MRSA, macrophages and maggots

Sarah Brocklesby

Introduction

The current problem of antibiotic resistance and the difficulties in controlling MRSA infection have led to increasing interest in maggot therapy for wound healing. The physiology regarding maggot therapy is not yet fully understood. This review explores what is known, as well as the physiology of wound healing. Maggot therapy appears to be successful because of its effect on pH and from mechanisms involving its secretions and its digestive system. The maggots also have an effective debriding action and growth-promoting effects.

Maggot therapy was used extensively, in wound healing, in the 1930s and 40s until the introduction of antibiotics made it obsolete.

However, the current problem of antibiotic resistance and the difficulties in controlling MRSA (methicillin-resistant *Staphylococcus aureus*) infection have resulted in an urgent search for alternative treatments, and hence an increasing use of maggot therapy once more. However, the physiology of maggot therapy is not yet fully understood.

Wound healing

Wound healing is an important physiological process, essential for the survival of all species (Ionoco et al, 1998). Shakespeare (1996) pointed out that the best wound care techniques assist the body's own healing process to progress to full healing. Research to date shows a harmony between the physiological action of maggot therapy and wound healing physiology that has not previously been acknowledged.

Maggots and wounds

Maggot therapy has been used for a wide range of wounds since its introduction as a therapeutic treatment for chronic pyogenic and tuberculous osteomyelitis (Baer, 1931). In the 1930s and 40s maggots were used extensively to treat suppurative infections including abscesses, burns, gangrene and chronic leg ulcers (Livingston and Prince, 1932). It has also been used for necrotic tumours (Bunkis et al, 1985), mastoiditis (Horn et al, 1976) and necrotising fasciitis (Gacheru, 1998).

Antibiotics and MRSA

Maggot therapy was dropped in favour of antibiotics, which were easier to administer and thought to be the definitive answer to the treatment of infection. Unfortunately, it has become apparent that bacteria have the ability to enhance their resistance to the agents employed to eradicate them — this is currently regarded as a major threat to public health (Wise et al, 1998). MRSA in particular is a major problem in wound healing. The tables may be about to be turn back in favour of maggot therapy in order to address this problem. The current strategy to minimise the use of antibiotics in medicine has resulted in a resurgence in the use of maggot therapy, making it vital that the physiology of such therapy be understood in order to fulfil modern requirements of evidence-based practice.

Entomological considerations

Myiasis is a condition caused by the infestation of fly larvae, which feed on, and therefore destroy, the dead or living tissues of a live host (Hall, 1995). The fly causing this condition can be classified according to its preferred feeding habit: live tissue (obligate parasites), or decaying organic matter, such as carrion or rotting vegetation (facultative parasites). Facultative parasites prefer to feed on dead material but can also lay

ARTICLE POINTS

1. Good wound care techniques assist wound healing physiology.
2. Maggots eradicate bacteria, debride wounds and facilitate faster healing.
3. Maggots have been seen to be effective against MRSA (methicillin-resistant *Staphylococcus aureus*).
4. Maggots work in harmony with human wound healing physiology.
5. Maggot therapy physiology mirrors macrophage action.

KEY WORDS

- **Wound healing physiology**
- **Maggot therapy**
- **Methicillin-resistant *Staphylococcus aureus***

Sarah Brocklesby is Podiatrist, South Bristol NHS Care Trust, formerly with United Bristol Healthcare Trust.

PAGE POINTS

1 Studies have sought to characterise the actions of maggots in the process of wound healing.

2 Maggots of the *Calliphoridae* family are those most commonly used in maggot therapy.

3 The rise in pH caused by the presence of maggots in the wound has a clinically significant bactericidal action.

4 Maggot secretions in the wound eliminate bacteria.

5 The maggot's peritrophic membrane protects it from infection and is useful in eliminating bacteria.

their eggs on a live host. Maggot therapy makes use of the mechanism of myiasis in a controlled way, with the choice of fly larvae being of vital consideration (Sherman et al, 2000).

Which fly ?

Maggots in the *Calliphoridae* family, which includes *Lucilia sericata*, are the flies most commonly used in maggot therapy. These are facultative parasites, and have been chosen because the larvae:

- Develop rapidly and therefore act quickly in the wound.
- Do not invade internal organs.
- Are easy to rear and sterilise.
- Prefer to feed on necrotic tissue (Hall, 1995).

Therapeutic action

Change in pH

Studies have sought to characterise the actions of maggots in the process of wound healing. The early studies began by confirming the observation that wound pH changed from acid to alkaline in the presence of maggots (Baer, 1931). It is known that extremes of acidity or alkalinity are lethal to most bacteria (Cruikshank et al, 1999). Several practitioners have documented bactericidal action resulting from a raised wound pH. (Baer, 1931; Livingston and Prince, 1932; Weil et al, 1933, Messer and McClellan, 1935; Teich and Myers, 1986). Thomas et al (1999) found that five of eight organisms tested had a slower growth at pH of 8 to 9. It can be accepted that the rise in pH caused by the presence of maggots in the wound has a clinically significant bactericidal action.

Specific bactericidal action

Practitioners have also sought to prove that bacteria are eliminated by maggot secretions in the wound. Simmons (1935) showed that bacterial growth is inhibited in the presence of maggot secretions, as compared with his control group, which grew prolifically.

This work was confirmed recently by Thomas et al (1999) using live maggots added to a suspension of *Staphylococcus aureus*. Results showed a gradual reduction of the bacteria, by surface counting techniques, to nil over three hours in the presence of maggots while the control group of uninhibited *Staphylococcus aureus* increased from 5 to approximately 22 colony-forming units over the same time. Further testing of maggot secretions by Thomas et al (1999) showed a similar result on multiple, isolated suspensions of *Staphylococcus aureus*.

Action against MRSA

Simmons (1935) and Thomas et al (1999) also studied a similar range of different bacteria reporting marked antibacterial action. Thomas et al (1999) included MRSA showing marked inhibition, which may prove to be of major importance in wound healing in the future. It should be noted that both research teams commented that the antibacterial action of maggot secretions was likely to be greater in vivo as the secretions are produced continuously.

In the digestive tract

In addition to the external effects of secretions on bacteria in the wound, it was found that the larvae also eliminated bacteria by ingestion. The larva's stomach comprises three sections; it has been shown both by culture of the contents of the separate sections (Robinson and Norwood, 1934) and by modern laser scanning (Mumcuoglu et al, 2001) that there is a gradual reduction of the presence of bacteria to 'practically nil' by the end of the digestive process. Mumcuoglu et al (2001) postulated that any bacteria that remained in the maggot would be contained within its peritrophic membrane (a tube-like membrane that is secreted at the entrance to the mid-gut in order to envelop incoming food), and therefore would not re-enter the wound. It was reported that bacteria were attracted to lectins in the membrane so strongly that they could not be removed (Peters et al, 1983 in agreement with Mumcuoglu, 2001). In addition, the peritrophic membrane is impermeable to bacteria and its function is to protect the maggot from infection (Zhuzikov, 1964).

Clinical utility

The above suggest a very useful clinical function in the ability of the maggot to eradicate any bacteria remaining in the wound.

Importance of debridement

It was the action of debridement by maggot larvae in wounds that was first noticed as being favourable to healing (Courtney et al, 2000). Debridement is still regarded as an important stage in wound healing; without it, wound healing may be delayed (Takemura et al, 1984). Stadelmann et al (1998) also explain that the physical condition of the wound affects its ability to heal and that the combination of necrotic wound tissue with increased infection prolongs the inflammatory stage, thus inhibiting the signals needed to activate macrophage cells to continue the healing process. Macrophages have a complex role including engaging in the phagacytosis of bacteria and the debridement of devitalised tissue as well as producing growth factors that specifically attract further cells needed in the process of healing (Slavin, 1996).

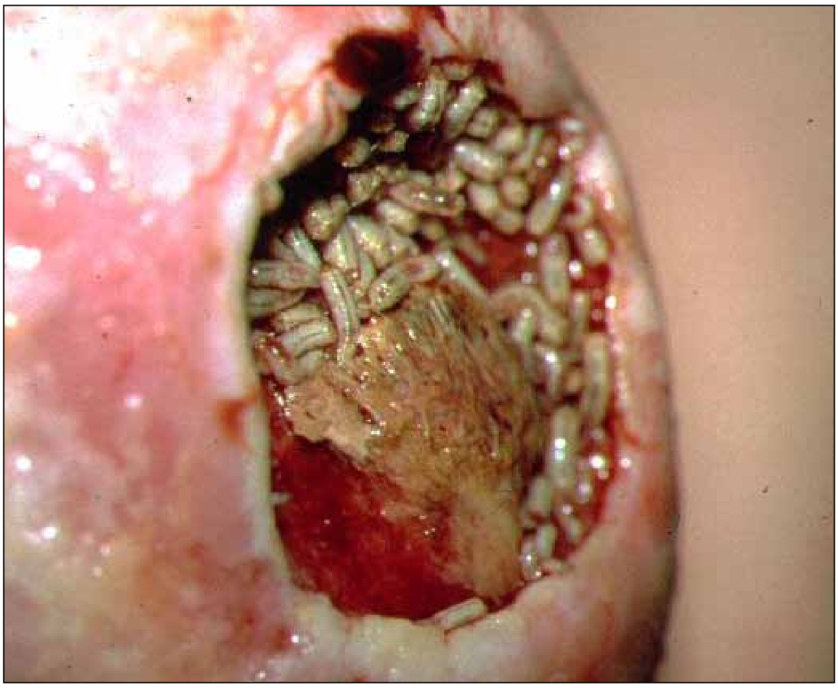
Maggots and debridement

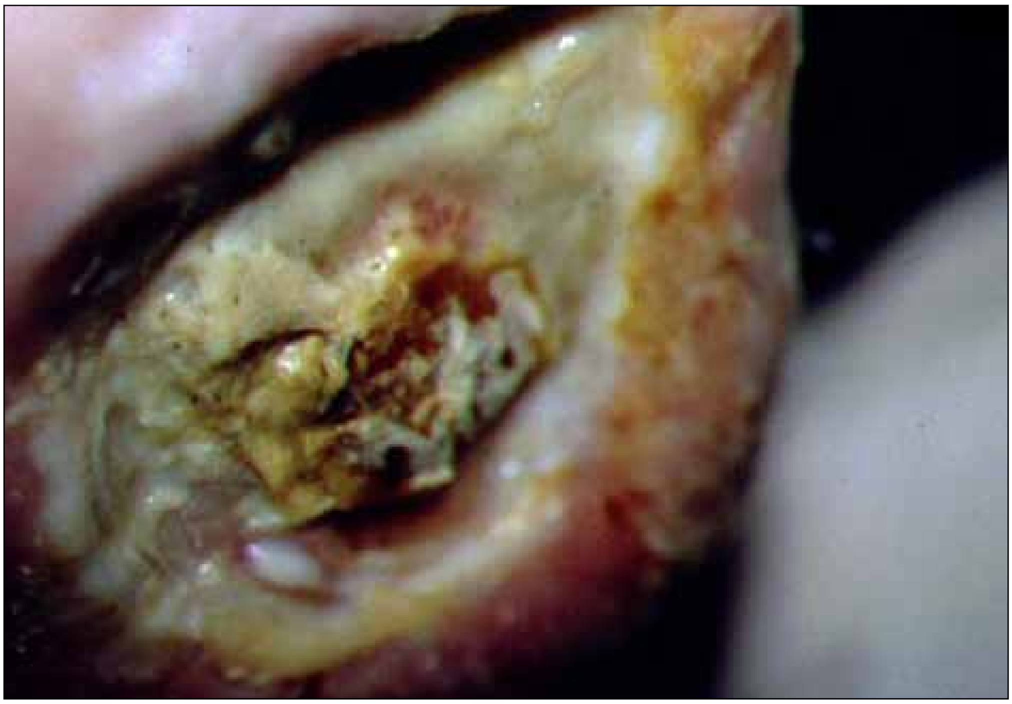
The author has considered the collective evidence regarding the ability of maggot therapy to debride wounds as no one researcher has produced proof by today's standards of scientific evaluation. It has been shown in laboratory testing that collagenases in maggot secretions act on slough in the wound (Hobson, 1931; Ziffren et al, 1964; Waterhouse and Irzkiewicz, 1957; Vistnes et al, 1981).

In addition, numerous clinical reports have documented the clinical observation of rapid and efficient wound debridement.

Growth promoting action

Baer (1931) noticed that larvae seemed to exert an additional biochemical action that speeded up wound healing. This has been reported several times since (Robinson,





A longstanding infected slough-covered ulcer, before (left) and after (above) treatment with maggots.

PAGE POINTS

1 Data strongly suggest that the maggot secretions interact with the body's own healing process to provide an enhanced wound healing environment.

2 There is a startling similarity between the actions of macrophages and maggots upon wound physiology.

3 Future work should focus on the use of maggot therapy in methicillin-resistant *Staphylococcus aureus* (MRSA) in wounds.

1935; Sherman et al, 2000), although there is no consensus on the mode of action to explain this observation.

In combination with growth factor

Prete (1997) compared the effects of maggot secretions with those of epidermal growth factor (EGF) on the growth of human fibroblasts, linking ancient and modern methods for the first time in the investigation of a growth-promoting action. EGF is one of several growth factors secreted by macrophage cells with specific functions to perform. It has been seen to stimulate new epithelial and fibroblast cells (Krishnamoorthy et al, 2001) but should be regarded as part of a set of interdependent interactions, which work together in the final phase of wound healing.

It was found that the combination of maggot secretions with EGF produced a significantly increased fibroblast growth rate in vitro, as compared with EGF or maggot secretions alone. These findings strongly suggest that the maggot secretions interact with the body's own healing process in order to provide an enhanced action in the final stage of healing.

Macrophages and maggots

Research has been progressing into the role of macrophages in the wound healing process. It is interesting to note a startling similarity between some of the actions of macrophages and the actions of maggots upon wound physiology. There is a similarity of action between:

- The phagacytotic elimination of bacterial cells by macrophages and the elimination of bacteria by maggots in wound healing.
- Cleansing of wound debris by macrophages, and the debriding action of maggots.
- The increase in fibroblast action by macrophages and the increased rate of healing in maggot-treated wounds.

More research is needed into the interactions between maggot secretions and other growth factors, particularly the fibroblast growth factor family, which also acts in the proliferative stage of healing.

It has become recognised that the actions of macrophages are essential and that healing will not occur without them. This may give an insight into the reasons for the success of maggot therapy in wound healing.

Conclusion

In this climate of uncertainty regarding the long-term viability of antibiotic use, we need to look for other ways of combating infection in wounds, and maintaining the conditions in the wound that will enable the wound physiology to go through its complex process to full healing. Maggot therapy has been seen to act on MRSA in wounds and constitutes another area in need of further confirmation, in order for the specialist practitioners in wound care to make an informed decision in line with the directive on evidenced-based practice.

In the case of wound healing, maggot therapy offers hope of a proven alternative to antibiotic therapy in the future, effective against a range of pathogenic bacteria including MRSA. ■

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