

Eat and heal. Past, present and future of maggot debridement therapy: a narrative review

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Article received 12 February 2024 and accepted 10 April 2025

SUMMARY

In medicine, fly larvae play a dual role: they can be both harmful causative agents of diseases and therapeutic agents. In fact maggot debridement therapy (biosurgery) is the controlled use of larvae to treat infected wounds and dates back to the beginnings of medicine. Ambroise Paré and Dominique-Jean Larrey pioneered the field of biosurgery before the 19th century, but it was John Forney Zacharias during the American Civil War who officially documented and promoted this medical application. The success of this method was immediate. Nevertheless, germ theory and the postulates of Robert Koch discouraged physicians from using potentially contaminated material such as larvae from the second half of the 19th century onwards. In the first half of the 20th century, however, the practice regained momentum thanks to the sterilization of fly eggs and the success of Dr. Stanton K. Livingston in the treatment of chronic osteomyelitis with biotherapy. The use of larvae for therapeutic purposes was discontinued after the Second World War due to the discovery of penicillin and is now receiving some attention again due to the emergence of antibiotic-resistant bacteria. Although biosurgery is rarely encouraged, the results of systematic reviews and meta-analyses support its use. Previous and current evidence shows that this practice may be as useful as ever in the age of antibiotic resistance. It is likely that larval therapy will be considered as a stand-alone tool in the near future.

Keywords: biotherapy, maggots, larvae, debridement, stewardship.

INTRODUCTION

In a fascinating perspective, dipterous (two-winged) larvae (maggots) perfectly mirror the definition of the ancient Greek term *pharmakon* (φάρμακον). As a matter of fact, maggots play a dual role in medicine: as a poison and as a therapeutic agent. Infestation of living human tissue with fly larvae that feed on the host's skin is known as myiasis and is a common tropical dis-

ease [1, 2]. However, the controlled use of fly larvae to treat infected wounds dates back in the history of humankind.

The practice is known as larval therapy, maggot debridement therapy (MDT) or biosurgery [3]. This treatment approach was primarily strengthened by the germ theory of disease in the late XIX century, before being displaced by the development of antibiotics in the mid XX century. Nowadays, in the XXI century, its use is experiencing a new phase of interest because of the scarcity of novel antibiotics retaining activity against multidrug-resistant organisms (MDROs).

This natural approach to eliminating bacteria and

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Figure 1 - Adult (male) of the “greenbottle flies” (*Lucilia sericata* Meigen, 1826). Some strains of this species are known as the “medicinal maggots”. Photo by P. Cerretti, Sapienza University, Rome.

debris from skin and soft tissue infections *Lucilia cuprina* has been widely used on battlefields around the world over the past centuries and is now being considered for civilian use in chronic wounds management. The “old way my mother show me” as reported by a practitioner in the United Kingdom during the 1970s [4]. In modern MDT, flies of the species *Lucilia sericata* (Figure 1) or *L. cuprina* are reared in insectaria, and the medicinal maggots are prepared aseptically under laboratory conditions using quality control procedures [5].

The aim of the present work is to provide a comprehensive history of MDT from the origins of this gruesome practice to its modern fields of application. The research has been carried out in scientific indexed databases such as PubMed and historical sources.

■ NOTES ON THE HISTORY OF MDT UNTIL THE MIDDLE OF THE 18TH CENTURY

There is evidence that MDT has been used by various cultures, such as the indigenous people of the Ngemba tribe in New South Wales, the hill tribe in northern Myanmar (Burma), the Mayan healers in Central America and Chinese medicine [3, 6].

In the tradition of Greek, Roman and Arabic medicine, there are no references to the use of maggots as a therapeutic agent. However, flies are cited as responsible for diseases and for their therapeutic effects. An Arabic medical author, Muhammad ibn Musa Ad-Damiri (1341–1405), in his attempt to

give a systematic account of natural history, reports: “I have carefully examined the fly, and found that it defends itself with its left wing, which is the one supposed to contain a [cause of] disease, just as the right one is supported to contain a remedy [for it]” [7].

Ambroise Paré (1509–1590) is generally credited with being the first to have noticed the beneficial effects of maggots on purulent wounds [3]. Paré indicates cases of “spontaneous” worm formation in putrid gunshot wounds and described patients who, against all odds, recovered from untreatable lesions during the Battle of St. Quentin in 1557. He reports in *Opera Ambrosii Parei Regis Primarii et parisiensis Chirurghi, Parisiis Apud Iacopum Du-Puys, 1582*: “Ad curam eiusmodi ulcerum praemissis generalibus, primus eximendi vermes erunt, inde exhausti veniet ille excrementitium humor, unde ipsis origo est. Itaque sequenti decocto: cui vis inest ipsorum necandorum, ulcus fovebitur: nam si quis tenet vivos omnes inde eximere, vehementer errant: saepe enim adeo tenaciter haerent ulceratae parti, ut sine summa vi, et doloris cruciatu avelli nequeant” [8].

Later, also Hieronymus Fabricius (1533–1619) noted the effect of maggots on wounds, while the success of Robert Hooke’s *Micrographia* (1665) increased the attraction for maggots and larvae [9, 10]. Of interest, the greatest naturalist (and physician) of the 18th century, Antonio Vallisneri (1661–1730), does not mention any therapeutic use of larvae or worms for men in his particularly comprehensive and learned work. It should be remembered that Vallisneri was one of the last epigones of Galenism in modern times.

■ FROM NAPOLEON’S CAMPAIGNS TO WORLD WAR II

A French surgeon, Baron Dominique-Jean Larrey (1766–1842), made the same observations as Ambroise Paré. While tending to the wounded soldiers of Napoleon’s army during the Egyptian expedition in Syria (1798–1801), he noticed that maggots removed necrotic tissue and had a positive effect on the remaining healthy tissue [3].

The first officially documented military application of MDT was reported by the surgeon John Forney Zacharias (1837–1901) during the American civil war (1861–1865): “[...] I first used maggots to remove the decayed tissue in hospital gangrene [...] In

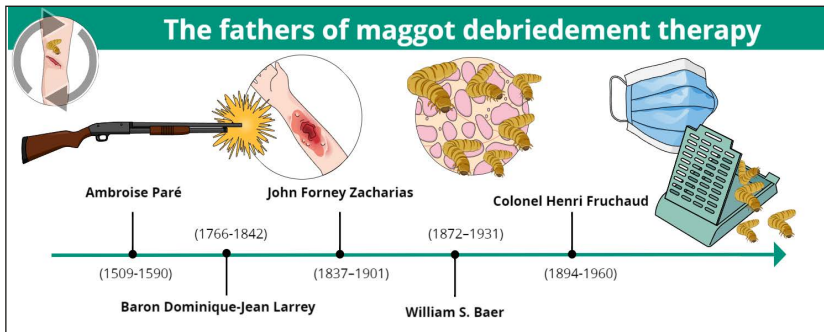


Figure 2

A graphic illustration of the men who have discovered and promoted the MDT until the discovery of penicillin at the end of World War II.

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." [11]. Nevertheless, in the period from 1860 to 1890, various contagious diseases were associated for the first time with certain specific microorganisms (e.g. leprosy, anthrax, typhoid, gonorrhea, tuberculosis and cholera). In addition, the prevailing scientific belief was that maggots were 'dirty' and introduced infections into wounds. Thus, the germ theory and the postulates established by Robert Koch (1843–1910) in the second half of the 19th century prevented doctors from applying contaminated material such as larvae to an open wound [3, 12].

William S. Baer (1872-1931), US Expeditionary Forces surgeon in France in 1917, reported during practice on battlefields: "[...] the wound filled with thousands and thousands of maggots [...] The sight was very disgusting [...] then the wounds were irrigated with normal salt solution [...] these wounds were filled with the most beautiful pink granulation tissue that one could imagine". After the European serendipitous observation in World War I, he experimented with MDT for osteomyelitis with encouraging results. The interest of the scientific community on biosurgery was back. Nevertheless, two treated patients developed tetanus and died. This prompted him to develop a method of rearing maggots in a sterile environment in line with the latest scientific theories of asepsis [13, 14]. Sterilization could be accomplished by soaking the eggs for one-half hour in a 1 to 1,000 solution of mercury bichloride containing 0.5 per cent hydrochloric acid, hatching them in sterile containers and feeding them on sterilized food. Baer's work spread like wildfire in North

America and Europe. In the 1930s and early 1940s, over a thousand hospitals used MDT to treat chronic wound infections and enthusiastic comments such as: "The maggots are more selective than my surgery" were reported from different countries. In 1935, this method was used by 585 surgeons in the United States and numerous biological laboratories were able to deliver aseptic "surgical maggots" by airmail in the same decade (e.g. Lederle Laboratories) [15, 16].

William S. Baer and one of his most famous students, doctor Stanton K Livingston, published in 1932 a report of 100 chronic infections resulting from fractures, tuberculous and pyogenic osteomyelitis following repeated amputations which had 95% cure rate. Mild or moderate infection healed in about six weeks; while severe cases required from three to six months of MDT [17].

It is interesting to note that in March 1942, during the World War II, when the American army introduced penicillin into clinical practice, Colonel Henri Fruchaud (1894-1960), professor of the surgical clinic in Angers (France), still encouraged MDT for ulcers and osteomyelitis. Nevertheless, Fruchaud's volume II *de la chirurgie de guerre*, which described MDT, was not published because of the advent of antibiotics. The biosurgery practice fell into oblivion again for some decades [18]. Figure 2 graphically illustrates the history of the so-called fathers of MDT until Colonel Henri Fruchaud and the advent of antibiotic mass distribution.

■ FROM WORLD WAR II TO THE END OF 21st CENTURY

After World War II, gradually, the use of MDT began to decline. This was attributed to the following circumstances:

Figure 3

Sterile maggots used for biotherapy. Images used with permission of the BioMonde Clinical Support Service.



1) the industrial production of antibiotics (first of all sulfonamides and then penicillin),
2) the improvement of surgical practices;
3) the production of new antiseptic agents [19]. Similarly, the academic interest dropped and until the late 1980s only few case reports have been published [19,20]. In the same period, the US Army continued to use MDT but only as a last therapeutic tool in extreme medical situations [21]. With the appearance of the first strain of *Staphylococcus aureus* resistant to methicillin (MRSA) in 1961 [22] the interest in MDT has resumed [23]. In the following decades few *in vitro* [24] and *in vivo* studies [25] on Maggot activity against MRSA have been published.

The late 1980s and early 1990s saw the birth of what we can call contemporary MDR. Three countries were mostly involved in the rediscovery of MDT: the United States (US), the United Kingdom (UK) and Israel [26]. In the US, in 1994, Ronald Sherman and Edward Pechter conducted a prospective study comparing MDT with standard treatment for pressure ulcers at the Veteran Administration Hospital Medical Centre in Long Beach, California [27]. Other studies followed this one and all found that MDT was superior to standard therapies [26]. In the same period, in Israel, Mumcuoglu successfully employed MDT for the treatment of ulcers in diabetic and non-diabetic patients [28]. In the UK, in 1995, Stephen Thomas and John Church, founded the Biosurgical Research Unit in Bridgend, South Wales, and started to produce sterile maggots. The Unit was composed of a fly room, where the adult insects were

kept, a clean room where the eggs were sterilized, a room for the breeding stock of larvae, and a room for patients' treatment [29].

In 2007 the Food and Drug Administration approved MDT for debriding non-healing necrotic skin and soft tissue wounds, including pressure ulcers, venous stasis ulcers, neuropathic foot ulcers, and non healing traumatic or post surgical wounds [30]. In 2010 also the European Medicines Agency approved MDT for sloughy and necrotic venous and mixed venous/arterial leg ulcers [31].

Nowadays, many countries worldwide use MDT for chronic wounds healing (Figure 3) and there are several specialized laboratories licensed to aseptically produce medical maggots in the US, the UK, Germany, Israel, Japan, Malaysia, and Thailand [26]. An International Conference on Biotherapy is organized periodically by the International Biotherapy Society since 1996, when the first one took place in Porthcawl, South Wales, UK [32]. According to the International Biotherapy Society, 80,000 patients have been treated with MDT in the last 25 years [32].

■ MDT APPLICATION IN RECENT GUIDELINES

Removal of devitalized tissue is essential for wound healing to occur. Necrotic tissue found in chronic wounds can impair healing and impede keratinocyte migration over the wound bed. Debridement can be accomplished using surgical, mechanical, autolytic, enzymatic, and biologic techniques. Biologic debridement using medical

grade maggots is a rapid and efficient debridement modality usually reserved for recalcitrant fibrinous wounds [33]. There appears to be mounting evidence that the secretions of maggots are capable of acting through a wide range of specific wound healing mechanisms and pathways. The powerful enzymes in their saliva dissolve necrotic tissue, which is ingested by the maggots. Because of the pain involved and the reluctance of patients and doctors, MDT is still rarely used [34]. A small number of studies have shown significantly favorable debridement results with the use of MDT, and more extensive and better powered comparative effectiveness studies are yet to be available to determine the exact clinical effectiveness of MDT.

A systematic review and meta-analysis investigated MDT in the treatment of chronically infected wounds and ulcers, considering healing rate and healing time among other outcomes. The results strongly suggest a significant positive effect of MDT on the healing rate of chronic wounds, and in four separate studies the authors showed that the time to healing for ulcers was significantly shorter in the MDT-treated group than in the control group. Notably, MDT had a significantly higher positive effect on wound healing compared to conventional therapies, with a pooled relative risk of 1.80 (95% CI 1.24-2.60). The time to healing of the ulcers was significantly shorter among patients treated with MDT, with a pooled standardized mean difference of -0.95 (95% CI -1.24, -0.65) [35].

More recently, a systematic review investigated the efficacy of MDT versus hydrogel dressings in the treatment of chronic wounds of different etiology, i.e. diabetic foot ulcers, pressure injuries, and vascular ulcers [36]. A total of five studies, including three randomized controlled trials, one retrospective and one prospective cohort study, for a total of 580 patients were retrieved [37-41]. Either bagged or loose larvae in a quantity ranging from five to eight per square centimeter of wound were employed. The duration for the application of larvae onto the wound prior to the removal of the dressing ranged from 48 to 96 hours. In chronic wounds treated with MDT, it was found that more granulation tissue was formed and the wound surface was reduced more rapidly. However, no effect on the disinfection of bacterial growth or on the duration of complete healing was noted. A

common adverse effect reported by patients was pain, especially after 24 hours of MDT application, which appeared to be related to the increasing size of the larvae [36].

In a randomized controlled trial comprising 140 patients with diabetic ulcers, Markevich *et al.* found that by the end of their 10-day study, wounds treated by MDT were covered with more healthy granulation tissue and were smaller in size than those of the control group [42]. Another study by Wilasrusmee *C et al.* compared the healing probability of diabetic foot ulcers treated with MDT versus conventional wound therapy and found a significantly better outcome for MDT [43]. Nevertheless, there have been clinical reports detailing little or no difference found in healing between MDT treated and conventionally treated wounds [44-46].

Critical limb ischaemia is a severe and debilitating condition which often manifests with recalcitrant ulcers in patients with peripheral arterial disease. MDT is generally not advisable on such ulcers because of poor oxygen provision to tissues. Interestingly enough, Maeda TM *et al.* measured an increase in skin perfusion pressure surrounding a post-amputation chronic wound after MDT administration for a patient with critical limb ischaemia [47]. Furthermore, there is some evidence that MDT can facilitate wound healing and potentially reduce the need for amputation [48].

■ FUTURE PERSPECTIVES OF MDT

In 2019 there were an estimated nearly 5 million deaths associated with bacterial antimicrobial resistance [49] and bacterial infections of the skin and subcutaneous systems ranked 6th as death associated infectious syndromes [49]. In clinical practice patients with subacute/chronic infections, especially when associated with biofilm and antibiotic resistant bacteria are extremely difficult to manage. During the last years we experienced the repurposing of some non-antibiotic "biologic" therapies such as bacteriophages and larval therapy.

In western world both UK and US use larval therapy in both community and hospital settings [50, 51] and the therapy is not necessarily administered by physicians [51]. From an economic point of view in 2009 a multicentre trial was published (22 UK centers, larvae vs hydrogel) and a cost ef-

fectiveness analysis was performed. Larvae treated patients costed 96 pound more per year, healed 2.42 days earlier and had a slightly better quality of life, however none of these differences were statistically significant therefore they concluded “larval therapy is likely to produce similar health benefits and have similar costs to treatment with hydrogel” [52] that is anyway a good result since maggots cost 40-60 times more than autolytic products. But a question arises: what happens to cost effectiveness if we select only cases infected with antibiotic resistant bacteria? We have no answer yet.

What we know is that *Lucilia* larvae excrete several antibacterial factors [53] and antimicrobial peptides [54-56] and maggot therapy has been demonstrated to act synergically with several antibiotics. In fact, when combined with maggot excretions/secretions, gentamicin minimum inhibitory concentration and minimum bactericidal concentration for *S. aureus* decreased, respectively 64- and 32- fold [57]. Moreover maggot excretions/secretions demonstrated to retain relevant anti-biofilm properties, also toward mature biofilm [58, 59] and biofilm is well known to delay wound healing [60]. Moreover maggot larvae are tolerant to maximum doses of antimicrobials [61]. In 2021 two cases of chronic wound infections caused by antibiotic resistant bacteria (carbapenem-resistant *Escherichia coli* and extended-spectrum beta-lactamase producing *E. coli*) and treated with maggot therapy were reported [62]. Given these premises the combination of maggot therapy and antibiotics for infected chronic wounds is appealing. A case-control study conducted in US patients with diabetic foot wounds found that patients who received maggot therapy had significantly more antibiotic-free days during the follow-up (126.8 ± 30.3 versus 81.9 ± 42.1 days; $P = .0001$) [63].

Another study that we can look at now with “stewardship eyes”, was published in 2004 and compared postoperative complications for patients who received presurgical maggot debridement ($n=10$) and for a matched group of patients who did not ($n=19$). No postoperative infections occurred in the maggot group while 32% of wound patients not treated presurgically with maggots developed postoperative wound infections (95% CI, 10-54%; $p<0.05$) [64].

It is likely that maggot therapy will be considered a full-fledged antimicrobial stewardship tool. Nar-

rowing analysis to chronic wounds infected with antibiotic resistant bacteria may bring out different cost effectiveness results.

■ CONCLUSIONS

The task of treating the suffering and human pain of war has always oriented the military medical mind more practically than theoretically, with a tendency to use what seems to work, regardless of the problems of acceptance [65]. MDT has been used in military medicine for centuries and has reached the civilian population only in the last one hundred years. It is always a question of time; cruel practices are accepted when they are necessary or clinically effective. It is our opinion that MDT should be studied in the field of antibiotic stewardship; especially in the context of chronic wounds infected with antibiotic resistant bacteria. In Mary Roach, in a brilliant book on the science behind war, states: “The maggot lives to eat”. We hope that in the near future we will be able to paraphrase the author and say: “The maggot lives to heal” [14]. Scalpels and broad spectrum antimicrobial agents in less than 100 mg [16, 66].

Conflict of interest

The authors declare no conflict of interest.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not for profit sectors.

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