

Important Notice:

1. Never Mix New Leeches Being Delivered with Earlier Lots of Leeches Still in Your Inventory!
2. Place Leeches in a clean Container with Fresh Distilled Water Immediately upon Receipt

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ATTENTION:

NEW IFU DOCUMENTATION ENCLOSED – PLEASE READ CAREFULLY:
SPECIFIC UPDATES INCLUDE

1. ANTIBIOTIC TREATMENT AGAINST AEROMONS INFECTION – PAGES 5 AND 6
2. RECOMMENDATIONS FOR IMMUNOCOMPROMISED OR IMMUNOSUPPRESSED PATIENTS – PAGES 5 AND 6
3. PREPARATION OF LEECHES FOR CLINICAL USE – PAGE 1
4. CARE OF LEECHES IN STORAGE – PAGE 2

I Labeling:

- A.) **Device Description:** Medicinal Leeches (Hirudo Medicinalis)
- B.) **Intended Uses:** An Adjunct to the healing of graft tissue when problems of venous congestion may delay healing, or to overcome problems of venous congestion by creating prolonged localized bleeding.
- C.) **Directions for Use:**

Applying Leeches

The animals should be applied in adequate numbers to the general area of maximal congestion. One or two leeches may be sufficient to treat the skin of a partially degloved finger, whereas a large flap may require six or more depending on initial clinical response. The head (or biting end) of the animal can be recognized by its searching movements, while the tail end is used mostly as a sucker for fixation. It is best to use the hungriest (normally the smallest) leeches first. Preferably do not use forceps forcibly on the leech.

1. A maximum of four hours prior to clinical use of a leech, rinse the animal twice with distilled water and place it in a container filled with clean distilled water. Double rinsing the leech prior to use is intended to reduce the number of bacteria that may be present on the leech's skin, thus reducing the risk of patient infection.
2. Clean patient's skin thoroughly with soap and water to remove all substances with strong odor or taste such as traces of operative prep fluids or saline. Rinse cleaned area with plain water.
3. Dampen a square of gauze on the patient with water and cut a 1cm hole in the middle. Place the gauze on the patient with the hole exposing the area to be treated. This will form a barrier to prevent the leech from wandering.
4. Steer the leeches head to the hole in the gauze. Attachment generally occurs quickly. However, if the leech is reluctant to bite, make a small needle prick on the skin to produce a tiny droplet of blood (which should result in enthusiastic attachment) or try another leech. Sugar or sweet substances are not necessary.
5. Once the leech is attached, it will likely remain safely in place until fully distended. The gauze square can be removed and used somewhere else without disturbing the animal. However, it is important that the site be checked continuously to make sure that the leech hasn't moved.
6. Leeches usually stay attached at a truly congested site for 30 to 60 minutes. If blood supply is poor (in which case the diagnosis of venous congestion is probably wrong), they may detach and attempt to wander to another site, for example nearby normal skin.
7. Leeches will simply drop off the skin when satisfied and not attempt to bite again. After the leech has feed and dropped off the patient, they must be segregated, anesthetized (see disposal) and discarded as any other infectious material. A leech must never be reused on the patient or any other patient.

II. Safety and Effectiveness Considerations

In order for the leeches to be ready for use, it is necessary to meet the following criteria for their care:

A.) Water:

Distilled water plus HIRUDOSALT is recommended. Hirudosalt is a specially formulated recipe for making up water ideally suited for the maintenance of the medicinal leech *Hirudo Medicinalis*. Leeches may also be kept in dechlorinated tap water. The ideal water for long term storage would be distilled water with Hirudosalt. Do not use distilled water alone as it will deplete the animals "ions". Simply stir 0.5g of Hirudosalt into each liter of water. The water is now ready for use. Aeration is unnecessary.

Change the water every other day or more often if it begins to look cloudy. If dead leeches are found when changing the water, dispose of them as indicated below ("Disposal") and increase the frequency of water changes to once a day. After three daily water changes without further leech mortality, you may return to changing the water every other day.

B.) Container:

A lid is essential. Leeches are amphibious and like to crawl about. The best container is one that has a wide opening at the top such as a large jar. This allows for easy access when dispensing leeches and can be easily covered by means of a piece of cotton fabric and a sturdy rubber band. If a lid is used, perforations are advised but they must be very small indeed, as the leech body is elastic and capable of going through remarkably small openings. So, do not overcrowd. No more than 50 leeches should go into a 10 liter container. We recommend that you place the container in a cool dark place that will provide temperature no higher than 50°F, or as close to 40°F as possible. Never put leeches in direct sunlight. If storage in a dark area is not possible, place a cover over the leech container when not in use. Leeches may also be kept in a refrigerator. In this case, it will be necessary to remove them from the refrigerator several hours before use, letting them stand at room temperature to allow them to recover their mobility.

C.) Container Disinfection:

Leeches from different lots must always be stored in separate containers. When all the leeches stored in a container have been used and disposed of, it is important to empty the container of any remaining water. Thoroughly rinse and disinfect the container in accordance with the disinfectant manufacturer's instructions. After disinfection, be sure to thoroughly rinse the container again with tap water in order to remove all traces of disinfectant, which may harm the leeches. After rinsing the container, refill it with distilled water plus HIRUDOSALT, as indicated above, before using it to store a new lot of leeches.

D.) Disposal:

Keep fed leeches in a separate container and properly discard as infectious material. Once used, leeches must never be reused on the same patient nor on another patient.

1. After detachment or removal from patient, leeches should be treated as a contaminated biohazard material. Each leech should be killed by immersion in 70% alcohol solution for 5-10 minutes and disposed with other biohazard materials.
2. Return unused leeches to the pharmacy to be put back in the container for storage.

E.) Mode of Action: prolonged localized bleeding

The leech's main therapeutic benefits are not derived from the average 5 ml of blood removed during the biting (although this may provide dramatic relief at first), but from the fact that each bite continues to ooze up to 150 ml of blood for an average of 10 or more hours. The goal is to produce a minimally adequate venous outflow from the tissue by adjusting the number of bite wounds to suite the clinical situation.

III. Indicators for Therapeutic use of Leeches**Plastic and Reconstructive Surgery**

Leeches are generally useful on any skin flap or other tissue suffering from impaired venous circulation. It is prudent that venous congestion be diagnosed before using leeches since they will not be helpful in cases of insufficient arterial flow. Note, also that insufficient arterial supply could lead to infection from any source, including leeches.

The following criteria may help in diagnosing a true venous problem in a flap:

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| 1) Skin Color | Dusky or bluish |
| 2) Capillary return brisker than normal (note that areas of fixed coloration are beyond salvage) | |
| 3) Pinprick response | Bleeding should be rapid and dark |
| 4) History | Known problems with veins at operation, either in pedicle or at the site of a microvascular anastomosis. |
| 5) Edema | Increasingly leeches are being used to treat severely edematous patients. |

IV. Contraindications for the leech: Arterial Insufficiency

Over the past several years countless patients have benefited from the use of leeches in microsurgery. As you know leeches are used to overcome the problem of venous congestion by creating prolonged localized bleeding uniquely characteristic of the leech bite. This artificial circulation gives the graft time to re-establish its own circulation, normally 3 to 5 days.

The practitioner should be aware, however that if the arterial supply is insufficient the graft is very vulnerable to infection from any outside source, including the leech.

It is well known that the leech gut contains an endosymbiotic bacteria such as **Aeromonas hydrophila** and **Aeromonas veronii**. These bacteria are true symbionts. They are a normal part of the leech gut flora and are, in fact essential for the leech growth and survival.

Aeromonas species are not at all uncommon, especially in water, and are normally not a pathogen. However, like most bacterial species, *Aeromonas* has been implicated as a pathogen in exceptional circumstances. While it usually can be knocked out with antibiotics such as those listed in the table shown on page 6, the practitioner should use discretion, especially when dealing with tissue which is or is likely to become compromised by poor arterial supply. Like any potent drug the clinician needs to weigh the potential benefits against possible risks.

The symbiotic role of the leech with multiple bacterial species present in the leech's digestive system and mouth cavity has been described in detail in literature, including *Aeromonas hydrophila*, *Aeromonas veronii*, *Aeromonas sobria*, *Ochrobacter anthroi*, *Acinetobacter Iwoffi*, *Rikenellaceae* and *Enterobacteriaceae* (Braga et al. 1990; Eroglu et al. 2001; Silver et al. 2007; Fraise et al. 2008; Laufer et al. 2008; Maetz et al. 2012; Verriere et al. 2015). These bacteria are essential to leech digestion of blood.

V. Warning

- A.) Leeches may wander from the wound site. This can be prevented by covering the animal with a secured, small, clear sterile inverted container, or by forming a barrier with dry towels or gauze.
- B.) After detachment or removal from patient, leeches should be killed by immersion in 70% alcohol solution for 5-10 minutes and disposed with other biohazard materials.
- C.) Persistent bleeding resulting in a significant blood loss has been reported after detaching leeches from a bite site. In some patients this blood loss has resulted in the need for a transfusion.

VI. Precautions

A.) Post-Bite Care of Wound

The major therapeutic effect of leech application occurs during the post-bite period and depends greatly on the care given to the bite wounds. Each bite must be encouraged to bleed by gentle removal of any locally forming clot at regular intervals. Clinical response of the tissue being treated should be closely observed during this period.

B.) General Patient Care

The area around the leech bite wounds should be routinely observed several times a day for local infection and swabs taken if indicated. If bleeding is severely prolonged, hemoglobin levels should be checked daily. It is quite possible for significant falls to occur.

Research indicates that after about 3 to 5 days, new vessel ingrowth around flap margins develops sufficiently to restore effective venous drainage. Therefore, it is important that treatment is not terminated too soon, but rather, continued over a period of time to avoid failure.

The property of the leech bite wound to continue bleeding, with encouragement, for 10 or more hours is related to pharmacologically active secretions (not anticoagulant alone) introduced by the leech bite. It has not been found possible to stimulate this effect by introducing conventional anticoagulants, such as heparin, into small stab wounds to the skin.

VII. Antibiotic Treatment

Warning – Risk of Infection

Development of infections is a significant risk to patients receiving leech therapy. Infection from *Aeromonas hydrophila*, (the leech's penicillin-resistant, obligate symbiote) has been reported in up to 20% of treated patients. An *Aeromonas hydrophila* infection may result in septicemia, gastroenteritis, hepatitis, pancreatitis, cholecystitis or pneumonia.

Prophylactic antibiotic treatment should be administered in accordance with appropriate hospital guidelines and the general state of health of the patient.

Specifically, a prophylactic single antibiotic treatment consisting of fluoroquinolones or sulfamethoxazole-trimethoprim is advisable for 7 days after completion of leech therapy. Sulfamethoxazole-trimethoprim and/or fluoroquinolone (example: ciprofloxacin) are most commonly recommended and may be useful in reducing the risk of infection.¹

Please see Table 1 on the next page for additional information regarding antibiotic application.

Immunocompromised or immunosuppressed Patients

In the case of immunosuppressed patients (aplasia, long-term corticosteroid therapy, chemotherapy, etc.), diabetics or persons suffering from chronic liver disease, a greater risk of infection exists, and particular caution is required when applying medicinal leeches.

¹Chepeha DB, Nussenbaum B, Bradford CR, Teknos TN, Leech therapy for patients with surgically unsalvageable venous obstruction after revascularized free tissue transfer. Arch Otolaryngol Head Neck Surg. 2002;128(8):960-965

In these cases, a prophylactic double antibiotic treatment consisting of fluoroquinolones and -in order of preference-sulfamethoxazole-trimethoprim OR third generation cephalosporin OR Piperacillin-tazobactam is recommended for 7 days after completion of leech therapy.

In all cases, antibiotic treatment must be administered with care and adjusted as indicated for the individual patient.

ANTIBIOTICS AGAINST AEROMONAS (THIS SUPERSEDES ALL OTHERS)

TABLE 1 Antimicrobial susceptibilities of 193 *Aeromonas* species

Antimicrobial agent	MIC breakpoint(s) ($\mu\text{g/ml}$)	Percentage (no.) of strains susceptible		
		All isolates (<i>n</i> = 193)	Clinical isolates (<i>n</i> = 144)	Environmental isolates (<i>n</i> = 49)
Amoxicillin (AMX)	8	1.6 (3)	0.7 (1)	4.0 (2)
Amoxicillin-clavulanate (AMC)	8/4	16.5 (32)	6.25 (9)	46.9 (23)
Norfloxacin (NOR)	4	100	100	100
Ciprofloxacin (CIP)*	1	100	100	100
Nitrofurantoin (NIT)	32	99.5 (192)	99.3 (143)	100
Trimethoprim (TMP)	8	92.7 (179)	91 (131)	97.9 (48)
Cephalothin (CEF)	8	27.4 (53)	20.8 (30)	46.9 (23)
Meropenem (MEM)	0.25	100	100	100
	1	100	100	100
	4	100	100	100
Gentamicin (GEN)	4	99.5 (192)	99.3 (143)	100
Tobramycin (TOB)	4	95.3 (184)	93.8 (135)	100
Amikacin (AMK)	16	100	100	100
Ceftriaxone (CRO)	1	96.9 (187)	95.8 (138)	100
Ceftazidime (CAZ)	0.5	97.4 (188)	96.5 (139)	100
	4	99.5 (192)	99.3 (143)	100
Aztreonam (ATM)	4	99.5 (192)	99.3 (143)	100
Ticarcillin-clavulanate (TIM)	16/2	91.2 (176)	88.9 (128)	97.9 (48)
	64/2	95.9 (185)	95.1 (137)	97.9 (48)
Trimethoprim-sulfamethoxazole (SXT)	2/38	98.9 (191)	98.6 (142)	100
Cefepime (FEP)	0.5	98.9 (191)	98.6 (142)	100
	8	100	100	100
Nalidixic acid (NAL)	16	96.9 (187)	97.9 (141)	93.8 (46)
Cefoxitin (FOX)	8	65.2 (126)	65.9 (95)	63.2 (31)
Piperacillin-tazobactam (TZP)	16/4	97.4 (188)	96.5 (139)	100
	64/4	98.9 (191)	98.6 (142)	100
Moxifloxacin (MXF)	1	98.9 (191)	99.3 (143)	97.9 (48)
Tetracycline (TET)	4	94.3 (182)	95.1 (137)	81.6 (40)
Cefazolin (CFZ)	2	20.7 (40)	8.2 (9) ^a	10.2 (5)
Doxycycline (DOX)	S, ≤ 4 ; I, 8; R, ≥ 16	97.9 (189)	97.2 (140)	100
Tigecycline (TGC)	S, ≤ 2 ; I, 4; R, ≥ 8	100	100	100
Colistin (CST)	S, < 2	44.5 (86)	39.5 (57)	59.1 (29)

from: Aravena-Román M, Inglis TJJ, Henderson B, Riley TV, Chang BJ, Antimicrobial Susceptibilities to *Aeromonas* Strains Isolated from Clinical and Environmental Sources to 26 Antimicrobial Agents Antimicrob. Agents Chemother. 2012, 56(2):1110.

Note that there are reports of *Aeromonas* resistant to ciprofloxacin.²

²Sartor C, Bornet C, Guinard D, Fournier PE Transmission of *Aeromonas hydrophila* by Leeches. Lancet 2013; 381:1686