Amphotericin B-loaded bone cement to treat osteomyelitis caused by *Candida albicans*

Fawziah Marra, PharmD;*§ Graham M. Robbins, MB BS;† Bassam A. Masri, MD;‡
Clive Duncan, MB, MSc;† Kishor M. Wasan, PhD;§ Evan H. Kwong;§ Peter J. Jewesson, PhD*§

Fungal pathogens are recognized as a potential cause of osteomyelitis. We describe a case of osteomyelitis due to *Candida albicans* in an adult who had undergone multiple revisions of a hip prosthesis. Treatment was with amphotericin B-loaded bone cement. We believe this is the first report of such treatment for fungal osteomyelitis.

Case report

A 59-year-old man (height 180 cm, weight 82 kg) was admitted to the Vancouver Hospital & Health Sciences Centre with a suspected infection after a second revision total hip arthroplasty. His medical history included an undiagnosed inflammatory arthropathy for which he had undergone a right-sided total hip replacement in 7 years earlier. This had been revised twice because of aseptic loosening, first 6 years after the original replacement and subsequently 2 months before the current admission. The erythrocyte sedimentation rate, C-reactive protein levels and intraoperative synovial tissue cultures obtained at the time of these revisions revealed no infection. His course after the second revision operation was uncomplicated until 10 days before this admission when he had night sweats, fever, redness and swelling over the right hip. He did not report any drug allergies and only reported taking diclofenac 50 mg orally twice daily, for his inflammatory arthropathy.

On admission, his vital signs included a blood pressure of 165/90 mm Hg, heart rate of 110 beats/min, and a body temperature of 38.1°C. Findings on physical examination were unremarkable except for an area of erythema over the medial portion of the wound on the right hip; the area from the right hip down to the knee was also edematous and tender. Ultrasonography revealed a small fluid collection from which 30 mL of turbid serosanguineous fluid was aspirated. This contained 19.7×10^9/L leukocytes (79% polymorphs, 5% lymphocytes, 16% monocytes), 81.5×10^9/L erythrocytes, 50 g/L protein and 0.3 mmol/L glucose.

Soon after admission, before we received the final culture results, the patient underwent removal of his infected arthroplasty with débridement and insertion of a prosthesis of antibiotic loaded acrylic cement (PROSTALAC), which included 2 antibiotics: vancomycin (Vancocin; Eli-Lily, Scarborough, Ont.) 1.0 g per package of Palacos (Smith & Nephew, Richards, Memphis, Tenn.) and tobramycin (Nebcin; Eli-Lily) 2.4 g per package of Palacos. All 4 tissue cultures from the right hip taken during this procedure showed occasional polymorphonuclear leukocytes, and no organisms were visible on Gram's staining. All specimens grew *C. albicans*, sensitive to amphotericin B (minimal inhibitory concentration [MIC] 0.12 mg/L), fluconazole (MIC 0.25 mg/L), flucytosine (MIC 1.0 mg/L) and itraconazole (MIC 0.03 mg/L).[1] In addition, microbiologic analysis of the fluid obtained from the preoperative aspirate also revealed 4+ polymorphonuclear leukocytes, but no organisms were seen on Gram's staining. Culture of this aspirate also grew *C. albicans*. Two sets of blood samples (4 tubes) were negative for *C. albicans*. Thus, a diagnosis of *C. albicans* infection of the right hip prosthesis was made, and the patient was started on fluconazole, 400 mg orally twice daily. However, over the next 3 weeks, the patient continued to drain moderate amounts of serosanguineous fluid from the wound and eventually showed a 1-cm long dehiscence in the proximal part of the wound. Because of our previous experience with antibiotic-loaded cement spacers in the treatment of bacterial and mycobacterial periprosthetic infections.[2–5] We decided to try a similar, but previously undescribed, technique as an adjunct to conventional surgical and medical treatment We modified our standard antibiotic-loaded spacer (PROSTALAC) by adding amphotericin B to the bone cement.

Amphotericin B-treatment regimen

A total of 750 mg of amphotericin B (15 vials of Fungizone, Squibb Pharmaceuticals, Montreal) sterile powder for injection were added to 4 mixes of Palacos polymethylmethacralate bone cement (Smith & Nephew Richards). The final dose of amphotericin B of 9 mg/kg total body weight was based on an empiric intravenous–bone cement conversion factor of 5–20 that we have historically applied to other anti-infectives. We considered that conventional amphotericin B represented our best choice for addition to bone cement based on the fact that it is a broad-spectrum agent with fungicidal activity, is heat stable to 170°C and is available in a sterile powder dosage form.[6] Although this patient was receiving fluconazole systemically at the time of the procedure and *C. albicans* was sensitive to this triazole, fluconazole is not available in a sterile powder formulation and therefore cannot be used in bone cement.

Surgical and amphotericin B loading procedures

Using our routine surgical technique, after excision of the sinus tract, we exposed and removed the previously implanted PROSTALAC. After thorough débridement, the acetabulum was reconstructed using a 42 × 32 mm PROSTA-LAC cup (Depuy, Warsaw, Ind.) with 2 mixes of cement containing a total of 400 mg amphotericin B. An antifungal femoral component was made using a 240-mm PROSTALAC femoral stem and 1 mix of cement containing 250 mg of amphotericin B. This was stabilized in the femur with a collar made from 1 mix of cement containing 100 mg of amphotericin B. There was between 5% and 10% wastage of antifungal-loaded cement, giving a total dose of amphotericin B of approximately 700 mg (between 675 and 713 mg). The wound was closed over 2 one-eighth-inch suction drains. These were clamped throughout the postoperative period, except when obtaining specimens of the periprosthetic fluid. Four intraoperative tissue specimens were taken and sent for bacterial culture and sensitivity (3 specimens) and fungal culture (1 specimen). All specimens revealed occasional polymorphs. No organisms were visible on Gram's staining. There was no bacterial growth after 5 days, and no evidence of fungus after 30 days of culture.

Sample collection and antifungal assay

Amphotericin B concentrations in blood and drainage fluid specimens were measured. Blood samples (6 mL of whole blood was allowed to clot, spun and serum harvested) were collected at 3, 6, 12, 26, 38, 50, 69, 93, 117, 141, 165, 189, 213 hours after insertion of the prosthesis. Drainage fluid specimens (20 mL) were obtained at 6, 12, 26, 50, 74, 98, 122 hours after insertion of the antifungal cement. Specimens were stored for up to 72 hours at –4°C before assay.

Amphotericin B quantification

Amphotericin B levels in serum and drainage fluid samples were determined by a high-pressure liquid chromatography methodology previously published by Wasan and colleagues.[7]

Clinical outcome

The patient's early postoperative course was uncomplicated, and the amphotericin B was well tolerated with no adverse clinical effects such as fevers, chills and rigors. The serum creatinine level on admission was 66 mmol/L and it remained stable (ranging from 66 to 72 mmol/L) throughout his hospital stay. The patient remained in hospital for an additional 2 weeks, during which time the fluconazole was continued at a rate of 400 mg orally twice daily. During this time, drainage from his wound decreased substantially

and he was able to move around with crutches; however, a sinus the size of a pinhead remained open on his hip wound. At discharge, the patient was treated with a hip spica cast, to reduce movement of the local tissues, and was given a prescription for fluconazole, 400 mg orally twice daily, to complete a 6-week course.

Unfortunately by 6 weeks after operation, soon after removal of the hip spica, and cessation of the fluconazole, the patient's wound drainage increased significantly. Additional specimens (7 hip joint fluid aspirates) were taken, and these revealed the presence of *Escherichia coli* in 4 specimens. Four weeks later the patient underwent operation for removal of the infected hip prosthesis and thorough débridement. Of 6 hip tissue culture specimens taken during this procedure, 3 grew *E. coli*, 1 showed no growth and the remaining 2 grew *Staphylococcus epidermidis* in broth only (considered to be a contaminant).

Amphotericin B concentrations

Serum amphotericin B concentration reached a maximum of 1.2 mg/L at 6 hours after implantation and then steadily declined such that no detectable levels of amphotericin B were observed 50 hours after implantation (Fig. 1). In the wound drainage, a maximal amphotericin B concentration of 3.2 mg/L was reached 50 hours after implantation (Fig. 2). This declined steeply over the next 24 hours to a concentration of 0.71 mg/L and then reached a plateau over the next
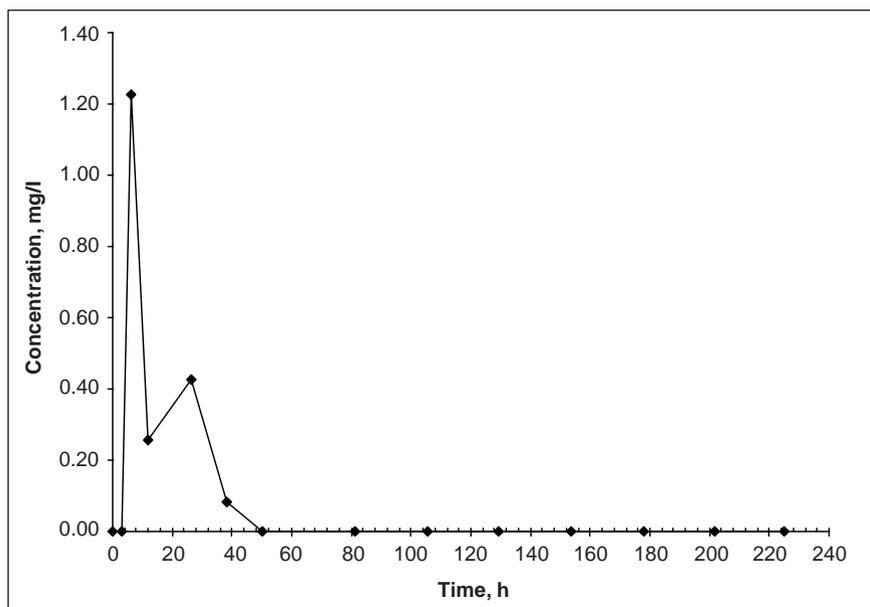

FIG. 1. Amphotericin B concentrations in plasma.

2 days (0.57 mg/L and 0.51 mg/L). No further samples were collected after day 5 as the clinical team felt that the risk of the patient getting a hospital-acquired wound infection was greater than the information available on the elution of amphotericin B from cement.

Discussion

To determine previous experience with amphotericin B-impregnated bone cement, we conducted a review of various online databases including the Cochrane Database of Systematic Reviews, Cinahl (1982–99), Current Contents (1996–present), EMBASE (1988–present), MEDLINE(1966–present) and PubMed using the search terms "amphotericin," "cement," "Candida albicans" and "osteomyelitis." This was supplemented by a review of the bibliographies of the articles identified. Although we found several reports of *C. albicans*-associated osteomyelitis, the patients had been treated with either intravenous amphotericin B,[8-19] fluconazole[20-23] or ketoconazole.[24,25] Despite our extensive review, we were unable to locate any previous reports of the use of amphotericin B in bone cement for the treatment of fungal infections of bone.

The use of antimicrobial-impregnated cement and beads to prevent and treat orthopedic infections was originally described in Europe almost 30 years ago.[26] The rationale for this is to provide high local drug concentrations while avoiding toxicity associated with systemic antibiotic administration.[27] Wininger and Fass[6] have recently summarized a list of the an-

timicrobial agents that have been incorporated into cement, including aminoglycosides, β-lactams, vancomycin, macrolides and polymyxins. No antifungal agents appeared on this list. Although somewhat dated, the survey by Fish and associates[28] also revealed no apparent use of amphotericin B-impregnated cement by the respondents.

Despite the advent of new antifungal agents in the past few years, amphotericin B remains the broadest spectrum antifungal drug available and the mainstay of treatment for fungal osteomyelitis, although a number of treatment failures have been reported.[9-19] Both fluconazole and ketoconazole have also been tried for the treatment of *C. albicans* osteomyelitis. Success with these fungistatic agents has also been mixed.[21-25] Although clinically efficacious, amphotericin B is also one of the most toxic antimicrobial drugs in use today. Common side effects of parenteral administration include immediate infusion-related reactions of hyperpyrexia, severe malaise and hypotension, acute renal failure, anemia, hypokalemia and occasional leukopenia and thrombocytopenia.[29] In sufficient concentrations, amphotericin B exhibits a pH-dependent fungicidal activity against susceptible pathogens. Amphotericin B inhibits the formation of the fungal cell membrane, and coincident binding to mammalian cell membranes is believed to cause polyene toxicity in man. This generally limits the systemic dose of amphotericin B to a maximum of 1 mg/kg daily.[29-31] Serum concentrations after intravenous administration appear to be dose-dependent. Peak levels (~1 h after infusion) ranging

between 1.0 and 2.4 mg/L following doses of 0.5 to 1.0 mg/kg have been reported by several investigators.[29,32] The drug has an initial serum elimination half-life of approximately 24 to 48 hours with a terminal half-life of about 15 days.[29] Amphotericin B has an apparent volume of distribution of 4 L/kg and the highest concentrations achieved are in lung, spleen and kidney. A high protein-binding (>90%) capacity likely accounts for the low tissue concentrations found in human studies. Most drug binding is to erythrocytes, cholesterol and lipoproteins. Fungicidal titres of amphotericin B are rarely identified in human tissues, and the bioavailability in infected tissue is often lower than that necessary for adequate responses.[33-35] Poor tissue bioavailability and toxic reactions associated with systemic administration of amphotericin B have resulted in investigations aimed at delivering amphotericin B directly to the target organ, in particular aerosolized and intracavitary instillations.[31]

This case report demonstrates that amphotericin B added to bone cement will result in diffusion of the drug to blood and local wound fluid. Although our patient demonstrated initial favourable clinical improvement, a secondary bacterial joint infection unfortunately developed and required further medical and surgical intervention. Measured serum and local drug concentrations were similar to those reported after typical systemic amphotericin B doses. Low drug concentrations in blood and wound fluid were not unexpected, considering the high degree of protein binding for this drug. It is also likely that the cement retained a significant portion of the amphotericin B. This has been described by investigators using antimicrobial-impregnated cement in patients undergoing hip arthroplasty and may explain why drug concentrations in blood declined rapidly despite the administration of a dose that was at least 10-fold that typically administered.[6] Similar to previous reports describing biphasic antibiotic release characteristics,[6] we measured the highest wound drainage drug concentrations during the initial 2 days after implantation. Local concentrations then dropped sharply and appeared to plateau at about 3 days, and we were able to detect stable amphotericin B concentrations for 5 days postoperatively. However, we were unable to obtain specimens be-
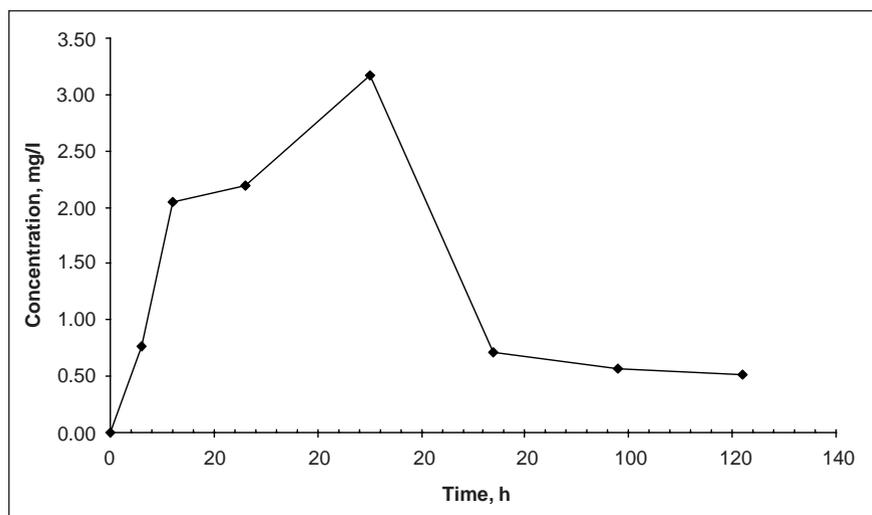
FIG. 2. Amphotericin B concentrations in wound drainage.

yond this period to determine the duration of this phenomenon.

It was interesting to note that the drug concentrations obtained in blood and wound fluid were above the MIC of *C. albicans* in our patient (MIC 0.12 mg/L). Although a standardized test has been produced by the National Committee for Clinical Laboratory Standards, studies correlating the data between in vitro antifungal susceptibility and clinical outcome are limited, and thus only tentative break points are set by the organization.[1,36] Fungal isolates with an MIC greater than 1 mg/L to amphotericin B are considered to be susceptible to this drug.

Our patient did not appear to experience any of the drug-related side effects that are commonly observed with amphotericin B, despite the similar blood concentrations. He did not complain of any of the typical infusion-related side effects and there was no evidence of diminished renal function during hospitalization. These observations suggest that local instillation of high doses of amphotericin B is safe. However, further investigation into the use of amphotericin B-impregnated cement is warranted to confirm therapeutic efficacy and establish an appropriate regimen.

References

1. National Committee for Clinical Laboratory Standards: *Reference method for broth dilution antifungal susceptibility testing of yeasts.* Proposed Standard M27-P. Villanova (PA): the Committee; 1992.

2. Masri BA, Duncan CP, Jewesson PJ, Ngui-Yen J, Smith J. Streptomycin-loaded bone cement in the treatment of tuberculous osteomyelitis: a new method of delivery. *Can J Surg* 1995;38:64-8.

3. Younger AS, Duncan CP, Masri BA, McGraw RW. The outcome of two-stage arthroplasty using a custom-made interval spacer to treat the infected hip. *J Arthroplasty* 1997;12:615-23.

4. Duncan CP, Beauchamp C. A temporary antibiotic-loaded joint replacement system for management of complex infections involving the hip. *Orthop Clin North Am* 1993;24:751-9.

5. Younger AS, Duncan CP, Masri BA. Treatment of infection associated with segmental bone loss in the proximal part of the femur in two stages with use of an antibiotic-loaded interval prosthesis. *J Bone Joint Surg [Am]* 1998;80:60-9.

6. Winnger DA, Fass RJ. Antibiotic-impregnated cement and beads for orthopedic infections. *Antimicrob Agents Chemother* 1996;40:2675-9.

7. Wasan KM, Brazeau GA, Keyhani A, Hayman AC, Lopez-Berestein G. Roles of liposome composition and temperature in distribution of amphotericin B in serum lipoproteins. *Antimicrob Agents Chemother* 1993;37:246-50.

8. Jonnalagadda S, Veerabagu MP, Rakela J, Kusne S, Randhawa P, Rabinovitz M. *Candida albicans* osteomyelitis in a liver transplant recipient: a case report and review of the literature. *Transplantation* 1996;62:1182-4.

9. Lafont A, Olive A, Gelman M, Roca-Burniols J, Cots R, Carbonell J. *Candida albicans* spondylodiscitis and vertebral osteomyelitis in patients with intravenous heroin drug addiction. Report of 3 new cases. *J Rheumatol* 1994;21:953-6.

10. Mullins RF, Still JM Jr, Savage J, Davis JB, Law EJ. Osteomyelitis of the spine in a burn patient due to *Candida albicans.* *Burns* 1993;19:174-6.

11. Corso FA, Shaul DB, Wolfe BM. Spinal osteomyelitis after TPN catheter-induced septicemia. *JPEN J Parenter Enteral Nutr* 1995;19:291-5.

12. Cooper P, Schofield B, Lennox DW, Ebert-Smith T. *Candida albicans* osteomyelitis in a patient with avascular necrosis of the hip. *Orthopedics* 1991;14:352-5.

13. Edelstein H, McCabe R. *Candida albicans* septic arthritis and osteomyelitis of the sternoclavicular joint in a patient with human immunodeficiency virus infection. *J Rheumatol* 1991;18:110-1.

14. Ackerman G, Bayley JC. *Candida albicans* osteomyelitis in a vertebral body previously infected with *Serratia marcescens.* *Spine* 1990;15:1362-3.

15. Levine M, Rehm SJ, Wilde AH. Infection with *Candida albicans* of a total knee arthroplasty. Case report and review of the literature. *Clin Orthop* 1988;226:235-9.

16. Neale TJ, Muir JC, Mills H, Horne JG, Jones MR. *Candida albicans* vertebral osteomyelitis in chronic renal failure. *Postgrad Med J* 1987;63:695-8.

17. Shaikh BS, Appelbaum PC, Aber RC. Vertebral disc space infection and osteomyelitis due to *Candida albicans* in a patient with acute myelomonocytic leukemia. *Cancer* 1980;45:1025-8.

18. Lertratanakul Y, Glassford GH, Rubinstein HM. Arthritis and osteomyelitis due to *Candida albicans:* a case report. *J Rheumatol* 1977;4:317-20.

19. Thomas FE Jr. Martin CE, Fisher RD, Alford RH. *Candida albicans* infection of sternum and costal cartilages: combined operative treatment and drug therapy and 5-fluorocytosine. *Ann Thorac Surg* 1977;23:163-6.

20. Flanagan PG, Barnes RA. Hazards of inadequate fluconazole dosage to treat deep-seated or systemic *Candida albicans* infection. *J Infect* 1997;35:295-7.

21. Arranz-Caso JA, Lopez-Pizarro VM, Gomez-Herruz P, Garcia-Altozano J, Martinez-Martinez J. *Candida albicans* osteomyelitis of the zygomatic bone. A distinctive case with a possible peculiar mechanism of infection and therapeutic failure with fluconazole. *Diag Microbiol Infect Dis* 1996;24:161-4.

22. Dan M, Priel I. Failure of fluconazole therapy for sternal osteomyelitis due to *Candida albicans. Clin Infect Dis* 1994;18:126-7.

23. Tang C. Successful treatment of *Candida albicans* osteomyelitis with fluconazole. *J Infect* 1993;26:89-92.

24. Bannatyne RM, Clarke HM. Ketoconazole in the treatment of osteomyelitis due to *Candida albicans. Can J Surg* 1989;32:201-2.

25. Dijkmans BA, Koolen MI, Mouton RP, Falke TH, van den Broek PJ, van der Meer JW. Hematogenous *Candida* vertebral osteomyelitis treated with ketoconazole. *Infection* 1982;10:290-2.

26. Buchholz HW, Engelbrecht H. Ueber die Depotwirkung einiger Antibiotica bei Vermischung mit dem Kinstharz Palacos. *Chirurg* 1970;41:511-5.

27. Henry SL, Galloway KP. Local antibacterial therapy for the management of orthopedic infections. Pharmacokinetic considerations. *Clin Pharmacokinet* 1995;29:36-45.

28. Fish DN, Hoffman HM, Danziger LH. Antibiotic-impregnated cement use in U.S. hospitals. *Am J Hosp Pharm* 1992;49:2469-74.

29. Gallis HA, Drew RH, Pickard WW. Amphotericin B: 20 years of clinical experience. *Rev Infect Dis* 1990;12:308-29.

30. Hay RJ. Antifungal drugs. *Q J Med* 1995;88:681-4.

31. Schmitt HJ. New methods of delivery of amphotericin B. *Clin Infect Dis* 1993;17 (Suppl 2):S501-6.

32. Nagata MP, Gentry CA, Hampton EM. Is there a therapeutic or pharmacokinetic rationale for amphotericin B dosing in systemic *Candida* infections? *Ann Pharmacother* 1999;30:811-8.

33. Powderly WG, Kobayashi GS, Herzig GP, Medoff G. Amphotericin B resistant yeast infection in severely immunocompromised patients. *Am J Med* 1988;84:826-32.

34. Collette N, van der Auwera P, Lopez AP, Heymans C, Meunier F. Tissue concentrations and bioactivity of amphotericin B in cancer patients treated with amphotericine B-deoxycholate. *Antimicrob Agents Chemother* 1989;33:362-8.

35. Christiansen KJ, Bernard EM, Gold JW, Armstrong D. Distribution and activity of amphotericin B in humans. *J Infect Dis* 1988;152:1037-43.

36. Ghannoum MA. Is antifungal susceptibility testing useful in guiding fluconazole therapy? *Clin Infect Dis* 1996;22(suppl 2):S161-5.