The Foot 39 (2019) 22–27

Contents lists available at ScienceDirect

The Foot

journal homepage: www.elsevier.com/locate/foot

Original Article

Adjuvant antibiotic loaded bio composite in the management of diabetic foot osteomyelitis — A multicentre study

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ARTICLE INFO

Keywords:
Diabetic foot
Chronic osteomyelitis
Antibiotic-loaded bio-composite
Cerament G

ABSTRACT

Background: Diabetic foot ulcers are associated with a high morbidity and are common cause of non-traumatic lower limb amputations. The effect of debridement and the use of an adjuvant local antibiotic carrier in the treatment of diabetic foot ulcers with osteomyelitis was evaluated.

Methods: A retrospective review of patients with diabetic foot ulceration and osteomyelitis treated by debridement with adjuvant local antibiotic was performed. Seventy patients with Texas Grade 3B & 3D lesions were included, with a mean age of 68 years. Cerament G, an antibiotic-loaded absorbable calcium sulphate/hydroxyapatite bio-composite was used along with intraoperative multiple bone sampling and culture-specific systemic antibiotics.

Results: Patients were followed up until infection eradication or ulcer healing. Mean follow up was 10 months (4–28months). Nine patients had Charcot foot deformity, 14 had peripheral vascular disease. 62% of patients had forefoot, 5% midfoot and 33% hind foot involvement. Fifty-three patients (87%) had polymicrobial infection. Staphylococcus aureus was the most common microorganism isolated. Infection was eradicated in 63 patients (90%) with mean time to ulcer healing of 12 weeks. Seven patients were not cured and required further treatment. Five patients had below knee amputation.

Conclusions: Adjuvant, local antibiotic therapy with an absorbable bio-composite can help achieve up to 90% cure rates in diabetic foot ulceration with osteomyelitis. Cerament G can act as effective void filler allowing dead space management after excision and preventing reinfection and the need for multiple surgical procedures.

Level of evidence: Level IV- case series.

1. Introduction

Diabetes is one of the most common chronic diseases in the UK and its prevalence is increasing. In 2013, there were almost 2.9 million people in the UK diagnosed with diabetes and this number will increase to 5 million by 2025. About 10% of all diabetics develop a foot ulcer at some point in their life [1]. Osteomyelitis of the foot is also common in individuals with diabetes mellitus [2,3]. Most diabetic foot infections occur with neuropathic ulcers, which serves as a point of entry for pathogens. Peripheral vascular disease often coexists with neuropathy that further delays wound healing. Diabetes is also the most common cause of non-traumatic limb amputation [1]. Amputations in diabetic patients carry a high morbidity and associated mortality [4]. These factors along with multidrug resistance and poor bone penetration of antibiotic agents make management of diabetic foot infection a major challenge [5,6]. In the present study, a multi-centre experience with the use of adjuvant local antibiotic carriers in the management of diabetic foot infection from two UK teaching hospitals is presented.

2. Materials and methods

A retrospective review of patients with diabetic foot ulceration and osteomyelitis treated with adjuvant local antibiotic Wythenshawe Hospital, Manchester University Foundation Trust and Frimley Park hospital, Frimley Health NHS Foundation Trust was conducted. Patient demographics, co-morbidities, presenting features and pre-operative

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https://doi.org/10.1016/j.foot.2019.01.005
Received 29 October 2018; Received in revised form 3 January 2019; Accepted 9 January 2019

Table 1
University of Texas diabetic wound classification.

University of Texas diabetic wound classification	
Stages	
A	No infection or ischemia
B	Infection present
C	Ischemia present
D	Infection and ischemia present
Grading	
Grade 0	Epithelialized wound
Grade I	Superficial wound
Grade II	Wound penetrates to tendon or capsule
Grade III	Wound penetrates to bone and joint

investigations were reviewed. Foot ulcers were classified according to the University of Texas Diabetic Wound Classification (Table 1).

Osteomyelitis in ulcer patients was defined as having visible exposed bone, bone palpable with a blunt probe, a red swollen toe with ulceration, a deep ulcer persistent over a bony prominence and the presence of a soft tissue sinus with purulentdischargem [7]. Surgical procedure involved careful and methodical bone and soft tissue debridement for infection source control, with multiple deep tissue sampling for microbiologic cultures. All clinically dead and necrotic tissue was removed. Antibiotic carrying bio-composite (Cerement G) was used as an adjuvant for dead space management. The Silo technique [8] was used for hind foot disease with antibiotic composite delivery into targeted pre-drilled holes, and intramedullary retrograde filling used for delivery in the forefoot. The antibiotic composite was preferentially applied to bone, but composite as beads were also applied to the soft tissues to manage any void after debridement. All procedures were carried out by specialist foot and ankle surgeons within a multi disciplinary (MDT) setup. The surgical wound was closed primarily where possible; otherwise a vacuum assisted closure (VAC) was applied. Systemic antibiotics were administered with microbiology advice and culture and sensitivity [8]. The duration of systemic antibiotics (enteral/parenteral) was decided on specialist advice and patient response. For the purposes of this study successful treatment was defined as eradication of infection with normalisation of inflammatory parameters and ulcer healing/stable ulcer. Failure of treatment was defined as failure to eradicate infection or recurrence of infection/ulcer at the same site within 4 months of intervention. Recurrence of infection or ulcer beyond 4 months of treatment or at a remote site was not considered as a failure of intervention (Figs. 1–3).

3. Results

Our multicentre study involved a total of 70 consecutive patients with diabetic feet. 59 (84%) were maleand 11 (16%) female. The average age was 68 years (range from 22 to 88). Sixty-three of our patients (90%) were type 2 diabetics and the rest 7 (10%) were type 1 diabetic. Forefoot involvement was most common with 43 (62%) cases, followed by the hind foot in 23 (33%) and the midfoot in 4 (5%). Thirty-six (51%) patients involved the left foot and 34 (49%) patient involved the right side. Nine patients had an associated Charcot foot deformity at presentation. Six patients with Charcot foot deformity had forefoot and 3 had mid foot ulcers. Fourteen (20%) patients had associated peripheral vascular disease with 8 having a re-vascularisation procedure. All patients had grade 3B (66) or grade 3D (4) ulcers according to the University of Texas classification. Among the 4 patients with grade 3D ulcer, 3 had forefoot and one had midfoot involvement. Peripheral neuropathy was observed in 60 patients (86%) in the study. Radiographs and magnetic resonance imaging (MRI) were available for all cases. Our preference of local antibiotic delivery system was Cerement G. The mean volume of bio composite used was 5 cc containing 87.5 mg (175 mg/10 ml) of gentamicin. Primary wound closure was possible in 55 (78%) patients with 15 (22%) having a VAC assisted closure. Polymicrobial infection was seen in 53 patients (87%) with mixture of gram positive, gram negative and anaerobes (Table 2). There was no growth obtained in 9 samples (13%). Staphylococcus aureus was the most common single infective organism seen in 47 (67%) patients. MRSA infection was isolated in 6 cases. Post-operative systemic antibiotics were given for mean 4 weeks (range 2–6) as per microbiology advice. All patients in our series were followed up until infection eradication, ulcer healing/stabilisation or failure of treatment. The mean duration of follow up was 10 months (range 4–28). One patient died due to unrelated causes. Successful treatment with eradication of infection was achieved in 63 (90%) cases. Ulcer healing was achieved in 57 (81%) cases. The remaining six patients achieved a stable wound with no signs of continued infection, erythema or discharge. Mean time to ulcer healing was 12 weeks (range 4–16 weeks). One 1st ray and one trans-metatarsal amputations were carried out. Failure of treatment occurred in 7 (10%) cases. Four of the failures (57%) involved the hind foot, 2 involved the forefoot and 1 the midfoot. All had established peripheral neuropathy. Five (7%) patients required a below knee amputation. Of the treatment failures which proceeded to an amputation, 2 had midfoot, 2 forefoot and 1 midfoot involvement. Significant vascular compromise was encountered in 3 (60%) patients with amputations. This included a patient with midfoot ulcer and femoro-popliteal bypass surgery, a patient with forefoot ulcer with popliteal artery stenting and a hind foot ulcer patient with posterior tibial artery occlusion. The fourth patient who required an amputation had type 2 diabetes, peripheral neuropathy and a static non-healing ulcer after 10 months of treatment. The final patient who required an amputation had a hindfoot ulcer with calcaneal osteomyelitis and learning disability. The other 2 failures included a patient with a hind foot ulcer had Type 2 diabetes, peripheral vascular disease and compliance issues, and in another hind foot case where the ulcer had not healed at 1 year with peripheral vascular disease requiring angioplasty at 6 months after the initial debridement and local antibiotic therapy (Table 3). In two patients, the primary ulcer healed but a new ulcer developed in a different part of the foot after 5 and 8 months respectively (relapse). There was no additional recurrence of infection seen in any patient and no local or systemic side effects presented in any patients during treatment. There were no iatrogenic fractures during the study duration. White discharge from the bio-composite was encountered in a few cases, but did not cause any concern (Table 4).

4. Discussion

Osteomyelitis of the diabetic foot is challenging to manage usually complicated by the presence of neuropathy, peripheral vascular disease and compromised immunity [9]. Surgical debridement is crucial in the treatment of chronic osteomyelitis in the diabetic foot. Bone infection, especially in the presence of necrosis, can be persistent because of impaired immunity and biofilm formation [10]. The biofilm, comprised of colonies of bacteria in a matrix of hydrated polysaccharides, protein and other molecules, is associated with a slower metabolism and a lower replication rate of bacteria, resulting in less effectiveness of antimicrobial agents [11,12]. The penetration of antibiotics in bone defects is poor and achieves only low local drug concentrations [13]. Local antibiotic delivery systems can deliver high local concentrations of antibiotic without any associated system toxicity [14]. The current authors believe this can be effective against residual biofilms. Locally delivered antibiotics can also diffuse into areas with poor perfusion. Effective treatment includes thorough excision of dead bone and the biofilm [14]. Management of dead space after bone and soft tissue debridement (source control) is also critical [14].

Antibiotic carriers can be classified as biodegradable or non-biodegradable. The most frequently used non-biodegradable gentamicin-containing carrier is polymethyl-methacrylate (PMMA). The rate of antibiotic release from PMMA bone cement relies on surface area of

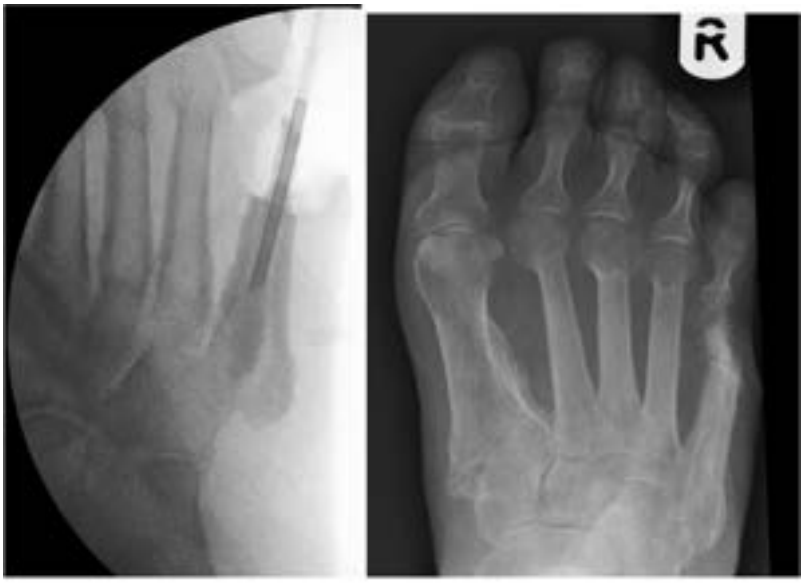


Fig. 1. (a-b) Intraoperative radiographs of application of Cerament G at the 5th Metatarsal and radiography after 2 months.

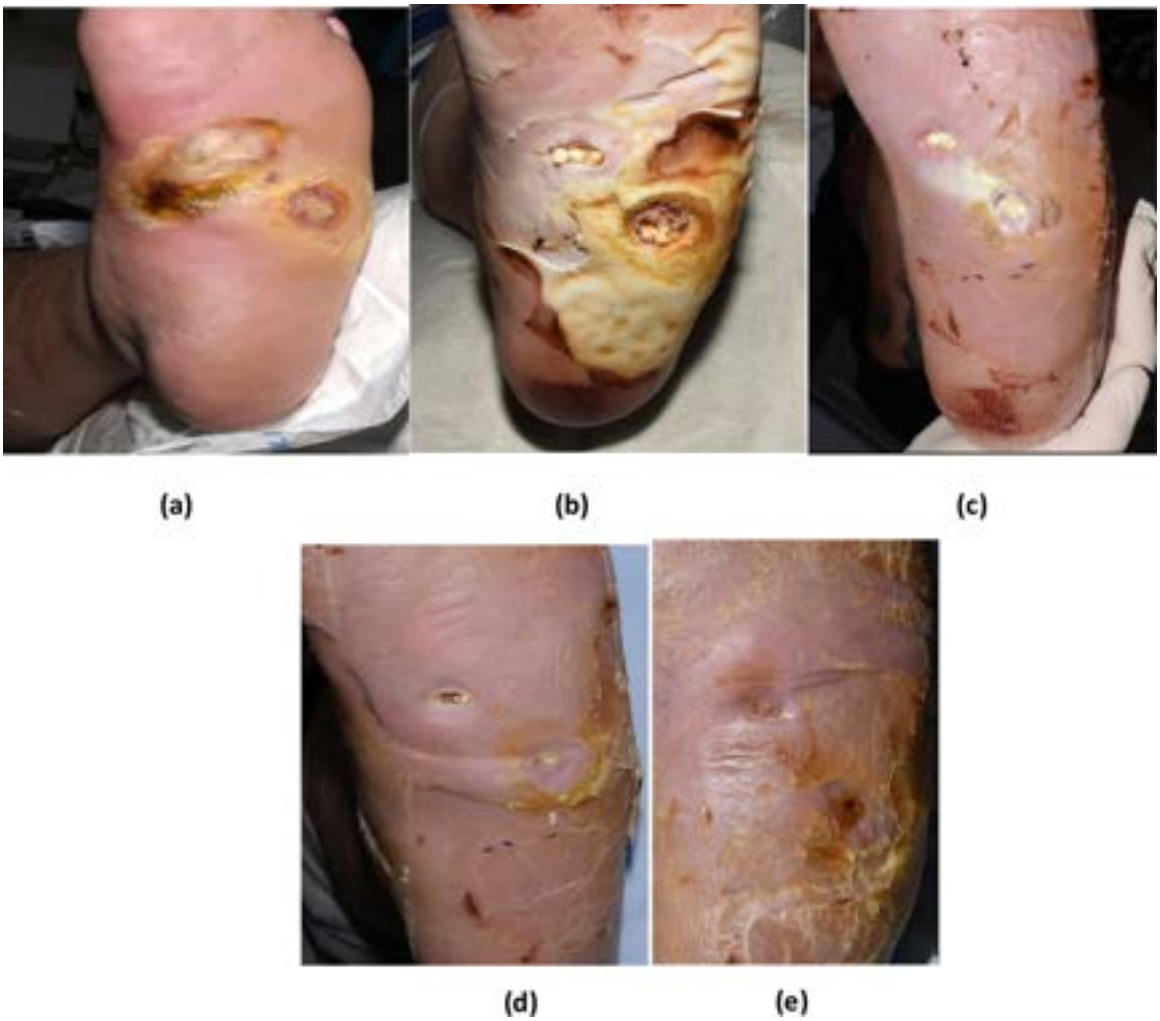


Fig. 2. (a–e) Midfoot osteomyelitis before surgery, immediately after surgery and 4, 6 and 12 weeks aftersurgery.

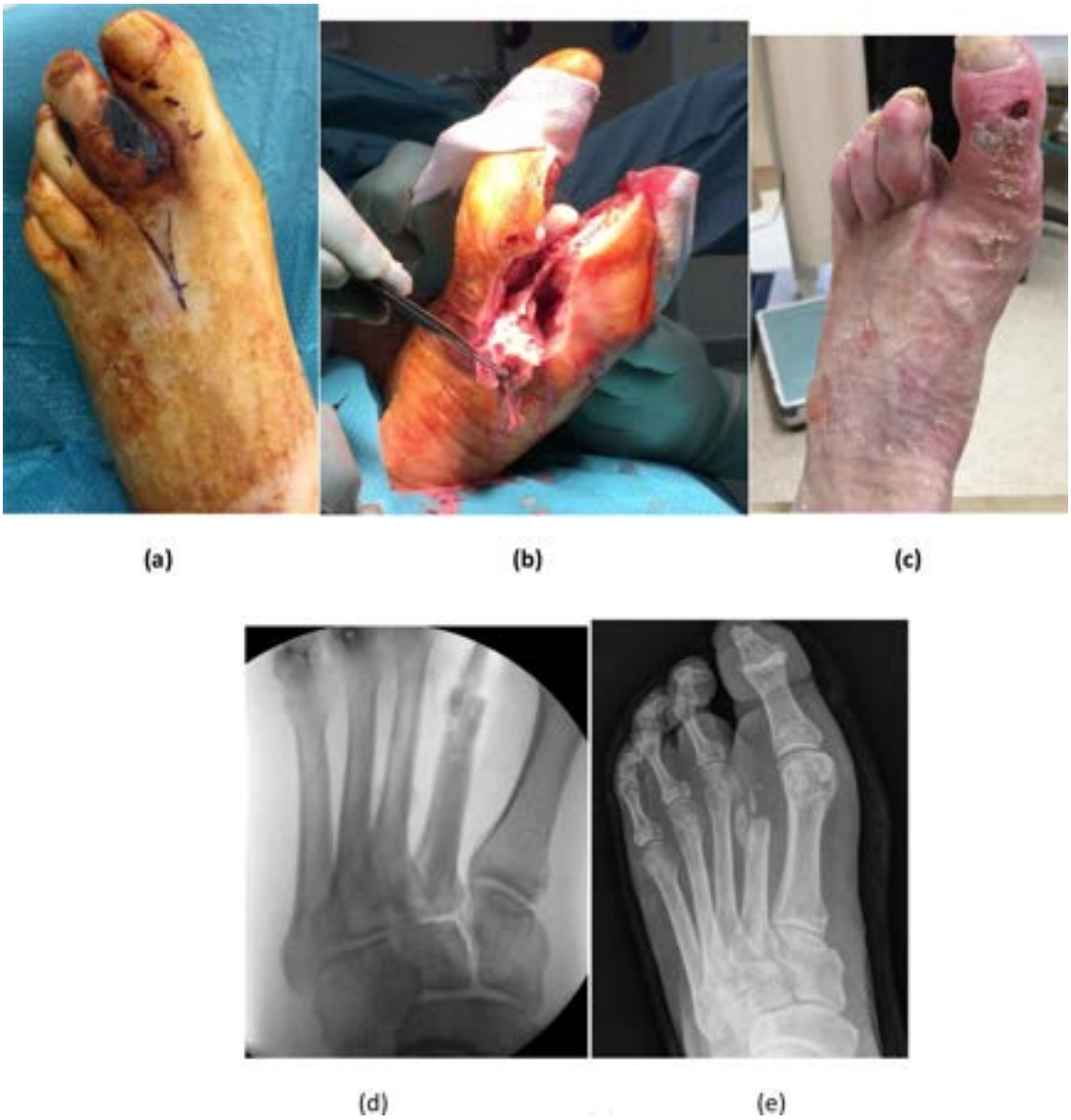


Fig. 3. (a–c) Second ray osteomyelitis before surgery, during surgery of ray amputation and 6 weeks after surgery. (d-e) Radiographs taken intraoperative and 2 months after surgery.

Table 2
Microbiology results from deep tissue cultures.

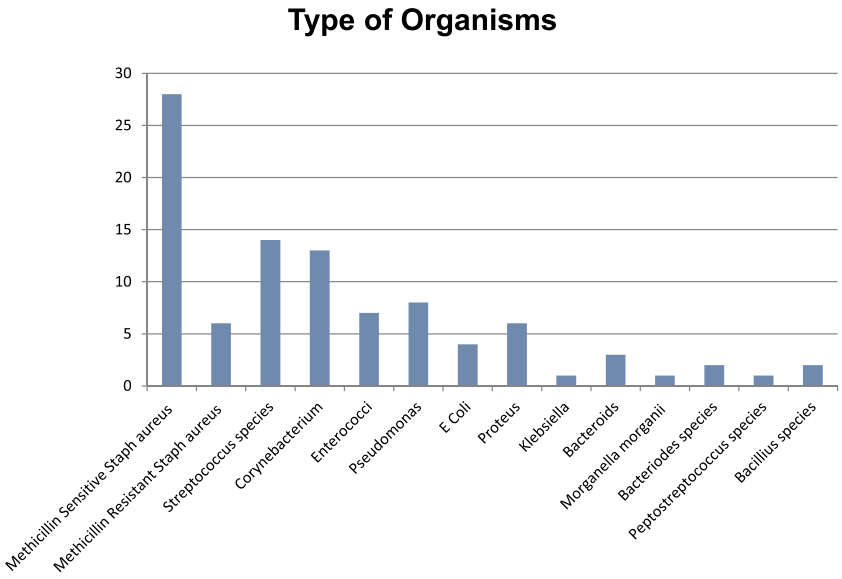
Organisms	Number
No growth	9 (13%)
Single organism — Staph aureus — 13%	8
Polymicrobial — 87%	53
Methicillin Sensitive Staph aureus	28
Methicillin Resistant Staph aureus	6
Streptococcus species	14
Corynebacterium	13
Enterococci	7
Pseudomonas	8
E Coli	4
Proteus	6
Klebsiella	1
Bacteroids	3
Morganellamorganii	1
Bacteriodes species	2
Peptostreptococcus species	1
Bacillius species	2

antibiotic spacer and concentration gradient between its surface and surrounding tissue [13]. The antibiotic release with PMMA is high during the first 2–3 days but quickly falls to sub therapeutic levels thus promoting multi drug resistance organisms and biofilm formation [15]. A further surgical procedure is required to remove PMMA bone cement and this increases patient morbidity, hospital stay and cost [16]. In recent years, new synthetic bone graft substitutes have been introduced, with the advantages of bio-absorbability, biocompatibility and osteoconductive properties [13]. Advantage of using a resorbable bone substitute over PMMA is that a one-stage treatment can be performed as carrier removal is not required. One of these products is a bio ceramic of hydroxyapatite particles embedded in an injectable synthetic calcium sulphate carrier (Cerament). The compressive strength provided by this injectable bio-ceramic is like that of cancellous bone to ensure at least the same mechanical stability as with autografts [17]. It provides a flowable delivery system and once mixed it forms a paste that can be injected into bone defects, completely filling the cavity without any dead space. This obliterates any areas that can harbor residual bacteria or small fragments of biofilm [18]. The Cerament G used

Table 3
Details of patents with failure of treatment.

	Part of foot	Age/sex	Side	Grade	Co morbidities	Outcome
Patient 1	Hind foot	62/male	left	3b	Type II DM, Learning disability, neuropathy	BK amputation after 1 year.
Patient 2	Hind foot	58/male	right	3b	Type II DM, Posterior tibial artery occlusion, insensate foot, neuropathy	BK amputation in 6 months
Patient 3	Hind foot	70/male	left	3b	Type II DM, peripheral vascular disease, poor compliance, neuropathy	Non-healing Ulcer after 1-year f/up
Patient 4	Hind foot	70/male	right	3b	Type II DM, peripheral vascular disease, angioplasty after 6 months of surgery, neuropathy	Non-healing Ulcer after 1-year f/up
Patient 5	Mid foot	72/male	left	3d	Type II DM, Charcot foot, CKD, Femoropopliteal bypass, neuropathy	BK amputation in 2 months
Patient 6	Fore foot	56/male	left	3b	Type II DM, neuropathy	BK amputation in 10 months
Patient 7	Fore foot	68/male	right	3b	Type II DM, neuropathy, popliteal artery Stenting	BK amputation in 3 months

Table 4
Graphical representation of type of organisms found in cultures with Staphlococcus aureus being the most common organism isolated.



in our study contains 17.5 mg/ml of gentamycin. The paste has been designed to have a neutral pH (7.0–7.2), so that it does not reduce the antibiotic activity. The mixing and injecting device ensures a homogeneous distribution of antibiotic so that it is made available for local elution and finally delivered in a controlled fashion. In vitro studies have shown that gentamicin elution from Cerament G has a high initial peak (> 1000 μg/ml) and remains above minimum inhibitory concentration (MIC) for at least 28 days. These levels of gentamicin can be effective in biofilm prevention and eradication. In vivo studies have shown that the bio-composite offers local gentamicin concentration levels 64–150 times higher than the minimal inhibitory concentration (MIC) for gentamicin-sensitive pathogens such as Staphylococcus aureus and Pseudomonas aeruginosa. The current authors also believe that local antibiotics are also effective against any residual bacteria in planktonic form after debridement. The initial dissolution of the calcium sulphate allows high early release of antibiotics leaving a more porous hydroxyl apatite scaffold to support ingrowth of blood vessels and subsequent new bone formation [19] with no secondary removal procedure required.

Cerament G has been used successfully as void filler for treatment of chronic osteomyelitis. McNally et al. reported a prospective study of 100 patients with chronic osteomyelitis in which single-stage treatment by Cerament G showed 96% eradication of infection and reduced hospital stay [18]. The studies for treatment of diabetic foot osteomyelitis with bio-absorbable bone void fillers are sparse. Armstrong et al. in 2001 presented application of antibiotic-impregnated calcium sulphate pellets improved the outcome of forefoot diabetic foot osteomyelitis [20]. Karr in 2011 presented a successfully managed single stage procedure for diabetic forefoot osteomyelitis with surgical bone resection and Vancomycin bone void filler [21]. Drampalos et al. in 2018 reported a single stage treatment of diabetic calcaneal osteomyelitis with Cerament G, in which the infection was eradicated in all patients [8]. There are no randomised control trials available.

Our data would suggest that adjuvant, local antibiotic therapy with an absorbable bio composite can help achieve up to 90% cure rates in diabetic foot ulceration with osteomyelitis. Our results of infection eradication and ulcer healing are comparable to those achieved by McNally et al. in the treatment of non-diabetic chronic osteomyelitis [18]. Cerament G can act as an effective void filler allowing dead space management after excision and preventing reinfection and thereby repeatsurgical procedures. We found a higher failure rate can be expected in hind foot disease (17%) in comparison to forefoot or mid foot ulceration due to inadequacy soft tissue coverage. We feel that the use of adjuvant local antibiotic therapy can potentially decrease the risk of amputations in this vulnerable and difficult to manage group of patients. Vascular compromise adversely affects outcomes with higher failure and higher amputation risk. As such, adjuvant local antibiotic may offer some bone preservation, help maintain length and function of the foot. Our data suggest that this is a safe procedure with no local or systemic adverse toxicity. The results presented in this paper is limited by the small numbers and the lack of a control group. Nonetheless, the literature is sparse, and additional randomized controlled trials (RCTs) are urgently needed to improve our understanding and guide treatment decisions.

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