Bio-Surgery: Medicinal Leech Therapy and Medical Maggots

Number: 0556

Policy

*Please see amendment for Pennsylvania Medicaid at the end of this CPB.

I. Aetna considers medicinal leech (Hirudo medicinalis) therapy medically necessary for any of the following conditions:

A. Poor venous drainage (venous congestion/venous outflow obstruction); or

B. Salvage of vascularly compromised flaps (muscle, skin, and fat tissue surgically removed from one part of body to another); or

C. Salvage of vascularly compromised replants (limbs or other body parts re-attached after traumatic amputation).

II. Aetna considers medicinal leech therapy experimental and investigational for treating cancer pain, complex regional pain syndrome (i.e., CRPS-I, CRPS-II), epicondylitis, epidermoid cysts (also called epidermal cysts or epidermal inclusion cysts), hematomas, hemorrhoids, knee osteoarthritis, inadequate arterial supply or tissue ischemia, low back pain, priapism,
rheumatoid arthritis and other musculoskeletal diseases, thumb osteoarthritis, and for all other indications because of insufficient evidence of its safety and effectiveness.

III. Aetna considers medical maggots medically necessary for the debridement of any of the following non-healing necrotic skin and soft tissue wounds:

   A. Chronic diabetic foot ulcers; or
   B. Neuropathic foot ulcers; or
   C. Non-healing traumatic or post surgical-wounds; or
   D. Pressure ulcers; or
   E. Venous stasis ulcers.

IV. Aetna considers bagged larval therapy an equally effective medically necessary alternative to medical maggot therapy.

V. Aetna considers bagged larval therapy/medical maggots experimental and investigational for all other indications (e.g., burn wounds and hand injury complicated by mycotic infection) because of insufficient evidence of its safety and effectiveness.

**Background**

**Medicinal Leech Therapy**

The medicinal leech, *Hirudo medicinalis*, has been used increasingly for relief of venous congestion, especially for salvage of compromised pedicled flaps and microvascular free-tissue transfer, digital re-implantation, and breast reconstruction. Leech therapy for compromised flaps is best used early since flaps demonstrate significantly decreased survival after 3 hours if venous congestion is not relieved. If
venous pooling occurs around a flap or replant, the skin becomes cyanotic, cool, and hard. If capillary refill time (CRT) remains more than 3 seconds the flap or replant will not survive. The objective of leech therapy is for the affected area to become pink and warm, with a CRT of less than 2 seconds.

When leeches begin feeding, they inject salivary components (e.g., hirudin) that inhibit both platelet aggregation and the coagulation cascade. This results in a marked relief of venous congestion. The anti-coagulant causes the bite to ooze for up to 48 hours following detachment, further relieving venous congestion. By feeding for 10 to 60 mins, leeches consume from 1 to 2 teaspoons of blood. Results from clinical studies showed that the success rate of salvaging tissue with medicinal leech therapy is 70 to 80%. On June 28, 2004, the Food and Drug Administration (FDA) had for the first time cleared the commercial marketing of leeches for medicinal purposes (in skin grafts and re-attachment surgery).

In an editorial that accompanied the article by Michalsen et al, Hochberg (2003) discussed some of the drawbacks of this paper. A lack of blinding of the patients as well as the researchers is a major pitfall because it raises concerns regarding measurement bias, especially since the outcome measures were all subjective. Also, 7 days is a short time frame for measuring the primary outcome measure since osteoarthritis (OA) is a chronic condition. Furthermore, patients in both groups seldom used rescue therapy, suggesting that, despite the observed significant differences in pain scores at day 7, both groups may have been satisfied with their responses to study interventions. Thus, it is still unclear whether leech therapy is effective in treating knee pain in patients with OA.

In an unblinded, randomized controlled trial with outpatients in a cross-over design with single interventions of either leeches or transcutaneous electrical nerve stimulation (TENS) as comparator, Stange and colleagues (2012) evaluated...
possible efficacy of medical leeches in the treatment of patients with active OA of the knee. Main outcome measures were change in Lequesne's combined index for pain and function and change (L.I.) and overall assessment of complaints by visual analog scale (VAS). Cross-over at day 42, with further observation period of 21 days. A total of 52 out of 72 screened patients were randomized (intent-to-treat) to initial treatment with either 8 leeches (group 1; n = 27 patients) or TENS (group 2; n = 25 patients). Due to phase effects, confirmatory evaluation had to be restricted to the first period. Between days 0 and 21, these researchers observed highly significant (p < 0.001) improvements for means of Lequesne's index from 12.07 to 9.37 and for VAS from 5.89 to 4.16 cm for leeches, but no significant differences for TENS. Effect size as group difference was -2.50 for L.I. (95 % CI: -3.88 to -1.11), resp. -1.86 cm for VAS (95 % CI: -2.85 to -0.87 cm). A total of 12 patients (5 in group 1, and 7 in group 2) did not finish the trial, mostly due to non-compliance (n = 6). No serious adverse effects were observed. The authors concluded that single leech therapy showed significant, relevant and sustaining effects, comparable to other trials with leeches. They stated that the method deserves further research, especially into mechanisms of possible specific effects and optimization of dosing by number of leeches and possible repeats.

Kalender and colleagues (2010) reported a case of severe pain related to advanced stage cancer successfully treated by self-applied leeches. A 62-year old male patient with synchronous renal cell carcinoma and leiomyosarcoma was admitted with severe pain in the lumbar region. The pain was refractory to radiotherapy, and systemic and epidural analgesic infusion. After 2 months, the patient came to the clinic in good condition free of pain. The patient reported outpatient self-treatment with 7 leeches to the lumbar region in the interim that resulted in complete healing of pain. The
authors concluded that this is the first report indicating possible activity of leeches in cancer pain. The finding of this case report needs to be validated by well-designed studies.

Rasi and colleagues (2014) observed a healthy 64-year old Iranian man, who presented with numerous asymptomatic multi-lobular oval-to-round well-defined 0.5 to 1.5 cm cystic lesions with central umbilication (central black eschar) over the upper portion of his chest. These investigators made the diagnosis of epidermoid cyst, giant comedone and leech bite on the basis of the constellation of clinical features. The patient was treated with oral ciprofloxacin at a dose of 2 g daily, and 2 % topical erythromycin solution. Despite improvement, the evidence of cystic lesions persisted. There was no history of similar lesions in any other family member.

There was no history of trauma. The patient was not using any topical or systemic medication. Two weeks before his visit, he had a history of leech therapy under the supervision of a general practitioner. His medical history was significant for leech therapy of the lesions, 5 days previously. He was followed-up for another 2 weeks and after disappearance of the inflammation, with the patient under local anesthesia, the well-circumscribed mass was completely evacuated with a sharp curette and comedone extractor. The patient was subsequently lost to follow-up. The authors concluded that considering the effectiveness of leeches, it would be favorable to breed a germ-free leech. In Iran, the use of the leeches in surgery, in recent years, has been infrequent. It appears that the positive effects of this ancient remedy may now be explained through scientific methods, promising potentially even more uses of this admirable creature in medicine.

Furthermore, an UpToDate review on “Overview of benign lesions of the skin” (Goldstein and Goldstein, 2014) does not mention the use of medicinal leech therapy as a therapeutic option for epidermoid cysts (also called epidermal cysts or epidermal inclusion cysts).
Osteoarthritis

Recently, leech therapy has also been suggested to be an effective treatment for rapid reduction of pain associated with OA of the knee (Michalsen et al, 2002). However, its effectiveness in treating OA of the knee needs to be validated in larger randomized controlled trials (RCTs). In a follow-up RCT, Michalsen et al (2003) evaluated the effectiveness of leech therapy for symptomatic relief of patients with OA of the knee (n = 51). Patients received a single treatment with 4 to 6 locally applied leeches (leech therapy group) or a 28-day topical diclofenac regimen (control group). The primary end point, pain at day 7, was reduced from a mean (+/- SD) of 53.5 +/- 13.7 to 19.3 +/- 12.2 after leech therapy compared with 51.5 +/- 16.8 to 42.4 +/- 19.7 with topical diclofenac. Although the difference between group pain scores was no longer significant after day 7, differences for function, stiffness, and total symptoms remained significant in favor of leech therapy until the end of study and for quality of life until day 28. The authors concluded that leech therapy helps relieve symptoms in patients with OA of the knee. The potential of leech therapy for treating OA and the pharmacological properties of leech saliva remain to be clarified.

Lauche and colleagues (2014) carried out a systematic review and meta-analysis of the effectiveness of medical leech therapy for OA of the knee. The PubMed/MEDLINE, Cochrane Library, EMBASE, Scopus, and CAMBASE databases were screened in August 2012 to identify RCTs and non-randomized controlled clinical trials (CCTs) comparing leech therapy to control conditions. Main outcome measures were pain, functional impairment, and joint stiffness. For each outcome, standardized mean differences (SMD) and 95% CIs were calculated. A total of 3 RCTs and 1 CCT were found, in which a total of 237 patients with osteoarthritis were included. Three trials had a low risk of bias. There was strong overall evidence for immediate (SMD = -1.05; p < 0.01) and short-term pain reduction (SMD = -1.00; p < 0.01), immediate
improvement in patients' physical function (SMD = -0.72; p < 0.01), and both immediate (SMD = -0.88; p = 0.04) and long-term improvement in their joint stiffness (SMD = -0.62; p < 0.01). Moderate evidence was found for leech therapy's short-term effects on physical function (SMD = -0.46; p < 0.01) and long-term effects on pain (SMD = -0.45; p < 0.01). Leech therapy was not associated with any serious adverse events. The authors concluded that this systematic review found moderate to strong evidence for the reduction of pain, functional impairment, and joint stiffness after medical leech therapy in patients with OA of the knee. They stated that given the low number of reported adverse events, leech therapy may be a useful approach in treating this condition. Moreover, they stated that further high-quality RCTs are needed for the conclusive judgment of its safety and effectiveness.

In a review on “Conservative treatment of thumb base osteoarthritis”, Spaans et al (2015) stated that there is insufficient evidence justifying the use of leech therapy.

An UpToDate review on “Complementary and alternative remedies for rheumatic disorders” (Panush, 2015) stated that “A list of all "non-mainstream" therapies touted for patients with rheumatic and musculoskeletal diseases would be extensive indeed. Prominent "complementary" and "alternative" remedies for rheumatic disorders include …. Newer biologic agents, such as monoclonal antibodies and interventions that perturb function of interleukins, cytokines, and similar mediators of inflammation/pain/immune responses, are exciting because of their therapeutic potential. These are not usually considered "alternative" remedies, but it bears noting that until safety and efficacy are established, they are not evidence-based mainstream therapies. Additional "complementary" and "alternative" remedies include other therapies (leeches, botulinus toxin, prayer, Ayurvedic medicine, and sitting in abandoned uranium mines) …. Pain relief from the application of leeches was reported in a study of
51 patients with osteoarthritis who were randomly assigned to have leeches (Hirudo medicinalis) or topical diclofenac applied to an affected knee [citing Michelson, et al., 2003]. Significantly more pain relief was reported with leeching than with diclofenac when assessed at seven days. The benefit persisted for up to 28 days and was associated with improvements in stiffness and function. The lack of blinding of patients and assessors is a major potential source of bias and diminishes confidence in the results. Use of leeches also carries a risk of cellulitis and septicemia due to Aeromonas hydrophilia that colonize medicinal leeches”.

In a prospective, single-center, randomized, single-blind and parallel group study, Isik and colleagues (2017) evaluated the effects of leech therapy in the treatment of knee OA in terms of duration of effectiveness and symptom relief and compared these results with TENS therapy. A total of 90 patients were included in the study, 46 in the leech group and 44 in the TENS group. Primary outcome measures were changes of the pain scores in VAS and Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) on the measurements day 0, 21 and 180. Secondary outcome measures were the changes in the sub-groups of the WOMAC scores. A total of 5 leeches were applied to the affected knee, once-weekly for 3 weeks. The VAS pain score showed a similar decrease in both groups in the evaluation on day 21 (p < 0.001). The course of the change of the VAS pain score in both groups was similar in the comparisons between groups. Long-term benefits of the TENS therapy group were slightly more than the leech therapy group. All the sub-scores of WOMAC in both therapy groups showed a similar decrease (p = 0.819). Throughout the study this decrease was statistically significant in both groups (p < 0.001). The authors concluded that leech therapy relieved symptoms in patients with OA of the knee and is as effective as TENS therapy in the management of OA of the knee. They stated that this treatment has the potential of being an additional or alternative therapy for the non-surgical management of OA of the knee.
Medicinal leech therapy is usually carried out for 4 to 5 days for patients with replant; it may be performed for 6 to 10 days for patients with compromised flaps.

A complication of leech therapy is the risk of infection; thus, it is recommended that therapy not be used in the presence of non-viable tissue.

Patients with HIV infection, or individuals taking immunosuppressive medications should not undergo leech therapy because of the risk of overwhelming bacterial sepsis.

**Priapism**

Asgari and colleagues (2017) noted that priapism is well-defined by persistent, painful penile erection that occurs without sexual stimulation. Currently, hirudotherapy is practiced to treat venous congestion and subsequent compartment syndrome. These investigators reported a case of priapism treated by leeches. A 26-year old subject was referred to the Razi Hospital Emergency Department, Guilan University of Medical Sciences, Rasht, Iran due to long-time spontaneous erections. The patient had no history of mental disorders, trauma or sickle cell anemia. These researchers inserted 2 leeches in each side of penile shaft for 2 hours, after a 1-hour break these investigators repeated the procedure for another cycle. At 2-day follow-up, subject had significantly decreased pain, though still had cavernosal swelling and tenderness to palpation. The patient was subsequently discharged after 3 days of admission. The pain and perineal swelling completely resolved over the course of 1 month. The authors concluded that that leech therapy was a possible, non-invasive, therapeutic option for priapism. These preliminary findings need to be validated by further investigation.

**Wound Healing and Other Investigational Indications**
Koeppen and colleagues (2019) noted that the use of medicinal leech therapy (MLT) is the subject of many articles describing basic pharmacological principles, application procedures, or safety and efficacy of the broad range of therapeutic indications. These investigators focused on the information gap between Eastern and Western medicine when medicinal leech therapy is used in wound healing. Impaired wound healing has serious consequences for patients’ health in a variety of clinical conditions. Western, Persian and Indian medicine appeared to apply different therapeutic approaches when using MLT for healing wounds. They examined a range of review articles, single-case reports and case-series studies on the use of MLT in wound healing. The various reports indicated that MLT has potential benefits for patients experiencing venous congestion of the skin and tissues, as well as varied types of ulcers. Such therapy is proven to have thrombolytic, anti-coagulant, blood and lymph enhancing, anti-inflammatory and pain-relieving effects. The specifics of these approaches are expected to stimulate further research on the use of MLT in wound healing. Although the use of MLT to relieve venous congestion following reconstructive and plastic surgery is well-known in Western medicine, its use in promoting wound healing in various ulcer forms, in the context of Ayurveda/Unani/Persian medicine, appeared largely restricted to Asian and Arabic spheres. The authors concluded that available references suggested that MLT for the wound-healing warrants further investigation in order to determine its potential as part of the modern therapeutic armamentarium. These researchers stated that the true value of MLT in wound healing should be elucidated by further investigations applying modern, evidence-based research methods. The same holds true for other indications where MLT is used, such as epicondylitis, hematomas, hemorrhoids, low back pain (LBP), as well as OA of knee and thumb.

Kulbida and associates (2019) reported on the findings of hirudotherapy in a patient with chronic complex regional pain syndrome (CRPS) in the right hand. CRPS is a multi-factorial
disease associated with disabling pain as well as sensory and motor deficits. The optimal therapeutic management is based on personalized multi-modal treatment approaches; however, hirudotherapy has not been described in the available literature. To-date, these researchers had completed 5 medicinal leech treatments. Altogether, hirudotherapy led to rapid and substantial relief of symptoms, especially with respect to pain intensity ratings and skin temperature asymmetries. Furthermore, the patient's active and passive agility of the affected limb improved obviously. Furthermore, an UpToDate review on “Complex regional pain syndrome in adults: Treatment, prognosis, and prevention” (Abdi, 2020) does not mention medicinal leech as a management / therapeutic option.

Contraindications

Sig and colleagues (2018) stated that medicinal leech therapy is not recommended when there is anti-coagulant therapy, bone narrow suppression, cachexis, chemotherapy, cirrhosis, dialysis, hemorrhagic diathesis, leukemia, and radiotherapy.

Medical Maggots

During the 1930s, maggot debridement therapy (MDT) was used routinely for treating bone and soft-tissue infections. Its use was supplanted by the introduction of new antibiotics and improvements in wound care. Recently, however, there has been a resurgence in the use of maggot therapy.

Medical maggots are blow fly (i.e., phaenicia sericata) larvae. Medical maggots, or larval therapy, is also known as maggot therapy, maggot dressings, green blow fly maggots, biosurgery, disinfected maggots, sterile maggots, therapeutic maggots, debriding maggots, maggot debridement therapy, or MDT dressings. Medical maggots secret digestive enzymes that selectively dissolve necrotic tissue, disinfect the wound, and stimulate wound healing.
Medical maggots received 510(k) marketing clearance by the FDA and are intended to debride non-healing necrotic skin and soft tissue wounds, including pressure ulcers, venous stasis ulcers, neuropathic foot ulcers, and non-healing traumatic or post-surgical wounds. According to information submitted by the manufacturer to the FDA, the fly eggs are chemically disinfected before being placed in sterile vials for transport. The dressings used to confine them on the wound are called "Creature Comforts" and are designed to create a confining "cage dressing." They are applied directly to the wound surface in a dose of 5 to 8 maggots per square cm. The dressings are left in place on the wound for a "cycle" of 48 hours (24 to 72 hours); 1 to 3 cycles are applied weekly. Most wounds require 2 to 6 cycles for complete debridement.

In a prospective study, Sherman et al (1995) evaluated the utility of maggot therapy (MT) for treating pressure ulcers in spinal cord injury patients. Eight patients received MT after a baseline assessment of healing under conventional therapy (defined as any therapy prescribed by the patient's primary care team). Surface area, tissue quality and healing rates were monitored weekly. Maggot therapy debrided most of the necrotic wounds within 1 week, which was more rapid than all other non-surgical methods. Wound healing was more rapid during MT than during antecedent conventional therapy (p = 0.01). No complications were noted.

In an abstract presented during the European Association for the Study of Diabetes Annual Meeting (2000), Markevich et al reported the results of a 30-month randomized, multi-center, double-blind controlled clinical trial of MT for diabetic neuropathic foot wounds as compared with conventional modern treatment in 140 diabetic patients. Sterile maggots (larvae) of the green-bottle fly (Lucilia sericata) were applied to the wound (6 to 10 per square cm) for 72 hours. At 10 days, granulation tissue covered greater than 50% of the wound in the MT group versus 34% in the control, and the wound area had decreased by greater than 50% in the MT group versus...
27% in the control. This may be a useful method for
debridement of necrotic tissue from diabetic foot wounds with
particular benefits in stimulating tissue growth and improving
the rate of healing (Bloomgarden, 2001).

Wayman et al (2000) examined the clinical efficacy and cost
effectiveness of larval therapy in the debridement of sloughy
venous ulcers. A total of 12 patients with sloughy venous
ulcers were randomized to receive either larval debridement
therapy (LDT) or a hydrogel (the control). Effective
debridement occurred with a maximum of 1 larval application
in 6/6 patients; 4/6 patients in the hydrogel group still required
dressings at 1 month. The median cost of treatment of the
larval group was £78.64 pounds compared with £136.23 pounds
for the control treatment group (p < 0.05).

Sherman (2002) compared MT versus conservative
debridement therapy for the treatment of pressure ulcers in
103 in-patients with 145 pressure ulcers. A total of 61 ulcers
in 50 patients received MT at some point during their
monitored course and 84 ulcers in 70 patients did not.
Debridement and wound healing could be quantified for 43
maggot-treated wounds and 49 conventionally treated
wounds. Eighty percent of maggot-treated wounds were
completely debrided, while only 48% of wounds were
completely debrided with conventional therapy alone (p =
0.021). Within 3 weeks, maggot-treated wounds contained 1/3
the necrotic tissue (p = 0.05) and twice the granulation tissue
(p < 0.001), compared to non-maggot-treated wounds. Of the
31 measurable maggot-treated wounds monitored initially
during conventional therapy, necrotic tissue decreased 0.2
square cm per week during conventional therapy, while total
wound area increased 1.2 square cm per week. During
maggot therapy, necrotic tissue decreased 0.8 square cm per
week (p = 0.003) and total wound surface area decreased 1.2
square cm per week (p = 0.001). The author concluded that
MT was more effective and efficient in debriding chronic
pressure ulcers than the conventional treatments prescribed, patients readily accepted MT and adverse events were uncommon.

Sherman (2003) retrospectively assessed the efficacy of MT for treating foot and leg ulcers in 18 diabetic patients who failed conventional therapy. Of the 20 non-healing ulcers, 6 wounds were treated with conventional therapy, 6 with MT, and 8 with conventional therapy first, then MT. Repeated measures ANOVA indicated no significant change in necrotic tissue, except when factoring for treatment (F [1.7, 34] = 5.27, p = 0.013). During the first 14 days of conventional therapy, there was no significant debridement of necrotic tissue; during the same period with MT, necrotic tissue decreased by an average of 4.1 square cm (p = 0.02). After 5 weeks of therapy, conventionally treated wounds were still covered with necrotic tissue over 33 % of their surface, whereas after only 4 weeks of therapy maggot-treated wounds were completely debrided (p = 0.001). Maggot therapy was also associated with hastened growth of granulation tissue and greater wound healing rates.

Sherman and Shimoda (2004) evaluated post-operative complications of pre-surgical wounds treated with MDT versus a matched group of patients who were not treated with MDT. Ten wounds were debrided by maggots within 1 to 17 days before surgical closure. Debridement was effective in all cases, and there were no post-operative wound infections. Six (32 %) of 19 wounds not treated pre-surgically with MDT developed post-operative wound infections (95 % confidence interval [CI]: 10 % to 54 %; p < 0.05). Pre-surgical MDT was effective in preparing the wound bed for surgical closure, without increased risk of post-surgical wound infection.

Armstrong et al (2005) assessed MDT in 60 non-ambulatory patients (mean age of 72.2 years) with neuro-ischemic diabetic foot wounds and peripheral vascular disease. Twenty-seven of these patients (45 %) healed during 6 months of review.
There was no significant difference in the proportion of patients healing in the MDT versus control group (57 % versus 33 %). Of patients who healed, time to healing was significantly shorter in the MT than in the control group (18.5 +/- 4.8 versus 22.4 +/- 4.4 weeks). Approximately 1 in 5 patients (22 %) underwent a high-level (above-the-foot) amputation. Patients in the control group were 3 times as likely to undergo amputation (33 % versus 10 %). Although there was no significant difference in infection prevalence in patients undergoing MT versus controls (80 % versus 60 %), there were significantly more antibiotic-free days during follow-up in patients who received MT (126.8 +/- 30.3 versus 81.9 +/- 42.1 days). Maggot debridement therapy reduced short-term morbidity in non-ambulatory patients with diabetic foot wounds.

Tantawi et al (2007) assessed the clinical and microbiological efficacy of MDT in the management of diabetic foot ulcers unresponsive to conventional treatment and surgical intervention. Consecutive diabetic patients with foot wounds were selected for MDT. Lucilia sericata medicinal maggots were applied to the ulcers for 3 days per week. Changes in the percentage of necrotic tissue and ulcer surface area were recorded each week over the 12-week follow-up period. Semi-quantitative swab technique was used to determine the bacterial load before and after MDT. The sample comprised 10 patients with 13 diabetic foot ulcers. The mean baseline ulcer surface area was 23.5 square cm (range of 1.3 to 63.1) and the mean percentage of necrotic tissue was 74.9 % (range of 29.9 to 100). Complete debridement was achieved in all ulcers in a mean of 1.9 weeks (range of 1 to 4). Five ulcers (38.5 %) were completely debrided with one 3-day MDT cycle. The mean reduction in ulcer size was significant at 90.2 % and this occurred in a mean of 8.1 weeks (range of 2 to 12). The mean weekly reduction in ulcer size was 16.1 % (range of 8.3 to 50). Full wound healing occurred in 11 ulcers (84.6 %) within a mean of 7.3 weeks (range of 2 to 10). The bacterial load of all ulcers reduced sharply after the first MDT cycle to
below the 10\textsuperscript{5} threshold, which facilitates healing. The authors concluded that the results highlight the potential benefits of MDT in diabetic wound care in developing countries and that MDT proved to be a rapid, simple and efficient method of treating these ulcers.

A review of MDT in chronic wound care by Chan et al (2007) stated that MDT has been shown to be a safe and effective means of chronic wound management, however, there are a number of limitations when considering its local applicability. Future development of the delivery system may help to overcome some of these limitations and improve its acceptability.

The VenUS II trial, a multi-center prospective clinical study compared the clinical and cost-effectiveness of 2 types of larval therapy (loose and bagged) with a standard debridement intervention (hydrogel). Patients (n = 267) with at least 1 venous or mixed venous and arterial ulcer with at least 25 \% coverage of slough or necrotic tissue, and an ankle brachial pressure index of 0.6 or more were enrolled in the study. The primary outcome was time to healing of the largest eligible ulcer. Secondary outcomes were time to debridement, health related quality of life (SF-12), bacterial load, presence of methicillin resistant Staphylococcus aureus (MRSA), adverse events, and ulcer related pain (VAS, from 0 mm for no pain to 150 mm for worst pain imaginable). The authors reported that time to healing was not significantly different between the loose or bagged larvae group and the hydrogel group (hazard ratio for healing using larvae versus hydrogel 1.13, 95 \% CI: 0.76 to 1.68; p = 0.54). Larval therapy reduced the time to debridement (hazard ratio 2.31, 95 \% CI: 1.65 to 3.2; p < 0.001). Health related quality of life and change in bacterial load over time were not significantly different between the groups. Seven percent of participants had MRSA at baseline and there was no difference found between larval therapy and hydrogel in their ability to eradicate MRSA by the end of the debridement phase (75 \% (9/12) versus 50 \% (3/6); p = 0.34),
although this comparison was under-powered. Mean ulcer related pain scores were higher in either larvae group compared with hydrogel (mean difference in pain score: loose larvae versus hydrogel 46.74 (95 % CI: 32.44 to 61.04), p < 0.001; bagged larvae versus hydrogel 38.58 (23.46 to 53.70), p < 0.001). The authors concluded that larval therapy did not improve the rate of healing of sloughy or necrotic leg ulcers or reduce bacterial load compared with hydrogel and was associated with significantly more ulcer related pain, but it did significantly reduce the time to debridement compared with hydrogel (Dumville et al, 2009).

To assess the cost-effectiveness of larval therapy compared with hydrogel in the management of leg ulcers, Soares et al (2009) carried out a cost-effectiveness and cost utility analyses alongside the VenUS II trial. The time horizon was 12 months and costs were estimated from the United Kingdom National Health Service perspective. Cost- effectiveness outcomes were expressed in terms of incremental costs per ulcer-free day (cost effectiveness analysis) and incremental costs per quality adjusted life years (cost utility analysis). The larvae arms were pooled for the main analysis. Treatment with larval therapy cost, on average, pound 96.70 (Euro 109.61; $140.57) more per participant per year (95 % CI: - pound 491.9 to pound 685.8) than treatment with hydrogel. Participants treated with larval therapy healed, on average, 2.42 days before those in the hydrogel arm (95 % CI: -0.95 to 31.91 days) and had a slightly better health related quality of life, as the annual difference in QALYs was 0.011 (95 % CI: -0.067 to 0.071). However, none of these differences was statistically significant. The incremental cost-effectiveness ratio for the base case analysis was estimated at pound 8,826 per QALY gained and pound 40 per ulcer-free day. Considerable uncertainty surrounds the outcome estimates. The authors concluded that debridement of sloughy or necrotic leg ulcers with larval therapy is likely to produce similar health benefits and have similar costs to treatment with hydrogel.
Guidance from the National Institute for Clinical Excellence (NICE, 2001) on the use of debriding agents for difficult to treat surgical wounds addressed the use of maggot therapy and other agents. The guidance states that there is no randomized controlled trial evidence to support any particular method of debridement for difficult to heal surgical wounds, but less robust studies suggest modern dressings (products thought to promote autolytic wound debridement, including hydrocolloids, hydrogels, polysaccharide beads/paste, foam dressings, and alginate dressings) as well as bio-surgical techniques (sterile maggots) may reduce pain and be more acceptable to patients. The guidance stated that, in the absence of sufficient evidence for or against any particular method of debridement, or for one type of modern dressing over another, the choice of debriding agent for difficult to heal surgical wounds should be based on impact on comfort, odor control and other aspects relevant to patient acceptability, type and location of wound, and total costs.

Igari et al (2013) noted that maggots are potent debriding agents capable of removing necrotic tissue and slough; however, it is still unclear which wounds are most likely to benefit from MDT. These researchers performed a retrospective review to gain insight into the patient and therapy characteristics influencing outcome. They reviewed patients with foot ulcers caused by critical limb ischemia, encountered during the period between June 2005 and May 2010. The treatment outcomes were defined as effective or ineffective. There were 16 patients with 16 leg ulcers. The patients were 13 men and 3 women, with an average age of 67.2 years (range of 47 to 85 years). Ten (63 %) of the 16 ulcers were treated effectively. According to uni-variate analyses, an ankle brachial pressure index (ABI) lower than 0.6 (p = 0.03) had a negative impact on the outcome of MDT; however, outcome was not influenced by gender, obesity, ischemic heart disease, diabetes mellitus, hemodialysis, smoking, or laboratory findings. The authors concluded that some patient characteristics, such as gender, obesity, ischemic heart
disease, diabetes mellitus, hemodialysis, and smoking, do not seem to contraindicate eligibility for MDT. However, a limb with an ABI lower than 0.6 is less likely to benefit.

Chronic Diabetic Foot Wounds

Shi and Shofler (2014) stated that maggot debridement therapy is used extensively in the United Kingdom in both community and hospital situations, but remains a potentially under-used modality in many wound care markets. It promotes wound healing by performing 3 key processes: (i) debridement, (ii) disinfection and (iii) growth-promoting activity. It can be used for the debridement of non-healing necrotic skin and soft tissue wounds, including pressure ulcers, venous stasis ulcers, neuropathic foot ulcers and non-healing traumatic of post-surgical wounds. The authors stated that with the increase in chronic diabetic foot wounds, maggot debridement therapy is a promising tool for health professionals dealing with difficult wounds.

Furthermore, UpToDate reviews on “Clinical manifestations, diagnosis, and management of diabetic infections of the lower extremities” (Weintrob and Sexton, 2016), “Management of diabetic foot ulcers” (McCulloch et al, 2016), and “Overview of treatment of chronic wounds” (Evans and Kim, 2016) do not mention the use of maggot as a therapeutic option for chronic diabetic foot wounds.

Sherman and co-workers (2003) evaluated the efficacy of MT for treating foot and leg ulcers in diabetic patients failing conventional therapy. Retrospective comparison of changes in necrotic and total surface area of chronic wounds treated with either MT or standard (control) surgical or non-surgical therapy. In this cohort of 18 patients with 20 non-healing ulcers, 6 wounds were treated with conventional therapy, 6 with MT, and 8 with conventional therapy first, then MT. Repeated measures ANOVA indicated no significant change in necrotic tissue, except when factoring for treatment (F [1.7,
During the first 14 days of conventional therapy, there was no significant debridement of necrotic tissue; during the same period with maggot therapy, necrotic tissue decreased by an average of 4.1 cm$^2$ ($P = 0.02$). After 5 weeks of therapy, conventionally treated wounds were still covered with necrotic tissue over 33% of their surface, whereas after only 4 weeks of therapy maggot-treated wounds were completely debrided ($P = 0.001$); MT was also associated with hastened growth of granulation tissue and greater wound healing rates. The authors concluded that MT was more effective and efficient in debriding non-healing foot and leg ulcers in male diabetic veterans than was continued conventional care.

In a prospective, case-control study of more than 18 months, Paul and associates (2009) examined the effectiveness of maggot debridement therapy (MDT) with the sterile larvae of Lucilia cuprina (a tropical blowfly maggot) for the treatment of diabetic foot ulcers (DFUs). Literature thus far has only reported results with the temperate maggot, Lucilia sericata. This study documented outcome in diabetic foot wounds treated with maggot debridement versus those treated by conventional debridement alone. In this series of 29 patients treated with MDT, 14 wounds were healed, 11 were unhealed and 4 were classified under others. The control group treated by conventional debridement had 30 patients of which 18 wounds were healed, 11 unhealed and 1 classified under others. There was no significant difference in outcome between the 2 groups. The authors concluded that MDT with L. cuprina is as effective as conventional debridement in the treatment of DFUs. It would be a feasible alternative to those at high risk for surgery or for those who refuse surgery.

Jordan and co-workers (2018) stated that MDT has a long and well-documented history. Once a popular wound care treatment, especially prior to the discovery of antibiotics, modern dressings or debridement techniques, MDT fell out of favor after the 1940s. With the increasing prevalence of
chronic medical conditions and associated complex and difficult-to-treat wounds, new approaches have become necessary to address emerging issues such as antibiotic resistance, bacterial biofilm persistence and the high cost of advanced wound therapies. The constant search for a dressing and/or medical device that will control pain, remove bacteria/biofilm, and selectively debride necrotic wound material, all while promoting the growth of healthy new tissue, remains elusive. On review of the current literature, MDT comes very close to addressing all of the previously mentioned factors, while at the same time remaining cost-effective.

Complications of MDT are rare and side effects are minimal. If patients and providers can look past the obvious anxiety associated with the management and presence of larvae, they will quickly see the benefits of this underutilized modality for healing multiple types of wounds. These investigators noted that according to the Centers for Disease Control and Prevention (CDC), an estimated 30 million Americans (9.4% of the U.S. population) had diabetes in 2015. This population is especially vulnerable and susceptible to poor wound healing, with the estimated annual cost of managing diabetic wounds in the U.S. exceeding $20 million, including more than 2 million workdays of lost productivity. Medical costs of treating a single diabetic ulcer can reach $10,000 and clinical non-response or progression of the disease process may result in an extremity amputation, with a median cost of $12,500. Diabetic extremity ulcers affect approximately 15% of the diabetic population, leading to about 70,000 amputations annually. The progression from diabetic peripheral vascular disease to chronic non-healing DFUs to terminal amputation is all too common; MDT could stall the progression of this condition, improving the prognosis even in recalcitrant cases. These researchers noted that 1 randomized trial suggested that MDT was more effective than hydrogel in reducing the wound area of DFUs. Another prospective, randomized study comparing the efficacy of MDT versus hydrogel showed improved debridement efficacy, but no difference in the rate of healing or ability to eradicate
methicillin-resistant S. aureus (MRSA) infection. While the same investigation suggested greater amount of ulcer-related pain with MDT compared to hydrogel, it also showed equivalent efficacy of loose versus bagged larvae. In yet another retrospective study comparing changes in necrotic and total surface area of chronic foot and leg ulcers in diabetic patients, patients were treated with either MDT, standard medical management, or routine surgical care. Maggot therapy was associated with faster debridement and wound healing than its therapeutic comparators. MDT-treated wounds saw a 50% reduction in necrotic surface area in as few as 9 days, compared to 29 days in the other groups. Moreover, within 2 weeks, MDT treated wounds contained only 7% necrotic tissue compared with 39% necrotic tissue for traditional management. Finally, within 4 weeks, wounds in the MDT group were completely debrided and contained 56% healthy granulation base, whereas wounds treated with conventional therapy retained 33% necrotic tissue coverage with only 15% granulation base. At the same time, the rate of complete wound closure was not significantly different between MDT and non-MDT approaches. Despite being limited by significant definitional heterogeneity and small size of source reports, a meta-analysis comparing the effectiveness of MDT versus non-MDT approaches, suggested that MDT may be superior to non-MDT modalities in achieving full wound healing, time to healing, and the number of antibiotic-free days.

In a RCT, Malekian and colleagues (2019) evaluated the antimicrobial effects of medicinal maggots of Lucilia sericata on Staphylococcus aureus and Pseudomonas aeruginosa on DFUs. The sample comprised 50 adult patients from the clinic of the Academic Center for Education, Culture and Research of Tehran University of Medical Sciences, Iran. All subjects who had at least 1 DFU present for at least 12 weeks, an ABI value of more than 0.6, and a hemoglobin A1c value of less than 8% were included in this study. Subjects were randomly selected for the maggot-treated (treatment) or conventional
treatment (control) group. Conventional treatments such as antibiotic therapy, debridement, and off-loading were done for both groups, but MT was added to the protocol of the treatment group. Bacterial burden was monitored and compared for both groups using cultures collected using swab technique. Wound secretions were measured and compared in both groups. The number of infected cases with S aureus in the treatment group was significantly reduced after 48 hours in comparison with the control group (p = 0.047). The number of infected cases with P aeruginosa was significantly reduced after 96 hours (p = 0.002). These researchers also found that wound secretions in the treatment group were significantly higher than in the control group (p < 0.00). The authors concluded that these findings indicated that MT is a safe and efficacious treatment of DFUs.

Furthermore, an UpToDate review on “Basic principles of wound management” (Armstrong and Meyr, 2019) states that “Maggot therapy has been used in the treatment of pressure ulcers, chronic venous ulceration, diabetic ulcers, and other acute and chronic wounds. The larvae secrete proteolytic enzymes that liquefy necrotic tissue, which is subsequently ingested while leaving healthy tissue intact. Basic and clinical research suggests that maggot therapy has additional benefits, including antimicrobial action and stimulation of wound healing. However, randomized trials have not found consistent reductions in the time to wound healing compared with standard wound therapy (e.g., debridement, hydrogel, moist dressings). Maggot therapy appears to be at least equivalent to hydrogel in terms of cost”.

Hand Injury Complicated by Mycotic Infection

Bohac and colleagues (2015) noted that complex injuries of the hand remain a therapeutic challenge for surgeons. These researchers presented the case of a male who suffered a devastating injury of the hand caused by a conveyor belt. The patient developed a progressive Absidia corymbifera infection
of the affected soft tissues. Initial treatments with serial surgical debridement and topical and intravenous itraconazole were unsuccessful in eliminating the infection. These investigators used maggot debridement therapy in a new special design to debride all necrotic, devitalized tissue and preserve only healthy tissue and functioning structures. This maneuverer followed by negative pressure therapy (NPT) allowed progressive healing. The authors concluded that in such complex hand injuries, maggot debridement combined with negative pressure therapy could be considered to achieve effective and considerable results, although future functional morbidity may occur. This was a single-case study; and its findings were confounded by the combined use of maggot and NPT. These preliminary findings need to be validated by well-designed studies.

Also, an UpToDate review on “Overview of hand infections” (Sebastin et al, 2016), does not mention the use of maggot as a therapeutic option.

**Burn Wounds**

Bian and associates (2017) stated that Lucilia sericata maggots have beneficial properties; however, their protective effects on burn wounds have yet to be fully elucidated. In the present study, a deep 2nd-degree burn rat model was used to examine the burn wound healing properties of aqueous extract of maggots (MAE). The anti-inflammatory, anti-oxidative and anti-bacterial activities were examined. In addition, the protein expression levels of Akt, vascular endothelial growth factor A (VEGFA) and nuclear factor-kB (NF-kB) were detected by Western blot. The findings of the present study revealed that MAE treatment increased burn wound healing and hydroxyproline content in the burn-treated rats. A total of 7 compounds (MAE-P1-P7) were separated from MAE and a comparative study was performed to identify the major active component. The results demonstrated that MAE-P6 exerted greater anti-bacterial activity compared with the other
compounds. MAE-P6 treatment reduced tissue levels of malondialdehyde, tumor necrosis factor-α and interleukin-6, and increased superoxide dismutase activity. Furthermore, MAE-P6 increased the expression levels of VEGFA and reduced NF-κB expression through Akt, which was verified by treatment with the Akt-specific inhibitor, LY294002. The authors concluded that to their best knowledge, the present study was the 1st to demonstrate the beneficial effects of MAE on burn wound healing via its anti-bacterial, anti-oxidative and anti-inflammatory activities. They stated that it is possible that MAE-P6 functions via the Akt/NF-κB signaling pathway to regulate the release of inflammatory cytokines and free radicals; MAE-P6 may also regulate angiogenesis and vasopermeability via the Akt/VEGFA pathway. These researchers stated that the findings of the present study suggested that MAE-P6 has multi-target mechanisms for improving burn wound healing, and therefore may provide useful information for the development of burn wound healing treatments.

CPT Codes / HCPCS Codes / ICD-10 Codes

Information in the [brackets] below has been added for clarification purposes. Codes requiring a 7th character are represented by "+":

<table>
<thead>
<tr>
<th>Code</th>
<th>Code Description</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Medicinal leech therapy:</td>
</tr>
<tr>
<td></td>
<td>There is no specific CPT code for medicinal leech therapy:</td>
</tr>
<tr>
<td>I87.1</td>
<td>Compression of vein</td>
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<tr>
<td>I87.2</td>
<td>Venous insufficiency (chronic) (peripheral)</td>
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<tr>
<td>I99.8</td>
<td>Other disorder of circulatory system</td>
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<tr>
<td>T86.820</td>
<td>Complications of skin graft (allograft) (autograft)</td>
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<tr>
<td>T86.829</td>
<td></td>
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<tr>
<td>Code</td>
<td>Code Description</td>
</tr>
<tr>
<td>----------</td>
<td>-------------------------------------------------------</td>
</tr>
<tr>
<td>T87.0x1 - T87.2</td>
<td>Complications of reattached extremity or body part</td>
</tr>
<tr>
<td>Z89.011 - Z89.9</td>
<td>Acquired absence of limb</td>
</tr>
</tbody>
</table>

ICD-10 codes not covered for indications listed in the CPB:

- B20: Human immunodeficiency virus [HIV] disease
- D80.0 - D89.9: Certain disorders involving the immune mechanism
- G89.3: Neoplasm related pain (acute) (chronic)
- G90.50 - G90.59: Complex regional pain syndrome I (CRPSI)
- K64.0 - K64.4 - K64.8 - K64.9: Hemorrhoids
- L72.0: Epidermal cyst
- M00.00 - M99.9: Diseases of the musculoskeletal system and connective tissue
- M17.0 - M17.9: Osteoarthritis of knee
- M19.041 - M19.049: Primary osteoarthritis, hand [osteoarthritis of the thumb]
- M54.5: Low back pain
- M77.00 - M77.02: Medial epicondylitis
- M77.10 - M77.12: Lateral epicondylitis
<table>
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<th>Code</th>
<th>Code Description</th>
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<tr>
<td>M79.81</td>
<td>Nontraumatic hematoma of soft tissue</td>
</tr>
<tr>
<td>N48.30 - N48.39</td>
<td>Priapism</td>
</tr>
<tr>
<td>Z21</td>
<td>Asymptomatic human immunodeficiency virus [HIV] infection status</td>
</tr>
</tbody>
</table>

**Medical maggots/Bagged larval therapy:**

**CPT codes covered if selection criteria are met:**

- **97602**  
  Removal of devitalized tissue from wound(s), non-selective debridement, without anesthesia (eg, wet-to-moist dressings, enzymatic, abrasion), including topical application(s), wound assessment, and instruction(s) for ongoing care, per session

**ICD-10 codes covered if selection criteria are met:**

- **E08.610 - E08.69**  
  Diabetes mellitus due to underlying condition with other specified complications
- **E09.610 - E09.69**  
  Drug or chemical induced diabetes mellitus with other specified complications
- **E10.621**  
  Type 1 diabetes mellitus with foot ulcer
- **E11.621**  
  Type 2 diabetes mellitus with foot ulcer
- **E13.621**  
  Other specified diabetes mellitus with foot ulcer
- **I83.001 - I83.029**  
  Varicose veins of lower extremities with ulcer
- **I83.201 - I83.229**  
  Varicose veins of lower extremities with ulcer and inflammation
- **L89.000 - L89.95**  
  Pressure ulcer
- **L97.101 - L97.929**  
  Non-pressure chronic ulcer of lower limb, not elsewhere classified
<table>
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<tr>
<th>Code</th>
<th>Code Description</th>
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<tr>
<td>L98.499</td>
<td>Non-pressure chronic ulcer of skin, not elsewhere classified</td>
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<tr>
<td>T81.89x+</td>
<td>Other complications of procedures, not elsewhere classified [non-healing surgical</td>
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<tr>
<td></td>
<td>wound]</td>
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<tr>
<td>Numerous</td>
<td>Open wounds, complicated [non-healing]</td>
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<tr>
<td>options</td>
<td>[Codes not listed due to expanded specificity]</td>
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<td>ICD-10 codes not covered for indications listed in the CPB (not all-inclusive):</td>
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<td>B49</td>
<td>Mycoses</td>
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<td>E10.622 -</td>
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<td>E10.69</td>
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<tr>
<td>E11.610</td>
<td>Type 2 diabetes mellitus with other specified complications</td>
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<td>E11.69</td>
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<tr>
<td>E13.610</td>
<td>Other specified diabetes mellitus with other specified complications</td>
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<tr>
<td>E13.620,</td>
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<tr>
<td>E13.622 -</td>
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<td>E13.69</td>
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<td>Open wound of hand [not covered for mycotic infections]</td>
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<td>S61.459</td>
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<td>T20.00xA</td>
<td>Burns and corrosions</td>
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<td>- T32.99</td>
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</table>

The above policy is based on the following
references:

Medicinal Leech Therapy

6. Goldstein BG, Goldstein AO. Overview of benign lesions of the skin. UpToDate [online serial]. Waltham, MA: UpToDate; reviewed April 2014.


19. Panush RS. Complementary and alternative remedies for rheumatic disorders. UpToDate [online serial]. Waltham, MA: UpToDate; reviewed April 2015.


Medical Maggots
1. Armstrong DG, Meyr AJ. Basic principles of wound management. UpToDate [online serial]. Waltham, MA: UpToDate; reviewed April 2019.


Amendment to
Aetna Clinical Policy Bulletin Number: 0556 Bio-Surgery:
Medicinal Leech Therapy and Medical Maggots

There are no amendments for Medicaid.