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Joint fluid concentrations of amphotericin B after local application with calcium sulphate—report of 2 cases

LARA POZZI,[1] MICHEL SCHLÄPPI,[1] FRANÇOISE LIVIO,[2] SAMUEL BLATTER,[1] YVONNE ACHERMANN[3,4] and PETER WAHL[1]

[1]Division of Orthopaedics and Traumatology, Cantonal Hospital Winterthur, Winterthur; [2]Service of Clinical Pharmacology, Lausanne University Hospital and University of Lausanne, Lausanne; [3]Division of Infectious Diseases and Hospital Hygiene, University Hospital Zurich; and [4]Internal Medicine, Hospital Zollikerberg, Zurich, Switzerland

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Fungal periprosthetic joint infections (PJI) are difficult to treat, due to important biofilm formation and limited local penetration of systemically administered antifungals. Calcium sulphate ($CaSO_4$) might be a promising carrier to increase local concentration of antifungals. We hypothesized that local amphotericin B release from $CaSO_4$ is high enough to significantly contribute to treatment of fungal PJI. We report joint fluid and serum concentrations of amphotericin B after local application with $CaSO_4$ as an implanted resorbable carrier material as adjunct to standard surgical and systemic antifungal treatment in two cases of PJI with *Candida* spp. Maximal joint fluid amphotericin B concentration was 14.01 mg/L 5 days after the second local administration of liposomal amphotericin in Case One and 25.77 mg/L 14 days after the second local administration in Case Two. Concentrations higher than minimal inhibitory concentrations (MIC) could be measured for 21 days and 17 days after local administration in Case One and Two, respectively. In Case Two, serum concentration of amphotericin B was <0.01 mg/L 3 days after local administration of 450 mg liposomal amphotericin B. No local or systemic adverse reaction was observed. Fungal PJI was successfully eradicated in both cases with a follow-up of 12 months in Case One and 20 months in Case Two. Application of amphotericin B-loaded $CaSO_4$ was associated with joint fluid concentrations higher than minimal inhibitory concentrations for *Candida* spp. for approximately 3 weeks, with the advantage that the carrier material dissolves spontaneously and does not require secondary removal. Relapse of fungal infections did not occur in these two patients.

Key words: Periprosthetic joint infection; fungi; amphotericin B; joint fluid; calcium sulphate.

Peter Wahl, Division of Orthopaedics and Traumatology, Cantonal Hospital Winterthur, Winterthur, Switzerland. e-mail: peter.wahl@ksw.ch

Fungal periprosthetic joint infections (PJI) are difficult to treat [1]. Treatment success rates are lower than in case of bacterial infection [1–4]. In fact, fungi are important biofilm formers [5,6] and penetration of systemically administered antifungals may be insufficient at the site of infection [7,8]. Therefore, antifungals may be applied locally to reach high concentration at the site of infection. However, release from polymethylmethacrylate (PMMA) bone cement, the most commonly used carrier material in orthopaedic and trauma surgery, proved to be insufficient [9–11]. *In vitro* release of amphotericin B from calcium sulphate ($CaSO_4$) has already been described [12], but to the best of our knowledge, there is no *in vivo* data. $CaSO_4$ has the advantage of dissolving over a period of weeks to months, thus entirely releasing any added drugs and requiring no surgical removal [13–15]. In addition, it does not cause a relevant third-body wear of joint replacement components, as it is a relatively soft material, particularly compared to PMMA [16]. We present observations from two patients with fungal PJI treated with local liposomal amphotericin B with $CaSO_4$ as an implanted resorbable carrier in addition to other systemically administered antifungals. These were unique occasions of adequate joint fluid sampling without interference from concomitant systemic administration of the same drug. Amphotericin B local concentrations were higher than *Candida* spp. minimal

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inhibitory concentrations (MIC) for approximately 3 weeks.

METHODS

Case one

A 73-year-old, morbidly obese (148 kg, BMI 47 kg/m^2) male with a history of diabetes and atrial fibrillation, underwent cemented total right knee arthroplasty (TKA). After two-stage revision for PJI with *Streptococcus dysgalactiae*, PJI with *Candida glabrata* was documented by two separate joint aspirations. Considering the causative microorganism and delay of 36 months since the index operation, another two-staged revision with short interval was performed with an articulated PMMA spacer. All six tissue biopsies at first stage confirmed growth of *Candida glabrata*. Antiinfectious treatment was enhanced by local application of $CaSO_4$ (50 mL Osteoset; Wright Medical, Arlington, TN, USA) loaded with liposomal amphotericin B (300 mg AmBisome; Gilead Sciences, Zug, Switzerland) at both stages. Radiographs are summarized in Fig. 1. Joint fluid concentrations documented by aspiration were significantly higher than MIC of amphotericin B for *Candida glabrata* (0.5–1 mg/L) 21 days after the first local administration of 300 mg amphotericin B and 12 days after the second administration (Fig. 2). All four tissue

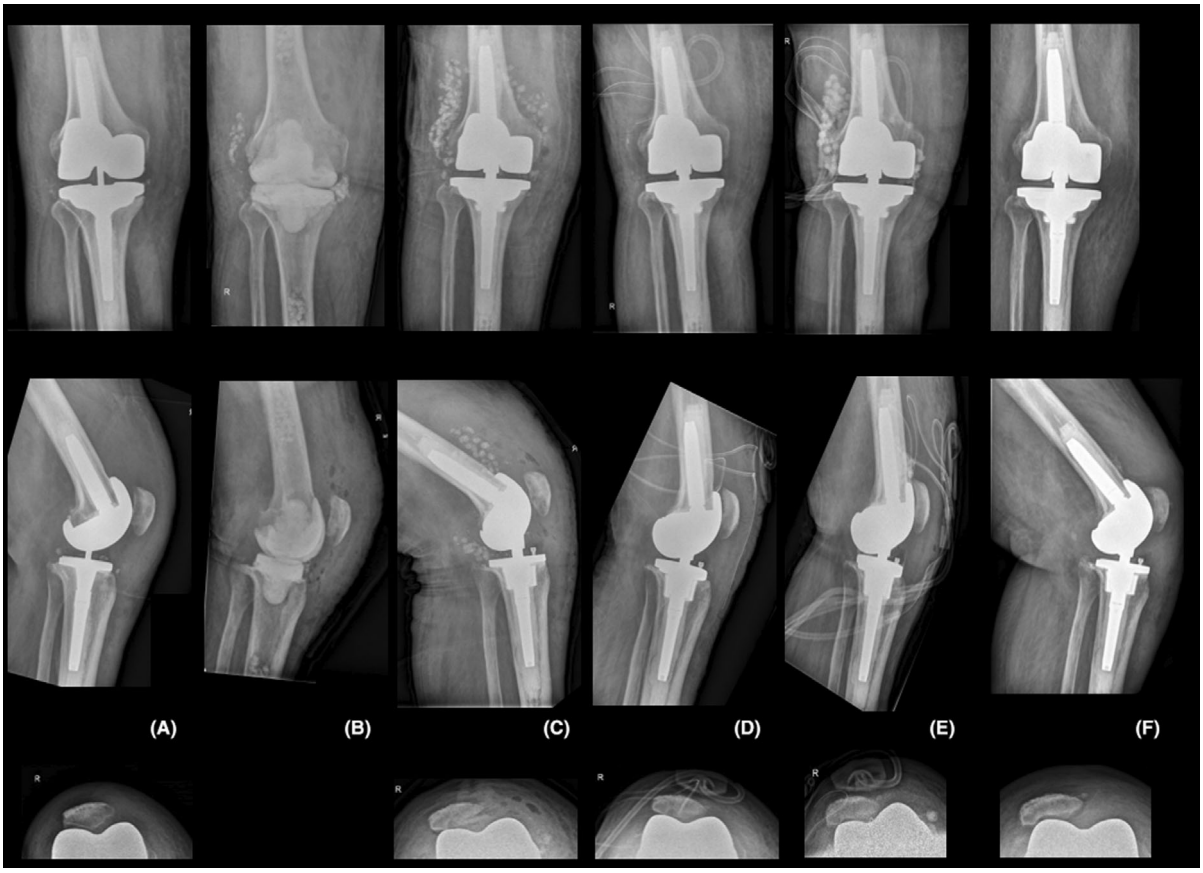

Fig. 1. Anteroposterior (upper row), lateral (middle row) as well as axial (lower row) radiographs of the affected knee of Case One. (A) Situation after re-implantation of a semiconstrained TKA as part of a two-staged revision due to PJI with streptococcus dysgalactiae. (B) After removal of the TKA as part of a two-staged revision due to PJI with *Candida glabrata*. An articulated, gentamicin- and vancomycin-loaded PMMA spacer was implanted. $CaSO_4$ loaded with amphotericin B was added. The pellets are visible intramedullary as well as within the joint cavity. (C) Situation after the second stage with re-implantation of a rotating hinge TKA with cemented stems and tibial cone with additional $CaSO_4$ loaded with amphotericin B added in the joint space. (D) Situation after revision 13 days after re-implantation due to persistent wound drainage, with exchange of the inlay and removal of the not yet resolved $CaSO_4$ pellets. (E) Situation after another revision with debridement and exchange of the inlay 27 days after the last revision due to late identification of *Corynebacterium tuberculostaericum* in subcultures from 3 out of 5 biopsies obtained at the last operation. The inlay was exchanged and $CaSO_4$ loaded with vancomycin (25 mL Osteoset with 2 g vancomycin) and amphotericin B (25 mL Osteoset with 150 mg liposomal amphotericin B) was locally added again. (F) Follow-up 2 months after the last revision. Note complete dissolution of the $CaSO_4$ pellets.

biopsies sampled at the second stage were sterile. Thirteen days after reimplantation, debridement with removal of the $CaSO_4$ was performed due to persistent wound drainage. Later wound healing was uneventful. Caspofungin (Cancidas, Merck Sharp & Dome, Lucerne, Switzerland) was used as systemic antimycotic treatment with 12 weeks duration, it was started on the day of the first stage revision.

Later, the subcultures of the thioglycolate broths identified *Corynebacterium tuberculostaericum* in three of the five tissue biopsies sampled at the last debridement as well as in on one of the four biopsies sampled at the second stage. Thus, another debridement with exchange of the inlay was performed 27 days after the last revision, adding $CaSO_4$ loaded with vancomycin (25 mL Osteoset with 2 g vancomycin Vancocin Teva Pharmaceuticals, Jona, Switzerland) and amphotericin B (25 mL Osteoset with 150 mg liposomal amphotericin B). Systemic antimicrobial treatment was expanded with daptomycin (Cubicin; Merck Sharp & Dome, Lucerne, Switzerland), administered parenterally for 8 weeks, followed by linezolid orally for 4 weeks.

At the latest follow-up, one year after the last revision, there were no signs for persistent infection and range of motion of the affected knee in flexion/extension was 120/0/0°.

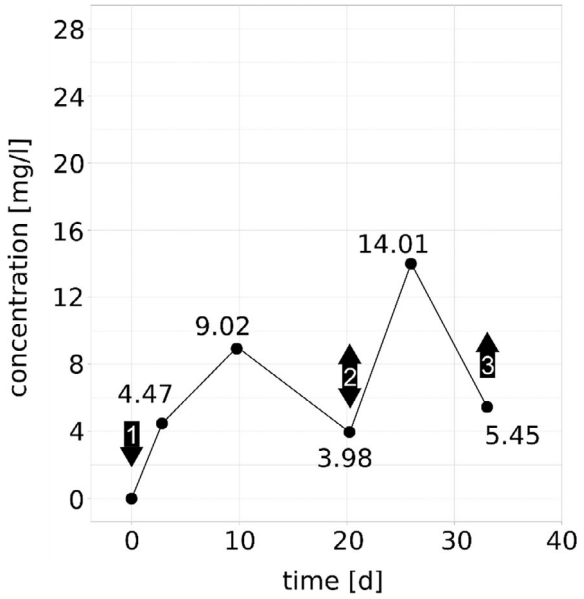

Fig. 2. Joint fluid concentrations of amphotericin B as observed in Case One. The individual points correspond to individual joint aspirations. The downwards arrow on Day 0 marks the first operation with implantation of $CaSO_4$ (50 mL Osteoset; Wright Medical) loaded with liposomal amphotericin B (300 mg AmBisome; Gilead Sciences). The double-ended arrow on Day 21 marks the second stage with removal of the PMMA spacer, component re-implantation and implantation of new $CaSO_4$ pellets loaded with amphotericin B (same quantities) after debridement of the residues from the first operation. Sampling ended as debridement with removal of the $CaSO_4$ residues was performed due to persistent wound oozing (upwards arrow).

Case two

A 57-year-old, overweight (90 kg, BMI 29 kg/m^2) male had bilateral total hip arthroplasty (THA) performed sequentially 2 years after bilateral resection arthroplasty due to septic arthritis and necrosis of the femoral heads in the context of intravenous drug abuse. After four revisions due to persistent wound drainage, dislocation and PJI with *Escherichia coli*, joint fluid aspiration of the left hip showed growth of *Candida tropicalis*. Considering a delay of 8 weeks since the last revision, the complexity of the reconstruction and well-fixed components, debridement with replacement of the modular components was performed. Considering soft tissue defects and the previous *Escherichia coli* PJI, treatment was enhanced with local application of liposomal amphotericin B, vancomycin and ceftriaxone (125 mL Osteoset, 450 mg liposomal amphotericin B, 2 g vancomycin, 2 g ceftriaxone Rocephin, Roche Pharma, Basel, Switzerland). On the third postoperative day, serum concentration of amphotericin B was <0.01 mg/L (reference values for therapeutic trough concentrations: 0.03–1.00 mg/L) [17]. Seventeen days later, open reduction had to be performed due to dislocation of the dual mobility THA. During this operation, 50 mL Osteoset with 300 mg liposomal amphotericin B was applied locally again, after removal of the residual pellets. Radiographs are summarized in Fig. 3. Fluconazole and later capsofungin were chosen as systemic therapy for 3 and 2 weeks, respectively. Because the patient suffered instability and PJI of the contralateral hip as well, repeated joint fluid aspirations of both hips were performed. The joint fluid concentrations of amphotericin B were higher than MIC for *Candida tropicalis* (MIC 0.5 mg/L) 17 and 31 days after the first local administration of 450 mg and the second administration of 300 mg amphotericin B respectively. However, 59 days after the second local administration, concentration measured was lower than MIC (Fig. 4).

Later, the patient suffered recurrent bacterial haematogenous PJI after resuming intravenous drug abuse and resection arthroplasty of both hips had to be performed. However, no more *Candida* spp. could be identified in the final tissue samples.

Amphotericin B assay

After aspiration, joint fluid samples were filled in serum separator tubes and sent to the Institute of Clinical Chemistry of the University Hospital Zurich for the assays. The samples were not frozen. The concentration of amphotericin B was measured by liquid chromatography coupled to tandem mass spectrometry (LC–MS/MS), a method fully validated and accredited according to ISO 17025.

DISCUSSION

To the best of our knowledge, this is the first clinical report on amphotericin B joint fluid concentrations after local administration with $CaSO_4$ as an implanted resorbable carrier material. Concentrations higher than MIC were measured in joint fluid samples over a period of approximately 3 weeks

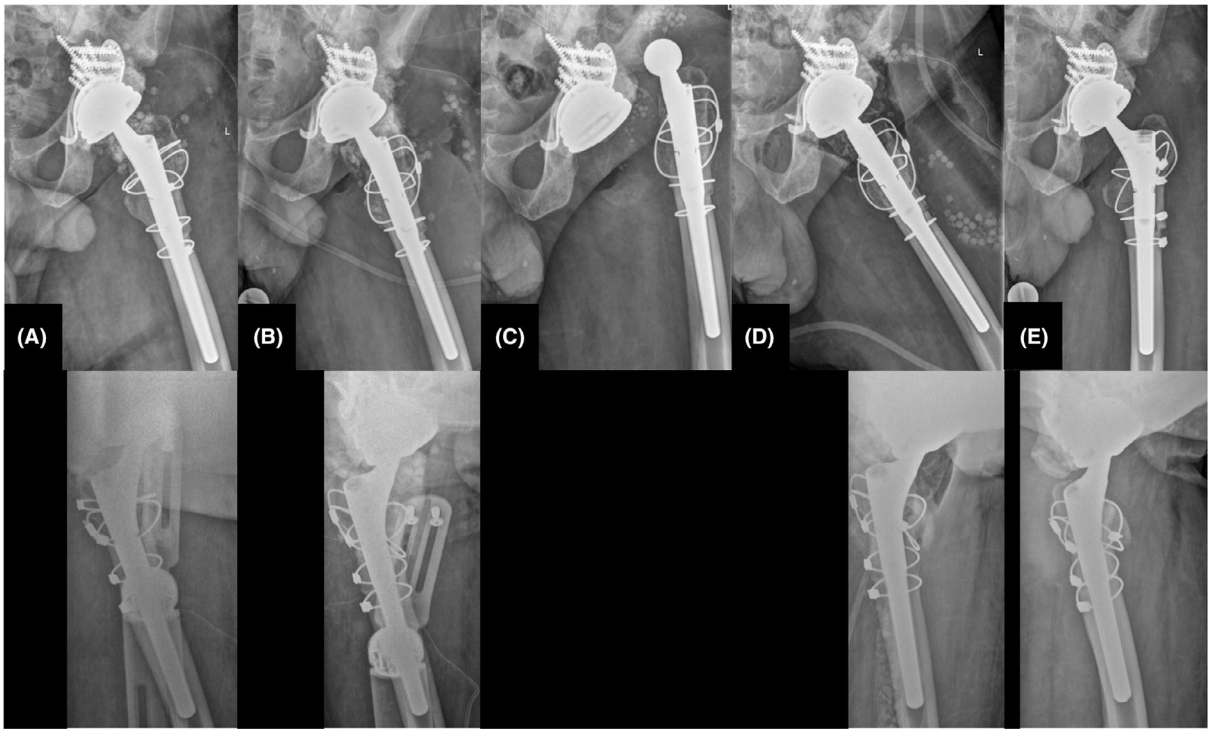

Fig. 3. Anteroposterior (upper row) and axial (lower row) radiographs of the left hip of Case two. (A) Situation before and (B) Situation right after revision with replacement of the modular components and application of $CaSO_4$ loaded with amphotericin B, vancomycin and ceftriaxone due to *Candida tropicalis* PJI developed within 4 weeks after treatment of *Escherichia coli* PJI. Note the periarticular, radio dense $CaSO_4$ pellets as well as on the axia views the metal strut that are part of the patient's abduction orthosis. (C) Anteroposterior radiograph of the dislocated THA 17 days after revision. No closed reduction of the dual mobility cup/head was possible, requiring open reduction. (D) Situation after open reduction and mesh tube (LARS; Corin, Buchs, Switzerland) reinforcement of the THA. After debridement, repeated application of $CaSO_4$ with amphotericin B was performed. (E) Follow-up 4 months after implantation of THA, 10 weeks after first revision and 8 weeks after the last implantation of $CaSO_4$ added with amphotericin B. not complete dissolution of the pellets.

after local administration in both cases, with concentrations as high as 25 mg/L. These local concentrations were much higher than serum concentrations commonly measured after systemic treatments (peak 1.5–3 mg/L, trough 0.03–1 mg/L) (Figs 2 and 4) [17–19]. Additionally, the measured concentrations were higher than ones needed for reduction in 50% of metabolic biofilm activity and most of the measured concentrations were higher than needed for reduction in 80% of metabolic biofilm activity for *Candida* spp. (0.29 and 7.89 mg/L respectively) [20]. The concentrations were also higher than reported after release from PMMA [9–11]. In Case Two, serum concentration was not detectable (<0.01 mg/L) 3 days after local application of 450 mg liposomal amphotericin B. There is a very low risk of systemic toxicity, as liposomal amphotericin B was administered locally on two occasions and the dosage was not higher than the daily recommended dosage for systemic treatment.

Amphotericin B is an intravenous antifungal agent that exerts its fungistatic and sometimes fungicidal activity by binding to ergosterol in the cytoplasmic membrane of the fungal cell [21]. Amphotericin B is characterized by a narrow therapeutic index. There are two distinct galenic forms of amphotericin B: the deoxycholate amphotericin B (Fungizone; Kohlpharma GmbH, Merzig, Germany) and the liposomal amphotericin B (AmBisome; Orifarm GmbH, Leverkusen, Germany). The liposomal form is less toxic, due to a gradual release of the antifungal agent from the liposomes. These two forms are not interchangeable, as their maximal recommended dosages and perfusion rates differ (Fungizone max 1.5 mg/kg/day infusion time 6 h, vs AmBisome max 6 mg/kg/day infusion time 2 h) [22]. Amphotericin B overdose can lead to hyperkalaemia, cardiac arrhythmia and multiorgan failure [21,23–26]. Cell lysis due to binding of amphotericin B to human cell membrane cholesterol in case of overexposure is the hypothesized mechanisms [21,27]. Fatal amphotericin B overdose have been reported, mainly in case of amphotericin B deoxycholate administration at the dosage

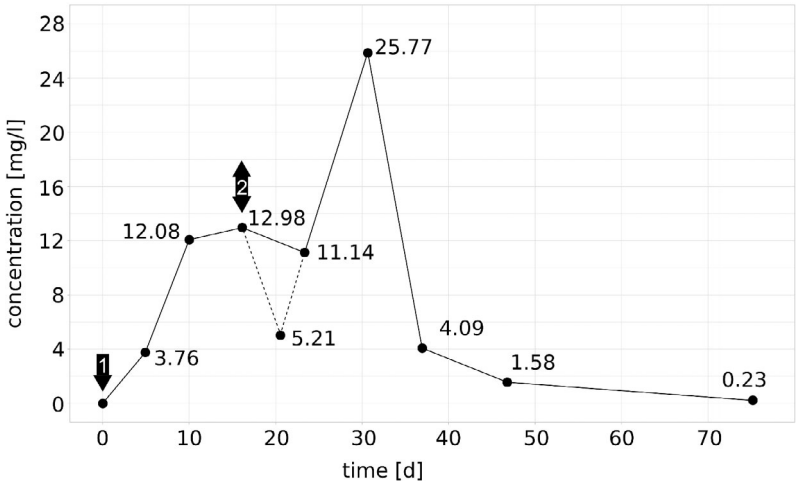

Fig. 4. Joint fluid concentrations of amphotericin B as observed in Case Two. The individual points correspond to individual joint aspirations. The downwards arrow on Day 0 marks the first septic revision due to *Candida tropicalis* with implantation of $CaSO_4$ (125 mL Osteoset; Wright Medical) loaded with liposomal amphotericin B (450 mg AmBisome; Gilead Sciences). The double-ended arrow on Day 17 marks the open reduction in the dislocated dual mobility THA with additional implantation of 50 mL of new $CaSO_4$ pellets loaded with 300 mg amphotericin B. the point at Day 21 connected with dotted lines corresponds to sampling from drain fluid and is potentially falsely low due to drug deposition along the tubing or displacement of the intraoperatively intra-articular placed tip of the drainage.

recommended for the liposomal form [23,24]. The release pharmacokinetics of liposomal amphotericin B administered off-label in $CaSO_4$ in a joint cavity have not been characterized. This observational study including two patients shows that a fraction of amphotericin B is released from the liposomes into the joint cavity over days and that it appears to be poorly absorbed systemically. Given the relatively high doses of amphotericin B administered in a limited space (joint cavity), the choice of the liposomal form seems safer than the deoxycholate. However, given the high local concentrations measured and the known toxicity of amphotericin B on cells, more data regarding safety are needed. These cases offered an exceptional occasion for documentation of joint fluid concentrations of locally applied antimicrobial drugs with an implanted resorbable carrier material. No systemic application or local release from additional PMMA interfered. One of the greatest limitations in understanding pharmacokinetics after local administration of antimicrobial drugs is sampling. Drains remove active drug from the site of infection and are thus counterproductive in case of local treatment. In addition, drains represent a potential source of superinfection, limiting the amount of time they can be left in place [28,29]. Joint aspirations are associated with pain, thus limiting sampling particularly during the early postoperative phase. The patients described accepted not only the treatment proposed but also the iterative joint aspirations.

Persistent wound drainage may be associated with implanted $CaSO_4$ [13]. However, a recently published review noted that this complication affects only 4% of the cases [30]. Optimal management remains a matter of debate, but commonly removal of the material is recommended in case of prolonged wound oozing, as it was performed in Case One. As the implantation of $CaSO_4$ may induce hypercalcaemia [31,32], monitoring of calcium blood levels, elimination of risk factors for hypercalcaemia, particularly interfering drugs, and adaptation of the quantities of material implanted to renal impairment are recommended. In both patients, *Candida* spp. was eradicated with a combination of local and systemic antifungal treatment as well as adequate surgical debridement. They both had several risk factors for PJI, such as male sex, diabetes and obesity [33–37]. In both cases, septic revision was complicated with superinfection with a new microorganism. However, new microorganisms cause up to two-thirds of persistent PJI [38,39].

In conclusion, after local administration with $CaSO_4$ as an implanted resorbable carrier material, amphotericin B showed prolonged local concentrations that were higher than usual MIC for *Candida* spp. There were no systemic adverse drug reactions, in accordance with the finding of the non-detectable serum concentration in Case Two and considering total local dose applied. However, further data from a larger cohort of patients are necessary for proper understanding of release kinetics.

Considering the low incidence of fungal PJI [40–42], a multicentre study is needed to obtain a larger study population. The local and systemic concentrations described in this report may be an encouraging basis for application of this technique.

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CONFLICT OF INTEREST

The authors have no conflicts of interest to declare.

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