Larva Therapy in Modern Wound Care: A Review

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Summary

This is a review of the reintroduction of larva therapy (LT) into modern wound care. Subjects addressed include the relevant larval biology, laboratory requirements for production for clinical use, patient selection, dressing techniques, clinical results and prospects for the future.

Introduction

The major prerequisites to wound healing, particularly in chronic wounds, are thorough debridement, reduction in pathogenic bacterial populations and adequate blood supply. Larval activity in wounds is unique in that there is liquefaction and removal of necrotic material, with concurrent ingestion and destruction of the contained bacteria, and apparent enhancement of granulation tissue formation. No other topical wound agent delivers a continuous supply of active debridement enzymes while also destroying bacteria.

LT is the clinical use of the larvae (maggots) of the blowfly *Lucilia sericata* in the management of open wounds and ulcers. This treatment method has been revived in the past decade, ini-tially in the USA [1-3], then in Israel [4] and the UK [5-8] and now in other countries in Europe. Much has been achieved in inte-grating LT into a variety of clinical situations, but there is still a great deal to be learnt.

Historical Background

The presence of 'worms' in wounds has been recorded since Biblical times [9]. Throughout the greater part of history, maggot activity has quite understandably been associated mostly with disease and death. In the past 400 years, military surgeons have reported on maggot infestation of wounds. Paré gives remedies for extracting them [10], while Le Dran writes: "The worms that sometimes generate in wounds, indicate no evil" [11]. Larrey, sur-geon general to Napoleon, writes of the Egyptian campaign that the majority of the wounded were afflicted with maggots but, far from prejudicing the wounds, the maggots accelerated heal-ing and never caused haemorrhage [12].

After World War I, surgeons took a bold step in culturing selected flies in the laboratory and actively placing maggots in chronic wounds, at first mostly in deep wounds with osteomyelitis. There is extensive literature from that period, when 'maggot therapy' became well-established, particularly in North America. Baer, and others, reported remarkable successes [13-20]. The pharmaceutical company Lederle produced maggots com-mercially for therapeutic use [21], and they were distributed to over 200 hospitals in the United States. However, the advent of antibiotics, and their obvious efficacy and relative ease of use, eclipsed other methods of microbial control and this, together with improvements in surgery, led to the decline of LT for about 60 years. Now, with the increasing incidence of bacterial resistance to antibiotics, the great expense and protracted de-velopment of new antibiotics and the high cost of prolonged treatment, there is a critical need for a review of other methods of bacterial control, especially with respect to wound healing.

Larval Biology

The larvae of *Lucilia sericata* – which are about 1 mm in length when they emerge fully formed from the egg – can start feeding immediately. Effectively, they have only one function: to feed and grow. They develop in three stages, or instars, shedding their outer skin between stages. The first instar larvae are the most susceptible to environmental change. Their mobility is assisted by mouth hooks, which are also used when feeding. Larvae exhibit social behaviour, especially when feeding. By congregating, they generate an increase in temperature, which accelerates their metabolism and enables the sharing of exo-enzymes. They are naturally very mobile in their search for food or shelter when preparing to pupate. In nature, where their

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Picture 1. A lower limb ulcer, with black and yellow necrotic debris at its base, immediately prior to larval therapy.

Picture 2. Larvae being removed from the wound 3 days later. Note the clean, well-debrided ulcer base.

feeding environment can vary considerably, larvae will be found mostly where temperature, humidity and aeration are optimal and there is safety from predation.

Larvae are semi-aquatic when feeding – their mouth parts must be in a fluid medium for the optimal action of their exoenzymes. Equally, however, their posteriorly-placed spiracles must be exposed to air, to allow them to respire. They must also have sufficient freedom to select their food source and remain undisturbed while they feed. Larvae are opportunists – that is, they will feed on any organic material that is readily broken down and digested – and are capable of simultaneously breaking down carbohydrates, fats and proteins. Under optimal conditions the larvae of *Lucilia sericata* will acquire their full size and weight (10-14 mm and 100-fold increase in body weight) in 48-72 hours. While actively feeding, their gut tube contains brown or grey material, which is visible since they are semi-transparent. When they stop feeding their gut becomes fully transparent, indicating their pre-pupal state.

Larvae are obviously exposed to secretions in a wound. If these secretions contain toxic products they may have a deleterious effect on the larvae. Most drugs administered to a patient will be expressed to some degree in the wound secretions, but the effects of varying concentrations of antibiotics on larvae have been studied and it has been shown that they are not adversely affected by the dose ranges commonly used clinically [22]. However, it is not yet known to what extent other drugs in wound secretions may have adverse effects. Until more information is available, it is advisable where possible to reduce other medication during LT.

There are other ways in which the wound environment may adversely affect larvae. All wounds generate secretions, some perhaps only minimally but others profusely. Larvae will not feed in dried-out or waterlogged wounds. Further, tight dressings will constrict or crush them, and some dressing materials can affect their growth [23].

Generally, however, larvae can survive a wide range of environmental conditions, provided they are allowed enough mobility to be selective.

Photophobia

Larvae are naturally photophobic and tend to migrate and feed under eschar or skin edges, to the extent that in some wounds they may temporarily seem to have disappeared. Some clinicians have used bright light to encourage the larvae to remain in the depths of the wound [24], but this is probably not necessary.

Pupation

Once they have stopped feeding larvae must find an appropriate environment for pupation. In nature this will usually be in the sub-soil under a carcass, where they burrow to a depth at which temperature and humidity are optimal for pupation. In such conditions, adults emerge from the pupae in about 5 days. In adverse climates they remain in the soil over winter, generally in the pre-pupal stage.

Adults

Adults can survive on sugar and water but need protein to become sexually mature and for female egg production. Females will lay up to 1000 eggs, in batches of 100-200, over a 3-week period. They survive for longer periods but their reproductive capacity declines after about 3 weeks. The whole cycle, egg to egg, can take as little as 16 days.

The Fly Culture Laboratory

The basic requirements for a fly culture laboratory are relatively simple but, to meet the high standards demanded of the clinical use of larvae, a number of factors must be considered [7, 8]. The adult flies must be caged in such a way that a mono-culture can be maintained. Environmental conditions, lighting, humidity and temperature should be controlled but need not be rigidly so. The most important prerequisite is that the larvae leaving the laboratory be supplied in bacteria-free containers. They will then need to acquire their hind gut microbial commensals but it is assumed that these will normally be found in chronic wounds.

The fly culture laboratory should be central to the area or region to be supplied. The laboratory established in the Surgical Material Testing Laboratory, Bridgend, UK is capable of culturing the flies in a bacteria-free state at every stage of their development cycle. This laboratory now has a mailing list of about 400 and has sent out over 3500 containers of bacteria-free larvae to destinations mostly in the UK but also, more latterly, in Europe. Postal and courier services in the UK have been used for delivery. Provided containers are well-aerated and kept humid and cool, and transit times are within 48 hours, larval survival rates can be kept high.

Though it is relatively inexpensive to culture flies, the laboratory standards required and the labour-intensive aspects of rendering the eggs and larvae bacteria-free prior to delivery necessitate appropriate staffing.

Picture 3. Staff in the 'biosurgery' laboratory in Bridgend, with the fly cages behind them *[photos courtesy of Andrea Andrews, lab manager (lower left) and Mary Jones, senior clinical research nurse (right)]*.

Patient Selection and Management

The author is not aware of any publications that provide guidelines on patient selection for LT. However, most patients with open wounds or ulcers containing infected, necrotic or semi-necrotic material can be considered for it. Conditions most commonly treated this way are diabetic foot ulcers and gan-grene, leg ulcers from vascular disease (arterial and venous), pressure sores and amputation sites. Other, less common conditions include fungating tumour ulcers and necrotizing fasciitis.

Because of its distinctive nature, LT has tended to be considered only as a last resort when standard treatment methods fail. However, the primary cause of chronicity in many wounds is the continuing presence of infected necrotic material, particularly if this is tethered to deeper structures. Thus, there is a place for LT to be administered at an earlier stage, and even in some cases as part of initial wound care. It should now be considered not as an alternative to established treatment methods but, rather, as an integral part of an overall treatment plan that may also necessitate other interventions, such as medication and surgery. This could include local surgery, such as skin grafting, and surgery at a distance, such as vascular reconstruction of a lower limb.

Since modern wound care is usually multidisciplinary, the ideal is for a given clinician – working with nurses trained in the wound dressing techniques – to take on the LT service, offering it to many departments within hospitals, and the community.

When a patient is initially assessed a treatment plan should be outlined, with the timing and expected duration of LT taken into account. It does not necessarily have to be undertaken in a hospital; it could be undertaken prior to admission to hospital for further treatment. A treatment 'cycle' – the period the larvae are in the wound – is generally 48-72 hours, depending on larval growth. Most patients will only need one or two cycles of treatment, lasting 2 to 3 days. However, some with complex wounds may need 10 cycles or more. Some conditions, such as diabetes, are progressive and may necessitate a number of sessions of LT, with intervals in between.

When LT is first advised some patients, and their carers, are naturally cautious about or opposed to such treatment. But, with sensitive explanations and an awareness of its efficacy – for instance, in overall reduction of wound pain and odour and accelerated healing rate – patients will not only accept it but positively collaborate in their wound management.

Dressing Techniques

These are relatively straightforward but have specific and well-documented, prerequisites [8]. Wound edges are protected by a hydrocolloid dressing or zinc-paste bandage, after which a nylon mesh is placed over the whole wound and secured. This confines the larvae but permits aeration and release of secretions, and is sufficiently transparent to permit observation and monitoring of larval activity. An absorbent superficial dressing is generally applied and changed as necessary. The arrangement of the dressing material can be complex in awkward situations or extensive wounds. If patients are otherwise mobile they can continue to be so, avoiding undue direct pressure on the wound and, if sitting or lying, adopting a posture that allows optimal drainage of the wound secretions.

Clinical Results

Clinical outcomes in LT can be defined as follows.

(i) **Complete**, where no further specific treatment is required after LT and there is full debridement and epithelialisation, leading to a stable, pain-free scar with no subsequent breakdown.

(ii) **Temporarily complete**, where a pain-free scar remains healed (as above) for a period but subsequently breaks down again.

(iii) **Relatively complete**, where LT debridement and reduction of wound infection allow further successful, specific treatment, such as skin grafting.

(iv) **Significantly beneficial**, where, although full wound healing has not occurred, there has been considerable long-term pain and odour relief, improvement in mobility, cessation of other treatments and early return home.

(v) **Partially beneficial**, where there has not been full wound healing but some improvement in the patient's clinical state, with reduction of specific symptoms such as pain, odour and wound secretion.

(vi) **Economical**, where LT is clearly cost-effective in comparison with other, similar wound treatment methods.

(vii) **Failed**, where LT is used inappropriately or is followed by no improvement, significant complications, morbidity or mortality.

With over 1500 patients treated this way in the UK over the past 4 years, individual clinicians and hospitals are now reporting on their clinical results. Reports to date – as presented at scientific meetings or by direct communication – have been uniformly positive, with the majority of patients benefiting from the treatment. Most would fit into categories (ii) to (vi) above.

Results for the first 33 patients with mixed aetiology treated with LT in the Churchill Hospital, Oxford, UK were as follows:

- 22 had varying grades of successful debridement, category (i) and (ii) above;
- six had no debridement, but these were mostly patients in whose deep pressure sores copious wound secretions drowned the larvae;
- three discontinued the treatment because of pain or for psychological reasons, and
- for two the results were inconclusive.

In a small 10-patient study of punch grafting immediately after LT, seven healed (two slowly) and in three treatment failed [25].

Analysis of 100 questionnaires sent out from the Bridgend fly culture laboratory has provided the following data.

- **Wound types**:
  - leg ulcers 55 per cent
  - pressure ulcers 26 per cent
  - necrotic toes or feet 8 per cent.

- **Wound condition prior to LT**:
  - 'sloughy' 90 per cent
  - 'necrotic' 38 per cent.

- **Wound condition following LT**:
  - 'completely debrided' 35 per cent
  - 'partially debrided' 55 per cent.

The number of treatment cycles was from one to five (median two), with granulation tissue present after debridement in 86 per cent of cases [2].

Studies on the clinical outcomes of LT are in progress in the UK. An initial report on these studies has been presented [26], with fuller reports to be published in the future [27].

Cost-effectiveness

In the UK, 'skin failure' is rapidly becoming "the National Health Service's costliest problem" [28]. Management of patients with long-term chronic ulcers, particularly when hospitalised, is expensive. LT may well prove to be cost-effective here in that it can be undertaken as much in the community as in hospitals; it can lead to a reduction in the need for antibiotics and consumables and release the staff, nurses and surgeons who would otherwise devote time to caring for such patients. Probably its most cost-effective aspect is when major surgery, such as below-knee or mid-thigh amputation, can be postponed or prevented.

A pilot study on LT's cost-effectiveness in chronic wounds has shown that it can reduce costs by up to 50 per cent [29]. It is estimated that, in the UK, the overall cost of a mid-thigh amputation – as might have to be performed for a diabetic patient with gangrene of the foot – is £50,000. There is anecdotal evidence that a number of patients have been saved from such major surgery, with larval activity leading to loss of toes but salvage of the foot. Such patients would fall into categories (ii) and (vi) above.

Complications

While no life-threatening complications have been reported to date, reported undesirable side-effects include pain, bleeding, dermatitis, fever, escapees and the potential for adverse immunological response.

Pain

Patients with a severe neurological deficit, such as paraplegics, will have no sensation in their wounds and will thus feel nothing during LT. Patients with painful ulcers, such as most of those with arterial insufficiency to the lower limbs, must be warned that pain might increase during treatment. This can be caused mechanically by migration of the larvae around the wound, par-ticularly when they are larger toward the end of treatment. Such pain can usually be treated adequately with appropriate pain relief. To lessen the risk of pain, treatment can be restricted to 24 hours, but several treatments with smaller larvae might then be necessary.

Bleeding

Larval activity in wounds does not usually cause bleeding. Reported cases have been mostly in the lower limbs and only to a minor degree. No severe bleeding has been reported. Bleeding generally responds to larvae removal and appropriate, simple haemostatic treatment, elevation of the part and local pressure.

Dermatitis

When confined to a wound with a restrictive dressing, larval feeding will be directed primarily at necrotic material; larval enzymes can, however, extend onto the surrounding skin, causing temporary dermatitis. This can usually be prevented by adequate protection of the wound margins.

Fever

Temporary pyrexia, limited to the time of treatment, has been reported in a few patients, but as yet with no identifiable cause.

Escapees

Wound dressing techniques and material are designed to keep larvae within the wound throughout the treatment period. If they do escape this may cause consternation, but they are harmless and can be readily destroyed.

Potential for adverse immunological response

With the profuse exo-enzymatic secretions elaborated by the larvae, it is to be expected that, in time, adverse immunological responses might be observed in some patients, particularly those who have had antecedent LT. However, there are as yet no re-ports of severe anaphylactic or local tissue reactions to larval activity in wounds.

Recent International Developments

Sherman reintroduced maggot (larva) therapy in California in 1990 and is the latter-day pioneer in this work [1-3, 23]. In 1995 he reported on his work at a European Tissue Repair Society work-ing party on wound debridement [5]. Following this, clinical trials were initiated in Oxford [25]. There was considerable media interest, which had a marked impact on public awareness and positively influenced the development of LT in the UK, leading to over 120 patients directly requesting treatment at that time.

International Biotherapy Society

The First World Conference on Biosurgery was held in May 1996. At the end of it the International Biotherapy Society (IBS) – whose object is to harness and use whole organisms, such as larvae and leeches, in modern medicine – was inaugurated. The IBS has held annual conferences ever since Dr Mumcuoglu hosted the third IBS conference in May 1998, and has reported on his work with LT in Israel [4].

Since 1995 there has been increasing interest in the use of LT in other European countries, notably Germany and Sweden, and several laboratories now supply larvae to centres in Germany. The most individually enterprising work in this respect is being done in the Ukraine, where Dr Markyvevich, despite financial and other constraints, has set up a small personal laboratory. By the time he reported on his work he had treated 30 patients [30].

Future Prospects

LT is now established in modern wound care, with larvae provided by dedicated fly culture laboratories in North America, Europe and Israel. The expectation is that there will be a steady increase in demand for LT, particularly as its efficacy and cost-effectiveness become more widely recognised. There remains, however, understandable caution and scepticism among clinicians, which can only be overcome by the positive findings of prospective clinical trials, which demand multi-centre collaboration, funding and time.

There is an overwhelming need for improved wound care facilities in countries medically under-provided for, mostly in the tropics; the hope is that once the advantages of LT are perceived in the developed world, low-cost local fly culture laboratories will be established in regional centres in the tropics, with a largely community-based service [31].

Global horizons for this work are expanding, as much in the clinical arena as the laboratory, and there is a great deal still to be discovered.

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Web sites

The laboratories in California, Israel and Wales now have Web sites, as follows.

- Dr Sherman, at <http://www.com.uci.edu/~path/sherman/home_pg.htm>.
- Dr Mumcuoglu, at <http://www.md.huji.ac.il/depts/parasitology/p-3-7.html>.
- Dr Thomas at <http://www.smtl.co.uk/>.

References

1. Sherman RA & Pechter EA. Maggot therapy: a review of the therapeutic applications of fly larvae in human medicine, especially for treating osteomyelitis. Med & Vet Entomol 1988; **2**:225-30.
2. Sherman R, Hall M & Thomas S. Medicinal maggots: an ancient remedy for some modern afflictions. Ann Rev Entomol. (In press)
3. Sherman RA, Wyle F & Vulpe M. Maggot therapy for treating pressure ulcers in spinal cord injury patients. J Spinal Cord Med 1995; **18**(2):71-74.
4. Mumcuoglu KY, Ingber A, Gilead L, Stessmann R, Friedmann R, Schulman H, Bichucher H, Ioffe-Uspensky I, Miller J, Galun R & Raz I. Maggot therapy for the treatment of diabetic foot ulcers. Diab Care 1998; **21**(1):2030-31.
5. Church JCT. ETRS working party consensus paper on wound debridement. Surgery 1995; **13**(10):228c-d.
6. Church JCT. Biosurgery. J Wound Care 1996; **5**(2):51.
7. Thomas S, Jones M, Shutler S & Jones S. Using larvae in modern wound management. J Wound Care (Suppl) 1996; **5**(2):60-69.
8. Thomas S, Andrews A & Jones M. The use of larval therapy in wound management. An update and detailed guide on the use of sterile larvae in chronic or infected wounds. J Wound Care 1998; **7**(10):521-24.
9. Job 7:5 Authorised version. 'My flesh is clothed with worms and clods of dust, my skin is broken and become loathsome'.
10. Pare A. Les Oevres d'Ambroise Pare 1579; Les Oevres d'Ambroise Pare 1652; 11A. Lyon; Pierre Rigaud. Translation from the Latin by Theodore Johnson 1678. London, Clark; X:249: XI:277. Selections from the Works of Ambroise Pare. By Singer 1924 p218.
11. Le Dran HF. A Treatise, or Reflections, Drawn From Practice, on Gun-shot Wounds. Printed for John Clarke under the Royal Exchange Cornhill, 1743 pp 174-75.
12. Larrey & Barron DJ. Observations on Wounds, and Their Complications by Erysipelas, Gangrene and Tetanus, etc. Translated from the French by EF Rivinus. Philadelphia: Key, Miekle and Biddle 1832 p34. Paris: Clinique Chirurgicale (Novembre) 1829 pp51-52.
13. Baer WS. The treatment of chronic osteomyelitis with the maggot (larva of the blowfly). J Bone Joint Surg 1931; **13**:438-75.
14. Buchman J & Blair JE. Maggots and their use in the treatment of chronic osteomyelitis. Surg Gynecol Obstet 1932; **55**:177-90.
15. Goldstein HI. Live maggots in the treatment of chronic osteomyelitis, tuberculous abscesses, discharging wounds, leg ulcers, and discharging inoperable carcinoma. Inter Clin 1932; **4**:269-81.
16. Livingston SK. Maggots in the treatment of chronic osteomyelitis, infected wounds, and compound fractures. Surg Gynecol Obstet 1932; **54**:702-06.
17. McLellan NW. The maggot treatment of osteomyelitis. Can Med Assoc J 1932; **27**:256-60.
18. Wilson EH, Doan CA & Miller DF. The Baer maggot treatment of osteomyelitis. Preliminary report of twenty-six cases. JAMA 1932; **98**:1149-52.
19. McKeever DC. Maggots in treatment of osteomyelitis – a simple, inexpensive method. JBJS 1933; **15**:85-93.
20. Robinson W. Progress in maggot therapy in the United States and Canada in the treatment of suppurative diseases. Am J Surg 1935; **29**:67-71.
21. Surgical maggots – Lederle. JAMA 1932; **98**:401.
22. Sherman RA, Wyle FA & Thrupp L. Effects of seven antibiotics on the growth and development of *Phaenicia sericata* (Diptera: Calliforidae) larvae. J Med Entomol 1995; **32**(5):646-49.
23. Andrews AM, Thomas S & Wilson M. The effect of hydrogels on maggot growth. Wound Repair and Regeneration 1998; **6**(5):A496.
24. Betune N. A case of chronic thoracic empyema treated with maggots. Can Med Assoc J 1935; **32**:301-02.
25. Doe PT, Hodman D, Church DUCT, Cherry G & Ran TAJ. Larvae and their use in chronic wounds – Experience in Oxford, 1997. (Unpublished report)
26. Courtesy M. Larva therapy in the UK. A review of clinical experiences to date and prospects for the future. Wound Repair and Regeneration 1998; **6**(5):A463.
27. Courtenay M. The use of larval therapy in wound management in the UK. J Wound Care 1999; **8**(4):177-79. (In press)
28. Dawe V. Health service pays high price for skin failure. Hosp Doctor 10 August 1995.
29. Walker M. 10.3.99. Personal communication.
30. Markyvevich Y. The use of larval therapy on diabetic patients in the Ukraine. Symposium on Chronic Wounds: Active Solutions, Pawthcawl, 18-19 June 1998.
31. Ryan TJ. The benefit of maggot debridement in the 1990s. Scars and Stripes. The News letter of the Wound Healing Society 1997 7(1):11-12.