Special Article

Maggot Debridement Therapy: From the Battlefields and Soldiers to Today's Clinical Trials

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Abstract

Background: Although the advances in contemporary medicine have helped to improve the healthcare services, the wounds that do not heal remain a problem. Patients' life expectancy has increased and many diseases are now considered chronic.
Objective or Aims: The present historical study explores the important use of Maggot Debridement Therapy in clinical practice from antiquity to this day.
Methodology: A literature review of both Greek and international literature was conducted. Popular data bases such as Pubmed, Medline, and Iatrotek were also used.
Results: Maggot therapy is a controlled therapeutic myiasis, during which, fly maggots are placed on the trauma and help to clean the dead and infected tissue. These maggots have been sterilized and have been bred in laboratories with strict quality control protocols. Usually, the preferred species for this particular type of treatment is the species *Lucilia sericata*.
Discussion: Maggot therapy first appeared at the beginning of civilization. From the Ngemba tribe to the Maya civilization, from army physicians during war campaigns to the 21^{rst} century, maggot therapy has been used to treat ulcers.
Keywords: maggot therapy, soldiers, wound healing, myiasis, *Lucilia sericata*

Introduction

Maggot therapy is used to clean dead tissue. It dates back to the beginning of civilization (Whitaker et al ,2007; Stadler, 2020). Maggot therapy had raised a lot of controversy and physicians did not usually prefer this type of treatment to clean a surgical wound. However, it is a safe, cheap, and simple treatment, with very good results and that is why it has been widely accepted (Stadler et al, 2015; Sherman, 2009). Today, both hospitalized and non-hospitalized patients with chronic, difficult to heal, diabetic ulcers can benefit from maggot therapy (Whitaker et al, 2007; Heitkamp et al, 2012; Peck et al, 2015; Jones et al, 2009; Cruz-Saavedra et al, 2016; Uysal et al, 2018; Meimeti et al, 2015). The main action of *Lucilia sericata* larvae is biological cleaning (scavenging, debridement) of necrotic tissue, especially of the yellow fibrous tissue that covers ulcers' bottom. It must be noted that *L. sericata* larvae's physical activity at ulcers' bottom consists one of the main reasons that made the U.S. Food and Drug Administration (FDA) classify them among the medical technology media (Sherman, 2014). They possess a wide range of matrix metalloproteinases (MMP), including serine proteases trypsin and chymotrypsin-type, one aspartic protease and one MMP exopeptidase-type, which can act at a wide range of pH (5.0-10.0). (Schmidtchen et al, 2003; Telford et al, 2010). More specifically, through ammonia secretion, the ulcer's area becomes alkalized; thus proteases like trypsin contribute to cell proliferation. The larvae antimicrobial activity is extremely important. Maggots control bacteria [both methicillin-sensitive (MSSA) and methicillin-resistant (MRSA) *Staphylococcus aureus*, *Streptococcus pyogenes* and partly *Pseudomonas aeruginosa*] through their digestion tract (Mumcuoglu et al, 2001; Bexfield et al, 2004; Kerridge et al, 2005)

Mechanism and Species of Larvae: The larvae act on the wound in three phases. The first phase is the debridement, the removal of the dead tissue, in order to improve the healing potential of the remaining healthy tissue (Sherman, 2014). Each maggot has the ability to remove up to 25mg of necrotic tissue within 24hrs. (Mumcuoglu, 2001) Debridement is achieved mechanically and chemically (Sherman, 2014; Naik et al, 2017). The mechanical debridement can be attributed to the tiny spines that cover the maggot's body, as well as its mouthpart hooks. Therefore, the maggots remove the necrotic tissue both by consuming it and by scraping it while they crawl along the wound. Moreover, due to the production of a large number of proteases, as already mentioned, the larvae are able to dissolve necrotic material (debris) chemically (Sherman, 2014). The second phase is disinfection, which is accomplished by the secretion and excretion of a mixture of proteolytic enzymes, such as lucifensin (a defensin), cyclo [Pro, Pro], *p*-hydroxyphenylacetic acid and *p*-hydroxybenzoic acid (Sherman, 2014; Naik et al, 2017; Huberman et al, 2007; Čeřovský et al, 2010). The last phase is healing (Sherman, 2014). After treatment with larvae an increased oxygenation and perfusion was observed (Wollina et al, 2002). This is probably due to the detection of certain amino acids in the maggots, such as L-histidine, 3-guanidinopropionic acid and L-valinol, substances that have been known to enhance the proliferation of the endothelial cells and angiogenesis (Bexfield et al, 2010). The most common insect species for maggot debridement therapy (MDT) are *Lucilia sericata* and *L. cuprina* (Diptera: Calliphoridae). Also, numerous other Calliphoridae have been used in MDT, such as *Calliphora vicina*, *Chrysomya rufifacies*, *Lucilia caesar*, *L. illustris*, *Phormia regina*, *Protophormia terraenovae*, as well as *Wohlfahrtia nuba* (Diptera: Sarcophagidae). (Grassberger et al, 2013) (Figures 1a,1b,1c)

Historical background of Maggot Therapy over the centuries

Maggot Debridement Therapy (MDT) is not a novel treatment; it dates back to the beginning of civilization. The oldest written reference may be found in the Old Testament, where a man's wound was infected by larvae of flies.

"My body is clothed with worms and scabs, my skin is broken and festering".

The Holy Bible, Old Testament, Job 7:5

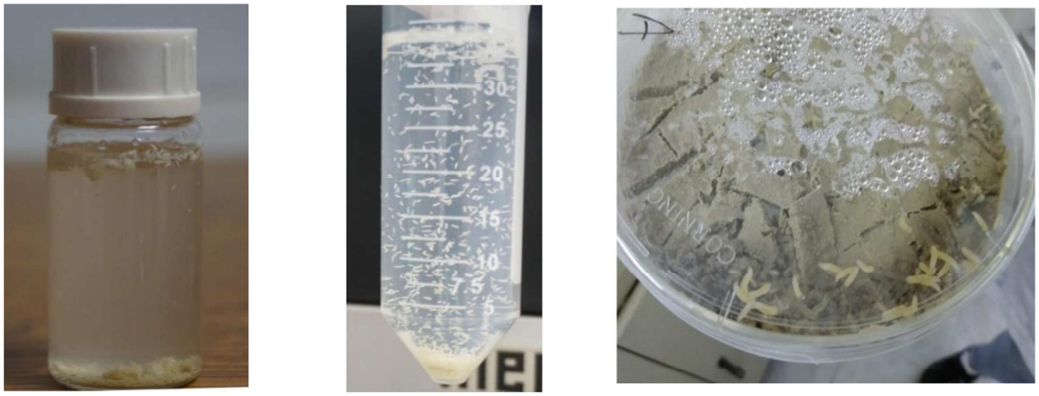
(New International Version (NIV), 2011)

Ancient Times

Different primitive civilizations, such as the Ngemba tribe of New South Wales, the Burmese Hill people in Northern Myanmar, and Mayan healers of Central America used fly larvae (Whitaker et al, 2007; Sherman et al, 2000; River, 1943; Nigam et al, 2010; Weil, 1933).

They soaked bandages in bovine blood and exposed them to the sun, so that the flies could lay their eggs and larvae (maggots) would appear. Then they applied the bandages on a trauma (Whitaker et al, 2007; Nigam et al, 2010; Weil et al, 1933).

Figure 1



1a **1b** **1c**

Figure 1a: Eggs of maggots

Figure 1b: Sterile maggots in vials

Figure 1c: Maggots for use in wounds

(photos from our Lab)

1510-1590

The French surgeon Ambroise Paré (1510-1590) was the first to describe the positive effect of fly larvae on soldiers' wounds. (Whitaker et al, 2007) No other references on MDT were found in the literature before Paré's novel descriptions during the 16th century (Graner, 1997). A particular case of a patient with a large, deep skull trauma was of great importance because Paré managed to observe the presence of maggots on the bone deficiency (Nigam, et al, 2010) and decided to allow the maggots' action. The patient recovered (Whitaker et al, 2007; Nigam, et al, 2010).

1766-1842

Baron Dominique-Jean Larrey (1766-1842), Napoleon's battlefield surgeon, noticed that maggots not only removed necrotized tissue from the trauma, but also cared for the rest of the healthy bone. Larrey first recorded the way maggots act in cases of trauma and recognized their beneficial effect during the Napoleonic wars (Whitaker et al, 2007; Sherman et al, 2000; Weil et al, 1933; Graner, 1997; Voyatzoglou et al, 1999; Larrey, 1832). Furthermore, his interest in troops' health in the battlefields led him to a revolutionary and original idea: a plan for the rapid evacuation of the injured through a medical transport vehicle, in an effort to avoid deaths due to bleeding. That invention made him the father of modern ambulance (Larrey, 1832; Skandalakis et al, 2006). In 1829, he claimed that "these insects accelerated cicatrization and shortened nature's work by eliminating the necrotic cells, because they devoured them without disturbing the live tissue" (Whitaker et al, 2007; Sherman et al, 2000; Weil et al, 1933; Graner, 1997; Voyatzoglou et al, 1999; Larrey, 1832). One of MDT's characteristics that aroused his interest was the improvement of inflammation and the reduction of pus, which was noticed by a male nurse in Mercy Hospital (Weil et al, 1933). Larrey notes in his book *Observations on*

Wounds, and their Complications By Erysipelas, Gangrene and Tetanus, and on the Principal Disease and Injuries of the Head, Ear, and Eye (1832) that the French Napoleonic campaign in 1798-1801 benefited by the use of fly maggots on several soldiers.

Nevertheless, despite their positive effect on wounds and the encouragement of the soldiers, Larrey resented the view of fly maggots because they grew rapidly and increased in size even within a day (Whitaker et al, 2007; Stadler et al, 2015; Larrey, 1832).

American Civil War (1861-1865) During the American Civil War (1861-1865), William Williams Keen (1837–1932), a military surgeon, claimed that fly maggots do no cause any harm in wounds, despite their repulsive appearance (Whitaker et al, 2007). Furthermore, John Forney Zacharias (1837–1901), a surgeon from Maryland, and Joseph Jones, a military doctor, were the first ones who used MDT during the American Civil War. Jones noticed that the use of fly maggots on numerous wounds did not affect the healthy tissue, only the necrotized, while J.F. Zacharias reported that fly maggots removed necrotized tissue from gangrene shortly after their application, saving numerous lives. (Whitaker et al, 2007; Graner, 1997; Voyatzoglou et al, 1999; Yan et al, 2018).

World War I (1914-1918) During the 1rst World War, mortality rates raised due to the injuries and the insufficiency of antiseptic methods (Whitaker et al, 2007; Sherman, 2009) .Fly maggots were unsuccessfully used in patients with osteomyelitis by the American military and orthopedic surgeon William Stevenson Baer (1872-1931). Baer was born in Baltimore and graduated from Johns Hopkins University in 1894. He served as a House Officer at Johns Hopkins Hospital in the surgical wing. The year 1917 was important for Baer because he became a Clinical Professor of Orthopedic Surgery at the Johns Hopkins University. One of his many accomplishments was the establishment of the Children's Hospital School in Baltimore. During the same year, he joined the American Expeditionary Forces in France, where he remained for 2 years. During this period, MDT aroused his interest (Baer, 2011; Wainwright, 1988). Baer was the first one to use fly maggots systematically on injuries and he discovered that in order to apply them on an injury, they have to be sterile (Whitaker et al, 2007; Sherman, 2009;Baer, 2011). Baer was considered to be the father of MDT, having the first scientific reference in the international bibliography, despite his not being the person who discovered it. During the 1rst World War, he used MDT on two soldiers in the battlefield with neglected fractures of the femoral bone and large abdominal wounds. After their transport to the hospital, Baer observed a lack of inflammation, pus, fever, and symptoms of sepsis. It was the overall good condition of the patients that impressed him the most. After removing the bandages, he noticed the formation of pink granular tissue (Weil et al, 1933; Graner, 1997; Baer, 2011; Wainwright, 1988; Ashley et al, 2018).Baer also observed that fly maggots tend to crowd in specific areas and that despite their need for air and sunlight, they seek shade, describing them *"like dogs that seek the shade"*. Thus, Baer placed artificial light on a scar The injuries healed, while bacteria like Staphylococcus, Proteus etc diminished, leading Baer to the conclusion that fly maggots restore the injury and affect bodily fluids, playing a key role in healing (Wainwright, 1988).

1929-1931

In 1929, Baer cured children suffering from osteomyelitis and injuries of the soft tissues and managed to publish his work in 1931 (Weil et al, 1933; Graner, 1997; Baer, 2011). With the aid of his colleagues, he managed to create methods for sterilizing the flies' eggs (Whitaker et al, 2007, Baer, 2011), but there were quite a few scientists that disagreed with MDT because its effect was not clear and knowledge was considered to be insufficient (Whitaker et al, 2007, Graner, 1997). Baer died in April 7, 1931. After his death, Stanton K. Livingston, one his students, continued the MDT, starting its wide application in wound healing in American hospitals (Whitaker et al, 2007;Graner, 1997). Livingston, who was Chief of the Orthopedics Service of the Edward Hines Jr. Veterans Administration Hospital at Hines, Illinois, contributed greatly with his research and effective treatment in wound healing, saving numerous veterans who did not lose their lower limbs. He published several papers; his last one being in 1942. After the fall of MDT, he stopped working as a clinical researcher and became Chief of Staff at the Albany VA Hospital until 1965. He is considered the savior of countless American soldiers, holding a special and honorable position in the

medical history of the American army (Graner, 1997).

World War II (1930-1940)

During the 2nd World War, military doctors of Burma used MDT and monitored the progress of the treatment (Whitaker et al, 2007). During the decade 1930-1940, numerous publications referred to MDT, since more than 300 American hospitals applied it for wound healing. Nevertheless, the discovery and wide availability of antibiotics, along with the amelioration of surgical practices that flourished during that era, led to the loss of interest for MDT application (Whitaker et al, 2007; Stadler et al, 2015; Sherman, 2009; Jones, 2009; Huberman et al, 2007; Yan et al, 2018; Huberman et al, 2007). This loss of interest started after the wide use of sulfonamides. Moreover, the production of penicillin (originally discovered in 1922, when Alexander Fleming noticed that this substance may suspend the development of staphylococci, streptococci, meningococci etc) started, along with the production of new antiseptic agents (River, 1943; Graner,1997; Voyatzoglou et al, 1999; Yan et al, 2018; Chain et al, 2005). So numerous traumas that in the past were cured with fly maggots, like osteomyelitis and soft tissue abscesses caused by bacteria, were less common due to the use of sulfonamides and penicillin (Sherman, 2009; Nigam et al, 2010). Furthermore, publications with MDT's successful results decreased, because it was considered an alternative solution for unfavorable conditions. In the 1950s, MDT was rarely used and less often reported (Whitaker et al, 2007; Sherman, 2009; Nigam et al, 2010; Voyatzoglou et al, 1999).

Late 20th Century

In 1980, the antimicrobial resistance of pressure ulcers and diabetic ulcers was common, while other treating methods were unsuccessful. The appearance of bacteria resistant to antibiotics such as MRSA, along with restrictions in the use of antibiotics, resulted in the return of MDT in hospitals (Sherman, 2009; Jones, 2009; Voyatzoglou et al, 1999; Malekian et al, 2019). Antibiotics do not remove necrotized tissue and sometimes decelerate the beneficial action of non-pathogenic microorganisms during healing. On the other hand, fly maggots eradicate bacteria and remove necrotized tissue, while they facilitate the development of granular tissue (Voyatzoglou, et al,1999; Nigam, 2016).Since 1989 in USA, and from the mid-1990s in the UK and Israel, MDT returned to successfully treat numerous patients (Mumcuoglu et al, 2001; Mumcuoglu et al, 1999). More precisely, Ronald Sherman and Edward Pechter brought MDT back to the spotlight and encouraged the use of maggots in the USA during the 1990s. (Naik et al, 2017). During that time, many studies were performed on patients with ulcers from MDT supporters, reporting faster removal of the necrotized tissue and faster healing rate, in comparison to other surgical treatments and techniques (Whitaker et al, 2007;Sherman, 2009; Huberman et al, 2007). An increase of its application was noticed, despite the hesitation of health professionals to its reintegration in the health system. Thus, MDT reappeared in the spotlight in the UK and the Biosurgical Research Unit was established in Bridgend, South Wales, producing since 1995 sterile maggots and exporting them to Europe (Whitaker et al, 2007).

21rst Century

In 2004, the U.S. FDA received a patent to breed maggots for pharmaceutical purposes, which would remove necrotic skin tissue and soft tissues (Grassberger et al, 2013; Sherman et al, 2018). During the same year, this particular type of maggot treatment was approved by the Health Authorities of Germany and Austria (Grassberger et al, 2013). In addition to that, in 2010, this type of treatment received approval from the EMA (European Medicines Agency) to be used in foot ulcers. Maggot therapy was included in the healthcare system in 2011 (Sherman, 2014; Sherman et al, 2001).It is estimated that 50.000 treatments take place every year and that fly maggots are bred in, at least, 25 laboratories (Sherman, 2009; Grassberger et al, 2013) and are then delivered in 40 countries, such as Argentina, Australia, Austria, Belgium, Brazil, Canada, China, Colombia, Czech Republic, Denmark, Ecuador, Egypt, France, Finland, Germany, Hungary, Indonesia, Iran, Italy, Israel, Japan, Kenya, Malaysia, Malta, Mexico, New Zealand, Norway, Philippines, Poland, Russia, Singapore, Slovakia, Slovenia, Saudi Arabia, South Africa, Spain, Sweden, Switzerland, Tanzania, The Netherlands, Thailand, Turkey, the UK, Ukraine, and the USA (Mumcuoglu, 2001; Mumcuoglu et al, 1999).

Today, many companies breed sterilized fly maggots in the USA, the UK, and in Germany,

Israel, Japan, Malaysia, and Thailand (Mumcuoglu et al, 1999).

Maggot therapy is a type of therapy for chronic wound healing, when the wounds do not respond to conventional treatments and surgical cleaning is not an option (Huberman et al, 2007).

Pioneers of contemporary MDR are Sherman in Europe and Mumcuoglu in Israel. They try to continue maggot therapy all over the world.

Conclusions

Maggot therapy can be applied to all kinds of trauma, such as diabetic foot ulcers, pressure wounds etc. and in areas that are difficult to treat. Maggots remove necrotic tissue without harming the healthy tissue, the blood vessels, and the tendons. MDT can be applied to both hospitalized and non-hospitalized patients. There are almost no side effects and it is a very quick and effective treatment for wound cleaning. It significantly reduces bacterial burden, while increasing tissue granulation and healing.

Maggot therapy can reduce the complications of chronic wounds and prevent limb amputations. Moreover, during this type of therapy, there is less need for antibiotics and hospitalization and patients do not need to visit the hospital very often. Maggot therapy can also improve patients' quality of life, since it reduces pain and bad odor. Maggot therapy is not only a low-cost and effective treatment, but also a way to significantly reduce the medical expenses for wound healing.

Abbreviations

FDA = Food and Drug Administration

MMP = matrix metalloproteinases

MSSA = methicillin-sensitive *Staphylococcus aureus*

MRSA = methicillin-resistant *Staphylococcus aureus*

MDT = maggot debridement therapy

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