ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Mar. 2009, p. 883–887 Vol. 53, No. 3
0066-4804/09/$08.00+0 doi:10.1128/AAC.00389-08

Continuous Cefazolin Infusion To Treat Bone and Joint Infections: Clinical Efficacy, Feasibility, Safety, and Serum and Bone Concentrations▽

Valérie Zeller,[1,2]* Frédérick Durand,[1,2] Marie-Dominique Kitzis,[3] Luc Lhotellier,[1] Jean-Marc Ziza,[2] Patrick Mamoudy,[1] and Nicole Desplaces[1,4]

Service de Chirurgie Osseuse et Traumatologique, Groupe Hospitalier Diaconesses-Croix Saint-Simon, 125, rue d'Avron, Paris 75020, France[1]; *Service de Médecine Interne et Rhumatologie, Groupe Hospitalier Diaconesses-Croix Saint-Simon, 125, rue d'Avron, Paris 75020, France*[2]; *Laboratoire de Microbiologie, Groupe Hospitalier Paris Saint-Joseph, 68, rue des Plantes, Paris 75014, France*[3]; *and Laboratoire de Biologie Médicale, Groupe Hospitalier Diaconesses-Croix Saint-Simon, 125, rue d'Avron, Paris 75020, France*[4]

Received 22 March 2008/Returned for modification 30 April 2008/Accepted 3 December 2008

Cefazolin has been used for many years to treat bone and joint infections. Because of its time-dependent antimicrobial activity, continuous infusion would potentially be beneficial. We report on the feasibility, safety, and efficacy of prolonged continuous intravenous cefazolin therapy in a cohort of 100 patients, their serum cefazolin levels, and the concomitant bone cefazolin concentrations in 8 of them. This retrospective cohort study included all the patients treated for bone or joint infection with a continuous cefazolin infusion administered over a 12-h period twice daily for ≥2 weeks. Drug monitoring was performed at least twice for all the patients. Serum and bone cefazolin concentrations were determined by standardized disk diffusion microbiological assays. The absence of clinical, biological, and radiological signs of infection after 2 years of follow-up and the same criteria after 1 year of follow-up defined cures and probable cures, respectively. The median treatment duration was 42 days, and the median daily cefazolin dose was 6 g. Half of the patients received parenteral antibiotic therapy on an outpatient basis. Two moderate-grade adverse events were observed. The median serum cefazolin concentrations were 63 μg/ml (range, 13 to 203 μg/ml) and 57 μg/ml (range, 29 to 128 μg/ml) on days 2 to 10 and days 11 to 21, respectively. The median bone cefazolin concentration reached 13.5 μg/g (range, 3.5 to 29 μg/g). The median bone concentration/serum concentration ratio was 0.25 (range, 0.06 to 0.41). Among 88 patients with a median follow-up of 25 months (range, 12 to 53 months), 52 were considered cured and 29 were considered probably cured. Thus, the treatment of bone and joint infections with a prolonged continuous intravenous cefazolin infusion was feasible, effective, well-tolerated, safe, and convenient, making it a strong candidate for home therapy.

No consensus guidelines on antibiotic therapy for bone and joint infections are currently available (20, 21, 25). So, treatment is still based on expert opinion. Because of the usual need for prolonged administration, the choice of the antibiotic(s) to be used relies on several characteristics: in vitro activity against the isolated microorganism(s), good or excellent bone penetration, and good tolerance.

Cefazolin is a semisynthetic cephalosporin with good in vitro activity against methicillin-susceptible staphylococci (MIC_{90}, 1 mg/liter) and nonenterococcal streptococci (MIC_{90}s, 0.1 to 2 mg/liter) (16) and with excellent tolerance and good bone diffusion (8, 9, 13). Several authors recommend the use of cefazolin for the treatment of bone and joint infections, particularly those due to *Staphylococcus aureus* (2, 21, 31), although only one study of this subject has been published to date (13).

The continuous intravenous administration of β-lactams can be an advantageous way to deliver these drugs, as their efficacy is time dependent; i.e., it increases with the time that the concentrations in serum exceed the MIC for the target pathogen (6, 17). When a molecule like cefazolin is stable over 24 h, the use of continuous infusion avoids the need for repeated intermittent injections, as the delivery device is refilled once or twice daily, which is particularly pertinent for parenteral antibiotic therapy on an outpatient basis (3, 27).

In our Department of Orthopedic Surgery, we treat numerous patients with bone and/or joint infections with continuous intravenous cefazolin, and almost half of them receive parenteral antibiotic therapy on an outpatient basis. The aim of this study was to evaluate the clinical efficacy, feasibility, and safety of the prolonged administration of continuous intravenous cefazolin in our cohort of patients and to determine their serum cefazolin levels and the bone concentrations in a few of them.

MATERIALS AND METHODS

Patients. This retrospective cohort study included all the patients treated in our department for a bone and/or joint infection with continuous intravenous cefazolin for ≥2 weeks and who had two or more serum cefazolin-concentration determinations. All the patients gave written informed consent before inclusion.

The following characteristics were noted for each patient: age, sex, weight, comorbidities (diabetes, malignancy that had developed within 5 years, immunosuppressive therapy, ischemic heart disease, chronic viral hepatitis, cirrhosis, splenectomy), American Society of Anesthesiology score (12), creatinine clearance (Cockroft-Gault formula), infection site, and the microorganism(s) isolated. All the pathogens were susceptible to cefazolin (MICs ≤ 8 mg/liter), as determined by the standard disk diffusion method of the Société Française de Microbiologie, and all the *Staphylococcus* strains were methicillin susceptible.

Drug administration. Cefazolin, administered intravenously through a central venous catheter, was initiated with a loading dose, infused over 10 min, of 1 g when the daily dose was ≤4 g or of 2 g when the daily dose was >4 g, followed

* Corresponding author. Mailing address: Service de Chirurgie Osseuse et Traumatologique, Groupe Hospitalier Diaconesses-Croix Saint-Simon, 125, rue d'Avron, Paris 75020, France. Phone: 33144641694. Fax: 33144643337. E-mail: vzeller@hopital-dcss.org.

▽ Published ahead of print on 15 December 2008.

TABLE 1. Main demographic and clinical characteristics of the 100 patients treated with continuous intravenous cefazolin

Characteristic	Value
Demographic	
Median (range) age (yr)	56 (18–92)
No. of males	55
Clinical	
No. of patients with American Society of Anesthesiology score ≥3	9
Median (range) wt (kg)	73 (45–130)
Median (range) creatinine clearance (ml/min)	110 (30–150)
Comorbidities (no. of patients)	48
Cardiovascular disease	9
Diabetes mellitus	7
Chronic inflammatory rheumatic disease	8
Malignancy	7
Obesity (BMI[a] ≥ 30)	9
Chronic viral hepatitis	3
Neuropsychiatric impairment	3
Other	6

[a] BMI, body mass index.

TABLE 2. Type of infection in and pathogens isolated from the 100 patients treated with continuous intravenous cefazolin

Characteristic	No. of patients
Type of infection	
Joint arthroplasty infection	44
Chronic osteomyelitis	34
Septic arthritis/osteoarthritis	16
Spondylodiscitis	2
Miscellaneous	4
Pathogen isolated	
Staphylococcus aureus	56
Coagulase-negative staphylococcus	9
Streptococcus spp	7
Gram-positive anaerobic bacteria[a]	18
Polymicrobial	8
Undetermined	2

[a] *Propionibacterium acnes*.

immediately by the continuous infusion of 60 to 80 mg/kg of body weight/day dissolved in 50 ml of 5% dextrose and administered over a 12-h period twice a day via an infusion pump. All patients received combined antibiotic therapy.

Patients were discharged to home with parenteral antibiotic therapy on an outpatient basis when the treatment duration exceeded 3 weeks, the local and general evolution of the infection was favorable, the function of the affected joint or limb had been recovered, the treatment was well tolerated, and they could be assisted at home with the performance of daily activities. At home, antibiotic therapy was administered twice a day by a visiting nurse through a portable infusion device, either a constant-infusion pump or an elastomeric infusion system. The other patients were transferred to a rehabilitation center or stayed in our unit until the end of parenteral therapy.

Treatment was monitored closely: during hospitalization, the patients were examined daily, and blood tests (blood counts and serum creatinine, liver enzyme, and C-reactive protein level determinations) were performed twice a week. At home, the visiting nurse evaluated the patients' conditions twice daily when the infusion pump was loaded and reported on the presence of adverse events (AEs) to the care team. Blood tests were performed once a week, and the results were sent to the patient's treating physician. All AEs considered by the treating physician to be related to cefazolin and classified as grade 2 to 5 (grade 2, moderate; grade 3, severe; grade 4, life-threatening or disabling; grade 5, death attributable to an AE), according to the Common Terminology Criteria for Adverse Events (CTCAE) (4), were reported.

Blood and bone sampling and drug analysis. Serum cefazolin levels were determined at least twice for each patient. The first blood sample was obtained between days 2 and 10 of cefazolin treatment, and the second was obtained between days 11 and 21, with a minimum of 5 days occurring between the times of collection of the two samples. Serum samples were stored at −20°C until they were assayed (which was on the same day that they were collected or the day after). Serum cefazolin concentrations were determined by the agar disk diffusion test (microbiological assay), as described by Klassen and Edberg (18) and Reeves et al. (23). Multiresistant *Bacillus pumilus* SJ15547 (resistant to rifampin [rifampicin; MIC > 128 mg/liter]; fosfomycin [MIC > 512 mg/liter], and fluoroquinolones [MIC > 64 mg/liter]) was used as the indicator organism. Aminoglycosides were inactivated with cellulose phosphate powder, which was included in the incubation with the serum specimen. The limit of quantification was 0.5 mg/liter, and the variation range was 5 to 11%.

The target serum steady-state concentration was 40 to 70 mg/liter; values below that range were considered underdosing, and those above that range were considered overdosing; the patients' daily cefazolin doses were increased or decreased (20 to 25% of the daily dose) accordingly.

For eight patients who received a continuous cefazolin infusion preoperatively for ≥2 days because of acute *S. aureus* sepsis, bone samples were obtained during surgery, pressed in sterile gauze to eliminate contaminating blood as much as possible, and stored at −80°C until they were assayed. Frozen bone samples were precisely weighed and crushed. The resulting powder was suspended in 0.1 M phosphate buffer (2:1, by volume; pH 6.6) for at least 24 h at 4°C. The homogenate was then centrifuged, and the antibiotic concentrations in the supernatant were determined as described above. A blood sample was concomitantly drawn to determine the bone concentration/serum concentration ratio.

Outcome. Patients were assessed for follow-up at 6 weeks, 3 months, 6 months, 12 months, and then once a year; for patients who had not been seen for >1 year, they or their general practitioners were contacted by phone. The following events were recorded: relapse, reinfection, and death. Relapse was defined as positive cultures of joint aspirate or intraoperative specimens that grew the same bacterium. Reinfection was defined as a new infection with another pathogen. Cure was defined as the absence of clinical, biological, and radiological signs of infection after 2 years of follow-up; and probable cure was defined as the same criteria for a cure but after 1 year of follow-up. If a patient had died, the cause of death was recorded. Death was considered infection related when it was associated with uncontrolled sepsis or treatment related when it was associated with a complication arising during or following surgery or while the patient was receiving antibiotic therapy and in the absence of severe sepsis.

RESULTS

Patients and treatment characteristics. One hundred consecutive patients hospitalized between February 2005 and May 2007 were included in this study. Ninety-four patients underwent surgery for their bone and joint infections. Their demographic and clinical characteristics and creatinine clearance rates are given in Table 1, the infection site and the isolated pathogen(s) are given in Table 2, and the characteristics of cefazolin treatment and the serum cefazolin steady-state concentrations are given in Table 3. Cefazolin doses were adjusted for 47 patients: between the first and second serum sampling for 32 patients and after the second sampling for 15 patients. For these 15 patients, a further serum sample was drawn 2 to 8 days after the dose adjustment to check that the serum concentration was within the therapeutic range. The adjustment was effective for all but five patients, who required further dose adjustment.

Two patients experienced cefazolin-related AEs. The first patient developed *Clostridium difficile* colitis, and the second became confused. In the latter patient, the concomitant serum cefazolin levels were very high (127 mg/liter), almost twice the upper limit targeted. Cefazolin was definitively stopped for the former patient and was intermittently stopped for the latter patient, whose daily dose was tapered. Both AEs disappeared and could be classified as CTCAE grade 2; no CTCAE grade 2 to 5 AEs were observed on the basis of blood test results.

TABLE 3. Main therapeutic characteristics of the 100 patients treated with continuous intravenous cefazolin

Therapeutic characteristic	Value
Median (range) daily dose (g)	6 (4–16)
Median (range) duration of treatment (days)	42 (14–82)
Antibiotic combined with cefazolin (no. of patients)	
Gentamicin followed by rifampin	59
Rifampin	29
Other	12
Median (range) serum cefazolin concn (mg/liter)	
Days 2–10	63 (13–203)
Days 11–21	57 (29–128)
Median (range) serum cefazolin concn (mg/liter)/MIC_{90} (mg/liter)[a]	60.75 (13–203)
No. of patients with dose adaptation	
Total	47
Increase	9
Decrease	38
No. of patients receiving outpatient parenteral antibiotic therapy	51
No. of patients with AEs	2

[a] MIC_{90} for cefazolin-susceptible staphylococcal strains, 1 mg/liter (16).

Bone cefazolin concentrations. Bone cefazolin levels were determined for eight patients. We obtained one bone sample from three patients, two samples from three patients, and three or four specimens from one patient each. The median duration of cefazolin therapy before sampling was 7 days (range, 6 to 62 days). The median cefazolin bone concentration and bone concentration/serum concentration ratio were 13.5 μg/g (range, 3.5 to 29 μg/g) and 0.25 (range, 0.06 to 0.41), respectively.

Outcome. The median follow-up time was 25 months (range, 12 to 53 months). Six patients were lost to follow-up before 1 year, and one patient died from an unrelated cause (cancer) within 1 year. Five other patients received long-term suppressive antibiotic therapy. These 12 patients were excluded from the outcome analysis.

Among the 88 remaining patients, 5 with *S. aureus* infection of the femur (1 patient), of the tibial stump (1 patient), after hip arthroplasty (1 patient), or after knee arthroplasty (2 patients) relapsed. No emergence of cefazolin resistance was observed. All five patients underwent further surgery and prolonged intravenous antibiotic therapy.

One patient died of a progressive deterioration of her general condition 6 months after surgery for the treatment of the infection. This patient's death was considered infection and treatment related.

Overall, 82 (93%) of the 88 patients were considered to have been cured (53 patients) or probably cured (29 patients).

DISCUSSION

The treatment of chronic bone and joint infections remains difficult. It requires a multidisciplinary approach that combines the identification of the responsible pathogen(s), surgical intervention, and prolonged antibiotic therapy. Cefazolin has been used for >30 years to treat bone and joint infections, because of its good activity against gram-positive cocci, especially methicillin-susceptible staphylococci; its excellent tolerance; its low cost; and its limited antimicrobial spectrum (13). No drug interaction has been observed. Because cefazolin exerts time-dependent antibacterial activity, its continuous infusion is potentially beneficial (17).

The results of our retrospective analysis of 100 patients treated with prolonged continuous cefazolin administration showed that this therapeutic mode is feasible, well-tolerated, safe, and convenient. These characteristics represent major advantages for the choice of drug(s) to be used for prolonged and parenteral antibiotic therapy on an outpatient basis. The latter has become a valid alternative for the treatment of bone and joint infections (3, 27). Only two moderate-grade AEs were observed in our patient cohort, and the AEs regressed after drug withdrawal in one patient and dose adjustment in the other. It is important to underline that drug monitoring was performed for all the patients, and the daily dose was adjusted accordingly for nearly half of them (47%). It is likely that the low AE rate was partly attributable to that close surveillance. We therefore recommend such drug monitoring.

The target range (40 to 70 mg/liter) was determined by considering that (i) the in vitro MIC for methicillin-susceptible staphylococcal strains is 1 mg/liter (16); (ii) peak serum bactericidal titers of ≥1/16 and trough titers of ≥1/4 predicted cure in patients with chronic osteomyelitis, whereas peak titers of <1/16 and trough titers of <1/2 predicted failure, as demonstrated by Weinstein et al. (30); (iii) the reported rates of cefazolin penetration into bone are 4 to 18% (8, 9, 13); (iv) a bone concentration/MIC ratio of 5 is required for time-dependent killing antibiotics (7); (v) we observed the absence of cefazolin toxicity at concentrations of <100 mg/liter; and (vi) small colony variants, which are embedded in their self-produced biofilm and which are known to be present in chronic bone infections, are more resistant to cell wall-active antibiotics (24). Although a reliance on the reported level of bone penetration and our calculation of the target serum cefazolin levels can be debated, we applied fundamental pharmacokinetic-pharmacodynamic parameters (7) to go beyond published medical findings to try to treat these difficult-to-treat infections with a continuous cefazolin infusion.

Serum cefazolin concentrations were determined at least twice for each patient. The median serum concentrations at the first and second determinations were within the target range (40 to 70 mg/liter), but for nearly half of the patients, the doses were adjusted and were tapered for 81% of the patients. These observations led us to lower the cefazolin starting dose from 80 to 60 mg/kg/day. A few reports on the serum cefazolin concentrations achieved during continuous infusion have been published (5, 15, 26, 28). In most of those studies, a single sample was obtained after 12 to 24 h of treatment; in one study (15), however, the patients were treated for at least 5 days before they were sampled. The mean serum concentrations ranged from 32 to 53 mg/liter, depending on the dose administered. Because β-lactams have time-dependent antimicrobial activity, a potential advantage could be exploited by maintaining local antibiotic concentrations permanently above the MIC of the isolated pathogen; this seems particularly relevant for slowly growing bacteria, which are observed in chronic osteitis and

implant-associated infections (7, 29). The results of several studies showed that the bone antibiotic concentration is proportional to its serum concentration (10, 11, 19, 30). Therefore, it is likely that constant serum concentrations yield constant bone concentrations. In our study, serum cefazolin levels were permanently and substantially above the MIC of the isolated pathogens (in vitro MIC of cefazolin-susceptible staphylococcal strains, 1 mg/liter [16]), as the median serum concentration/MIC ratio for *Staphylococcus* was 60.75 (range, 13 to 203). It should be kept in mind that pharmacokinetic-pharmacodynamic relationships use serum concentrations as a surrogate marker for tissue concentrations, which are difficult to obtain and which have several limitations (22). Numerous studies with animals and a few clinical trials have shown that the duration of time that the serum concentration exceeds the MIC of the pathogen is highly predictive of drug efficacy (1, 7). Theoretically, the use of very high constant antibiotic concentrations is not necessary to kill bacteria, but in chronically infected bone, bacteria undergo major metabolic changes. Their growth rate is slowed markedly, leading to the development of small colony variants (24), which exhibit increased resistance to cell wall-active antibiotics.

Determination of the bone cefazolin levels in eight of our patients confirmed that this antibiotic penetrates into bone. We observed intra- and interindividual variations of those concentrations, which ranged from 3.5 to 29 μg/g, whereas the levels in serum continuously ranged from 45 to 86 μg/ml, thereby confirming previously reported data (9, 14, 19). That cefazolin diffusion into bone is heterogeneous and dependent on the type of bone and the presence or absence of inflammation and/or necrosis tends to support the use of high-dose antimicrobial therapy. Furthermore, important limitations of the measurement of antibiotic concentrations in tissue homogenates must be taken into consideration (22).

The efficacy of cefazolin for the treatment of bone and joint infections has been evaluated only once, by Fass (13). Cefazolin was administered intermittently either intravenously or intramuscularly to 16 patients. Fifteen patients were considered cured, but only 6 of them were followed for at least 12 months. In our study, outcome analysis for 88 patients with at least 12 months of follow-up showed that 93% had no signs of infection. Five patients, all with *S. aureus* infections, relapsed with the same susceptible strain. No obvious cause of relapse (inappropriate surgery or antibiotic therapy, low serum cefazolin concentration, poor treatment compliance, severe immunodeficiency) could be identified.

Our study has some limitations. The first is its retrospective design. Nevertheless, all the patients were managed according to our standardized local protocol, and weekly blood tests were always performed. Therefore, it seems unlikely that we could have missed grade 2 to 5 AEs, as AEs were noted in the patients' charts. Second, keeping in mind the technique applied and the fact that only eight patients' bones were sampled only once, the antimicrobial bone concentrations measured should be viewed with prudence. Indeed, measurements of the amount of drug in those tissue homogenates alone cannot provide information on the compartment (e.g., cell, interstitial fluid, or vascular compartment) into which the drug penetrates or the activity of the drug at the infection site, nor can they ascertain the efficacy of the drug. However, clinical evidence of the efficacy of antimicrobial therapy is needed before its use can be recommended (22). Third, patient follow-up was <2 years for one-third of our cohort. Follow-up for 2 years is generally required before patients with chronic osteomyelitis or infections after arthroplasty can be defined as being cured. Later relapses or reinfections could have been missed. Finally, our cohort included patients with different infections that were at different sites and that were caused by different pathogens. A prospective study that includes a homogeneous population is required to ascertain the efficacy of this treatment for a specific infection.

In conclusion, prolonged treatment of bone and joint infections with continuous intravenous cefazolin is feasible, effective, well-tolerated, safe, and convenient to administer, making continuous cefazolin a strong candidate for home therapy.

ACKNOWLEDGMENTS

We thank Janet Jacobson for editorial assistance.
No financial support was received.
None of the authors has a conflict of interest to declare concerning this report.

REFERENCES

1. **Ambrose, P. G., S. M. Bhavnani, C. M. Rubino, A. Louie, T. Gumbo, A. Forrest, and G. L. Drusano.** 2007. Pharmacokinetics-pharmacodynamics of antimicrobial therapy: it's not just for mice anymore. Clin. Infect. Dis. **44:** 79–86.
2. **Barberan, J.** 2006. Management of infections of osteoarticular prosthesis. Clin. Microbiol. Infect. **12:**93–101.
3. **Bernard, L., L. El-Hajj, B. Pron, A. Lotthé, V. Gleizes, F. Signoret, P. Denormandie, J. L. Gaillard, and C. Perrone.** 2001. Outpatient parenteral antimicrobial therapy (OPAT) for the treatment of osteomyelitis: evaluation of efficacy, tolerance and cost. J. Clin. Pharm. Ther. **26:**445–451.
4. **Cancer Therapy Evaluation Program.** 31 March 2003. Common terminology criteria for adverse events, version 3. DCTD, NCI, NIH, DHHS, Bethesda, MD. http://ctep.cancer.gov.
5. **Connors, J. E., J. T. Dipiro, R. G. Hayter, K. D. Hooker, J. A. Stanfield, and T. R. Young.** 1990. Assessment of cefazolin and cefuroxime tissue penetration by using a continuous infusion. Antimicrob. Agents Chemother. **34:** 1128–1131.
6. **Craig, W. A., and S. C. Ebert.** 1992. Continuous infusion of β-lactam antibiotics. Antimicrob. Agents Chemother. **36:**2577–2583.
7. **Craig, W. A.** 1998. Pharmacokinetic/pharmacodynamic parameters: rationale for antimicrobial dosing of mice and men. Clin. Infect. Dis. **26:**1–12.
8. **Cunha, B. A., H. R. Gossling, H. S. Pasternak, C. H. Nightingale, and R. Quintiliani.** 1977. The penetration characteristics of cefazolin, cephalothin, and cephradine into bone in patients undergoing total hip replacement. J. Bone Joint Surg. Am. **59A:**856–859.
9. **Cunha, B. A., H. R. Gossling, H. S. Pasternak, C. H. Nightingale, and R. Quintiliani.** 1984. Penetration of cephalosporins into bone. Infection **12:**80–84.
10. **Dellamonica, P., E. Bernard, H. Etesse, and R. Garraffo.** 1986. The diffusion of pefloxacin into bone and the treatment of osteomyelitis. J. Antimicrob. Chemother. **17:**93–102.
11. **Desplaces, N., P. Mamoudy, F. Ducroquet, P. Larrouturou, and M. D. Kitzis.** 1997. Vancomycine en perfusion continue et infections ostéo-articulairesà staphylocoques multirésistants. Med. Mal. Infect. **27:**969–974.
12. **Dripps, R. D., A. Lamont, and J. E. Eckenhoff.** 1961. The role of anaesthesia in surgical mortality. JAMA **178:**261–266.
13. **Fass, R.** 1978. Treatment of osteomyelitis and septic arthritis with cefazolin. Antimicrob. Agents Chemother. **13:**405–411.
14. **Fitzgerald, R. H.** 1984. Antibiotic distribution in normal and osteomyelitic bone. Orthop. Clin. N. Am. **15:**537–546.
15. **Howard, G. W., E. J. Begg., S. T. Chambers, J. V. Brincat, M. Zhang, and C. M. Kirkpatrick.** 2002. Free and total cefazolin plasma and interstitial fluid concentrations at steady state during continuous infusion. J. Antimicrob. Chemother. **50:**429–432.
16. **Karchmer, A. W.** 2000. Cephalosporins, p. 274–291. *In*: G. L. Mandell, J. E. Bennett, and R. Dolin (ed.), Principles and practice of infectious diseases, 5th ed. Churchill Livingstone, Philadelphia, PA.
17. **Kasiakou, S. K., G. J. Sermaides, A. Michalopoulos, E. S. Soteriades, and M. E. Falagas.** 2005. Continuous versus intermittent intravenous administration of antibiotics: a meta-analysis of randomised controlled trials. Lancet Infect. Dis. **5:**581–589.

18. **Klassen, M., and S. C. Edberg.** 1996. Measurement of antibiotics in human body fluids: techniques and significance, p. 230–295. *In* Antibiotics in laboratory medicine, 4th ed. The Williams & Wilkins Co., Baltimore, MD.
19. **Kolzcun, M., C. L. Nelson, M. C. McHenry, T. L. Gavan, and P. Pinovich.** 1974. Antibiotic concentrations in human bone. J. Bone Joint Surg. Am. **56A:**305–310.
20. **Lazzarini, L., B. A. Lipsky, and J. T. Mader.** 2005. Antibiotic treatment of osteomyelitis: what have we learned from 30 years of clinical trials? Int. J. Infect. Dis. **9:**127–138.
21. **Lew, D. P., and F. A. Waldvogel.** 2004. Osteomyelitis. Lancet **364:**369–379.
22. **Mouton, J. W., U. Theuretzbacher, W. A. Craig, P. M. Tulkens, H. Derendorf, and O. Cars.** 2008. Tissue concentrations: do we ever learn? J. Antimicrob. Chemother. **61:**235–237.
23. **Reeves, D. S., R. Wise, J. M. Andrews, and L. O. White.** 1999. Clinical antimicrobial assays. Oxford University Press Inc., New York, NY.
24. **Sendi, P., M. Rohrbach, P. Graber, R. Frei, P. E. Ochsner, and W. Zimmerli.** 2006. *Staphylococcus aureus* small colony variants in prosthetic joint infection. Clin. Infect. Dis. **43:**961–967.
25. **Stengel, D., K. Bauwens, J. Sehouli, A. Ekkernkamp, and F. Porzsolt.** 2001. Systematic review and meta-analysis of antibiotic therapy for bone and joint infections. Lancet Infect. Dis. **1:**175–188.
26. **Thys, J. P., B. Vanderkelen, and J. Klastersky.** 1976. Pharmacological study of cefazolin during intermittent and continuous infusion: a crossover investigation in humans. Antimicrob. Agents Chemother. **10:**395–398.
27. **Tice, A. D., S. J. Rehm, J. R. Dalovisio, J. S. Bradley, L. P. Martinelli, D. R. Graham, R. B. Gainer, M. J. Kunkel, R. W. Yancey, and D. N. Williams.** 2004. Practice guidelines for outpatient parenteral antimicrobial therapy. Clin. Infect. Dis. **38:**1651–1672.
28. **Waltrip, T., R. Lewis, V. Young, M. Farmer, S. Clayton, S. Myers, L. A. Gray, and S. Galandiuk.** 2002. A pilot study to determine the feasibility of continuous cefazolin infusion. Surg. Infect. **3:**5–9.
29. **Weinstein, M. P., C. W. Stratton, H. B. Hawley, A. Ackley, and L. B. Reller.** 1987. Multicenter collaborative evaluation of standardized serum bactericidal test as a predictor of therapeutic efficacy in acute and chronic osteomyelitis. Am. J. Med. **83:**218–222.
30. **Wichmann, A., P. Lattke, A. Hartmann, W. Jaross, and K. J. Schulze.** 2002. Bestimmung von Levofloxacin-Spiegeln im humanen Knochengewebe. Krankenhauspharmazie **23:**207–212.
31. **Zeller, V., and N. Desplaces.** 2006. Antibiothérapie des infections ostéo-articulairesà pyogènes chez l'adulte: principes et modalités. Rev. Rhum. **73:**129–135.