Bibliography*: Thermosurgery in Dermatology

*Selected, quality filtered, not subject to external review

Policy Issue: A representative of Thermosurgery Technologies Inc. (TTI) (Phoenix, AZ) asked the VA National Director of Surgery within the Office of Patient Care Services (OPCS) to consider the evaluation and use of TTI's ThermoMed™ Model 1.8 in VA.

This request is being handled by the VA Technology Assessment Advisory Group (TAAG) within OPCS, which was created to deliver evidence-based recommendations for use of new technologies in VA in a timely manner. As part of this process, the VA Technology Assessment Program (VATAP) is charged with providing the best available evidence on a topic to the TAAG within a brief time period. The evidence would help support guidance for acquisition and use of ThermoMed™ in VA.

Background: The ThermoMed™ Model 1.8 is a portable, battery-operated device that delivers precisely controlled localized current field radio frequency heat to selectively destroy diseased tissue. TTI received FDA 510(k) approval for the ThermoMed™ Model 1.8 as a Class II device based on its substantial equivalence to predicate devices currently marketed in the US. FDA-approved indications for use include: warts, molluscum contagiosm, angioma, fibroma, seborrehic keratoses, acrochordon, syringoma, hydrocystoma, calvus, actinic keratoses, keloids, epidermoid cysts, cystic acne, cutaneous Leishmaniasis, atypical mycobacteria, dermatophytosis, and, most recently, basal cell carcinoma. [1]

Of particular interest to VA policy makers is the evidence for the use of ThermoMed™ to treat basal cell carcinoma and cutaneous leishmaniasis.

Basal cell carcinoma[2]

Skin cancer is a growing public health concern. More than 1.0 million estimated new cases of skin cancer were diagnosed in the United States in 2008, and the vast majority of cases were nonmelanoma types. Basal cell carcinoma (BCC) is the most common form of nonmelanoma skin cancer. BCC is slow growing, rarely metastasizes, and primarily affects individuals of light complexion. It tends to occur more often in individuals at lower latitudes, with increased sun exposure, of increasing age (> 40 years) and on sun-exposed areas of the skin, especially the head and neck. BCC can cause extensive tissue destruction, particularly on the face, resulting in significant cosmetic disfigurement if not treated early or adequately.

Treatment

The goals of treating skin cancer include early and complete removal of the entire tumor and the preservation or restoration of normal function and bodily appearance. The overall cure rate for BCC ranges from 85% to 95% and is directly related to the stage of the disease (early detection) and the type of treatment used. The first line of treatment is often simple excision with frozen or permanent sectioning for margin evaluation, but several alternatives exist: Mohs micrographic surgery, electrodesiccation and curettage, cryosurgery, carbon dioxide laser, radiation therapy, intralesional therapy with interferon alpha, photodynamic therapy, immunomodulators and chemotherapy.

A recent Cochrane review of interventions for BCC, excluding thermotherapy, found overall very little good quality research on treatments for BCC despite a large volume of work on the

[1] http://www.fda.gov/cdrh/pdf6/K063748.pdf accessed March 13, 2008.
[2] http://www.cancer.gov/cancertopics/types/skin NCI Skin Cancer Treatment (PDQ®), accessed March 13, 2008.

subject.[3] In terms of low recurrence and early treatment failure rates, surgery appears to be the most effective treatment followed by radiotherapy. Cosmetic outcomes appear better with photodynamic therapy than surgery, but long term follow up data are needed. Other treatments appear promising, but few have been compared to surgery. Most trials have only evaluated low risk BCCs, the results of which would not necessarily apply to individuals with the more invasive morpheaform (sclerosing) type BCC.

Cutaneous leishmaniasis[4,5]

Leishmaniasis is a collection of parasitic infectious diseases caused by species of *Leishmania* transmitted by the bite of a sand fly. Leishmaniasis is found largely in tropical and subtropical areas of the world ranging from rain forests in Central and South America to deserts in Southwest Asia, placing millions of people at risk for leishmaniasis infection or disease if they live in or travel to endemic areas.

There are several different forms of Leishmaniasis. The most common forms cause skin infections (cutaneous leishmaniasis or CL) or infect the internal organs such as the liver, spleen, or bone marrow (visceral leishmaniasis or VL). The number of new cases of CL each year in the world is estimated to be 1.5 million with 90% of cases located in Southwest Asia. Ninety percent of the estimated 500,000 new cases of VL annually live in India, Bangladesh, Nepal, Sudan, and Brazil.

Since 2003, 853 U.S. soldiers deployed to Afghanistan and Iraq have been diagnosed with CL and five with VL.[6] The majority of infections occurred in the early years of combat operations (August 2002-February 2004) prior to implementing preventive measures to decrease the risk for CL in military personnel. *L. major* was the most common species among CL infections, and *L. infantum* was considered the probable agent of VL.[7]

CL may present as a non-healing ulcerative lesion developing at the site of the sand fly bite (localized), as multiple non-ulcerative nodules (diffuse), or as destructive mucosal inflammation. The first sign of infection is typically an erythema which develops into a papule and then a nodule that progressively ulcerates over a period of 2 weeks to approximately 6 months. Localized CL varies in severity, clinical appearance, and time to spontaneously cure, which may take months or years. Less frequently, CL may spread through lymphatic channels and cause sporotrichoid disease presented as subcutaneous nodules. In rare cases and depending on the Leishmania species (primarily *L. braziliensis*), if left untreated, CL may spread to the nose or mouth and cause sores (mucosal leishmaniasis) that might not be noticed until years after the original skin sores have healed, and large lesions (caused primarily by *L. mexicana*) that appear nodular or vegetative or lesions involving cartilage may not heal at all.

Diagnosis of CL can be complicated by other endemic causes that present with a similar clinical spectrum. Therefore, parasitological confirmation is important to the diagnosis of CL and choice of treatment.

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[3] Bath-Hextall FJ, Perkins W, Bong J, Williams HC. Interventions for basal cell carcinoma of the skin. Cochrane Database of Systematic Reviews 2007, Issue 1. Art. No.: CD003412. DOI: 10.102/14651858. CD003412.pub2.
[4] http://www.cdc.gov/Ncidod/dpd/parasites/leishmania/factsht_leishmania.htm accessed March 14, 2008.
[5] MMWR Weekly;April 2, 2004;53(12):264-5. http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5312a4.htm accessed March 14, 2008.
[6] DASG-PPM-NC March 29, 2006 Information paper. Leishmaniasis And Other Parasitic Diseases Among Soldiers Deployed To Southwest Asia.
[7] Under Secretary for Health. Department of Veterans Affairs. Under Secretary for Health's Information Letter. Guidance for the Diagnosis and Treatment of Leishmania Infection. IL 10-2004-013. October 6, 2004.

Treatment[8,9]

The goals of CL treatment are to accelerate cure in order to reduce scarring and to prevent disease spread or relapse, while weighing maximal benefit and minimal harm to the patient. Magill[10] stresses that the treatment recommendations for the many different forms of CL are not straight forward, and the clinical reality of North American practitioners perhaps has been oversimplified:

> *"…The current reality, however especially in North America, is a "one size fits all" recommendation based on parenteral SbV [pentavalent antimony]. The heterogeneity and diversity of syndromes seen in clinical practice result in patients who present with a complex spectrum of lesions that are associated with cosmetic and functionally important considerations. Evidence-based treatment recommendations that apply to all the leishmaniases do not exist and experts disagree on the optimal individual case management."*

History and appearance of the lesion (size, number and location), parasitic strain, as well as clinician experience, patient preferences and cost-effectiveness considerations, will influence choice of treatment. Small (< 2 cm diameter) or sparse (5-10) lesions, and old epithelialized lesions are often left untreated. While CL is not life threatening, the permanent scarring from resolution of disease on its own can be severe, resulting in a mutilating appearance, or may become symptomatic because of secondary bacterial infection.

If treatment is indicated, local and systemic options exist, each with their own risks and benefits that must be weighed. Local treatments may be used to treat persons with a few, small sized lesions and for cosmesis without toxic systemic side effects. Local treatment options include:

- Physical methods—cryotherapy, surgical excision or curettage, or heat (delivered by cauterization, infrared or heat lamps, or radiowaves)
- Topical therapy—paromomycin phosphate (not commercially available in the US, but can be compounded)
- Intralesional injections—with pentavalent antimonials (but experience with this route of administration in the US is very limited)

Systemic therapy is used in more severe cases of CL with persistent (> 6 months duration), actively ulcerated lesions, multiple (≥ 3) or large lesions (> 2 cm in diameter), and for sores located on joints, hands, feet, face or ears that are not amenable to local treatment options. Pentavalent antimonials (meglumine antimoniate and sodium stibogluconate) are the principal parenteral drug therapies used to treat CL. They can be used in the US by physicians under an Investigational New Drug protocol on file with FDA. They are available to civilian physicians from the Parasitic Disease Drug Service of the Centers for Disease Control and Prevention and to military personnel from the Infectious Disease Service of the Walter Reed Army Medical Center in Washington DC.

Pentavalent antimonials can have serious, albeit reversible, toxicity effects including musculoskeletal pains, renal failure, and fatigue, plus high associated medical costs. Time commitment, drug-resistance, immunosupression and poor patient compliance may further affect treatment responsiveness. Other drug therapies have been tried but have limited

[8] Reithinger R, Dujardin J-C, Louzir C, et.al. Cutaneous Leishmaniasis. Lancet. 2007;7:581-596.
[9] Minodier P and Parola P. Cutaneous Leishmaniasis treatment. Travel Medicine and Infectious Disease. 2007;5:150-58.
[10] Magill AJ. Cutaneous Leishmaniasis in the Returning Traveler. Infect Dis N Am. 2005;19:241-66.

efficacy, eg. Amphotericin B deoxycholate for treatment of *L. braziliensis* and for second-line treatment of pentavalent antimonial failures.

No FDA-approved oral agents are indicated for Leishmaniasis. However, azole antifungal compounds such as fluconazole and itraconazole have shown antileishmanial activity *in vitro* and limited efficacy in clinical trials, and may be given alone or with pentavalent antimonials. Other oral agents are currently under investigation. In short, Magill (2007) summarizes the state of CL treatments today:

> *"Treatment options for CL, especially in North America, are limited and not satisfactory for optimal management of the individual patient. The diversity of clinical presentations can only be addressed satisfactorily at the extremes of the spectrum with cryotherapy or SSG [sodium stibogluconate]. Many patients present with lesions not suitable for local or physical methods, but not severe enough for toxic or poorly tolerated systemic treatment. An efficacious, well-tolerated, nonparenteral, systemic treatment is missing…"*

Interest in heat therapy devices have grown based on the concept that Leishmania amastigotes are susceptible to temperatures 39ºC or higher. Recently, thermotherapy using Thermomed™ has been introduced to the U.S. armed forces as a portable, easy-to-use local treatment option for CL.

Methods: To meet the immediate information needs of its client, first VATAP queried members of the International Network of Agencies for Health Technology Assessment (INAHTA)[11] electronically via their listserv on March 13, 2008 for existing reviews or reports in process on the ThermoMed™ system for either clinical indication.

Searches and Inclusion Criteria

VATAP then conducted searches on MEDLINE, EMBASE, BIOSIS, Science Citation Index, and Diogenes on Dialog© from 1990 to March 2008 as well as The Cochrane Library. Searches were done to capture research using the following concepts: cutaneous leishmaniaisis, basal cell carcinoma, keratoses, cystic acne, warts, fibroma; or any cutaneous, skin, or dermatologic condition using electrocautery, electrosurgery, electrodesiccation, radiofrequency, thermosurgery, thermomed, or thermotherapy.

Criteria for inclusion of studies in this review were:

- FDA-approved devices using ThermoMed™ or similar radiofrequency heat therapy devices for cutaneous Leishmaniasis or ThermoMed™ for treatment of basal cell carcinoma;
- Existing systematic reviews or health technology assessments on the topic;
- For primary studies, at least ten study subjects in each treatment arm;
- Full text to capture study details sufficient for table abstraction;
- The most recent or largest version of a study from the same investigators (to eliminate redundancy).

Case reports, meeting abstracts and articles not published in English were excluded from review. One reviewer (Adams) selected citations for full-text retrieval, reviewed all articles, abstracted information, and prepared this review.

[11] www.inahta.org

Results: The searches and hand searching of end references of retrieved articles identified 288 references, of which 45 were retrieved for further review as potentially relevant background material or primary studies.

Basal cell carcinoma
FDA 510(k) data suggested no histological evidence of tumor at three months follow up after a single treatment session and high patient satisfaction; the few reported side effects were localized mild infection, post treatment pain, and light headedness.[12] VATAP found no published evidence for the use of ThermoMed™ for treatment of basal cell carcinoma in the peer reviewed literature.

Cutaneous leishmaniasis
Seven primary studies met inclusion criteria for review: five randomized controlled trials (RCT) (Sadeghian 2007; Lobo 2006; Aronson 2005; Reithinger 2005; Navin 1990) and two case series (Willard 2005; Velasco-Castrejon 1997). See Tables 1 and 2.

Of note, in searches of end references VATAP identified one meeting abstract by Aronson (2004)[13] describing preliminary results of a RCT comparing intravenous sodium stibogluconate (SSG) versus thermotherapy in treating cutaneous *L. major* in U.S. military personnel, but VATAP did not identify any follow up full text of the study in the searches. However, this study group reported one-year follow up data in another abstract in 2005[14], which the author provided to VATAP (personal communication: N. Aronson March 31, 2008). Because the study was conducted in U.S. military personnel exposed in Iraq and is relevant to the health status of current veterans, an exception to the inclusion criteria was made and the abstract information was included in Table 1. Their results suggested "…*less systemic toxicity and good efficacy when compared to 10 days of intravenous SSG therapy. Follow-up photographs suggest similar late cosmetic effects.*"

All but one RCT (Sadeghian 2007) used a radiofrequency heat device by Thermosurgery, Inc. RF heat was administered at 50ºC for 30 seconds until the lesion was covered, but administration varied from a single session (Lobo 2006; Aronson 2005; Reithinger 2005) to weekly sessions for several weeks (Sadeghian 2007; Navin 1990). Sadeghian (2007) used a radiofrequency heat generator (4 MHz, maximum output 90 W) by Ellman International, Inc. (New York, USA), which produces a variety of FDA-approved radiosurgical devices for use in dermatology, although treatment for cutaneous Leishmaniasis is not stated as a specific indication for use in its on-line product information.[15]

All used pentavalent antimonials as control groups with varying dosage schedules and administration (intramuscular, intralesion, or IV), and only Navin (1990) included a placebo heat therapy group. All but one (Sadeghian 2007) reported the Leishmania species from confirmed diagnoses that were endemic to their geographic region, but only Aronson (2005) included *L. major* which is the most prevalent species among OEF/OIF military personnel.

[12] http://www.fda.gov/cdrh/pdf6/K063748.pdf accessed March 19, 2008.
[13] Aronson N, Wortmann G, Byrne W, et al. A randomized trial of sodium stibogluconate versus heat therapy in cutaneous Leishmania major [abstract P428]. In: Program and abstracts of the 44th Interscience Conference on Antimicrobial Agents and Chemotherapy (Washington, DC). Washington, DC: American Society for Microbiology, 2004:452.
[14] Aronson N, Wortmann G, Oster C, Byrne W, Kester K, Bernstein W, Marovich M, Yoon I, Polhemus M, Benson P. A randomized trial of sodium stibogluconate versus thermotherapy in cutaneous Leishmania major. Late breaker, 54th annual meeting of the Am Soc Tropical Medicine and Hygiene, Washington DC, Dec 2005.
[15] http://www.ellman.com/products/medical/dermatology.htm accessed March 31, 2008.

All reported using a randomization process of varying detail which resulted in comparable baseline statistics across study groups. Groups were comprised primarily of adults with no prior history of Leishmania diagnosis or treatment and with disease of variable duration and severity at presentation. Lesions were generally small, variably defined as 1-10 cm in diameter, and numbers of lesions ranged from 1 or 2 to less than 20 per subject. Pregnant women, young children and those with significant underlying diseases were excluded due to the toxicity of pentavalent drug therapy. Subjects with lesions of the ear, on the face, or on joints or fingers were excluded in most studies because these locations are not amenable to localized heat therapy. Treatment efficacy (cure) was reported in terms of visual complete or partial reepithelialization, the proportion of complete healing at the conclusion of follow up, or time to cure. Follow up time periods ranged from 28 days to 52 weeks. Loss to follow up was minimal, except Reithinger (2005) which experienced 40% lost to follow up. Reported adverse effects associated with ThermoMed™ were blistering and secondary bacterial infections which were successfully treated with antibiotic therapy.

The two case series (Willard 2005; Velasco-Castrejon 1997) in Table 2 tested the feasibility of, and described the clinical experience with, ThermoMed™ in US soldiers at Fort Campbell and in a primary care setting in Mexico, respectively. In general, ThermoMed™ was found to be safe, well-tolerated and efficacious. Adverse effects were minimal, but local anesthetic was required and wound care for blistering and oozing required daily dressing changes for several days. The convenience of one-day treatment, acceptable cosmesis, and low associated costs and compliance requirements relative to other drug therapy regimens may provide another treatment alternative to those patients with less severe CL:

- smaller size;
- few lesions;
- no evidence of lymphatic spread, or
- CL infected with certain species eg. *L. mexicana*, that prove difficult to heal.

For patients with more severe CL or with lesions on the face, exposed surfaces, or over joints, pentavalent antimonials are still the drugs of choice.

Conclusions/discussion: The variability in study protocols make it difficult to draw firm conclusions about the treatment efficacy of radiofrequency heat therapy using ThermoMed™ relative to available therapies for which greater clinical experience exists or for which different dosage schedules than those used in earlier studies are now recommended.

In general, ThermoMed™ as a single session local treatment option appears well-tolerated with local anesthesia and without exaggerated scarring or color changes. Evidence suggests that the optimal candidates for ThermoMed™ are patients with less severe forms of infection in areas of the body that are appropriate for heat therapy and without evidence of lymphatic spread. Post treatment wound care is essential, as blistering and secondary infection are the most common adverse effects. There is no consensus regarding the appropriate length of follow up, but evidence of complete or partial healing occurred within two months in the majority of cases. Longer follow up is desirable to detect recurrence or document slower healing lesions.

Anecdotal evidence in Lobo (2006) suggested a systemic cytokinine response effect in both treatment groups, but further study is needed to determine if all lesions of a patient with multiple lesions require local heat therapy. Further study is also needed to determine if degree of healing and duration of infection at clinical presentation and Leishmania species play important roles in treatment effectiveness.

Wortmann (2005) summarized the state of thermotherapy with ThermoMed™ for treatment of CL as follows:

> *"In summary, thermotherapy with a LCF-RF [localized current field-radio frequency] device is an important and useful addition to existing treatment modalities;;;The device will be especially useful in situations involving large numbers of patients (in which injections with antinomy are impractical); for children (because intralesional injections with antimony are painful); for patients with small, localized lesions; and, potentially, in cases refractory to antimony therapy. There are, however, few data on the efficacy of the device for treatment of large lesions, lesions associated with regional adenopathy, and lesions caused by species (such as L. braziliensis) known to spread outside of the apparent skin lesion and cause late-onset mucosal disease. Significant rates of soft-tissue infection after use have been reported in some studies, and there are scant data on the long-term risk of scarring and keloid formation after treatment.*
>
> *The LCF-RF device is a technically sophisticated piece of machinery, and its portability and ease of use offer effective therapy to many patients who might otherwise, because of the cost of the unavailability of other therapies, go untreated. Still, the underlying principle (the physical destruction of the parasite, along with some of the host tissue) is not that much different from other direct local therapies, and it is sobering to realize just how far the treatment of cutaneous Leishmaniasis has not advanced over the centuries. Stir the cauldron and sprinkle antimony, or reach for the smoldering brand and cauterize? Between the toxicities of antimony, the medical incongruity of burning a lesion to save the skin, and the modest effectiveness of other, alternative therapies, it is clear that the treatment of cutaneous Leishmaniasis is far from its apogee. We still lack a safe, affordable, and effective treatment, and although LCF-RF device is one more stone laid on the path, we still have a long road to travel."*

Full published results from Aronson and colleagues at Walter Reed Army Medical Center comparing a current therapeutic regimen of SSG versus ThermoMed™ would help inform the knowledge base of available treatment options that are most relevant to US military personnel and veterans exposed to endemic areas in present war zones.

Regarding ThermoMed™ for treatment of basal cell carcinoma, Bath-Hextall (2007) lists implications for future research of BCC treatments in general:

- Promising preliminary results from an ongoing long-term study of imiquimod versus surgery should be confirmed before routine use.
- Clinical trials comparing other alternatives to excisional surgery with long-term follow up data (at least three years) should be conducted before recommending for routine use.
- Future trials should make clear which type of BCCs are being studied with respect to size, location and histological types; morpheaform type and recurrent malignancies should be analyzed separately.
- Assessment of adverse effects should include pain, cosmetic appearance and costs.

Table 1. Controlled Trials of Localized Radiofrequency Heat for Treatment of Cutaneous Leishmaniasis

Study attributes	Sadeghian 2007	Lobo 2006	Aronson 2005 (abstract only)	Reithinger 2005	Navin 1990
Study location	Iran	Brazil	Walter Reed AMC	Kabul	Guatemala
Intervention: Radiofrequency heat therapy	• Instrument=RF heat generator by Ellman International, NY, USA • Heated to 50ºC surface temp for 30 s once weekly X 4 consecutive weeks	• Instrument= Thermosurgery, Inc. • Single session heat at 50ºC applied for 30 s at each adjacent area of lesion until completely covered, taking 4-5 min. • Meglutamine antimonite given at day 28	• Instrument=ThermoMed by Thermosurgery, Inc • 50ºC for 30 s in one session • Followed for 10 days	• Instrument=ThermoMed by Thermosurgery, Inc • Single session ≥ 1 consecutive application of 50ºC for 30 s, depending on lesion size • Patients not cured after 100 days got IM or IL SSG	• Instrument=Thermosurgery ™ by RDM International (Phoenix AZ) • 50ºC for 30 s given 1/week X 3 weeks
Control group(s)	IL Meglumine antimoniate (Glucantime®, Sanofi-Aventis, France) Dose: 0.1-4 mL (85 mg pentavalent antimony/ml) once weekly X 4 consecutive wks	IV Meglutamine antimonite (Glucantime®; Rhodia) , 20 mg/kg/d X 20 days	• IV sodium stibogluconate (SSG) 20 mg/kg/day for 10 doses	• IL generic SSG, 5 injections of 2-5 ml/5-7 days for up to 29 days, or • IM injection of SSG 20 ml/mg/kg up to max dose of 850 mg for 21 days	• IM Meglutumine antimonate (MA) (850 mg daily X 15 days, or • Placebo heat therapy with no heat
Sample size (N subjects)	Heat=57 (83 lesions) Control=60 (94 lesions)	Heat= 17 Control=20	Heat=27 SSG=27	Those who completed study IL SSG=93/146 (64%) IM SSG=58/117 (49.5%) Heat=108/138 (78%)	IM MA= 22 Heat=22 Placebo=22
Leishmania species	Not reported	Confirmed or likely *L. braziliensis*	*L. major*	*L. tropica*	*L. m. mexicana* (20%) *L. b. braziliensis* (60%) Unknown (20%)
Inclusion criteria	• Smear positive Leishmania diagnosis • Antroponotic CL • Seen at skin diseases and Leishmaniasis research center	67 adults screened: • ≤ 2 lesions total • ≤ 10 cm in size • No ML involvement • Compliant with protocol • No prior history of Leishmaniasis or tx for it	Confirmed cutaneous *L. major* infection	431 subjects at a Leishmaniasis center from Jan-Sept 2003: • 1 suspected CL lesion • Age > 5 years	80 Guatemalan soldiers who sought treatment for suspected CL • Ages 18-60 • Confirmed diagnosis • Lesion size < 25 cm^2
Exclusion criteria	• Pregnant women • Children < 5 years • Prior antileishmanial therapy • Significant underlying diseases • Patients with facial lesions	• Pregnant women, children • Contraindications to drug, • Prior antileishmanial therapy or history	• Facial lesions • Non L. major infections • Those with > 20 lesions	• Pregnant women • Breast feeding women • Prior antileishmanial therapy or history • Major surgery in prior 3 months • Uncontrolled medical condition • Unavailability for follow up • Lesions near eyes, nose, lips	• Women or children • Prior antimonial treatment • No serious medical problems • No visual evidence of mucosal involvement • Lesions of the ear, near the eye, or on finger

Study attributes	Sadeghian 2007	Lobo 2006	Aronson 2005 (abstract only)	Reithinger 2005	Navin 1990
Baseline characteristics (severity of infection, age, sex, duration of complaint)	Matched for age, sex, duration of disease, type, number and site of lesions	• Comparable baseline • More patients with 2 lesions in control group but not statistically significant	• 53/57 were male • Median age=24 (range, 18-57) • 59% white, 21% black, 14% Hispanic • Median # skin lesions=2 (range 1-17) • Median lesion size= 133mm^2 (range, 9-1548) • Median lesion presence=123 days (range, 45-270)	• Comparable baseline characteristics • 43% patients with facial lesions • 38% on hands, 16% on legs, 2% on arms	• Comparable baseline stats among groups • 68% with only one lesion • Lesions apparent on average 58 days prior to seeking tx • 53 (80%) patients with infecting parasite identified
Randomization	Yes, computerized	Yes, details not described	Yes, details not described	Yes, details described	Yes, details not described
Blinding of patients, health workers, and study personnel	Health worker conducting F/U evaluation was blinded to treatment	Not reported	Not reported	Blinded follow up	Patient blinded to heat and placebo tx
Loss to follow up	None	1 in heat group	None	172/431 (40% overall)	Follow up at week 9 (100%),13 (100%), 26 (97%) and 52 (95%) after start of tx
Intention-to-treat analysis	Yes	Yes	?	Yes	No
Length of follow up	• Weekly during 4 weeks of treatment • Monthly for 6 months	Outcomes at 14 days, 28 days	• 12 months	4 patient follow up visits End point=100 days	• Up to 52 weeks from start of therapy • Patients with partially reepithelialized lesions at week 13 were removed from study and given MA
Outcome measure(s)	• Complete=lesions flattened, no induration, epidermal creases appeared • Partial=lesion size decreased but no epidermal creases • Poor= size of induration was unchanged or increased	• Lesion healing, and size plus biopsy at days 14 and 28 • Systemic cytokine production by PBMCs (TNF-α, IFN-γ, IL-5, IL-10) at day 0, 14 and 28 • Healing=decrease in lesion size and > 50d% reepithelialization of ulcer	• Visual healing at 2 months	• Tx efficacy=% cured at 100 days, time to cure, odds for cure • Cure=complete reepithelialization of CL lesion with no evidence of papules, inflammation or induration	• Clinical response at 2,6, 9,13, 26 and 52 • Clinical response= complete reepithelialization and no evidence of papules, inflammation or induration • Reactivated lesion = appearance of a lesion within or at the border of previous lesion • New lesions that appeared after tx, but were not defined as tx failure • Clinical response and cosmetic outcome photographed at week 9, 26, and 52

Study attributes	Sadeghian 2007	Lobo 2006	Aronson 2005 (abstract only)	Reithinger 2005	Navin 1990
Results					
Treatment effect	• Analyzed by patient: Complete, partial and poor responses were 80.7%, 12.3% and 7% in heat group vs. 56.7%, 24.9% and 18.4% in control group, respectively (P=0.02). • Analyzed by lesion: Complete, partial and poor responses were 80.7%, 12% and 7.3% in heat group vs. 55.3%, 21.3% and 23.4% in control group, respectively (P=0.001). • Mean scar size significantly less in Heat group 11.2 ± 4.7 mm vs. Controls 14.8 ± 5.5 mm (P< 0.05) • No relapse from lesions with complete response in either group after follow up	• Partial healing: 12/16 (75%) in heat group and 18/20 (90%) in control group • Complete healing: 1 in heat therapy vs. 2 in control group • No healing: 3 in heat group • No statistically sig difference on overall response rates between two groups (χ^2=4.14; P=0.1261), nor did size influence healing • Parasite burden at day 14: heat group=25% negative biopsies plus a reduction in parasitism intensity in 2 patients • Control group=64% negative biopsies	• Incomplete healing at 2 months: SSG=7% vs. Heat=27% (p=0.076) • No other later relapses • All electing crossover treatment responded • 12 month photos show similar scarring between treatment groups	Cure rates (ITT var†): • Heat=75/138 (54%) • IM SSG=70/117 (60%) • IL SSG=105/146 (72%) • No relapses Time to cure (median, days): • Heat= 53 days vs. Il SSG (75 days) or IM SSG (> 100 days) (P=.003) Odds of cure (ITT var†): (OR, 95% CI) • IL SSG vs. Heat =2.15 (1.28-3.63) (*P*< .01) • IL SSG vs. IM SSG=1.72 (0.99-2.98) (*P*< .05) • IM SSG vs. Heat =1.25 (0.74-2.13) • No stat sig differences noted across groups in rate of secondary infections before or after treatment	Analyzed by patient: • At week 13, complete response and parasitologically negative lesions: • MA, 16/22 (73%); • localized heat, 16/22 (73%); and • placebo, 6/22 (27%). Cure rate for those with *L. braziliensis* infection: • MA 11/14 (79%); • heat 9/14 (64%); • placebo 0/11. • Cure rates varied across species: Placebo response rate was higher in *L.mexicana* (5/7) species than in *L. braziliensis* (0/11) (*P*=0.002; Fisher's exact test) • 5 patients developed new *L. braziliensis* lesions during f/u, likely due to new infection from re-exposure
Adverse effects	• Heat group=satellite lesion after tx (1) • Control group=allergic reactions eg. erythema, edema, pruritus around lesion (4 patients with 10 lesions), sporotrichoid lesions (4), satellite lesions after tx(3)	• Secondary bacterial infection: Heat (7), control (1) • Note: in one heat-treated patient, the untreated lesion on opposite leg healed as rapidly as the treated lesion	SSG group: • Pancreatic toxicity (85%) • Liver (41%) • Fatigue (85%) • Musculoskeletal symptoms (67%) Heat group: • Blistering (85%) • Secondary infection (19%)		Celllulitis in heat group (2 at beginning and 4 during tx) successfully tx with dicloxacillin
Conflict of interest	Statement present: none declared	Statement present: None declared	No statement	Statement present: • Reithinger is part-time employee with Thermosurgery • Other authors have no conflicts	No statement
Comments		• Results suggest a systemic cytokine response in both groups, but cause (due to therapy vs. healing process) is inconclusive	Conclusion: "*Using a FDA-cleared device, thermotherapy for localized cutaneous L. major has less systemic toxicity and good efficacy when compared to*	• Species may affect effectiveness of Thermomed--*L. major* is less temperature resistant than *L. tropica*. • Patient compliance is a	• Reepithelialization with heat was slower than with MA =less acceptable to patients and difficult to access need for further tx, but rapid

Study attributes	Sadeghian 2007	Lobo 2006	Aronson 2005 (abstract only)	Reithinger 2005	Navin 1990
		• Controlled study is needed to determine if all lesions on a patient with multiple lesions need to be treated • Large controlled trial comparing heat vs. Glucantime with 10-year follow up has been initated	*10 days of intravenous SSG therapy. Follow-up photographs suggest similar late cosmetic effects"*	problem with IM injections (painful)	response with MA did not always result in lasting cure. • Both tx more effective than placebo • Higher thermal doses at different administrations are needed to detect improvement in response rates without increasing adverse effects

†=ITT var, analysis including patients LTFU during treatment, who were considered to have experienced cure, and including patients LTFU after treatment completion, who were considered to have experienced treatment failure.

LTFU, loss to follow up

Table 2. Case series of localized radiofrequency heat therapy for treatment of Cutaneous Leishmaniasis

Study attributes	Willard 2005	Velasco-Castrejon 1997
Objective(s)		Test feasibility of ThermoMed for treatment of CL presenting to primary care facilities and a regional hospital in an endemic area
Perspective	Retrospective	Prospective
Intervention (s)	Soldier chose treatment options offered based on clinical presentation: • Pentostam (for confirmed disease only) • oral fluconazole • Itraconazole • Thermomed single session • Cryotherapy single session • No treatment	Thermomed • Single session ≥ 1 consecutive application of 50ºC for 30 s, depending on lesion size • 11 patients received additional treatment to ensure complete coverage of entire lesion
Study group(s)	OEF/OIF soldiers at Ft. Campbell, KY with suspected or confirmed CL disease Confirmation by smear, PCR or biopsy Suspected based on exposure history and skin lesions suspected as CL	Patients with confirmed CL from five health jurisdictions in Tabasco, Mexico Diffuse CL excluded 63% male Ages 2-75 years Lesion history range 1 month to > 3 years Location of lesion: 42% upper extremeties 11% on ear cartilidge No tx history < 60 days
Sample size	Confirmed=181 Suspected=56	N=201, 122 available for evaluation at end of 4 weeks, 191 available at 8 weeks
Leishmania species	*L. major*	*L. mexicana*
Length of follow up	Variable	8 weeks
Outcome measure(s)	Not defined	Complete cure= reepithelialization and no induration or discoloration
Results		
Treatment effect	Treatment failure/treated in confirmed cases: • Pentostam (N/A) • oral fluconazole (4/15) • Itraconazole (0/2) • Thermomed (1/26) • Cryotherapy (0/4) • No treatment (72)	Complete cure=181/191 (90%) or > if consider that nonreturners were completely healed
Comments	• Practitioners deemed treatment safe, well-tolerated and largely effective • Soldiers generally satisfied with Thermomed, had little post treatment pain, no exaggerated scarring, atrophy or color changes. One day treatment offered convenience and increased compliance with tx. • Disadvantages of Thermomed: • Local anesthetic needed • Blistering and oozing for several days post tx • Daily dressing changes for up to 2 weeks.	• This form of treatment proved to be effective and convenient for use in primary health care facilities in Mexico and has many advantages over traditional forms of therapy • Convenience and low cost may improve access to technology and tx compliance

Study attributes	Willard 2005	Velasco-Castrejon 1997
	• Expense=> $20,000 per unit • Cryotherapy used for small, nonfacial lesions and for satellite papules near resolving lesions after Thermomed • Pentostam recipients had complicated lesions on face, over joints, or on exposed surgaces or large (> 3.5 cm diameter) lesions.	
Conflict of interest statement	Statement present: none reported	• Statement present: none reported

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