Surgical debridement and gentamicin-loaded calcium sulphate/hydroxyapatite bone void filling to treat diabetic foot osteomyelitis

Kor Hutting, Jaap van Netten, Jan Dening, Wouter ten Cate and Jeff van Baal

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Key words

- Amputation prevention
- Biodegradable bone graft substitute
- Calcium sulphate hydroxyapatite
- Charcot neuroarthropathy
- Diabetic foot osteomyelitis
- Local antibiotic treatment

Authors

Kor Hutting is Surgical Resident, Department of Surgery, Ziekenhuisgroep Twente, Almelo, The Netherlands; Jaap van Netten, is Human Movement Scientist, affiliated to the Department of Surgery, Ziekenhuisgroep Twente, Almelo, The Netherlands, and the Department of Rehabilitation, Academic Medical Centre, Amsterdam University, Amsterdam, The Netherlands; Jan Dening is Radiologist, Department of Radiology of Ziekenhuisgroep Twente, Almelo, The Netherlands; Wouter ten Cate is Trauma Surgeon, Department of Surgery, Ziekenhuisgroep Twente, Almelo, The Netherlands. Jeff van Baal is Vascular Surgeon, Department of Surgery of Ziekenhuisgroep Twente, Almelo, The Netherlands, and Honorary Visiting Professor, Cardiff University, UK

This is a case study of a patient with a difficult-to-manage diabetic foot ulcer with osteomyelitis in a severely deformed foot complicated by Charcot neuropathy. The foot was treated using surgical debridement and gentamicin-loaded calcium sulphate/hydroxyapatite (CaS/HA) bone void filling, offloading and systemic antibiotics after unsuccessful standard treatment. The article includes a discussion of the literature that supports the use of surgical debridement and antibiotic-loaded CaS/HA bone void filling and how it can be used to treat DFO, avoiding the need for amputation.

Osteomyelitis is diagnosed in 50–60% of patients who have been hospitalised for diabetic foot infections (Lipsky et al, 2016). Besides standard-of-care offloading, optimisation of glycaemic control and arterial vascularisation, the treatment of diabetic foot osteomyelitis (DFO) involves long-term systemic antibiotics and surgical debridement (Lipsky et al, 2016). Diabetic foot ulcers with osteomyelitis are difficult to heal, resulting in high amputation rates (6–14%) (Mutluoglu et al, 2013).

Recently, the local antibiotic therapy antibiotic-loaded calcium sulphate/hydroxyapatite (CaS/HA) has been used to treat DFO with promising initial results (Karr, 2011; Whisstock et al, 2015; Drampalos et al, 2017; Niazi et al, 2019) and this was the treatment used in the following case study.

Case study

The patient was a 49-year-old white woman who had hypertension and type 1 diabetes for 20 years with peripheral neuropathy but without peripheral artery disease. She used valsartan (160 mg once daily), hydrochlorothiazide (25 mg once daily) and insulin (glargine, Lantus® and aspart, NovoRapid®). She had no allergies. Her right foot was severely deformed due to Charcot neuroarthropathy-related collapse and transmetatarsal amputations of the first and second rays and cuboid exostectomy due to recurrent infected foot ulcers (*Figure 1*). Her previous ulcers had not been complicated by DFO. Despite the foot deformities, the patient was able to mobilise and weight-bearing was possible with orthopaedic footwear.

The patient presented at a multidisciplinary diabetic foot unit with a recurrent plantar ulcer which was about 3 cm^2 located centrally over the collapsed midfoot. Pre-existent oedema of the entire foot was seen with generalised erythema and a locally elevated temperature on the dorsum of the midfoot. Instability of the foot was clearly present in the tarsometatarsal and midfoot joints.

It was possible to reach multiple dislocated loose bone fragments on the midfoot level using forceps. The patient's vital signs were normal with a temperature of 37.7°C. PEDIS classification (Schaper, 2004) of the ulcer was P1 (no symptoms or signs of peripheral artery disease in the affected foot and palpable dorsal pedal and posterior tibial arteries), E3 (ulcer size of 3 cm^2), D3 (ulcer involvement of all subsequent layers of the foot, including bone and joints), I3 (erythema >2 cm surrounding the ulcer, swelling, warmth, discharge and suspicion of osteomyelitis but no systemic inflammatory response signs), S2 (loss of protective sensation on the affected foot).

The authors hospitalised the patient and prescribed intravenous amoxicillin/clavulanate

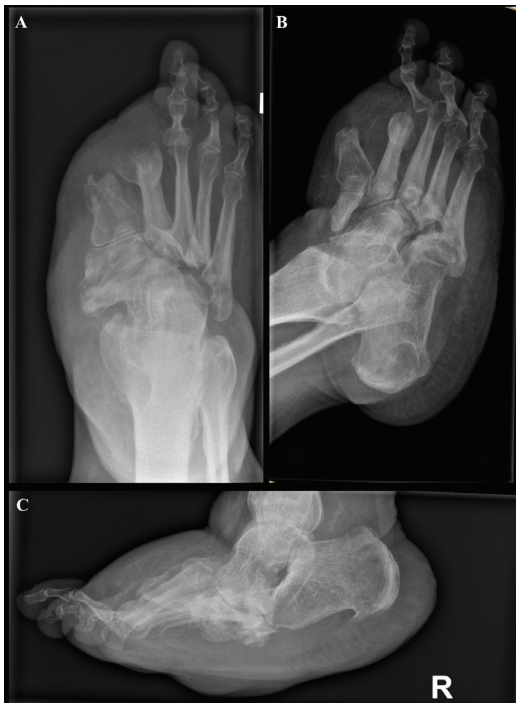

Figure 1. A: Non-weight-bearing dorsal–plantar, B: oblique and C: lateral radiographs. Previous transmetatarsal amputations of the first and second rays and typical 'rocker bottom' deformity (reduced calcaneal inclination and collapse of the midfoot and tarsometatarsal joints) with plantar protrusion of the cuboid bone due to Charcot neuroarthropathy.

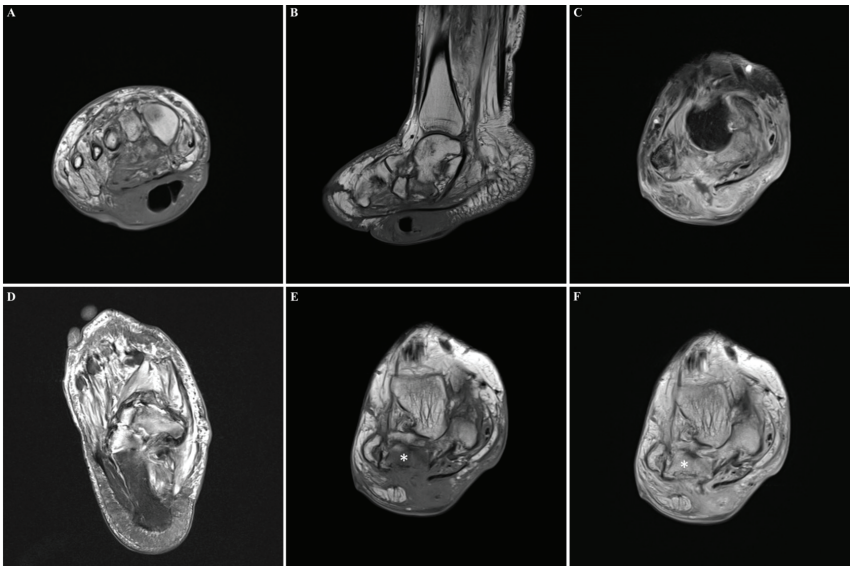

Figure 2. MRI. A: T1 weighted, turbo spin echo sequence (TSE) coronal view and B: sagittal views. Low signal intensity areas in the plantar soft tissue with swelling and a plantar gas collection showing inflammation and abscess. C: T1 weighted, TSE, fat suppression (FS) post-gadolinium contrast coronal view. High signal intensity area corresponding with the low inflammation and plantar abscess in A and B. D: Proton density (PD) weighted, FS, transversal view. Extensive high signal intensity areas in the soft tissues and navicular, cuneiform and cuboid bones representing oedema. E: T1 weighted, TSE, pre-gadolinium contrast coronal view and F: and post-gadolinium contrast coronal view. Extensive low signal intensity areas in soft tissues and the cuboid bone (marked with) on E corresponding with high signal intensity on F representing gadolinium uptake in the corresponding oedematous soft tissues and osseous structures described in D, suggesting osteomyelitis and soft tissue inflammation.*

(1,000/200 mg, four times daily). Laboratory findings showed a normal white blood cell count (7.6 x 10^9/L) and an elevated C-reactive protein level (20 mg/L). Magnetic resonance imaging (MRI) showed inflammation of the soft tissues around the ulcer with an underlying abscess and oedematous bones and bone marrow on the level of the collapsed midfoot (*Figure 2*). These findings confirmed osteomyelitis of the midfoot but did not rule out secondary Charcot neuropathy, which was suspected due to the instability of the foot, oedema, erythema and warmth.

The authors advised offloading with strict bedrest to prevent further damage to the foot. Urgent surgical debridement was performed with drainage of the abscess and partial resection of the infected remnants of the lateral cuneiform bone underlying the ulcer tract. Gentamicin-impregnated collagen sponges were put in place and the wound was partially closed. Further resection of the infected tarsals was not performed because we expected this could cause damage that could render the foot non-functional. Bedrest was continued postoperatively and intravenous antibiotics flucloxacillin (12 g, once daily) and oral ciprofloxacin (500 mg, twice daily) were prescribed based on cultures of the resected bone, positive for *Staphylococcus aureus* and *Klebsiella pneumoniae* (resistant to amoxicillin/clavulanate and piperacillin/tazobactam). No further healing was observed after 2 weeks and the oedema, erythema, elevated temperature and midfoot instability persisted. The authors discussed lower leg amputation with the patient, which she refused.

As a final attempt for limb salvage, an extensive surgical debridement of the ulcer and infected bones of the midfoot was performed, which included complete resection of the cuboid bone, after which the bone void was filled (about 18 cm^3) with gentamicin-loaded CaS/HA, and the skin was closed (*Figure 3*). The aim was to eradicate the infection and to regain osseous stability of the midfoot joints. The operation was performed under general anaesthesia and a pressure tourniquet was used. The authors prescribed 5 days of strict bedrest postoperatively after which total contact cast (TCC) immobilisation was started.

Serous wound leakage persisted for 3 weeks, which required a removable TCC to allow wound

Article points

1. Osteomyelitis leads to a high risk of amputation despite surgical debridement, systemic antibiotics and offloading.
2. Local antibiotic-loaded calcium sulphate/hydroxyapatite has been introduced to treat osteomyelitis with promising results.
3. Local antibiotic treatment could enable single-stage treatment of diabetic foot osteomyelitis, removing the need for systemic antibiotics
4. Further research is required regarding procedures, postoperative treatment and outcomes.
5. Local antibiotic therapy with antibiotic-loaded calcium sulphate/hydroxyapatite should be considered to reduce the risk of amputation after unsuccessful conventional treatment of osteomyelitis.

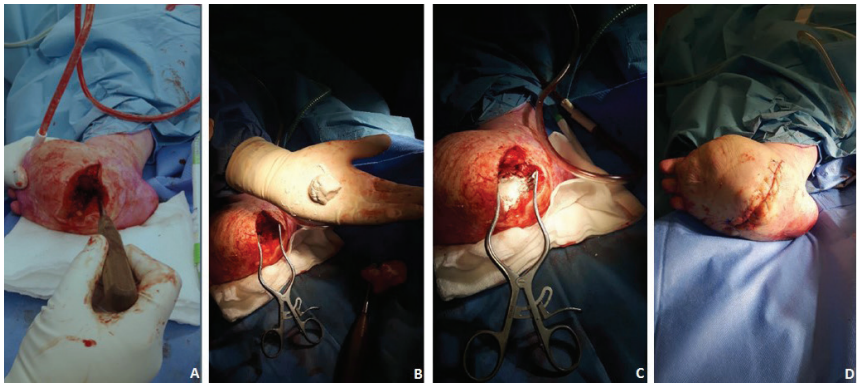

Figure 3. Surgical debridement and bone void filling with gentamicin-loaded calcium sulphate–hydroxyapatite (CaS/HA). A: Extensive surgical debridement of the ulcer and infected bones of the midfoot, including complete resection of the cuboid bone. The resultant bone void was about 18 cm³. B: Preparation of gentamicin-loaded CaS/HA, which was exposed to open air until the viscosity was dough-like. C: Complete filling of the bone void with gentamicin-loaded CaS/HA. D: Primary wound closure to fixate CaS/HA in the bone void.

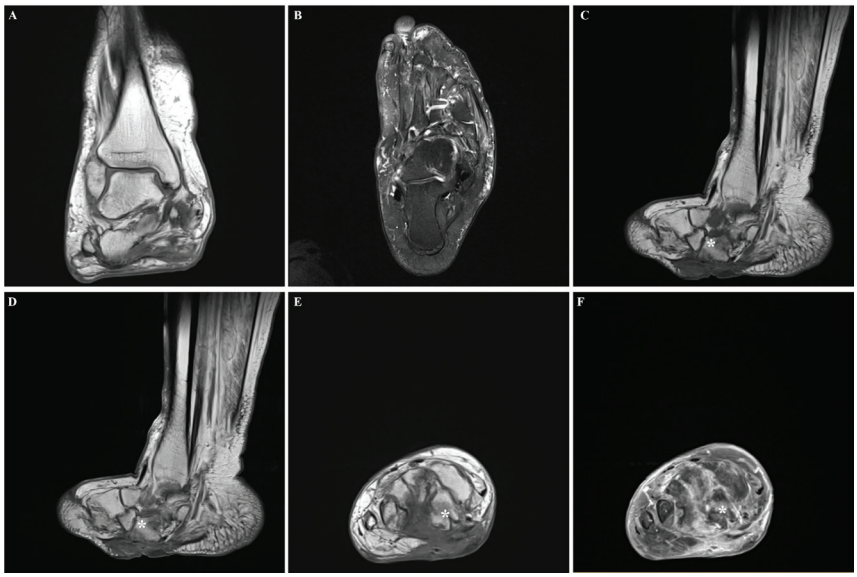

*Figure 4. MRI 7 months after surgical debridement and filling the bone void with gentamicin-loaded CaS/HA. A: T1 weighted, turbo spin echo (TSE) sequence, coronal view. Decrease of low signal intensity areas in soft tissues and osseous structures when compared with preoperative MRI. B: T2 weighted, TSE, fat suppression (FS), transversal view. No high signal intensity areas in osseous structures representing no residual areas of bone marrow oedema and a minor area of high signal intensity in the soft tissues representing oedema. C: T1 weighted, TSE, pre-gadolinium contrast sagittal view and D: post-gadolinium sagittal view. Decreased low signal intensity area in the soft tissues. The decrease of signal intensity of the navicular bone (marked with *) after gadolinium contrast suggest some degree of sclerosis. E: T1 weighted, TSE, coronal view. Fibrous tissue is shown on the plantar aspect of the foot with oedema in the central compartment of the foot. The reduction in signal intensity of the medial cuneiform bone (marked with *) suggest postoperative osseous oedema. F: T1 weighted, TSE, FS, post-gadolinium contrast, coronal view. Persistent gadolinium uptake in the soft tissue and medial cuneiform bone (marked with *) suggests postoperative oedema.*

care. This delayed hospital discharge by two weeks. Systemic amoxicillin/clavulanate (500/125 mg, three times daily) was continued postoperatively despite resistance of the isolated Klebsiella pneumonia, since clindamycin and ciprofloxacin were not tolerated by the patient. Intra-operative bone cultures were negative.

The authors observed gradual healing of the ulcer and improvement in MRI findings at monthly outpatient visits. At 4 months, ulcer healing was complete and systemic antibiotics were stopped. At 7 months postoperatively, normal foot stability without signs of inflammation was found. MRI showed further reduction of oedema of the tarsals and the underlying soft tissues (*Figure 4*). The authors then stopped TCC immobilisation and the patient started weight-bearing mobilisation with custom-made orthopaedic footwear. At final follow-up, 1-year postoperatively, there were no recurrent ulcers or signs of Charcot neuroarthropathy (*Figure 5*) and radiography showed no signs of residual osteomyelitis (*Figure 6*).

Discussion

Local antibiotic treatment

Various techniques and materials have been developed for local antibiotic treatment since the introduction of joint arthroplasties in the 1970s. Non-biodegradable polymethyl methacrylate (PMMA) in preformed beads has mostly been used as a carrier material for local antibiotic treatment (Gogia et al, 2009). Filling of bone voids with antibiotic-loaded PMMA beads is easy and it improves dead space management after surgical debridement and reduces the need for systemic antibiotics. Disadvantages are partial retention of antibiotics in the PMMA beads and the requirement of further surgery to remove the beads after treatment (Gogia et al, 2009).

Many biodegradable materials have been developed to improve local antibiotic treatment, ranging from protein-based materials, such as collagen, to bone grafts and bone graft substitutes, such as calcium sulphate and hydroxyapatite, to synthetic polymers (McLaren, 2004). CaS/HA composite (Cerament™, BoneSupport) has recently been introduced as a biodegradable bone graft substitute. This material acts as an osteoconductive scaffold to improve healing of bone defects and

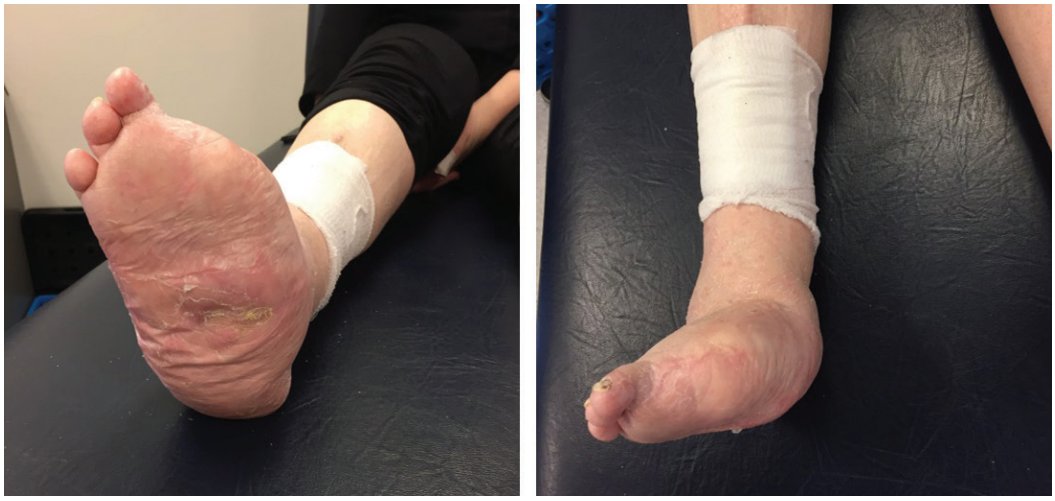

Figure 5. 12 months after the debridement of the diabetic foot ulcer with osteomyelitis and subsequent bone void filling with gentamicin-loaded CaS/HA. The ulcer was completely healed without recurrent ulcers or clinical signs of Charcot neuroarthropathy.

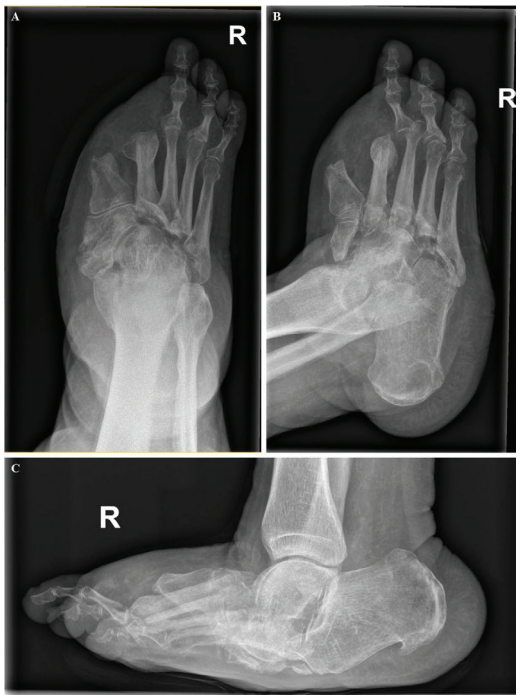

Figure 6. Non-weight-bearing dorsal – A: plantar , B: oblique and C: lateral ankle view radiographs 12 months after the debridement of the diabetic foot ulcer with osteomyelitis and subsequent bone void filling with gentamicin-loaded CaS/HA. Cortical reaction and demineralisation of the tarsal bones and metatarsals was found to be reduced when compared with preoperative radiographs, suggestive of healed osteomyelitis. Remnants of the calcium sulphate-hydroxyapatite composite bone graft substitute are visible.

can be loaded with antibiotics (gentamicin or vancomycin) for local antibiotic treatment (Nilsson et al, 2013).

Previous studies showed that a gradual release of gentamicin from CaS/HA results in a local concentration above the minimal inhibitory concentration for about 4 weeks (Stravinskas et al, 2016). Complete reabsorption of the material requires about 2 years (Stravinskas et al, 2016).

Treatment outcomes in previous studies

Initial results of the treatment of post-traumatic osteomyelitis with surgical debridement and bone void filling with antibiotic-loaded CaS/HA are promising (McNally et al, 2016; Stravinskas et al, 2016). Specific results of this treatment for DFO were studied by Niazi et al (2019), where 63 out of 70 patients with DFO achieved wound healing by surgical debridement and bone void filling with gentamicin-loaded CaS/HA, in addition to culture-specific systemic antibiotics. Another study by Drampalos et al (2017) described the healing of 12 patients with calcaneal DFO after surgical debridement and holes drilled in the adjacent bone and filled with gentamicin-loaded CaS/HA in combination with systemic antibiotics for 6–12 weeks. Whisstock et al (2015) described the successful treatment of 16 out of 20 patients using surgical debridement and gentamicin-loaded CaS/HA bone void filling without systemic antibiotics.

Karr (2011) reported the successful treatment of a patient with methicillin-resistant *Staphylococcus aureus* DFO using surgical debridement including minor amputations and filling of the bone voids with vancomycin-loaded CaS/HA beads, in addition to oral trimethoprim/sulfamethoxazole for 2 weeks.

Charcot neuroarthropathy

The success of the treatment in this case study supports these previously published successes. The management of the patient was more complicated due to her severely deformed and deformed foot due to chronic Charcot neuroarthropathy, which is a reason for exclusion in most studies on the management of diabetic foot infections. Charcot neuroarthropathy-related foot deformation increases the risk of recurrent plantar ulcers and leads to a higher risk of lower-limb amputation compared with people with diabetic foot ulcers without Charcot neuroarthropathy (Sohn et al, 2010). Suspected secondary Charcot neuroarthropathy activity further complicated this treatment, requiring seven months of TCC immobilisation.

The observed symptoms of inflammation at presentation — oedema, elevated temperature, erythema and instability of the tarsometatarsal and midfoot joints — were suggestive of Charcot neuroarthropathy activity but obviously overlap with symptoms of extensive infection. MRI did not distinguish between Charcot neuroarthropathy activity and osteomyelitis in this case since bone and bone marrow oedema on the midfoot level is present in both pathologies (Ertegrul et al, 2013). These MRI findings in the presence of an underlying ulcer confirm osteomyelitis, but do not rule out secondary Charcot neuroarthropathy activity. Of the Charcot neuroarthropathy-related symptoms, mainly the instability improved slowly, requiring seven months of TCC immobilisation, even though the wound healing was complete after four months without signs of persistent infection. Ignoring secondary Charcot neuroarthropathy activity may have led to early weight-bearing mobilisation of the foot with the risk of further damage.

Antibiotics

In this case study, systemic antibiotics were prescribed perioperatively and postoperatively for a duration of 4 months. The literature suggests that the treatment of osteomyelitis with antibiotic-loaded calcium sulphate-based bone graft substitutes can be successful without systemic antibiotics (Gauland, 2011). However, most previous studies on local antibiotic treatment of osteomyelitis by antibiotic-loaded CaS/HA provided systemic antibiotics for about 3 months (McNally et al, 2016; Drampalos et al, 2017).

The authors prescribed systemic antibiotics since we were aiming for limb salvage in a severely threatened foot with a difficult-to-treat infection and it was decided that it would be irresponsible to stop the antibiotics until all signs of infection were absent and wound healing was complete.

Initial clinical experience

The authors found surgical debridement and gentamicin-loaded CaS/HA bone void filling quick and easy to achieve. No local or systemic complications of the material or the required procedures occurred. Serous wound leakage was witnessed for about 3 weeks, which has been reported in previous studies of antibiotic-loaded CaS/HA and does not indicate persistent or recurrent infection (Drampalos et al, 2017). The authors performed surgical debridement and subsequent gentamicin-loaded CaS/HA bone void filling as a second stage after initial standard-of-care was unsuccessful. Although unintended, multiple stages of surgical treatment are often required in the standard treatment of DFO.

Conclusion

In this case study, the authors presented the successful treatment of a difficult-to-manage diabetic foot ulcer with DFO in a severely deformed foot complicated by Charcot neuroarthropathy, by using surgical debridement and gentamicin-loaded CaS/HA bone void filling, offloading and systemic antibiotics after unsuccessful standard treatment. This result adds credibility to the promising initial results showing how effective surgical debridement and antibiotic-loaded CaS/HA bone void filling can be when treating DFO. This treatment has potential benefits, when compared with the current conventional treatment, by enabling single-stage treatment and making long-term systemic antibiotics unnecessary. More research is required regarding potential procedures, postoperative treatment, such as offloading and systemic antibiotics, and comparisons with conventional treatment

of DFO before this treatment modality can be implemented as an addition to standard care. For now, it should be considered for patients who do not heal after standard-of-care treatment for DFO to prevent amputations in this vulnerable group of patients. ■

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