course of antimicrobial therapy in osteomyelitis complicated by vascular disease or diabetes, signs of recurrence in these patients may call for earlier amputation or for excision of infected bone rather than successive courses of intravenous antimicrobial agents. Surgery is more likely to be appropriate and cost-effective when infection involves a digit other than the great toe, affects a bone that is not essential to the foot's architecture, or has already destroyed the integrity of the foot (40–42). Conversely, if a major amputation is required, aggressive attempts at limb salvage are preferable from a cost perspective (40,43) and in terms of quality of life (44–46). Both amputations and recurrences may be prevented by longer courses of intravenous therapy, prolonged oral antimicrobial therapy after outpatient parenteral antimicrobial therapy, improved host defenses, nutrition supplements, special surgical procedures, and enhanced home care (1,2,16,20,47); all of these treatments should be studied rigorously.

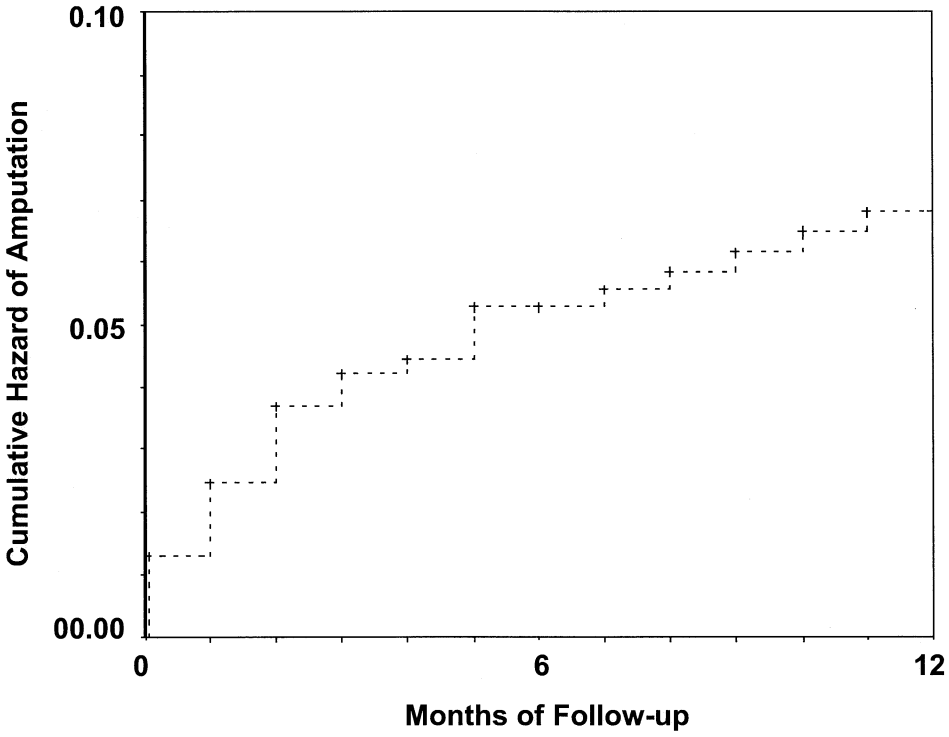

Figure. Time to amputation during first 12 months of follow-up constructed using Kaplan-Meier techniques. N represents the number of patients with information available at the designated months of follow-up. A total of 27 amputations or bone excisions were performed, of which 18 were done during the first 3 months.

The lack of a clear association between older age (>70 years) and the likelihood of recurrence was unexpected. Although some decline in host defenses occurs with age, these age-related factors are apparently less important than others in predicting outcome.

Among patients with osteomyelitis due to *S. aureus*, there were clear differences in response to different antimicrobial agents that were independent of age, vascular disease, and diabetes. The rate of recurrence after vancomycin therapy was more than twice that for β-lactams. The reasons for this are unclear, but suboptimal results have been reported with other infections (48–51). Review of the records did not indicate that the treatment course was any shorter with vancomycin, or that a com-

Table 2. Recurrence of Osteomyelitis, by Age, Diabetes, and Peripheral Vascular Disease*

Characteristic	No. of Patients	No. of Relapses (%)	No. of Reinfections (%)	No. of Other Recurrences (%)	Total No. of Recurrences (%)	Odds Ratio (95% Confidence Interval)	*P* Value
Age							0.58
≤70 years	383	21 (6)	11 (3)	81 (21)	113 (30)	1.0	
>70 years	71	1 (1)	6 (8)	16 (23)	23 (33)	1.2 (0.7–2.0)	
No diabetes or peripheral vascular disease	258	10 (4)	5 (6)	44 (17)	59 (23)	1.0	
Diabetes	129	3 (2)	8 (6)	35 (27)	46 (36)	1.9 (1.2–3.0)	0.01
Peripheral vascular disease	10	2 (20)	1 (10)	4 (40)	7 (70)	7.9 (2.0–31)	0.003
Both diabetes and peripheral vascular disease	44	7 (16)	3 (7)	16 (36)	26 (59)	4.9 (2.5–9.5)	<0.001

* Data about diabetes or peripheral vascular disease were missing in 13 patients. Relapse was defined as recurrence with original pathogen. Reinfection was defined as recurrence with new pathogen.

Table 3. Recurrence by Antimicrobial Therapy for Osteomyelitis Associated with *Staphylococcus aureus* (n = 246 patients)

Antimicrobial Agent	No. of Patients	No. of Relapses (%)	No. of Reinfections (%)	No. of Other Recurrences (%)	Total No. of Recurrences (%)	Relative Risk (95% Confidence Interval)*	*P* Value
Oxacillin/nafcillin/methicillin	56	5 (9)	1 (2)	10 (18)	16 (29)	1.0	
Cefazolin	46	3 (7)	1 (2)	12 (26)	16 (35)	1.1 (0.5–2.2)	0.80
Ceftriaxone	110	8 (7)	2 (2)	22 (20)	32 (29)	0.8 (0.4–1.5)	0.53
Vancomycin	17	2 (12)	0 (0)	7 (41)	9 (53)	2.5 (1.1–5.6)	0.04
Other	17	1 (6)	0 (0)	5 (29)	6 (35)	1.3 (0.5–3.0)	0.6

* Cox regression analysis adjusted for diabetes, peripheral vascular disease, and age >70 years.

plicating foreign body (one of nine of failures vs. one of eight successes) was responsible. It is possible that failures may be due to inadequate levels or limited bactericidal activity, as has been reported in endocarditis associated with *S. aureus* (51,52). It has also been suggested that vancomycin may be less effective against methicillin-susceptible strains of staphylococci than more commonly used β-lactams (48).

The rates of recurrence associated with *S. aureus* were as low with cephalosporins as with penicillinase-resistant penicillins, which are the standard of therapy. This was true of cefazolin as well as ceftriaxone, which was the most frequently used antimicrobial agent. The success with ceftriaxone was not expected because the minimum inhibitory concentrations with *S. aureus* are generally higher than with penicillinase-resistant penicillins. The long half-life of ceftriaxone may account for the better outcomes (53,54). The outcomes with ceftriaxone in treating osteomyelitis are also consistent with a recent smaller series (9).

ACKNOWLEDGMENT

We gratefully acknowledge the contributions of Kim Burgess, Michael Sullivan, Philip Craven, James DeMaio, Larry Schwartz, Peter Marsh, and the staff of Infections Limited for their help in performing this study and reviewing the findings.

REFERENCES

1. Mader JT, Calhoun J. Osteomyelitis. In: Mandell GL, Bennett JE, Dolin R, eds. *Principles and Practice of Infectious Diseases.* 5th ed. Philadelphia, Pennsylvania: Churchill Livingston; 2000:1182–1196.
2. Lew DP, Waldvogel FA. Osteomyelitis. *N Engl J Med.* 1997;336: 999–1007.
3. Waldvogel FA, Vasey H. Osteomyelitis: the past decade. *N Engl J Med.* 1980;303:360–370.
4. Tice AD. Outpatient parenteral antibiotic therapy. Management of serious infections. Part II: amenable infections and models for delivery. Osteomyelitis. *Hosp Pract.* 1993;28:36–39,60–61.
5. Wininger DA, Fass RJ. Antibiotic-impregnated cement and beads for orthopedic infections. *Antimicrob Agents Chemother.* 1996;40: 2675–2679.
6. Mader JT, Ortiz M, Calhoun JH. Update on the diagnosis and management of osteomyelitis. *Clin Podiatr Med Surg.* 1996;13:701–724.
7. Tice AD. Outpatient parenteral antimicrobial therapy for osteomyelitis. *Infect Dis Clin North Am.* 1998;12:903–919.
8. Mader JT, Shirtliff M, Bergquist SC, Calhoun J. Antimicrobial treatment of chronic osteomyelitis. *Clin Orthop.* 1999;360:47–65.
9. Guglielmo BJ, Luber AD, Paletta D Jr, Jacobs RA. Ceftriaxone therapy for staphylococcal osteomyelitis: a review. *Clin Infect Dis.* 2000; 30:205–207.
10. Poretz DM. Outpatient parenteral antibiotic therapy. *Int J Antimicrob Agents.* 1995;5:9–12.
11. Mader JT, Shirtliff M, Calhoun JH. Staging and staging application in osteomyelitis. *Clin Infect Dis.* 1997;25:1303–1309.
12. Waldvogel FA, Medoff G, Swartz MN. Osteomyelitis: a review of clinical features, therapeutic considerations and unusual aspects (first of three parts). *N Engl J Med.* 1970;282:198–206.
13. Waldvogel FA, Medoff G, Swartz MN. Osteomyelitis: a review of clinical features, therapeutic considerations and unusual aspects (second of three parts). *N Engl J Med.* 1970;282:260–266.
14. Waldvogel FA, Medoff G, Swartz MN. Osteomyelitis: a review of clinical features, therapeutic considerations and unusual aspects (third of three parts). *N Engl J Med.* 1970;282:316–322.
15. Dich VQ, Nelson JD, Haltalin KC. Osteomyelitis in infants and children. *Am J Dis Child.* 1975;129:1273–1278.
16. Dunkle LM, Brock N. Long-term follow-up of ambulatory management of osteomyelitis. *Clin Pediatr.* 1982;21:650–655.
17. Dirschl DR. Acute pyogenic osteomyelitis in children. *Orthop Rev.* 1994;23:305–312.
18. Peltola H, Unkila-Kallio L, Kallio MJT, et al, for the Finnish Study Group. Simplified treatment of acute staphylococcal osteomyelitis of childhood. *Pediatrics.* 1997;99:846–850.
19. Christiansen P, Frederiksen B, Glazowski J, Scavenius M, Knudsen FU. Epidemiologic, bacteriologic, and long-term follow-up data of children with acute hematogenous osteomyelitis and septic arthritis: a ten-year review. *J Pediatr Orthop B.* 1999;8:302–305.
20. Bamberger DM, Daus GP, Gerding DN. Osteomyelitis in the feet of diabetic patients: long-term results, prognostic factors, and the role of antimicrobial and surgical therapy. *Am J Med.* 1987;83:653–660.
21. Gilbert DN, Tice AD, Marsh PK, Craven PC, Preheim LC. Oral ciprofloxacin therapy for chronic contiguous osteomyelitis caused by aerobic gram-negative bacilli. *Am J Med.* 1987;82:254–258.
22. Gentry LO, Rodriguez-Gomez G. Ofloxacin versus parenteral therapy for chronic osteomyelitis. *Antimicrob Agents Chemother.* 1991; 35:538–541.
23. Lew DP, Waldvogel FA. Quinolones and osteomyelitis: state-of-the-art. *Drugs.* 1995;49(suppl 2):100–111.
24. Stengel D, Bauwens K, Sehouli J, Ekkernkamp A, Porzsolt F. Systemic review and meta-analysis of antibiotic therapy for bone and joint infections. *Lancet Infect Dis.* 2001;1:175–188.

25. Carek PJ, Dickerson LM, Sack JL. Diagnosis and management of osteomyelitis. *Am Fam Physician.* 2001;63:2413–2420.
26. Rissing PJ. Antimicrobial therapy for chronic osteomyelitis in adults: role of the quinolones. *Clin Infect Dis.* 1997;25:1327–1333.
27. Bamberger DM, Daus GP, Gerding DN. Osteomyelitis in the feet of diabetic patients. Long-term results, prognostic factors, and the role of antimicrobial and surgical therapy. *Am J Med.* 1987;83:653–660.
28. Calandra GB, Norden C, Nelson JD, Mader JT. Evaluation of new anti-infective drugs for the treatment of selected infections of the skin and skin structure. Infectious Diseases Society of America and the Food and Drug Administration. *Clin Infect Dis.* 1992;15(suppl 1):S148–S154.
29. Nathwani D, Tice A. Ambulatory antimicrobial use: the value of an outcomes registry. *J Antimicrob Chemother.* 2002;49:149–154.
30. Tice AD. Osteomyelitis. Special Report. *Scientific American Medicine.* New York, New York; 1997:55–59.
31. Tice AD. An office model of outpatient parenteral antibiotic therapy. *Rev Infect Dis.* 1991;13(suppl 2):S184–S188.
32. Tice AD. The office/clinic model for outpatient parenteral antimicrobial therapy. Special Report. Scientific American Medicine. New York, New York; 1997:12–14.
33. Tice AD. *Handbook of Outpatient Parenteral Therapy for Infectious Diseases.* New York: Scientific American; 1997.
34. 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.
35. Diabetes-related amputations of lower extremities in the Medicare population—Minnesota, 1993–1995. *MMWR Morb Mortal Wkly Rep*. 1998;47:649–652.
36. Hospital discharge rates for nontraumatic lower extremity amputation by diabetes status— United States, 1997. *MMWR Morb Mortal Wkly Rep*. 2001;50:954–958.
37. Ouriel K. Peripheral arterial disease. *Lancet.* 2001;358:1257–1264.
38. Luther M, Lepantalo M, Alback A, Matzke S. Amputation rates as a measure of vascular surgical results. *Br J Surg.* 1996;83:241–244.
39. Feinglass J, Brown JL, LoSasso A, et al. Rates of lower-extremity amputation and arterial reconstruction in the United States, 1979 to 1996. *Am J Public Health.* 1999;89:1222–1227.
40. Lipsky BA. Osteomyelitis of the foot in diabetic patients. *Clin Infect Dis.* 1997;25:1318–1326.
41. Lipsky BA, Pecoraro RE, Wheat LJ. The diabetic foot. *Infect Dis Clin North Am.* 1990;4:409–432.
42. Tan JS, Friedman NM, Hazelton-Miller C, Flanagan JP, File TM Jr. Can aggressive treatment of diabetic foot infections reduce the need for above-ankle amputation? *Clin Infect Dis.* 1996;23:286–291.
43. Gibbons GW, Habershaw GM. Diabetic foot infections: anatomy and surgery. *Infect Dis Clin North Am.* 1995;9:131–142.
44. Pittet D, Wyssa B, Herter-Clavel C, Kurtsteiner K, Vaucher J, Lew PD. Outcome of diabetic foot infections treated conservatively: a retrospective cohort study with long-term follow-up. *Arch Intern Med.* 1999;159:851–856.
45. Pell JP, Donnan PT, Fowkes FG, Ruckley CV. Quality of life following lower limb amputation for peripheral arterial disease. *Eur J Vasc Surg.* 1993;7:448–451.
46. Lavery LA, van Houtum WH, Ashry HR, Armstrong DG, Pugh JA. Diabetes-related lower-extremity amputations disproportionately affect Blacks and Mexican Americans. *South Med J.* 1999;92:593–599.
47. Widmer AF. New developments in diagnosis and treatment of infection in orthopedic implants. *Clin Infect Dis.* 2001;33(suppl 2): S94–S106.
48. Gonzalez C, Rubio M, Romero-Vivas J, Gonzalez M, Picazo JJ. Bacteremic pneumonia due to *Staphylococcus aureus*: a comparison of disease caused by methicillin-resistant and methicillin-susceptible organisms. *Clin Infect Dis.* 1999;29:1171–1177.
49. Fowler VG Jr, Kong LK, Corey GR, et al. Recurrent *Staphylococcus aureus* bacteremia: pulsed-field gel electrophoresis findings in 29 patients. *J Infect Dis.* 1999;179:1157–1161.
50. Fowler VG Jr, Sanders LL, Kong LK, et al. Infective endocarditis due to *Staphylococcus aureus*: 59 prospectively identified cases with follow-up. *Clin Infect Dis.* 1999;28:106–114.
51. Small P, Chambers HF. Vancomycin for *Staphylococcus aureus* endocarditis in IV drug abusers. *Antimicrob Agents Chemother.* 1990; 34:1227–1231.
52. Levine DP, Fromm BS, Reddy BR. Slow response to vancomycin or vancomycin plus rifampin in methicillin-resistant *Staphylococcus aureus* endocarditis. *Ann Intern Med.* 1991;115:674–680.
53. Craig WA. Pharmacokinetic/pharmacodynamic parameters: rationale for antibacterial dosing of mice and men. *Clin Infect Dis.* 1997; 26:1–12.
54. Leggett JE. Ambulatory use of parenteral antibacterials. *Drugs.* 2000;59:1–8.