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Definitive single-stage surgery for treating diabetic foot osteomyelitis: a protocolized pathway including antibiotic bone graft substitute use

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Abstract

Background: Diabetic foot ulcers (DFUs) are a challenging complication of diabetes mellitus, often leading to poor clinical outcomes and significant socioeconomic burdens. We evaluated the effectiveness of a definitive single-stage protocolized surgical management pathway, including the use of local antibiotic bone graft substitute, for the treatment of infected DFUs with associated osteomyelitis.
Methods: A retrospective cohort study was conducted. Medical records were extracted (from January 2017 to December 2020) to establish a database consisting of patients who underwent surgical intervention for the treatment of an infected DFU with osteomyelitis. Patients were divided into conventional (control) and protocolized (intervention) surgical groups depending on the treatment received. Clinical outcomes were assessed over a 12-month follow-up period.
Results: A total of 136 consecutive patients were included (conventional = 33, protocolized = 103). The protocolized group demonstrated a statistically significant reduction in the mean number of operations performed per patient (1.2 vs. 3.5) ($P < 0.001$) and a shorter accumulative hospital length of stay (12.6 vs. 25.1 days) ($P < 0.001$) compared to the conventional group. Major amputation rates were significantly lower in the protocolized group (2% vs. 18%) ($P < 0.001$). Within 12 months of surgical intervention, the protocolized group exhibited an ulcer healing rate of 89%, with a low rate of recurrence (3%).
Conclusion: The protocolized surgical pathway, including local antibiotic bone graft substitute use, demonstrated superior outcomes compared to conventional management for the treatment of infected DFUs with osteomyelitis. Further research is needed to evaluate the cost-effectiveness and generalizability of this approach.

Introduction

Diabetes mellitus (DM) is a prevalent metabolic condition that imposes significant morbidity and mortality.[1] The most common complication of DM is the development of peripheral neuropathy which affects up to 50% of individuals with the condition.[2] As protective sensation in the lower extremities is lost, patients become vulnerable to repetitive unrecognized trauma, which often leads to soft tissue ulcerations. Once a foot ulcer develops, infection and osteomyelitis typically ensue in up to 60% of instances, dramatically increasing the risk of hospitalization, limb amputation and premature mortality.[3–5]

Prompt and appropriate treatment of a diabetic foot ulcer (DFU) is paramount in promoting ulcer healing and preserving mobility. Traditionally, management combines off-loading, wound dressings, optimization of glycaemic control and administration of antibiotics.[6] If these fail or if moderate to severe infection is present, surgical debridement is then indicated whereby devitalized tissue and bone are resected, aiding the formation of a healthy granulation wound bed.[7] Despite this being the accepted standard of care at most centres, the prognosis for infected DFUs remains poor with rates of ulcer healing, recurrence, lower limb amputation and mortality over 12-months reported as 46%, 10%, 17% and 15%, respectively.[8]

The socioeconomic implications associated with DFUs are also considerable. Patients treated for infected DFUs often have prolonged hospitalizations and require multiple returns to theatre for surgical debridement, which combined account for ~60% of the overall cost burden.[9] These costs are substantially increased if a lower limb amputation is performed, not only in direct hospital expenditures but also indirectly in the form of reduced productivity and premature mortality.[10] The current 5-year mortality rate following a lower limb amputation for diabetic foot disease is ∼50%, which is comparable to cancer.[11]

In view of the above, interventions that can improve the quality and efficiency of care for patients with DFUs are clearly needed. In recent years, one such intervention has been the creation of in-hospital multidisciplinary treatment pathways. These protocol-driven services enable standardized and evidenced based care to be delivered in emergent settings and have been shown to improve outcomes.[12] However, they also require substantial collaborative effort, resources and expertise to develop and maintain thus presenting a potential barrier for their widespread adoption.[13] At present, clinical practice in Australia remains variable and surgical management of DFUs is often not dictated by best practice guidelines.[14]

A further intervention that has gained clinical interest in the management of DFUs is the use local antibiotic delivery as an adjunct to surgical debridement.[15] In particular, the combination of calcium sulphate (CAS) and hydroxyapatite (HA) as a biocompatible and biodegradable injectable mixture with osteoconductive properties has been gradually introduced into clinical care. The above mixture is usually loaded with either gentamicin (17.5 mg/mL: Cerament G; BoneSupport, Lund, Sweden) or vancomycin (66 mg/mL CS/HA: Cerament V), and demonstrates promising results for treating chronic osteomyelitis and augmenting bone defects.[16,17] Clinical data investigating the use of local antibiotic bone graft substitute in the context of diabetic foot infections remains sparse.[18–21]

We conducted a retrospective cohort study to evaluate the outcomes of a protocolized surgical management pathway including local antibiotic bone graft substitute delivery (in the form of Cerament G/V) for the treatment of infected DFU with associated osteomyelitis. Knowledge of a comparative advantage between conventional and protocolized approaches may help guide clinical practice and assist with optimizing the treatment of diabetic foot infections.

Methods

Study setting and local practice

At our centre, surgical management of patients with DFUs is shared by the orthopaedic and vascular subspecialties (Fig. 1). Referral to the appropriate surgical team is contingent on whether the patient has co-existing occlusive peripheral arterial disease (PAD), defined at the bedside by the absence of pedal pulses to palpation. The orthopaedic department only manages diabetic patients without occlusive PAD. Patients can be referred to our service from the emergency department, affiliated peripheral hospitals as well as general practitioners and podiatrists within the local network.

Between November and December 2018, the orthopaedic department formulated a specialized Foot and Ankle Reconstruction Unit in response to the increasing prevalence of diabetic foot disease in our community. Shortly thereafter a protocol for the surgical management of infected DFUs was developed in accordance with best available evidence and departmental expertise. A predominant change that was instigated was the routine use of Cerament G and/or V in the setting of diabetic foot osteomyelitis. Cerament G was usually preferred due to its broader spectrum, as gentamicin effectively targets most Gram-negative bacteria as well as Gram-positive Staphylococcus. Conversely, Cerament V was only selected if prior microbiological results had excluded Gram-negative bacterial infection or if methicillin resistant forms of Staphylococcus were expected. Other relevant features and differences of conventional and protocolized management of infected DFUs are outlined in Table 1.[22,23]

Patient selection and data source

Only patients who received surgical care directly from the senior author (BM) were considered for inclusion (Fig. 1). Diagnosis related group (DRG) admission codes were used to establish a deidentified electronic database. Consecutive patients who underwent surgical debridement for the treatment of a DFU with osteomyelitis between January 2017 and December 2020 (i.e., immediate 2 years pre- and post-protocolized management) were selected. A diagnosis of osteomyelitis was made based on clinical presentation (i.e., probe-to-bone test), radiological evidence and/or an intraoperative bone biopsy.[24] Radiological evaluation was predominantly based on x-ray and computed tomography (CT), with magnetic resonance imaging (MRI) not routinely performed. Patients were divided into the conventional (control) and protocolized (intervention) arms accordingly and paired with their relevant clinical outcome measures. A minimum 12-months of post-operative follow-up was required. Patients who self-discharged against medical advice or who were non-compliant with post-operative and follow-up instructions were excluded.

Outcomes

The primary clinical outcome considered in the study was the number of operations performed at the same limb site per patient during a 12-month period. If a re-operation was performed for any reason other than infection control (e.g., adjustment of an external fixator) this 'event' was not counted as an additional operation.

Secondary outcomes evaluated included length of hospital stay (LOS) and rates of major amputation (i.e., any amputation proximal to the tibio-talar joint).

The decision to perform a re-operation or major amputation was based on the clinical judgement of the treating surgeon.

Statistical analysis

Data analyses were performed using JASP© statistical software (Version 0.16) (https://jasp-stats.org/). Student's t or Mann–Whitney U tests were used to compare continuous variables and a chi-squared test was used to compare categorical data. Results were deemed statistically significant when the P-value was <0.05.

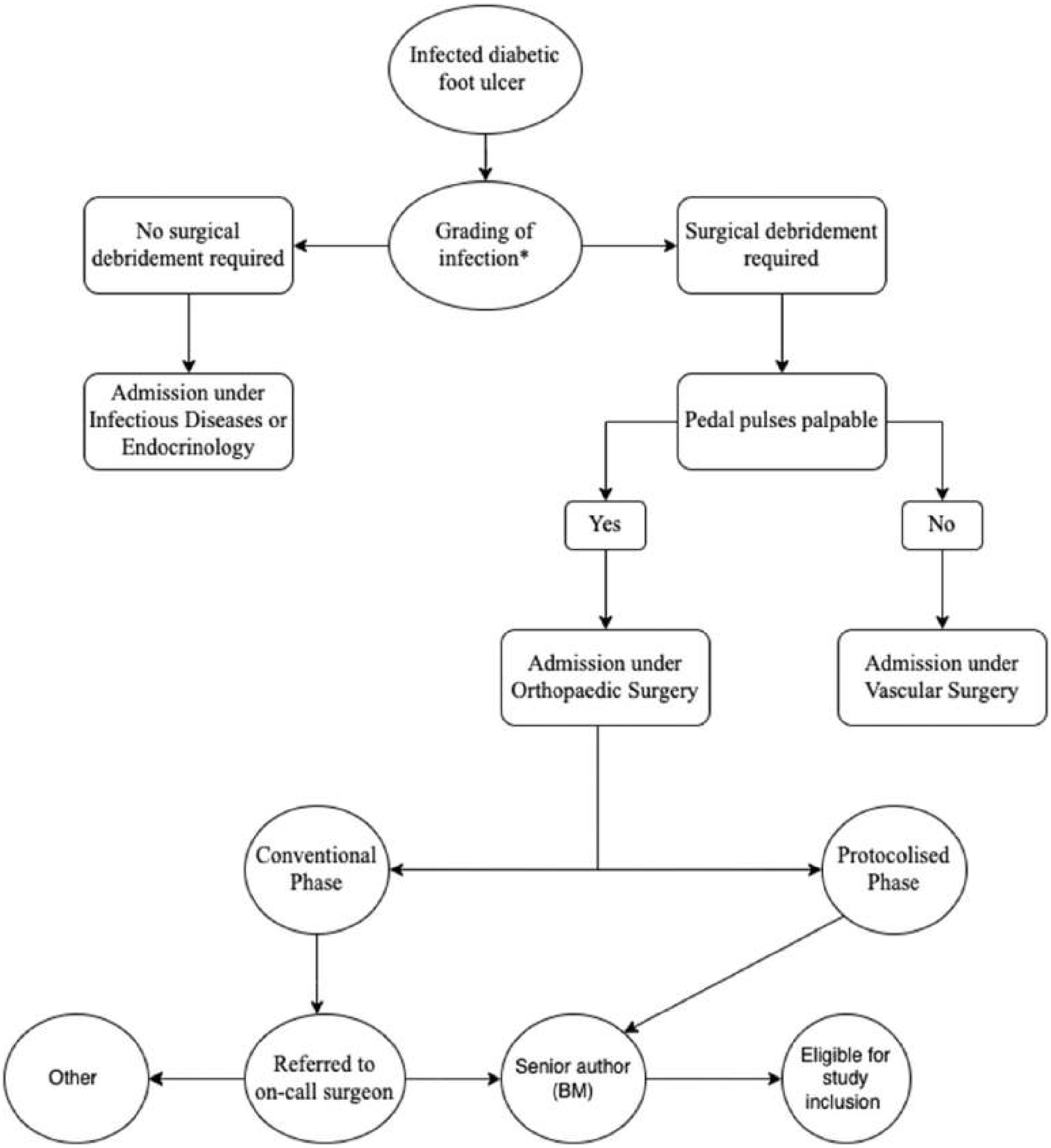

Fig. 1. Institutional referral pathway and study inclusion eligibility of patients with infected diabetic foot ulcers. During the conventional phase, infection severity was based on the clinical assessment of the referring physician (with no objective method). During the protocolized phase, infection severity was based on the International Working Group on the Diabetic Foot (IWGDF) classification system. Ulcers with mild infection (equivalent to IWGDF Grade 2) were managed conservatively, whilst those with moderate or severe infection (IWGDF Grade 3 or 4) warranted surgical debridement.

Ethics

Ethics approval was sought and granted by the Nepean Blue Mountains Local Health District Human Research Ethics Committee (2020/STE02676).

Results

A total of 136 consecutive patients were included in this study (conventional, $n = 33$; protocolized, $n = 103$). There were seven patients lost to follow-up (conventional, $n = 4$; protocolized, $n = 3$) and thus excluded from the study. Baseline patient characteristics were similar between the two cohorts in terms of gender ratios, age and body max index (BMI) (Table 2). Similarly, there were no differences observed between the groups in relation to relevant biomarkers including glycated haemoglobin (HbA1c), serum albumin and glomerular filtration rate (eGFR). Ulcers were most often localized to the forefoot followed by the midfoot and hindfoot in both groups.

Table 1 Outline of infected diabetic foot ulcer management at Nepean Hospital

Phase	Summary
Conventional	• Patients with infected DFUs referred to the on-call orthopaedic surgeon • Assessment and management varied and based on the discretion of the admitting surgeon • No consistent approach to surgical debridement and largely performed by orthopaedic trainees • Local antibiotics (Cerament or otherwise) not applied • Superficial swabs frequently used to guide antibiotic therapy • Multidisciplinary involvement during admission not routine and only available on request of the admitting surgeon • Upon discharge, patient follow-up conducted at an outpatient orthopaedic clinic with or without a consultant present
Protocolized	• All patients with infected DFUs referred to an on-call foot and ankle specialist • Defined pathway for pre-operative assessment (e.g., ulcer characterization, presence of neuropathy, associated foot deformity/contracture) and investigations (e.g., bloods, imaging, nutritional status) • Infection severity is stratified using IWGDF classification system,[22] dictating the need and timing of surgical debridement. Moderate (Grade 3) and severe (Grade 4) infections undergo surgical debridement <24 and <8 h, respectively • Surgical debridement performed according to the red-amber-green principle,[23] combined with tendon balancing procedures to correct foot biomechanics as required • No superficial swabs/tissue samples collected. Multiple deep samples collected with clean instruments during debridement • Cerament G or V routinely administered for all patients with osteomyelitis. The mixture is prepared according to the product instructions and up to 10 mL injected to fill the intramedullary canal/cancellous structure of the infected bone • Post-operative wound review performed on the ward. Criteria for return to theatre include persisting necrotic tissue, purulent discharge, stagnant or rising inflammatory markers and/or imaging suggesting ongoing infection • Patients receive routine endocrinology reviews and are administered systemic antibiotics on the advice of the infectious disease team • Upon discharge, patient follow-up conducted at a weekly, consultant-led, diabetic foot clinic, staffed with specialist wound care nurses and podiatrist

DFU, diabetic foot ulcer; IWGDF, International Working Group on the Diabetic Foot.

Patients in the conventional group had a significantly higher mean number of operations performed per patient (3.5 vs. 1.2; $P < 0.001$) and accumulated a longer hospital LOS (25.1 vs. 12.6 days; $P < 0.001$) when compared with the protocolized group (Table 3). Major amputations were more frequently required and performed among patients in the conventional group (6/33, 18%) as opposed to the protocolized group (2/103, 2%) (<0.05). These consisted of five transtibial and one transfemoral amputations in the conventional group and two transtibial amputations in the protocolized group. One patient in the protocolized group underwent a total calcenectomy for infection control after systemic antibiotics were required to be ceased due to medical reasons. This decision came after the patient chose not to proceed with a transtibial amputation.

Ulcer healing was only assessable in the protocolized group (excluding those who underwent major amputation) with data available for the majority of patients (98/103, 95%). Within 12-months of initial surgical debridement 89% (87/98) of patients demonstrated complete resolution of the ulcer or progressive epithelialization with no evidence of ongoing infection. Three treatment failures (3/87, 3%) occurred with patients having recurrence of the ulcer with infection despite the ulcer initially being declared healed. In all three cases, the ulcer was located on the forefoot. A small number of patients ($n = 10$) experienced a serous wound drainage (locally termed 'Cerament ooze') post-operatively. This is usually resolved within 2 weeks without intervention. No major complications or adverse events were encountered. Data regarding rates of ulcer healing in the control group was not available.

Discussion

The treatment of infected DFUs with osteomyelitis is challenging and requires a multidisciplinary approach.[25] Complicating factors include the high incidence of peripheral neuropathy among this patient demographic which often delays their presentation to medical care, as well as the co-existence of micro and macrovascular complications which markedly compromise host immunity.[26,27] In this context, rapid and thorough surgical debridement is typically necessary for eliminating infection, promoting ulcer healing, as well as mitigating the risk of sepsis and limb amputation.

The present study evaluated the clinical outcomes of a definitive single-stage surgical protocol for the treatment of infected DFUs with osteomyelitis. We compared the results of this approach to our previous conventional management and found that a protocolized pathway was associated with a significant reduction in both the number of operations performed, as well as hospital LOS and major amputation rates per patient in a 12-month period. It is important to note that the clinical 'components' included in our protocolized surgical pathway are not conjectural but rather based on well-established evidence,[12,22,23,28,29] a detailed overview of which can be found elsewhere.[13,30] However, it is likely that maximum benefit is only derived when these components are combined and adhered to in synergistic fashion.

One feature of the protocol design that is based on emerging evidence but arguably offers the most advantage is the routine application of antibiotic bone graft substitute. Over the last few years, the use of Cerament has continued to gain prominence in the treatment of osteomyelitis, initially in the setting of traumatic open fractures (chronic osteomyelitis) before expanding into other fields including revision arthroplasty and diabetic foot disease.[16,20,31] To the best of our knowledge, only one other smaller study has attempted to quantify the impact of antibiotic bone graft substitutes on hospital LOS and limb amputation rates relating to infected DFUs.[32] Our results

Table 2 Baseline patient characteristics

	Conventional (*N* = 33)	Protocolized (*N* = 103)	*P*-value
Gender (male), *n* (%)	24 (73)	80 (78)	0.56
Age (years), mean (SD)	61 (10)	59 (13)	0.43
Side (left foot), *n* (%)	21 (64)	52 (50)	0.19
BMI (kg/m^2), mean (SD)	30 (5)	33 (8)	0.10
HbA1c (%), mean (SD)	8 (2)	8 (2)	0.62
Serum albumin (g/L), mean (SD)	30 (6)	29 (6)	0.21
eGFR (ml/min/1.73 m^2), *n* (%)			0.09
>60	20 (61)	67 (65)	
20 to 60	13 (39)	28 (27)	
<20	0 (0)	8 (8)	
Ulcer site, *n* (%)			0.31
Forefoot	23 (70)	62 (60)	
Midfoot	6 (18)	21 (20)	
Hindfoot	4 (12)	14 (14)	
Other (distal tibia/fibula)	0 (0)	6 (6)	
Local antibiotics, *n* (%)			
Cerament G	0 (0)	73 (71)	
Cerament V	0 (0)	29 (28)	
Cerament G + V	0 (0)	1 (1)	
No. of positive bone cultures	30/33	95/103	0.07
Monomicrobial	9	51	
Polymicrobial	21	44	
P. aeruginosa	3	10	
Methicillin Resistant S. aureus	3	15	

BMI, body mass index; HbA1c, glycated haemoglobin.

Table 3 Clinical outcomes measured over 12-months

	Conventional (*N* = 33)	Protocolized (*N* = 103)	*P*-value
No. of operations, *n* (%)			
1	7 (21)	89 (86)	
2 to 3	12 (36)	12 (12)	
4 to 5	8 (24)	2 (2)	
6 or more	6 (18)	0 (0)	
No. of operations, mean (SD)/median (IQR)	3.5 (2)/3 (3)	1.2 (1)/1 (0)	<0.001
LOS (days), mean (SD)/median (IQR)	25.1 (25)/19 (16)	12.6 (14)/7 (8)	<0.001
Major amputations, *n* (%)	6 (18)	2 (2)	<0.001
Ulcer healing rate[†], *n* (%)	-	87 (89)	
Ulcer recurrence rate[‡], *n* (%)	-	3 (3)	

[†]Ulcer healing was only assessable in the protocolized management group (excluding those who underwent major amputation). Data were available for the majority of patients in this group (*n* = 98, 95%).

[‡]Ulcer recurrence rate was calculated patients for whom an ulcer was initially declared healed (*n* = 87). LOS, length of hospital stay; Major amputation defined as amputation above the tibiotalar joint.

not only help validate their findings but also additionally assess re-operation rates, an equally important clinical endpoint, offering further insight regarding the efficacy of these therapies for treating diabetic foot infections.

The local delivery of antibiotics at the time of surgical debridement represents an important adjunct to surgical management. This strategy allows high local antibiotic concentrations to be achieved exclusively at the site of infection, a key advantage considering that vascular supply is frequently compromized in diabetic limbs and leads to poor penetration of systemic antibiotics to affected areas.[33] Pharmacokinetic studies have shown that Cerament G achieves local gentamicin concentrations >100 times greater than the minimum inhibitory concentration (MIC) of clinically relevant organisms, with levels then remaining in therapeutic range for at least 28 days.[34,35] Similar results have been reported for Cerament V.[36,37]

Relating to this, we found an ulcer healing rate of 89% for patients treated with Cerament. Additionally, rates of recurrence in this cohort were low at 3%. Although we were unable to draw direct comparisons to our own control group, these findings are promising when we consider that ulcer healing and recurrence rates within 12-months of 46% and 10%, respectively, have been reported in the literature.[8] To explain this, it is likely that the very high local antibiotic concentrations conferred by Cerament overcomes the bacterial resistance and polymicrobial biofilm formation characteristically associated with diabetic foot infections.[38,39] Importantly, these high local concentrations are generally safe for patients as noted in our study among others.[21]

Considering the above, by optimizing local antibiotic delivery, the prescribing of systemic antibiotics may be better rationalized. Current guidelines for treating diabetic foot osteomyelitis recommend that systemic antibiotic be used for a period of 4 to 6 weeks post-debridement.[40] Such prolonged duration of therapy can certainly increase the risk of toxicity, antibiotic resistance and costs.[41] In this setting, the use of local antibiotic delivery may potentially shorten the duration of systemic antibiotic required, thus limiting adverse effects and other associated drawbacks including poor patient compliance.[42] Of note, further research is still required to define the minimum duration of systemic antibiotics, that when combined with local antibiotic delivery, offers a comparable clinical efficacy to prolonged therapy.

Dead space management following surgical debridement is also of clinical relevance. Resection of infected tissue and necrotic bone can lead to the formation of large cavities that then fill with haematoma.[43] This creates a conducive environment, low in oxygen and pH, in which residual bacteria can proliferate thus increasing the likelihood of infection recurrence. Furthermore, osseous defects post-debridement may undermine skeletal stability and predispose patients to delayed pathological fractures.[44] Although not formally assessed in our study, existing evidence suggests that Cerament, in its liquid and injectable form, is a highly effective method for filling osseous dead space, remodelling into host bone within 6–12 months.[45] Importantly, there is no current published evidence to suggest that the use of Cerament can lead to development of heterotrophic ossification.

Our study has a number of limitations. The single centre retrospective design can be a source of selection bias, limiting the generalizability of our results. Moreover, only the senior author (BM) was permitted to use Cerament during the study period via an 'Authorized Prescriber' scheme, as the product was not listed on the Australian Register of Therapeutic Goods (ARTG) prior to August 2021. As such, all patients in the protocolized phase were admitted under the care of and had surgical debridement performed by an experienced subspecialist foot and ankle surgeon. This may not be practical at some institutions (including our own, during the conventional phase) who delegate such procedures to orthopaedic trainees. Additionally, there were differences in patient sample sizes between the conventional and protocolized groups which may have influenced the comparisons drawn. This is attributed to the fact that on-call duties and management of DFUs was shared among different consultants in our department during the conventional phase of the study. To eliminate potential surgeon-specific confounding factors in the conventional phase, we intentionally chose to only include patients who presented when the senior author (BM) was on-call or who were referred to the senior author (BM) by other surgeons.[46] Finally, we were limited in the scope of demographic details and follow-up data available for the conventional management group. Medical records during this period were largely handwritten and the relevant data were often unavailable or difficult to reliably interpret namely in relation to ulcer healing rates as patient follow-up was not performed in a dedicated diabetic foot clinic. Future prospective studies are welcomed to overcome these limitations and validate our findings.

Conclusion

Compared to conventional surgical management, a definitive single-stage surgical protocol (including the routine use of Cerament) for the treatment of diabetic foot osteomyelitis can lead to a reduction in the number of operations performed, hospital LOS and rates of major lower limb amputation. Further studies are needed to assess the cost effectiveness of this approach.

Author contributions

Jason Chow: Conceptualization; data curation; investigation; methodology; writing – review and editing. **Sahand Imani:** Investigation; project administration; visualization; writing – original draft. **Isuri Kavisinghe:** Data curation; investigation; project administration; writing – review and editing. **Rajat Mittal:** Conceptualization; formal analysis; methodology; writing – review and editing. **Brian Martin:** Conceptualization; methodology; resources; supervision; writing – review and editing.

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Conflicts of interest

BM holds consultancy agreements with BoneSupport® and Orthofix®, in addition to owning shares in BoneSupport®.

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