

Maggot debridement therapy: the current perspectives

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Abstract: Chronic wounds remain a challenge to most healthcare systems worldwide despite the technological advances we have seen to date. Many chronic non-healing wounds require alternative approaches, in addition to standard conventional therapies. Maggot debridement therapy (MDT) or the use of maggots to treat wounds is one such therapy that has been in use for centuries. We conducted a review of articles published in PubMed, NICE evidence documents, and linked literature with the aim of providing a brief perspective on the evolution of MDT, and the context in which maggot therapy is currently used along with evidence behind such methods.

Keywords: wound healing, maggot debridement therapy, debridement, *Lucilia sericata*, chronic disease, larva

Introduction

The burden of wounds is probably as old as mankind itself. Even with vast advances in today's healthcare technology, the management of chronic wounds still poses a significant challenge to the medical world.^{1,2} The cost to the National Health Service of caring for patients with a chronic wound is conservatively estimated at £2.3b to £3.1b per year (at 2005–2006 costs); it is around 3% of the total estimated expenditure on health (89.4b).³ The total cost of managing patients with wounds, originating in primary care, accounted for nearly 6% of the total expenditure on the health service in Wales, at an average cost of £1727 per patient.⁴ A high proportion of chronic wounds remain unhealed for long periods, and this may be due to the use of inappropriate or ineffective therapies, as clinical staff are not trained or aware of optimal ways of managing such patients. Many patients with chronic wounds tend to have other underlying conditions making wound healing extremely difficult even where specialized care is provided in order to expedite the process. Many chronic non-healing wounds therefore require targeted approaches rather than the standard conventional therapies.

Maggot debridement therapy (MDT) or the use of maggots to treat wounds is one such therapy that has been in use for centuries.⁵ Larvae of the green bottle fly *Lucilia sericata* are used in MDT. An important step in assisting chronic non-healing wounds progress through healing is wound bed preparation. This is usually achieved by effective debridement technique to remove devitalized tissue, including slough and eschar. The methods of debriding a wound can be classified as surgical, autolytic, mechanical, enzymatic, or biological.⁶ MDT mainly helps in wound healing by debridement of necrotic tissue by both mechanical and biochemical means. Mechanical debridement is achieved by the “mouth hooks” of the maggots and their rough bodies that

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scratch the necrotic tissue.⁷ They may also secrete a mixture of proteolytic enzymes (trypsin and chymotrypsin-like collagenase) that lyse nonviable tissue, making it easier for the maggots to digest.⁸ This article provides a brief perspective on the evolution of MDT and the context in which maggot therapy is currently being used along with evidence behind such methods.

Methods

The evidence that forms the basis of this article was identified by searching PubMed, using a two-layer search method using; “Wounds and injuries,” “Ulcers,” and “Debridement” and “Larva*,” “*Lucilia sericata*” (the widely used binomial nomenclature for the larvae used in MDT), and “Maggot” in titles/abstract. Other literature linked to the articles found on PubMed searches was also used. Major texts in the field were reviewed, including the evidence-based guide to maggot therapy in wounds. Well-conducted systematic reviews were included as part of the evidence base, as well as authoritative articles about the wound healing and suggested best practice guides. We also looked at appraised literature from the National Institute of Clinical Excellence (NICE) evidence search.

Historical use of maggots in wound treatment

The history of wound care probably dates back to the origin of human species. Wounds can naturally heal by themselves, but humans have noticed several natural remedies that would speed up the process, especially if the wounds were chronic. The use of insects or their products is not new; honey⁹ from bees, cobwebs,¹⁰ ant-heads¹¹ to aid wound closure, and leeches¹¹ to help draw excessive wound congestion have all been tried in the past. Maggot therapy is one such ancient method that has stood the test of time and is still being widely used to achieve wound debridement in difficult and chronic wounds. According to Fleischmann et al, “Australian aborigines have used maggots to clean wounds for thousands of years.”¹²

Many military surgeons noted that soldiers whose wounds became infested with maggots healed better. Ambroise Paré (1509–1590) was a notable barber surgeon who served in the French army.¹³ Paré in the battle of St. Quentin (1557) observed that when maggots were present in suppurating wounds, they healed faster. However, at the time this observation did not result in a new treatment modality. Again, in the 1800s, Napoleon’s battlefield surgeon, Dominique Larrey (1766–1842) noted the beneficial effects of maggots on wounds sustained by soldiers during an expedition to Syria.¹⁴

While Larrey noticed their benefits, he had not deliberately placed blowfly larvae on the wounds. He said they were “greedy only after putrefying substances, and never touch the parts which are endowed with life”.¹⁴ Despite all efforts, Larrey’s wounded soldiers were not willing to have the crawling larvae on their wounds and, yet again, did not result in the adoption of this as a new modality of treatment for wounds. Similar observations were made by American Civil War surgeons who ultimately realized that maggots could have beneficial effects. Confederate Surgeon Joseph Jones, for example, reported that “a gangrenous wound which had been thoroughly cleansed by maggots healed more rapidly than if it had been left by itself.”¹⁵ John Forney Zacharias (1837–1901), a surgeon from Maryland during the American civil war was the first to officially document maggot therapy, which he explains as having saved many lives. Later during the First World War, William Baer (1872–1931) noted that maggots assisted in the healing of fracture wounds.¹⁶ However, while undergoing MDT, some of his patients with fractures died of secondary bacterial infections such as tetanus and gas gangrene. Then after several experiments, Baer successfully devised a method to produce sterilized maggots that would not spread these clostridial infections. Despite the method being expensive, maggots were cultured during that time, and MDT saw one of its peaks in the 1930s. Another contemporary surgeon, Duncan McKeever (1905–1959) credited Baer for the use of maggot therapy in osteomyelitis, and he describes in great detail an inexpensive and easy method of the production of non-sterile maggots and how to apply them in chronic osteomyelitis.¹⁷ MDT was widely used until after the Second World War, when the discovery of antibiotics and the development of better surgical techniques pushed it to the background.¹⁵

Renaissance in the new era

Ronald Sherman, a strong advocate, was the key figure for its revival. In the 1990s, he established a small fly-culturing facility in the Veteran Administration Hospital Medical Centre in Long Beach, California, USA to produce sterile larvae.¹⁸ He was one of the first to conduct a prospective-controlled study that looked at maggot therapy in treating pressure ulcers in spinal cord-injury patients.¹⁹ Eight patients received MDT after a baseline assessment of healing under conventional therapy. Maggot therapy led to a more rapid removal of debris than all other non-surgical treatments and had a faster healing rate. No complications were seen. At around the same time, he developed an optimal dressing design which was a two-layered cage-like dressing; the

bottom layer of which comprised a hydrocolloid pad, applied to the surrounding healthy skin and covered by a fine chif-fon or nylon mesh.²⁰ The renaissance of MDT in the United Kingdom can be attributed to Dr John Church, an orthopedic surgeon who, along with Dr Stephen Thomas, opened the first Larval Therapy Research Unit at Bridgend, South Wales in 1995.²¹ German and Belgian factories have also distributed fly larvae in Europe since 1998.¹⁸

In 2000, Wayman et al²² published one of the first conducted randomized-controlled trials (RCTs) on the effectiveness of MDT. They considered a small sample (12 patients) with venous leg ulcers who were treated with MDT or hydrogel. Six wounds in the MDT group had debrided faster (2–3 days) than in the control arm (>1 month). In the same year (2000), another large RCT was conducted by Markevich et al.^{23,24} They included 140 patients with non-healing diabetic neuropathic foot wounds. Compared with conventional therapy, the MDT wounds were successfully debrided twice as often in the 10-day follow-up period (51.1% of MDT patients versus 27% of controls, $p < 0.05$). Complete healing during the observed time period was twice as frequent as conventional therapy (7.1% of MDT patients and 2.8% of controls). Dumville et al in the UK in 2009 conducted the largest RCT.²⁵ They included 267 venous or mixed venous arterial ulcers that were treated either with MDT (free living or loose larvae) or hydrogel, and followed up for 12 months in a three-armed trial. They concluded that “Larval therapy did not improve the rate of healing of sloughy or necrotic leg ulcers or reduce bacterial load compared with hydrogel but did significantly reduce the time to debridement and increased ulcer pain.”²⁵ Paul et al, also in the same year (2009), conducted a case control series of MDT on diabetic foot ulcers.²⁶ In this series, they included 29 patients and 30 controls; there was no significant difference in outcomes between the two groups. They concluded that MDT is as effective as conventional debridement in the treatment of diabetic foot ulcers. They suggested that MDT would be a feasible alternative to those at high risk for surgery or for those who refuse surgery. Another retrospective study by Wang et al followed 25 diabetic foot ulcers and 18 pressure ulcers in spinal cord-injury patients treated with either MDT or traditional dressings.²⁷ The MDT group had a significantly shorter time to achieve bacterial negativity, healthy granulation, and complete healing. Finally, the most recent RCT was conducted in 2014 at the Wound Healing Research Unit, Cardiff University by Mudge et al.²⁸ This study compared the clinical effectiveness of a larval therapy dressing (Bio-FOAM) with a standard debridement technique (Purilon gel; hydrogel) in terms of time to debridement of venous or mixed

arterial/venous leg ulcers. Out of 88 subjects who were included, 64 completed the study. With withdrawn subjects excluded from the analyses, the ulcers that debrided in the larvae arm were 96.9% compared with only 34.4% from the hydrogel arm. Subjects in the MDT arm experienced more ulcer-related pain or discomfort than the subjects in the hydrogel arm. The authors, based on the trial, suggested that provision of pain relief, patient education, and treatment concordance are important factors to be considered to achieve effective and efficient MDT.

Other clinical studies

Cambal et al published their findings of the MDT method in chronic conservative non-treatable leg ulcers in patients in whom conventional therapy failed.²⁹ All ulcers were healed or minimized in size at 4–8 weeks of follow-up. Tantawi et al studied 13 diabetic foot ulcers in 10 patients treated with MDT.³⁰ Complete debridement was achieved at a mean of 1.9 weeks, and 85% of the ulcers healed within a mean of 7.3 weeks. The bacterial load of all ulcers reduced sharply after the first MDT cycle which probably contributed to healing. Marineau et al studied complex diabetic foot wounds, studying a 23-person cohort that included 11 cases of osteomyelitis, 13 patients with poorly controlled diabetes, and five patients with end-stage renal failure on chronic hemodialysis.³¹ In 17 of 23 patients with multiple comorbidities, the treatment of their complex diabetic wounds by MDT resulted in improvement or cure. Gilead et al conducted a retrospective study of patients treated with MDT in their facility.³² Out of 723 ambulatory and hospitalized patients treated with MDT, 90.5% had leg ulcers and 48% had diabetic foot ulcers. Complete debridement was achieved in 82.1% of cases, partial debridement in 16.8%, and treatment was ineffective in 1.1%. Increased pain with MDT was seen in 38% of the treated patients.

There has been a rising trend in the use of MDT after the 1990s. The contexts in which it was used are reflected in the published case reports during the time. It is interesting to note that there were only two case reports within our searches between 1975 and 1990, and 22 case reports were found after 1990. The revival of MDT around the time coincides with the rise of antibiotic resistance,^{33,34} which rendered one of the main modalities of wound treatment ineffective. This is probably why the use of MDT began to rise, but in most cases as the last resort when other modalities failed. MDT was used for a range of wounds ranging from the common venous and diabetic ulcers to more complex and rare forms of chronic wounds. Table 1 presents an overview of the context in which MDT has been used.

Table 1 Clinical case studies of MDT

Wound type	Year	Country	Outcome
1 Complex hand injury complicated by mycotic infection ³⁵	2015	Slovakia	MDT followed by negative pressure therapy allowed progressive healing
2 Diabetic foot ulcer colonized by multidrug resistant bacteria ³⁶	2015	Brazil	MDT used for 43 days resulted in a reduction of necrotic tissue and the ulcer size
3 Maggot debridement therapy for critical limb ischemia ³⁷	2014	Japan	Wound healing was successfully activated by MDT, leading to complete healing within 2.5 months after MDT. Significant increase in skin perfusion pressures was also noted
4 Warfarin-induced skin necrosis diagnosed on clinical grounds and treated with maggot debridement therapy ³⁸	2013	UK	Combination of surgical and maggot debridement resulted in sufficient recovery for skin grafts to be applied and amputation avoided
5 Tropical diabetic hand syndrome ³⁹	2013	China	Significant wound debridement was achieved with MDT
6 Poorly healing periorbital wound ⁴⁰	2012	Germany	Good results obtained
7 Infective wound in a patient with severe burn injury ⁴¹	2012	China	Necrotic tissues cleared up, and eventually fresh granulation tissue grew. Wound healed by skin grafting
8 Postsurgical wound infection in scoliosis ⁴²	2011	South Korea	All wound healed completely within 5.2±1.8 weeks of MDT
9 Treatment for Leishmaniasis ulcers ⁴³	2008	Venezuela	Healthy scar formation and wound healing was observed after therapy
10 Pyoderma Gangrenosum ⁴⁴	2008	Switzerland	Reduced survival of maggots (<i>Lucilia sericata</i> sp.) led to ineffectiveness of this therapy
11 Mixed arterial-venous ulcer ⁴⁵	2008	The Netherlands	Serious bleeding requiring transfusion
12 Degloving injuries to both lower extremities. MDT was used in view of patient's faith. Surgical debridement and blood transfusion were not consented to in this case. ⁴⁶	2008	Canada	Good result, wounds later healed by grafting
13 Maggot debridement therapy in the palliative setting ⁴⁷	2007	The Netherlands	Wound pain was diminished, the odor reduced, and the wound showed signs of healing
14 Necrotizing fasciitis of the leg following a simple pelvic fracture ⁴⁸	2006	The Netherlands	Repeated surgical debridement, broad-spectrum antibiotic therapy, MDT, and topical negative pressure therapy were used. The wound finally closed
15 Severely infected wound after forearm replantation ⁴⁹	2006	China	Successful debridement achieved
16 Foot ulcer secondary to malignant adenocarcinoma ⁵⁰	2004	UK	Successful debridement achieved
17 Degloving injury to the foot with a trans-metatarsal amputation and extensive soft tissue loss ⁵¹	2003	USA	Successfully allowed complete wound closure without any additional interventions
18 Severe ischemic infected ulcer of the foot in a diabetic patient ⁵²	2003	Belgium	Successful debridement achieved
19 Limb salvage after bilateral lower extremity fourth-degree burns ⁵³	2000	USA	Therapy successful
20 Chronic bilateral plantar foot ulcer of several years' duration ⁵⁴	1995	USA	One foot was treated with MDT showed successful outcome whereas the contralateral foot showed no improvement
21 Venous stasis ulcer ⁵⁵	1996	USA	Therapy successful
22 Observation of maggot infested wound in a facial tumour ⁵⁶	1985	USA	Debridement achieved
23 Intractable subacute mastoiditis ⁵⁷	1976	USA	Therapy successful
24 Elephantiasis nostras verrucosa ⁵⁸	2014	USA	Therapy was successful but resulted in hyperammonemia as a complication

Abbreviation: MDT, maggot debridement therapy.

MDT has been used in traumatic, surgical, arterial, venous, and malignant wounds (Table 1). Maggots have also been used in other wounds caused by infections, infestations, drugs, and wounds related to autoimmune conditions. We have identified 24 different clinical situations where MDT has been tried. MDT was successful in 22 out of 24 clinical scenarios. MDT did not help to achieve good results in a case of Pyoderma Gangrenosum where the poor survival of the maggots rendered the therapy ineffective, and in another case of mixed arterial and venous ulcer where bleeding complication was seen. However, the evidence from these case reports can only be considered as anecdotal.

Meta-analyses of MDT studies

A systematic review by Zarchi and Jemec compiled three RCTs and five non-randomized studies, focusing on the debriding potential of MDT.⁵⁹ They noted that the design of the studies was suboptimal, with differences in the use of other therapies, such as compression, that may influence both debridement and healing process between the compared groups, as well as short follow-up times. They concluded that poor quality of the data used for evaluating the efficacy of MDT called for more and better designed clinical trials. Wilasrusmee et al found MDT helpful in the treatment of chronic ulcers with a 20% greater chance of wound healing as compared to conventional therapies.⁶⁰ Tian et al (2013) reviewed the efficacy of MDT compared with standard of care for diabetic foot ulcers.⁶¹ Four studies (356 participants) were meta-analyzed with the conclusion that the evidence for MDT was too weak to routinely recommend it for treatment. Larger studies and sample sizes to assess the efficacy and safety of MDT in the treatment of diabetic foot ulcers were recommended. The recent systematic review by Sun et al (2014) looked at the use of MDT in the treatment of chronically infected wounds.⁶² In these meta-analyzed data, the pooled relative risk was 1.80 (95% [CI 1.24–2.60]). Subgroup analysis revealed that the combined relative risks were 1.79 (95% [CI 0.95–3.38]) for patients with diabetic foot ulcers, and 1.70 (95% [CI 1.28–2.27]) for patients with other types of ulcers. The time to healing of the ulcer was significantly shorter among patients treated with MDT.

Current use of MDT

Currently, MDT is used mostly when other conventional therapies fail or when non-surgical debridement of the wound is being considered. NICE (UK) suggests considering MDT in chronic pressure ulcers if debridement is needed, but sharp debridement is contraindicated, or if there is associated

vascular insufficiency. The Health Service Executive (Republic of Ireland) in their evidence based wound management guidance suggest that in general, removal of all necrotic or devitalized tissue by various methods including MDT leads to a more normal wound-healing process. Maggots received marketing clearance as “medical devices” by the US Food and Drug Administration in January 2004, making them the first live organism marketed in the United States for medical purposes and treatment is currently reimbursable by Medicare.⁶³ The Welsh guidelines recommend that an overall clinical decision has to be made when rapid debridement of devitalized tissue is required to achieve wound healing and then an assessment for suitability of the wound before MDT is commenced.⁶⁴

Currently, there are two methods of larval application. The first method is using larvae sealed within a dressing called biobag. They come in varying sizes to match different wound sizes. The larvae remain sealed inside the biobag throughout the treatment period. The other method is to use free-range larvae applied directly on the wound. Biobags can be left in place up to 4 days and free-range larvae are also left in the wound for up to 4 days per application. The number of applications required for complete wound debridement depends on the type of wound and ranges from one to several per treatment session.

Indications and cautions for use

The most important part of managing a wound is addressing the underlying condition that causes it. MDT can play an adjunct role to wound care. MDT can be used for any type of chronic wounds that have moist slough or necrotic tissue on its floor where urgent surgical debridement (eg, necrotizing fasciitis) is not indicated, possible or refused by the patient. MDT should be used cautiously under close supervision near exposed blood vessels, organs, or wounds body cavities.^{18,64} Bleeding complications have been encountered with previous use of MDT, and close observation of the therapy is required when used in patients with bleeding tendencies, for example, Warfarin induced coagulopathy.^{45,65}

Back to the future

There is a rise in the number of people living with long-term conditions; one of the main reasons why we will see an increase in prevalence of chronic and complicated wounds that are resistant to conventional therapies. The evidence for MDT is encouraging, and we will continue to see a rising trend in its use. Currently, the literature that can provide level 1 evidence is, however, sparse. Most studies so far look

at proximal short-term outcomes that present a short-sighted view of measuring success of MDT. RCTs of MDT that can capture both proximal and distal outcomes need longer term of follow-up and are expensive and challenging to design. There is a need for more such trials to be conducted in the future that ultimately provide better levels of evidence. Another method to capture more distal outcomes would involve observational studies of large patient cohorts or databases such as Clinical Practice Research Datalink⁶⁶ and Health Wise Wales.⁶⁷ This method can also be a good way of sharing clinical and patient experiences.

There has been a renewed interest in MDT and its role as a form of antimicrobial treatment for infected wounds. With the emergence of antimicrobial resistance, we are again likely to see its increased use in drug-resistant wound infections. Systematic reviews evaluating MDT have highlighted its successful role in treatment of Gram-positive and Gram-negative bacterial strains, including *Staphylococcus aureus*, *Pseudomonas aeruginosa*, Methicillin-resistant *Staphylococcus aureus*, and other drug-resistant pathogens.^{62,68} However, no direct anti-microbial effect of MDT was observed in an in vitro study by Cazander et al,⁶⁹ but other clinical studies have confirmed a decrease in bacterial load following its use.⁶⁸ The main mechanism of antimicrobial activity has been thought to be by the destruction of bacteria in the hind gut of the larvae.⁷⁰ Other mechanisms include excretion of waste products like ammonia by the larvae, and secretion of other bactericides that may be responsible for combating bacterial pathogens.⁷¹ Evans et al have shown that the larvae of medicinal maggots also have antifungal activity.⁷² More research is needed to demonstrate the indirect antibacterial activity observed in clinical studies, such as the possible presence of the immuno-modulatory effect of MDT.

Another field for future research is the potential of MDT to promote wound healing by stimulating tissue regeneration. High levels of gamma-interferons and interleukins have been shown in maggot excretions.^{70,71} Inappropriate complement activation has been thought to cause tissue destruction, and complement reducing substrate has been identified by Cazander et al in maggot secretions.⁷³ This substance could lead to a novel treatment option subject to its detailed identification and reproduction, possibly by recombinant technology. Human growth factors have also been shown to promote wound healing. Further research is underway, where genetic engineering techniques have been used to produce transgenic larvae that can secrete human growth factors such as the human platelet derived growth factor (PDGF-BB).⁷⁴ “Will this be the first step in developing a novel and cost-effective

technique of delivering a variety of growth factors and antimicrobial peptides into the wound environment?” is a question that only time can answer.

Conclusion

Management of chronic wounds still poses a huge challenge, and many chronic wounds require other unconventional therapies in order to achieve healing. MDT is one such alternative therapy that has been used for centuries for wound debridement, and now has re-emerged as an effective option for many wound types. Almost all literature published so far is in support of the use of MDT, however, level 1 evidence is sparse, and more work is needed to further establish the evidence base. Recent research into the cellular mechanisms of action of MDT and genetic engineering techniques may result in novel and innovative therapies in the future that have the potential to revolutionize wound healing.

Disclosure

The authors report no conflicts of interest in this work.

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