
Cutaneous leishmaniasis in soldiers from Fort Campbell, Kentucky returning from Operation Iraqi Freedom highlights diagnostic and therapeutic options

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Background: Cutaneous leishmaniasis (CL), rare in the first Gulf War, is common in American troops serving in Operation Iraqi Freedom. Awareness of the clinical features and treatment options of CL would benefit clinicians who may encounter soldiers, as well as civilians, returning from the Middle East with skin lesions.

Objective: Our purpose was to describe our clinical experience in treating soldiers with CL.

Methods: From December 2003 through June 2004, approximately 360 of an estimated 20,000 soldiers returning from a yearlong deployment in Iraq with skin lesions suspected of being CL were examined by dermatologists. We summarized CL diagnoses, laboratory evaluations, and treatments, including localized heat therapy (ThermoMed model 1.8; ThermoSurgery Technologies, Inc, Phoenix, Ariz), oral fluconazole, cryotherapy, and itraconazole.

Results: Among 237 soldiers diagnosed with CL, 181 had one or more laboratory confirmations, most by Giemsa-stained lesion smears and polymerase chain reaction (PCR). PCR was positive for all 122 smear-positive and 26 biopsy-positive lesions and all 34 smear negative and all 3 biopsy-negative cases. Primary outpatient treatments, including ThermoMed (n = 26), oral fluconazole (n = 15), cryotherapy (n = 4), and itraconazole (n = 2), were safe and tolerable. Treatment failure occurred in 2 fluconazole recipients and was suspected in 1 ThermoMed and 2 fluconazole recipients. Seventy-two soldiers elected no treatment.

Limitation: This was a retrospective study.

Conclusion: Approximately 1% of Ft Campbell troops returning from Iraq were diagnosed with CL, most by laboratory confirmation. PCR appeared to be the most useful diagnostic technique. Among outpatient treatments, ThermoMed and cryotherapy had favorable safety and efficacy profiles. (J Am Acad Dermatol 2005;52:977-87.)

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The Middle East is an endemic region for cutaneous leishmaniasis (CL), generally caused by one of three *Leishmania* species that include *L major*, *L tropica*, and *L aethiopicum*.¹⁻³ CL in this geographic location is called Old World leishmaniasis, also commonly known as “Baghdad boil.”³ CL is considered a localized disease, typically presenting as one or more papules or nodules that eventually ulcerates. Untreated CL self-heals 12 to 18 months after a lesion has reached maximal size, but usually with a variable amount of scarring. CL may disseminate through lymphatic channels and cause sporotrichoid disease, manifested by subcutaneous nodules that may contain organisms.^{4,5} However, systemic multiple organ disease is atypical and has

only been reported in a few American soldiers with CL caused by *L tropica* who served in the first Gulf War (1991; Operation Desert Storm).^{6,7} Mucocutaneous leishmaniasis, endemic to Central and South America, is caused primarily by *L braziliensis*, organisms with a tropism for mucous membranes of the nose and mouth. Rarely, Old World CL caused by *L major* or *L aethiopicum* may develop into mucocutaneous disease, but this may represent direct extension from skin lesions rather than metastatic spread of organisms.⁸⁻¹⁰

In Operation Iraqi Freedom (OIF), many soldiers are expected to acquire CL, nearly all caused by *L major*.^{11,12} Despite the self-healing nature of CL, prompt diagnosis and therapy, especially for lesions on the face or exposed areas of the extremities, or over joints, may reduce healing time, prevent the stigma of an exposed ulcerated lesion, and, importantly, improve the cosmetic appearance of the residual scar.^{12,13} US Army soldiers with suspected CL may undergo one or more laboratory procedures for parasitologic confirmation to include lesion smear, biopsy, polymerase chain reaction (PCR) or, less commonly, culture.¹¹ Local treatment options include cryotherapy and ThermoMed (model 1.8; ThermoSurgery Technologies, Inc, Phoenix, Ariz), a device with FDA 510K clearance that delivers localized radiofrequency-generated heat directly to a lesion through a set of prongs placed onto the lesion.¹⁴ Systemic treatments include Pentostam (GlaxoSmithKline; Research Triangle Park, NC), a parenterally delivered pentavalent antimony compound (heavy metal) associated with transient but important side-effects,¹⁵⁻¹⁷ and oral fluconazole, a second-line therapy administered daily for 6 weeks.¹⁸

From December 2003 through June 2004, the Dermatology Service at Ft Campbell, Kentucky, examined approximately 360 soldiers who had returned from a yearlong deployment in Iraq with skin complaints suspected as being CL. Most were assessed by Giemsa-stained lesion smear, punch biopsy, or PCR of lesional material. Among 237 soldiers diagnosed with CL, 181 had one or more confirmatory laboratory diagnostic procedures; many elected to receive therapy. Characteristics of the soldiers with CL and the diagnostic and therapeutic outcomes from Ft Campbell are summarized.

PATIENTS, METHODS, AND TREATMENTS

Between December 2003 and June 2004, an estimated 20,000 soldiers returned to Ft Campbell, Kentucky, after a year-long tour in Iraq. Any soldier with a skin complaint was first seen by a primary care provider at the designated health-screening site. Any

soldier with lesions suspected of being CL was referred to the dermatology service for further evaluation. In order of highest likelihood for CL, most soldiers were assessed by a Giemsa-stained lesion smear, PCR of lesional material, or a punch biopsy. All sampling techniques were done with the patient under local anesthesia using 1% or 2% lidocaine containing epinephrine. Punch biopsy specimens were obtained by standard technique, targeting the lesion edge. Smears were obtained by removing the scale crust from the edge of a lesion, followed by scraping of the lesion base with a No. 15 or similar surgical blade and placement of lesional material on several glass slides, as described elsewhere.¹⁹ Samples for PCR were obtained from biopsy or lesional scrapings and placed in 70% ethanol until analysis. The smears were stained with a stock Giemsa solution (Fisher Scientific, Catalogue No. 23-264983) according to a standardized operating procedure and biopsy specimens were stained with hematoxylin-eosin or Giemsa.

Paraffin-embedded biopsy specimens and smears were interpreted by experienced pathologists or parasitologists at Ft Campbell, the Armed Forces Institute of Pathology (Washington, DC), or the Walter Reed Army Institute of Research (Silver Spring, Md), according to standardized operating procedure. For smears, each slide was generally reviewed for at least 10 minutes before declaring "no amastigotes seen," denoted as a negative result in this study. Genus-specific PCR was conducted at the Leishmania Diagnostics Laboratory, Walter Reed Army Institute of Research, according to established methods.^{12,20} This laboratory is certified by the College of American Pathologists and the Clinical Laboratory Improvement Program (Department of Defense equivalent of CLIA) for *Leishmania* in vitro culture, smear preparation and interpretation, and PCR for genus and speciation (*L major*). In any soldier, one or more conclusive laboratory assessments (smear, PCR, or biopsy) qualified as a "confirmed" case.

Some soldiers returned to Ft Campbell with an established diagnosis of CL by smear, PCR, or biopsy and were seeking treatment. Other soldiers with an exposure history and skin lesions suspected as being CL but with inconclusive or lack of any laboratory work-up were classified as "clinical diagnoses." Criteria for a clinical diagnosis included history of a papule or nodule that repeatedly ulcerated and crusted for at least 90 days and, on examination, was either a nonerosive, nonulcerated, erythematous to violaceous plaque that, by history, was decreasing in size for the past 4 to 6 weeks, or a scar consistent with CL (atrophic or hypertrophic, hyperpigmented, or

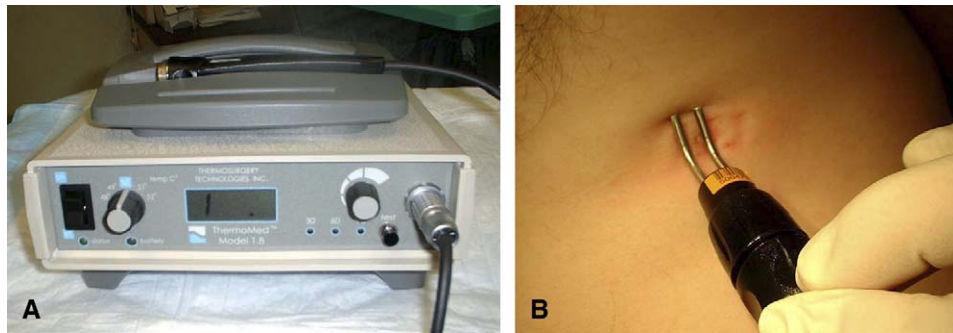


Fig 1. **A,** ThermoMed device. **B,** Metal prongs placed over lesional skin delivers localized radiofrequency heat at 50°C to an approximately 1-cm² area.

violaceous cicatricial plaque). In most cases, oral antibiotic therapy had failed to resolve the lesion. Because this was a retrospective analysis, a negative laboratory work-up did not necessarily alter the original clinical impression and a clinical diagnosis of CL was reported as such.

Soldiers with laboratory-confirmed or clinically diagnosed CL were counseled on the natural history of CL and the treatment options available. These included two systemic therapies, parenteral Pentostam and oral fluconazole, and two localized therapies, ThermoMed and cryotherapy.¹⁴ Because CL is self-healing, the option of observation without treatment was also discussed. The final decision on treatment was made by the soldier, but systemic therapy was limited to laboratory-confirmed cases.

Pentostam, a parenterally administered pentavalent antimony compound, has been used for many years in US soldiers with all forms of leishmaniasis.^{15,21} In our study, referral for Pentostam was offered to soldiers with facial lesions, those on exposed areas of the extremities, or those over joints. Pentostam is administered as an investigational new drug to inpatients at Walter Reed and Brooke Army Medical Centers in Washington, DC, and San Antonio, Texas, respectively, for 10 to 20 days.²¹ The other systemic therapy, oral fluconazole, is not approved by the Food and Drug Administration for CL but was offered as a second-line therapy on the basis of a 2002 report whereby CL due to *L major* may have resolved slightly faster when 200 mg of fluconazole was administered daily for 6 weeks under direct observation.¹⁸ Eventually, we offered itraconazole (200 mg twice daily for 6 weeks) as a second-line treatment, a therapy shown to have modest success in CL.^{4,22-25}

Fig 1 shows the ThermoMed device, a radiofrequency heat delivery system in which two prongs are placed over anesthetized lesions in a grid-like fashion (approximately every 1 cm²) for 30-second treatment periods at the target temperature until

the entire lesion, and up to 0.5 to 1 cm of normal-appearing surrounding skin, has been treated.^{14,26} The target temperature between the prongs is 50°C.¹⁴ In all patients, 1% or 2% lidocaine without epinephrine was used to anesthetize the lesion and surrounding skin before therapy. All lesions treated with ThermoMed then had gentamicin ointment applied and were covered with a standard gauze bandage. Patients returned the following day for bandage change and general assessment and then self-applied gentamicin ointment and a new bandage daily for up to 2 weeks or until the lesion was healed (complete re-epithelialization without residual ulcer or crust). Longer term follow-ups to assess response and healing were scheduled between 2 and 6 months, depending on soldier availability.

For cryotherapy, liquid nitrogen was sprayed by using a Cry-Ac-3 device (spray tip "B," Brymill Cryogenic Systems, Ellington, Conn) on lesional and up to 0.5 cm of surrounding normal-appearing skin to cause frosting for at least 30 seconds, followed by one re-treatment after a slow thaw. No anesthetic was used. Soldiers receiving cryotherapy or fluconazole were instructed to visit the clinic in 1 month and then approximately every 3 months as available to assess for treatment response, recurrence, and adverse sequelae, such as exaggerated scarring, atrophy, or color changes, at lesion sites.

RESULTS

Patients and diagnoses

Table I summarizes the clinical characteristics of soldiers diagnosed with CL. The majority of soldiers had been assigned to northern Iraq, especially the northwest quadrant. Sporotrichoid spread was noted in 7 cases, manifested as ulcers with one or more proximal subcutaneous nodules without surface changes (Fig 2). There were no signs of spread beyond the skin and regional lymph nodes. None of the soldiers had mucosal lesions.

Table I. Characteristics of 237 soldiers diagnosed with cutaneous leishmaniasis

| | Laboratory confirmed (n = 181) | Clinical diagnosis* (n = 56) |
|---|-----------------------------------|---------------------------------|
| Gender | 176 men, 5 women | 54 men, 2 women |
| Areas of Iraq assigned (No.) [†] | | |
| Northeast | 81 | 23 |
| Northwest | 169 | 53 |
| Southeast | 8 | 6 |
| Southwest | 17 | 9 |
| No. of lesions per patient (No.) | 1 (73) | 1 (25) |
| | 2 (43) | 2 (20) |
| | 3 (21) | 3 (3) |
| | 4 (22) | 4 (3) |
| | 5 (9) | 5 (4) |
| | 6 (6) | 6 (1) |
| | 7 (6) | |
| | 13 (1) | |
| Mean No. of lesions per person | 2.5 | 2.0 |
| Mean diameter of largest lesion (cm) (range) [‡] | 2 (0.3-5) | 1.3 (0.3-3.8) |
| Lesion location | | |
| Face only (No.) | 8 | 0 |
| Extremities-trunk only (No.) | 163 | 56 |
| Both areas (No.) | 10 | 0 |
| Lesion(s) over a joint (No.) | 55 | 11 |
| Sporotrichoid spread (No.) | 7 [§] | 0 |

*Based on history and skin lesion morphology only (19 with inconclusive laboratory evaluations).

[†]Reflects multiple assignments for some soldiers.

[‡]For persons with ≥ 2 lesions.

[§]Does not include 1 patient with suspected fluconazole failure.

The flow chart depicted in Fig 3 shows 237 soldiers diagnosed with CL divided between laboratory-confirmed and clinically diagnosed cases. Among 181 soldiers with laboratory-confirmed CL, conclusive assessments were as follows: smear/PCR (n = 106), a single method (n = 59), PCR/biopsy (n = 12), smear/PCR/biopsy (n = 3), and smear/biopsy (n = 1). In soldiers with 2 or more lesions, the most clinically suggestive lesion for CL was usually evaluated. As initial diagnostic steps, we generally obtained smears from lesions highly suspected to be CL (crusted erosion or ulcer) and biopsy specimens on equivocal lesions or those appearing as "late-stage" CL. A biopsy was also conducted on any lesion highly suspected to be CL that was smear negative.

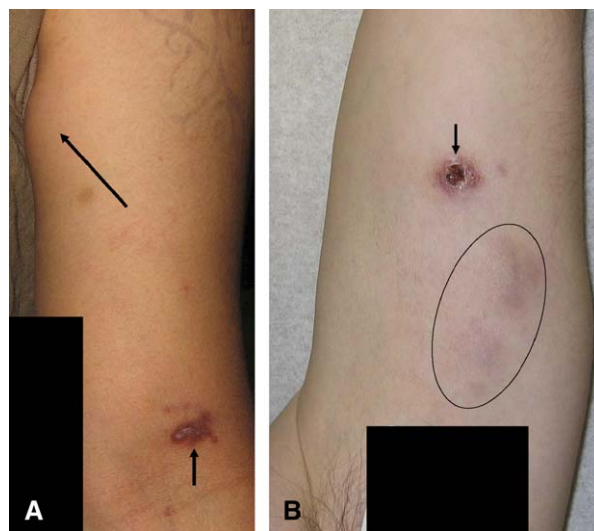


Fig 2. A and B, Sporotrichoid CL. Primary CL lesions on upper and medial arm (*short arrows*) with proximal spread denoted by *long arrow* and *circle*, respectively.

Among 156 soldiers with laboratory-confirmed CL lesions that were smeared, there were 122 positive and 34 negative outcomes (78% and 22%, respectively). PCR confirmed all 122 smear-positive and all 34 smear-negative lesions, as well as all 26 biopsy-positive and all 3 biopsy-negative lesions. There were no instances of a smear-positive lesion or biopsy-positive lesion that was negative on PCR. Soldiers who had PCR and biopsy procedures but no smear were generally those whose lesions had been sampled in the field and sent to the United States for assessment.

Fifty-six soldiers had clinical diagnoses of CL, 19 of whom had inconclusive laboratory results (Fig 3) as follows: 17 smear-negative lesions (12 of which underwent PCR and were negative), one biopsy-negative/PCR-negative lesion, and one biopsy-negative lesion. In 37 soldiers with a clinical diagnosis of CL but without any laboratory work-up, records indicated that logistical issues, patient unwillingness, or lesions in advanced stages of healing (re-epithelialization) that may have prevented adequate smear and PCR sampling affected conduct of diagnostic assays. All lesions in this subgroup were on the extremities or trunk and, in most, had been present for many months. In accordance with a retrospective study, clinical diagnoses of CL remained in the records of these soldiers and were reported as such.

Treatments and responses

Fig 3 shows that among laboratory-confirmed CL cases, watchful observation was the most commonly selected option. Pentostam and ThermoMed were

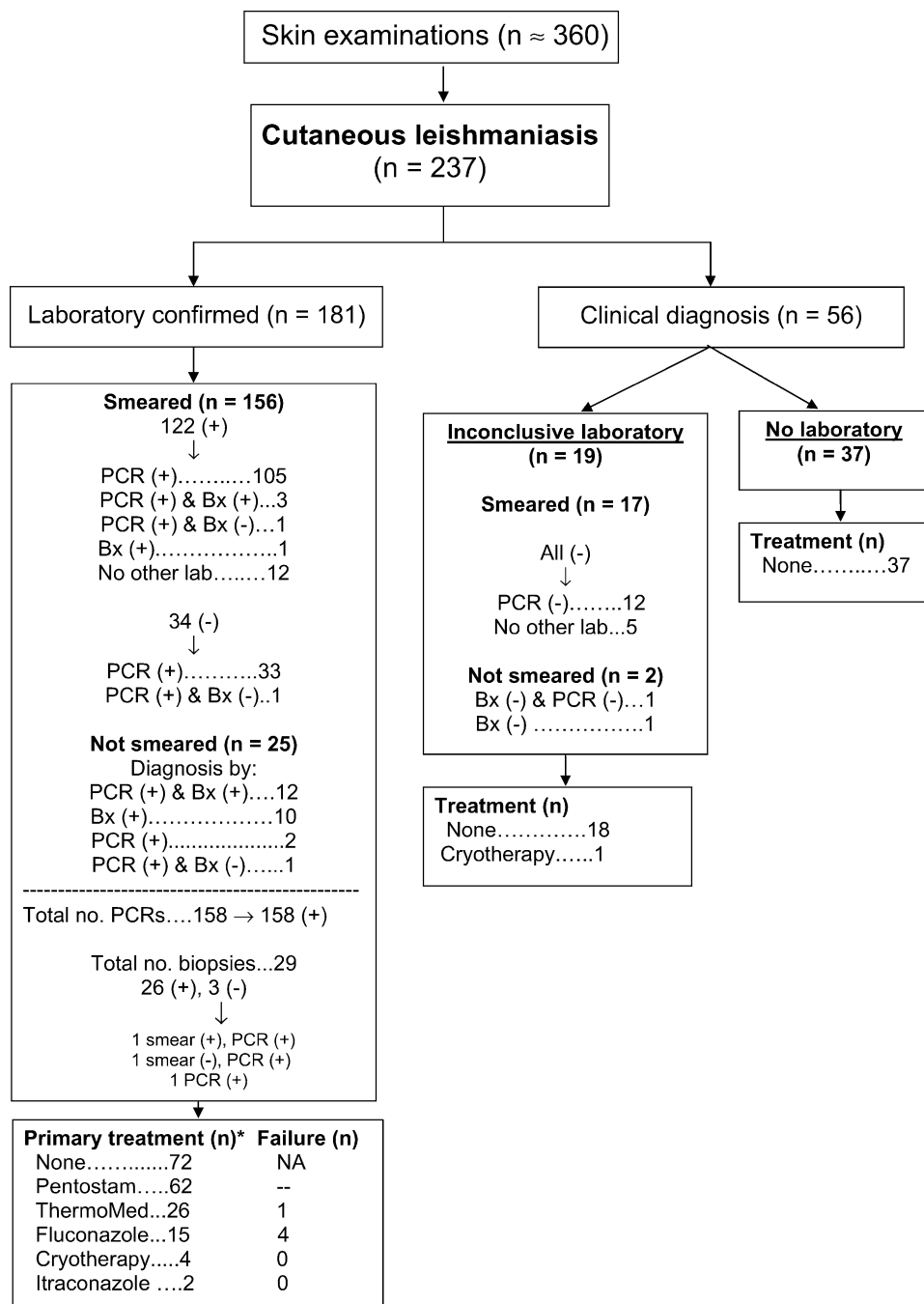


Fig 3. Flow chart depicting CL diagnoses, diagnostic outcomes, and treatments. *Bx*, Biopsy, *NA*, not applicable; *PCR*, polymerase chain reaction.

the most common treatments. Because Pentostam is administered as an investigational new drug under human use protocols, patient outcomes are reported separately.¹¹

ThermoMed treatment was administered to 26 soldiers with confirmed CL (Table II). During and immediately after ThermoMed treatment, painless edema and bullae occurred on the treated sites that generally persisted for up to 1 week (Fig 4). By

history, compliance for dressing changes and gentamicin ointment application for up to 2 weeks was excellent. Twenty soldiers attended follow-up at 2 months or more, 8 of whom also attended additional follow-up at 5 or more months (Table II). One patient who showed signs suspicious for fluconazole failure was re-treated with ThermoMed and seen at 6 weeks on his discharge from the Army (Table III).

Table II. Characteristics of 26 soldiers receiving ThermoMed therapy at Ft Campbell as a primary treatment

| | |
|---|--|
| Gender | 24 men, 2 women |
| Laboratory confirmed CL | 26 |
| No. of lesions per patient (No.) | 1 (11) |
| | 2 (7) |
| | 3 (5) |
| | 4 (1) |
| | 5 (2) |
| Mean size of largest lesion (cm) (range)* | 2.2 (0.7-3.6) |
| Lesion location | |
| Face only (No.) | 0 |
| Extremities-trunk only (No.) | 26 |
| Both areas (No.) | 0 |
| Lesion(s) over a joint (No.) | 6 |
| Sporotrichoid spread (No.) | 2 |
| Follow-up (No.) | |
| ≤ 2 wk | 22 [†] (all lesions healing) |
| 1-2 mo | 10 (11 visits; most lesions healed or healing) |
| >2 mo | 15 (24 visits [‡] ; all lesions healed [§]) |

*For persons with ≥ 2 lesions.

[†]Discharged from Army (n = 3), no show (n = 1).

[‡]Longest follow-up, 5 mo (n = 2); ≥ 6 mo (n = 6).

[§]Except one suspected treatment failure.

There was one suspected ThermoMed treatment failure in a soldier with a single lesion on the upper arm. The patient presented with ringlike erythema overlying the lesion 1 day after ThermoMed therapy (a single pass), but disclosed a recent tick bite in the area. She was treated empirically with doxycycline, 100 mg twice daily for 21 days. At the 2-month follow-up, a 1-cm indurated erythematous plaque was found surrounding the CL scar, suggestive of pyoderma. A culture was not done, and the patient was treated empirically with cephalexin (Keflex), 500 mg 3 times a day, for 14 days. At a follow-up visit 4 months after ThermoMed treatment, the central plaque had decreased in thickness but was surrounded by an annular erythematous patch approximately 6 cm in diameter (Fig 5). The overlying crust was debrided and the serous exudate grew *Staphylococcus epidermidis*. A punch biopsy specimen and PCR were negative for CL. Despite incon-



Fig 4. CL lesion immediately after ThermoMed treatment showing bullae and oozing.

clusive laboratory findings, the soldier elected to be re-treated with itraconazole (200 mg twice daily for 6 weeks). At a 3-week follow-up visit, the lesion was resolving.

In one soldier who had 4 lesions treated with ThermoMed after suspected fluconazole failure, 3 lesions resolved and a persistent crust developed in the other. Debridement of the crust revealed an erosion, but no deep ulceration. Gentamicin ointment was applied, and the lesion resolved. Two soldiers with sporotrichoid CL who had small satellite lesions surrounding their ulcers were treated with ThermoMed only at the ulcer sites. Within 1 month, both showed slightly more prominent satellite lesions around the treated ulcers (Fig 6, A). The papules were treated with single doses of cryotherapy and resolved (Fig 6, B). None of these lesions was considered a ThermoMed therapy failure.

There was one confirmed bacterial infection after ThermoMed therapy. The patient presented 8 days after ThermoMed therapy with yellow, tender, granulation-like tissue surrounded by erythema over one treated leg lesion that grew methicillin-sensitive *Staphylococcus aureus* and group B streptococcus. Treatment with cephalexin resolved the infection.

All soldiers expressed general satisfaction with ThermoMed therapy and all dermatology providers deemed the treatment safe, well tolerated, and largely effective. Among 54 treated lesions, including those on dark-skinned persons, no unusual or unexpected sequelae occurred (eg, exaggerated scarring or color change) beyond those previously described in CL and other conditions (Fig 7).^{14,26-28}

Table III. Characteristics of suspected and laboratory-confirmed oral fluconazole failures in CL

| Patient No. | Initial laboratory confirmation | Dose (duration) | Clinical indication of treatment failure | Laboratory indication of treatment failure | Re-treatment | Comment |
|-------------|---------------------------------|--------------------|---|--|--------------|---|
| 1 | PCR (+) | 200 mg bid (6 wk) | Nonresolving elbow lesion | Smear, biopsy, culture inconclusive | None | Discharged from Army |
| 2 | Biopsy (+) | 200 mg bid (6 wk) | Nonresolving lesions L cheek and ear | Smear (+), PCR (+) | Pentostam | Deployed |
| 3 | Biopsy (+), PCR (+) | 200 mg bid (3 wk)* | Progressive arm, neck lesions with sporotrichoid spread | Smear (+), PCR (+), culture (+) | Pentostam | All lesions resolved with mild scarring |
| 4 | Biopsy (+) | 200 mg bid (6 wk) | Nonresolving lesions on R thigh and calf | None | ThermoMed | 3 of 4 lesions healed at 6-wk follow-up |

bid, Twice daily; *L*, left; *PCR*, polymerase chain reaction; *R*, right.

*Discontinued because of rising ALT level and progressive lesions (see "Results" section in text).



Fig 5. CL lesion on upper arm as suspected ThermoMed treatment failure 4 months after treatment shows central ulcer and surrounding erythematous plaque (*circle*); however, biopsy and PCR assays were negative for CL.

Fifteen soldiers elected to self-administer oral fluconazole. Two suspected and two laboratory-confirmed treatment failures occurred, including in one soldier in whom a transient rise in alanine aminotransferase levels (ALT) developed after 3 weeks of treatment (pretreatment, 52 U/L; after 3 weeks of treatment, 113 U/L; 2 weeks after treatment discontinued, 52 U/L; ALT normal reference range 0–45 U/dL) (Table III). The posttreatment PCR was positive for the two failures, but confirmation was also made by smear-positive or culture-positive assays. Cryotherapy, elected by a small number of soldiers, was well tolerated, with no indication of treatment failure during routine follow-up visits.

Among 7 soldiers with confirmed CL showing sporotrichoid spread, 3 were referred for Pentostam, two received ThermoMed therapy (described earlier) and 2 elected a trial of itraconazole (200 mg

twice daily for 6 weeks) after being counseled on the side-effect profile and failure rate of fluconazole in earlier treated soldiers. Sporotrichoid disease was not necessarily a requisite for systemic therapy. Both soldiers who received itraconazole as their primary treatment had opted for no therapy immediately after diagnosis and then, over a period of several months, developed more prominent lesions. After several weeks of itraconazole, both soldiers showed at least a 50% decrease in the size of the subcutaneous nodules and modest re-epithelialization of the ulcers.

Among the soldiers with a clinical diagnosis of CL, only one soldier elected therapy (cryotherapy). None of the 37 soldiers lacking laboratory evaluation elected therapy. All soldiers in the clinical diagnosis group did well, and there was no evidence that any lesion worsened or persisted beyond a residual scar in those who attended periodic follow-up visits.

DISCUSSION

This retrospective study summarizes the diagnostic methods, treatments, and related considerations in soldiers with CL that may be beneficial to clinicians who encounter active-duty soldiers, deactivated reservists re-entering the civilian sector, or civilians returning from Iraq or other parts of the Middle East with skin lesions.¹² Indeed, OIF is likely to continue for many years with a large number of soldiers and, to a lesser degree, civilians, likely to acquire CL.^{11,12}

Among an estimated 20,000 US Army soldiers returning to Ft Campbell in late 2003 and the first half of 2004, at least 5% were estimated to have skin complaints, 25% of whom we diagnosed with CL. In



Fig 6. **A**, CL lesion on upper arm 1 month after ThermoMed treatment of central primary lesion; untreated satellite papules (*arrows*) became accentuated. **B**, Satellite papules treated with cryotherapy had resolved 3 weeks later. Note improved primary lesion site with centrally regressing scar.

comparison, up to 10% of civilian travelers returning from tropical destinations may report a dermatosis, but CL typically accounts for less than 5% of the dermatoses.²⁹⁻³² Most soldiers had been assigned to northern Iraq at some point during their tour, especially northwest Iraq in or around the cities of Tikrit, Kirkuk, Tal Afar, and Salaymaniya where CL is considered highly endemic.³³ The use of personal protective measures, such as permethrin-impregnated bed nets and uniforms and insect repellent, is highly encouraged and proven to reduce sandfly exposure, but compliance appears modest.¹²

Among 181 laboratory-confirmed cases of CL in our series, PCR was the most useful diagnostic procedure in establishing a diagnosis. PCR was positive in all 122 smear-positive and all 26 biopsy-positive cases, as well as in all 34 smear-negative and all 3 biopsy-negative lesions. There were no instances of a smear-positive or biopsy-positive lesion that was PCR negative. These observations parallel a recent study indicating that among 4 diagnostic techniques for CL, including smear, biopsy, PCR, and culture, PCR was most sensitive and highly specific.¹⁹ Accordingly, PCR appears to be approaching a “gold” standard among the currently available diagnostic methods and is quickly moving from a research tool to a standard assay for CL, with clinical certification expected in the future.^{12,19} Nonetheless, as initial diagnostic steps, we recommend Giemsa-stained smears of lesions highly suspected of being CL (ie, crusted erosion or ulcer) and biopsies for questionable lesions or those

suggestive of “late stage” or resolving CL. A biopsy should also be conducted on any lesion highly suspected of being CL that is smear-negative.

CL acquired in the Middle East is commonly caused by *L major* or *L tropica*. Recently, isoenzyme analysis for *Leishmania* speciation conducted early in OIF, a painstaking procedure requiring cultured organisms, found that 304 of 308 samples (99%) were *L major*.¹² There have been at least 4 cases of visceral leishmaniasis (kala-azar) in soldiers deployed to Iraq, but this disease typically presents with systemic symptoms and no skin lesions.^{11,12} Mucocutaneous leishmaniasis is a potentially destructive condition endemic to Central and South America, caused primarily by *L braziliensis*. Rarely, CL caused by *L major* or *L aethiopica* may develop mucocutaneous involvement, but this may represent direct extension from skin lesions and, to date, has not been reported in any soldier.⁸⁻¹⁰

Among confirmed CL cases, smear positivity rates were 78% (122/156); among the small number undergoing biopsy, positivity rates were 90% (26/29), similar to that previously reported.¹⁹ Proper interpretation of a lesion smear requires adequate sampling, high-quality Giemsa staining, and a substantial amount of time and rigor by an experienced reader, factors that may contribute to the discordance with PCR. In clinically diagnosed CL, however, all 12 lesion samples undergoing PCR were negative, underscoring that even with high clinical suspicion, some presumptive diagnoses may be true negatives



Fig 7. **A**, CL lesion on upper arm approximately 3.5 cm in diameter at presentation. **B**, Five months after ThermoMed therapy, lesion is well healed with minimal scarring and slight pink discoloration.

or will remain inconclusive by even the most sensitive laboratory method. Notably, most lesions in the clinically diagnosed group with inconclusive PCR or smear results were “old” lesions with various degrees of re-epithelialization that can be expected to be parasitologically negative. Because the systemic therapies are associated with a spectrum of untoward effects, they were offered only to those with laboratory-confirmed CL, a conservative approach that we generally recommend.

Among several outpatient treatments offered at Ft Campbell, we were encouraged by ThermoMed, a portable, battery-operated device that delivers superficial 50°C localized radiofrequency-generated heat through a set of prongs placed directly on the lesion.²⁶ ThermoMed treatment for CL is based on the concept that *Leishmania* amastigotes die at temperatures of 39°C or higher.^{34,35} ThermoMed has been used to treat civilians with CL in Mexico, Central America, and Afghanistan with seemingly acceptable curative and cosmetic results.^{14,26}

In October 2004, ThermoMed received FDA 510K clearance for use in 16 benign conditions, including CL (US FDA, Oct 2004). Soldiers treated with ThermoMed at Ft Campbell were generally satisfied, had little posttreatment pain, and healed without exaggerated scarring, atrophy, or color changes. Moreover, all treatments were on a single day, underscoring convenience and eliminating compliance issues. The drawbacks of ThermoMed included administration of local anesthetic, blistering (near painless) and oozing for several days after treatment, and daily dressing changes for up to 2 weeks. ThermoMed units are relatively expensive, costing more than \$20,000 per unit.

Among ThermoMed-treated patients, only one had a posttreatment bacterial infection, a concern given the burnlike nature of this treatment. Notably,

our patients applied gentamicin ointment to the ThermoMed-treated sites; gentamicin is a broad-spectrum aminoglycoside that may even have modest activity against *Leishmania* parasites not unlike paromomycin ointment,^{36,37} a related aminoglycoside preparation used successfully to treat CL in some countries.^{2,16} ThermoMed probably kills only a modest proportion of parasites, especially in larger lesions, but may hasten resolution by causing a localized immune response when antigen is released by killed parasites.^{14,26} For the single suspected ThermoMed failure, the treated lesion developed an annular erythematous patch around the primary plaque that was biopsy negative and PCR negative for CL. We speculate as to whether this lesion resulted from leishmanial antigen release after ThermoMed therapy, followed by a modestly robust immune reaction.

Soldiers who were referred for Pentostam therapy generally had “complicated” lesions, including those on the face, over joints, or on exposed surfaces, or large lesions (diameter generally >3.5 cm). Some soldiers chose oral fluconazole, a convenient, generally well-tolerated, off-label, non-first-line therapy administered at 200 mg daily for 6 weeks, which may slightly lessen healing time.¹⁸ In the current study, fluconazole compliance was not closely monitored as in an earlier study,¹⁸ and 4 of 15 soldiers showed signs of failure (2 with laboratory confirmation), including one patient who also had a transiently elevated ALT level after 3 weeks of therapy.

Some anecdotal reports suggest *L major* may be more responsive to azoles than *L tropica*.^{38,39} Itraconazole, a newer azole that has shown variable rates of success in CL (including sporotrichoid CL), was offered as an alternate to fluconazole after we observed poor responses in 4 of 15 soldiers treated with fluconazole.^{4,22-25} Itraconazole was chosen by

two soldiers with sporotrichoid disease and by one in whom ThermoMed therapy had presumptively failed. Notable improvement or lesion resolution occurred within weeks, suggesting that itraconazole may warrant further evaluation as a second-line treatment for some patients. Sporotrichoid disease is not considered a requisite for systemic treatment.

Cryotherapy, used in the Middle East for many years with good results,⁴⁰ was used in 5 soldiers with small, nonfacial lesions and on satellite papules that developed near several resolving primary lesions after ThermoMed treatment. This treatment is relatively simple to administer but requires training to avoid adverse sequelae, such as dyspigmentation in dark skinned persons. Notably, approximately 40% of the soldiers with confirmed CL and nearly all with clinically diagnosed CL elected no treatment and did well, underscoring the self-healing nature of CL caused by *L major*.

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Cutaneous leishmaniasis diagnostic support is available free of charge at the Centers for Disease Control and Prevention (Atlanta, Ga) or the Leishmania Diagnostics Laboratory, Walter Reed Army Institute of Research (Silver Spring, Md). The Web site address that provides links to these sites is <http://www.pdhealth.mil>.

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