Review Article

Maggot debridement therapy: A practical review

Ashley Jordan[1], Neeraj Khiyani[2], Steven R. Bowers[3], John J. Lukaszczyk[1,3], Stanislaw P. Stawicki[4]

Departments of [1]Surgery and [4]Research and Innovation, St. Luke's University Health Network, [2]Medical School of Temple/St. Luke's University Hospital Campus, [3]Wound Care Center, St. Luke's University Health Network, Bethlehem, PA, USA

Abstract

Maggot debridement therapy (MDT) has a long and well-documented history. Once a popular wound care treatment, especially prior to the discovery of antibiotics, modern dressings or debridement techniques, MDT fell out of favor after the 1940s. With the increasing prevalence of chronic medical conditions and associated complex and difficult-to-treat wounds, new approaches have become necessary to address emerging issues such as antibiotic resistance, bacterial biofilm persistence and the high cost of advanced wound therapies. The constant search for a dressing and/or medical device that will control pain, remove bacteria/biofilm, and selectively debride necrotic wound material, all while promoting the growth of healthy new tissue, remains elusive. On review of the current literature, MDT comes very close to addressing all of the previously mentioned factors, while at the same time remaining cost-effective. Complications of MDT are rare and side effects are minimal. If patients and providers can look past the obvious anxiety associated with the management and presence of larvae, they will quickly see the benefits of this underutilized modality for healing multiple types of wounds.

The following core competencies are addressed in this article: Medical knowledge, Patient care, Practice-based learning and improvement.

Keywords: Clinical review, larval therapy, maggot debridement therapy, wound care

Address for correspondence:
Dr. Stanislaw P. Stawicki, Department of Research and Innovation, St. Luke's University Health Network, Bethlehem, PA 18015, USA.
E-mail: stawicki.ace@gmail.com
Received: 16.02.2018, **Accepted:** 14.03.2018

INTRODUCTION AND HISTORICAL PERSPECTIVE

The use of maggots in wound healing is among the best-studied direct medical applications of invertebrates.[1,2] For centuries, leeches, maggots, and various invertebrate-based medicinal products and treatments have been used in traditional medical practices worldwide. There is evidence for the medical use of maggots dating back to the 1500s with documentation from Ambroise Paré (1509–1590), Dominique Jean Larrey (1766–1842), as well as surgeons in the Confederate Army during the US Civil War.[3] During World War I, wounds infested by maggots were commonly seen among battlefield soldiers, as reported by William S. Baer, a notable physician and surgeon of that era.[4] He noted that wounds infested with maggots did not appear to be equally infected or swollen when

Access this article online	
Quick Response Code:	Website: www.ijam-web.org
	DOI: 10.4103/IJAM.IJAM_6_18

How to cite this article: Jordan A, Khiyani N, Bowers SR, Lukaszczyk JJ, Stawicki SP. Maggot debridement therapy: A practical review. Int J Acad Med 2018;4:21-34.

compared to non-maggot bearing wounds. Moreover, maggot-containing wounds were described as having clean and healthy appearing "pink granulation tissue," prompting Baer to clinically apply and report on early maggot debridement therapy (MDT) in the setting of complicated wounds and osteomyelitis.[3-5] Early results of his MDT experiences were published in the late 1920s and early 1930s.[4,6] Within 5 years of Baer's groundbreaking work, it was estimated that >1000 American, Canadian, and European surgeons have adopted MDT in their wound care practices.[4,7] While the majority of doctors were pleased with MDT, some of the drawbacks included difficulty obtaining maggots, the expense ($5 in 1933), and the tedious effort required to construct a restrictive dressing that would prevent maggots from leaving the wound site.[8]

The use of MDT thrived until the development and introduction of penicillin in the 1940s.[4] Osteomyelitis and soft tissue abscesses, primary indications for MDT, became less common as a result of increasingly widespread early treatment of infections with antimicrobial agents such as sulfonamides and penicillin.[4] By the 1950s, the use of MDT decreased markedly, likely due to the combination of the introduction of antibiotics, concurrent improvements in surgical techniques, and general advances in wound care.[4] Maggot therapy became a "last resort" treatment used in cases where antibiotics, surgery and modern wound care failed to achieve adequate or complete healing.[9]

In recent years, MDT has experienced resurgence due to the appearance of highly specific circumstances. More specifically, the emergence of antibiotic resistance prompted a renewed search for alternative approaches to managing chronically infected wounds.[10,11] At the same time, the availability of better chemical disinfectants, advanced wound coverage materials, and the widespread availability of reliable overnight shipping services, made the application of MDT increasingly attractive through the advent of "germ-free" maggots that can be quickly and inexpensively delivered to the treatment location, and applied to the wound using custom-made, cage-like dressings.[10,12]

Further advances in this area came in 2004 when the U.S. Food and Drug Administration (FDA) approved MDT as a "prescription only" treatment; more specifically, maggots were approved as a single-use "medical device."[4,5,13] In some other countries, such as the UK, maggots are actually regulated as a drug.[4] The U.S. FDA official indications for maggot therapy are for "debriding chronic wounds, such as pressure ulcers, venous stasis ulcers, neuropathic foot ulcers and nonhealing traumatic, or postsurgical wounds."[9] Today, any licensed physician in the U.S. can prescribe MDT.[9]

With MDT becoming increasingly popular, scientific studies have led to the defining and recognition of four major "actions" associated with this form of wound therapy: Debridement, disinfection, stimulation of healing, and biofilm elimination.[4,14] Arora *et al*. demonstrated that the antibacterial activity in excretions/secretions of *Lucilia cuprina* maggots seems to act synergistically with concurrent antibiotic treatment for *Staphylococcus aureus*.[15] It has also been postulated that maggot secretions may have an anti-inflammatory effect on cutaneous wounds.[16] Increasing awareness of clinical benefits of MDT led to more targeted, evidence-based use of this modality for "niche indications" such as problematic wounds, diabetic ulcers, venous ulcers, chronic pressure ulcers, reduction of bacterial load in wounds, osteomyelitis, cancer, and burns.[10,17-23]

METHODS

A comprehensive query of major medical search engines was conducted, including Bioline International, EBSCOhost, Google™ Scholar, and PubMed. The following list of search terms, in various combinations was used: "maggot," "wound," "maggot debridement," "maggot debridement therapy," "larval debridement therapy." Related and associated articles, when available, were also included after critically reviewing their content for relevance and quality. Literature reports most closely associated with the focus of this review were included as part of the general discussion, topic-specific considerations, or both. In addition, wound type-specific references were tabulated according to the corresponding clinical subject area [Table 1][31,33,42,62,68,69,72,73,75,76,83,89,102,104,109-111].

MAGGOT BIOLOGY

Maggots are fly larvae or immature flies, just as caterpillars are immature butterflies or moth larvae.[9,22,23] On hatching, 1st stage larvae are roughly 2 mm long and grow to about 5 mm before shedding their skin. The 2nd stage larvae grow to about 10 mm before they shed

Table 1: Listing of selected literature sources in each major clinical category discussed in this review. The table concludes with a listing of reported complications of larval therapy

Study (reference)	Year	Type of report	Number of patients	Clinical details
Diabetic wounds				
Sherman[68]	2003	Retrospective cohort	18	MDT was more effective and efficient in debriding nonhealing foot and leg ulcers in male diabetic veterans than conventional care
Marineau *et al*.[62]	2011	Case series	23	MDT resulted in favorable outcomes in 74% of patients. Six formed granulation tissue over exposed tendons, preventing the need for tendon excision
Tian *et al*.[69]	2013	Meta-analysis	356	Current evidence does not support routine MDT application for diabetic wounds. Larger studies are needed to assess the better define benefit (s) safety of MDT in the treatment of diabetic foot ulcers
Venous ulcers				
Dumville *et al*.[33]	2009	Randomized, controlled trial	267	Larval therapy did not improve the rate of healing or reduce bacterial load. However, it did reduce time required to debride
McInnes *et al*.[72]	2013	Case report	1	The report suggests that MDT may have utility in the setting of a venous ulcer contaminated with multidrug-resistant organisms
Davies *et al*.[73]	2015	Randomized control trial	40	A randomized comparison of MDT + compression versus compression therapy alone in the management of venous ulcers. Although wound debridement was more efficient in the MDT group, no subsequent improvement was noted in ulcer healing
Arterial ulcers				
Nordström *et al*.[75]	2009	Case report	1	Authors describe the use of MDT in a palliative setting at home to decrease odor from a gangrenous wound. The report also demonstrates the use of MDT in the setting of an arterial ulcer.
Igari *et al*.[76]	2013	Retrospective cohort	16	The study suggests that patients with an ankle-brachial index <0.6 may be less likely to benefit from MDT. History of peripheral artery disease by itself was not considered a contraindication to MDT
Burns				
Wu *et al*.[83]	2012	Case report	1	The case demonstrates that MDT is a viable alternative to surgical debridement of infected wounds, especially when the latter may be contraindicated
Cancer				
Lin *et al*.[31]	2015	Case report	1	The case describes the use of MDT in Kaposi's sarcoma wound to avoid amputation and possible death from infection. MDT also provide a bridge that allowed chemotherapy and antiretroviral therapy to become effective
Nwaeburu *et al*.[42]	2016	Case series	5	The authors present five cases where MDT was used to treat, but not necessarily cure, nonhealing wounds and ulcers caused by superficial tumors. MDT was found helpful in reducing tumor size
Gericke *et al*.[102]	2007	Case report	1	The case describes an 82-year-old-male who developed an orbital infection following left orbital exenteration. His wound therapy utilized *Lucilia sericata* maggots, placed within the orbital wound, contained in a biobag. Each treatment involved 50 larvae, and after second larval application of 4 days, the orbit was free of purulence. Local wound treatment involving twice daily azidamfenicol was continued to prevent recurrent infection
Less common/proposed applications				
Pliquett *et al*.[110]	2003	Case report	1	Management of wounds associated with calciphylaxis in a 53-year-old-woman is described. MDT was utilized as "last resort therapy" and the patient died from recurrent wound infections, sepsis, and exacerbations of renal failure. It is proposed that MDT be utilized earlier in the course of calciphylaxis (e.g., when ulcerations initially appear)
Borst *et al*.[89]	2014	Case report	1	The authors report the use of MDT to treat elephantiasis. The case also describes hyperammonemia as a potential side effect of MDT in humans
General/multipurpose applications				
Steenvoorde *et al*.[111]	2007	Case series	101	A total of 117 infected wounds with signs of gangrenous of necrotic tissue were present in 101 study patients. Within this group, 72 patients were classified as high-risk for surgery (e.g., ASA III or IV). Overall, 69% of patients had good clinical results. In terms of specific diagnoses, all wounds of traumatic origin healed completely while all wounds with septic arthritis failed to respond to MDT. Multivariate analysis demonstrated that chronic limb ischemia (OR, 7.5); the depth of the wound (OR, 14.0); and patient age >60 years (OR, 7.3) negatively affected outcomes

Contd...

Table 1: Contd...

Study (reference)	Year	Type of report	Number of patients	Clinical details
		Reported complications of MDT		
Guerrini[104]	1988	Animal study	12	Sheep infested with *Lucilia cuprina* larvae suffered from ammonia toxicity and alkalosis which can cause immunosuppression
Steenvoorde and van Doorn[109]	2008	Case report	1	Clinical report of massive hemorrhage associated with MDT
Borst *et al*.[89]	2014	Case report	1	The authors report hyperammonemia as a potential side effect of MDT in humans

MDT=Maggot debridement therapy, ASA=American Society of Anesthesiologists, OR=Odds ratio

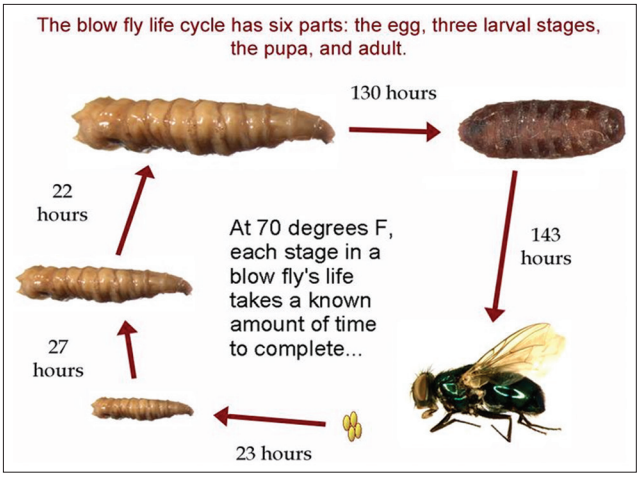

Figure 1: Life cycle of a blowfly (Source: Cleveland Museum of Natural History, reproduced with permission; URL: https://www.nlm.nih.gov/visibleproofs/galleries/technologies/blowfly.html)

their skins to become 3rd stage larvae. The 3rd stage grows to approximately 15–20 mm before wandering off as prepupae.[22] Apart from the change in size, there is little variation among the three stages of larvae. The most distinctive feature separating larvae of different stages is the structure of the posterior spiracles, through which the larvae respire.[22] Figure 1 provides a simplified overview of relevant larval developmental biology.

The larval, or maggot, stage of fly development is the primary feeding stage.[24] Fly larvae are very efficient feeders, with specialized mouth hooks allowing them to literally rake in decaying or necrotic flesh.[25] Their rear ends consist of a chamber, in which their anus and posterior spiracles (used for breathing) are located.[25] Between their heads and their tails there is a muscular, segmented body, a simple intestine and a pair of proportionately very large salivary glands.[26] Larvae are covered by spines that scrape along the wound and help loosen debris.[27,28] They have mandibles which help with maggot movement and contrary to popular belief, are not involved in the consumption of tissue.[26] Instead, maggots secrete and excrete alimentary enzymes which begin digestion of necrotic tissue outside their body.[27] Various components of these secretions include allantoin, sulfhydryl radicals, calcium, cysteine, glutathione, embryonic growth-stimulating substance, growth-stimulating factors for fibroblasts, carboxypeptidases A and B, leucine aminopeptidase, collagenase, and serine proteases.[29,30]

The movement of the maggot over the wound, spreading its alimentary secretions as it goes, further increases debridement activity.[31,32] In fact, an *in vivo* study demonstrated that larval therapy was associated with faster debridement process than hydrogel application.[33] The digestive enzymes also have the ability to prevent, inhibit, and break biofilms of many bacteria, except pseudomonas and some other Gram-negative pathogens, commonly found on prosthetics.[34,35] Maggot enzymatic digestion can be very intense, leading to focal liberation of significant amounts of heat within the center of the wound.[36] As a result, actively feeding maggots often migrate to the edge of the wound to cool down. The liberation of heat increases both the rate of putrefaction and the rate of digestion.[22] Cazander *et al*. demonstrated that thermal changes within maggots' enzymes may help facilitate their ability to reduce the activation of the human complement system.[37]

Not all fly species are safe and/or effective for use in medical applications. The flies that are most commonly utilized for maggot therapy are sheep blowflies (Calliphoridae) and the species most commonly used is *Phaenicia (Lucilia) sericata*, the green blowfly.[38,39] This specific fly has been managed in pure culture for over 20 years,[23] with efforts ongoing to create transgenic *Lucilia* sericata larvae capable of producing a human growth factor.[39] Studies on the application of other fly species, such as *Protophormia terraenovae*, *L. cuprina*, *L. illustris*, and *Phormia regina* have also been published.[18,40,41]

EFFECTS OF MAGGOT DEBRIDEMENT THERAPY ON HUMAN TISSUE

On a molecular level, MDT has been found to influence three major processes: angiogenesis, inflammation,

and cell migration.[42] Three proangiogenic factors have been identified in maggot secretions: l-histidine, 3-guanidinopropionic acid, and l-valinol.[42] Dried secretions from *L. sericata* larvae increased wound capillary density and VEGF-A mRNA protein expression in a rat model.[43] In addition, the presence of maggot secretions may be associated with increased production of pro-angiogenic growth factors from anti-inflammatory macrophages,[44] as well as the differentiation of macrophages and monocytes. In one study, larval secretions influenced monocytes to differentiate into anti-inflammatory macrophages.[44] Another study showed that maggot secretions inhibit the production of pro-inflammatory cytokines (e.g., tumor necrosis factor-alpha) while upregulating anti-inflammatory cytokines (e.g., interleukin-10) in dose-dependent fashion, likely through a cAMP-mediated process.[45]

Cazander, *et al*. collected samples of larval excretions from disinfected maggots.[37] When added to donated human sera from preoperative and postoperative patients, these excretions resulted in decreases in complement protein (C3 and C4) activation by up to 99% (preoperative group) and up to 55% (postoperative group), pointing to a powerful effect of MDT on complement-mediated inflammatory response.[37] Researchers are currently working to isolate modulators of inflammation in maggot excretions in hopes to identify clinically relevant substances affecting not only complement activation but also the proteolytic, antimicrobial, and growth promoting activity of MDT.[4,5] Among other potentially beneficial actions of larval secretions, the presence of increased microvascular epidermal cell migration was shown.[46]

MEDICAL RATIONALE FOR MAGGOT DEBRIDEMENT THERAPY

The increasing prevalence of chronic medical conditions and nonhealing wounds is one of the consequences of the ability of modern medical advances to prolong life.[4] Diseases that were once fatal have evolved into chronic ailments that result in cardiovascular risk factors associated with the emergence of nonhealing wounds.[47] Given current demographic trends, the number of susceptible patients is bound to increase, especially among populations that actively use pharmacological modulators of wound healing.[4,48] Because of the growing need for effective clinical approaches to chronic wound management, numerous new treatment modalities were introduced over the past two decades, including hyperbaric oxygen administration, negative pressure wound therapy, topical growth factor applications, enzymatic wound debridement, and many others.[49-52]

In general, effective wound care begins with properly conducted debridement, which in turn results in a lower infectious burden and improved wound status through the removal of necrotic, contaminated tissue and microbial biofilm. Mechanical, surgical, autolytic as well as enzymatic methods have all been utilized as mechanisms for debridement.[53,54] Each of these techniques has associated disadvantages such as limited efficacy, need for anesthesia, complaints of significant pain as well as mechanical and/or cellular damage to the underlying healthy tissue.[40]

MDT is the intentional application of live, "medical grade" fly larvae to wounds to effect debridement, disinfection, and ultimately wound healing.[4,55] The process begins with predetermined species of maggots undergoing chemical disinfection. Historically, the availability of inexpensive, well-contained, viable, and germ-free maggots has been a major barrier to wider implementation of MDT.[4] Improved disinfectants and rearing techniques have simplified the production of germ-free maggots.[4,23] Expeditious delivery of maggots is now possible through multiple overnight courier services.

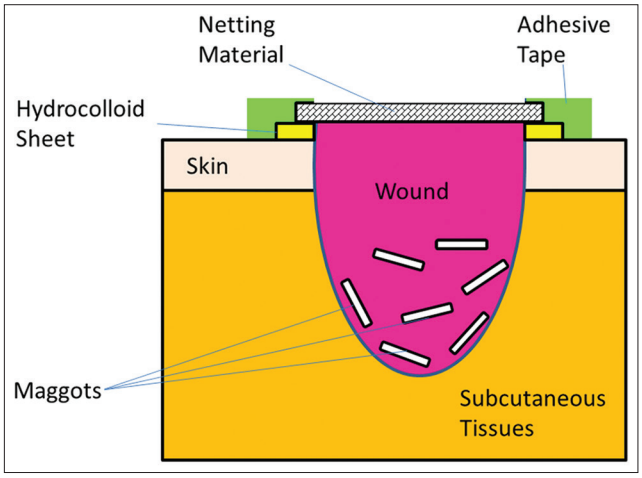

Figure 2: An example of a "confinement" dressing, with the wound itself serving as the bottom of the "container" that holds the larvae. Applied circumferentially around the cutaneous wound edges is the protective hydrocolloid sheet, over which the netting material is placed. Once secured with adhesive tape, the top portion of the dressing effectively prevents larvae from migrating out of the wound

Modern dressing materials have simplified the larval debridement procedure and minimized the risk of uncontained maggots.[4] Appropriately fashioned dressings now consist of improved adhesives and synthetic materials which provide maggots with an environment suitable for debridement while preventing uncontrolled migration and patient/provider discomfort. There are two major variants of specialized MDT dressings – the confinement and the containment types.[4,57] In confinement dressings, the wound floor acts as the bottom limit of the enclosure, allowing direct maggot-to-wound contact [Figure 2]. In containment dressings, maggots are enclosed within a sealed pouch [Figure 3] that is then placed on top of the wound, with no direct maggot-to-wound contact.[12,56] Although somewhat counter-intuitive, MDT approaches based on containment and confinement dressings have been shown to be equally effective.[8,33] Overall, the above evidence supports the importance of larval secretions (in addition to any direct mechanical action) in delivering beneficial wound outcomes, in addition to any direct physical interactions (e.g., larval movement and the ingestion of necrotic material) between maggots and the wound surface.[4,8,12,58] The FDA classification of maggots under the label of "medical device" reflects, in a way, the fact that maggots aggressively search the wound bed for necrotic material, consuming more and more necrotic tissue and gaining access to increasingly deeper tissue layers within the wound.[4,59] Chambers *et al*. provide compelling experimental evidence that the proteinases present in larval excretions/secretions help in the breakdown of fibrin and play a role in the subsequent remodeling of extracellular matrix components.[60] Zhang *et al*. further suggest that fatty acid extracts from *L. sericata* larvae may promote wound healing by enhancing angiogenic activity.[43] Potential benefits of MDT are summarized in Figure 4.

Figure 3: An example of a "containment" dressing or a "biobag" used in maggot debridement therapy. The permeable bag allows larval secretions to interact with the wound while at the same time preventing the maggots from migrating. Modified from Williams *et al*.,[56] under the terms of Creative Commons Attribution License

MAGGOT DEBRIDEMENT THERAPY IN DIABETIC WOUNDS

According to the Centers for Disease Control and Prevention (CDC), an estimated 30 million Americans (9.4% of the U.S. population) had diabetes in 2015.[61] This population is especially vulnerable and susceptible to poor wound healing, with the estimated annual cost of managing diabetic wounds in the U.S. exceeding $20 million, including more than 2 million workdays of lost productivity.[62] Medical costs of treating a single diabetic ulcer can reach $10,000 and clinical nonresponse or progression of the disease process may result in an extremity amputation, with a median cost of $12,500.[63] Diabetic extremity ulcers affect roughly 15% of the diabetic population, leading to approximately 70,000 amputations annually[4,42,61,64,65] The progression from diabetic peripheral vascular disease to chronic nonhealing foot ulcers to terminal amputation is all too common. MDT can stall the progression of this condition, improving the prognosis even in recalcitrant cases.[66]

One randomized trial suggested that MDT was more effective than hydrogel in reducing the wound area of diabetic foot ulcers.[67] Another prospective, randomized study comparing the efficacy of MDT versus hydrogel showed improved debridement efficacy, but no difference in the rate of healing or ability to eradicate methicillin-resistant *S. aureus* (MRSA) infection.[33] While the same investigation suggested greater amount of ulcer-related pain with MDT compared to hydrogel, it also showed equivalent efficacy of loose versus bagged larvae.[33] In yet another retrospective study comparing changes in necrotic and total surface area of chronic foot and leg ulcers in diabetic patients, patients were treated with either MDT, standard medical management, or routine surgical care.[68] Maggot therapy was associated with faster debridement and wound healing than its therapeutic comparators.[68] MDT-treated wounds saw a 50% reduction in necrotic surface area in as few as 9 days, compared to 29 days in the other groups. Moreover, within 2 weeks, MDT treated wounds contained only 7% necrotic tissue compared with 39% necrotic tissue for traditional management. Finally, within 4 weeks, wounds in the MDT group were completely debrided and contained 56% healthy granulation base, whereas wounds treated with conventional therapy retained 33% necrotic tissue coverage with only 15% granulation base.[68] At the same time, the rate of complete wound closure was not significantly different between MDT and non-MDT

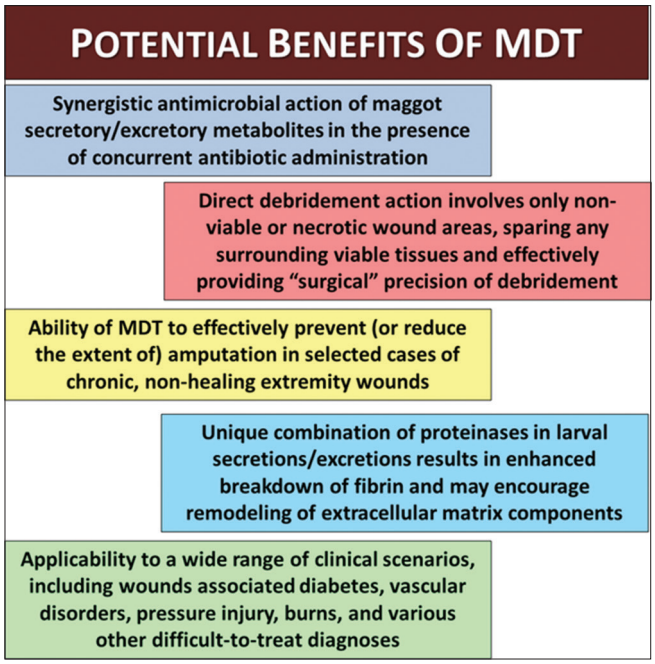

Figure 4: List of selected benefits of maggot debridement therapy based on the current literature review

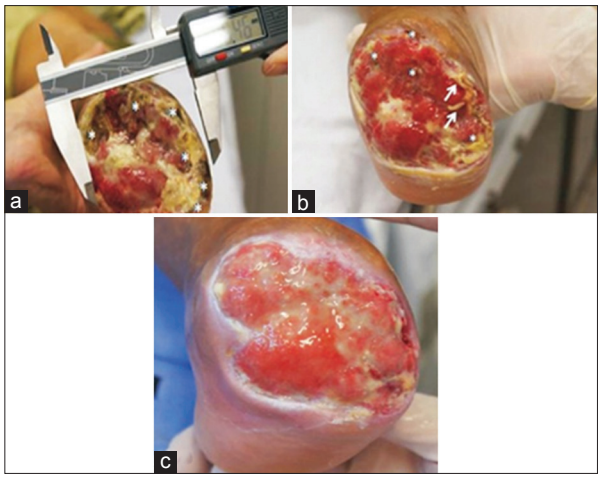

Figure 5: An example of a diabetic foot ulcer before, during and after maggot debridement therapy. (a) Baseline measurement of the extent of necrosis and initiation of treatment (day 1). Asterisks represent the areas of tissue necrosis. (b) Patient's foot ulcer during active treatment with maggot therapy (day 14). The asterisks represent areas of tissue necrosis and the arrows indicate the larvae of *Chrysomya megacephala*. (c) Patient's foot ulcer after treatment with maggot therapy (day 43). Source: Pinheiro, *et al*. Indian J Med Res 2015;141 (3):340-2. Images used under the terms of the Creative Commons Attribution-Noncommercial-Share Alike 3.0 Unported, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited

approaches.[68] Despite being limited by significant definitional heterogeneity and small size of source reports, a meta-analysis comparing the effectiveness of MDT versus non-MDT approaches, suggested that MDT may be superior to non-MDT modalities in achieving full wound healing, time to healing, and the number of antibiotic-free days.[69] An example of a diabetic foot ulcer treated with MDT is provided in Figure 5.[70]

MAGGOT DEBRIDEMENT THERAPY IN VENOUS EXTREMITY ULCERS

Chronic venous ulcers affect approximately 2.5 million adults in the U.S., and are characterized by the presence of venous insufficiency, hemosiderin deposition, and lipodermatosclerosis.[71] Traditional management options include debridement of the ulcer, skin grafting, venous stripping or ligation, and sclerotherapy.[71] Despite treatment, over half of these ulcers fail to heal after a year of therapy.[71] The application of MDT shows some promise in this challenging area of wound care.

In one case-based experience with the use of MDT in the setting of chronic venous ulceration, favorable outcome was reported despite the presence of multidrug-resistant bacteria including MRSA, vancomycin-resistant enterococci, and multiresistant *Psuedomonas aeruginosa*.[72] Following 3 weeks of combined MDT and antibiotic treatment, wound cultures showed no growth and the clinical team proceeded with skin grafting plus negative pressure wound therapy.[72] At discharge, the patient was noted to have 90% graft take, but after several months experienced a recurrence requiring further therapy.[72]

A randomized trial comparing the efficacy of compression bandage alone versus compression bandage plus MDT in the treatment of chronic venous ulcers showed that compression plus larval therapy improved wound outcomes in the first 4 days but failed to affect the 12-week healing rates.[73] Evidence shows that if the underlying venous insufficiency is corrected, ulcerations will heal despite the presence of devitalized tissue, as corroborated by findings from the VenUS II trial.[33] It has also been demonstrated that larvae beneath the bandages may stay unharmed during the 4 days of MDT treatment, suggesting limited need for elaborate specialty dressings.[73] Limitations of this study included a small sample size, lack of long-term result evaluation, and the potential presence of patient/venous ulcer selection bias.[73]

MAGGOT DEBRIDEMENT THERAPY IN ARTERIAL EXTREMITY ULCERS

Ischemia has traditionally been considered a relative contraindication for MDT.[20] In the absence of

adequate arterial perfusion, revascularization is required to support wound healing.[74] If this is not feasible, amputation may be required.[20,74] Beyond these general guidelines, there is no formal quantitative definition of circulatory function required for MDT to be successful. Consequently, the utility of MDT in the setting of arterial extremity ulcers has been predominantly limited to defining the level of viable tissue and thus guiding amputation planning.[20]

One clinical report suggests that the use of MDT in ischemic extremity ulcers may have utility in the setting of a gangrenous wound of the foot, provided that revascularization attempts are made.[75] In that particular case, MDT was initiated to reduce patient discomfort and odor while trying to prevent an amputation.[75] Following a femoro-femoral bypass and eight MDT treatments, necrotic soft-tissue was effectively debrided, and the foot wound began to heal.[75] Another small study evaluated management of leg ulcers in 16 patients suffering from peripheral arterial disease, with MDT effectively facilitating healing in 10 cases.[76] The authors determined that ankle-brachial index of <0.6 may be associated with unfavorable MDT outcomes in the setting of ischemic leg ulcers.[76]

MAGGOT DEBRIDEMENT THERAPY IN PRESSURE ULCERS

Pressure ulcers are among the most common adverse events seen within the healthcare setting. Although incidence and prevalence may vary depending on the institution and setting, it is estimated that over 2.5 million individuals in the United States will develop pressure ulcers annually.[77] This equates to a significant financial burden as well as an increased mortality rate for patients who develop this dreaded complication.[77] In fact, the overall associated cost is estimated to be between $9.1 and $11.6 billion, and more importantly about 60,000 attributable deaths.[78] The standard treatment approach consists of appropriate "offloading" of the area of injury, in addition to excellent nursing care and the use of pressure redistribution devices including specialized mattresses and seat cushions.[79] As with all other types of wounds, debridement may become necessary, along with appropriate specialty care management. These ulcers may require weeks to months of debridement, often contain extensive amount of necrotic tissue, and can be malodorous and difficult to handle in the outpatient setting. MDT may be used to reduce the number of debridements required which may decrease pain, bleeding, length of admissions, and overall costs.

In one study, looking at 103 inpatients with 145 pressure ulcers, 80% of MDT-treated wounds were deemed to be successfully debrided while only 48% were completely debrided using conventional therapy alone.[80] In the same study, it was noted that within 3 weeks the MDT-treated wounds contained approximately one-third of the amount of necrotic tissue and twice the granulation tissue compared to nonmaggot-treated wounds.[80] In another small prospective controlled study looking at eight spinal cord injury patients with pressure ulcers that had been treated with conventional nonsurgical approach, MDT was shown to significantly decrease the amount of necrotic tissue seen after 1 week, as well as reduce the time to heal.[81] Additional clinical investigation, looking at 25 patients with intractable wounds, including lower extremity and pressure ulcers, demonstrated that MDT was able to achieve complete debridement in >88% of wounds.[82] In all of these studies, MDT was shown to be a safe, simple, effective, and an inexpensive alternative to conventional therapy of pressure ulcers.

MAGGOT DEBRIDEMENT THERAPY AND BURN INJURIES

A relatively recent case report demonstrated the applicability of MDT in the treatment of extensive thermal injuries.[83] A 59-year-old patient presented with severe, full-thickness burns over 60% of his total body surface area, with concurrent extensive muscle necrosis.[83] Following escharotomies and initial resuscitation, debridement of necrotic muscle proved difficult, mainly due to the lack of clear boundaries between normal and necrotic tissue. Skin allografting was performed, followed by the development of fevers, abdominal distension, and generalized clinical deterioration.[83] The allogenic skin was removed, and extensive soft-tissue necrosis was discovered.[83] Initial consideration of surgical debridement was abandoned because the amount of resected tissue would not be compatible with meaningful functional survival.[83] As an alternative option, MDT was utilized to more selectively debride necrotic areas.[83] The patient defervesced approximately 24 h after the initiation of MDT, followed by general clinical improvement. By day 6, large areas of granulation tissue were readily apparent.[83] No complications were reported during the

follow-up period, and subsequent serial skin grafting was performed to cover the wounds.[83] Of interest, the authors noted that MDT was much more effective on necrotic muscle than on necrotic tendons, skin, or adipose.[83]

ONCOLOGIC APPLICATIONS OF MAGGOT DEBRIDEMENT THERAPY

Although the application of MDT in the oncology setting does not treat cancer, this modality can provide benefit in the following therapeutic areas: mass debulking of necrotic tumor, drainage reduction, and odor control.[20] Literature is scant regarding MDT use for oncologic indications, consisting mainly of case reports in the setting of ulcerating tumors. Despite these limitations, some generalizations can be made. For example, malignant tissue in inoperable ulcerating sarcomas and breast carcinomas was noted to be readily susceptible to the beneficial activity of maggots.[42] The larvae attacked any abnormal structure(s) within the wound, clearing away malignant tissue and leaving behind healthy granulation bed.[42] In addition, the associated odor and pain improved, with some evidence of wound closure tendencies.[84]

In one striking case, a necrotic squamous cell carcinoma of the face was noted to be infested with blowfly larvae.[85] Because the wound contained no evidence of surrounding cellulitis or adenopathy, it was decided to leave the larvae in place, and by the 3rd day, the wound was devoid of any residual necrotic tissue.[85] A similar case was described involving a deteriorating squamous cell carcinoma refractory to chemotherapy, radiotherapy, and conventional wound management until successful MDT application.[42] Wounds associated with Kaposi sarcoma have also been successfully treated with MDT. Similar to applications in other oncologic settings, larval therapy may help debride, disinfect, and heal necrotic Kaposi sarcoma wounds, potentially preventing morbid outcomes such as amputation or severe soft-tissue infection.[31] To summarize, key palliative benefits of MDT in the setting of difficult-to-treat, cancer-related wounds include better control of infection, odor, drainage, and avoidance of extensive and potentially deforming surgeries.[31]

MAGGOT DEBRIDEMENT THERAPY FOR ELEPHANTIASIS NOSTRAS VERRUCOSA

Seen very rarely, elephantiasis nostras verrucosa (ENV) is a dermatologic condition that complicates chronic lymphedema.[86] It typically presents with dermal fibrosis, hyperkeratotic, papillomatous, verrucous lesions, often accompanied by episodic infections of involved tissues.[87] Affected anatomic areas have been described as having cobblestone-like appearance in the setting of severe, nonpitting, fibrotic edema.[88] Known risk factors for ENV include recurrent cellulitis, previous surgery/trauma, obesity, congestive heart failure, and radiation exposure.[88]

In a recent case report, the use of MDT was shown to be effective in treating ENV.[89] Over a period of 28 days, the patient underwent a combination therapy consisting of surgical debridement and MDT for the right lower extremity ENV.[89] Larvae were placed over the wounds for 48–72 h at a time, allowing the affected tissue to become soft and the hyperkeratotic areas to slough off, with impressive end result.[89] The authors describe transformation of dark, edematous, woody, and malodorous tissues into much thinner, softer, and pinker ones. Most importantly, the patient's pain improved significantly, restoring his ability to ambulate.[89] Although the conventional therapy for ENV is surgical, operative debridement can be very difficult given the texture and tissue consistency of ENV. Presurgical treatment with 10% salicylic acid is often necessary to soften these lesions before debridement. In the above-described case, MDT was able to reduce the presurgical preparation time from 1 month (typical duration) to 2 days.[89] Further investigation is clearly warranted in this highly specialized area of wound care.

COST-EFFECTIVENESS OF MAGGOT DEBRIDEMENT THERAPY

The approximate cost of medical maggots is currently between $80 and $100 per treatment. Although it may seem expensive, this range is roughly equivalent to what it was about 90 years ago when adjusted for inflation.[4] The majority of the cost is attributable to labor and quality control expenditures, and although MDT in the U.S. is generally covered by third party payers, this remains inconsistent.[4] MDT is generally considered both clinically and fiscally prudent due to its documented effectiveness, simplicity, safety, applicability to a broad range of settings (e.g., hospital, clinic, home), and the ability for a wide range of caregivers to apply it (e.g., physicians, nurses, patients, and family members).[4]

It has been noted that MDT may be more cost-effective than conventional wound therapy in certain clinical

settings and/or conditions.[4,9] One study examined cost-effectiveness of MDT compared to other conventional wound care approaches in the setting of venous stasis ulcers.[9] The median cost of an MDT treatment (including the price of larvae) was significantly lower (£78.64) when compared to £136.23 per-treatment cost in the control group.[9] In addition, the MDT group required less nursing time per ulcer treated than the standard "hydrogel dressing" group (three nursing visits in MDT group vs. 19 visits in the standard treatment group).[9] The median cost of nursing per ulcer was £53.85 for standard therapy versus £10.77 for MDT group.[9] Even after including the cost of larvae (£58.00 per treatment) the median amount of "dressings" was still lower for the MDT group (£67.87 vs. £89.55).[9] When all of the above are compiled into monthly cost data, MDT was about 50% less expensive than the comparator therapy (£492 including larvae vs. £1054 in the hydrogel group).[9]

It is important to note that MDT, based on previous observations, may be associated with better clinical outcomes. The fact that debridement occurred more rapidly in patients undergoing MDT is difficult to quantify from economic standpoint.[40] However, the combination of indirect benefits of MDT (e.g., more effective debridement) and lower reported costs (e.g., clinical materials and labor) presents a compelling argument in favor of larval therapy.[4,9] One can likewise extrapolate that MDT, associated with more rapid debridement, would also be associated with an earlier hospital discharge and thus financial benefits of shorter duration of stay.

ADVERSE EFFECTS OF MAGGOT DEBRIDEMENT THERAPY

As with other medical modalities, MDT has a number of associated side effects and risks, from localized tissue discomfort, to infection, to the sight of escaping maggots.[90] By far, the most common adverse effect of MDT is significant pain,[91,92] with approximately 5%–30% of patients reporting this complaint.[4,68,80,93] It is important to note, however, that most patients who complain of pain during MDT also report some degree of "baseline" pre-MDT pain. The skin, especially around the wound, tends to be sensitive to motion, pressure, and the liquefied necrotic drainage associated with maggot secretions.[94-96] The perception of movement becomes more apparent after 24 h of therapy due to increase in larval size. This uncomfortable sensation can be ameliorated by applying fewer or smaller larvae over the wound bed while also actively removing larvae before they become too large.[91] In terms of the sensory perception of pain, patients most often report either throbbing (pressure-like) or a sharp (knife-like) sensation.[20] Multimodality analgesia can help control the pain, especially when the latter occurs in the presence of associated hyperalgesia and central sensitization.[97-99] Preemptive analgesia may also be helpful, particularly when treating patients with known predisposition for acute-on-chronic pain exacerbations.[99,100]

Some degree of anxiety is also common among both patients and providers.[91] One survey showed that health-care professionals and administrators are much more likely to be repulsed by the thought of maggot dressings than the actual patient suffering with the chronic wound.[4,101] Patients may have some anxiety but are generally very accepting of MDT as a treatment option. The most effective way of addressing patient anxiety is by providing the recipient with more control over their treatment.[91] The availability of 24 h/day access to immediate and direct medical assistance can help with anxiety. At the same time, pharmacologic adjunctive therapy can be useful as well.[20] An important component of the overall strategy to reduce both patient and provider anxiety is education about MDT, optimally with inputs from experienced wound care experts, as well as former MDT patients.[102,103]

It has been observed that the digestive enzymes released by maggots may be associated with the appearance of erythema or cellulitis.[96] Mumcuoglu recommends that this complication can be avoided by applying plaster or hydrocolloid dressing around the periphery of the wound.[96] Related to this local tissue reaction is the frequently reported sensation of "tickling" or itching of the anatomic region being treated.[96]

First documented in sheep infested with >15,000 larvae, hyperammonemia is an uncommon side effect of MDT.[104] This ammonia toxicity as a result of an extreme larval burden is called "blow fly strike" that can result in reduced immune function, encephalopathy, and coma in most severe cases.[105] It was subsequently documented in humans by Borst, *et al*.[89] The increase in ammonia itself may be involved in the antimicrobial and wound healing activity of MDT.[106] Borst *et al*.[89] also demonstrated that serum ammonia levels trended predictably with increases in larval load. Consequently, high larval loads

must be avoided to minimize morbidity.[20,107] It is also recommended that a baseline serum ammonia level be established prior to initiating MDT and that monitoring be continued throughout treatment. Any changes in mental status in a patient undergoing MDT should prompt ammonia level verification. Adherence to the recommended density of 5–10 maggots/cm^2 can also help mitigate the risk of "blow fly strike."[20]

Escaping of larvae or even mature flies is a possibility during MDT.[10,108] Larvae do occasionally get loose as they migrate away from the warm environment of the wound bed in search of necrotic tissue. This is most commonly seen when maggot dressings are left in place for more than 48 h.[8] Transitioning to an adult fly typically takes 1–2 weeks; the chance that larvae would go without being noticed for such an extended period of time is unlikely. However, cases where dressings are intentionally or unintentionally left in place are not out of the realm of possibility.

Another rare side effect is maggot invasion of healthy tissue. It is important to note that only a few larval species have been used in medical applications with success.[107] *L. sericata* is the most commonly prescribed larval type. This is primarily because it was discovered that larvae of this species starved when only granulation tissue remained in a wound.[84] However, there still have been reports of *L. sericata* feeding on healthy human tissue, resulting in a theory that some strains of this species were able to retain a degree of invasiveness in humans.[96,107]

Although no allergic reactions have been attributed to MDT larvae, allergies to various wound dressing materials are possible.[96] It is important to remember that the use of nonsterile maggots can be associated with septicemia.[96] This, in turn, highlights the importance of ensuring the availability of high quality, reliable sources of medically suitable larvae.

Finally, serious bleeding in a patient undergoing MDT was reported.[109] In that particular case, the patient was being treated with approximately 200 maggots while at home. A visitng nurse performing a dressing change reported severe bleeding at the wound site and rushed the patient to the hospital. It was estimated that 500 mL of blood was lost at the scene. During the initial evaluation at the hospital, the wound was judged to be healing adequately as there was granulation tissue present without visible necrosis. Shortly afterwards, the patient's blood pressure fell suddenly to 72/24 mmHg, necessitating blood transfusion and inpatient admission. Patient has subsequently normalized and was discharged after 4 days in the hospital, without further complications.[109] Table 1 provides a summary of complications encountered with MDT.[31,33,42,62,68,69,72,73,75,76,83,89,102,104,109-111]

CONCLUSIONS

Modern MDT is based on established clinical evidence and has resulted in substantial wound care advances. MDT is most often used in chronic, nonhealing wounds; however, it was also found to be useful in a variety of other specialized wound applications, including postsurgical wounds, burns, necrotic fungating tumors, osteomyelitis, and necrotizing fasciitis. High-risk medical patients, including those with chronic diabetes and vasculopathy have benefited greatly from MDT.

For extremity wounds, benefits of MDT may be greatest before infection or vascular compromise become limb threatening.[4] One of the advantages of MDT is that it is not operator dependent.[8] Many of the drawbacks of MDT have been successfully addressed through advances in materials manufacturing and transportation making maggot therapy readily available, reliable, economically viable, and simple to implement.[4] Specialty laboratories currently supply medical-grade maggots to therapists and patients in more than 30 countries.[4] Complications of MDT, for vast majority of patients, are minimal and easily treatable. Thus, MDT appears to be a great tool for supplementing surgical treatment or primary therapy in patients who are not surgical candidates. Given many unexplored areas of clinical application of MDT, this valuable wound management option should be studied further.

Financial support and sponsorship
Nil.

Conflicts of interest
There are no conflicts of interest.

Ethical conduct of research
Established ethical guidelines for research were utilized during the conduct of this project. Neither IRB approval nor informed consent were required because no human participants were involved.

REFERENCES

1. Cherniack EP. Bugs as drugs, part 1: Insects: The "new" alternative medicine for the 21st century? Altern Med Rev 2010;15:124-35.

2. Porshinsky BS, Saha S, Grossman MD, Beery Ii PR, Stawicki SP. Clinical uses of the medicinal leech: A practical review. J Postgrad Med 2011;57:65-71.
3. Manring M, Calhoun JH. Biographical sketch: William S. Baer (1872–1931). Clin Orthopaed Relat Res 2011;469:917-9.
4. Sherman RA. Maggot therapy takes us back to the future of wound care: New and improved maggot therapy for the 21st century. J Diabetes Sci Technol 2009;3:336-44.
5. Gabrielsen P. How Maggots Heal Wounds; 2012. Available from: http://www.sciencemag.org/news/2012/12/how-maggots-heal-wounds. [Last accessed on 2016 Nov 11].
6. Baer WS. The classic: The treatment of chronic osteomyelitis with the maggot (larva of the blow fly). 1931. Clin Orthop Relat Res 2011;469:920-44.
7. Robinson W. Progress of maggot therapy: In the United States and Canada in the treatment of suppurative diseases. Am J Surg 1935;29:67-71.
8. Opletalová K, Blaizot X, Mourgeon B, Chêne Y, Creveuil C, Combemale P, *et al.* Maggot therapy for wound debridement: A randomized multicenter trial. Arch Dermatol 2012;148:432-8.
9. Wayman J, Nirojogi V, Walker A, Sowinski A, Walker MA. The cost effectiveness of larval therapy in venous ulcers. J Tissue Viability 2000;10:91-4.
10. Steenvoorde P. Maggot debridement therapy in surgery. Department Surgery, Faculty of Medicine/Leiden University Medical Center (LUMC). Leiden University; 2008.
11. Parnés A, Lagan KM. Larval therapy in wound management: A review. Int J Clin Pract 2007;61:488-93.
12. Grassberger M, Fleischmann W. The biobag – A new device for the application of medicinal maggots. Dermatology 2002;204:306.
13. Arnold C. New Science Shows How Maggots Heal Wounds; 2013. Available from: https://www.scientificamerican.com/article/news-science-shows-how-maggots-heal-wounds/. [Last accessed on 2016 Nov 11].
14. Cazander G, van Veen KE, Bouwman LH, Bernards AT, Jukema GN. The influence of maggot excretions on PAO1 biofilm formation on different biomaterials. Clin Orthop Relat Res 2009;467:536-45.
15. Arora S, Baptista C, Lim CS. Maggot metabolites and their combinatory effects with antibiotic on *Staphylococcus aureus*. Ann Clin Microbiol Antimicrob 2011;10:6.
16. Li X, Liu N, Xia X, Zhang S, Bai J, Wang J, *et al.* The effects of maggot secretions on the inflammatory cytokines in serum of traumatic rats. Afr J Tradit Complement Altern Med 2013;10:151-4.
17. Sherman RA, Tran JM, Sullivan R. Maggot therapy for venous stasis ulcers. Arch Dermatol 1996;132:254-6.
18. Sherman RA, Pechter EA. Maggot therapy: A review of the therapeutic applications of fly larvae in human medicine, especially for treating osteomyelitis. Med Vet Entomol 1988;2:225-30.
19. Bonn D. Maggot therapy: An alternative for wound infection. Lancet 2000;356:1174.
20. Sherman RA. Maggot therapy for foot and leg wounds. Int J Low Extrem Wounds 2002;1:135-42.
21. Thomas S, Jones M, Shutler S, Jones S. Using larvae in modern wound management. J Wound Care 1996;5:60-9.
22. The_Australian_Museum. Decomposition: Fly Life Cycle and Development Times; 2015. Available from: http://www.australianmuseum.net.au/decomposition-fly-life-cycles. [Last accessed on 2016 Nov 11].
23. Labs M. Medical Maggots™ (maggot therapy, maggot debridement therapy, MDT, biotherapy, biosurgery, biodebridement, larval therapy); 2017. Available from: http://www.monarchlabs.com/mdt. [Last accessed on 2017 Aug 08].
24. Amendt J, Campobasso CP, Gaudry E, Reiter C, LeBlanc HN, Hall MJ, *et al.* Best practice in forensic entomology – Standards and guidelines. Int J Legal Med 2007;121:90-104.
25. Ubero-Pascal N, Paños Á, García MD, Presa JJ, Torres B, Arnaldos MI, *et al.* Micromorphology of immature stages of sarcophaga (Liopygia) cultellata pandellé, 1896 (Diptera: Sarcophagidae), a forensically important fly. Microsc Res Tech 2015;78:148-72.
26. Lowne BT. The Anatomy, Physiology, Morphology and Development of the Blow-Fly:(Calliphora Erythrocephala.) A Study in the Comparative Anatomy and Morphology of Insects; with Plates and Illustrations Executed Directly from the Drawings of the Author; Vol. 2. 1895.
27. Sherman RA. Mechanisms of maggot-induced wound healing: What do we know, and where do we go from here? Evid Based Complement Alternat Med 2014;2014:592419.
28. Francesconi F, Lupi O. Myiasis. Clin Microbiol Rev 2012;25:79-105.
29. Gottrup F, Jørgensen B. Maggot debridement: An alternative method for debridement. Eplasty 2011;11:e33.
30. Terra WR, Ferreira C. Insect digestive enzymes: Properties, compartmentalization and function. Comp Biochem Physiol B 1994;109:1-62.
31. Lin Y, Amin M, Donnelly AF, Amar S. Maggot debridement therapy of a leg wound from Kaposi's sarcoma: A Case report. J Glob Oncol 2015;1:92-8.
32. Nigam Y, Morgan C. Does maggot therapy promote wound healing? The clinical and cellular evidence. J Eur Acad Dermatol Venereol 2016;30:776-82.
33. Dumville JC, Worthy G, Bland JM, Cullum N, Dowson C, Iglesias C, *et al.* Larval therapy for leg ulcers (VenUS II): Randomised controlled trial. BMJ 2009;338:b773.
34. Renner R, Treudler R, Simon JC. Maggots do not survive in pyoderma gangrenosum. Dermatology 2008;217:241-3.
35. Romanò CL, Toscano M, Romanò D, Drago L. Antibiofilm agents and implant-related infections in orthopaedics: Where are we? J Chemother 2013;25:67-80.
36. Hall RD. The forensic entomologist as expert witness. Forensic Entomology: The Utility of Arthropods in Legal Investigations. Vol. 1. CRC Press: Boca Raton, Florida; 2001. p. 379-400.
37. Cazander G, Schreurs MW, Renwarin L, Dorresteijn C, Hamann D, Jukema GN, *et al.* Maggot excretions affect the human complement system. Wound Repair Regen 2012;20:879-86.
38. Nigam Y, Dudley E, Bexfield A, Bond AE, Evans J, James J. The physiology of wound healing by the medicinal maggot, *Lucilia sericata*. Adv Insect Physiol 2010;39:39.
39. Linger RJ, Belikoff EJ, Yan Y, Li F, Wantuch HA, Fitzsimons HL, *et al.* Towards next generation maggot debridement therapy: Transgenic lucilia sericata larvae that produce and secrete a human growth factor. BMC Biotechnol 2016;16:30.
40. Zarchi K, Jemec GB. The efficacy of maggot debridement therapy – A review of comparative clinical trials. Int Wound J 2012;9:469-77.
41. Nuesch R, Rahm G, Rudin W, Steffen I, Frei R, Rufli T, *et al.* Clustering of bloodstream infections during maggot debridement therapy using contaminated larvae of protophormia terraenovae. Infection 2002;30:306-9.
42. Nwaeburu CC, Alishlash O. Maggot therapy and cancer. Research & reviews. Res J Biol 2016;4:28-32.
43. Zhang Z, Wang S, Diao Y, Zhang J, Lv D. Fatty acid extracts from *Lucilia sericata* larvae promote murine cutaneous wound healing by angiogenic activity. Lipids Health Dis 2010;9:24.
44. van der Plas MJ, Baldry M, van Dissel JT, Jukema GN, Nibbering PH. Maggot secretions suppress pro-inflammatory responses of human monocytes through elevation of cyclic AMP. Diabetologia 2009;52:1962-70.
45. van der Plas MJ, van Dissel JT, Nibbering PH. Maggot secretions skew monocyte-macrophage differentiation away from a pro-inflammatory to a pro-angiogenic type. PLoS One 2009;4:e8071.
46. Wang SY, Wang K, Xin Y, Lv DC. Maggot excretions/secretions induces human microvascular endothelial cell migration through AKT1. Mol Biol Rep 2010;37:2719-25.
47. Sanders LJ, Robbins JM, Edmonds ME. History of the team approach to amputation prevention: Pioneers and milestones. J Vasc Surg 2010;52:3S-16S.
48. Stadelmann WK, Digenis AG, Tobin GR. Physiology and healing dynamics of chronic cutaneous wounds. Am J Surg 1998;176:26S-38S.
49. Thackham JA, McElwain DL, Long RJ. The use of hyperbaric oxygen therapy to treat chronic wounds: A review. Wound Repair Regen 2008;16:321-30.
50. Cipolla J, Baillie DR, Steinberg SM, Martin ND, Jaik NP, Lukaszczyk JJ, *et al*. Negative pressure wound therapy: Unusual and innovative applications. OPUS 2008;12:15-29.

51. Ramundo J, Gray M. Enzymatic wound debridement. J Wound Ostomy Continence Nurs 2008;35:273-80.
52. Brown GL, Curtsinger L, Jurkiewicz MJ, Nahai F, Schultz G. Stimulation of healing of chronic wounds by epidermal growth factor. Plast Reconstr Surg 1991;88:189-94.
53. Arabloo J, Grey S, Mobinizadeh M, Olyaeemanesh A, Hamouzadeh P, Khamisabadi K, *et al.* Safety, effectiveness and economic aspects of maggot debridement therapy for wound healing. Med J Islam Repub Iran 2016;30:319.
54. Patry J, Blanchette V. Enzymatic debridement with collagenase in wounds and ulcers: A systematic review and meta-analysis. Int Wound J 2017;14:1055-65.
55. Pickles SF, Pritchard DI. Endotoxin testing of a wound debridement device containing medicinal *Lucilia sericata* larvae. Wound Repair Regen 2017;25:498-501.
56. Williams KA, Cronje FJ, Avenant L, Villet MH. Identifying flies used for maggot debridement therapy. S Afr Med J 2008;98:196-7.
57. Musculoskeletal_Key. Clinical Application of Maggots; 2016. Available from: https://www.musculoskeletalkey.com/clinical-application-of-maggots/. [Last accessed on 2017 Dec 10].
58. Blake FA, Abromeit N, Bubenheim M, Li L, Schmelzle R. The biosurgical wound debridement: Experimental investigation of efficiency and practicability. Wound Repair Regen 2007;15:756-61.
59. FDA 510(k) Summary; 2007. Available from: https://www.accessdata.fda.gov/cdrh_docs/pdf7/K072438.pdf. [Last accessed on 2017 Dec 11].
60. Chambers L, Woodrow S, Brown AP, Harris PD, Phillips D, Hall M, *et al.* Degradation of extracellular matrix components by defined proteinases from the greenbottle larva lucilia sericata used for the clinical debridement of non-healing wounds. Br J Dermatol 2003;148:14-23.
61. Promotion National Center for Chronic Disease Prevention and Health Promotion. National Diabetes Statistics Report, 2017; 2017. p. 1-20.
62. Marineau ML, Herrington MT, Swenor KM, Eron LJ. Maggot debridement therapy in the treatment of complex diabetic wounds. Hawaii Med J 2011;70:121-4.
63. Davis WA, Norman PE, Bruce DG, Davis TM. Predictors, consequences and costs of diabetes-related lower extremity amputation complicating type 2 diabetes: The fremantle diabetes study. Diabetologia 2006;49:2634-41.
64. Association, A.P.M. Diabetic Wound Care; 2017. Available from: http://www.apma.org/Learn/FootHealth.cfm?ItemNumber=981. [Last accessed on 2017 Aug 29].
65. American Diabetes Association. Statistics about Diabetes. 2017. [Last accessed on 2017 Jul 19].
66. Mat Saad AZ, Khoo TL, Halim AS. Wound bed preparation for chronic diabetic foot ulcers. ISRN Endocrinol 2013;2013:608313.
67. Markevich YO, McLeod-Roberts J, Mousley M, Melloy E. Maggot therapy for diabetic neuropathic foot wounds: A randomized study. Diabetologia 2000;43:A15.
68. Sherman RA. Maggot therapy for treating diabetic foot ulcers unresponsive to conventional therapy. Diabetes Care 2003;26:446-51.
69. Tian X, Liang XM, Song GM, Zhao Y, Yang XL. Maggot debridement therapy for the treatment of diabetic foot ulcers: A meta-analysis. J Wound Care 2013;22:462-9.
70. Pinheiro MA, Ferraz JB, Junior MA, Moura AD, da Costa ME, Costa FJ, *et al.* Use of maggot therapy for treating a diabetic foot ulcer colonized by multidrug resistant bacteria in Brazil. Indian J Med Res 2015;141:340-2.
71. Dua A, Desai SS, Heller JA. The impact of race on advanced chronic venous insufficiency. Ann Vasc Surg 2016;34:152-6.
72. McInnes W, Ruzehaji N, Wright N, Cowin AJ, Fitridge R. Venous ulceration contaminated by multi-resistant organisms: Larval therapy and debridement. J Wound Care 2013;22:S27-30.
73. Davies CE, Woolfrey G, Hogg N, Dyer J, Cooper A, Waldron J, *et al.* Maggots as a wound debridement agent for chronic venous leg ulcers under graduated compression bandages: A randomised controlled trial. Phlebology 2015;30:693-9.
74. Taylor LM Jr., Hamre D, Dalman RL, Porter JM. Limb salvage vs. amputation for critical ischemia. The role of vascular surgery. Arch Surg 1991;126:1251-7.
75. Nordström A, Hansson C, Karlström L. Larval therapy as a palliative treatment for severe arteriosclerotic gangrene on the feet. Clin Exp Dermatol 2009;34:e683-5.
76. Igari K, Toyofuku T, Uchiyama H, Koizumi S, Yonekura K, Kudo T, *et al.* Maggot debridement therapy for peripheral arterial disease. Ann Vasc Dis 2013;6:145-9.
77. Bauer K, Rock K, Nazzal M, Jones O, Qu W. Pressure ulcers in the United States' inpatient population from 2008 to 2012: Results of a retrospective nationwide study. Ostomy Wound Manage 2016;62:30-8.
78. AHRQ. Preventing Pressure Ulcers in Hospitals; 2014. Available from: https://www.ahrq.gov/professionals/systems/hospital/pressureulcertoolkit/putool1.html. [Last accessed on 2018 Feb 15].
79. Reilly EF, Karakousis GC, Schrag SP, Stawicki SP. Pressure ulcers in the Intensive Care Unit: The 'forgotten'enemy. Opus 2007;12:17-30.
80. Sherman RA. Maggot versus conservative debridement therapy for the treatment of pressure ulcers. Wound Repair Regen 2002;10:208-14.
81. Sherman RA, Wyle F, Vulpe M. Maggot therapy for treating pressure ulcers in spinal cord injury patients. J Spinal Cord Med 1995;18:71-4.
82. Mumcuoglu KY, Ingber A, Gilead L, Stessman J, Friedmann R, Schulman H, *et al.* Maggot therapy for the treatment of intractable wounds. Int J Dermatol 1999;38:623-7.
83. Wu JC, Lu RR, Huo R, Fu HB. Maggot therapy for repairing serious infective wound in a severely burned patient. Chin J Traumatol 2012;15:124-5.
84. Weil GC, Simon RJ, Sweadner WR. A biological, bacteriological and clinical study of larval or maggot therapy in the treatment of acute and chronic pyogenic infections. Am J Surg 1933;19:36-48.
85. Bunkis J, Gherini S, Walton RL. Maggot therapy revisited. Western J Med 1985;142:554.
86. Turhan E, Ege A, Keser S, Bayar A. Elephantiasis nostras verrucosa complicated with chronic tibial osteomyelitis. Arch Orthop Trauma Surg 2008;128:1183-6.
87. Iwao F, Sato-Matsumura KC, Sawamura D, Shimizu H. Elephantiasis nostras verrucosa successfully treated by surgical debridement. Dermatol Surg 2004;30:939-41.
88. Dean SM, Zirwas MJ, Horst AV. Elephantiasis nostras verrucosa: An institutional analysis of 21 cases. J Am Acad Dermatol 2011;64:1104-10.
89. Borst GM, Goettler CE, Kachare SD, Sherman RA. Maggot therapy for elephantiasis nostras verrucosa reveals new applications and new complications: A Case report. Int J Low Extrem Wounds 2014;13:135-9.
90. Woo KY, Harding K, Price P, Sibbald G. Minimising wound-related pain at dressing change: Evidence-informed practice. Int Wound J 2008;5:144-57.
91. Sherman RA, Mendez S, McMillan C. Using maggots in wound care: Part 1: Learn about this simple, effective, low-risk, low-cost wound debridement technique. Wound Care Advisor 2014;3:12.
92. O'Connell K, Wardlaw JL. Unique therapies for difficult wounds. Today's Vet Pract 2011;1:10-6.
93. Sherman RA, Sherman J, Gilead L, Lipo M, Mumcuoglu KY. Maggot débridement therapy in outpatients. Arch Phys Med Rehabil 2001;82:1226-9.
94. Hollinworth H. The management of patients' pain in wound care. Nurs Stand 2005;20:65-6, 68.
95. Sherman RA, Mendez S, McMillan C. Using maggots in wound care: Part 1. Wound Care Advisor 2014;3:12-9.
96. Mumcuoglu KY. Clinical applications for maggots in wound care. Am J Clin Dermatol 2001;2:219-27.
97. Kehlet H, Jensen TS, Woolf CJ. Persistent postsurgical pain: Risk factors and prevention. Lancet 2006;367:1618-25.
98. Joshi GP. Multimodal analgesia techniques and postoperative rehabilitation. Anesthesiol Clin North America 2005;23:185-202.
99. Woolf CJ, Chong MS. Preemptive analgesia – Treating postoperative pain by preventing the establishment of central sensitization. Anesth Analg 1993;77:362-79.
100. Dahl JB, Møiniche S. Pre-emptive analgesia. Br Med Bull 2004;71:13-27.
101. Sherman RA, Nguyen H, Sullivan R, Mendez S, Carmean M.Why not maggots? Factors affecting therapists' decisions about using maggot debridement therapy. In: Presented at: 20th Annual Symposium on

Advanced Wound Care and Wound Healing Society Meeting. Tampa, FL; 28-1 April-May, 2007.
102. Gericke A, Hoffmann EM, Pitz S, Pfeiffer N. Maggot therapy following orbital exenteration. Br J Ophthalmol 2007;91:1715-6.
103. Fullerton D, *et al*. http://bjo. bmj. com. orbit, 2005;89:1445-8.
104. Guerrini VH. Ammonia toxicity and alkalosis in sheep infested by *Lucilia cuprina* larvae. Int J Parasitol 1988;18:79-81.
105. Guerrini VH. Excretion of ammonia by *Lucilia cuprina* larvae suppresses immunity in sheep. Vet Immunol Immunopathol 1997;56:311-7.
106. Robinson W. Ammonium bicarbonate secreted by surgical maggots stimulates healing in purulent wounds. Am J Surg 1940;47:111-5.
107. Sherman RA, Hall MJ, Thomas S. Medicinal maggots: An ancient remedy for some contemporary afflictions. Annu Rev Entomol 2000;45:55-81.
108. Wollina U, Karte K, Herold C, Looks A. Biosurgery in wound healing – The renaissance of maggot therapy. J Eur Acad Dermatol Venereol 2000;14:285-9.
109. Steenvoorde P, van Doorn LP. Maggot debridement therapy: Serious bleeding can occur: Report of a case. J Wound Ostomy Continence Nurs 2008;35:412-4.
110. Pliquett RU, Schwock J, Paschke R, Achenbach H. Calciphylaxis in chronic, non-dialysis-dependent renal disease. BMC Nephrol 2003;4:8.
111. Steenvoorde P, Jacobi CE, Van Doorn L, Oskam J. Maggot debridement therapy of infected ulcers: Patient and wound factors influencing outcome – A study on 101 patients with 117 wounds. Ann R Coll Surg Engl 2007;89:596-602.