Title

Complex Foot Infection Treated with Surgical Debridement and Antibiotic Loaded Calcium Sulfate - A Retrospective Cohort Study of 137 Cases.

Abstract

Complex foot infections involving bone and soft tissue in patients with co-morbidities such as diabetes and peripheral arterial disease (PAD) are a cause of significant hospital admission. They are associated with substantial economic costs to health services worldwide. Historically, severe foot infection has been treated with surgical debridement and prolonged courses of systemic antibiotics. Prolonged systemic antibiotic use increases the risk of drug side effects, antimicrobial resistance and Clostridium difficile infection. The purpose of this study was to investigate whether surgical debridement and implantation of antibiotic loaded calcium sulfate is effective in the resolution of foot infection and wound healing. A retrospective cohort study of 137 consecutive cases of osteomyelitis (127) or significant soft tissue infection (10) over 62 months from 02/2013 – 04/2018 was conducted following local ethical approval. All cases of infection were treated with surgical debridement and local antibiotic-loaded calcium sulfate. The primary outcomes of infection resolution, time to healing and duration of post-operative antibiotics were measured. In 137 cases, 88.3 % of infections resolved. Infection was eradicated in 22 patients without post-operative systemic antibiotics. 82.5% of wounds healed, with an average healing time of 11.3 weeks. Healing time was significantly increased for the co-morbidities of diabetes and PAD (p=<0.05) and for those requiring prolonged systemic postoperative antibiotics. Conservative surgical debridement and implantation of local antibiotic impregnated calcium sulfate is safe and effective in managing complex foot infections. We advocate early surgical intervention before deeper tissue involvement to help preserve lower limb structure and function.

Key words:

diabetes, foot ulceration, local antibiotics, osteomyelitis, peripheral arterial disease

Level of Clinical Evidence:

3

Introduction

Worldwide diabetic foot ulceration prevalence is estimated at 6.3%; ranging from 3% in Oceania to 13% in North America (1) with foot ulcers developing in 9.1-26.1 million people with diabetes annually around the world (2). Fifty percent of these ulcerations become infected, resulting in high rates of hospitalization, increased morbidity and potential lower limb amputation (3) with mortality rates at 70% within five years of below-knee amputation (2).

Diabetic foot infection (DFI) particularly osteomyelitis (OM) is difficult to treat due to multidrug resistance and poor penetration of antibiotics into bone (4). There is no agreed treatment strategy and the role of antimicrobial therapy and surgery is not sufficiently clarified (5). Relying on systemic antibiotics for complex lower limb infection can often lead to prolonged treatment that is often ineffective (6) for multiple reasons, including resistance, formation of biofilms (7) and circulatory impairment (8). Systemic antibiotics are also associated with adverse events (7,9,10) including liver and renal impairment (11) and increased incidence of Clostridium difficile, the leading cause of health-care associated infective diarrhea (12).

The use of local antibiotic delivery systems have become much more common practice over recent years (4) as successfully demonstrated by multiple surgical centers (7,8,11,13-19). The aim is to provide a high concentration of antibiotics locally, to eradicate infection and subsequently aid limb preservation. This study aims to support the use of this treatment option, as an adjunct or alternative to systemic antibiotics alone. The study reports on 137 consecutive cases over 62 months. All cases had foot infection and underwent conservative surgical debridement and local administration of antibiotic loaded calcium sulfate (ALCS) (Stimulan Rapid Cure®, Biocomposites, Keele, UK) with or without additional postoperative systemic antibiotics. Stimulan Rapid Cure® is approved as a carrier for antibiotics, for use in infected bone and soft tissue voids.

Calcium sulfate (CS) belongs to a synthetic ceramic group of bone graft substitutes (18) shown to be biocompatible and biodegradable (6). It is indicated for bone and soft tissue infections (20) although different calcium sulfate products have different approvals. The purity of medical grade CS ensures predictable in-vitro dissolution after 3-4 weeks (20). Evidence for its use has been promising; Laycock et al (21) demonstrated in-vitro antibiotic efficacy for 20 days using a range of antibiotics, while Kanellakopoulou et al (22) noted sustained release of moxifloxacin from CS for 35 days in animal models with osteomyelitis. Gauland (11) meanwhile evaluated 323 patients who had osteomyelitis of the lower extremity and found 279 of 323 healed without the need for additional intra-venous antibiotics.

The study objectives were to: determine whether conservative surgery with antibiotic loaded calcium sulfate beads effectively resolved infection; healed complex wounds and reduced the necessity for, or duration of, postoperative systemic antibiotics. The secondary objectives were to determine comorbidities which affect wound healing within the sample, and to identify adverse effects of the calcium sulfate treatment strategy.

Patients and Methods

A double-center, retrospective observational cohort study was performed by medical record review of all patients undergoing surgical debridement of complex foot infection, over a 62 month period from 02/2013- 04/2018. Patients were recruited from two hospitals under the care of one surgical team (FW, RM, AB). The medical records of 137 consecutive cases of complex foot infection treated with surgical debridement were reviewed. All surgery was performed between February 2013 and April 2018. The curtailment of date of the study was July 18th, 2018. Primary outcomes were infection resolution, time to wound healing and duration of post-operative systemic antibiotics. Secondary outcomes were medication side effects and comorbidities associated with delayed wound healing. Permission to review notes was granted by the local UK National Health Service clinical effectiveness team.

One hundred and thirty-seven consecutive patients were involved in the study, 117 (85.4%) males and 20 (14.6%) female; 113 (82.5%) had a diagnosis of diabetes; 24 (17.5%) had a diagnosis of Peripheral Arterial Disease (PAD). All cases of surgical debridement with ALCS were included, no patients were excluded. The independent variables of interest were: Gender and the comorbidities of diabetes and/or PAD. The outcome measures of: Infection resolution (y/n), healing (y/n); time to healing (weeks), postoperative systemic antibiotics treatment (y/n) and duration of postoperative antibiotic treatment (weeks) were collated by the surgical team (RM,FW,AB). This was achieved via the review and abstract of data from medical records, laboratory reports and radiographic images (RM,FW,AB) (23). The outcomes assessors consisted of the surgical team undertaking the surgical debridement (RM,FW,AB).

Complex foot infection was defined as all cases of OM or significant soft tissue infection. OM was diagnosed through positive probe-to-bone test (24) and radiographic findings demonstrating cortical disruption, periosteal reaction and bone destruction, or by bone biopsy. Soft tissue infection (STI) was diagnosed from clinical signs, in line with the Infectious Diseases Society of America (IDSA) guidelines (25) and by positive microbial culture of tissue sampling. PAD was determined by the presence or absence of palpable dorsalis pedis and posterior tibial pulses. Time to healing was defined as the time (in weeks) taken to achieve intact skin postoperatively. Infection resolution was determined by the eradication of all clinical signs and symptoms (following IDSA guidelines) combined with radiological evidence of no progression of osteomyelitis. Culturing wounds without clinical signs of infection has no predictive value for outcomes and therefore was not utilized to determine the presence or absence of infection (26)

Intervention

All patients underwent surgical debridement as day case surgery utilizing a regional ankle block. The patients were positioned supine; a pneumatic ankle tourniquet was applied in all cases with the exception of those with medial vessel calcification. The foot was elevated and swabbed with Iodinated Povidone and then draped utilizing aseptic non-touch technique. Where a tourniquet was applied the foot was then exsanguinated with a single use Esmarch bandage and the tourniquet inflated to 100mmHG above systolic blood pressure. Surgical debridement was performed and non-viable tissue excised. This was followed by high-volume irrigation using a 50/50 mix of iodinated povidone and sodium chloride solution 0.9% of between 100 and 500 ml, depending of the wound dimensions. Tissue samples were taken and sent for microbiological and histological testing.

ALCS was prepared in theatre by mixing vancomycin (1 g) in powder and gentamicin in liquid (3 ml/120 mg) with 5 cm3 of calcium sulfate hemihydrate. This was subsequently placed in a mold mat to produce multiple beads. Setting time is variable dependent on the antibiotic selection (approximately 5 minutes). The synthetic biocompatible material acts as a drug delivery system (15) for the antibiotic. Gentamicin and vancomycin were selected for their broad spectrum characteristics, predictable and rapid setting times with the carrier vehicle. Irrespective of microbiological sensitivities, this combination has been shown to provide better in vivo results than empiric antibiotics or those selected based on culture and sensitivity data (11). The set beads were then implanted deep within the wound and the medullary cavity of resected bone to enable optimum penetration. Up to 5 cm3 was implanted depending on the size of the void.

When appropriate, surgical closure was achieved with 3.0 prolene sutures to retain the antibiotic loaded beads. Appropriate sterile dressings were applied and the patient was discharged on the same day. Postoperative review took place within 2-3 days (FW, RM). Some patients were immobilized in a cast to expedite postoperative healing. All patients were advised to rest and elevate the affected limb for a minimum of two weeks after the surgery. Twenty-two patients were discharged without systemic postoperative antibiotics the remainder had antibiotics for between 2 days and 84 days, (mean - 18.6 days). The decision to supply or withhold systemic antibiotics was primarily dependent on the severity of the infection. Where infection was known to be antibiotic resistant or with systemic involvement then oral or IV antibiotics were administered in addition to the calcium sulfate implantation.

Statistical Plan

For time to healing low numbers of events precluded multiple regression approaches. This outcome was modelled using a series of uncontrolled logistic regression analyses and a series of uncontrolled Cox time-to-event analyses. Cases in which healing was not achieved by the curtailment of the study were recorded as right-censored observations, with the date of censoring set at the curtailment of the study on July 18th 2018. For all models, p-values, odds/hazard ratios and associated 95% confidence intervals were reported. Survival curves were constructed considering the event of healing for all variables revealed to be significantly associated with the time-related outcome. Whilst infection resolution Yes/No (a binary response) was recorded, the exact time to infection resolution could not be established from the note review.

Results

Valid data was obtained between 02/2013 and 04/2018 from 137 patients. Sample characteristics are summarized in Table 1. Of 137 patients infection was resolved in 121 (88.3%) with the remaining 16 (11.7%) unresolved or lost to follow-up. 109 patients achieved healing (79.6%) and 16 (20.4%) patients did not achieve healing. The logistic regression analyses revealed that in uncontrolled models, age ($p=0.036$) and post-operative duration of antibiotics ($p<0.001$) were significantly associated with time to healing at the 5% significance level. No other variable achieved statistical significance at the 5% significance level. With no a priori hypotheses, only the postoperative duration of antibiotics parameter would be considered to show significance following a correction for multiple comparisons. The odds ratio of 0.999 (95% confidence interval 0.999 to 1.00) revealed that the odds of healing decreases by about 0.7% with each additional week of antibiotic duration (3% with each additional month). Parameters of all logistic regression models are given in Table 2.

The Cox time to event analyses revealed that in uncontrolled models postoperative duration of antibiotics ($p=0.042$), diabetes status ($p=0.046$) and PAD (p<0.001), were significantly associated with time to healing at the 5% significance level (Table 3). No other variable achieved statistical significance at the 5% significance level. With no a priori hypotheses, only the PAD parameter would be considered to show significance following a correction for multiple comparisons. The hazard ratio of 0.329 (95% confidence interval 0.180 to 0.602) revealed that the "hazard" of healing in those with PAD was approximately one third those with no PAD. Parameters of all models are given in Table 3.

Survival curves for patients discriminated by duration of post-operative antibiotics (dichotomized into up to 1 month and over 1 month), by diabetes status and by presence or absence of PAD are presented in Figs. 7-9. The ungrouped survival curve for healed wounds alone is presented in Fig. 10.

The proportion of unhealed ulcerations drops rapidly in all patients during the initial 25 weeks, with little substantive difference between groups up to that point. Beyond that point, greater levels of healing are observed in patients with postoperative antibiotics up to 1 month, with no diabetes and with no PAD. However, this latter effect may be a sampling artefact: low numbers of patients with PAD (n=24) and those without diabetes (n=24) limits the power of the analysis.

Discussion

Resolution of Infection

In 137 consecutive cases of osteomyelitis (127) and soft tissue infection (10) 88.3 % of infections resolved and 11.7% did not or lost to follow-up. This compares similarly with Kapur et al (27) where 50 patients with diabetes underwent surgical debridement and antibiotic implantation for osteomyelitis of the foot, with 7 (14%) patients requiring further surgery within 12 months related to their initial procedure. Thus this preliminary study suggests that this is a safe and effective method in reducing the need for amputation. Limitations of the study were that some patients had concurrent systemic antibiotic management and some peri-operative data was not available for review to allow further analysis.

Most studies into surgical debridement, combined with the use of local delivery of antibiotics, utilized systemic antibiotics postoperatively (17,28,29). Our study demonstrates a similar approach in many respects, with the exception that systemic antibiotics were not supplied postoperatively in all cases. Twenty-two patients were treated successfully for infection with ALCS but no systemic antibiotics. Patil et al (30) treated 106 diabetic lower limb infected patients with ALCS and found 98 (92%) with no recurrence of infection. Interestingly, only 28 (26%) received supplementary systemic antibiotics. The mean follow up period however was short at 92 days and debridement was described as radical. This may suggest that systemic antibiotic therapy may not be required for all cases following surgical debridement and topical antibiotic treatment.

For those assessed as requiring additional systemic postoperative antibiotics, the authors (RM,FW) utilized a greater proportion of oral antibiotics (58.4% patients compared with IV antibiotics 24.1% patients) than in comparable studies. Of this sub-set, Infection resolved in 87.5% and 87.9% which demonstrates a similar outcome. It could be posited that, the route of antibiotic administration had little bearing on successful infection eradication. This is supported by the findings of many previous studies which back up the high bioavailability and efficacy associated with oral therapy (31,32,33)

Systemic antibiotic efficacy may be limited by impaired blood flow of infected bone resulting in low penetration at the infection site [8,9,10]. The study found that only one patient (n=1/24) with PAD had infection which was unresolved and required further debridement. This may suggest that local implantation is an important route of administration for this cohort of patients, and may perhaps be a viable alternative to parenteral treatment where vascularity is compromised (34).

However, it is not certain that the local implantation of antibiotics alone is responsible for the eradication of infection and this may be attributed to the surgical debridement. In this study, surgical debridement was conservative in nature with every effort to preserve structure and function, devitalized infected tissue was excised and thorough irrigation was performed significantly reducing the local bacterial burden (35). Lazaro-Martınez et al (5) reaffirms this who found no significant difference in 52 patients with diabetic foot osteomyelitis (DFO) as randomized into either a group receiving up to 90 days of systemic antibiotics or in a group undergoing surgery. Results demonstrated primary healing in 75% compared to 86.3% for the antibiotic and surgery groups respectively and healing achieved in 7 and 6 weeks. There was however, a short follow-up period of 12 weeks and relatively low sample size.

It is difficult to determine specific reasons why some of our infections were not eradicated, but it may be due, primarily to multi-resistant organisms and, in some cases, incomplete surgical debridement.

Healing Times and Impact of Co-morbidities

Healing was defined once complete epithelialization had taken place, which includes the incision line and any associated ulceration. Our results demonstrate that 82.5% of patients healed following surgical intervention and antibiotic packing with a mean average healing time of 11.3 weeks. The remaining 17.5% episodes that did not heal either required further debridement, died before the wound had healed, were lost to follow-up or did not heal by the curtailment of the study of July 18th 2018. In comparison with other studies, Pyho et al (36) found 14 (48%) neuropathic heel ulcers healed that underwent surgery with or without some form of antibiotic bone substitute. Patients with critical limb ischemia however were excluded and the follow up-period was only 350 days. Wai Chon et al (29) noted 16 (84%) of patients with diabetic foot ulceration undergoing debridement, lavage and administration of ALCS healed within 1 month. Gauland (11) found that 70% of patients healed in a group of 323 with osteomyelitis of the lower extremity who underwent surgery and local antibiotic implantation while Grannon and Pierides (37) noted a healing rate of 23% with a further 69% on a healing trajectory in a group of patients with diabetes with recalcitrant foot osteomyelitis which had previously failed to heal with long courses of systemic antibiotics or had relapsed. Jogia et al (38) meanwhile analyzed 109 patients with diabetes and subsequently underwent local antibiotic implantation for osteomyelitis. Mean average postoperative healing time was 6 weeks, although PAD was excluded and all patients received systemic antibiotics and offloading. In another study, Jogia et al (16) retrospectively analyzed 20 patients with diabetes over 18 months with forefoot osteomyelitis. Median healing time was 5 weeks, with all patients achieving healing and no episodes of recurrence within 12 months.

Healing rates and times in our study were summarized and analyzed over subgroups based on antibiotic administration, with minimal difference between those who had postoperative systemic antibiotics, compared to those that did not; revealing no evidence for improved healing using antibiotics. However, the precision of the analysis is limited by the low frequency of patients who had no postoperative antibiotics. Those that had antibiotics up to one month were significantly more likely to heal than those who received antibiotic administration over one month (Fig. 7); suggesting that the use of prolonged antibiotics does not heal wounds. This may be because those who had resistant infections may have had continued antibiotic administration and therefore more likely to predispose to a poor outcome with increased healing times. It may also be the case that subjects who had prolonged courses of antibiotics may have had a greater propensity to an unsalvageable wound that was unlikely to heal. In a non-randomized study with limited sample size it is not possible to adjust for such potential confounders.

A similar consecutive retrospect study conducted by Dekker et al (39) suggested ALCS may not be beneficial. They compared patients who underwent surgical debridement without ALCS, to a combination of debridement and local implantation of antibiotics. There was no significant difference between the two groups in healing time. Similarly, in a retrospective comparative study, Qin et al (40) compared surgical debridement with surgical debridement and implantation of ALCS in DFO and found no improvement in the latter group in healing rate, healing time or amputation rate. It did however; find that ALCS can prevent the recurrence of DFO demonstrating 0% recurrence compared to 36% recurrence in the debridement group alone.

Unsurprisingly, a diagnosis of diabetes also had a significant effect on healing rates (Table 1); with 22 out of 24 (91.7%) non diabetes patients healing compared to 87 out of 113 (77%) diabetic patients. Time to healing was also found to be significantly increased in those patients with diabetes and hence likely to predispose to a poorer outcome (Fig. 8) although low numbers of patients with diabetes reduced the power of the analysis. Tsourdi et al (41) refers to many mechanisms of the deleterious effect of diabetes on wound healing, including: extrinsic factors, such as repeated mechanical stress from an insensate foot due to neuropathy; as well as intrinsic factors, including ischemia from micro and macrovascular disease, the direct effect of hyperglycemia on collagen synthesis, and the clinical correlation of hyperglycemia and poor wound healing.

Diabetes substantially increases the risk of peripheral arterial disease, with vascular diseases, particularly atherosclerosis, a major cause of disability and death (42). We found that those patients with PAD had poor healing rates and times. Only 50% of patients with PAD healed, compared to 89.8% with no PAD. Similarly, there were significantly reduced levels of healing over time (Fig. 9) with overall mean healing of 16.4 weeks in those with PAD compared to 10.7 weeks in patients with no PAD; although data was only available for 11 patients in the vascular impairment group because 50% failed to heal, requiring further debridement or amputation.

Systemic Postoperative Antibiotics

Systemic antibiotics have well documented disadvantages, including: antimicrobial resistance and toxic effects with liver and renal impairment. These effects are all too common particularly in patients who may already be susceptible to organ failure; with wide-ranging cost implications arising from the cost of the drugs, administration costs, blood monitoring and managing adverse effects. Finding novel ways to reduce the use of systemic antibiotics is of paramount importance in future management of eradicating infection and reducing antibiotic resistance (37). Our study questions the absolute requirement for systemic antibiotics in all cases once surgical debridement and antibiotic loaded calcium sulfate beads have been implanted for foot infection. In this study 23 (16.8%) patients did not receive postoperative systemic antibiotics in comparison to 114 (83.2%) patients who received IV or oral systemic antibiotics for a mean average duration of 18.6 days and ranging from 1-84 days. Of this latter group 22 (19.3%) patients only received them for up to 48 hours for prophylaxis. Based on the findings of this and other studies, the authors question the value of short postoperative courses of antibiotics due to the successful outcomes in the non-postoperative antibiotic group. No data however, was available on two (1.5%) patients. Fleiter et al (7) found that 13 out of 20 patients did not require concomitant systemic antibiotics in a caseload of post traumatic/postoperative bone infections, with 20% requiring further surgery due to recurrence of infection which the authors ascribe to incomplete debridement. Jogia et al (16) found that the mean duration of postoperative antibiotics for a similar cohort of patients to ours after locally administered antibiotics was 14 days in a sample size of 20 patients. In another study by Jogia et al (38), a case series of 109 patients received 1.4 weeks (10 days) of postoperative systemic antibiotics but with a mean duration of 8 weeks preoperatively. Grannon and Pierides (37) found 77% required post-operative antibiotics for a mean 7 weeks duration in comparison to 82.4% in our study with a mean duration of only 18.6 days.

The majority of our patients underwent surgical debridement and local antibiotic implantation for infection of bone as opposed to soft tissue infection totaling 127 out of 137 (92.7%) cases. This may be because many patients are often referred on to a specialist team belatedly when the infection has already taken hold, crossed tissue planes and infected deep tissues. On this basis, we encourage early referral to a specialist team and have a low threshold for early surgical intervention and local antibiotic-loaded administration, ensuring a more direct route to help preserve structure and function and prevent amputation. We have also used this method for prophylaxis in patients with high predilection for infection in foot surgery, which has been shown to be previously effective (43).

Adverse Effects

A secondary objective was to determine any adverse effects of antibiotic loaded calcium sulfate. We noted no adverse reactions including any local or systemic toxicity but it was noted that dissolution of ALCS did cause some skin maceration in some cases to varying degrees which may have affected healing times. However, Khansa et al (44) found overall complication rates between patients packed with ALCS and those that were not were similar (43.8% vs. 51.9%, p=0.54) in 120 stage 4 pressure ulcers but there were only 16 ulcers in the ALCS group. Jogia et al (16) meanwhile noted no adverse reactions in 20 patients and Patil et al (30) found none in 106 patients with implantation of ALCS. Inflammatory reactions have been observed previously in the literature suspected to be due to the calcium rich fluid causing transient cytotoxic effects

(34) but overall it has been shown to be safe [8] with no nephrotoxic or hepatotoxic effects (7,22,44).

Other Outcomes

Analysis of the results highlighted other unforeseen trends which were not originally sought. For example, it was noted that 113 of our patients had diabetes all of which had peripheral neuropathy of varying degrees. Of interest was that all but six of the remaining 24 patients in the non-diabetic group had peripheral neuropathy due to other causes including spina bifida, alcoholic neuropathy or neuropathy of unknown cause. Although there may have been various factors contributing to their ulceration and infection such as hyperglycemia, PAD, foot deformity and social factors in these cases, neuropathy was a likely major underlying contributing factor to their foot disease.

The large proportion of men in the study (85.4%) suggests a greater predilection to diabetic foot disease in males than females, consistent with other studies (45,46). Possible reasons include males having a much greater chance of developing peripheral neuropathy, more likely to smoke and increased rates of PAD. This lower risk in females has also been attributed to increased joint mobility, lower foot pressures and hormonal differences which are believed to enhance neural protection (45, 46).

Strengths and Limitations

A significant strength of this paper was that all of the surgery was performed by the same surgical team experienced in diabetic foot surgery minimizing bias and allowing consistency of results.

In terms of limitations, a small proportion of the patients were lost to follow-up. These patients were all located out of area and had been followed by the initial referring center. Those centers were contacted to provide postoperative patient data but some did not respond. In addition, we could not provide data on which patients may have had preoperative systemic antibiotics and the duration of the preoperative therapy. Healing times, meanwhile, may have been influenced by each patient’s individual postoperative regime. For example, where appropriate, some patients were casted postoperatively, which has been shown to expedite healing (47,48) others were not. Eradication of infection and healing times would have also been dependent on glycemic control, and it would have therefore been useful to have noted HbA1c results at the time of surgery. Finally, determining when the infection was eradicated would have given a wider range of statistical data but this is very difficult to determine.

Further studies, particularly randomized controlled trials would be useful to compare surgical debridement, thorough irrigation and use of ALCS to surgical debridement and thorough irrigation alone. However, from an ethical and moral perspective it could be considered a high-risk strategy when the consequences of failure are possible amputation.

In conclusion, a combination of conservative surgical debridement and implantation of ALCS would appear to be safe and effective in managing complex foot infection, and may reduce the requirement for prolonged postoperative courses of systemic antimicrobials potentially reducing the associated financial cost, adverse reactions and often toxic effects of these drugs. We would advocate early surgical intervention in appropriate cases, to prevent deeper tissue involvement preserving lower limb structure and function. However, the literature shows contradictory low-level evidence into the effectiveness of the use of ALCS. This highlights the requirement for further larger scale prospective studies into the efficacy of this potentially useful treatment modality.

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Tables

Variable	**Healed (*n*=109)**	**Not healed (*n*=28)**	**All cases (*N*=137)**
Post-operative duration of antibiotics (days) (mean (SD))	17.5 (18.9)	23.9 (23.2)	18.6 (19.8)
PAD			
No PAD	97 (89.0%)	16 (57.1%)	113 (82.5%)
PAD	12 (11.0%)	12 (42.9%)	24 (17.5%)
Post-operative antibiotic delivery method			
None prescribed/no data	18 (16.5%)	5 (17.9%)	23 (16.8%)
IV	24 (22.0%)	10 (35.7%)	34 (24.8%)
Oral	67 (61.5%)	13 (46.4%)	80 (58.4%)
Gender			
Male	93 (85.3%)	24 (85.7%)	117 (85.4%)
Female	16 (14.7%)	4(14.3%)	20 (14.6%)
Age (years) (mean (SD))	60.1 (13.1)	54.3 (8.67)	60.7 (12.7)
Diabetes status			
Non-diabetic	22 (20.2%)	2 (7.1%)	24 (7.5%)
Diabetic	87 (79.8%)	26 (92.9%)	113 (92.5%)

Table 1: A statistical description of the cases

Variable	**P-value**	**Odds ratio (OR)**	**95% CI for OR**
Age	0.036	1.05	(1.00, 1.01)
Gender Male (reference) Female	 0.801	 1.22	 (0.256, 5.84)
Diabetes status Non-diabetic (reference) Diabetic	 0.234	 0.284	 (0.0360, 2.26)
Method of antibiotic delivery[1] Oral (reference) IV	 0.750	 0.829	 (0.260, 2.64)
PAD No PAD(reference) PAD	 0.577	 1.56	 (0.330, 7.34)
Post-operative duration of antibiotics (days)	<0.001	0.999	(0.999, 1.00)

[1]Analysis conducted on all cases with recorded method antibiotic delivery (*n*=114)

Table 2: Uncontrolled Logistic Regression Model Parameters

Variable	**P-value**	**Hazard ratio (HR)**	**95% CI for HR**
Age	0.959	1.00	(0.984, 1.02)
Gender Male (reference) Female	 0.725	 0.909	 (0.553, 1.55)
Diabetes status Non-diabetic (reference) Diabetic	 0.046	 0.689	 (0.386, 0.992)
Method of antibiotic delivery[1] Oral (reference) IV	 0.571	 0.874	 (0.547, 1.39)
PAD No PAD (reference) PAD	 <0.001	 0.329	 (0.180, 0.602)

Post-operative duration of antibiotics (days)	0.042	0.988	(0.977, 1.00)

[1]Analysis conducted on all cases with recorded method antibiotic delivery (n=114)

Table 3: Uncontrolled Cox Regression Model Parameters

Figure Legend/s

Figure 1 Preoperative Photograph of Right Foot Second Metatarsophalangeal Ulceration with Underlying Osteomyelitis

Figure 2 Preoperative X-ray of Right Forefoot in Dorsoplantar View Demonstrating Second Metatarsophalangeal Joint Osteomyelitis

Figure 3 Intraoperative Photograph Following Second Metatarsophalangeal Joint Excision and Lavage with Antibiotic Loaded Calcium Sulphate Beads In situ

Figure 4 Intraoperative Photograph following Second Metatarsophalangeal Joint Excision and Lavage with Antibiotic Loaded Calcium Sulfate Following Wound Closure

Figure 5 Six Weeks Postoperative Photograph of Plantar Aspect of Foot Following Surgical Debridement and Implantation of Antibiotic Loaded Calcium Sulfate Demonstrating Healed Ulceration

Figure 6 Six Weeks Postoperative Photograph of Dorsal Healed Surgical Wound Following Surgical Debridement and Implantation of Antibiotic Loaded Calcium Sulfate

Figure 7 Survival Curve for Patients with Post-operative Antibiotics of Duration up to One Month, and Over One Month

Figure 8 Survival Curve for Patients with and without Diabetes

Figure 9 Survival Curve for Patients with and without Peripheral Arterial Disease

Figure 10 Survival Curve for Healed Wounds

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