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Case Report

Successful Treatment of *Candida Albicans*–Infected Total Hip Prosthesis With Staged Procedure Using an Antifungal-Loaded Cement Spacer

Jenneke J. Deelstra, MD,*† Danielle Neut, PhD,*† and Paul C. Jutte, MD, PhD*

Abstract: We present a rare case of an immunocompetent host who developed a *Candida albicans*–infected total hip prosthesis. The infection could not be eradicated with debridement and extensive antifungal therapy. Our patient first underwent a resection of the proximal femur and local treatment with gentamicin-loaded cement beads. In a second procedure, a handmade cement spacer impregnated with voriconazole, amphotericin B, and vancomycin was placed. After 3 months of additional systemic antibiotic therapy, the patient remained afebrile, and a tumor prosthesis was placed. Six years postoperatively, she is doing well, walking with a small limp and no signs of recurrent infection. This is the first report on elution of voriconazole and amphotericin B from bone cement delivered at clinically significant concentrations for at least 72 hours.
Keywords: revision hip arthroplasty, joint infections, fungal infection, bone cement, hip spacer.

Periprosthetic joint infections are one of the most dreaded and complex complications of total joint arthroplasty [1]. Periprosthetic infections with fungi, although rare, represent a therapeutic challenge for which clear guidelines have not yet been established [2]. With few reported cases and the variety of treatment regimens used, no single, definite protocol has emerged for the treatment of these infections. Most experience to treat fungal joint infections is with intravenous systemic drug therapy [3]. Amphotericin B and fluconazole are regarded to be the drugs of choice for systemic administration in patients who have *Candida* infections. However, amphotericin B is one of the most toxic drugs; side effects include immediate infusion-related reactions of hyperpyrexia, severe malaise and hypotension, renal failure, anemia, hypokalemia, and occasional leucopenia and thrombocytopenia [4]. Local antifungal administration can be used to achieve much higher concentration (up to 1000-fold) than what systemic antifungals can achieve, without the systemic side effects.

Most patients require removal of the components and resection arthroplasty to cure a periprosthetic joint infection [5]. A 2-stage revision for infected totally replaced hip joints may involve a temporary spacer impregnated with antibiotics allowing elution of antibiotics directly into the infected tissue bed, filling the dead space, maintaining soft-tissue length, and allowing limited walking before placing the new prosthesis [6]. The utility of antibiotic-impregnated cement spacers for bacterial periprosthetic joint infections was first reported around the 1990s [7]. However, little is known about cement depot delivery of antifungal agents for treatment of periprosthetic infections, and literature shows a problem regarding the impregnation of bone cement with antifungal agents. In vitro studies of amphotericin B– and fluconazole impregnated cement have shown poor elution characteristics for both agents [5,8].

Our case describes an immunocompetent patient with *Candida albicans*–infected total hip prosthesis. The patient was successfully treated with a segmental resection, rigorous debridement, and a staged conversion using a

*From the *Department of Orthopedic Surgery, University Medical Center Groningen, The Netherlands; and †Department of Biomedical Engineering, University Medical Center Groningen, The Netherlands.*
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Reprint requests: Paul C. Jutte, MD, PhD, University Medical Center Groningen, Department of Orthopedic Surgery, PO Box 30.001, 9700 RB Groningen, The Netherlands.

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spacer, created with a long gamma nail coated with cement and impregnated with high contents of voriconazole, amphotericin B, and vancomycin. To our knowledge, there are no previous case reports of antifungal-impregnated cement spacers with proven clinical high local concentrations of these agents for at least 72 hours.

Case Report

A 73-year-old woman was admitted with a left femoral neck fracture type Garden 1 after a fall in October 2002. Initially, she received conservative treatment for this fracture. In April 2003, she returned to the hospital with increasing pain in her left leg. Plain x-rays showed a femoral head necrosis, and the decision was made to place a total hip prosthesis. During the reposition maneuver, a mid-shaft femur fracture occurred, which was managed with a dynamic compression plate with 14 holes. She had persistent wound leakage after 10 days and elevated C-reactive protein (96 mg/L), so on suspicion of a periprosthetic joint infection, the patient was taken to the operating room for extensive debridement and deep cultures. The wound cultures showed coagulase-negative staphylococci sensitive for vancomycin and rifampicin. She received these antibiotics intravenously, and after 6 weeks of treatment, she was clinically stable and discharged from the hospital with a non–weight-bearing regime for 3 months and a full weight-bearing regime after that period.

Six months later, she returned to the hospital with a plate fracture, probably related to a fall, and a revision osteosynthesis was planned. During the procedure, 4 tissue cultures were taken from the fracture side, the plate was revised, and allograft bone was placed. One of the cultures was positive for *C albicans*. In consultation with the microbiologist, this was considered contamination of the culture and was not targeted with antibiotics. Another 6 months later, she fractured her proximal femur and the dynamic compression plate again while walking with full weight bearing. Infection pseudoarthrosis was suspected, and it was decided to remove the implant and obtain 6 cultures. Gentamicin-loaded cement beads were placed to fill the dead space, and traction was given to keep soft-tissue length. It was felt necessary to exactly establish the kind of infection before a definitive treatment plan could be made. Of 6 cultures, 4 were positive for *C albicans* and coagulase-negative staphylococci. Systemic fluconazole as well as vancomycin was given. It was a difficult nursing situation and decubitus started to develop. In close collaboration with a microbiologist, a pharmacist, and local and foreign experts new management was decided.

A second, more extensive debridement was done, the acetabular component was removed, and a cement spacer was created by using a long gamma nail (Stryker, Mahwah, NJ) coated with 4 batches of Palacos RG bone cement (Heraeus, Wehrheim, Germany) (Fig. 1). We incorporated powdered antibiotic (500 mg gentamicin and 1000 mg vancomycin) and powdered antifungal (1000 mg voriconazole and 250 mg amphotericin B) into 40 g of polymethyl methacrylate (PMMA) bone cement. Consequently, the total antimicrobial content was approximately 7% wt/wt.

Once the cement became sufficiently doughy, it was hand-molded around the nail, and a cement head was clayed manually. The spacer was stable, and it allowed a good range of motion. Rotational stability was provided by locking the nail with the distal screw. Serum and drain fluid levels for voriconazole and amphotericin B were determined 24, 48, and 72 hours after surgery (see Table). The direct postoperative course was unremarkable, with nice wound healing. Our patient's previous left leg pain decreased dramatically. Five weeks after the initial spacer placement, our patient was given oral suppressive treatment with fluconazole and was discharged, weight bearing as tolerated, to a nursing home. At the 3 months of follow-up, the patient remained clinically stable, and laboratory findings were normal. She was able to transfer short distances without pain and practice her muscles. The spacer was removed, and a tumor prosthesis was placed (GMRS; Stryker), and the cup (SHP; Biomet Orthopedics, Warsaw, IN) was fixed with a full dose of Simplex P bone cement (Stryker), hand-mixed with voriconazole (Fig. 1). Tissue cultures were negative, and there were no further postoperative complications. Six years after placement of the tumor prosthesis, our patient is still satisfied and mobilizing fully weight bearing with 1 cane, blood parameters for infection remain normal, and radiographs show no evidence of loosening or infection.

Discussion

Standard spacers and commercial devices such as the PROSThesis of Antibiotic Loaded Acrylic Cement (PROSTALAC; DePuy, Leeds, United Kingdom) have different sizes of the femoral component to fulfill patient needs [9]. For cases with severe femoral bone loss, there are not many options available though. Rodriguez and Ziran [10] reported the case of a handmade antibiotic-coated gamma nail as a temporary spacer during staged reconstruction of an infected proximal femur nonunion. They recognized using the gamma nail as a cost-effective alternative for commercially available, prefabricated spacers. Besides filling the dead space and preventing limb shortening, our spacer should eradicate the fungal infection. There is no consensus regarding the type and dose of antifungal agents that can be used to mix with bone cement to treat periprosthetic joint infection. Pharmacokinetics, safety, published reports, drug interactions, and isolate susceptibility must be considered when selecting a therapy [11]. Furthermore, the drugs should be heat-stable and easy to dissolve in water. Theoretically, amphotericin B seems to be an ideal agent

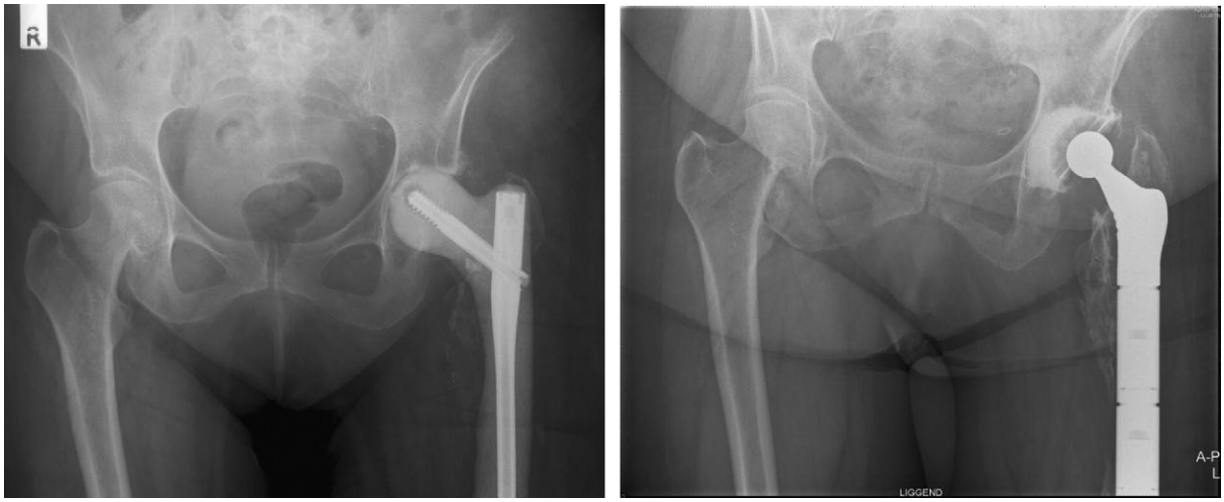

Fig. 1. X-ray of the hip. Left: AP image of the custom-made spacer impregnated with voriconazole, amphotericin B, vancomycin, and gentamicin; Right: anteroposterior image of the definite GMRS prosthesis.

to be mixed with bone cement because of its heat stability, broad antimicrobial spectrum, and availability in powder form [2,12]. In vitro research, however, showed very low elution of amphotericin B from Simplex bone cement [8]. Marra et al [4] performed an in vivo study of the elution of amphotericin B from Palacos bone cement (Heraeus, Werheim, Germany). They detected a maximum wound fluid concentration of 3.2 mg/L and an undetectable serum concentration 50 hours postimplantation. The concentrations of antifungal agents mixed with the bone cement powder in both studies were subsequently lower compared with our impregnated cement. In a large, multicenter study, Kullberg et al [13] state that voriconazole is as effective as the commonly used strategy of amphotericin B in nonneutropenic patients for the treatment of candidemia, including *C albicans*. In a recent report, Rouse et al [14] added voriconazole to Simplex cement and gained a concentration above the minimal inhibitory concentrations (MIC) 90 value for *C albicans* in the continuous flow chamber experiments. Their experiment, however, was not performed in a clinical situation.

In our case, the elution of both voriconazole and amphotericin B was good; this report documents clinically detectable elution of these agents from bone cement for at least 72 hours. Moreover, all the elution levels of the antifungals were well above the MIC levels determined for *C albicans* in accordance with the National Committee for Clinical Laboratory Standards M27-A2 (see Table). The higher the antimicrobial content in bone cement, the more porous the cement matrix will become. Because porosity determines antimicrobial release [15], our detectable elution can be explained with the high content of antimicrobials. This content was chosen based on expert opinion and scarce literature, susceptibility of the *Candida* isolate, elution profiles of Palacos cement for other antimicrobials, and safety levels of the different drugs we used. However, with the increase in the amount of antimicrobials incorporated, the hardening time of the cement becomes considerably reduced [16], and it requires some skills to prepare spacers within the time available. Furthermore, the acrylic cement becomes brittle when the content of antimicrobials becomes too high, and consequently, the spacer will lack sufficient strength for our load-bearing application.

We believe that the combination of systemic and local antifungals mixed in bone cement is a good solution to treat severe fungal joint infections, as is local application of vancomycin to treat and/or prevent bacterial infections [3]. As a result of our experience with this patient, we suggest close cooperation between various disciplines to ensure proper management and a successful outcome after a rare type of periprosthetic infection.

Table. Elution Levels of Amphotericin B and Voriconazole 24, 48, and 72 Hours After Spacer Implantation

	Drain (μg/mL)			Serum (μg/mL)			MIC (μg/mL)		
Antifungals	24 h	48 h	72 h	24 h	48 h	72 h	Range	MIC 50	MIC 90
Amphotericin B	0.6	1.2	1.1	0.1	0.1	0.1	0.06-1.0	0.25	1.0
Voriconazole	5.0	5.0	5.0	0.389	0.442	0.571	0.015-0.03	0.01	0.03

* Minimal inhibitory concentrations determined for *C albicans* in accordance with the National Committee for Clinical Laboratory Standards M27-A2.

In addition, our patient had no risk factors for a fungal infection. *Candida* infection should be considered in all cases, even in immunocompetent hosts, and not be regarded as "contamination".

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