Case Study

Maggot debridement therapy for the treatment of diabetic foot ulcers: robbing the rich past to give to the sore

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Key Learning Points
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The lifetime risk of a diabetic patient developing diabetic foot ulcers lies between 15-25%[1]. Good diabetic foot care therefore forms a cornerstone of care for diabetic patients and focusses on prevention, management of chronic wounds and early identification and treatment of acute infections. Diabetic foot ulcers can acutely present as diabetic foot sepsis, which can be ultimately limb or life threatening and requires early aggressive management with antibiotics and emergency surgical debridement. The number of lower limb amputations secondary to diabetes has reached an all-time high in England, with 26,378 recorded from 2014-2017, an increase of 19.4% from 2010-2013[2]. Amputations impact patients' quality of life, independence and carry a significant cost to the health service – limb preservation is therefore critical. This case describes a case of a 57-year-old diabetic patient who presented with severe diabetic foot sepsis leading to multiorgan failure. It provides a brief overview of the history and evidence base supporting maggot debridement therapy. Most importantly, the case demonstrates the combination of aggressive surgical debridement early in the patient's admission with subsequent use of maggot debridement therapy (MDT) for selective debridement of necrotic tissue. MDT was successfully used to complement ongoing antibiotic therapy and reduce repeated surgical debridement, thus allowing the preservation of healthy tissue. The case ultimately highlights the important role of specialist, multidisciplinary diabetic foot care in the management of diabetic foot ulcers.

Abstract

A diabetic foot ulcer (DFU) is a complication of diabetes mellitus that results in significant morbidity and mortality. The lifetime risk of a patient with diabetes developing a DFU is 15-25%[1]. Furthermore, the incidence of DFUs is increasing in line with the growing burden of diabetes worldwide. Lower limb amputation is a devastating consequence of DFU infection that impacts quality of life, independence and is associated with significant financial cost to the healthcare system. Maggot debridement therapy (MDT) involves the application of sterile larvae, usually of the species Lucilla sericata (common green bottle fly), which remove devitalised tissue to promote wound healing. This historical therapy re-emerged in the 1990s to combat the increasing incidence of recalcitrant wounds, such as DFUs. Since its reintroduction, there has been ongoing debate in the medical literature regarding the efficacy of MDT in the treatment of DFUs and other chronic wounds. We present the case of a 57-year-old male admitted with diabetic foot sepsis and multiorgan failure and discuss how MDT was used to complement initial surgical and antibiotic

management. A 14-day course of MDT improved wound debridement and decreased necrotic tissue burden, after which no further surgical interventions were needed. This case provides further evidence that MDT is effective in the selective debridement of necrotic tissue and can aid the preservation of limb length in DFU patients, thereby highlighting the importance of MDT in multispecialist diabetic foot care.

Introduction

Diabetic foot ulcers are a prevalent complication of diabetes mellitus that result in significant morbidity and mortality. A diabetic foot ulcer (DFU) is defined as a foot affected by ulceration that is associated with neuropathy and/or peripheral arterial disease in the lower limb of a patient with diabetes. A population-based cohort study in the UK found that the development of a DFU is associated with 5% mortality within the first 12 months and 42% within 5 years[3]. Furthermore, DFUs are the most common foot injuries leading to lower limb amputation[4], with 20% of moderate or severe DFU infections resulting in some level of amputation, which greatly impacts health-related

quality of life[5]. Between 15-25% of people with diabetes will develop a foot ulcer and this is expected to increase as the number of people diagnosed with diabetes increases[1]. This prevalence creates a significant healthcare expenditure burden. Indeed, the cost of treating DFUs in the UK for the year 2010/2011 was £1bn, which is expected to rise to over £2bn by 2035/2036[6].

Debridement, the removal of devitalised tissue from the wound to expose healthy tissue, is an essential component of DFU care. It supports granulation tissue formation and re-epithelization to promote wound healing, whilst also aiding infection control through the removal of devitalised tissue that serves as a nidus for bacterial proliferation[7-9]. This makes debridement perhaps the most important part of wound management; however, it must not be seen in isolation, but rather as a key element of effective wound care. The gold-standard form of debridement is widely considered to be surgical (sharp) debridement, which classically involves the direct removal of necrotic tissue with a scalpel blade[8]. This method gives the most accurate assessment of wound depth and severity, while also being extremely efficient, making it first line in medical emergencies of life and limb. However, it is non-selective, with the removal of viable tissue an inevitable limitation and dependent on the skill of the professional. Additionally, such procedures are expensive, with NHS theatre costs estimated to be in excess of £1,200/h[10]. Furthermore, not all patients are suitable surgical candidates.

Maggot debridement therapy (MDT) involves the application of sterile larvae, usually of the species Lucilia sericata (common green bottle fly), in a form of controlled therapeutic myiasis (maggot infestation of a live host). The mechanism of action of MDT involves both mechanical debridement through their specially adapted mandibles and the grinding of their rough bodies on the necrotic tissue, alongside biochemical debridement through the various excretions and secretions that dissolve the devitalised tissue[7,9]. These processes act synergistically, with the action of their 'mouth hooks' distorting cell membranes and enabling the entry of various proteolytic enzymes into the cell, which is broken down to form a semi-liquid tissue that is ingested[11]. Furthermore, laboratory studies have revealed that Lucilia sericata larvae decrease wound pH and produce bacterial enzymes that directly contribute to wound disinfection and biofilm inhibition and eradication[12-14]; while also directly stimulating wound healing[7,15].

The beneficial effect of maggots on wound healing has been known for centuries, with military surgeons such as Baron Larry (of Napoleon fame) noting that of the many soldiers abandoned on the battlefield, those whose wounds became infested with maggots seemed to fair better and their wounds heal faster than their counterparts[9]. The treatment was pioneered by William Baer (1872-1931), an orthopaedic surgeon at John's Hopkins Hospital, who had himself observed the medicinal effect of maggots on the wounds of two soldiers during the First World War. He carried this observation across to civilian surgery and employed the larvae of Lucilia sericata for the treatment of children with osteomyelitis in 1929[16]. Baer observed that MDT resulted in faster debridement, reduced bacterial growth and decreased odour compared to chemical or conventional dressings. Throughout the 1930s MDT was used widely with over 90% of doctors reporting that they were very pleased with the treatment[17]. However, the discovery of Penicillin by Alexander Fleming in 1928[18] and the widespread production and use of this first antibiotic led to the disappearance of MDT for infected wounds, a process

that was probably compounded by parallel advancements in surgery and anaesthesia[19]. By the late 1980s antimicrobial resistance was becoming an increasingly common problem; the prevalence of DFUs, venous ulcers and pressure sores were all on the rise too, and conventional wound care seemed ill-prepared to combat the snowballing number of recalcitrant wounds. This was the backdrop for the a re-examination of MDT and led to its reintroduction in the UK during the 1990s[20]. Some divergence has emerged in in the medical literature regarding the efficacy of MDT in the treatment of diabetic foot ulcers and other chronic wounds. Here we present a case where MDT was used to treat a DFU following initial surgical and antibiotic management to enhance the selective debridement of necrotic tissue and preserve limb length.

Case history

A 57-year-old male was admitted with rapidly progressing sepsis secondary to an infected DFU. Over the preceding week a relatively dry left third toe necrosis had advanced to wet necrosis with forefoot and midfoot soft tissue infection. His past medical history included ischaemic heart disease with a myocardial infarction (MI) six months previously, managed with a coronary artery bypass graft and warfarin for a post-MI ventricular thrombus. He had known peripheral arterial disease (PAD) and was suffering with acute-on-chronic critical limb ischaemia likely precipitated by embolization of the ventricular thrombus. The patient also had type 2 diabetes mellitus (T2DM) with previous periods of poor glycaemic control and suffered from peripheral neuropathy. On examination he had no palpable pulses below the level of the femoral arteries bilaterally and had a palpable collection on the sole of the left foot. Blood results revealed a raised white cell count (34.96 x 109 cells/L) and C-reactive protein (273.0 mg/L). They also showed an elevated international normalised ratio (>17) and alkaline phosphatase level (861 IU/L). Furthermore, a radiograph of the left foot showed diaphyseal periostitis and irregularity of the head of the proximal phalanx of the third toe – signs suspicious for early osteomyelitis. The patient received co-amoxiclav (1200 mg, TDS, IV) and metronidazole (500 mg, TDS, IV) to treat the sepsis and prothrombin complex concentrate to reverse the deranged clotting. He was then expedited to theatre in the evening for amputation of the third toe with extensive surgical debridement. The following day the patient received a popliteal and posterior tibial artery angioplasty. Such an intervention was already planned to take place, as he had recognised occlusive PAD at these sites, but this was brought forward as he needed urgent restoration of perfusion to the ischaemic tissue to facilitate wound healing.

Despite aggressive source control, the patient continued to deteriorate, developing stage two acute kidney injury and acute liver failure, prompting escalation of antibiotic therapy to piperacillin-tazobactam (4.5 g, TDS, IV). The patient was broached with the possibility of a more significant amputation, but he was keen to preserve his leg if at all possible. He went on to receive three further episodes of surgical debridement and amputation of the neighbouring second toe over the next three weeks in repeated attempts to control the source of infection. Diagnosed through a proximal bone biopsy taken during the final surgical intervention, the amputation of the neighbouring second toe, the causative organism was cultured to be a methicillin-sensitive Staphylococcus Aureus. This was confirmed by a later blood culture and the bacteraemia was treated with flucloxacillin (2 g, QDS, IV).
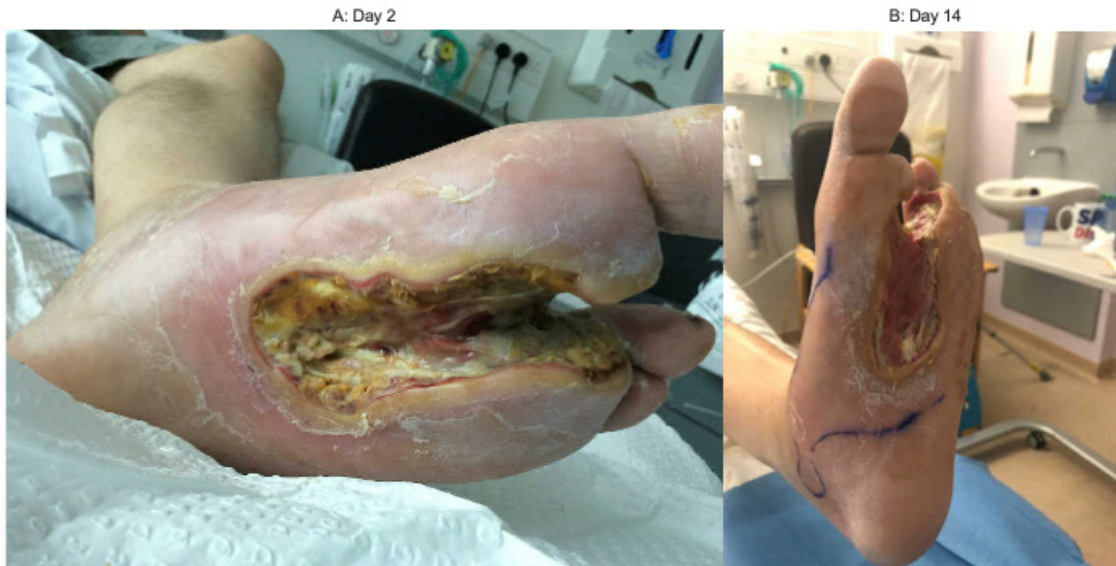
Figure 1: Effect of MDT on wound healing.
Photographs taken at day 2 (A) and day 14 (B) following the initation of MDT.

Upon discharge, the patient was switched to ceftriaxone (2g, OD, IV), in order for the Outpatient Parenteral Antimicrobial Therapy (OPAT) team to continue treatment at home. IV antibiotics were delivered for 4 weeks from the date of the first negative blood culture, followed by another 2 weeks of oral flucloxacillin (1g, QDS).

The use of MDT was first discussed one week after admission, as the sloughy appearance of the wound indicated it may benefit from larval debridement. However, the appearance of moist necrosis on the edges of the wound two days after the initiation of MDT necessitated further invasive surgical debridement, limiting the efficacy of this first round of treatment. However, after the amputation of the neighbouring second toe the use of MDT was revisited. The wound was healing minimally, and it was hoped that MDT could accelerate this process. MDT was re-initiated one week following the amputation and after 7 days of active treatment the wound bed had greatly improved, with increasingly healthy granulation tissue present with no evidence of necrosis or ongoing infection. MDT continued for another 7 days with continued improvement to the wound and was halted after a total of 14 days (Fig.1) after which the patient was transitioned to Protosan® wound irrigation solution in preparation for his return home. The patient was discharged four days after the cessation of MDT. He was admitted for a total of 40 days.

Discussion

This patient, with a severely infected diabetic foot ulcer, received a 14-day course of MDT following amputation, surgical debridement and antibiotic therapy. Comparison of Fig.1A and Fig.1B show that the wound underwent substantial healing during this period of active MDT, with the final result appearing more superficial and containing an increased proportion of shiny red granulation tissue. There may have also been a decrease in wound surface area, although this is difficult to tell due to the absence of scale markers in the photographs. Thus, use of MDT in this patient appears to have improved wound debridement with a decrease in necrotic tissue burden. The patient's survival and recovery from sepsis was likely due to antibiotic and supportive management alongside surgical source control. But MDT appeared to play a key role in the preservation of limb length, including of the tripod foot (enables even weight distribution and normal gait), through its selective debridement of necrotic tissue and the negated need for further surgery – including more extensive amputation. Thus, the combination of initial, aggressive surgical management with downstream MDT proved effective in preserving limb function and improving quality of life for the patient, which highlights its importance in multispecialist diabetic foot care.

MDT has been used in variety of chronic wounds including pressure sores, venous leg ulcers and diabetic foot ulcers. However, the literature is sparse, with the evidence supporting MDT coming from a handful of small clinical trials with conflicting results. Dumville et al.[21] published the results of the largest randomised control trial (RCT) evaluating the use of MDT in the BMJ in 2009. In this study, a cohort of 267 patients in the UK were randomised to receive either larval therapy or hydrogel, a moisture-retention dressing that acts to amplify the inherent autolytic debridement ability of the body by enhancing the action of our own phagocytic cells and endogenous enzymes. The trial showed that MDT significantly reduced the time to debridement. However, larval therapy did not improve the rate of healing or reduce bacterial load compared with hydrogel and significantly increased ulcer pain. Nevertheless, Sun et al.[22] published a systematic review of MDT for chronically infected wounds and ulcers in the International Journal of Infectious Diseases in 2014, which showed that MDT had a significant positive effect on both healing rate and time to healing versus control therapies. Furthermore, MDT was also associated with decreased amputation rates and reduced antibiotic usage. Of the 12 studies identified by the authors, six were RCTs, two were prospective cohort studies and four retrospective analyses. These studies had a sample size ranging from 12-267 and median value of 76. The relatively small number of studies identified reflects the scarcity of literature on MDT, but also limits the statistical rigour of the results, as does the small sample sizes used in the many of the studies. Additionally, the control therapies varied between studies, with some using hydrogel, others using surgical debridement and/or conservative wound care. This variability may have influenced the effect estimation of MDT. Finally, in some non-RCTs, MDT may have been used as a salvage tool when all else had failed, which would lead to biased healing outcomes.

There have been only 2 RCTs evaluating the use

of MDT for DFUs. The first was by Markevich et al. (2000)[23], who recruited 140 patients with non-healing diabetic neuropathic foot ulcers and randomised them to receive either conventional treatment with hydrogel or MDT and followed subjects for 10 days. In the larvae group, 36/70 patients (51%) showed a wound area reduction of more than 50% compared with 19/70 (27%) of patients in the hydrogel control group, a statistically significant result. Complete wound healing was higher in the MDT group (7.1% vs 2.8% in the control group), but this failed to reach statistical significance, which is not surprising given the short length of the study. Caution should be noted as the only data available from this study is taken from this very early time frame (10 days). The study was intended to be reported over a period of 30 months, but the initial conference report is all that has been published to-date. Indeed, a Cochrane review (2010)[24] on the debridement of diabetic foot ulcers concluded that there is insufficient evidence of the effects of larval therapy on diabetic foot ulcers. Due to the lack of 1a evidence, NICE guidelines do not recommend the use of MDT for DFU, with current UK prescriptions at the discretion of the clinician. Malekian et al (2019)[25] published a recent RCT evaluating the use of MDT as an adjuvant therapy in the context of Staphylococcus Aureus and Pseudomonas aeruginosa DFU infection in a cohort of 50 patients in Iran. Patients in the control arm received conventional therapy, including surgical debridement, antibiotics and offloading; patients in the treatment arm received conventional therapy alongside MDT. Using cultures collected through wound swabbing, the authors found that the use of adjuvant MDT significantly reduced the bacterial burden of S.aureus after 48 hrs and P.aeruginosa after 96 hrs. This RCT suggests that a benefit when MDT is incorporated into conventional therapy. However, the small and homogenous patient cohort again limits the generalizability of these outcomes.

Our review of the literature herein reveals a lack of rigorous RCTs evaluating the use of MDT to treat DFUs and chronic wounds more widely. There are several possible explanations. Due to the nature of MDT, it is difficult to blind patients to the use of larvae and there is substantial difficulty in recruiting sufficient numbers of patients to generate statistically significant results. Additionally, possibly due to the historic nature of the treatment, there appears to be compliancy in gathering fresh data to thoroughly examine the efficacy of the treatment in the current treatment landscape. However, scarcity of published literature on the subject may be also reflection of negative publication bias.

Current practice is that MDT is prescribed on a case-by-case basis when indicated by expert opinion, most commonly a vascular surgeon, often after the failure of conventional therapies. MDT does appear to perform well as a therapy of last resort, with the limb salvages rates possibly as high as 40-50%[9,26-29]. However, like other wound treatments, MDT is likely to be most effective when delivered early, before the infection has reached life/limb-threatening levels[19]. Thus, MDT does have the potential to be a valuable first line therapy when used in parallel with conventional interventions, especially when speed, selectivity and bioburden are key aspects of management. In the future, MDT may come to play an increasingly important role in the management of wounds infected with antimicrobial resistant organisms. Bowling et al (2007)[30] reported that MDT resulted in the eradication of 92% of DFUs after an average of 19 days, delivering effective treatment faster and more cheaply than vancomycin. MDT provides a novel option to combat this ever-growing health crisis.

However, despite the potential of MDT, many challenges remain. Firstly, the cost-effectiveness of MDT is contested. In the economic analysis of Dumville et al (2009)[21], the authors reveal that larval therapy cost, on average, £96.70 more per participant per year than hydrogel[31]. Yet, while the unit cost of MDT is higher than other wound care products, MDT is considered to be cost-effective in comparison to surgical debridement. Thomas et al (2006)[32] report that the use of maggot therapy for 30% of refractory diabetic ulcers in need of debridement could save the NHS approximately £50 million annually. Another practical challenge is that due to licencing considerations, MDT is only available on prescription, unlike other wound care products. This has led to the underutilisation of MDT.

Adverse events associated with larval therapy include MDT-associated pain, which has been reported in 5-30% of patients[21,26,33,34]. This phenomenon is more often observed in patients who experienced pain before the initiation of MDT and hence proper patient identification and management with analgesia should limit its occurrence. The prospect of maggot escape is also an intrinsic risk of MDT. However, the introduction of modern 'maggot containment dressings' minimises this possibility. These single-piece, cage-like dressings are specifically designed for MDT to provide maggots with complete access to the wound without allowing them to crawl out[7,19]. Finally, given that maggots are highly perishable, delays in transportation can result in product inviability on arrival. Therefore, robust courier services must be in place. However, as research accumulates and the mechanisms behind MDT become better understood, the possibility of maggot-derived products substituting MDT becomes greater. Such an advance would overcome many of the current limitations of MDT and is undoubtably an exciting future prospect. But for now, we will have to rely on what nature has provided and humans gracefully harnessed.

Conclusion

Herein we present a case where MDT was used to aid the preservation of limb length and improve the clinical outcome of a patient with severe DFU infection. MDT is effective in the selective debridement of necrotic tissue, but due to the few numbers of rigorous RCTs published to-date, there is lack of evidence to support its use. Despite this, there is a substantial body of literature further down the evidence hierarchy pyramid that supports the use and benefits of MDT. Looking forward, the future of MDT may be decided by its performance against antimicrobial resistant organisms. But for now, in the battle against an increasingly common enemy of the DFU, the choice of whether we rely on modern surgical and antibiotic weaponry, or hijack this rich resource from the past, remains entirely at the discretion of the expert clinician.

Conflicts of interest
None.

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Consent
The patient has consented to the publication of this case study.

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