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# Use of maggots in the care of WOUNDS

By STEVE THOMAS, PHD, FRPHARMS, and PAMELA McCUBBIN, BSc, PhD

Most people, health professionals included, would be concerned at the thought of leaving 300 maggots to roam free on any sort of wound. The final article in our special feature discusses this unusual form of treatment

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Introducing maggots into open wounds helps to prevent or combat wound infections by taking up and destroying bacteria

The wound-cleansing properties of maggots were first used in Western medicine by surgeons during the American Civil War, although their effectiveness in preventing infection in battle injuries had been recognised for centuries.<sup>1</sup> From the end of the 1914–18 war until the dawn of the antibiotic era in the 1940s, maggots were widely used in clinical practice to treat osteomyelitis<sup>2–8</sup> and chronic or acutely infected soft tissue injuries, including

abscesses, carbuncles,<sup>2</sup> leg ulcers, pressure ulcers, mastoiditis,<sup>9</sup> and compound fractures.<sup>2</sup>

The use of maggots in clinical practice was revived in the United Kingdom in 1995 when the Biosurgical Research Unit (BRU), part of the Surgical Materials Testing Laboratory, was established in the Princess of Wales Hospital in Bridgend, specifically to produce sterile maggots for use in wound management.

The BRU has since supplied over 20,000 treatments under the brand name LarvE to more than a thousand centres. Several reviews on maggot therapy have also been published, which describe in detail the his-

tory of the technique and the mechanisms of action of maggots.<sup>1,10,11</sup>

## MECHANISM OF ACTION

Maggots secrete a powerful mixture of proteolytic enzymes that break down slough and necrotic tissue into a semi-liquid form that they can ingest. During this process, the actively feeding maggots also take up and destroy bacteria, and thus help to prevent or combat wound infections,<sup>12–16</sup> including those caused by antibiotic-resistant organisms such as methicillin-resistant *Staphylococcus aureus* (MRSA).<sup>17,18</sup>

## EVIDENCE

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Several papers have described the use of maggots in a variety of wound types, including pressure sores,<sup>11,19,20</sup> leg ulcers,<sup>11,20</sup> diabetic foot wounds,<sup>11,21-26</sup> traumatic wounds,<sup>20</sup> various types of surgical wounds,<sup>27-29</sup> burns,<sup>30</sup> an infected insect bite<sup>31</sup> and necrotising fasciitis of the neck.<sup>32</sup> One study also presented convincing evidence for the cost-effectiveness of sterile maggots compared with the use of a hydrogel dressing designed to promote autolytic wound debridement in the treatment of venous leg ulcers.<sup>33</sup>

#### PRESENTATION

LarvE is supplied as sterile pots containing approximately 300 maggots. The pots are secured with a cap bearing a membrane filter that allows the passage of air but which prevents the ingress of micro-organisms. Recently, maggots have also been made available in net bags that resemble tea bags, and although these appear to offer practical advantages in terms of ease of application and removal, research has shown that even on relatively flat or open wounds, the feeding mechanisms and therefore the growth rate of maggots applied in this way are significantly impaired when compared with the "free-range" variety. This obviously has important implications for their wound debriding activity.<sup>34</sup>

For cavity wounds, sinuses, or wounds with a significant degree of undermining, experience suggests that maggots in bags will do little to facilitate debridement or combat infection. It is strongly recommended, therefore, that the use of maggots in bags be restricted to situations where the application of free-range maggots is contra-indicated by the nature or position of the wound (eg, pressure sores close to the anus). It should also be remembered that the plethora of evidence in support of the clinical use of maggots previously cited relate to the use of free-range maggots and cannot be used to support the effectiveness of maggots applied in net or foam bags.

A simple calculator has been devised to provide practitioners with general guidance on the number of pots required for a particular patient. This takes account of the size of the wound and the amount of slough present.<sup>35</sup> Copies of this calculator are available upon request from the BRU.

#### LEGAL STATUS

When the BRU first began to produce sterile maggots for medicinal use, guidance was sought from both the Medicines Control Agency and the Medical Devices Agency about the legal status of such maggots. The advice received indicated that sterile maggots, like leeches, were not classified as medicinal products or med-

ical devices as defined by the relevant legislation and therefore were not subject to any regulatory control. As a result, maggots offered for medicinal use can, in theory, be produced under uncontrolled conditions by individuals with no knowledge of the basic requirements of good manufacturing practice.

#### QUALITY ISSUES

Despite the lack of regulatory control, the BRU decided to apply the highest possible quality standards to the production of LarvE, by drawing upon the pharmaceutical and microbiological expertise available in the department.

Sterile maggots are produced by chemically sterilising the eggs of the greenbottle fly, *Lucilia sericata*, which are collected on the liver of pigs from adult flies kept in cages in the laboratory. The sterilised eggs are allowed to hatch upon a sterile agar-based substrate and the young larvae are transferred into sterile containers to await delivery by courier. Some quality issues that should be given attention include the use of the correct species of greenbottle fly and the maintenance of the sterility of the maggots.

The identity of the fly species used at the BRU has been confirmed by the entomology department of the Natural History Museum in London.

Manipulation of the sterilised eggs and the young hatchlings is performed inside laminar airflow cabinets by staff trained in aseptic technique. Maggots, being living organisms, have a limited "shelf life" and unlike most pharmaceutical products, cannot be placed in quarantine for 14 days while awaiting the results of a full sterility test. The sterility of the maggots is therefore assured by process validation and careful monitoring of the microbiological status of each batch at every stage of the production process. All aspects of maggot production and distribution are comprehensively documented so that should a batch recall be necessary, this can be accomplished easily and effectively, assuming of course that the maggots have not already been applied to a wound.

As part of the production validation process, some batches of maggots are tested for the presence of endotoxins, which are components of the cell wall of Gram-negative bacteria. Endotoxins, which are heat stable and not destroyed by most sterilisation methods, are potent modulators of the human immune system, causing monocytes in the blood stream and related tissue macrophages to release fever-inducing mediators such as interleukin-1. The testing is performed in the laboratory using the *Limulus amoebocyte lysate* (LAL) technique, which uses an aqueous extract of blood cells from the horseshoe crab *Limulus polyphemus*. In the presence of endotoxins, proteins in LAL are activated. This then initiates a cas-

cade of reactions resulting in the formation of a clot that is preceded by a change in turbidity. The development of this turbidity is measured quantitatively using a kinetic turbidometric technique.

Endotoxin levels in the maggots are measured because they provide a useful indicator of the general "cleanness" of the final product. The measured levels of endotoxins on LarvE, determined in this way, are well within the recommended limits for medical devices.

#### YELLOW CARD REPORTING

Each container of LarvE now contains a "yellow card" that clinicians are encouraged to complete and return to the BRU. This card has been designed to obtain information on treatment outcomes and adverse events associated with novel forms of therapy.

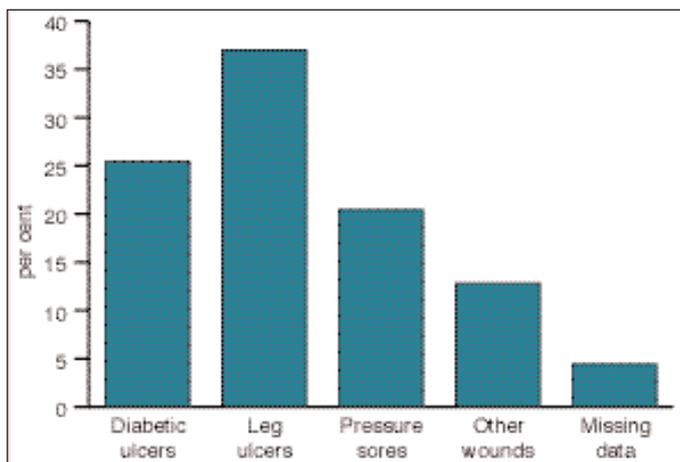
The container is also accompanied by a Databank that describes, among other things, the method of use and contraindications. To date, a total of 343 yellow cards have been returned, which represents about 2 per cent of the number of cards sent out. Some of the findings from these returned cards are described below.

In all, 51 per cent of the patients were female and 43 per cent were male. The gender of the remaining 6 per cent was not recorded. The majority of treated wounds were leg ulcers, but significant numbers of diabetic ulcers and pressure sores were also dressed with maggots (Figure 1, p269). Most wounds (about 90 per cent) were described as "sloughy" although a significant number also contained necrotic tissue. Not surprisingly, many wounds were also described as infected or malodorous (Figure 2, p269). In addition, 56 per cent of wounds only had a single application of maggots. A further 28 per cent had two applications and 7 per cent of wounds had three applications. The remaining wounds had four or more applications, apart from the 4 per cent for whom no data were provided.

The total number of pots applied to each wound is shown in Figure 3 (p270), which indicates that the majority, about 68 per cent, had a maximum of two pots applied throughout the treatment.

Treatment outcomes are summarised in Figure 4 (p270). These outcomes indicate that 25 per cent of wounds were fully cleansed with a single application of maggots and a further 58 per cent were improved by the treatment. Only 4 per cent of wounds were said to have deteriorated during maggot therapy.

The effect of maggot therapy on wound pain was also investigated. Figure 5 (p270) shows that 25 per cent of patients experienced increased discomfort with maggots, although 17 per cent reported a reduction in



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Figure 1: Wound types

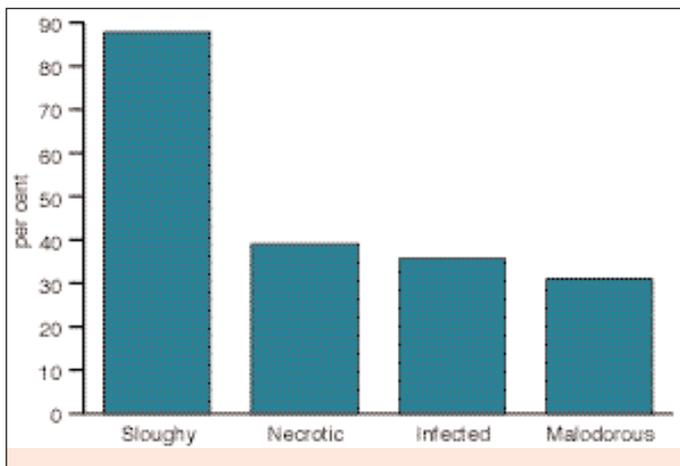


Figure 2: Description of wounds before treatment

pain. A more detailed analysis of the data revealed that an increase in wound pain was most likely to occur in patients with leg ulcers. This confirmed the results of previous observations that patients with ischaemic leg ulcers often required additional analgesia when treated with maggots. A reduction in pain was most commonly noted with pressure sores. There were a total of 60 adverse events recorded. Of these, 27 related to increased wound pain, and seven to bleeding from the wound. In one case it was reported that a patient was pyrexial during maggot therapy. The remaining adverse events included poor survival of the maggots, problems with "escapee" maggots and irritation of surrounding skin by wound exudate.

When clinicians were asked to rate the success of the maggot treatment, 248 (72 per cent) rated the treatment as good or very good (Figure 6, p270). Only 33 of them (11 per cent) rated it as poor or very poor. This was largely due to maggots failing to survive (16). Some of the other reasons include maggots escaping (3) and the pain associated with treatment (3).

**DISCUSSION**

In their natural state, flies and maggots are heavily contaminated with bacteria, which must be eliminated if they are to be used in the treatment of human wounds. The BRU is continually improving its production techniques to ensure that the maggots it provides are free from bacteria and their breakdown products and thus suitable for their intended purpose.

The success of treatment with LarvE has been such that most practitioners have now accepted that sterile maggots represent a cost-effective alternative to the use of hydrogels or enzymatic agents for cleaning infected or necrotic wounds and, in extreme cases, the only alternative to surgical intervention, including ampu-

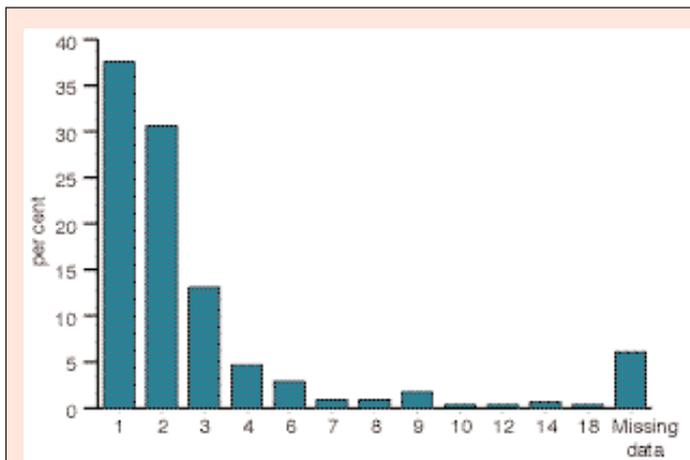


Figure 3: Total number of pots applied per wound

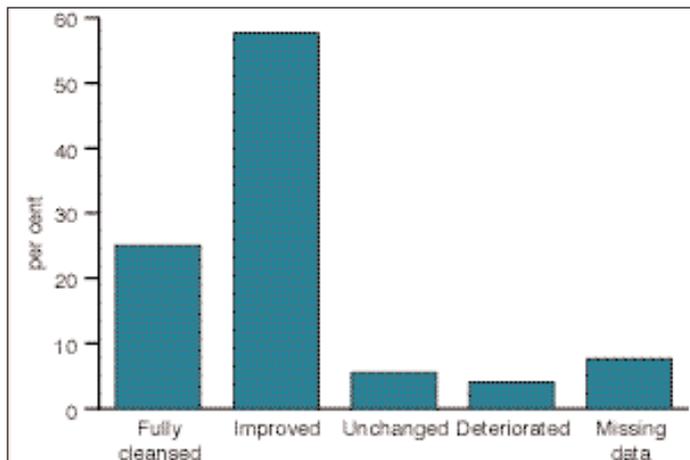


Figure 4: Treatment outcomes

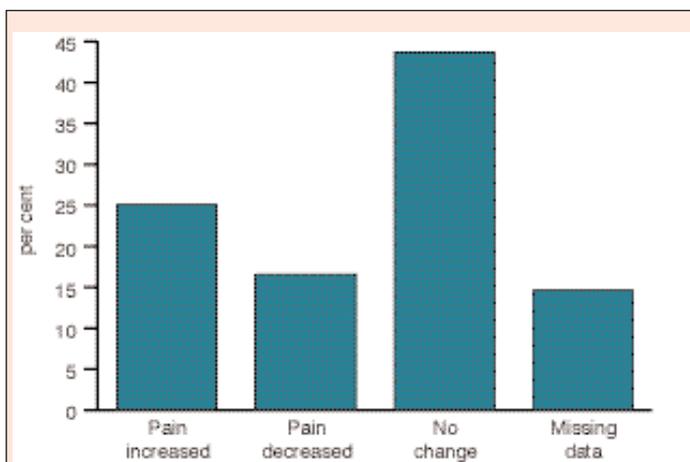


Figure 5: Effect of maggots on wound pain

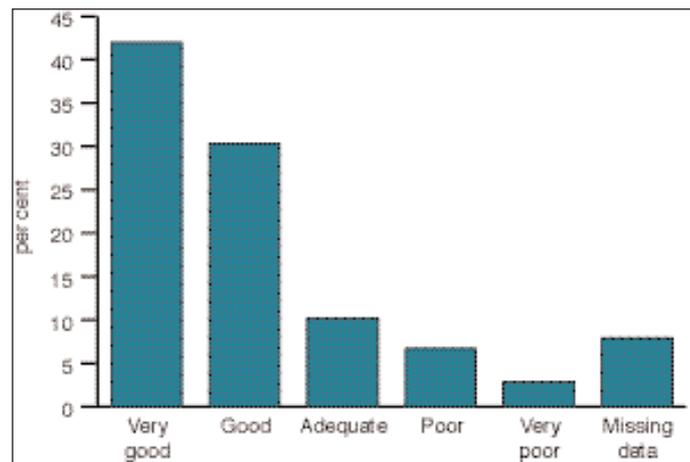


Figure 6: Overall success of LarvE treatment

tation. Although large randomised controlled trials have yet to be undertaken, the analysis of yellow cards provides further support for the benefit of maggots. However, it is recognised that information obtained by the use of forms such as yellow cards may be less reliable than that produced by the use of more structured data collection systems.

The yellow cards used for reporting are entitled "Feedback/adverse event reporting form". Therefore, it is not unreasonable to suggest that they would be used to report adverse events more frequently than favourable treatment outcomes. In practice, however, this does not seem to be the case, as the results of the analysis show. Of particular importance is the finding that 25 per cent of wounds were fully cleansed, the majority with a single application of maggots lasting about two to three days, and a further 58 per cent were improved. This compares favourably with debridement rates achieved with hydrogels of 21 per cent in three weeks or 33 per cent in 28 days.<sup>36</sup>

The most important criticism of maggot therapy is that it can increase wound pain, particularly in ischaemic leg ulcers. These are frequently already quite painful. This problem can often be overcome by increasing the patient's analgesia, removing the maggots from the wound after two days instead of three or by using a reduced num-

ber of maggots. In some instances, however, there is no alternative but to terminate treatment prematurely. The other important, albeit relatively rare problem, is that of bleeding from the wound. The real incidence of this is not known, but it was reported on seven of the yellow cards returned to the BRU. It is assumed that if this was regarded as a significant problem, all or most incidents would be reported. In percentage terms therefore, bleeding probably occurs in less than 0.1 per cent of wounds treated. Despite these problems, however, it is reassuring to note that 72 per cent of users rated the treatment as good or very good. Even though the use of maggots in "tea bags" is an attractive concept, it is not recommended for routine use because treatment times are greatly extended, but if circumstances prevent the use of free-range maggots, the BRU can provide them in this way if required.

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