Larval therapy from antiquity to the present day: mechanisms of action, clinical applications and future potential

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When modern medicine fails, it is often useful to draw ideas from ancient treatments. The therapeutic use of fly larvae to debride necrotic tissue, also known as larval therapy, maggot debridement therapy or biosurgery, dates back to the beginnings of civilisation. Despite repeatedly falling out of favour largely because of patient intolerance to the treatment, the practice of larval therapy is increasing around the world because of its efficacy, safety and simplicity. Clinical indications for larval treatment are varied, but, in particular, are wounds infected with multidrug-resistant bacteria and the presence of significant co-morbidities precluding surgical intervention. The flies most often used in larval therapy are the facultative calliphorids, with the greenbottle blowfly (*Lucilia sericata*) being the most widely used species. This review summarises the fascinating and turbulent history of larval therapy from its origin to the present day, including mechanisms of action and evidence for its clinical applications. It also explores future research directions.

In the twenty first century, when modern medicine fails, it is often useful to draw ideas from ancient treatments. The therapeutic use of fly larvae to debride necrotic tissue, also known as larval therapy,[1] maggot debridement therapy[2] or biosurgery,[3] dates back to the beginnings of civilisation. Despite repeatedly falling out of favour and the persistent public disdain which hampers its acceptance, the practice of larval therapy is increasing around the world because of its efficacy, safety and simplicity.[4] The flies most often used in larval therapy are the facultative calliphorids, with the greenbottle blowfly (*Lucilia sericata*) being the most widely used species.[5] Clinical indications for larval treatment include infected or necrotic wounds of all types. Candidates for the treatment generally have non-acute external wounds for which one or more courses of alternative treatments have failed.

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HISTORY OF LARVAL THERAPY

> 'My body is clothed with worms and scabs, my skin is broken and festering…'
> *The Holy Bible*, Old Testament, Job 7:5.

Larval association with infected wounds has been reported since ancient times, with the Old Testament being the oldest written piece to cite the infestation of an infected wound of a man by fly larvae (myiasis).[6]

Evidence exists that larvae have been used for the last thousand years by various ancient cultures, such as the aboriginal Ngemba tribe of New South Wales,[7] the Hill people of Northern Myanma (Burma)[8] and the Mayan healers of Central America.[9] Anthropological research suggests that the Maya soaked dressings in the blood of cattle and exposed them to the sun before applying them to certain lesions, expecting the dressings to squirm with maggots.[7]

The French surgeon, Ambroise Pare (1510–1590), was the first doctor to note the beneficial effect of fly larvae for wounds. His early descriptions, however, emphasised the destructive nature of the maggot, and he conscientiously tried to protect the wounds of his patients from infestation.[10 11] The turning point came when he observed a case of a deep wound that had penetrated a patient's skull. A number of months after the injury, a large number of maggots emerged from the wound. Although a piece of bone the size of a hand was lost, the patient nevertheless recovered.[10] After this, Pare would allow maggots to continue to survive in wounds for extended periods in an attempt to facilitate recovery.[10]

Another French surgeon, Baron Dominique-Jean Larrey (1766–1842), who treated the injured of Napoleon's army, observed that during the Egyptian expedition in Syria, maggots of the "blue fly" only removed dead tissue and had a positive effect on the remaining healthy tissue.[12] Larrey's written observations clearly described the role of fly larvae in wound cleaning.[8]

The first officially documented application of maggots was performed by John Forney Zacharias (1837–1901), a surgeon from Maryland during the American civil war (1861–1865):

> "During my service in the hospital at 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 used them afterwards at various places. I am sure I saved many lives by their use, escaped septicaemia, and had rapid recoveries."[13]

William Williams Keen (1837–1932), who was a surgeon of the army of the North States, also

reported the presence of fly larvae in wounds and noticed that, despite their sickness-inducing appearance, they had no disadvantageous effect.[14]

At this time, popular scientific belief was that maggots were ''dirty'' and introduced infections to wounds. The germ theory of the microbiologists, Robert Koch and Louis Pasteur, during the second half of the 19th century finally stopped any willingness of doctors to apply contaminated matter to an open wound. By the end of the 19th century, there were hardly any doctors left who would support the use of non-sterile fly larvae for the public.

During World War I, mortality from open wounds increased to 70%.[15] The available antiseptic tools were often not sufficient. In 1917, William S Baer, a military surgeon in France, reported his treatment of open fractures and stomach wounds with maggots. In 1929, during his appointment as Professor of Orthopaedic Surgery at the Johns Hopkins University, Baer recalled and utilised his experiences during the war.[15] He chose 21 patients with failed primary treatment for osteomyelitis. He exposed the wounds to maggots and found that, 2 months after the initiation of treatment, all of the patients' wounds had healed.[15]

Larval therapy was subsequently the fastest and most successful mode of treatment for chronic osteomyelitis. To minimise the disgust of patients, as well as staff, and to avoid the migration of larvae, doctors created net-cage bandages to cover and hide the larvae. To reduce the strong itching effect that larvae caused on healthy skin, Baer covered the border of wounds with a special bandage. However, the contamination of some wounds with *Clostridium tetani* and *Clostridium perfringens* led him to the conclusion that sterile maggots needed to be applied. Baer worked together with some colleagues to create specific flies for use in therapy and they developed a number of different methods to sterilise the eggs.[16]

A large number of Baer's colleagues disliked the use of maggots in wound healing as there was little knowledge of the mechanism of action. Once Baer died, Stanton Knowlton Livingston, one of Baer's students, became the authority in the field of maggot therapy.[17] Livingston was such a strong advocate that he used an extract as a vaccine for his patients, who often reacted badly.[18]

''Maggot therapy'' experienced a real boom from then on despite some doubtful experiments. Military doctors north of Burma during World War II observed the therapeutic application of the fly larvae by the local population.[19] More than 300 US American hospitals introduced maggots into their programme of wound healing between 1930 and 1940, and in this period more than 100 publications appeared.

Unfortunately for the proponents of maggot therapy, in the early to mid 1940s the use of sulphonamides was already widespread. Penicillin was produced industrially from 1944 onwards, and the development of new antiseptics led to a rapid decline in the use of larval therapy. With the exception of sporadic publications of hopeless cases where the use of fly larvae was successful,[20 21] the academic interest was lost. The public showed distain,[22] and in 1988 Wainwright brought the majority opinion to a point:

> ''…Fortunately maggot therapy is now relegated to a historical backwater, of interest more for its bizarre nature than its effect on the course of medical science … a therapy the demise of which no one is likely to mourn…''[23]

At the same time, Craig[24] described in the *US Army Special Forces Medical Handbook* that the use of fly larvae in military life-threatening situations was a useful alternative. Here the treatment of wounds with fly larvae was seen as a last therapeutic tool only in extreme situations.[25]

Larval therapy's renaissance in clinical practice started much sooner after this particular decline.[26] In the USA, Ronald Sherman and Edward Pechter have been strong advocates of the technique.[4 27] At the beginning of the 1990s, Sherman established a small fly-culturing facility in the Veteran Administration Hospital Medical Centre in Long Beach (California) to meet the need for the production of sterile larvae. In prospective controlled studies during the 1990s, maggot therapy was compared with conventional therapies in the treatment of wounds in patients with decubitus ulcers.[2] Maggot therapy led to a more rapid removal of debris than all other non-surgical treatments, and had a faster healing rate. In necrotic wounds with an average surface area of 13 cm^2 (5–30 cm^2), the healing rate was about 1.5 weeks on average, as assessed by the successful removal of debris, in comparison with 4 weeks for conventional methods.[2] Wounds that were increasing by 22% surface area per week before treatment with larvae reduced their area on average by 20% per week after its use. Furthermore, Sherman[28] experimented with different bandages in order to ensure optimal controlled clinical use of maggot therapy.

The renaissance of larval therapy in the United Kingdom can be attributed to John Church, a retired orthopaedic surgeon who, with Stephen Thomas, set up the Biosurgical Research Unit in Bridgend, South Wales. Since 1995, the unit has commercially distributed sterile larvae.[4] German and Belgian factories have distributed fly larvae in middle Europe since 1998. Since 1996, an annual world meeting on larval therapy, or biosurgery as it was then being called, has taken place. This meeting is called the International Conference on Biotherapy, organised by the International Biotherapy Society (IBS).

MECHANISMS OF ACTION

Most flies that facilitate myiasis belong to one of three major families: Oestridae, Sarcophagidae or Calliphoridae. Only a minority of the approximately 80 000 species have properties that enable medical use. Larvae of the greenbottle fly, *L sericata*, are currently used routinely.[29] The beneficial properties of this

Box 1: Milestones in the history of larval therapy

- The French surgeon Ambroise Pare (1510–1590) notes the beneficial effect of maggots
- The American Surgeon Forney Zacharias (1837–1901) officially documents their use during the American Civil War (1861–1865)
- In 1929, William Baer reports a case series of osteomyelitis treated with larval therapy based on his observations during World War I
- Ronald Sherman and Edward Pechter rediscover and promote the use of larval therapy in the USA in the 1990s

Box 2: Mechanisms of action

- Production of natural antibiotic-like agents
- Alkalinisation of wounds with secreted ammonia, inhibiting bacterial growth
- Injection of microorganisms
- Production of substances to induce wound healing

subtype of maggot include: exclusive feeding on necrotic tissues, congregation in vivo, and ability to breed and sterilise in vitro.[1] The key morphological features of medically important flies have been described by Lane and Crosskey.[30] The mechanisms by which larvae kill bacteria in wounds are not fully understood, but include the production of natural antibiotic-like agents,[31] the modification of wound pH, and the ingestion and destruction of bacteria as part of normal feeding processes. Growth-promoting agents have also been detected in larval secretions,[32] a finding that is consistent with the clinical observation that the introduction of larvae often causes a previously indolent wound to heal rapidly.

In order to debride necrotic tissue, larvae produce a mixture of proteolytic enzymes, including collagenase, which break down the necrotic tissue to a semi-liquid form, which can then be absorbed and digested.[33] Debridement is facilitated by wound disturbance as the larvae crawl around the tissue using their mouthhooks.[34] Their antibacterial properties are designed for self-defence; it is believed that they ingest microorganisms, which are then destroyed in their gut.[32] There is evidence that they secrete chemicals with a broad-spectrum bactericidal effect. They also secrete ammonia, causing wounds to become more alkaline, which is believed to inhibit bacterial growth. Further studies of the screwworm suggest that phenylacetic acid and phenylacetaldehyde produced by *Proteus mirabilis*, a commensal of the larval gut, may contribute to the antibacterial effect of larvae.[35 36] In vitro, live maggots kill or inhibit the growth of a range of pathogenic bacteria, especially *Staphylococcus aureus* and Group A and B streptococci. They show some activity against *Pseudomonas* species but none against *Escherichia coli* or *Proteus* spp.[37] Several substances secreted by maggots have been found to stimulate wound healing, with larval secretions inducing fibroblast migration into the wound space, facilitating tissue regeneration.[38] As a result, maggots eliminate odours and kill malignant tissue,[39] producing a clean wound, free from necrotic residues.[40]

CURRENT APPLICATIONS

Treated wounds decrease by an average of 4.1 cm ($p = 0.02$) over a 14-day period with larval therapy when compared with dressings alone.[41] This is accompanied by a reduction of necrotic tissue by 33% in a 4-week period.[41] Exudate, wound odour and pain scores are all significantly decreased when larval therapy is compared with conventional dressings.[42] Taking into account a number of clinical criteria, wound scores have been significantly improved when larval therapy is compared with dressings alone (a mean (SD) decrease of 13.5 (1.8) to 6.3 (2.7), $p<0.001$). Wound healing has also been shown to be significantly more rapid with the addition of larval therapy.[43]

There is evidence in the literature of the successful use of larval therapy for traumatic wounds that fail to heal, such as pressure ulcers, diabetic ulcers, decubital ulcers, neurovascular and vascular ulcers,[44 45] osteomyelitis,[46] florid necrotising fasciitis,[47] postsurgical wound infections, and burns.[48] Life-threatening temporal mastoiditis[20] and perineal gangrene[21] have also been treated with maggot therapy after unsuccessful antibiotic and surgical treatments. It has a role in the palliative care of certain types of tumour or fungating lesions when surgical intervention is not possible because of anatomical location or significant co-morbidity.[49] Larval therapy may be used for infections associated with peripheral vascular disease, although results are often poor in the late stages.[50]

The few contraindications to the use of larval therapy comprise restricted use around wounds with organs or blood vessels exposed, although they may be used around blood vessels with careful nursing observation. Caution should be used around fistulae. There is no evidence that larvae are affected by any antibiotic, chemotherapy or radiotherapy.[51]

Some authors advocate the use of larval therapy for the treatment of Fournier's gangrene[22] and even necrotising fasciitis,[34] but this is not to be advocated unless in conjunction with aggressive surgical debridement or when there are overwhelming clinical indications and circumstances precluding surgical intervention. Larvae have been reported to be a source of infection in themselves, so caution should be used for septic patients where their use may confuse the clinical picture.[52]

ADMINISTRATION OF LARVAE

To apply larval therapy, a wound-sized hole is cut out of hydrocolloid dressing, a self-adhesive wafer with an outer semipermeable membrane. This both protects the skin from irritation by the maggot's proteolytic enzymes and forms the base of the adhesive dressing.

The sterile maggots are then moved from their container on to a special piece of nylon netting placed on a non-woven swab to draw away moisture. The netting is then ''bunched up'' to create a cage for the larvae, which is then placed on the wound. This is stuck to the hydrocolloid dressing by waterproof adhesive tape. The dressing is finally covered with a simple absorbent pad held in place with adhesive tape or a bandage.

FUTURE APPLICATIONS

As public acceptance and medical awareness of larval therapy increases,[51 53] it may be more widely used for superficial infection in the future. Early application should be considered to clean up a problematic or infected wound, which in many cases would obviate the need for topical or systemic antimicrobial treatment.[4] In the face of ever increasing antibiotic resistance, chronic infections, immunosuppressive illnesses and diabetes, larval therapy may even become first line treatment for some infections, although it has stiff competition from novel techniques such as tissue engineering[54] and modern wound dressings such as vacuum therapy.[55] Early clinical experience suggests that it could be a formidable weapon against difficult cases of methicillin-resistant *S aureus*.[37 56 57]

Many current uses of larval therapy remain improperly assessed. Randomised trials for the efficacy of larval therapy are scarce, and there is a need to define acceptable criteria for clinical outcomes and guidelines for best practice before carrying them out.[5] The ongoing VenUS II trial will begin to

Box 3: Applications of larval therapy

- Any superficial wound excluding those with organs or blood vessels exposed
- Aggressive superficial infection in conjunction with surgical debridement and antibiotics
- Some types of fungating cancers

Box 4: Future directions

- Multidrug-resistant infections
- Early, community based application
- Prospective, randomised control trials
- Elucidation of exact mechanisms of action and application of this knowledge to create more efficacious treatments

provide answers to these questions.[58] Infected limbs with peripheral vascular disease often receive larval treatment as a last resort, when conventional treatments, including repeated courses of antibiotics, have failed. Early aggressive surgical debridement with intravenous antibiotics and larval therapy in combination may be more effective than these treatments alone. There is very little published work on maggot therapy for non-healing infected burns and tumours, where surgical intervention is contraindicated. Prospective, randomised controlled trials in these areas are indicated. Such trials would most likely need collaboration between multiple units to facilitate patient numbers and a suitable study power.

The biosurgical research unit in Wales produces sterilised eggs which have been raised through bacteria-free adult flies. If this can be scaled up, it will eliminate the need for time-consuming sterilisation procedures. Laboratory studies are underway to isolate and identify enzyme systems and antimicrobial agents produced by different species of fly, which may shed more light on the mechanism of action.[59] This research may yield topical or intravenous therapies with improved efficacy, without the need for maggot application.

As wound healing evolves and expands as a medical specialty, it should be possible to encourage more hospital practitioners to use larval therapy. As most wounds are treated in the primary care setting, there may be benefit in encouraging general practitioners to prescribe larval therapy in the home.[54] This should prove to be cost effective, decreasing hospital admissions and the need for surgical intervention.

CONCLUSIONS

From antiquity to the present day, it seems that the unassuming larva is being embraced by twenty first century mainstream western medicine and has a fixed base in literature and history.

Larval therapy can be used for any infection, but is currently used for problematic wounds that are often poorly responsive to conventional treatment. Increased awareness may facilitate its use in conjunction with established treatments, hopefully in the setting of prospective clinical trials.

Larval therapy benefits patients through rapid wound debridement, elimination of infection and odour, and possible prevention of amputation. It may decrease overall antibiotic use, prevent hospital admission, and decrease outpatient visits. From a pragmatic point of view, larval therapy is relatively cheap and may save money by those factors mentioned above and by reducing bed occupancy. As antibiotic resistance becomes increasingly prevalent,[60 61] this ancient remedy may once again be at the forefront of human survival.

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MULTIPLE CHOICE QUESTIONS (TRUE (T)/FALSE(F); ANSWERS AFTER THE REFERENCES)

1. With regard to the application of larval therapy:

(A) Larval therapy cannot be used for wounds containing methicillin-resistant *S aureus*
(B) Larval therapy is commonly applied as a first line treatment for venous ulcers
(C) Patients are averse to larval therapy as it increases odour
(D) Larval therapy may be used in patients undergoing chemotherapy
(E) Some antibiotics kill the larvae

2. With regard to the mechanism of action of larvae:

(A) The exact mechanisms are precisely mapped
(B) Ammonia is produced by the larvae
(C) Mouth hooks allow the larvae to hold their exact position once placed
(D) Enzymes produced by the larvae break down healthy tissue
(E) Larvae ingest microorganisms which are destroyed in their gut

3. To apply larval therapy:

(A) The maggots are placed in your hand during transfer
(B) A net cage is created to place the larvae in the wound
(C) A silicone dressing is used to hold the net in place
(D) The larvae must be in contact with the surrounding skin for proper debridement
(E) A non-woven swab is used to draw away moisture

4. Problems with larval therapy include:

(A) Public acceptance
(B) The therapy is usually painful
(C) It is very time consuming for nursing staff to look after
(D) A lack of randomised control trials
(E) The cost

5. Larval therapy may be used to treat:

(A) Any superficial infection
(B) Certain types of fungating cancers
(C) Infected burns
(D) Osteomyelitis
(E) Abdominal infections with exposed bowel

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ANSWERS

1. (A) F, (B) F, (C) F, (D) T, (E) F;
2. (A) F, (B) T, (C) F, (D) F, (E) T;
3. (A) F, (B) T, (C) F, (D) F, (E) T;
4. (A) T, (B) F, (C) F, (D) T, (E) F;
5. (A) T, (B) T, (C) T, (D) T, (E) F.