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MAGGOT DEBRIDEMENT THERAPY (MDT): IT IS SAFE AND ECONOMIC FOR TREATING A DIABETIC FOOT ULCER

By

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Abstract

Diabetic foot ulcer (DFU) is the major global and devastating complication of diabetes mellitus that affects at least 20% of diabetic patients during their lifetime. This article presents an overview of the research evidence on maggot debridement therapy that serves as a guide to health professionals who may be users of this form of treatment now and in the future.

Key words: Diabetic foot ulcer, Maggot debridement therapy, Review.

Introduction

Patients with diabetes have difficulty healing wounds especially in the elderly whose numbers are increasing, resulting in rising cost for the delivery of health care (Sherman 2009). Diabetes mellitus is a public health challenge worldwide, and roughly 25 % of patients with diabetes in developing countries developed at least one foot ulcer during their lifetime (Melmed *et al*, 2011). The gravest outcome of an ulcerated foot is amputation, leading to premature death and larger economic costs. For standard care plus temperature monitoring compared to sub-optimal care the ICER rises to US$16, 124 per death averted and averts 1,385 deaths (Cárdenas *et al*, 2011). Based on the NIH and clinical excellence strategies, the early management of DFU could reduce the risk of complications such as preventable amputations and possible mortality, and also can improve overall quality of life. Diabetic foot infections are associated with substantial morbidity and mortality (Boulton *et al*, 2008).

The preventative strategy such as standard care not only improves the current level of care, but also leads to economic benefits in terms of societal cost-savings. Since prevention must be provided to a large number of patients at high-risk of ulceration, total costs of the prevention strategies are high; however, in the case of standard care plus temperature monitoring, the costs of thermometers would decline over time after the initial investment. For this strategy, even if the cost of the thermometer was zero, the strategy of standard care plus temperature monitoring would be cost-effective but not cost-saving. In the future, temperature monitoring technology may be integrated with electronic and mobile health prevention platforms that could further reduce the costs of personnel and phone services and make the intervention even more attractive.

Review, Discussion and Comments

Nowadays, some herbal products have shown therapeutic effects on healing of DFU as olive oil in combination with routine cares is more effective than routine cares alone (Nasiri *et al,* 2015), or applying 500 to 1000 mg of vancomycin powder prior to skin closure in diabetic patients who are not allergic to vancomycin (Wukich *et al*, 2015). Also, Plasma Heat Shock Proteins 70 and 47 levels gave good results in animal models (Zubair and Ahmad, 2015).

Maggots in medicine: Throughout recorded the history maggots have been used therapeutically to clean out the necrotic wounds, an application known as maggot as maggot therapy. Fly larvae that feed on dead tissue can clean wounds and may reduce bacterial activity and the chance of a secondary infection. They dissolve dead tissue by secreting digestive enzymes onto the wound as well as

actively eating the dead tissue with "mouth hooks," two hard, probing appendages protruding on either side of the mouth (David and William, 2006).

In Ancient Egyptian Papyrus, skin diseases was Known as leprosy. Myiasis (Miasis) was named after Hore (1854). Imhotep" the one who comes in peace, is with peace" used myi- asis in treating wounds and its skin for surgical sutures (Morsy, 2014)

If one went to the ancient time, as early as 520 B.C., Herodotus the "Father of History," described a case of facultative myiasis in a woman. "No sooner had she returned to Egypt, than she died a horrible death, her body seething with maggots while she was still alive." The Holy Bible alludes several times to maggots infesting human flesh. In Job7:5, the afflicted Job states "My flesh is clothed with maggots and clouds of dust, my skin rotted and fouled a fresh" In Acts 12: 23, it is recorded that King Herod died 5 days after being smitten with gangrene, during that time maggots bred in gangrenous mass. But, historical descriptions are not restricted to man. In the Hortus-Sanitatis published in An-twerp, Belgium in 1521, there are woodcuts that imply that the authors were aware of life cycle of flies that would swarm on maggot-infested meat and would attack a dead or dying animal (Greenberg, 1973). Hope (1840) coined the term "*Myiasis"* to refer to the diseases resulting from dipterous larvae as opposed to those caused by other insect larvae (the term for this was *scholechiasis*), and described several cases of myiasis from Jamaica caused by unknown larvae, one of which resulted in death, Colloquialisms for the myiasis include fly-strike, blowfly strike, and the victim or the tissue may be described as flyblown (Show, 1974). Name of the condition was derived from the ancient Greek μυῖα (*myia*), meaning "fly". Myiasis, a term introduced by William Hope in 1840, referred to the invasion of tissues and organs of animals and human wounds and certain body cavities by the dipteran larvae, which manifests as subcutaneous furunculoid or boil-like lesions (Kathleen, 2005).

Maggot therapy (also known as maggot debridement therapy (MDT), larval therapy, larva therapy, larvae therapy, biodebridement or biosurgery): is a type of biotherapy involving the intentional introduction by a health care practitioner of live, disinfected green bottle fly larvae into non-healing skin and soft tissue wound(s) of a human or other animal for the purpose of selectively cleaning out only the necrotic (dead) tissue within a wound in order to promote wound healing. Maggot therapy has a long history and prehistory (Nigam and Morgan, 2016). The indigenous people of Australia used maggot therapy, and so, do the Hill Peoples of Northern Burma, and possibly the Mayans of Central America. Surgeons in Napoleon's armies recognized that wounded soldiers with myiasis were more likely to survive than those without the infestation. In the American Civil War, army surgeons treated wounds by allowing blowfly maggots to clean away the decayed tissue. Dr. William Baer, an orthopedic surgeon at Johns Hopkins during the late 1920s, used maggot therapy to treat a series of patients with osteomyelitis, an infection of bone or bone marrow. The idea was based on an experience in the World-War I in which two soldiers presented to him with broken femurs after having lain on the ground for seven days without food and water (William, 1931).

Mumcuoglu (2001) reported that the sterile maggot debridement therapy (MDT) was first introduced in the US in 1931 and was used until mid-1940s in over 300 hospitals. With the antibacterial advent, MDT became rare until the early 1990s, but re-introduced first in the US, and later in Israel, the UK, Germany, Sweden, Switzerland, Ukraine and Thailand. Maggots were approved by the FDA as a "medical device" only in 2004 (along with leeches in the same year).

Scavée *et al.* (2003) in Belgium reported a case of a diabetic patient with severe ischa-

emic infected ulcer of the right foot, successfully treated with maggot therapy.

Martini and Sherman (2003) in Brazil reported that maggot therapy is used in chronic wounds to remove necrotic tissue, stimulate granulation tissue formation and kill bacteria. They added that in diabetic foot ulcers with the problem of bacterial resistance, this therapy proved as an alternative treatment for treating chronic ulcers infected with multidrug-resistant bacteria in a diabetic patient. Rita (2004) reported that maggots were the first live organism to be marketed in the US according to FDA regulations, and approved for treating neuropathic (diabetic) foot ulcers, pressure ulcers, venous stasis ulcers, and traumatic and postsurgical wounds that are unresponsive to conventional therapies

Chan *et al*. (2005) in Hong Kong repored eight cases of (*Chrysomya bezziana* seven cases & *Calliphora* spp one) nosocomial human myiasis, which were nursing home residents with an average age of 81.8 years. Seven patients were bedridden with advanced dementia. Four patients had preexisting wounds. Five had poor oral hygiene and four of those were on tube feeding. All of the five patients with poor oral hygiene suffered from oral myiasis. Two patients had vaginal infestations and one had wound myiasis in his diabetic foot ulcer.

Steenvoorde (2005) in the Netherlands performed a retrospective analysis using a visual analogue scale (VAS) was for 41 patients treated with MDT for non-healing wounds (22 men and 19 women; average age: 67 years). Average wound duration was 14 months (range: two weeks up to 132 months). Maggots were applied using the contained or the free-range techniques. Paracetamol (1g three times daily) and Durogesic plaster (25 microgm. every three days and 50 microgm. the day before the maggot change) were given for pain relief in the outpatient clinic. They found that Diabetic patients experienced the same amount of pain before and during MDT. Eight / 20 non-diabetic patients experienced more pain during MDT than before; the remaining non-diabetic patients had the same amount of pain before and during the therapy. The difference between diabetic and non-diabetic patients was statistically significant ($p<0.05$) for all applications combined. They concluded that options included hospital admission, using the contained method of application or, in the worst case scenario, cessation of treatment and that standardized but individually tailored pain management protocol is mandatory.

Parnés and Lagan (2007) in the UK stated that debridement is an essential component of wound care as the presence of devitalised tissue can impede the healing process. Larval therapy has been used for the debridement of wounds for several hundred years. They added that wound must be of a type which can benefit from the application of maggot therapy. A moist, exudating wound with sufficient oxygen supply is a prerequisite. Not all the wound-types were suitable: wounds which are dry or open wounds of body cavities do not provide a good environment for maggots to feed. In some cases it may be possible to make a dry wound suitable for larval therapy by moistening it with saline soaks, applied for 48 hours. The patients and doctors may find maggots distasteful, although studies have shown that this does not cause patients to refuse the offer of maggot therapy.

Gupta (2008) reviewed of some of the most relevant literature regarding maggot therapy makes it clear that some factors beg a final conclusion such as patient and physician factors regarding maggot therapy, care of larvae, the indications, benefits and precautions of maggot debridement therapy (MDT). MDT has been given the fashionable name of myiasis or bio-surgery. Maggots used in MDT are not the same as that of the house fly (*Musculus* sp.) but are now specially bred larvae of the *Lucilia sericata*. These larvae have the property of not damaging healthy dermis and subcutaneous tis-

sue but can destroy healthy epithelium; thus, epithelium protection is mandatory in MDT.

Tantawi *et al*. (2010) in Egypt reported an accidental involvement of *L. cuprina* in MDT in Alexandria, which proved to be safe and effective. Laboratory colonies of *L. sericata* (species regularly used in MDT) at the Alexandria Faculty of Science were renewed by *Lucilia* flies collected as third instar larvae on exposed rabbit carcasses. Flies from the new colonies were successfully used to heal the diabetic foot wounds of two patients at Alexandria Main University Hospital. Analysis of DNA sequences and adult and larval morphology then revealed that these flies were and still are *L. cuprina.* Breeding of this species in carrion in Alexandria is a new record. Despite the safety of this strain of *L. cuprina* in MDT, entomologists rearing blow flies for the purpose of wound debridement should regularly maintain high quality assurance of their species' identity to avoid possible clinical complications that may result from the introduction of an unexpected and invasive species to their laboratory colonies.

Marineau *et al*. (2011) in USA mentioned that the growth and aging of the population of Hawai'i with a high incidence of diabetes needed more effective strategies to manage complicated wounds healing. They reported none of the 23 patients refused MDT due to a version of this treatment modality and the majority of patients had minimal discomfort. In the 17 of 23 patients with the multiple comorbidities, the treatment of the complex diabetic wounds by MDT resulted in complete improvement or cure.

Tian *et al*. (2013) stated that maggot therapy improved healing in chronic ulcers. In the diabetic foot ulcers there is tentative evidence of benefit In 2004, the FDA cleared maggots for the usage as a medical device in the United States for the purpose of treatment of citation needed; non-healing necrotic skin and soft tissue wounds, pressure ulcers, venous stasis ulcers, neuropathic foot ulcers or non-healing traumatic or post-surgical wounds

Experimentally Hassan *et al*. (2014) used *Lucilia cuprina* maggots for the treatment of diabetic foot wounds. An artificial wound was made in diabetic foot of rabbit. The maggots were sterilized and put directly on the wound after dressing the wound without using any antibiotics. Several cycles of maggots were put on the wound. They concluded that the treatment of the diabetic foot was observed after 13 days. After this period the wound was completely healed and become free of microbial contamination. The new tissues were observed to close the wound.

Theoretically Wang *et al.* (2014) mentioned that maggot debridement therapy played an important role in treatment of diabetic foot ulcers and other chronic infectious wounds cause of this is its extremely low drug resistance and that the microbe stimulated maggot or it a derivative of normal sterile maggot, could exhibit stronger bacterial or bactericidal effects. Methods of the pretreatment on maggot was different germ solution were artificially mixed and added with originally sterile maggots, the novel secretions were collected. Some was demonstrated by plate test and telescope analysis. They hypothesized that maggot especially the larvae of *Lucilia sericata* conducted as the germ irritant receptor, and diversed germs interacted with it, at last, novel secretions/excretions result would offer a great help to the general surgery clinicians as well as researchers interested in novel antibiotics discovery.

Olea *et al*. (2014) reported the first case of myiasis in a diabetic foot of a 54-year-old male patient. They added that the main factor that favored the development of myiasis is due to diabetes, which caused a loss of sensibility in the limb that resulted in late consultation.

Shi and Shofler (2014) in USA maggot debridement therapy is used extensively in the UK in both community and hospital situ-

ations, but remains a potentially under-used modality in many wound care markets. It promotes wound healing by performing three key processes: debridement, disinfection and growth-promoting activity. They added that it could be used for the debridement of non-healing necrotic skin and soft tissue wounds, including pressure ulcers, venous stasis ulcers, neuropathic foot ulcers and non-healing traumatic of post-surgical wounds. With the increase in chronic diabetic foot wounds, maggot debridement therapy is a promising tool for health professionals dealing with difficult wounds..

Demirel *et al*. (2014) in Turkey stated that the diabetes, coronary artery disease and low socio-economic level as well as the presence of an open, neglected wound were attributed as the most important predisposing factors that led to the development of myiasis in this patient. It should be kept in mind that the diabetic patients with open wounds may develop myiasis especially in the summer months and larvae can cause progressive wound infection.

Sun *et al.* (2015) in China utilized human umbilical vein endothelial cells (HUVECs) to explore responses to the maggot excretions/ secretions on markers of angiogenesis and proliferation. They reported that the neo-granulation and angiogenesis in diabetic foot wounds after MDT. Moreover, significant elevation in CD34 and CD68 levels was also observed in treated wounds. In vitro, ES increased HUVEC proliferation, improved tube formation, and increased expression of vascular endothelial growth factor receptor 2 in a dose dependent manner. They concluded that MDT and maggot ES could promote diabetic foot wound healing by the up-regulating endothelial cell activity.

Góngora *et al*. (2015) in Colombia evaluated extracts taken from *S. magellanica* 3rd instar larvae fat body and haemolymph using a diabetic rabbit model as compared to the effect obtained with the same substances taken from *Lucilia sericata* larvae. Alloxan (a toxic glucose analogue) was used to induce experimental diabetes in twelve rabbits and were infected with the *Staphylococcus aureus* and *Pseudomonas aeruginosa*. The wounds were successfully treated with haemolymph and lyophilized extracts from the blowflies' larvae fat bodies. Each wound was then evaluated by rating scales and histological analysis. More favorable scores were recorded on the PUSH and WBS scales for the wounds treated with fat body derived from the larvae of both species compared to that with haemolymph; but, wounds treated with substances from *S. magellanica* gave better evolution. Histological analysis revealed that treatment led to tissue proliferation and more effective neovascularisation in less time with both species' fat body extracts compared to treatment with just haemolymph. *Sarconesiopsis magellanica* (Diptera: Calliphoridae) is a known potential mechanical vector of viruses, bacteria, protozoa, and helminthes (Amat, 2009).

Pinheiro *et al*. (2015) in Brazil studied the efficacy reports of maggot therapy in treating diabetic foot ulcer infected with multidrug resistant microorganisms. A 74 year old female patient with diabetes for over 30 years was treated with maggot therapy using larvae of *Chrysomya megacephala*. The microbiological samples collected were *Escherichia coli, Klebsiella pneumoniae* and *Pseudomonas aeruginosa*. The therapy done for 43 days resulted in a reduction of necrosis and the ulcer's retraction of 0.7 cm in area. Analysis of the bacteriological swabs revealed the presence of. Further studies need to be done to confirm the role of maggot therapy in wound healing using a large sample and a proper study design.

Klaus and Steinwedel (2015) reported that the maggot debridement therapy (MDT) was experiencing resurgence as an effective alternative to conventional mechanical debridement in non-healing wounds, especially those with antibiotic-resistant organisms. MDT has antibiotic, antifungal, and anti-inflammatory properties. They added that the Military use was on the rise.

Linger *et al*. (2016) in USA stated that diabetes and its concurrent complications impact a significant proportion of the population of the US and create a large financial burden on the American health care system. The FDA-approved the maggot debridement therapy (MDT), the application of sterile laboratory-reared *Lucilia sericata* larvae to wounds, proved a cost-effective and successful treatment for diabetic foot ulcers and other medical conditions. Human platelet derived growth factor-BB (PDGF-BB) is a secreted dimeric peptide growth factor that binds the PDGF receptor. PDGF-BB stimulates cell proliferation and survival, promotes wound healing, and has been investigated as a possible topical treatment for non-healing wounds. Genetic engineering has allowed for expression and secretion of human growth factors and other proteins in transgenic insects. They presented a novel concept in MDT technology that combined the established benefits of MDT with the power of genetic engineering to promote healing. The focus of this study is to create and characterize strains of transgenic L. sericata that express and secrete PDGF-BB at detectable levels in adult hemolymph, whole larval lysate, and maggot excretions/ secretions (ES), with potential for clinical utility in wound healing. They concluded that robust, inducible expression and production of human PDGF-BB protein from two conditional expression systems in transgenic *L. sericata* larvae. The tetracycline-repressible system prov-ed to be the promising as PDGF-BB protein was detectable in larval ES following induction. The system could potentially be used to deliver a variety of growth factors and anti-microbial peptides to the wound environment with the aim of enhancing wound healing, thereby improving patient outcome in a cost-effective manner.

As to the diabetic hand ulcer: Jiang *et al*. (2013) Diabetic patients with infectious hand ulceration, known as tropical diabetic hand syndrome (TDHS), are generally less well recognized than those with foot ulcers. Maggot debridement therapy (MDT) is usually used for the treatment of the diabetic foot ulcers and, in such wounds; the remarkable wound cleansing properties can be of considerable value. They present a case of TDHS in a 51-year-old man with type II, hypertension and dilated cardiomyopathy, in which conventional therapy had minimal effect, but significant wound debridement was achieved with MDT. They suggested that MDT may be a cost-effective alternative to conventional treatments for the debridement of TDHS.

Nursing role: Courtenay *et al*. (2000) in England collected prospective data to examine the current use of larva therapy (LT). Quantitative information was collected on 70 patients treated in nine hospitals. LT is used primarily to treat leg ulcers and generally involves three applications of larvae at the two to three day intervals. This method was judged effective in wound debridement and promoted the growth of granulation tissue. The wound exudate, odor, infection and pain are all reduced by the treatment. Adverse reactions are infrequent but include pain, bleeding, pyrexia and influenza-like symptoms. Prevention of hospital admission and surgery, reduced need for antibiotics and reduced hospital stay are all identified as outcomes of LT. The nurse practitioners who used LT believed it to have an important role in wound management. A randomized clinical trial, comparing LT with other debriding agents, was a must for evaluation of cost effectiveness.

Thomas (2002) reported that the standard technique recommended for relatively small wounds involves the initial application of a hydrocolloid sheet with a hole cut to the size and shape of the wound. This protects the intact skin from attack by the maggots' enzymes. Once in place, the maggots are introduced into the wound and covered with a piece of sterile nylon net that is supplied with each container of larvae. The net must be fixed to the hydrocolloid using water-

proof adhesive tape to form a 'cage' that retains the maggots in the wound. The pores in the net allow the maggots to breathe and facilitate drainage of liquefied necrotic tissue and serous exudate. The process is extremely simple, taking only a few moments to perform. A layer of moist gauze is placed over the net to prevent the maggots from drying out in the early stages of their development.

The dressing must be then covered with a simple absorbent pad, held in place with adhesive tape or a bandage. For areas that are more difficult to dress, such as the toes or feet, the nylon mesh is supplied heat-sealed into a bag or sleeve that is taped to strips of hydrocolloid dressing placed above and/or below the wound. For patients whose skin is too fragile to permit the use of adhesive dressings, or those who are allergic to hydrocolloid dressings, zinc oxide paste could be used to protect the skin and form a seal with the nylon net.

Raynor *et al*. (2004) in the UK investigated the effect of larval therapy and hydrogel on both the bacteriology and healing of leg ulcers. They compared the clinical and cost effectiveness of two types of larval therapy (loose and bagged) with a standard debridement intervention (hydrogel) in terms of effects on time to complete healing, time to debridement, wound microbiology, cost of treatment and health-related quality of life. They concluded design of the trial outlines the eligibility criteria for patients and discusses the nurses' role.

Gwynne and Newton (2006) in the UK reported that there were several methods of wound debridement and the appropriate one should be chosen for maximum effectiveness. They added that that practitioners and nurses must have a working knowledge of a wide variety of debridement methods and that they should recognize their own professional limitations and the need for referral for expert advice. They overviewed the indications, cautions and contraindications of the most commonly used methods of debridement at the disposal and to look briefly at some less often used alternatives

Chan and Zang (2007) stated that nurses have the responsibility to educate patients with correct and updated information on diabetes and maggot therapy; therefore, the knowledge should be provided and maintained to a certain standard. The lack of the knowledge among nursing staff has contributed to diabetes patients receiving inadequate health care instruction. As indicated by the results of this study, 'tailor-made' educational programmes should be designed to meet the learning needs of each subgroup. Expertise and nurse education should be recognized when such educational programmes were designed. Keast (2007) in Canada stated that the nursing staff must play a vital role in education about foot care to all people with diabetes and their families. Nurses' education should be tailored to meet each individual's needs and risk factors, using the principles of nurse's education. Education should be provided in several sessions over time, using a variety of teaching methods. It is essential to evaluate whether the nurse has understood the message, is motivated to act and has sufficient self-care skills.

In Egypt, Steyskal and El-Bialy (1967) listed the Egyptian Diptera, among which 184 were myiasis producing dipterous flies. They were in alphabetical orders; Calliphoridae (12 species), Gasterophilidae (5 species), Muscidae (63 species), Oestridae (5 species), Piophilidae (2 species) and Sarcophagidae (97 species) and gave key for families identifications. Shaumar *et al*. (1989) established a key of all known Egyptian species of Calliphoridae to genera and species accompanied by the synonyms in the light of modern taxonomic concepts. Eight genera are recorded including 14 species and added *Hemipyrellia pulchra* (Wied) as a record. The myiasis varies widely in the forms it takes and its effects on the victims. Such variations depend largely on the fly species and where the larvae are located.

Some flies lay eggs in open wounds, other larvae may invade unbroken skin or enter the body through the nose, ears, oral cavity and/or vagina. In Patton's categorization (1922), there are two main groups of myiasis-causing species: the specific parasites, which must develop on live hosts; and the semi-specific parasites, which usually develop on decaying organic matter, such as carrion, feces and rotting vegetation, but may also deposit their eggs or larvae on live hosts. Zumpt (1965) termed the specific parasites obligatory and the semi-specific parasites facultative. Diagnosis of myiasis depends on the demonstration of larvae on the host's tissues or organs. Correct identification of the larvae is important for the initiation of appropriate treatment and establishment of the preventive measures. The risk factors that potentially cause myiasis are the exposure of ulcers and hemorrhoids, bacterial infection of wounds or natural cavities, poor personal hygiene, alcohol-related behaviors such as lack of sensitivity and sleeping outdoors, lesions resulting from itching in patients with pediculosis, and extreme lack of personal hygiene (Morsy, 2012a, b).

However, only a small number of flies that cause human myiasis are used in medicine (Francesconi and Lupi, 2012). Chaiwong *et al*. (2014) in Northeast Thailand reported that *Chrysomya megacephala* (Fabricius) (Diptera: Calliphoridae) and *Musca domestica* L., (Diptera: Muscidae) are synanthropic flies which are adapted to live in close association with human habitations.From 994 individual flies collected by a sweep net (555 *C. megacephala* and 439 *M. domestica*), they isolated 15 bacterial genera from the external surfaces, comprising ten genera of gram-negative bacteria and five gram-positive bacteria. The commonest from both species were coagulase-negative *Staphylococci*, followed by *Streptococcus* group D non-enterococci. Human pathogenic enteric bacteria isolated were *Salmonella* sp., *Shigella* sp., *Escherichia coli* O157:H7, *Salmonella typhi, Bacillus* sp., and *Enterococcus* sp., of which *S. typhi* is the first report of isolation from these fly species. Other human pathogens included *Staphylococcus aureus* and *Pseudomonas aeruginosa*. Not only were the number of *C. megacephala* positive for bacteria significantly higher than for *M. domestica*, but they were also carrying ~11-12 times greater bacterial load than *M. domestica*. They suggested that both fly species should be considered potential mechanical vectors of bacterial pathogens associated with human habitations year-round. Gilead et al. (2012) summarized experience of the medicinal maggots use for the debridement of necrotic chronic wounds and to try and identify prognostic factors for debridement success and associated pain. They found that number of treatments was 1–48 (mean=2.98; median=2) and the treatment duration varied between one and 81 days (mean=4.65; median=3). In 357 patients (82.1%) complete debridement of the wound was achieved, while in 73 patients (16.8%) the debridement was partial and in five (1.1%) it was ineffective. The increased pain or discomfort during MDT was in 38% of the patients. They concluded that MDT proved to be a very safe, simple and effective treatment modality for chronic wounds in ambulatory and hospitalized patients Ma *et al*. (2012) in USA identified the putative interkingdom signals for the bacterium and flies, reasoned by swarming was used by this bacterium to cover food resource and required bacterial signaling, the same bacterial signals used for swarming to communicate with blow flies. Using transposon mutagenesis, they identified six novel genes for swarming (ureR, fis, hybG, zapB, fadE and PROSTU _03490), and hypnotized that fly attractants, lactic acid, phenol, NaOH, KOH and ammonia, restore swarming for cells with the swarming mutations. Hence, compounds produced by the bacterium that attract flies also are utilized for swarming. In addition, bacteria with the swarming mutation rfaL attracted fewer blow flies and reduced the number of eggs laid by the flies. They identified several

interkingdom signals between *P. mirabilis* and blow flies. Bunchu *et al.* (2014) in in Northeast Thailand isolated *Toxocara* eggs from *C. megacephala* collected from the fresh-food markets, garbage piles, school cafeterias, and paddy fields but not from restaurants, and concluded *C. megacephala* was a potential carrier of *Toxocara* eggs than *M. domestica*.

The maggots have four principal actions: 1- Debridement (Chan, *et al*, 2007), 2- Disinfection of the wound, 3- Stimulation of healing (Sherman, 2014), and 4- Biofilm inhibition and eradication (Sherman, 2009). Sherman (2014) in USA reported that medicinal maggots were believed to have three major mechanisms of action on wounds, brought about chemically and through physical contact: debridement (cleaning of debris), disinfection, and hastened wound healing. Je added that until recently, most evidence for these claims was anecdotal; but the past 25 years have seen an increase in the use and study of maggot therapy. Controlled clinical studies are now available, along with laboratory investigations that examine the interaction of maggot and host on a cellular and molecular level. He examined the salient data, make sense, where possible, of seemingly conflicting evidence, and reexamined the paradigm for maggot-induced wound healing. He concluded that the clinical and laboratory data strongly support claims of effective and efficient debridement, and that the clinical evidence for hastened wound healing was meager, but laboratory studies and some small, replicated clinical studies strongly suggested that maggots do promote tissue growth and wound healing, though it is likely only during and shortly after the period when they are present on the wound. The best way to evaluate-and indeed realize-maggot-induced wound healing may be to use medicinal maggots as a "maintenance debridement" modality, applying them beyond the point of gross debridement.

Singh *et al*. (2015) in USA characterized the bacteria associated with different life stages of *L. sericata* (Meigen) and *L. cuprina* (Wiedemann) and in the salivary gland of *L. sericata* by using 16S rDNA 454 pyrosequencing. Bacteria associated with the salivary gland of *L. sericata* were characterized using light and transmission electron microscopy (TEM). The results showed that the majority of bacteria associated with these flies belong to phyla Proteobacteria, Firmicutes, and Bacteroidetes, and most bacteria are maintained intragenerationally, with a considerable degree of turnover from generation to generation. In both species, second-generation eggs exhibited the highest bacterial phylum diversity (20 % genetic distance) than other life stages. *Lucilia* sister species shared the majority of their classified genera. Of the shared bacterial genera, Providencia, Ignatzschineria, Lactobacillus, Lactococcus, Vagococcus, Morganella, and Myroides were present at relatively high abundances. Lacto-bacillus, Proteus, Diaphorobacter, and Morganella were the dominant bacterial genera associated with a survey of the salivary gland of *L. sericata*. TEM analysis showed a sparse distribution of both Gram-positive and Gram-negative bacteria in the salivary gland of *L. sericata*. There was more evidence for horizontal transmission of bacteria than there was for trans-generational inheritance. Several pathogenic genera were either amplified or reduced by the larval feeding on decomposing liver as a resource. They concluded that the information on bacterial communities associated with different life stages of *Lucilia* and their horizontal and trans-generational transmission might help in the development of better vector-borne disease management and MDT methods.

Consequently, for effective usage Brundage *et al*. (2016) in USA reported that effective MDT required aseptic technique to prevent the unintentional introduction of pathogenic bacteria into a wound to be debrided; yet the external surface of Calliphoridae eggs is often heavily contaminated with bac-

teria. They evaluated the efficacy of ten disinfection techniques involving immersion, rinse, or a combination of both in formalin, Lysol, formaldehyde, bleach, ethanol, Sporgon, or benzalkonium chloride. All techniques resulted in significant decreases in culturable, aerobic bacterial load on *Lucilia cuprina* eggs a 10 minute 3% Lysol immersion was the most efficacious, disinfecting 96.67% of egg samples, while resulting in 31.84% egg mortality. The 5% formalin immersion was least efficacious, disinfecting only 3.33% of *L. cuprina* egg samples, while resulting in 33.51% egg mortality. A formaldehyde immersion, one of the most commonly used disinfection techniques, was moderately effective, disinfecting 66.7% of egg samples, while resulting in 40.16% egg mortality. For the *Chrysomya rufifacies* and *Cochliomyia macellaria* egg samples, the 10 minute 3% Lysol immersion disinfected 100% of the samples, and for *Lucilia sericata*, 80% of egg samples, while resulting in 33.97%, 7.34%, and 36.96% egg mortality, respectively. H2 CO disinfected 16.67% of *Ch. rufifacies*, 26.67% of *C. macellaria*, and 56.67% of *L. sericata* egg samples, while resulting in 21.98%, 10.18%, and 32.19% egg mortality, respectively. Due to its high disinfection the efficacy and relatively low egg mortality, a ten minutes 3% Lysol immersion is recommended for sterilizing Calliphoridae eggs prior to rearing of larvae for use in the MDT.

Conclusion

The impaired wound healing is a common and costly problem for those with diabetes worldwide. The current enthusiasm for the maggot debridement has been fueled more by anecdotal reports and personal experience than by scientific studies.

The present analysis demonstrated that the maggot therapy is more effective and efficient in debriding non-healing foot and leg ulcers in diabetic male veterans than the typical conventional treatment currently prescribed. Maggot therapy was also associated with a more rapid decrease in wound size and an increase in granulation tissue, making the wounds ready for surgical closure. The higher number of patients actually achieving complete wound closure within the 8-week study period (14% with maggot therapy vs. 0% with conventional therapy) did not reach statistical significance. These findings support the benefits of maggot therapy claimed by earlier and ongoing researches.

The present review showed that the maggot debridement therapy benefits reported for the pressure and venous stasis ulcers could also be realized by the diabetic patients with chronic ischemic and neuropathic wounds. Thus one should not consider maggot therapy only as a last resort (an alternative to amputation); rather than using MDT earlier during the course of therapy, as a second- or third-line option.

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