REVIEW ARTICLE

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Clinical Applications for Maggots in Wound Care

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Abstract

Maggot debridement therapy (MDT) was first introduced in the US in 1931 and was routinely used there until mid-1940s in over 300 hospitals. With the advent of antibacterials, maggot therapy became rare until the early 1990s, when it was re-introduced first in the US, and later in Israel, the UK, Germany, Sweden, Switzerland, Ukraine and Thailand.

Sterile maggots of the green bottle fly, *Lucilia* (*Phaenicia*) *sericata*, are used for MDT. Up to 1000 maggots are introduced in the wound and left for 1 to 3 days. MDT could be used for any kind of purulent, sloughy wound on the skin, independent of the underlying diseases or the location on the body for ambulatory as well as for hospitalized patients. One of the major advantages of MDT is that the maggots separate the necrotic tissue from the living tissue, making a surgical debridement easier. In 80 to 95% of the cases, a complete or significant debridement of the wound is achieved. As therapy progresses, new layers of healthy tissue are formed over the wounds. The offensive odor emanating from the necrotic tissue and the intense pain accompanying the wound decrease significantly. In a significant number of patients, an immediate amputation can be prevented as a result of MDT. In other cases, a more proximal amputation could be avoided. It is also possible that in patients with deep wounds, where septicemia is a serious threat, this can be prevented as a result of MDT.

The majority of patients do not complain of any major discomfort during the treatment. Psychological and esthetic considerations are obvious. Maggots can occasionally cause a tickling or itching sensation. Approximately 20 to 25% of the patients with superficial, painful wounds, complain of increased pain during treatment with maggots, and are treated with analgesics.

MDT has been proven to be an effective method for cleaning chronic wounds and initiating granulation. It is a simple, efficient, well tolerated and cost-effective tool for the treatment of wounds and ulcers, which do not respond to conventional treatment and surgical intervention.

'My flesh is clothed with maggots and clods of dust
My skin rotted and fouled afresh'

(Job VII, 5)

The beneficial effect of fly larvae for wounds was first observed by Ambroise Pare in the 16th Century. Baron Larrey, physician-in-chief to Napoleon's armies and Dr Joseph Jones, a medical officer during the American Civil war, while working with soldiers who remained wounded for several days in the battle field, observed that maggots destroyed only dead tissue, and not viable tissue.[1]

Maggot debridement therapy (MDT), also called larva therapy, the intentional treatment of suppurative skin infections with the larvae of calliphorid flies, was first introduced by Baer in 1931.[2] This method was used extensively in the 1930s and early 1940s in over 300 hospitals in the US alone,[3-5] but was abandoned with the introduction of antibacterials and the use of aggressive surgical debridement. Between 1950 and 1980 MDT was used only occasionally as salvage therapy for skin and soft tissue wounds, which did not respond to surgery and antibacterials.[6-10] Since 1989 in the US,[11-13] since the mid 1990s in Israel[14-16] and the UK[17,18] and more recently in Sweden,[19] Germany,[20] Switzerland,[21] Austria, Ukraine, Thailand and Canada,[22] MDT was re-introduced for the treatment of intractable wounds. In the last 5 years, more than 15 000 maggot treatments have been dispatched to over 650 centers in the UK.[23] In Germany within one year 215 patients received approximately 1000 maggot treatments.[20] During the last 10 years nearly 10 000 patients have been treated worldwide by this method.[22]

This method is used when antibacterial treatment, surgical debridement, hydrocolloid dressings, drainage and other conventional methods do not halt the progressive tissue destruction. The poor blood supply to the deep wound and the consequent inability of immunologic mediators and systemic antibacterials to reach the infected area prevent healing. For earlier reviews on this topic the reader is referred to Pechter and Sherman,[8] Chernin,[1] and Thomas et al.[17]

An International Biotherapy Society for the promotion of MDT was created in 1996 and since then 5 international conferences on biotherapy have been held. Details about the organization, the conferences and links to different biotherapy institutions can be found on the Internet at: http://www.homestead.com/biotherapy.

1. Production of Maggots

The larvae of the green bottle fly, *Lucilia* (*Phaenicia*) *sericata* are used for MDT (fig. 1). Various techniques are used for the production of sterile maggots. In our laboratory flies are fed with a 20% sugar solution and pieces of liver or meat are used to induce oviposition.[24-26] Eggs are removed from the liver, separated, surface sterilized and transferred to a sterile medium. Two to 36 hours after hatching the larvae are separated from the medium, transferred to a sterile container and used for therapy. When necessary, sterile maggots are kept at 5 to 8°C for up to 5 days without losing their viability.[16]

Sterile maggots are being produced and marketed by 1 company in the UK and 2 companies in Germany as well as by a number of laboratories in the US, Israel, Sweden, Switzerland, Austria and Ukraine.

2. Suitable Dressings

Most practitioners use a cage-like dressing. For this purpose an adhesive dressing is applied on the periphery of the wound. A hydrocolloid dressing can be cut and applied such that it covers only the skin peripheral to the wound. A sterile piece of fine nylon or dacron netting, slightly larger than the wound but smaller than the first layer of tape or hydrocolloid is attached with adhesive tape on the top of the first layer, leaving an opening through which the maggots are introduced. The netting allows air to reach the maggots and facilitates the drainage of liquefied necrotic tissue through the top of the dressing with the help of absorbing gauze and pads.[27]

Recently, the 'Biobag' method was introduced for MDT. Maggots are enclosed between two 0.5mm thin layers of polyvinylalcohol-hydro-sponge netting, which are glued together over a small cube of a spacer material. The maggots are thus able

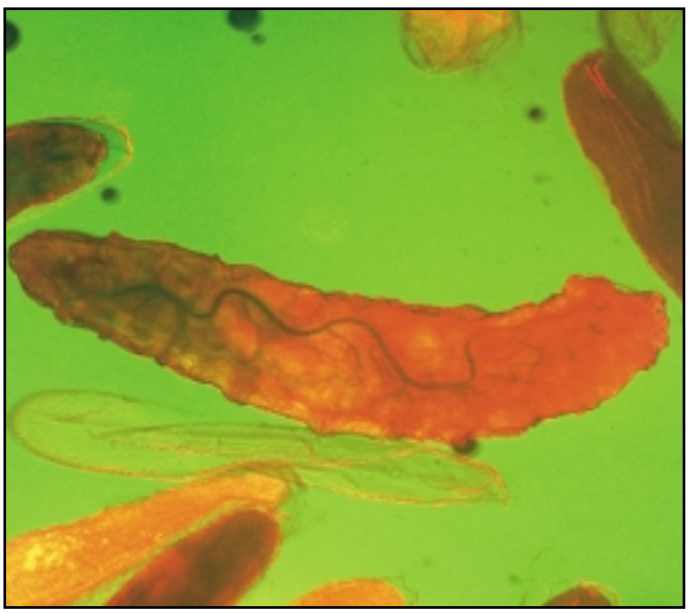

Fig. 1. First instar of the green bottle fly maggot, *Lucilia* (*Phaenicia*) *sericata.*

to feed through the dressing and their secretions reach the wound in order to control infection and stimulate healing. The suggested advantages of this method are: (i) reduced pain as there is no mechanical irritation of the wound edges by growing maggots; and (ii) the maggots cannot escape from the 'Biobag', which is essential for hospital hygiene and patients acceptance of MDT.[28] However, preliminary studies in our laboratory showed that the debridement is less effective because the 'Biobag' restricts movement of maggots on the wound.

3. Wound Types

MDT could be used for any kind of purulent, sloughy wound on the skin, independent of the underlying diseases or the location on the body. MDT can be used for ambulatory as well as for hospitalized patients.[29] The average age of the patients treated using this method has ranged from 65 to 75 years.[16,29,30] MDT has been used successfully for abscesses, burns, cellulitis, gangrene, and ulcers due to arterial disease, venous stasis, lymphostasis, Burger's disease, neuropathies, paraplegia, hemiplegia, osteomyelitis mastoiditis, thalassemia, polycythemia, dementia and basal cell carcinoma.[2,5,6,14] This method has been recommended especially for patients with diabetic foot ulcers and pressure ulcers.[12,13,16]

Most of the wounds treated by MDT are chronic wounds. In the 120 patients who have been treated by our team, the wounds had been present for 1 to 240 months (median 5 months, average 14). Before MDT, patients were treated with 3 or more conventional methods. In 87.3% of the patients wounds were located on the leg or foot, while in 22.7% of the patients, mainly pressure sores, the wounds were located in the sacral area. Approximately one-third of the patients with leg ulceration were potential candidates for amputation or major surgical interventions. In all cases where MDT is to be applied, informed consent must be obtained from the patient or from the legal guardian.[15,16]

4. Illustrative Case Reports

A 57-year-old man had had a diabetic foot ulcer for about 3.5 months (fig. 2a). Previously, he had been treated with conventional wound treatment methods but the wound did not heal and caused a lot of pain. The patient was treated in the Department of Dermatology of the Hadassah Hospital in Jerusalem. A single treatment with approximately 100 maggots cleaned the wound within 19 hours (fig. 2b). During this time the patient experienced an increase in pain and was treated with analgesics. After MDT the patient was transferred to the plastic surgery department of the same hospital for skin grafting.

Fig. 2. (**a**) Foot ulcer of a 57-year-old patient with diabetes mellitus. The wound was previously treated with conventional methods for 3.5 months. Before maggot therapy the wound was covered with purulent material. (**b**) The same wound after a single treatment with approximately 100 maggots, which completely debrided the wound within 19 hours.

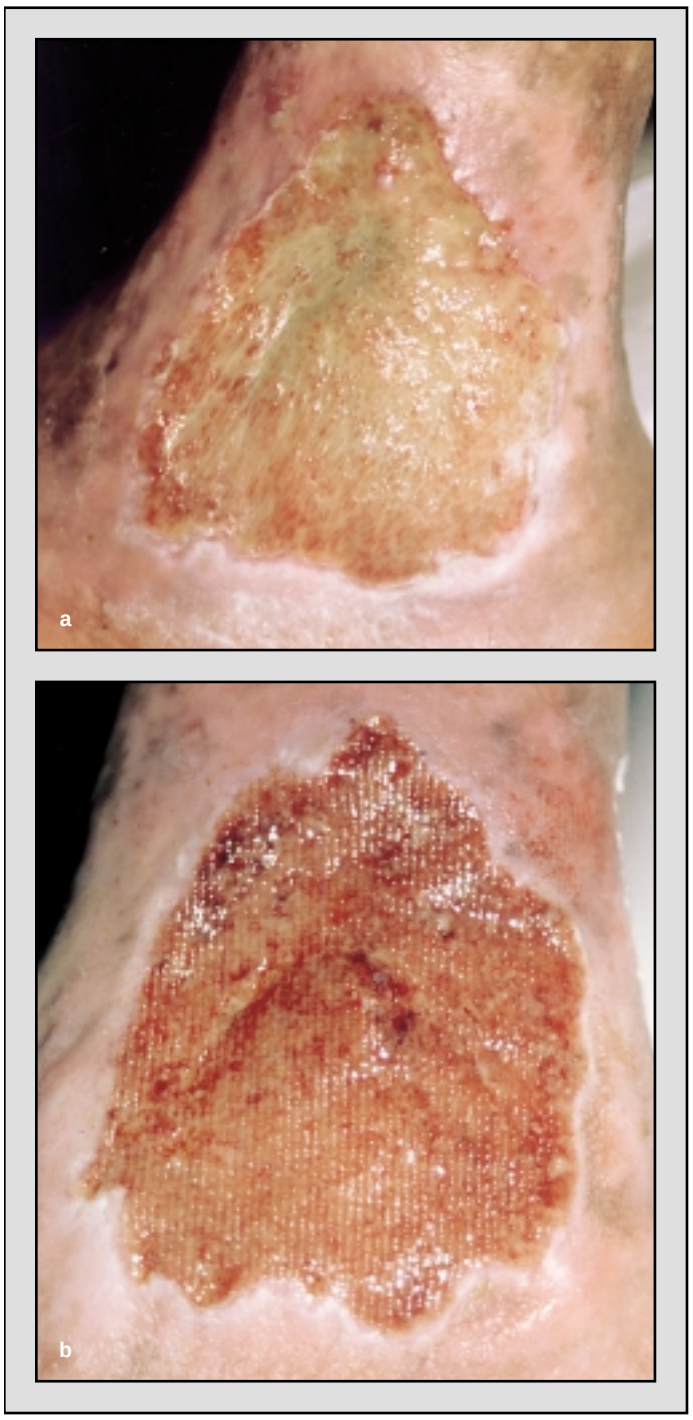

Fig. 3. (**a**) Left ankle of a 66-year-old man with venous stasis who presented with a painful ulceration, which had been present for over 12 months. (**b**) The same wound after treatment with 200 maggots, which succeeded in debriding the wound completely within 18 hours.

A 66-year-old man with venous stasis presented with a painful ulceration on the left ankle, which had been present for over 12 months (fig. 3a). The wound was treated with 200 maggots, which succeeded in debriding the wound completely within 18 hours (fig. 3b).

5. Treatment Methods

Physicians, nurses, nursing assistants, physical therapists and entomologists, are able to administer MDT. The treatment should be performed under the supervision of a physician who is responsible for the treatment even if he or she is not the person applying the therapy. Although MDT could be applied in any department of the hospital, most patients are treated in the geriatric, orthopedic and dermatology departments.[12,13,16,30]

One of the most problematic aspects of MDT is the size and number of maggots applied to the wound. Companies normally sell tubes containing approximately 200 maggots. For smaller wounds less than 200 maggots should be used, while for larger wounds up to 1000 maggots could be applied.[16,30] Although 10 maggots/cm^2 necrotic area has been suggested,[17] it is difficult to measure the exact surface of the necrotic tissue and even more so its depth.

Companies supply newly hatched maggots, which are applied to the wound and left for 48 to 72 hours. In our laboratory, we leave the maggots to develop on their substrate until they are 14 to 16 hours old and then apply then to the wound. A maggot develops very rapidly between 16 and 40 hours after hatching from egg and consumes approximately 20 to 25mg of food during this period (fig. 4). Accordingly, 400 to 600 maggots (16 hours old) could consume 10 to 15g of necrotic tissue within 24 hours. Although it is more convenient to leave small maggots on the wound for 2 to 3 days, larger maggots replaced every 24 hours debride the wound faster and more effectively.

The size of the wound usually determines the number of treatments; this can vary between 1 and 48 (median 4).[16] The treatment can last for a period of 1 to 210 days (median 6).

When maggots are left more than 24 hours on the wound, the outer absorbent dressing should be changed as often as required. After each treatment cycle, maggots are washed out of the wound with a jet of sterile physiological saline, and if necessary, removed with forceps. Any remaining maggots can be easily removed the next day when they are ready to leave the wound and pupate in a dry environment.

One of the major advantages of MDT is that the maggots separate the necrotic tissue from the living tissue, making a surgical debridement easier. The latter should be used as often as possible during MDT to remove larger pieces of necrotic tissue

so that the debridement of thin layers of purulent material over the living tissue is left to the maggots.

We recommend photographing the wound after each treatment or once a week. Description of the wound, that is, necrosis, drainage and purulence is recorded during each visit and the odor of the wound and any pain experienced by the patient should also be noted.

6. Results of Treatment

In 80 to 95% of the cases a complete or significant debridement of the wound is achieved.[2,16,30] As therapy progresses, new layers of healthy tissue are formed over the wounds. The offensive odor emanating from the necrotic tissue and the intense pain accompanying the wound decrease significantly.

In a prospective controlled study to evaluate the utility of MDT for treating pressure ulcers in spinal injury patients it was found that wound healing was more rapid during MDT than during antecedent conventional therapy.[12] No complications related to MDT were observed.

In a significant number of patients, an immediate amputation can be prevented as a result of MDT.[14-16,29,30] In other cases a more proximal amputation could be avoided.[31] It is also possible that in patients with deep wounds, septicemia is a serious threat, this too, can be prevented as a result of maggot therapy. After MDT, the wound can be treated until it is healed with conventional methods such as skin grafting, hydrocolloid dressings or disinfectants.

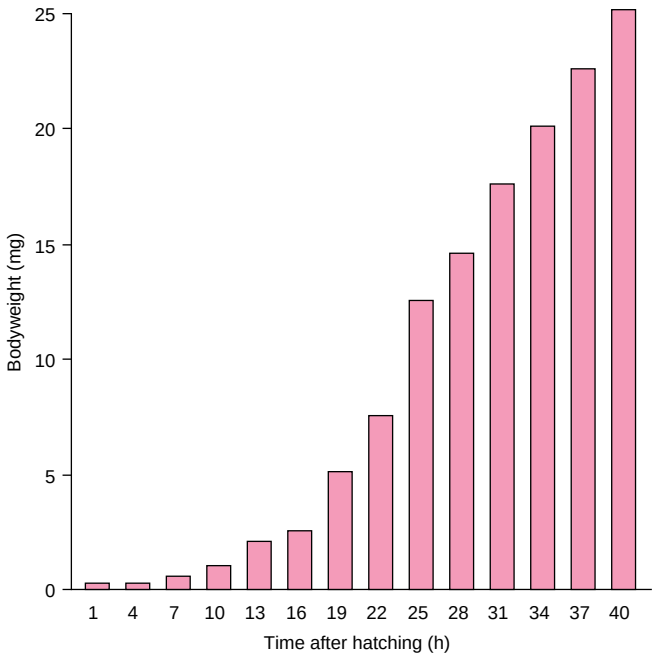

Fig. 4. Average bodyweight of maggots during 40 hours after hatching from the eggs.

In a survey conducted in 1935, Robinson[32] found that 91.2% of the more than 600 responding surgeons commented favorably about their experiences with MDT. A study examining the current status of MDT in the UK, showed that all 23 hospital nurses interviewed were in favor of this treatment method. MDT was considered a last resort, when other forms of wound treatment had proven unsuccessful and was particularly effective in wounds contaminated by methicillin-resistant *Staphylococcus aureus* (MRSA). The prevention of surgery, the reduction in hospital admissions and use of antibacterials, and the shortening of hospital stays, were all clinical outcomes identified by interviewees.[33] In the US and Israel over 95% of the therapists and 90% of the patients were satisfied with MDT.[29]

7. Adverse Effects

The majority of patients do not complain of any major discomfort during the treatment. Physicians, nurses and patients are at first disturbed by the idea of treating or being treated with maggots. Psychological and esthetic considerations are obvious. Most of patients can easily be convinced to undergo such a treatment by showing them photographs of previous treatments or giving them a thorough explanation and appropriate literature about the advantages and disadvantages of this method. Therapists may reduce the anxiety of ambulatory patients by providing 24 hour/day telephone access to medical assistance.[29]

Escaping maggots could be unpleasant for patients, their relatives and medical staff. Care should be taken to restrict the maggots to the area of the wound, using appropriate dressings. In some cases of pressure sores, which are located close to the anus, maggots can escape from the dressing, when the tapes do not adhere properly to the skin due to moisture from urine, or feces in this area. In these cases the 'Biobag' could be helpful.

The digestive enzymes of the maggots can cause erythema or cellulitis. Therefore, the periphery of the wound should be protected by the plaster or hydrocolloid dressing, keeping the maggots only within the wound.

Although maggots will always look for necrotic tissue and slough as a food source, they should not be left on a completely debrided tissue, as they could cause some damage to living tissue if they have no other choice.

A special device should be built for ambulatory patients with plantar wound ulcers in order to prevent them from squashing the maggots.

Crawling maggots can occasionally cause a tickling or itching sensation. Approximately 20 to 25% of the patients with su-

perficial, painful wounds, complain of increased pain during treatment with maggots, and should be treated with analgesics. Pain has rarely prompted discontinuation of therapy.[16]

No allergic reactions related to maggots have been described. It is possible that ammonium salts produced by maggots,[34] if not absorbed properly by gauze, could increase the body temperature of the patient. In rare cases, a bleeding of the wound has been observed. If non-sterile maggots are used there is a danger of septicemia.[2,21] Special attention should be given to patients allergic to the maggot dressings.

Fetor was noted by few patients and therapists, and probably resulted from the liquefaction of necrotic tissue, followed by the vaporization of volatile products of putrefaction.[29] Ammonium salts excreted by maggots and the odor of bacteria such as *Pseudomonas* might contribute to fetor, which could be prevented by frequent changes of the gauze and pads covering the box-dressing.

8. Mechanisms of Wound Healing

Different mechanisms of wound healing by maggots have been suggested.

8.1 Debridement

Medicinal maggots feed primarily on necrotic or partially decomposed material within the ulcer. They reach necrotic tissue and slough even in the smallest crevices, and debride the wound without harming healthy tissue in a manner resembling microsurgery. The maggots anchor themselves with their mouth hooks on the substrate and scavenge small particles. Salivary enzymes, which dissolve the necrotic material, are excreted into the wound. The pre-digested material including bacteria is then ingested by the maggot. Proteolytic enzymes of the gut are excreted[35,36] and are probably responsible for partial digestion of the necrotic tissue.

Maggots excrete collagenases, which digest the fine strands of connective tissue that support muscle fibres. Optimum pH for the collagenases is about 8 to 9, which is most probably attained in the wound by the maggot's excretion of ammonia and salts by the maggots.[37]

8.2 Disinfection

The serous exudate caused by the irritating effect of maggots crawling in the wound as well as excretory products of the maggots lead to mechanical washing of the wound. This is especially effective when there is continuous drainage of the wound through a rich layer of gauze and pads.

Bacteriological examination of infected wounds before initiation of maggot therapy, followed by subsequent cultures at each dressing, have shown that there is a marked decrease in infection as the treatment progressed.[38] Simmons[39] sprayed the maggots periodically with water, and found that the antibacterial substance is also excreted. This substance was tested on 7 species of bacteria, which are of etiological importance in pyogenic infections, and showed that 5 to 10 minute exposures were usually sufficient to kill all the microorganisms.[40] Lappin-Scott[41] found that maggots reduced the number of bacteria in a culture of resistant *Staphylococcus aureus* over a period of 5 days. A marked antimicrobial activity was detected in the maggot secretion when used against Streptococcus A and B and *S. aureus*.[42]

In order to investigate the relative abundance and viability of the bacteria in the successive regions of the alimentary tract of the maggot, Robinson and Norwood[43] placed sterile maggots on infected wounds and removed them after 24 to 48 hours. The maggots were dissected and the crop and a 2cm long piece of the midgut and hindgut were removed and smeared on a blood agar plate or macerated in nutrient broth. All the crops were infested heavily with bacteria, whereas 60.7% of the midguts, and only 7.1% of the hindguts were infested slightly with bacteria. The bacteria were later identified as *S. aureus* and *Streptococcus* spp. They concluded that a large number of bacteria were destroyed as they passed through the tubular midgut of the maggot, and almost complete destruction of any remaining organisms occurred in the hindgut.

Green fluorescent protein-producing *Escherichia coli* were used to investigate the fate of bacteria in the alimentary tract of sterilely grown maggots using a laser scanning confocal microscope.[44] A computer program was applied to analyze the intensity of the fluorescence and to quantify the number of bacteria. The crop and the anterior midgut were the most heavily infected areas of the intestine. A significant decrease in the amount of bacteria was observed in the posterior midgut. The number of bacteria decreased even more significantly in the anterior hindgut and practically no bacteria were seen in the posterior end, near the anus. The viability of bacteria in the different gut sections was examined. It was shown that 66.7% of the crops, 52.8% of the midguts, 55.6% of the anterior hindguts and 17.8% of posterior hindguts harbored living bacteria. In conclusion, during their passage through the digestive tract the majority of *E. coli* was destroyed in the midgut. Most of the remaining bacteria were killed in the hindgut, indicating that the feces were either sterile or contained only small numbers of bacteria.

An antibacterial agent from homogenized maggots was partially purified using a high-performance liquid chromatography column. The fractions harboring the antibacterial agent were iden-

tified by a zone inhibition assay with *Micrococcus luteus* as the indicator bacteria.[45] Proteases abolished all antibacterial activity indicating that the active agent is a protein or a peptide. The apparent molecular weight of the agent is 6000, determined by the activity on a sodium dodecyl sulfate-polyacrylamide gel electrophoresis (SDS-PAGE) gel. The purified antibacterial agent from maggots caused efflux of potassium ions from the bacterial cells, indicating that the mode of action of this peptide is similar to many other natural antibacterial peptides. The antibacterial agent had a wide spectrum of activity against many resistant pathogen strains including Gram-negative bacteria such as *E. coli, Salmonella* and *Pseudomonas aeruginosa* and Gram-positive bacteria such as *S. aureus, Staphylococcus epidermidis, Listeria* and clinical isolates of MRSA. The maggot secretions were purified as above and some fractions have been shown to possess an antibacterial activity against *M. luteus.*

In addition to the antibacterial substances, maggots also possess diverse proteolytic enzymes, which are capable of digesting bacteria.[35,37,46] It is possible that bacteria are lysed by the varying pH- values in the alimentary tract.[47,48] As these antibacterial substances and the proteolytic enzymes of the gut are excreted to the environment, bacteria are also destroyed on the wound.

8.3 Initiation of Granulation

The excretion products of the maggots contain ammonia, urea and allantoin, which are known to stimulate granulation.[39,49-52] In addition maggot excretions contain calcium carbonate, which changes the wound pH from acid to neutral or slightly alkaline (pH 7 to 8), and which also has a stimulatory effect on granulation.[40] Furthermore the continuous crawling of the maggots might aid in the formation of granulation tissue by mechanical stimulation of viable tissue.

In order to study the mechanisms by which the excreta of maggots of *L. sericata* stimulate granulation of the debrided wound and the immune system of the patient, their potential to excrete cytokines in vitro has been evaluated.[53] High levels of interferon-γ (20 to 35 pg/ml) and interleukin (IL)-10 (7 to 27 pg/ml) were found in 5 and 8, samples, respectively, as compared to the negative controls (<3.4 and <6.8 pg/ml, respectively). However, soluble IL-2 receptor activity was not detected in any of the extracts. Although no clear trend towards T helper (TH) 1 or TH2 cytokines was observed, it was concluded that maggot excretions contain specific cytokines, which could contribute to the quick granulation in debrided tissue seen during maggot therapy.

8.4 Improvement of Blood Circulation

It was shown that after MDT there is a significant improvement of tissue oxygenation, as well as a decrease in wound edema.[54]

9. The Future for Maggot Debridement Therapy

The ever-growing number of patients treated by MDT in different countries in the last 10 years, indicate that this method will become one of the alternative methods for the treatment of chronic wounds in modern medicine.

Prospective studies using ambulatory and hospitalized patients and comparison of MDT with conventional wound healing techniques are warranted. The time is now opportune for multicenter clinical trials, which should also prove the cost-effectiveness of the method. Further studies related to patients' perspectives and concerns could improve the acceptability of MDT.

Once the safety and efficacy of MDT and its cost effectiveness are demonstrated in randomized clinical trials, an increased support for this method by the public, hospitals and health insurance companies can be expected. As the use of maggot therapy increases, this modality will become an accepted part of outpatient medical practice. The spread of maggot therapy throughout the world will increase.

Characterization of the antibacterial substance(s) in the body and excretions of the maggots would help demonstrate their efficacy in destroying bacteria inside the body of the maggot and in their environment (in this case the wound). Studies of the proteolytic enzymes will indicate how the wound is debrided and study of the cytokines and salts excreted by maggots will explain how the maggots initiate granulation of tissue within the debrided wound. Comparative studies will also show us how maggots could be used more effectively (number, size, period of treatment).

The use of maggots other than *L. sericata,* such as *Phormia regina*[6,55] *P. terranenovae*[21,40] and *Calliphora vicina*[56] should be encouraged. New dressings should be developed to minimize the possibility of maggots escaping and to reduce pain.

The potential benefits of MDT in developing countries is obvious, although largely unrealized. A simple, inexpensive and effective wound treatment method can help a large number of people with chronic wounds, for example, for those walking barefoot, who are bitten or stung by animals, walk on mines and live in poor hygienic conditions.

10. Conclusions

Maggot therapy has long been recognized as a successful method for cleaning soft tissue infections. The emergence of an-

tibacterial-resistant bacteria, and the recognition that currently available surgical and pharmaceutical tools cannot heal all chronic wounds, has led hospitals to open their doors to maggot therapy once again.

MDT has been shown to be an effective method of cleaning chronic wounds and initiating granulation. It is a simple, efficient, well tolerated and cost-effective tool for the treatment of wounds and ulcers, which do not respond to conventional treatment and surgical intervention.

Although MDT hastens wound-healing, the primary task of this method is to completely debride the wound from slough and necrotic tissue and transform the chronic wound to an acute one, which can then be treated with any suitable conventional method.

As with any conventional wound treatment method, MDT is optimized by collaboration between biotherapists, plastic, vascular and orthopedic surgeons, podiatrists, and dermatologists and internists.

There is no doubt that MDT has now re-established itself as a valid option in current orthopedic, dermatologic and geriatric infection management, which merits wider acceptance, especially as those patients most likely to benefit are almost by definition disadvantaged. They include the elderly, people with severe diabetes mellitus, people who have had limbs amputated and those with chronic sepsis. MDT will belong to the standard armamentarium against infections of the skin in modern wound care.

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