Maggot debridement therapy in surgery

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Chapter

1

Introduction

A long history of maggot therapy

Maggot-therapy is a medical curiosity that has had little influence on the course of modern medicine.[2] This statement might have been true as late as 1988,[3] but now with more than 100 papers published on the subject in the past decade alone, it's no longer true. Maggot debridement Therapy (MDT) has been used in many cultures and has been used in wound healing for centuries.[4,5] There are reports of the successful intentional use of maggots by Ngemba-tribes in Australia[6], in the province of Yunan in China[7] and the Mayan Indians.[8] The oldest known written record in which myasis (human infested with maggots) is described, is the Old Testament. The first European medical reference to maggots appeared in the Hortus Sanitatus in 1491.[5] This book was probably written by its printer, Jacob Meydenbach. It is a collection of herbal knowledge drawn from medieval and classical authors, such as Galen, Albertus Magnus and Dioscorides.

Ambroise Paré (1509-1590) is credited as the father of modern MDT.[9] He was the first to observe the beneficial effects of fly larvae on wounds. He described a patient who, against all odds, recovered. He believed however, that the observed 'wurms' were the result of 'Generatio Spontane' (this theory introduced by Aristotle, states that from an individual of one species a total different species could develop). In literature, there is no evidence that Paré intentionally used maggots as a method to clean or heal wounds. The only reference is the often-cited case that occurred in 1557 at the battle of St. Quentin, when Paré observed soldiers whose wounds were covered in maggots. He mainly described the negative effects of the maggots and above all did not know the relationship between flies, eggs and maggots.[10-11]

Baron Larey (1766-1842), a famous surgeon in the army of Napoleon Bonaparte, wrote about soldiers who had maggot infested wounds, but was frustrated that it was difficult to persuade his patients to leave the maggots in place. He believed that "maggots promoted healing without leaving any damage".[9]

During the American Civil War a group of imprisoned Confederate medical officers were forced to leave the wounds of their patients undressed, as they were denied bandages. They found that many of the larva-infested wounds cleared up quickly, while many of the Union wounded died.[12] Zacharias, a Confederate surgeon was the first to intentionally apply maggots to the wounds of soldiers, in order to clean and debride them.[13]

A famous quote of Zacharias: *'During my service in the hospital in Danville, Virginia, I first used maggots to remove the decayed tissue in hospital gangrene and with eminent satisfaction. In a single day they would clean a wound much better than any agents we had at our command….. I am sure I saved many lives by their use, escaped septicaemia, and had rapid recoveries.'*

The first surgeon to use MDT on patients in hospital was the orthopedic surgeon William Baer. In the 1920s he was faced with a group of untreatable patients with severe osteomyelitis (antibiotics had not yet been discovered). He successfully treated many patients by means of maggots, and because of his success the therapy became regularly used in the United States.[13] Dr Baer however, experienced problems with sterility, with subsequent tetanus developing in some of his patients. By 1934 more than 1,000 surgeons were using maggot therapy. Surgical maggots were commercially available from Lederle Corporation.[14] With the introduction of antibiotics in the 1940s, the use of maggots declined. MDT fell into oblivion due to the fact that antibiotics such as

sulphonamides and penicillin were industrially fabricated. In the years to come, MDT was (Chapter 14) largely abandoned, with some case reports being published in the mean time. In 1989 Dr. Ronald Sherman rediscovered MDT. He acknowledged that despite modern wound treatment, not all wounds healed. He started rearing larvae and used them successfully in a controlled trial on decubital ulces.[15] Another factor might have been the appearance of antibiotic-resistant bacteria (eg, methicillinresistant Staphyloccocus Aureus), in which case MDT seemed to work very efficiently.[16]

At the same time in England Dr. John Church[17;18] and Steven Thomas[19;20] were involved in MDT. The Biosurgical Research Unit at SMTL commercially rears maggots; Biomonde does so in Germany.

MDT in the Netherlands

Dr. Gerrolt Jukema was the surgeon who introduced maggot therapy in the Leiden University Medical Center in 1999.[21] A patient with a severe crush injury of both feet was treated with maggots in order to salvage at least one of his limbs. Against all odds, both wounds healed with good functional and cosmetic result.[22] Maggot therapy has been known in the Netherlands for a longer period, as can been seen, for instance, in the fact that Military Services in the Netherlands equipped its soldiers who were going to Korea (in the 1950's) with the basic knowledge regarding maggot therapy, how to apply it in order to treat wounded soldiers awaiting pick-up by the helicopters (which at that time could sometimes be a couple of days).[23] Unfortunately, the Dutch Institute for Military History could not find any records on this.[24]

MDT was introduced at the Rijnland Wound Center in 2002. The first few patients were treated with maggots derived from Leiden University Medical Center. The first patient treated was a patient who suffered from a severely infected below-knee amputation, which in the surgeon's opinion needed to be converted to an above-knee amputation. The patient however, persuaded the surgeons to try a period of maggot therapy about which he had read in a lay Dutch newspaper. After treatment of the first few (5) patients, we held our first presentations for general physicians[25] and discussed our results with doctors and nurses of our hospital.[26] This led to publications in the lay press[27], leading to more patients coming to our hospital with the question whether or not their wounds could be treated with MDT.

We have argued that maggot therapy should not only be reserved for the wounds that are difficult to heal, but could also be used as a first-line treatment.[28] However, with the start of our Rijnland Wound Center there were many unanswered questions and these have become the basis of this thesis. With maggot therapy we were able to get a lot of wounds in the granulating phase. However, we found that sometimes it is actually more difficult to close the cleaned wounds for which we have proposed several options, like Topical Negative Pressure Therapy[29], Oasis Wound Matrix[30] and many others, this eventually cumulating in our first organised wound symposium of the Rijnland Hospital on 11th September 2006 and the treatment of our 150th patient (with MDT) in February 2007.

Revival of MDT

Maggot therapy has seen a real revival, in the period 2004-2006, 60 papers were published on MDT, and on Pubmed almost 200 articles can be found. MDT has been approved by the FDA (Food and Drug Administration) and is now a medical device (issue 510(k)33391). Dr. H. Wolff, from Sweden, wrote her thesis on 'Studies of Chronic Ulcers & Larval Therapy' in 2004. The International Society of Biotherapy was founded in 1996, to investigate and develop the use of living organisms, or their products, in tissue repair.

Their 7th meeting was held in Seoul Korea in June 2007.[31] Currently 300 centers in the United States and about 1,000 centers in Europe are using MDT.[32] In these days of evidence based medicine, we must conclude that there is no evidence from multiple, large, randomised studies, simply because there have not been any, although one is currently on its way in England. It is a trial on the effectiveness of MDT in chronic venous leg ulcers, including a total of 600 patients.[33] We believe however, that randomised studies can only be performed if some of the basic questions are answered, such as which factors influence the effectiveness of MDT. The group of Petherick et al. questioned themselves, for example, about patient acceptability, which in our opinion is a very important question.[34] If a randomised study is undertaken without reference to factors influencing the outcome, these studies will have confounding factors. In this thesis, I will answer some of these basic questions.

MDT is a form of debridement; a biological debridment. Some wounds can better be treated with surgical debridement, others perhaps with chemical debridement. Debridement in its different forms will now be outlined.

Debridement

The term "debridement" comes from the French desbrider, meaning "to unbridle". Debridement refers to the removal of dead, damaged, or infected tissue in order to improve the healing potential of the remaining tissue.[35] Debridement as a medical term was probably first used by surgeons working in war zones, who recognised that grossly contaminated soft tissue wounds had a better chance of healing (and the soldier of surviving) if the affected tissue was surgically removed to reveal a healthy bleeding wound surface.[36] It seems that the chronic wound does not progress through the stages of wound healing (hemostatis, inflammation, proliferation and maturation) but the healing progress stagnates in the inflammatory phase. If necrotic tissue is left intact, it is very difficult to maintain a moist wound environment, to keep the wound free from infection, prevent excessive inflammatory response and to ensure the closure of wound edges.[37] If the wound is not debrided the healing process will be impeded. Another point is that if necrotic tissue is not removed, the open wound or ulcer cannot be properly assessed.[36] Other consequences of not debriding a wound is imposition of additional metabolic load, psychological stress, compromising skin restoration, abcess formation, odour, nutritional loss and sub-optimal clinical and cosmetic outcome.[38] Debridement additionally removes senescent cells from the wound bed.[39] Senescent cells are cells that (due to aging) have a reduced growth capacity, are morphologically changed and have an over-expression of certain matrix proteins.[40] By removing necrotic tissue, the increased bacterial burden is reduced (traditionally considered greater than 105 colonies per gram of tissue). It is known from earlier studies that wounds exhibiting increased bacterial burden have reduced healing responses when compared to wounds containing fewer bacteria.[41] Biofilms (communities of bacteria and other organisms that are embedded with an extrapolyosaccharide matrix) have detrimental effects on wound healing; debridement may also help remove these biofilms.[42] Debridement, which results in bleeding, stimulates the production of growth factors. Platelets control bleeding and form a platelet plug. In addition, activated platelets release various growth factors and cytokines.[43] These act as chemoattractants for inflammatory cells and mitogens for fibroblasts and epithelial cells, all crucial components of proper wound healing.[42] There is no level 1 evidence that debridement (in any form) has a beneficial effect on wound healing[44], compared to no debridement. However, international consensus is that debridement is a vital adjunct in the care of patients with chronic wounds.[45;46] There are several methods of

debridement: surgical, mechanical, autolytic, chemical, enzymatic and biological.[47] It's not clear which method of debridement is to be preferred. Each method seems to have its own indications and contra-indications. In a published review on debriding agents for surgical wound healing by secondary intention, it was concluded that there is proof of the effectiveness of autolytic debridement; they could find no studies into the other forms of debridement.[47] In studies on diabetic patients, enzymatic debridement was found effective (3 Randomised controlled trials); there was no proof in favour of surgical debridement (1 RCT) or maggot therapy (1 RCT).[46] It seems that not all necrotic wounds can be addressed with the same debriding method. The different debridement methods will subsequently be discussed, with figures that illustrate each method.

Biological Debridement (Maggot Debridement Therapy)

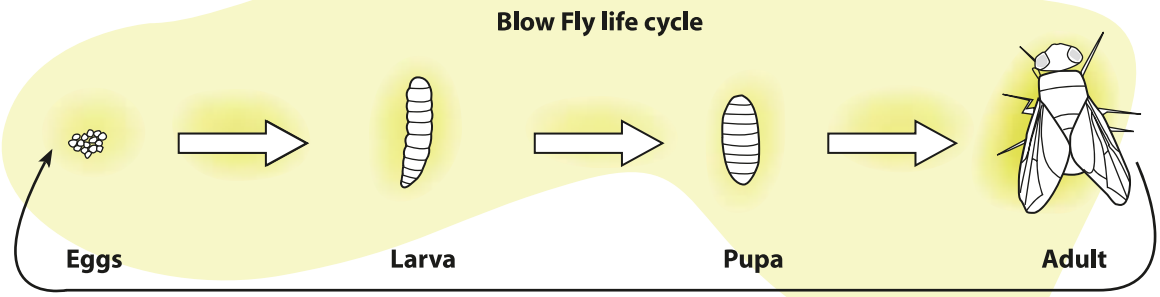

Figure 1: Showing the life cycle of the blow fly.

It is important to realize that the larvae of the blow fly (lucilia sericata) is the stage of the maggot's development in which it can be used for MDT. The larvae are relatively small (<2 mm) when they are applied and can grow up to 1 cm in 2 to 3 days. In order to complete the cycle the larvae will need to pupate (at a lower temperature than the human body temperature). The cycle **(see Figure 1)** takes about 14 days to be complete. The larvae will never stay on the wound for this long, for they are changed 2 to 3 times per week. The maggots are put in place on the wound. There are several application techniques, which will be described in detail in chapter 4. The larvae are sterilized in a specialized production facility. They can be easily obtained from Tuesday till Friday (if ordered the day before). In the Netherlands larvae can be obtained by BiologiQ (Apeldoorn, The Netherlands).

It is still not clear how maggot therapy works. It is probably more complicated than the mere washing out of bacteria by the serous exudate or the simple crawling of the larvae in the wound. 'Maggots move over the surface of the wound, secreting proteolytic enzymes that break down dead tissue, turning it into a soup which they then ingest'.[48] The mechanism for the beneficial effect of maggot therapy is likely their extracorporal digestive system. Maggots produce enzymes such as tryptase, peptidase, and lipase and release these into their environment. This may help break down debris and necrotic tissue, while leaving healthy tissue unharmed. The resulting semiliquid debris is absorbed and digested by the maggots.[49-51] They act as necrophages and destroy bacteria.[48;52] In addition, maggots secrete allantoin, ammonia, and calcium carbonate, which produce an alkaline environment.[53] This acts as a barrier against bacterial colonization and stimulates the growth of granulation tissue.[13] Also, the crawling of

maggots in the wound is thought to create a mechanical stimulus for the growth of granulation tissue.[54] Besides, they produce growth stimulating factors[55], which have been shown to promote the growth of fibroblasts.[49] Nigam et al. recently published an article discussing evidence supporting the potent antibacterial action of maggot secretions. Besides debridement and desinfection, a third important factor of MDT is discussed: enhanced healing.[56]

Figure 2: Production facility of maggots in Germany (Biomonde).

Figure 3: Showing the non-sterile part of maggot rearing. Some maggot larvae are grown into the adult stage (fly) in order to keep the production going.

Figure 4: The eggs intended for use in MDT are sterilized. Cultures are taken, in order to prevent induction of infection in patients. In all maggot treatments performed in the LUMC and Rijnland Wound Center Leiderdorp, this has never occurred.

Surgical Debridement

Surgical debridement refers to the extensive removal of tissue, sharp debridement refers to minor tissue sparing debridement that can be repeated and can be performed at the bedside of the patient or in a procedure (surgical) room.[36] Necrotic tissue is removed, using a scalpel, scissors, forceps or a curette. This is especially indicated if a rapid debridement is needed, it can be done at the patient's bedside. It seems ideal if there is a large quantity of necrosis that needs to be removed.[57] Surgical debridement is the only debriding method if the patient has systemic signs caused by the wound (e.g., sepsis or cellulitis).[42] One should consider bleeding problems in patients with clotting/bleeding disorders or patients on anticoagulant therapy. Another problem is that surgical debridement is not always very selective, for viable tissue lying adjacent to the necrosis can be removed.[58] Surgical debridement requires special training and expert comfort level and anatomic knowledge.[59] Sometimes an operating room or anesthetics are needed for extensive procedures, this limits the possibility of repeated surgical debridements. A new alternative is the use of a laser which both cuts and cauterizes.[42]

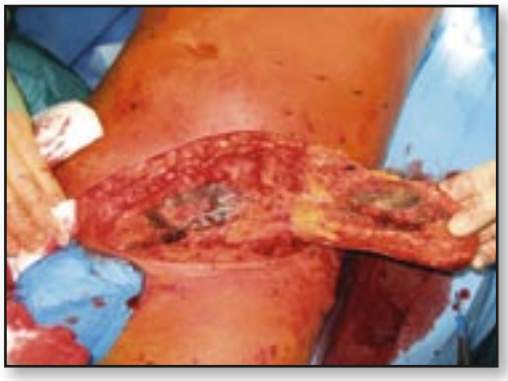

Figure 5: Showing a patient with a necrotizing fasciitis, for which surgical debridement is performed.

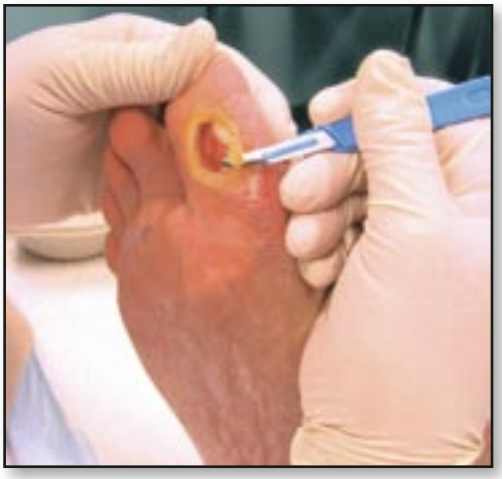

Figure 6: Sharp debridement of a diabetic neuropathic ulcer, using a scalpel.

Mechanical Debridement

In mechanical debridement, non-discriminatory physical forces are used in order to remove necrotic tissue and debris from the wound surface. The traditional wet-to-dry treatment consists of a moist dressing applied to the wound, which is subsequently removed when the dressing has dried out. It seems ideal for larger wounds, and for patients unfit for surgery. The main disadvantage is that it is non-selective and painful. Other problems include the frequent dressing changes, maceration of surrounding skin, and bleeding, while the time-consuming and labor-intensive characteristics of MDT further aggravate the patient's discomfort. Dressing fibers stick to the wound which can cause a foreign-body reaction. This method now seems outdated, with the current availability of other methods.[42] Rehydration can ease the removal of the surface eschar and debris on the surface of the wound. Hydrotherapy or wound irrigation is a relatively slow technique that uses moving water to dislodge loose debris. There is little evidence to support its effectiveness. The danger of cross infection should be taken into account when using hydrotherapy. Health care professionals need personal protective equipment with a view to aerosolization. There is also a theoretical risk of fluid embolism and promotion of infection if irrigation is too vigorous. Other forms of mechanical debridement include high-pressure irrigation and whirlpool baths. In this way, wounds are debrided using water, but these methods may also result in periwound maceration. Other forms of mechanical debridement are ultrasonic therapy and laser therapy.
A relatively new method using Fluidjet Technology (Versajet Hydrosurgery System®, Smith & Nephew, Hull, UK) seems promising for hard-to-heal leg ulcers.[60]

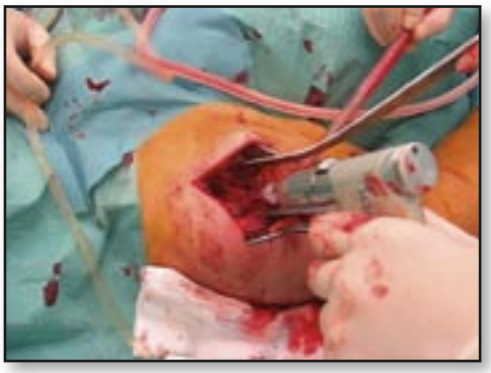

Figure 7: After surgical debridement, hydrotherapy is applied to clean the infected shoulder joint. In this figure the use of a Hydrojet® is demonstrated.

Autolytic Debridement

In autolytic debridement, the body's own enzymes and moistures are used to rehydrate, soften and finally liquefy necrosis and slough. It relies on enhancing the natural process of selective liquefaction, separation and digestion of necrotic tissue and eschar from healthy tissue that occurs in wounds because of macrophage and endogenous proteolytic activity.[59] Autolytic processes are accelerated if there is a moist environment.[61] It is a somewhat selective method, for only necrotic tissue is liquefied. When this therapy is used, occlusive or semi-occlusive dressings are used for lysosomal enzymes to have a better contact with the wound.[62] One of the main disadvantages is the slow speed, the chances of (anaerobic) infection and the chances of maceration of the surrounding skin.

Autolytic debridement is recognised to be effective in the maintenance phase of debridement. Examples of this treatment method are the use of hydrocolloids, hydrogels, alginates and transparent films. This method is selective and causes little or no pain. However, autolytic debridement may be slow.[42]

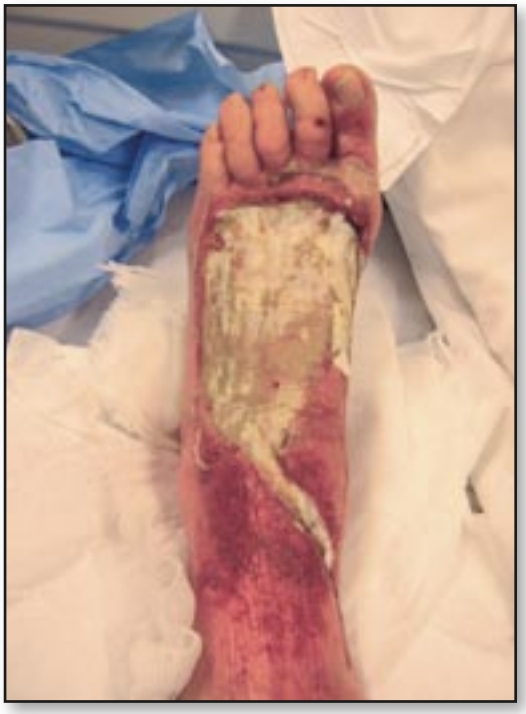

Figure 8: A wound covered in yellow slough is treated with an analginate dressing for further debridement. In this case Kaltostat® (Convatec, The Netherlands) was used.

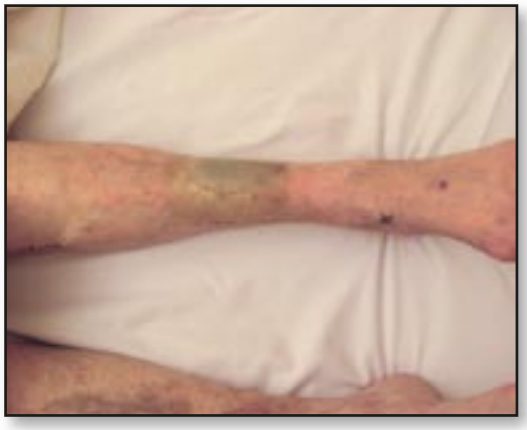

Figure 9: Showing an arterial ulcer of the left lower leg treated with a hydrocolloid dressing (Duoderm, ConvaTec, The Netherlands) in order to achieve autolytic debridement.

Enzymatic Debridement

In enzymatic debridement preparations are used such as streptokinase or streptodornase or bacterial-derived collagenases. Streptokinase and streptodornase aim to break down and rehydrate the necrotic tissue. Despite their availability for more than 30 years, there is little evidence to prefer the use of these to alternative methods. This process relies on the addition of proteolytic and other exogenous enzymes on the wound surface. These enzymes break down necrotic tissue and can be effectively combined with moist wound healing. Bacterial-derived collagenases show great potential and may promote healing.[63] The two most widely used proteolytic enzymes in Europe are fibrinolysin/desoxyribonuclease (Elase®) and collagenase (Novuxol®). In a study on collagenase in decibutal ulcers these seemed more effective than autolytic debridement.[64] In retrospective studies it seems effective for hard-to-heal ulcers.[65] Enzymes are inactivated by heavy metals (silver, zinc), which may be introduced from some wound care products, such as antimicrobial dressings (e.g. Actisorb Silver®, Flammazine®) and detergents present in skin cleansing agents inactivate enzymes. Care must be taken therefore, to use enzymatic debridement agents such as collagenases in the correct care sequence if they are to be maximally effective.[59] The products originate from very different sources, for example Elase® from bovine pancreatic tissue and Novuxol® from Clostridium histolyticum. However, several products are used for enzymatic debridement, ranging from pineapples and papaya to plankton and the newest product is a silicone-based controlled-release device for accelerated proteolytic debridement.[66] Combinations of enzymatic products like crab and krill are also available.[67] It seems we have not seen the end of enzymatic debridement yet, with new preparations and combinations being studied.

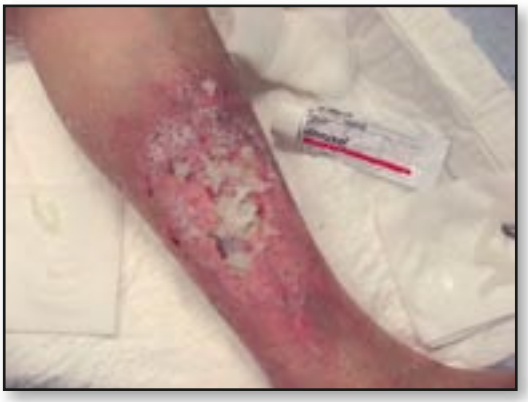

Figure 10: A painful necrotic ulcer treated daily with Novuxol® (Smith and Nephew, The Netherlands).

Chemical Debridement

Chemical debridement is not widely used due to the fact that it causes pain and also because the healthy underlying tissue is damaged during the therapy.[37] Another problem is that its effectivity is debated.[68] It is non-selective. Some authors call all chemical and enzymatic debridement chemical debridement. However, this is not right.[69] Sodium hypochlorite (Dakin's solution), hydrogen peroxide, povidonc-iodine and acetic acid all damage the cells needed for healing, such as fibroblasts. Some clinicians feel that these

antiseptic solutions can be used in case of infected wounds, for the prevention of the spread of infection takes priority over the protection of the few cells needed for healing.[70]

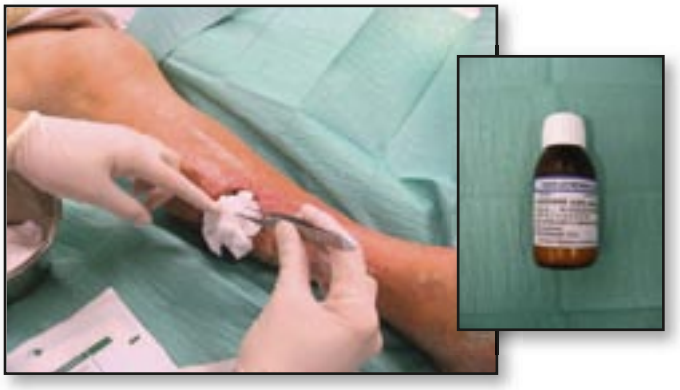

Figure 11: Sodium hypochlorite is applied to the wound. There are different treatment protocols, some prescribing the application for 15 minutes, three times a day.

Outline of the thesis

In chapter 1 of this thesis the history of maggot debridement therapy has been discussed. Starting from the oldest records of maggots known, until more recent history: the introduction of MDT in the Netherlands. There are six forms of debridement, biological debridement (MDT) is one of these methods. All different debridement methods have been briefly discussed.

In chapter 2 basic observations of MDT are described: histopathological, microbiological and laboratory investigations.

In chapter 3 a study is described in which patient-, wound- and therapy factors influencing the outcome of MDT are studied.

In chapter 4 two different application techniques are described and compared.

Chapter 5 consists of case reports and case series, such as MDT in amputation sparing surgery, MDT in breast-conserving therapy, MDT in necrotizing fasciitis, MDT in order to improve the outcome for infected amputation stumps and MDT in a palliative setting.

In chapter 6 adverse effects and safety issues are discussed: in particular the YUK-factor, bleeding complications and pain management.

In chapter 7 two articles are described in which possible contra-indications for MDT are discussed: smoking and chronic limb ischemia.

The general discussion is found in chapter 8, followed by a summary in English and in Dutch. References are published separately as is the publication list and the curriculum vitae.