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Mini Review

Maggot therapy-related zoonotic diseases and modern larval therapy solutions to ensure safety

Masoud Ahmadnejad[1*], Ata Kaboudari[2]

1- Department of Internal Medicine, Faculty of Veterinary Medicine, Urmia University, Urmia, Iran
2- Department of Food Hygiene and Quality Control, Faculty of Veterinary Medicine, Urmia University, Urmia, Iran
* **Corresponding author**: *ahmadnejad.masoud@gmail.com*
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Summary

Larva therapy or maggot therapy is a new treatment used mainly for some skin diseases such as diabetic wounds and skin tumors. The use of larval therapy can improve the success and speed of wound healing. In this treatment, fly larvae are used for the treatment process. In the past, diseases such as tetanus and erysipelas have been seen in larval therapy. New methods of producing sterile larvae have significantly reduced the risk of these diseases in patients. Microbial control of larvae produced prior to wound placement can be a very effective method of immunizing larval therapy. Despite the possibility of various diseases due to larval therapy, with proper quality control and microbial program, the infection can be minimized. Several methods have been introduced for sterilizing larvae. The use of disinfectants in the egg stage can reduce the possibility of microorganisms in the larvae used.

Keywords: Infectious Disease, *Clostridium tetani*, *Erysipelothrix rhusiopathiae*, *Providencia stuartii*, Sterilization

Introduction

Maggots (fly larvae) are often highly specialized for living in environments with a high level of humidity. A few species are internal parasites of animals or humans. When maggots infest humans or other vertebrates, it is called "myiasis" (Hosni et al., 2019). Flies causing myiasis are either obligate parasites that develop only on live hosts or facultative parasites that develop on either live hosts or carrion (Hall and Wall, 1995). The naturally-occurring myiasis can be beneficial, but sometimes it can be harmful, depending upon the type of maggots and the circumstances surrounding the infestation. The known beneficial application of myiasis is for the

treatment of wounds that called "Maggot therapy" or "Larval therapy" (Thomas, 2003).

Today, various treatment methods have been studied for the treatment of various diseases. One of the most important of these methods is 'Biotherapy". Maggot or larval therapy is a subset of biotherapy (Naik and Harding, 2017). Larval therapy is one of the modern methods of treatment in medicine and veterinary sciences. In this method, the use of sterile fly larvae is used to treat human and animal wounds. In the methodology of this treatment method, the larvae of *Lucilia sericata* (common green bottle fly) are used. The performance of modern larval therapy in the treatment of diabetic and infectious wounds is outstanding. In some cases, larval therapy heals wounds faster and better than conventional methods (Kenawy and Abdel-Hamid, 2020).

In this article, one of the main problems in larval therapy has been studied, and problem management methods have been presented. For this purpose, a systematic search and review of the available published articles on the different aspects of larval therapy using "wound debridement, larval therapy, maggot therapy, and *L. sericata*" as keywords were performed on Pub Med and internet-based ones. In addition, several related web pages were accessed.

Problems in Non-Sterile Larvae

Larval therapy is an invasive treatment (Kenawy and Abdel-Hamid, 2020). Because this treatment is associated with an open wound, the components must be sterile. If complete sterilization is not observed, some problems may occur (Thomas, 2003). Some larval-treated wounds were infected with *Clostridium tetani* and *Clostridium perfringens*. Therefore, efforts to produce sterile larvae began (Whitaker et al., 2007).

In some cases of old larval therapy using non-sterile larvae, tetanus and erysipelas were seen. It has never been proven that these infections originate from larvae. However, the scientists decided to disinfect the larvae and use them in treatment, after which they are called Medical Maggots Larvae (Sherman, 2002).

Cases of blood infections with *Providencia stuartii* and *Candida albicans* have been observed in patients treated with larval therapy. Although the association of these infections with larval therapy was not confirmed, changes were made in subsequent larval therapies. The larvae used by *Protophormia terraenovae* suddenly changed to *L. sericata*, and the disinfection method was modified. None of the patients had blood

infections after changes in follow-up (Nuesch et al., 2002).

According to various reports, it can be concluded that due to non-sterile larval therapy, three types of infectious diseases are very common in patients treated with larval therapy that causes of these three types of diseases are: *C. tetani*, *Erysipelothrix rhusiopathiae*, and *P. stuartii*.

Clostridium tetani

Tetanus is a human-animal disease caused by the toxin of *C. tetani*, characterized by muscle spasms and dysfunction of the autonomic nervous system (Yen and Thwaites, 2019). *C. tetani* is one of a genus of obligate anaerobic, saprophytic, gram-positive bacteria that well known for its toxin-producing ability making it one of the most dangerous of its genus. This bacteria is spore-forming that can withstand extreme temperature conditions in both indoor and outdoor environments. Tetanus spores can survive in the environment for many years and are often resistant to heat and disinfectants (George et al., 2020).

The disease is well controlled in developed countries and is rare but common in developing countries. The disease is often transmitted by the bites of wild and domestic carnivores and controlled by vaccines. The person has an arduous treatment process after being infected (Yen and Thwaites, 2019). In many tropical and subtropical countries with low vaccination coverage and inadequate medical care, it is still widely distributed (Stock, 2015).

Tetanus affects all mammals, although susceptibility to the disease is variable; horses and primates are more susceptible than carnivores. Larval therapy is more used in humans and, among animals, in horses. Therefore, the probability of contracting tetanus due to this treatment in horses is very high and is of special importance (Van Galen et al., 2017). For the management of tetanus, neutralization of free circulating toxin, adequate antibacterial, and symptomatic therapy, as well as intensive care of the patient are essential. For prophylaxis of the disease, active tetanus toxoid vaccination is the choice method (Stock, 2015).

Erysipelothrix rhusiopathiae

E. rhusiopathiae is a gram-positive, motionless or very little motion, capsule-free, microaerophilic, rod-shaped, and slightly curved bacteria. This bacteria is a zoonosis pathogen and causes several diseases. The most important of which are erysipelas, arthritis, and sepsis. The disease is common in humans in people who deal with animals, such as veterinarians and farmers (Ugochukwu et

al., 2019). Pigs, sheep, chickens, ducks, and horses have been reported to be natural hosts of *E. rhusiopathiae* (Principe et al., 2016). However, other domestic animals and humans are occasionally infected by the organism; hence the disease is of zoonotic importance (Quinn et al., 2002).

This bacteria causes three forms of the disease, which include hyperacute, acute, and chronic (Micaelo et al., 2016). In various forms of the disease, the most important part is endocarditis caused by bacteria, which is very dangerous and deadly (Wang et al., 2020). The zoonotic importance of this disease is very high due to its prevalence. It can also cause disease and infection due to its easy passage through the skin barrier of the body, including during larval therapy (Krauss et al., 2003; Quinn et al., 2002). In the case of this disease, antibiotics (Penicillin and Amoxicillin) should be used for treatment along with serum therapy and local treatment of the wound and its disinfection (Kayser, 2005).

Providencia stuartii

P. stuartii is a Gram-negative, motile via flagella and non-sporulating bacteria that can grow in anaerobic conditions (Liu et al., 2020). This bacterium can cause disease in two ways, including in the urinary tract and, more importantly, through wounds (McHale et al., 1981). The possibility and ability of bacteria to transmit through wounds can be very dangerous during larval therapy (Kenawy and Abdel-Hamid, 2020).

At larval therapy, one should be very careful about this bacterium and the infection caused by it because the treatment of this disease is more difficult due to the microbial resistance created (Lin et al., 2017; Molnár et al., 2019).

Production of Sterile Larvae

To obtain sterile larvae, the eggs collected from a particular species (often *L. sericata*) are washed with special solutions. Several methods have been proposed for sterilizing larvae (Weil et al., 1933; Simmons, 1934; Sherman et al., 2000). Washing the larvae with dilute sodium hypochlorite and then mercury chloride or formaldehyde solution is one method to sterilizing the larvae. Satisfactory sterilization using 5% formalin, 1% sodium hydroxide has been reported. The main limitation of sterile larval production methods is that high concentrations of disinfectants will kill fly eggs (Sherman et al., 2000). Exposing the larvae for 20 minutes in saline with 2.5% formaldehyde and 1% sodium sulfite produced excellent results in controlling bloodstream infections in patients (Nuesch et al., 2002).

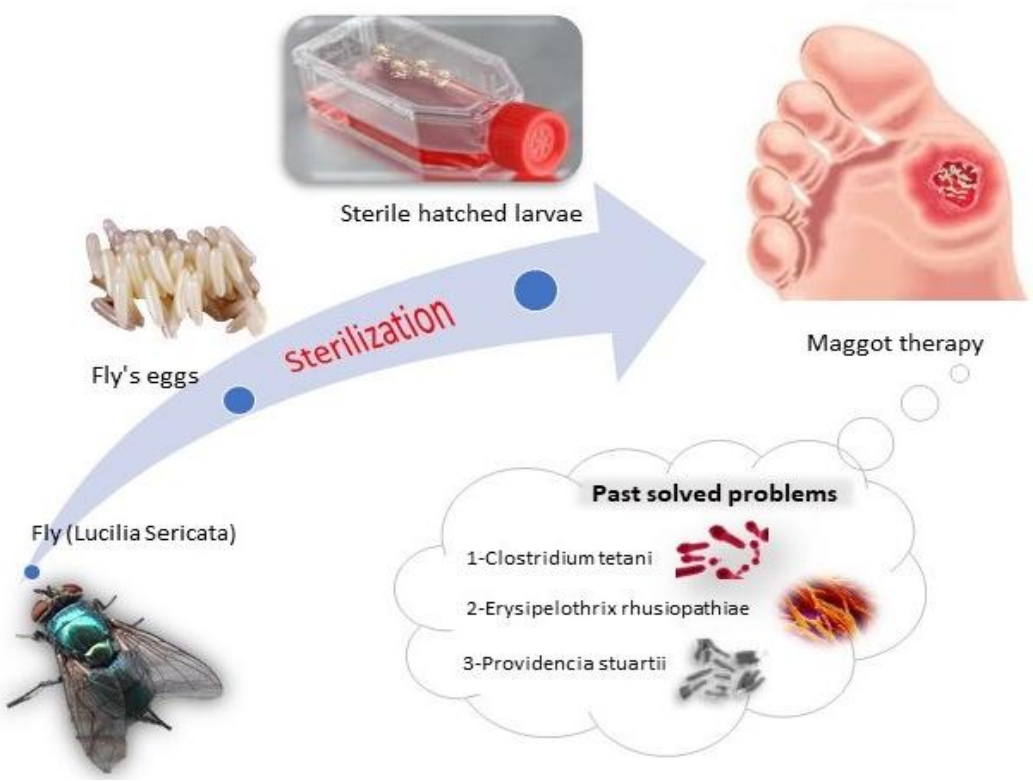

Fig. 1. Schematic of maggot therapy and sterilization to prevent related infections.

In another proposed method, the eggs are first washed with dilute sodium hypochlorite solution (5%) and then with sterile water. The eggs are then stirred in 4% formaldehyde and washed again with sterile water. After this operation, the fly eggs are placed on the fresh liver or meat agar media to hatch at 37 ˚C for 48 hours. After hatching, the larvae are used in human and animal larval therapy. Numerous brands sell these larvae in ready-made containers in the culture media. Some packages are inside special nets (Biobags®) placed on the wound in the same way and do not even need to remove the larvae from the culture media (Kenawy and Abdel-Hamid, 2020).

To prevent problems and diseases caused by larval therapy, quality, and microbial control in all stages of production and use of larvae is necessary. Establishing random microbial quality control methods on the produced larvae reduced post-larval infections to zero (Nuesch et al., 2002).

Conclusion

Although non-sterile larvae have been used for larval therapy in previous years, the cases of dangerous diseases such as tetanus and erysipelas have been seen. But, in recent years, disinfection methods have been used to produce sterile larvae and old concerns have been mostly resolved. With modern methods of producing sterile larvae, these larvae can be used with high confidence and without any worries about the occurrence of infectious diseases in the treatment of various human and animal wounds. However, there is still an incentive to research newer and safer methods of producing sterile larvae.

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Conflict of Interest Statements

The authors declare that they have no conflict of interests.

Ethical Approval

Not applicable

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