Avoiding Long Antibiotic Regimen For Diabetic Foot Osteomyelitis Through Application Of Bioresorbable Calcium Sulfate Beads Impregnated With Tobramycin And Vancomycin: A Case Presentation

Catherine Boucher DPM, **Marie-Christine Torchon** DPM and **Sébastien Hains** DPM

Abstract: Diabetic foot osteomyelitis, given the multiple comorbidities of the patient, antibiotic resistance and potential for recurrence, poses a significant challenge for the treating clinicians and patients alike. Combinations of intravenous (IV) and oral (PO) antibiotic therapy, with or without surgical debridement, are standard treatment methods. The authors present a case of osteomyelitis cured through the application of bioresorbable calcium sulfate beads impregnated with tobramycin and vancomycin as an adjunct to surgical bone debridement. Simple offloading using isolation in felt was employed. This approach led to the complete healing of the infection and ulcer without recurrence, thereby avoiding hospitalization and amputation.

Key words: *osteomyelitis, diabetic foot, diabetic foot infection, antibiotics, antibiotic therapy, antibiotic beads, tobramycin, vancomycin*

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Infections of the diabetic foot, including osteomyelitis, present challenges at multiple levels for both clinicians and affected patients. Over a third of diabetic patients develop foot wounds during their lifetime, more than half of which complicate into infections involving soft tissues and bones.[1] Diabetic foot osteomyelitis (DFO) results from peripheral neuropathy causing insensitivity in the foot, allowing wounds to progress painlessly and unfavourably without strict offloading and regular monitoring. Intermittent loading of the wound directs surface bacteria towards deeper tissues, promoting their propagation. They are associated with high morbidity, prolonged hospital stays, amputations and significant health-care costs. In Canada, 70% of non-traumatic lower limb amputations in hospitals are diabetes-related, with 85% preceded by plantar ulcers.[2,3] Therefore, these comorbid patients require comprehensive management when ulceration with osteomyelitis occurs. However, there currently exists no precise consensus on treatment selection.

Historically, aggressive surgery with amputation was considered the treatment of choice, often leading to poor wound healing, further ulcers and the need for more proximal amputations. Today, systemic antibiotic therapy is prioritized, whether

parenteral, enteral or a combination, although detailed consensus on preferred antibiotics, route of administration or optimal treatment duration remains lacking. Oral therapy has shown similar efficacy to IV treatment, with lower costs and fewer side effects, but limitations persist, particularly in patients with concurrent arterial and kidney diseases, complicating antibiotic and dose selection.[4]

Many clinicians are now considering the use of local antibiotics for DFO. These methods have been studied and applied in non-diabetic orthopedic surgery and trauma, primarily using non-resorbable polymethylmethacrylate (PMMA) beads and more recently resorbable calcium sulfate beads.[5,6] These treatments aim to prevent infection from orthopedic implants and/or treat osteomyelitis.

Local delivery of antibiotics via resorbable calcium sulfate beads is relevant in DFO treatment due to their advantages: potential reduction in required antibiotic quantities, ability to achieve high local concentrations, limited systemic absorption, minimal side effects and safety in relation to antibiotic resistance.[7,8] During the beads' degradation, additional antibiotic is released, which prolongs their action, preventing biofilm formation on their surface.[9] Beads can also act as filling agents following resection of the affected bone.

This clinical case presents a patient with diabetic foot ulcer complicated by contiguous osteomyelitis and recurrent bone exposure, ultimately cured with the assistance of tobramycin and vancomycin-impregnated calcium sulfate beads as adjuncts to surgical debridement.

Case Presentation

A 57-year-old man with a medical history of type II diabetes since 2010, treated with insulin, presented with peripheral neuropathy, atherosclerotic vascular disease (ASVD) with a right femoropopliteal bypass in 2019. He is an active smoker (35 pack-years) with chronic obstructive pulmonary disease, congestive heart failure, hypertension, dyslipidemia, multiple osteomyelitis episodes in the right foot (2013, 2014, 2016, 2017, 2019) leading to amputations (right 4th metatarsal head in 2014, right 3rd toe and 3rd metatarsal head in 2012) and benign prostatic hyperplasia. He has been followed at the University Podiatric Wound Care Clinic at Lanaudière's Hospital in Québec since 2016. His lower limb vascular status shows right ankle-brachial index (ABI) of 0.94 and left ABI of 0.84. It should be noted that in diabetic patients with ASVD, the ABI measurement has low diagnostic sensitivity due to frequent peripheral arterial calcification.[10] Auditory Doppler would be a more representative measure of arterial status. In his case, the right posterior tibial and dorsal pedis arteries are biphasic (Saint-Bonnet stage A) and left arteries are monophasic with systolic crest blunting (Saint-Bonnet stage CD).[11]

On May 15, 2023, the patient presented a wound under the 2nd right metatarsal, chronicized since March 2022 due to non-compliance with offloading and suboptimal hygiene exacerbated by his physical maintenance work as a hunting and fishing outfitter. The wound now exposed the metatarsal head with a communicating sinus to the 2nd right toe medially. Heat, swelling and significant erythema are noted at the 2nd toe, radiating to the forefoot, but without systemic involvement. The patient cannot specify how long his right foot has been in this condition, but a month earlier during a podiatry appointment, no signs of infection were noted around the wound measuring 2.5x1.3x0.2 cm under the 2nd metatarsal.

The patient has a history of 2nd metatarsal head osteomyelitis, noted in July 2022 and treated with piperacillin/tazobactam for only five days, as the patient refused longer IV treatment. A switch to oral trimethoprim/sulfamethoxazole (TMP/SMX) for six weeks was implemented at that time. Healing of the osteomyelitis was confirmed by the normalization of the C-reactive protein and disappearance of bone contact on examination, but the ulcer persisted.

A radiograph on May 15, 2023, showed signs of osteomyelitis, metaphyseal-diaphyseal osteolysis with eccentric cortical rupture of the 2nd metatarsal head and periosteal reaction at the base of the proximal phalanx (See Figure 1).

Figure 1: Dorsoplantar (DP) X ray of the right foot, May 15, 2023

A conservative surgical debridement with sterile saline water of the wound was performed to remove calluses causing pressure on the wound and dead tissue. The application of an absorbable dressing under the 2nd metatarsal wound and a 1/4-inch wick for the 2nd toe to be changed every two days was performed. The recommendation to wear a short pneumatic offloading boot at all times was reiterated, since the wound is on a weight-bearing surface and a prescription of amoxicillin/clavulanate PO for four weeks was started because of the wound infection. A deep wound pus culture at that time revealed infection with *Staphylococcus epidermidis* and complex *Enterobacter cloacae*, both resistant to penicillin, prompting a change in antibiotics to TMP-SMX PO for two weeks on June 2nd. Blood test results showed an increase in the C-reactive protein to 10.6 mg/L, but no increase in leukocytes.

At the follow-up on May 19, no improvement of the wounds or the infection was noted in the patient's condition (See Figures 2 & 3). Therefore, 10 absorbable calcium sulfate beads in a mixture of 10 mL of the beads with 3 mg of tobramycin and 1 g of vancomycin were applied to both wounds as a local antibiotic treatment. Non-adherent dressings were now recommended for dressing changes.

Figure 2: Wound under the head of the 2nd right metatarsal bone exposing the bone, May 19, 2023

Figure 3: Transfixing wound on the 2nd right toe with redness and swelling of the toe, May 19, 2023

Four days later, on May 26, the patient mentioned feeling a burning sensation in his foot as the only side effect of the beads. This was only one day after the application of the beads. On physical examination, signs of infection persisted without improvement of the wounds, but without systemic infection symptoms. The wound edge was macerated, with serous discharge soiling the dressing by 40%, which was the norm for the patient even well before beads application. The treatment plan was maintained.

On June 2, the 2nd metatarsal head was now mobile at the centre of the wound. At this time, a diabafoam (made of plastazote and poron) sole with an isolation under the 2nd metatarsal head was applied in the offloading boot. Knowing he would not comply with complete offloading in the boot, pieces of 10 mm felt covering the forefoot with isolation at the 2nd metatarsal head were provided to the patient for his work boots. Plain radiographs (See Figure 4) showed that the beads applied on May 19 were no longer visible.

Figure 4: DP X-ray of the right foot, June 2, 2023

Despite the continued evolution of his condition, the patient refused to be seen in Infectious Diseases or Orthopaedics. He also rejected recommendations of complete bed rest and IV antibiotic therapy.

On June 9, no improvement was noted in the patient's condition, therefore a better control of the infection source was needed. Under sterile protocol, the right 2nd metatarsal head was resected via the wound with a double-action bone cutter and rongeur. Subsequently, 15 Stimulan Rapid Cure® beads of the same tobramycin mixture with vancomycin were inserted into and around the osseous resection site. A non-adherent greasy dressing, to be changed in two days, was applied. In addition, a new 10 mm felt piece with an isolation under the 2nd metatarsal head was adhered to the dressing

directly on the foot. The patient was advised on the importance of wearing the felt sole and the offloading boot at all times. A plain X ray was taken to ensure proper bead placement and complete transverse resection of the 2nd metatarsal head (See Figure 5).

Figure 5: DP X-ray of the right foot with antibiotics beads

Figure 6: DP X-ray of the right foot, August 28,2023

At the four-day post-op follow-up, the patient reported no pain or other side effects but had not changed his dressing as recommended. He claimed to have worn the offloading boot at all times but still seemed to be 'working with it' and the felt sole. Significant improvement in wound size and appearance was noted. Now linear and measuring 1x0.4 cm, the wound showed no signs of infection.

During follow-ups from July to September 2023, the wound continued to shrink, and probe-to-bone disappeared. Plain X rays taken on August 28 showed the disappearance of antibiotic beads and bone remodeling distally to the diaphysis of the 2nd metatarsal (See Figure 6).

As of September 6, 2023, the wound under the 2nd metatarsal was completely healed. Offloading with diabafoam and a felt sole in his shoes was continued until a custom accommodative foot orthosis was provided on March 26, 2024. More than 12 months post-op, there was no recurrence of the ulcer or osteomyelitis under the right 2nd metatarsal (See Figures 7 & 8).

Figure 7: Healed wound under right foot, September 6, 2023

Figure 8: No recurrence of the wound, May 13, 2024

Discussion

Treating diabetic foot osteomyelitis (DFO) poses a significant challenge due to the increasing prevalence of antibiotic-resistant bacteria and poor antibiotic penetration into bone. It is a costly complication of diabetic foot ulcers for patients and health-care systems. Despite adequate surgical and medical treatment, the recurrence rate of DFO exceeds 40%, thereby increasing the risk of major amputation.[12,13] Most of these patients also suffer from peripheral arterial disease, which further limits the effectiveness of systemic antibiotic therapy.[14] Minimum inhibitory concentration (MIC), the lowest concentration of antibiotic that inhibits bacterial growth, plays a crucial role in selecting appropriate antibiotics and their mode of administration. While current systemic antibiotics generally achieve sufficient concentrations to reach the target MIC, the biofilm present in these infections significantly increases antibiotic tolerance, sometimes up to 1000-fold, rendering MIC alone insufficient for predicting treatment efficacy.[15] In the vast majority of cases, microorganisms involved in DFO are organized within biofilms.[16,17] Therefore, it is essential to treat with antibiotics that penetrate bone well and maintain activity against bacteria in reduced metabolic states typical of biofilms. Several in vitro studies have demonstrated the effectiveness of absorbable calcium sulfate beads against bacterial biofilms, supporting their use in this context. [18-22]

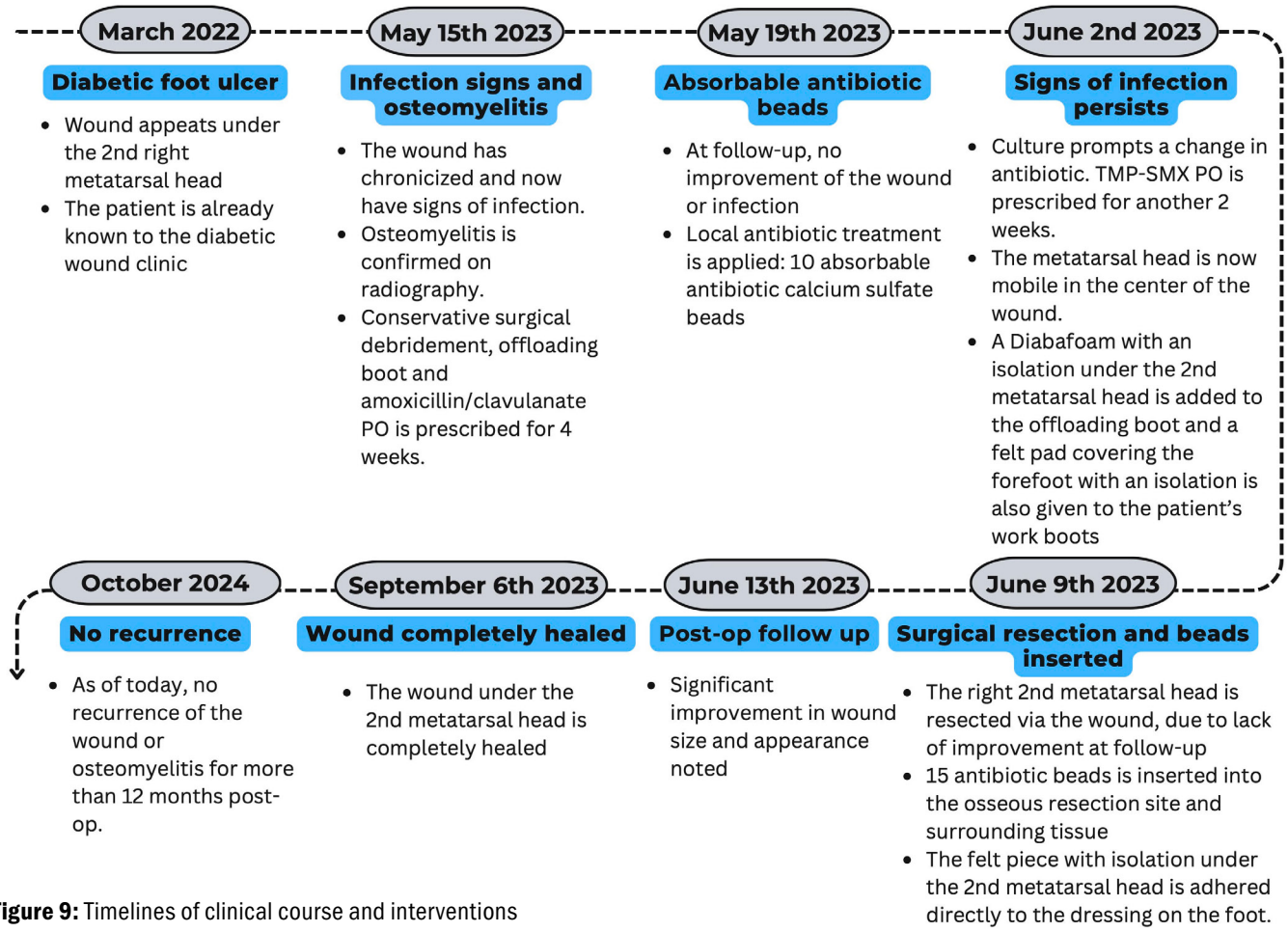

Figure 9: Timelines of clinical course and interventions

Furthermore, local administration of antibiotics via beads has been shown to achieve antibiotic concentrations more than 50 times higher than necessary to inhibit many bacteria found in intra-articular infections.[19,20]

Antibiotic-loaded bioresorbable calcium sulfate beads have been used for several years primarily for musculoskeletal infections (bone, soft tissue) with varying efficacy rates.[23,24] However, few published studies have evaluated their effectiveness for diabetic foot infections, most being case series with short-term follow-ups (less than three months).[25-29] A retrospective cohort study from 2024,[30] evaluating recurrence of DFO, found high rates of ulcer persistence and osteitis recurrence at 12 months among 45 patients who underwent surgical intervention with 10 mL calcium sulfate beads containing either vancomycin, tobramycin, gentamicin, linezolid or meropenem, along with a systemic antibiotic treatment. They noted increased wound drainage (in 28 patients) associated with ulcer persistence at three and six months as the main side effect. In contrast, our case study shows eradication of osteomyelitis without recurrence of osteomyelitis or ulcer at 12 months and no increase in exudate following beads application. We believe that resection of the infected 2nd metatarsal head with application of fewer mL of beads into the wound, along with pressure-relieving measures to prevent maceration, contributed to this outcome. A case series from 2021[31] demonstrated similar results. Out of 106 patients requiring surgical intervention for osteomyelitis, ranging from debridement to amputation, and receiving adjuvant bioresorbable beads with meropenem, colistin or vancomycin, 98 showed no recurrence of infection (follow-up up to 16 weeks). A recent review by Chatzipapas et al. (2021)[32] presents findings that differ from those of

our clinical case. The review analyzed 16 studies on local antibiotic delivery systems in DFO, including three randomized controlled trials (RCTs). The RCTs indicated that gentamicin-impregnated collagen sponges significantly improved clinical healing rates and slightly reduced hospitalization duration. However, retrospective studies on antibiotic-impregnated calcium sulfate beads showed non-significant improvements in healing parameters and no reduction in post-operative complications. Their results suggest that while certain local antibiotic delivery methods may offer benefits, the efficacy of antibiotic-loaded beads, particularly calcium sulfate-based ones, remains inconclusive. This contrasts with our findings of a successful healing using antibiotic loaded beads.

In 2011, Gauland used bioresorbable beads for lower limb osteomyelitis treatment without oral or IV antibiotics in 354 patients followed over five years.[13] Over 86% of patients showed wound healing without infection after surgical debridement and the application of antibiotic-impregnated bioresorbable beads. These results raise questions about the necessity of surgical debridement for local antibiotic application. This was evaluated in a retrospective cohort study of 50 patients, comparing the efficacy of calcium sulfate beads in healing osteomyelitis with and without surgical debridement.[31] Their results showed no significant difference in healing time between the two groups.

With increased use of bioresorbable calcium sulfate beads comes the discovery of associated complications. The main side effect in soft tissues appears to be increased wound drainage, promoting maceration in surrounding tissues and slowing healing time.[33] One explanation may be the more superficial placement in soft tissues for DFO compared to deeper placement in bones for knee orthopedic procedures. Using an adequate quantity of beads relative to wound size may help reduce drainage.[33] No systemic or local complications related to antibiotic beads use were noted in our patient's case.

To reduce recurrences and promote healing, it is crucial to manage underlying conditions predisposing patients to osteomyelitis episodes. This involves relieving pressure on the wound through offloading or surgically correcting foot deformities.[14] In this clinical case, isolation in 10mm felt ultimately allowed the patient to adhere to wound offloading, after attempts with a short pneumatic offloading boot that the patient could not properly wear. This technique, not tried earlier in the wound's evolution, was more suited to the patient's lifestyle and activities. We believe this contributed to osteomyelitis healing. Felt is an effective offloading modality, reducing pressure on the ulcer by 49%.[34] It requires regular changes, as its effectiveness diminishes to 32% after one week.[33]

Complications related to diabetic foot cost the Canadian health-care system over $150 million CAD annually.[5] The cost of Stimulan Rapid Cure® calcium sulfate bead treatment at time of publication is $870 CAD for 10 mL, and the cost of vancomycin and tobrsmycin is $48.23 CAD.[36] Less than a third of the mixture (beads and antibiotics) was applied to this patient for both combined applications. The total cost of this treatment would be $306.08 CAD, not including professional fees. By comparison, a six-week IV ertapenem antibiotic treatment in the province of Québec, excluding hospitalization costs and health-care professional fees, costs $2,337.75 CAD.[36]

IV treatment improves treatment adherence compared to oral treatment but entails significant costs and multiple complications. A study by Henry and Lundy[37] on systemic antibiotic treatment of hand osteomyelitis mentions an average cost of $482.85 USD for a patient taking oral antibiotics vs $21,646.90 USD for IV treatment in the United States. According to the OVIVA[4] study, switching from IV to oral antibiotics reduces hospitalization duration and associated costs. Although oral treatment seems an interesting option, it also has limitations such as longer antibiotic duration, increasing the risk of side effects, including *Clostridium difficile* diarrhea and antibiotic resistance. Thus, local antibiotic offers several advantages for DFO's treatment, both microbiologically and economically. The relevance

of this particular clinical case lies in the clinical healing of osteomyelitis and ulcers in 12 weeks without recurrence at 12 months. It is interesting to note that PO antibiotic treatment followed by administration of tobramycin and vancomycin-loaded calcium sulfate beads in the wound alone showed little improvement in the patient's clinical condition. Rather, complete healing was achieved with necrotic bone tissue resection combined with bead cavity filling and felt offloading. Additionally, the ease and speed of performing the procedure in an outpatient setting without hospitalization represent additional significant strengths of this clinical case. Indeed, like this patient, the diabetic population with DFO unfortunately does not always have the motivation or willingness for complete multi-day hospital-based care, given their history of multiple amputations and IV antibiotics. In this case, the 2022 DFU became chronic and infected primarily due to lack of adherence to offloading and regular wound care follow-ups. Given the patient's categorical refusal to consult with infectious disease or orthopaedic specialists, post-resection local antibiotic treatment with work-adapted offloading helped avoid hospitalization and amputation. However, this case presentation is limited by its single-patient design, which prevents generalization of the findings, and the lack of long-term comparative data to assess the broader efficacy of antibiotic beads in DFO.

Conclusion

Biodegradable calcium sulfate antibiotic beads impregnated with tobramycin and vancomycin have proven to be an effective adjunct local antibiotic therapy option in the treatment of diabetic foot osteomyelitis following surgical resection of infected bone. In the context of an integrated approach for patients without significant vascular compromise, they enable targeted treatment of infection combined with surgical offloading, resulting in durable healing without transfer lesions. These beads have demonstrated efficacy in resolving persistent infections, even alongside systemic antibiotic therapy and despite the patient's adamant refusal of infectious disease and orthopaedic consultations. This treatment modality is particularly beneficial in cases of polymicrobial osteomyelitis, offering flexibility to locally combine different antibiotics specific to isolated pathogens while achieving maximum concentrations with minimal or no systemic effects.

Moreover, this treatment is cost-effective and requires fewer resources compared to conventional intravenous antibiotic therapies. It is hoped that this article will increase awareness of this therapeutic approach, making it accessible to more patients and thereby reducing the human and financial burden associated with DFO, which often leads to hospitalizations and lower limb amputations. In conclusion, well-designed double-blind randomized controlled trials are needed to confirm whether the use of local antibiotics improves the healing of diabetic foot osteomyelitis and reduces recurrence rates.

Patient consent and Ethical Approval: Written informed consent was obtained from the patient for the publication of this case report, with the inclusion of clinical details and accompanying images. The authors have ensured that all identifying information has been removed to protect patient confidentiality. Authors were informed by Research Direction of Lanaudière's Hospital that ethical approval was not required for this case report, since it describes a single clinical case without experimental interventions.

Catherine Boucher DPM is in private practice and a third-year medical student at Université de Montréal, Québec, Canada

Marie-Christine Torchon DPM is Professor of Clinical Sciences Podiatric Medical Program, Université du Québec à Trois-Rivières, Québec, Canada

Sebastien Hains DPM is Professor of Clinical Sciences Podiatric Medical Program, Université du Québec à Trois-Rivières, Québec, Canada.

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