PREVENTING INFECTIVE COMPLICATIONS FOLLOWING LEECH THERAPY: IS PRACTICE KEEPING PACE WITH CURRENT RESEARCH?

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Background: Despite several publications strongly advocating prophylactic antibiotics during leech therapy, and recent primary articles shedding new light on the microbiota of leeches, many units either do not use antibiotic prophylaxis, or are continuing to use ineffective agents. *Methods:* A 5-year follow-up of plastic surgery units in the United Kingdom and the Republic of Ireland was conducted in 2007 to ascertain current practice regarding the use of prophylactic antibiotics with leech therapy. A comprehensive literature search investigated primary research articles regarding the microbiota of leeches to update the reconstructive surgery community. *Results:* Despite published evidence to support the use of prophylactic antibiotics during leech therapy, 24% of units do not use antibiotic prophylaxis and 57% of those using antibiotics are using potentially ineffective agents. Advanced molecular genetic techniques, which allow accurate characterization of both culturable and nonculturable microbiota of the leech digestive tract, show a wider diversity than at first thought, with variable antiobiotic resistance profiles. *Conclusions:* Despite infection due to leech therapy being a well known and relatively common complication, many units are not using appropriate antibiotic prophylaxis. © 2009 Wiley-Liss, Inc. Microsurgery 29:619–625, 2009.

Blood letting and the therapeutic use of medicinal leeches dates back to ancient Egypt.[1] Decades of reports of leech therapy in plastic and reconstructive surgery[2] and more recently the application of leeching for diverse medical problems such as chronic pain syndromes associated with degenerative diseases[3–5] have given leech therapy multiple roles in modern day medicine. Their popularity has indeed varied over the years, having been used by plastic,[6–9] maxillofacial,[10] and other reconstructive surgeons[11,12] to aid salvage of compromised pedicled flaps,[2,13] microvascular free-tissue transfers,[6,14–16] venously congested digits,[8,17–24] nipples,[25,26] ears,[27–32] lips,[33,34] nasal tips,[11,35] and even the penis.[12] Peer-reviewed evidence suggests that the survival of compromised, venous-congested tissues is improved by early application of a leech.[36–38] The leech simulates venous circulation until the congested tissue reestablishes venous capillary circulation. The benefits of leech therapy were only relatively recently acknowledged with The Food and Drug Administration of the United States approving the use of *Hirudo medicinalis* as a medical device in 2004.[39] While most commercial suppliers sell medicinal leeches as *H. medicinalis*, a recent study revealed that the annelids sold were genetically distinct from *H. medicinalis* and were identified as *H. verbana* by Siddall et al.[40] Bely et al. encourage the increased use of "DNA Barcodes" such as COI gene sequences to reveal genetic variations in leeches,[41] while DeSalle et al. advocate a more cautious approach until the barcode reader is reliable and the taxonomic community is in agreement.[42] Whether clarification of these differences will have any medical or microbiological importance remains to be demonstrated. In this study, we refer to medicinal leeches as *H. medicinalis* unless the animals were specifically identified as *H. verbana*. An overview of the anatomy, physiology, and mechanisms of action of the medicinal leech relevant to the reconstructive surgeon is summarized elsewhere.[43]

A high incidence of infection during and after application of medicinal leeches has been widely reported despite external decontamination. The exact incidence of leech-associated infection associated with postoperative use is difficult to assess, with incidences ranging from 2.4% to 36.2% being reported in the literature[8,36,44–46] (see Table 1). At least one clinical study has demonstrated that limiting leech application to tissue with clear evidence of arterial circulation while giving patients antibiotics effective against leech enteric flora during leech therapy can eliminate leech-related soft-tissue infection.[47] Despite several publications advocating prophylactic antibiotics to combat leech-borne infections,[7–9,44,48–52] we were aware of many units either not using antibiotic prophylaxis at all, or continuing to use inappropriate agents.

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Table 1. Chronological Table Summarizing the Published Infection Rates Following Leech Therapy in the Medical Literature

Number of patients	Period (years)	Infection rate (%)	Authors	Year
30	3	20	Mercer et al.[45]	1987
42	Not stated	7	Lineaweaver et al.[8]	1992
18	5	11	De Chalain et al.[36]	1996
122	5	4.1	Sartor et al.[46]	2002
47	2	36.2	Bauters et al.[44]	2007

With the knowledge of the microbiota of the leech digestive tract continuing to grow, the last decade has shown that the bacterial community is much more complex than previously documented. More accurate identification and antibiotic sensitivity testing has allowed an exponential increase in relevant data regarding leech microbiota. A limitation of the clinical articles that previously characterized the digestive tract microbiota of leeches was that these studies were purely culture based. It is now widely recognized that >99% of microbes are at present unculturable[53] and modern techniques must be used to identify theses symbionts.

In this article we present the results of a 5-year follow-up national survey of antiobiotic prophylaxis during leech therapy and draw on the combined wisdom of both the microbiological and plastic surgery community to discuss the implications of our findings including an up-to-date discussion concerning leech borne infections and appropriate evidence-based treatment.

METHODS

A telephone survey of all 62 plastic surgery units in the United Kingdom and the Republic of Ireland was conducted in August 2007. The names, addresses, and phone numbers were obtained from the British Association of Plastic, Reconstructive and Esthetic Surgeons Website (www.bapras.co.uk). Information was obtained from the senior sister on the Plastic and Microsurgery ward who had first hand experience of the use of leeches on the unit, and was responsible for the supervision of antibiotic administration and leech application.

Five simple questions were asked:

1. Are leeches used postoperatively by the plastic surgeons in your unit?
2. How many times per year on average are leeches used?
3. Do you use antibiotics routinely postoperatively when leeches are applied?
4. If yes: What antibiotics do you use?
5. Were there written protocols for the use of leeches?

This questionnaire was accompanied by an extensive literature search to investigate primary research papers regarding the microbiota of leeches and update the reconstructive surgery community.

RESULTS

Accurate information was gained from 55 of the 62 units (89% response rate). Of these, 49 (90%) had used leeches postoperatively in the salvage of compromised free flaps or digital replants within the last 5 years. On average, 23 units used leeches one to five times per year, 15 units used leeches 6–10 times per year, four units used leeches 11–15 times per year, and seven units used leeches more than 16 times per year. Twelve units (24.5%) did not use any antibiotic prophylaxis before or during leech therapy. The remaining 37 units used a range of prophylactic antibiotics routinely during leech application including coamoxiclav, metronidazole, benzyl penicillin, ciprofloxacin, and flucloxacillin. Written protocols concerning the use of leeches were available in 39 units (80%) and 49 units (100%) routinely kept leeches in the hospital pharmacy overnight (see Figs. 1–4). In the figures, "other" antibiotics include metronidazole, cephalosporins, and trimpethoprim.

DISCUSSION

This study confirms that the majority of plastic surgery units in the United Kingdom and Ireland use medicinal leeches to improve drainage from venously congested tissues or extremity replants postoperatively, but despite strong supportive evidence, 24.5% of units fail to use any antibiotic prophylaxis. The total percentage of units using prophylactic antibiotics has decreased from 2002 to 2007 from 92.5% to 75.5%, although the number of units using reliably effective antibiotics such as fluoroquinolones has improved from 22% in 2002% to 43% in 2007[9] (see Fig. 4).

Leech-Borne Infection: Clinical Aspects

The leech bite is created by three jaws, each containing 60–100 pairs of cutting teeth, forming the characteristic Y-shaped tri-radiate conformation 1 mm in diameter and up to 1.5 mm in depth.[54,55] These specially adapted jaws pierce the host tissues in order to feed on blood. The combination of local tissue damage, along with contact between the oral and digestive tract flora (including both the leech crop and intestine) and the patient means that a potential for infection exists. Although the use of leeches in the treatment of arthritis and other medical conditions seems to be associated with negligible risks of infection, the venous congestion in plastic surgery patients requiring treatment seems to lead to a localized area of immunocompromise that is more susceptible to infection. The exact incidence of infection is difficult to assess, with incidences ranging from 2.4% to 36.2%[8,36,44–46] being reported in the literature.

Extensive studies have been carried out on the surface, mouth, and digestive tract microbiota of leeches, which show *Aeromonas* spp. to be prominent in the resident flora.[36,47,48,53,56–60] The most recent of these primary research articles was able to identify both culturable and unculturable isolates. The most common clinical presentation of *Aeromonas* infection in humans is of cellulitis,[61,62] often with a foul odor, complicated by subcutaneous abscess formation. In severe cases, extensive tissue loss and septicemia has been reported.[63] *Aeromonas* seems to have an affinity for muscle tissue, and is capable of producing extensive proteolytic enzymes leading to a picture resembling clostridial myonecrosis with gas production.[64] Of most concern to microsurgeons is the ability of *Aeromonas* to invade the walls of blood vessels with resultant vasculitis, thrombosis, and hemorrhagic necrosis.[65] In immunocompetent patients, surgical site infections (SSIs) due to leech application may result in additional antibiotic therapy, extended hospital stays, rehospitalization, or removal of nonviable tissues.[46] Chalain's meta-analysis reported on a total of 19 cases of aeromonas infection (nine replants, three free flaps, and seven pedicled flaps) with an overall salvage rate of the tissues in the presence of infection of 31.8%, compared with an expected salvage rate of 60–80% in noninfected tissues.[36] As one would expect, neutropenic and immunocompromised patients seem to be more at risk. Leech-borne infections are by no means heterogenous in presentation; delayed presentations have been recently reported

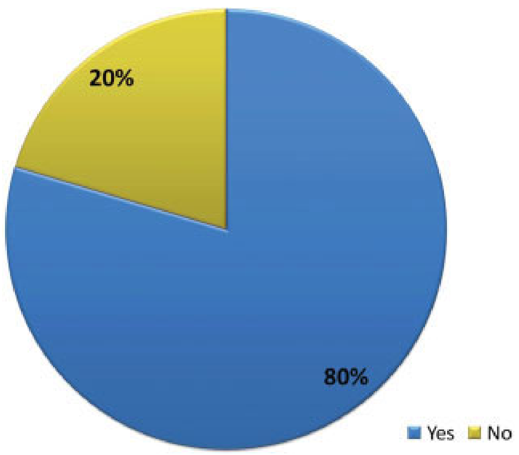

Figure 1. A pie chart showing the percentage of units in the United Kingdom with and without a written protocol for leech therapy. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

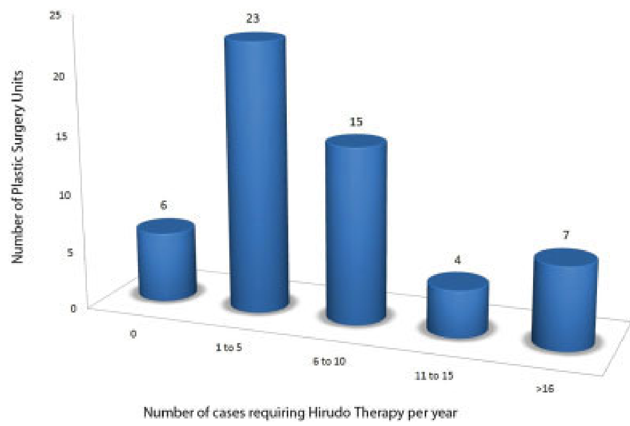

Figure 2. A bar chart showing the approximate number of cases per year requiring leech therapy in each unit in the United Kingdom. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

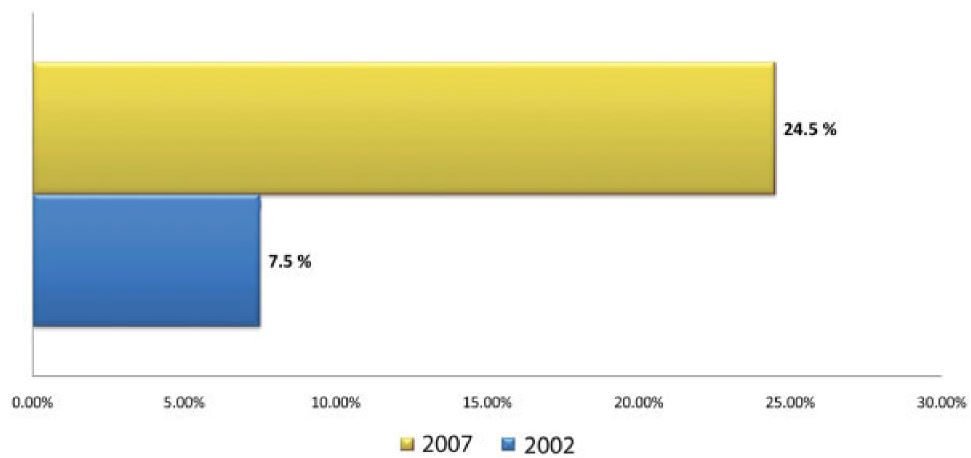

Figure 3. A bar chart showing the percentage of United Kingdom units not using any antibiotic prophylaxis during leech therapy in 2007 compared with 2002. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

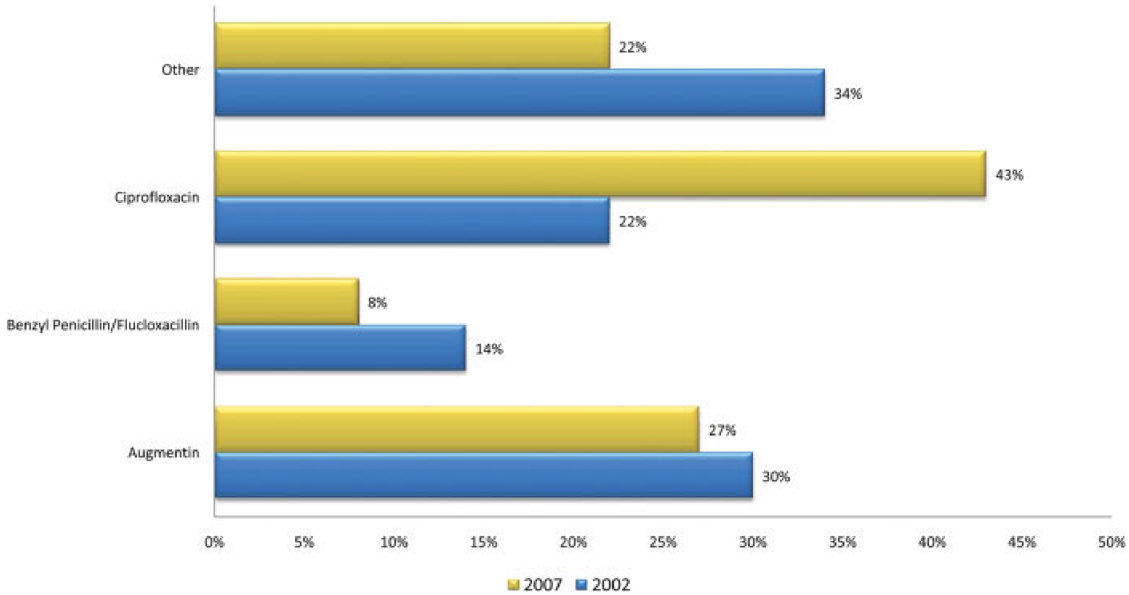

Figure 4. A bar chart showing the percentage of units using specific antibiotic prophylaxis in 2007 compared with 2002. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

in escharotic flaps[66] and a case of meningitis due to leech-borne infection has previously been reported.[67]

Leech-Borne Infection: Microbiology

Since 1976 three Aeromonas genospecies (*Aeromonas hydrophila*, *Aeromonas veronii*, and *Aeromonas caviae*) have been subdivided into 14 species.[68] A combination of molecular and biochemical studies has revealed the digestive tract of *H. verbana* contained *A. veronii*[69,70] and not *A. hydrophila*. Soft-tissue infections due to *A. hydrophila* have been widely reported as a complication of leech application but may well be due to *A. veronii*,[58] which has a similar clinical presentation. Apart from *A. hydrophilia*, pathogens causing wound infection following Hirudo therapy reported in the literature include *Serratia marcescens*,[71] *Aeromonas sobria*,[72] *and Vibrio fluvialis*.[73] The accurate identification is challenging because commercial identification kits frequently misidentify the species and such kits could report *A. veronii* biovar sobria as *Aeromonas sobria*. The single report of *Vibrio fluvialis* associated infection may well have been misnamed, as the API20E method was used for identification purposes and the microbe was almost certainly an *Aeromonad*.[74] The API20E® test (bioMerieux) was used in the older studies to identify *Aeromonas* species. Although it is still used today, it is rather imprecise when compared with molecular genetic analysis. The test consists of a plastic strip of 20 individual, miniaturized tests tubes (cupules) each containing a different reagent used to determine the metabolic capabilities, and, ultimately, the genus and species of enteric bacteria in the family Enterobacteraceae. Interpretation of the 20 reactions plus a separate oxidase reaction is converted to a digital code which is compared with a known database of bacteria.

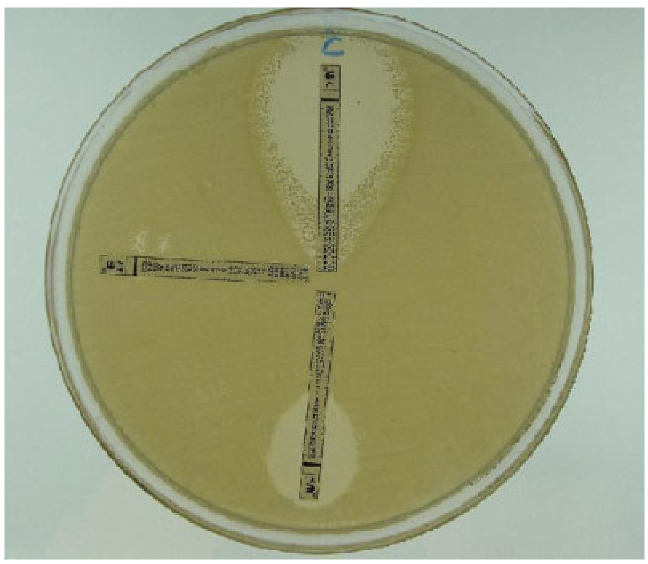

Figure 5. E test® results showing the susceptibility of Aeromonas veronii *to ciprofloxacin (top center), the complete resistance to ampicillin (middle left), and intermediate resistance to augmentin (amoxycillin and clavulanic acid) (bottom middle). [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]*

Knowledge of the diversity, virulence, and infections caused by *Aeromonas* spp. continues to increase rapidly.[75] Of potential clinical importance is the increasing incidence of multidrug resistance among *Aeromonas* spp. isolates that have been observed in aquaculture worldwide. This increasing incidence of resistance is due to the horizontal transfer of mobile genetic elements such as plasmids and class 1 integrons.[76] High levels of resistance to first-generation cephalosporins[44] and penicillins[75–77] (via β-lactamases), tetracyclines,[76] and augmentin[76–79] have been observed in studies, whereas fluoroquinoles seem to be consistently active.[44,48,57,66,75–77]

We performed a preliminary study to illustrate the antibiotic resistance profile of *A. veronii* to plastic surgeons considering using leeches in their practice. We identified a leech (*H. medicinalis*) by comparing with color charts[80] and isolated *A. veronii* in the laboratory from the leech crop using previously described techniques.[81] The identity of *Aeromonas* was confirmed using the API20E test and more accurate molecular genetic analysis. After plating a lawn of *A. veronii*, three Etest® strips comprising predefined gradients of antibiotic concentrations on strips of plastic were used to determine the on-scale minimum inhibitory concentration (MIC in μg/ml) of ciprofloxacin, ampicillin, and augmentin. Following 48 hours of incubation, the Etest® results showed the susceptibility of *A. veronii* to ciprofloxacin (top center), the complete resistance to ampicillin (middle left), and intermediate resistance to augmentin (bottom middle) (see Fig. 5).

One of the limitations of this study is the lack of culture-based data from patients with infections following leech therapy. In an ideal world, a large prospective study would report on the clinical outcome and infection rate following leech therapy, along with an analysis of the microbiota and resistance profiles. The use of leeches is often a last resort, unplanned, and out of hours. Personal opinions and experience of their use varies from surgeon to surgeon. To coordinate the collection and analysis of this data would be incredibly difficult considering the diversity of units using leeches and the lack of a centralized database.

Considering the efficacy of leeches, it would be favorable to breed a germ-free leech. Unfortunately, *H. medicinalis*'s obligatory symbiotic relationship with *A. veronii* seems to preclude this.[53,58,81–83] Future research could potentially be targeted toward breeding less pathogenic genotypes which retain only the proteolytic determinants with the caveat that germ-free animals are susceptible to colonization by potentially more virulent bacteria.

CONCLUSIONS

Infection due to leech therapy is a well-known complication with rates of up to 36.2% in recent studies. Many units are not using appropriate antibiotic prophylaxis. There is known resistance of *Aeromonas* species to commonly used agents such as penicillins and augmentin. The recommended antibiotic at the present time is ciprofloxacin, which has favorable resistance profiles and good oral bioavailability.

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