

Article

Antibiotic-Loaded Hydroxyapatite Ceramic in the Management of Diabetic Foot Osteomyelitis: An Investigation of Factors That Determine Patient Outcomes

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Abstract: Background: Diabetic foot osteomyelitis is a complex condition to manage, with substantial risk of treatment failure, which could necessitate major amputations. Surgical debridement and prolonged systemic antibiotic therapy have been the mainstay of treatment, but recurrence rates remain high. The use of adjuvant local antibiotic therapy has been proposed as a potential adjunct to improve outcomes. **Methods:** This retrospective study involved 113 patients with diabetic foot osteomyelitis, who underwent debridement and application of antibiotic-loaded hydroxyapatite ceramic from the year 2018 to 2023. Clinical outcomes of interest were eradication of infection, ulcer healing, recurrence of infection, prevention of major amputation and mortality rate. Patient-associated factors were identified and analysed. **Results:** Eradication of infection was achieved in 96%, healing of ulcer in 93% and limb salvage in 95% of patients. The mortality rate at 1 year was 5.4%. Peripheral arterial disease, HbA1c and CRP levels were statistically significant in affecting treatment outcomes. Other factors had no impact on the treatment success. **Conclusions:** This is the largest single-centre study involving Cerament G and V in the management of diabetic foot osteomyelitis and the first investigating the specific factors associated with outcome goals. The use of these antibiotic-loaded carriers demonstrated excellent eradication of infection, healing of ulcer and limb salvage and prevention of recurrence of infection.



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Keywords: diabetic foot ulcer; diabetic foot osteomyelitis; diabetic foot infection; local antibiotic; biocomposite; Cerament

1. Introduction

Diabetes mellitus remains among the most prevalent metabolic disease affecting 588.7 million people worldwide, with diabetes-related expenditures exceeding USD 1 trillion for the first time in 2024 [1]. Patients suffering from this condition have a lifetime risk of developing a diabetic foot ulcer of up to 25% [2]. The risk of major lower limb amputation in diabetic foot ulcer varies according to region and has been reported to be up to 52% [3]. A study conducted in the UK even reported a 17% amputation rate within 1 year from initial presentation of an ulcer [4]. This condition imposes a significant burden on the healthcare system, with a reported 5-year mortality rate of 50% in diabetic patients with a foot ulcer and up to 80% in patients with diabetic-related amputations [5].

The development of ulceration in diabetic patients has been attributed to multifactorial complications of diabetes mellitus, which include peripheral neuropathy, peripheral vascular disease, altered immune response, structural deformity and repetitive minor trauma.

Newer studies have accredited advanced glycation end products (AGE) through receptor-mediated signalling cascade activation leading to a pro-inflammatory state, ultimately inducing direct damage to nerves and vessels [6]. The development of non-invasive tests such as skin autofluorescence (SAF) in detecting AGE has the potential to predict diabetic foot ulcer occurrence [7]. Despite the best efforts in managing such ulcers, the recurrence rate after ulcer healing is approximately 40% in a year and 60% in 3 years [8]. Direct spread of infection through an ulcer to the underlying bone leads to osteomyelitis in up to 20% of patients, severely complicating the management [9].

The routine management of diabetic foot osteomyelitis involves radical debridement to remove infected tissue and necrotic bone, which may include bone resection or partial amputation. This is followed by targeted systemic antibiotic therapy for a long duration and frequent dressings or additional surgeries for wound closure after eradication of infection. The recurrence of infection, however, was reported to be above 56% and amputation was 83% within 1 year in the presence of osteomyelitis [10]. Bone and soft tissue void after debridement poses a significant challenge as it delays wound healing, increases risk of reinfection and produces structural vulnerability. The presence of multi-drug resistance microorganisms associated with diabetic foot osteomyelitis along with poor penetration of systemic antibiotics further hinder successful management [11].

Improved management of bone void is crucial in order to achieve optimal outcomes in treating diabetic foot osteomyelitis. The use of an antibiotic-incorporated synthetic bone graft substitute which integrates ideal properties such as bioabsorbability, biocompatibility and osteoconductivity has been reported to be beneficial in the management of bony defects [12]. Earlier experience in this centre demonstrated infection healing of 73.2% in patients with the use of a local antibiotic biocomposite compared to 20.4% with the current standard of care [13]. This present study intends to evaluate the effectiveness of antibiotic-loaded hydroxyapatite ceramic (Cerament[®], Bonesupport, Lund, Sweden) in the eradication of infection, wound healing, the prevention of recurrence of infection and limb salvage for diabetic foot osteomyelitis. We further aim to assess patient factors which are associated with treatment outcomes.

2. Materials and Methods

This is a retrospective study involving all patients with diabetic foot osteomyelitis treated with antibiotic-loaded hydroxyapatite ceramic (Cerament G and V) in Wythenshawe Hospital, Manchester University Foundation Trust from 2018 to 2023. After considering the inclusion and exclusion criteria, 113 patients were included in this study. Informed consent was obtained from the patients. Information on patient demographics, comorbidities, clinical features, infective status, investigations, surgical procedures, antibiotic treatment and outcomes were collected from the hospital electronic data base system.

Inclusion criteria were consecutive patients 18 years and above with diabetic foot osteomyelitis treated with Cerament application. Exclusion criteria were patients without diabetes, less than 18 years old, lacking evidence of osteomyelitis and lost to follow-up. Osteomyelitis in our study is defined clinically as having an ulcer over a bony prominence, exposed bone or purulent discharge through a soft tissue sinus, supported by elevated infective markers, including white blood cell count and C-reactive protein (CRP) with further confirmation by magnetic resonance imaging (MRI). In cases where the diagnosis is uncertain, further three-phase bone scans were utilised. Body mass index (BMI) was classified based on the National Institute for Health and Care Excellence (NICE) guidelines which defines underweight as BMI less than 18.5, normal as 18.5 to 24.9, overweight as 25.0–29.9, obesity as 30–39.9 and severe obesity as more than 40 [14]. HbA1c in our study is measured in mmol/mol and further divided into good diabetes control from 42 to 58 mmol/mol,

suboptimal control 59–75 mmol/mol and poor control when more than 75 mmol/mol [15]. Chronic kidney disease is diagnosed from an estimate glomerular filtration rate according to NICE guidelines and defined in this study as less than 60 mL/min/1.73 m² (Grade 3a) [16]. Peripheral arterial disease (PAD) in this study was defined in agreement with several guidelines by an ankle brachial pressure index < 0.9 [17]. This was further confirmed by Duplex ultrasound in all our patients to identify the extent and level of disease.

All included patients underwent methodical debridement of bone and soft tissue for infection source control with multiple deep tissue and bone samplings for culture and sensitivity by foot and ankle consultants. Necrotic bone and infected tissue were removed until visible healthy tissue followed the application of antibiotic-carrying biocomposite (Cerament G or V). The silo technique was often utilised for hindfoot involvement with the delivery of a biocomposite through pre-drilled holes and forefoot involvement through retrograde intramedullary filling [18]. The antibiotic biocomposite was preferentially applied to bone or as beads to soft tissue to manage the post-debridement void. The surgical wounds were closed primarily, if possible, or a vacuum-assisted closure (VAC) was applied otherwise. Cerament G was more commonly utilised due to the broad spectrum nature of gentamicin, while Cerament V containing vancomycin was preferred if previous cultures involved methicillin-resistant *Staphylococcus aureus* (MRSA) and excluded a gram-negative microorganism.

Patients were followed up by a multidisciplinary team (MDT) involving foot and ankle surgeons, podiatrists, infective disease specialists, diabetologists, plastic and vascular surgeons, diabetes specialist nurses and physiotherapists. The duration of antibiotics was decided during MDT meetings, based on culture and sensitivity, patient clinical response and infective markers. In this study, we define eradication of infection as clinical improvement and resolution of infective markers and ulcer healing as complete re-epithelisation of the wound. Recurrence of the ulcer is defined as the development of a new, full-thickness lesion at the site of a previously healed wound within the study period. All the patients were closely followed up for a minimum duration of 1 year with clinical photographs of wounds, serial radiographs and infective parameters.

To ensure an adequate sample size, we applied Cochran's sample size formula for the finite population. Niazi's study was previously the largest study demonstrating a good clinical outcome with the use of an adjuvant antibiotic biocomposite in the management of diabetic foot osteomyelitis, involving 70 patients [19]. Setting the margin error value as 0.05, confidence interval at 95% Z and drop-out rate of 20%, it was recommended to have at least 77 patients to answer the research question. Our study included 113 participants, providing a sufficient sample size to achieve statistical power and effectively validate the observed clinical outcomes.

Statistical analyses were performed to identify factors that affect clinical outcomes. A chi-square test was adopted for the analysis of categorical variables while a Fisher's test was employed for cell frequencies less than 5. The *p*-value was set at <0.05 for significance. Confidence intervals (95% CI) were reported where appropriate to support the interpretation of associations. Kaplan–Meier survival analyses were performed for the assessment of time-dependent outcomes, including eradication of infection and ulcer-healing duration, and log-rank tests were used to compare survival distributions between subgroups (e.g., PAD vs. non-PAD, HbA1c categories). No other regression modelling or multiple testing correction was applied in this study as the comparison variable did not have the same units to compare with.

3. Results

Our study involved 113 patients with a mean age of 63.5 years (range 29 to 91 years) and consisted of 85 (75%) males and 28 (25%) females. The body mass index (BMI) average was 33.1 (range 20.6 to 64) with one underweight, 25 normal, 31 overweight, 42 obese and 14 severely obese. In total, 67 (59%) were non-smokers, and 46 (41%) were smokers. Hindfoot involvement was most common with 60 (54%) cases, followed by forefoot with 41 (37%) cases and midfoot with 10 (9%) cases. A total of 32 (29%) patients suffered from associated Charcot arthropathy, and 42 (37%) had chronic kidney disease. A total of 51 (45%) patients had peripheral vascular disease with involvement at the level of common femoral artery (CFA) in four cases, superficial femoral artery (SFA) in five, popliteal artery (POPA) in sixteen, tibioperoneal trunk (TPT) in ten, both anterior tibial artery (ATA) and posterior tibial artery (PTA) in five, ATA alone in six and PTA alone in five (Figure 1). HbA1c levels averaged 66.7 mmol/mol (range 30–135) with 33 (29%) well controlled, 35 (31%) suboptimal and 45 (40%) poorly controlled. The C-reactive protein level at time of surgery averaged 114.49 (range 4 to 451). In total, 88 (78%) of the cases involved Cerament G, while 25 (22%) involved Cerament V.

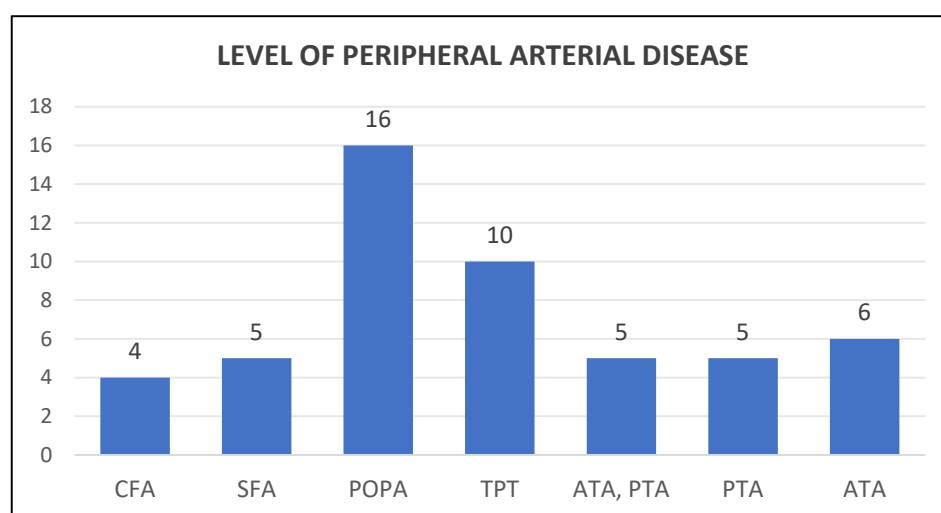


Figure 1. Demonstration of level of PAD.

Cultures demonstrated 85 (75%) cases of polymicrobial involvement, 27 (24%) monomicrobial and one case where no growth was obtained. Among them, 58 cases (52%) involved a gram-positive microorganism, 19 (17%) a gram-negative one and 35 (31%), both. Based on cultures, the most common microorganism involved is Staph. Aureus, and the distribution is demonstrated (Figure 2). The duration of antibiotics mean in weeks was 6.86 (range 2–20 weeks) with a duration of up to 4 weeks in twenty-nine cases, 4.1–8 weeks in sixty-five, 8.1–12 weeks in thirteen and more than 12 weeks in six cases.

Eradication of infection was achieved in 108 (96%) cases at a mean duration of 8.84 weeks (range 2–24 weeks). PAD was statistically significant in relation to eradication of the infection, while BMI and PAD were found to be significantly related to the duration of eradication of infection (p -values < 0.05). Healing of ulcer was attained in 105 (93%) cases with mean duration of 16.3 weeks (range 4–54 weeks). PAD and HbA1c were significantly associated with ulcer-healing status, while HbA1c levels and age were significantly affiliated with duration of ulcer healing (p -values < 0.05). Recurrence of the ulcer occurred in 23 cases (20%); all twenty-three of the cases underwent a second debridement, while six of them required a third debridement. With regard to recurrence, 65.2% of cultures at repeated debridement show similar microorganisms. Recurrence of the ulcer has a statistical association with PAD, HbA1c and initial CRP levels (p -value < 0.05) (Table 1).

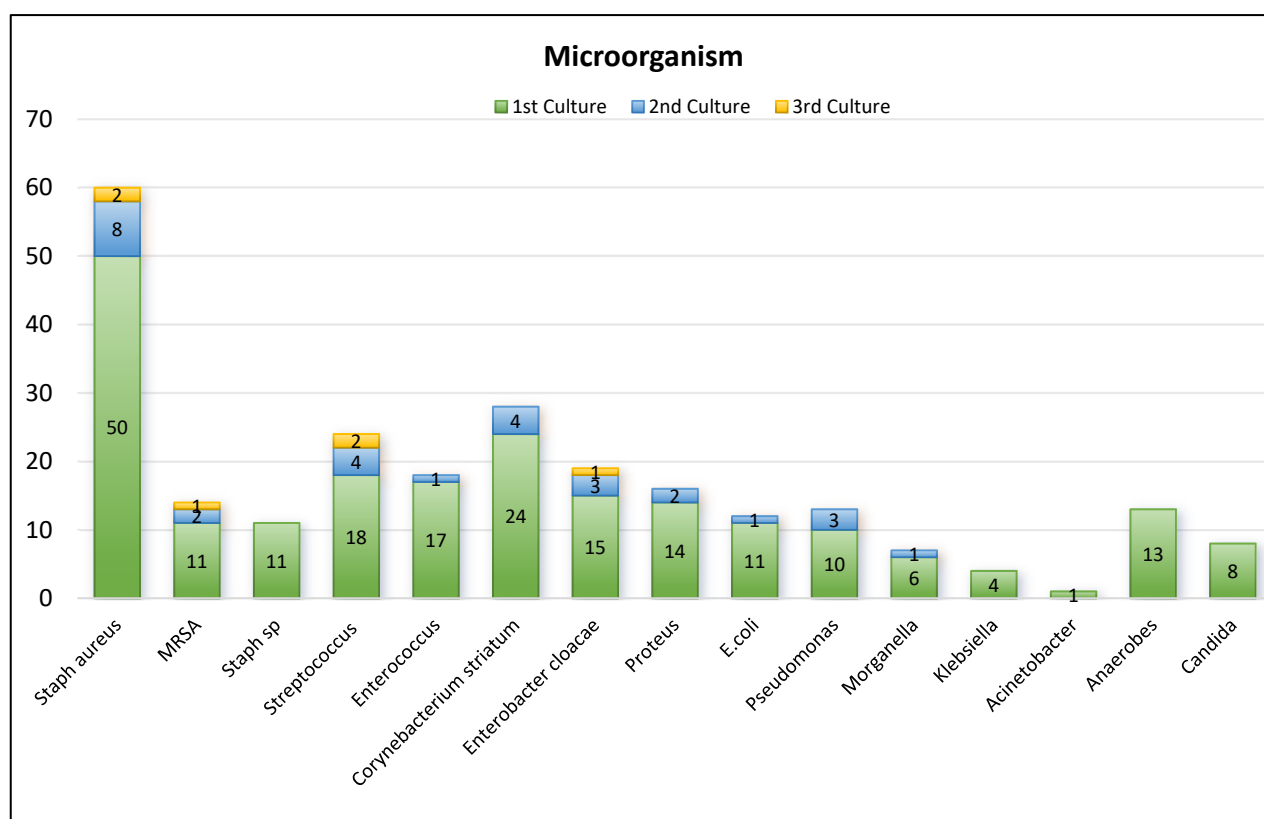


Figure 2. Graphical representation of microorganisms found in cultures.

Table 1. Statistical representation of factors affecting outcomes (significant is highlighted in bold and when p -value is <0.05 at 95% confidence interval).

	Infection Eradication	Infection Eradication Duration	Ulcer Healing	Ulcer- Healing Duration	Recurrence of Ulcer	Limb Salvage	Mortality
Age	0.51	0.43	0.20	0.04	0.75	0.26	0.28
Gender	0.33	0.38	0.09	0.08	0.11	0.17	0.25
BMI	0.54	0.04	0.74	0.11	0.16	0.28	0.18
Smoker	0.33	0.18	0.18	0.19	0.07	0.18	0.29
Part of Foot	0.20	0.56	0.32	0.72	0.23	0.15	0.73
Charcot	0.46	0.55	0.43	0.29	0.18	0.24	0.08
PAD	0.02	0.04	0.02	0.07	0.00	0.05	0.15
CKD	0.38	0.22	0.63	0.40	0.31	0.27	0.00
HbA1C	0.15	0.07	0.02	0.00	0.01	0.07	0.07
CRP	0.34	0.19	0.17	0.09	0.01	0.27	0.02
Poly/Mono	0.42	0.20	0.70	0.28	0.33	0.35	0.51
Gram Stain	0.58	0.22	0.92	0.12	0.22	0.26	0.87
Antibiotics	0.22	0.38	0.36	0.03	0.13	0.86	0.76
Cerament	0.28	0.09	0.13	0.21	0.19	0.21	0.09

Survival analyses were further performed to determine prognostic indices of various factors to duration-based outcomes. The good HbA1c control group demonstrated faster eradication of infection compared to the suboptimal and poor control groups (Figure 3).

Shorter duration of ulcer healing was also significantly observed in the good HbA1c control group compared to the suboptimal group and longest in the poor control group (Figure 4). Patients with PAD demonstrated a longer duration of ulcer healing compared to patients without (Figure 5).

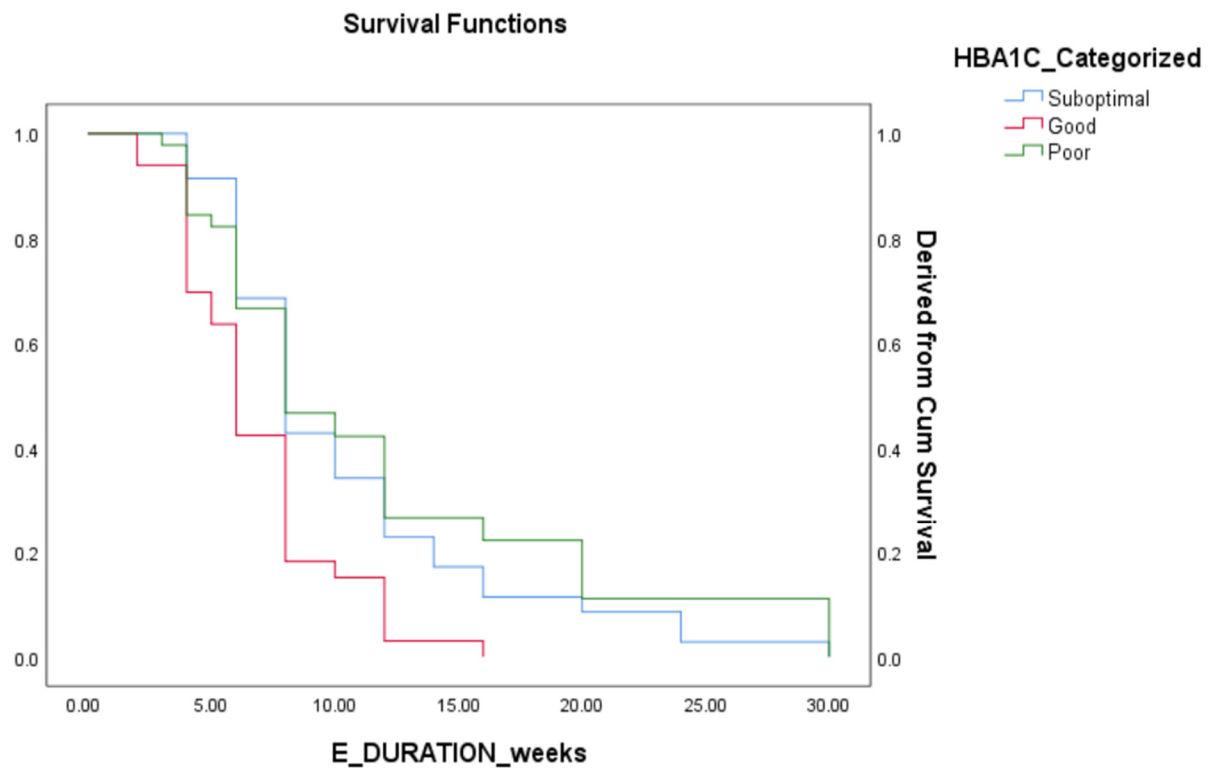


Figure 3. Kaplan–Meier chart demonstrating infection eradication duration based on HbA1c level.

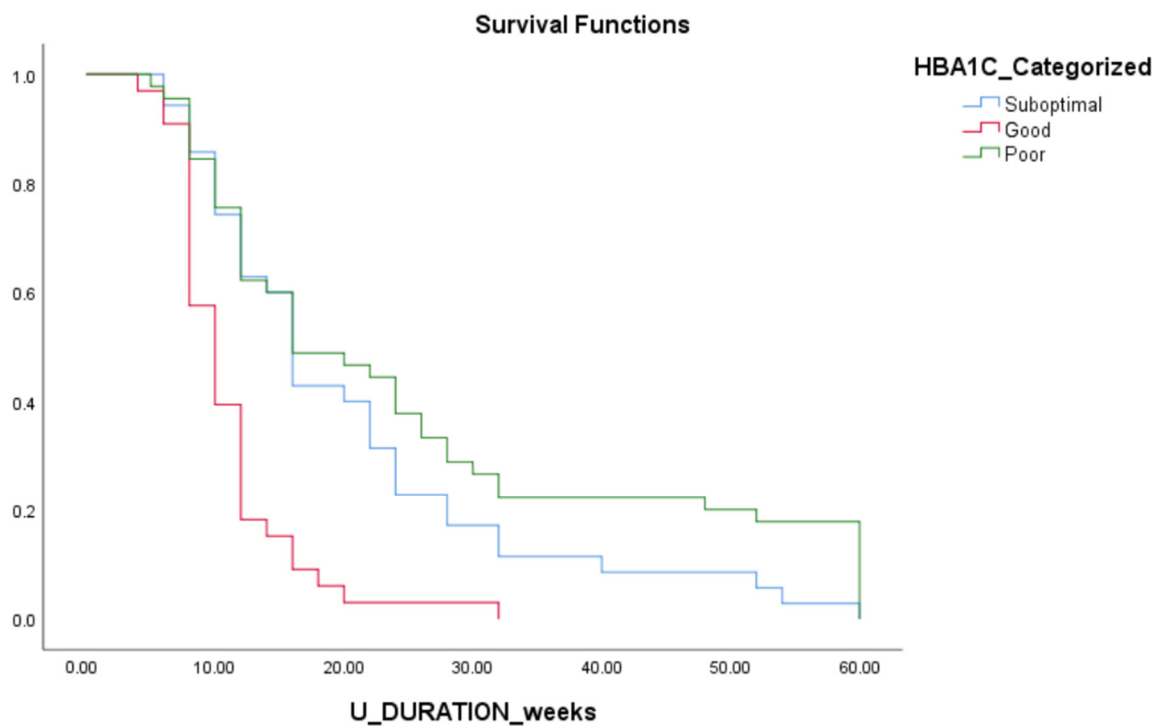


Figure 4. Kaplan–Meier chart demonstrating ulcer-healing duration based on HbA1c level.

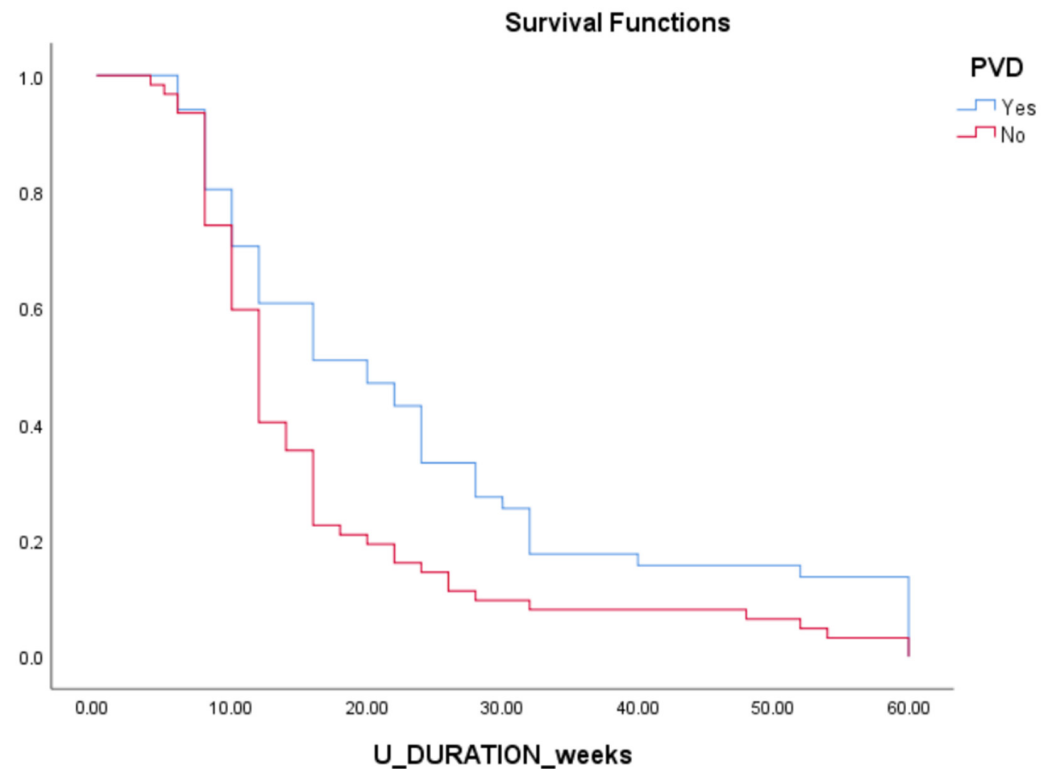


Figure 5. Kaplan–Meier chart demonstrating duration of ulcer healing based on PVD.

Limb salvage was obtained in one hundred seven (95%) patients, while six (5%) patients underwent below knee amputation. PAD was found to be statistically significant in relation to limb salvage (p -value < 0.05). At the end of this study, 84 (74%) patients were still alive, while 29 (26%) were deceased. A total of six patients succumbed within the first year of diagnosis, nine at the second, seven at the third, four at the fourth and three at the fifth year (Figure 6). We report that the 1-year mortality rate for this study is 5.30%. CKD and CRP levels were found to be significantly associated with patient mortality (p -values < 0.05).

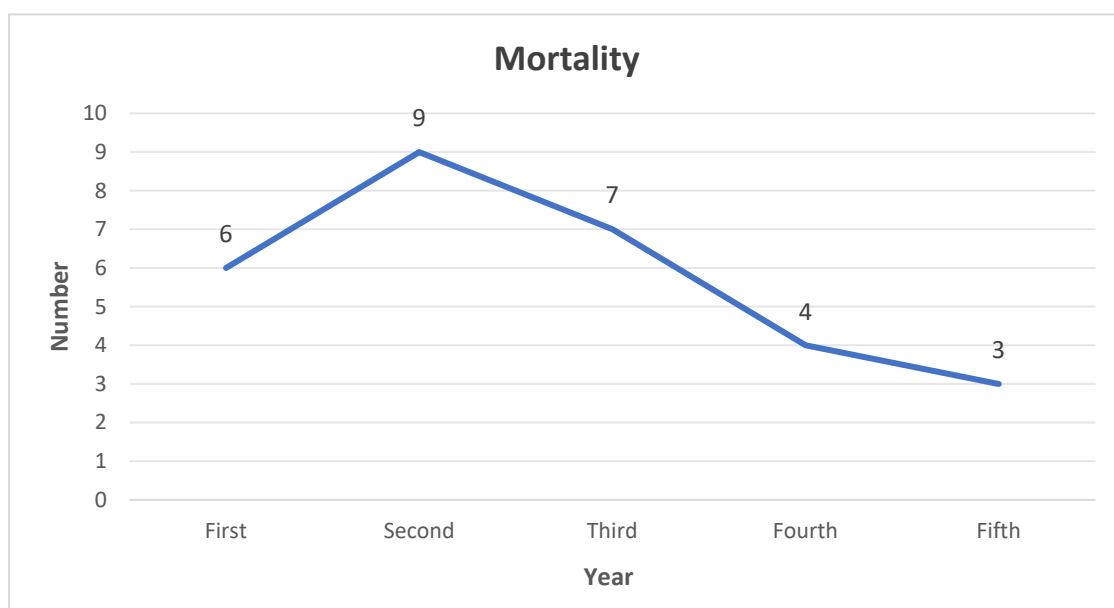


Figure 6. Mortality number according to years.

4. Discussion

The presence of osteomyelitis in diabetic foot infections is complicated and often requires meticulous debridement with a longer duration of antibiotics. Debridement is usually radical, involving osteotomies and resection to achieve successful eradication. This leads to potential dead space with the altered structure and load-bearing properties of the foot. The presence of biofilms along with a defective immune system make eradication of infection challenging. Biofilms, which are aggregates of bacterial colonies encapsulated in self-produced extracellular polymeric substances with quorum-sensing capability, protect bacterial cells from a host immune response, antimicrobials and oxidation processes [20]. A study involving *Staphylococcus aureus* biofilms in diabetic foot infections revealed that most antibiotics tested required much higher doses to achieve a minimum biofilm inhibitory concentration (MBIC) and minimum biofilm eradication concentration (MBEC) in relation to the minimum inhibitory concentration (MIC). They further report that the resistance of biofilms to the concentration of antibiotics were 10 to 1000 times compared to the concentration required to eliminate free-living bacteria [21].

Antibiotics in diabetes patients are aggravated by various factors, such as poor oral absorption, reduced compliance and drug interactions. Hyperglycemia is reported to adversely affect intestinal motility, gastric emptying time and overall mean absorption time [22]. A systemic review that analysed bone penetration in various groups of antibiotics revealed bone concentrations were much lower than serum concentrations and reported inadequate bone penetration for penicillin and the cephalosporin groups. The efficacy of systemic antibiotics is further aggravated by the presence of bone defects and vascular pathologies, including PAD, which results in a low concentration of antibiotics locally. Studies involving PAD patients revealed that 33–50% of subjects did not achieve satisfactory antibiotics bactericidal activity based on tissue concentration for at least 50% of the time [23].

The introduction of a local antibiotic delivery system has the potential to overcome the limitations of systemic antibiotics. The ability to deliver a higher concentration of antibiotics will be effective in dealing with biofilm-producing microorganisms without the systemic side effects. Studies have demonstrated the good elution capability of Cerament G with a high local antibiotic dose exceeding MIC for most gentamicin-susceptible microorganisms during the 28-day test period [24]. The capability to act as a dead space filler while providing structural support would be ideal in the management of this condition. In this study, we utilise the advantages of the injectable composites, Cerament G and V, in the management of diabetic foot osteomyelitis. This injectable bioceramic material consists of 60% calcium sulphate and 40% hydroxyapatite, which provides a compressive strength similar to cancellous bone, thus contributing to sufficient mechanical stability in addition to possessing osteoinductive properties [25]. The use of Cerament in osteoporotic vertebral fractures has reported good tolerance to motion load stresses and resorption of the product at an equal rate with new bone formation [26].

Our present study demonstrates an eradication of infection rate of 96% with the use of Cerament G and V in the management of diabetic foot osteomyelitis. There is a significant improvement compared to our previously published multicentre study with a success rate of 90% [19]. The success of eradication may be attributed to antibiotic elution from Cerament G and V achieving a high initial peak of more than 1000 µg/mL, with up to 150 times higher than the minimal inhibitory concentration for up to 3 months, potentially eradicating the biofilm as well [27]. This study further reports a successful healing of ulcer rate of 93%, which is higher than our previous study published with 80% [19]. The calcium sulphate and hydroxyapatite components provide a supportive scaffold for blood vessel in-growth and new bone formation, ensuing a healthy wound bed for ulcer healing.

This study reported a 20% recurrence rate of ulcers, which is substantially lower than other studies with a rate of 37 to 58% when treated with conventional debridement and systemic antibiotics [28,29]. We achieved limb salvage in 95% of our patients, with six patients (5%) undergoing lower extremity amputation. Various studies have demonstrated a higher amputation rate of 10.0 to 58.8% in the presence of diabetic foot ulcer, with a reported odds ratio of 3.7 in the presence of osteomyelitis [30]. This study also reported a mortality rate of 5.4% at 1 year, which is significantly lower than other studies demonstrating a mortality rate of up to 13.2% [31]. This could be associated with the eradication of infection and wound-healing rate, thereby preventing amputation, which is a significant contributing factor to the mortality rate.

Diabetic foot osteomyelitis is particularly difficult to manage due to the systemic effects of hyperglycemic status in diabetes mellitus affecting all components of proper wound healing, namely neuropathy, vasculopathy and immunopathy [32]. The presence of other conditions, such as PAD, metabolic syndrome, CKD and Charcot neuropathy, may further complicate the treatment outcome. Age was found not to directly impair wound healing but the higher prevalence of comorbidities, alteration in aging skin and altered wound-healing process at the molecular level during haemostasis, inflammation, proliferation and tissue remodeling phases may lead to a delay in healing [33]. Our study reports a statistically significant association between the increase in age and prolonged duration of wound healing, similar to other studies involving a much larger patient cohort [34]. There was, however, no association between age and eradication of infection duration, limb salvage or recurrence of ulcers.

Obesity has been reported to impact wound healing, mainly due to the prolonged inflammatory state with elevated pro-inflammatory cytokines resulting in an impaired immune response during the healing phases [35]. This study reports a significant association between BMI and eradication of infection duration but not with ulcer healing, recurrence of infection or amputation. PAD directly impairs blood supply and has been reported to have poorer prognosis, delayed wound healing, a higher recurrence of infection and a higher risk of amputations [36]. The pattern of PAD in diabetes patients is also known to be more complicated due to defective arterial remodeling leading to diffuse involvement with the failure of the compensatory vessel lumen enlargement and with a more distal predominance [37]. Our study demonstrates a significant association of PAD with success in the eradication of infection, duration of eradication, ulcer healing, recurrence of ulcer and limb salvage.

HbA1c is the most common tool in diagnosing and monitoring the control of diabetes mellitus. A hyperglycemic state has been reported to impair wound healing directly by the alteration in keratinocyte migration and reactive oxygen species causing oxidative stress [38]. Higher HbA1c levels were reported to be associated with longer duration of wound healing, increased non-healing ulcers and higher risk of amputation [39,40]. The present study reports a significant association of HbA1c levels with success in wound healing, duration of wound healing and recurrence of ulcers. Chronic kidney disease is known to influence wound healing due to a uraemic state adversely affecting fibroblast proliferation, collagen production and platelet function, leading to delayed granulation and cell proliferation [41]. At later stages of the disease, acid-base disorders, electrolyte imbalance, oedema and secondary hyperparathyroidism may further impair healing. CKD has also been reported to be associated with a higher mortality risk and lower extremity amputations [42]. Our study demonstrates a similar association only in terms of mortality.

CRP is a valuable infective marker for the diagnosis and monitoring of diabetic foot infections by estimating the infective burden and extent of disease. In terms of outcomes, the initial CRP value was reported to be associated with treatment failure, namely persistence

of infection and amputation risk [43]. In this study, initial CRP was demonstrated to have a significant association with the recurrence of ulcers and mortality. Other parameters such as gender, BMI, smoking status, part of foot, Charcot arthropathy, microorganism factors and duration of antibiotics do not have any bearing on the final treatment outcomes. These parameters should not serve as a barrier to limb salvage surgery as predictable good results can be achieved regardless of the use of antibiotic-loaded calcium sulphate ceramic.

We acknowledge that there are several limitations to our study. This is a retrospective study describing the use of a single technique of local antibiotic therapy. This study lacks a control group for better comparison, which would be more significant in reflecting clinical outcomes and identifying factors affecting the outcomes. A longer follow-up duration would improve the assessment of long-term outcomes, especially with regard to long-term recurrence and mortality.

5. Conclusions

This is the largest single-centre study involving Cerament G and V in the management of diabetic foot osteomyelitis and the first to evaluate factors associated with the outcome goals. The addition of antibiotic-loaded hydroxyapatite ceramic demonstrated excellent clinical outcomes with regard to eradication of infection, healing of ulcer, recurrence of ulcer, limb salvage and mortality rate. Based on the results, HbA1c and PAD were the only modifiable factors which could promote better outcomes, highlighting the importance of diabetic control and treatment of underlying PAD. All other parameters have no impact on treatment outcomes, and predictable good results can be obtained irrespectively.

Author Contributions: Conceptualisation A.P.; data collection: K.M.T., J.M. and S.M.; writing, literature review and editing: K.M.T.; supervision: A.P. All authors have read and agreed to the published version of the manuscript.

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Institutional Review Board Statement: The study was conducted in accordance with the Declaration of Helsinki, and approved by the Institutional Review Board of Department of Clinical Audit (protocol code ID 910512024 and approval date 15 April 2024). Following a discussion with the hospital trust Research and Innovation Department and use of the NHS Health Research Authority's online tool, the project was deemed to be a service evaluation. Further ethical approval was not required as patients' management was not affected in any way, and treatment had already been provided.

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Data Availability Statement: The datasets presented in this article are not readily available because of privacy restrictions. Requests to access the datasets should be directed to the corresponding authors.

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Conflicts of Interest: The authors declare no conflicts of interest.

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