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**UNDER SECRETARY FOR HEALTH'S INFORMATION LETTER**

# GUIDANCE FOR THE DIAGNOSIS AND TREATMENT OF LEISHMANIA INFECTION

**1.** This Under Secretary for Health Information Letter provides information to Department of Veterans Affairs (VA) clinicians examining veterans of Operations Iraqi Freedom and Enduring Freedom who may have acquired leishmaniasis while on active duty during recent military operations in Southwest (SW) Asia.

## 2. General Issues

a. Leishmaniasis is an infectious disease transmitted by the bite of infected sand flies. It is caused by *Leishmania* sp., an obligate intracellular protozoa. The disease predominantly manifests in SW Asia either in a cutaneous (skin) form or in a visceral (internal organ) form that affects the liver, spleen, and bone marrow. Different species of *Leishmania* tend to cause different forms of the disease.

b. Leishmaniasis is found in approximately 90 tropical and subtropical countries around the world and in southern Europe. More than 90 percent of the cases of cutaneous leishmaniasis occur in Afghanistan, Algeria, Brazil, Iran, Iraq, Peru, Saudi Arabia, and Syria. More than 90 percent of the world's cases of visceral leishmaniasis occur in Bangladesh, Brazil, India, Nepal, and Sudan. Rarely, people living in rural southern Texas develop cutaneous leishmaniasis. No cases of visceral leishmaniasis are known to have been acquired in the United States (U.S.). Leishmaniasis was diagnosed in 32 out of the 700,000 U.S. troops deployed to the Persian Gulf in 1990 and 1991.

c. Travelers of all ages are at risk for leishmaniasis when they visit endemic areas. Leishmaniasis usually is more common in rural than urban areas, but it is found in the outskirts of some cities.

d. Leishmaniasis is spread by the bite of certain species of phlebotomine sand flies. Sand flies become infected by biting an infected animal. Rodents and dogs are likely reservoirs in SW Asia of this zoonotic infection. Because sand flies do not make noise when they fly, their presence may not be recognized. Also, sand flies are very small and may be hard to see. Sand flies usually are most active from dusk to dawn.

e. Rarely, visceral leishmaniasis is spread from a pregnant woman to her unborn child. Leishmaniasis also can be spread by blood transfusions. However, leishmaniasis is not contagious by casual contact; for example, a person cannot be infected from touching a *Leishmania* skin sore.

f. People with cutaneous leishmaniasis usually develop skin sores within a few weeks (sometimes as long as months) of when they were bitten. People with visceral (internal) leishmaniasis usually become symptomatic within several months (rarely longer than a year) of when they were bitten. The last case of leishmaniasis among veterans of the 1991 Gulf War was diagnosed 2 years after the end of hostilities; no new cases have been diagnosed among Gulf War troops in over a decade.

## 3. *Leishmania* Infection Among Current U.S. Troops

a. The impact of leishmaniasis on U.S. military personnel currently deployed to SW Asia has been substantial. Since January 2003, over 600 U.S. troops have been diagnosed with cutaneous leishmaniasis (CL). Several hundred additional soldiers may have been infected. Nearly all cases of CL were acquired in Iraq and were found to be caused by *Leishmania major.*

b. To date, visceral leishmaniasis (VL) has been diagnosed in two soldiers who deployed to Afghanistan in support of Operation Enduring Freedom. One soldier stationed in the Baghdad area for 11 months also has been recently diagnosed with VL. *Leishmania infantum* is considered the probable etiologic agent of VL in Afghanistan and Iraq.

***NOTE:*** *These findings indicate that CL is a much greater health threat than VL for U.S. troops currently serving in SW Asia.*

## 4. Cutaneous Leishmaniasis (CL)

a. CL typically presents as one or more skin sores, papules, or nodules, either painful or painless, with or without a scab, that develop weeks to months after a person is bitten by infected sand flies. In SW Asia, the skin lesions are commonly called “Baghdad boil.”

b. If untreated, the sores can last from weeks to years. The sores can change in size and appearance over time. They often develop raised edges and a central crater, which may look like a volcano. The sores can be painless or painful when secondarily infected by bacteria. Some patients have swollen lymph nodes near the sores.

c. The skin lesions caused by CL usually go away on their own. While CL is not life threatening, the skin lesions may take months to years to heal and can result in permanent scarring. ***NOTE:*** *Health care personnel need to focus on the possibility of leishmaniasis in slowly or non-resolving skin lesions among soldiers redeploying from Iraq and Afghanistan.* No general screening tests are currently available for CL. Diagnosis involves a combination of compatible symptoms, objective signs, and laboratory findings.

## 5. Visceral Leishmaniasis (VL)

a. VL, also known as kala-azar, is typically a more severe disease than cutaneous infection. Patients with VL often present with fever, weight loss, and an enlarged spleen and liver. Some patients have swollen lymph glands. Certain blood tests are abnormal. For example, patients usually have low blood counts, including anemia, leukopenia, and thrombocytopenia, and often have elevated liver function tests.

b. The most common manifestations of VL (fever, weight loss, enlargement of the spleen and liver, and anemia) characteristically develop months, but sometimes years, after a person becomes infected. In the Gulf War of 1991, soldiers with VL often presented with symptoms more than 5 months after leaving the Persian Gulf.

c. For the two recent U.S. veterans with VL who served in Afghanistan, their illness began from 3 to 14 months after leaving the theater of operations. Both presented with fever, cachexia, hepatosplenomegaly, pancytopenia, and hypergammaglobulinemia with hypoalbuminemia. Leishmanial parasites were found only on liver biopsy. In the VL case diagnosed in a veteran of the war in Iraq, the presentation was similar but the bone marrow biopsy showed parasites and allowed isolation of the parasite in culture. In all three cases of VL, the commercially available rK39 serology (Kala-azar detect, Inbios, Seattle, WA) was positive.

d. When symptomatic, untreated VL can be a very severe disease. However, visceral disease from the Middle East is usually milder with less specific findings than VL from other areas of the world.

e. Because symptoms are non-specific and often start after redeployment, there is frequently a delay in diagnosis of VL. ***NOTE:*** *VL needs to be considered in any veteran with documented, chronic fever returning from an endemic area*. Other diseases that can present with a similar clinical picture include: mononucleosis syndromes, tuberculosis, brucellosis, syphilis, salmonella infection, malaria, lymphoma/leukemia, solid malignancies, and Acquired Immune Deficiency Syndrome (AIDS).

## 6. Guidance

a. Every VA primary care provider, infectious disease specialist, and dermatologist needs to be familiar with the clinical manifestations and treatment of CL and VL.

b. VA health care providers need to consider leishmaniasis among veterans who were deployed to SW Asia and who have unexplained persistent skin rashes or persistent febrile illnesses, especially if associated with other clinical manifestations like splenomegaly and pancytopenia. VA health care providers need also to be prepared to address the concerns of veterans who are unlikely to have leishmaniasis and to explain when invasive diagnostic tests are unnecessary.

c. For suspected cases of leishmaniasis infection, specialty assistance from local infectious disease consultants, dermatologists, and pathologists needs to be sought. For the diagnosis and treatment of suspected cases, both the U.S. military and the Centers for Prevention and Disease Control (CDC) can be of substantial help. Contact information for leishmaniasis include the following:

(1) For questions about veterans deployed previously to SW Asia, contact the Deployment Health Clinical Center of the Department of Defense, telephone 866-559-1627 or at http://www.pdhealth.mil. Specific information on clinical management, military policies, and education and training materials on leishmaniasis can be obtained at http://www.pdhealth.mil/leish.asp.

(2) For evaluation or consultation involving veterans with suspected or confirmed cases of leishmaniasis, clinicians can contact the Infectious Disease Service of either Walter Reed Army Medical Center (DC), telephone 202-782-1663, 202-782-6740, and/or 202-782-8691 or Brooke Army Medical Center (San Antonio, TX), telephone 210-916-5554 and/or 210-916-1286.

(3) Diagnostic support can also be obtained by contacting the director of the leishmaniasis diagnostic laboratory at Walter Reed Army Institute of Research (Silver Spring, MD), telephone 301-319-9956.

(4) The Armed Forces Institute of Pathology (AFIP) has established a registry for both cutaneous and visceral leishmaniasis. The point of contact at AFIP is Colonel Peter McEvoy (mcevoy@afip.osd.mil).

(5) The CDC can be contacted at 1-800-311-3435, or by sending an inquiry at http://www.cdc.gov/netinfo.htm. The drug sodium stibogluconate is available under an Investigational New Drug protocol from the CDC Drug Service. Additional information can be found on the Division of Parasitic Diseases' website: http://www.cdc.gov/ncidod/dpd/parasites/leishmania/factsht_leishmania.htm.

**7. References.** Useful references about leishmaniasis include:

a. Herwaldt BL. "Leishmaniasis," Lancet. 354:1191-9; 1999.

b. Herwaldt BL, Stokes SL, Juranek DD. "American Cutaneous Leishmaniasis in U.S. Travelers." Annals of Internal Medicine. 118:779-84; 1993.

c. Berman JD. Human Leishmaniasis: Clinical, Diagnostic, and Chemotherapeutic Developments in the last 10 Years," Clinical Infectious Diseases. 24:684-703; 1997.

d. Desjeux P. "Leishmaniasis: Public Health Aspects and Control," Clinical Dermetology. 14:417-23; 1996.

e. Ohl CA, Hyams KC, Malone JD, Oldfield E. "Leishmaniasis among Desert Storm Veterans: A Diagnostic and Therapeutic Dilemma," Military Medicine. 158:726-729; 1993.

f. Veterans Health Initiative Independent Study Guide: Endemic Infectious Diseases of Southwest Asia Independent Study; found at: http://www.va.gov/vhi.

g. CDC. Update: "Cutaneous leishmaniasis in U.S. Military Personnel -- Southwest and Central Asia, 2002-2004," MMWR. 53:264-265, April 2, 2004.

h. CDC. "Two cases of Visceral Leishmaniasis in U.S. Military Personnel - Afghanistan, 2002-2004," MMWR. 53:265-268, April 2, 2004.

i. Slide set with good pictures of pathology: "Leishmaniasis Briefing, Leishmaniasis Working Group, July 2004," at http://www.pdhealth.mil/downloads/Leishmaniasis_Brief_0704.ppt.

**8. Contact.** Questions regarding this information letter may be addressed to the Office of Public Health and Environmental Hazards (13) at (202) 273-8579.

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**ATTACHMENT A**

## DIAGNOSIS OF LEISHMANIASIS

### 1. Cutaneous Leishmaniasis (CL)

a. The diagnosis of cutaneous leishmaniasis can be difficult, even with typical skin lesions. Identification of the parasite is required to confirm the diagnosis. Special military and Centers for Prevention and Disease Control (CDC) laboratories can do microscopy, culture and Polymerase Chain Reaction (PCR) of clinical specimens. A skin scraping is usually the first approach for diagnosis. Skin biopsy with touch preps may be preferred if the differential diagnosis includes other skin diseases. However, a properly performed skin scraping may have equal diagnostic yield.

b. In order to provide an optimal specimen, debridement and cleaning of the ulcer base must be vigorous and complete. Infiltration of local anesthetic with epinephrine (except where contraindicated) is encouraged to facilitate debridement necessary to get an adequate specimen. Healing, re-epithelialized ulcers should be scraped or biopsied only when the results will impact treatment. Specimens containing only keratinized epithelium are inadequate.

c. The following information on scraping and biopsy procedures was provided by the Department of the Army, Office of the Surgeon General, Falls Church, VA:

(1) Criteria for scraping or biopsy:

(a) Any patient who has had a non-healing skin lesion (does not have to be an open, weeping ulcer) for greater than 3 to 4 weeks should be suspected of having leishmaniasis.

(b) Suspected cases need to be placed on a course of antibiotic therapy for 7 to 10 days with an antibiotic that has proven activity in Iraq (current recommendation is Augmentin 875 milligrams (mg) twice a day ( BID) for 7 to 10 days) to help rule-out a primary bacterial infection and to treat any complicating secondary infection.

(c) At the conclusion of therapy, the patient needs to be seen by the same practitioner and a decision made as to whether the course of antibiotics was effective. If the lesion has persisted or worsened, a scraping or biopsy needs to be performed.

(2) Scraping procedure:

(a) Clean area and surrounding ulcer base with alcohol pads and allow to dry.

(b) Anesthetize with lidocaine 1 percent or 2 percent with epinephrine 1:100,000 (unless the epinephrine is contraindicated due to anatomic site).

(c) Two tissue smears are performed by horizontally scraping (lightly enough to elicit an exudates, but not vigorously enough to cause bleeding) the base of the underlying ulceration with a #15 blade (this often requires removal of the overlying crusted debris). The dermal tissue is then thinly applied in a circular fashion to a dime to nickel sized area in the center of the slide. Minimize blood, epithelium (keratinocytes), and purulence on the specimen.

(d) Additionally, material from the scrapings (and even the overlying crusted debris) should be inserted into a small vial of 95 percent to 100 percent ethanol for PCR analysis.

(e) Ensure slides are labeled per the format of the affiliated pathology department and submit per their protocol. If pathology services are unavailable locally, ship per address in subparagraph 2c. Work closely with pathologists to verify adequacy of tissue smear samples.

(3) Biopsy or touch prep-impression smear procedure:

(a) An area of the lesion needs to be cleaned thoroughly with alcohol pads and dried.

(b) The anticipated area of biopsy needs to be anesthetized as described in subparagraph 1c(2).

(c) A 4 millimeter (mm) sterile disposable punch or sterile scalpel (#15, #11, or #10) needs to be used to remove a piece of tissue approximately 3 to 4 mm in circumference and approximately 1 mm deep from the edge of the lesion. Lesions on the face, anterior of the neck, and near larger vessels and/or nerves need to be biopsied with extreme caution and a simple surface scraping as described may be preferred to a true biopsy.

(d) The biopsy needs to be placed on a sterile, clean, dry gauze 2”x2” pad briefly to absorb excess blood on the tissue that may interfere with the reading of the touch preparations.

(e) The tissue needs to be grasped with forceps and impression smears made on clean slides (4 for each biopsy) by rubbing the tissue gently across the surface of the slide in a circular motion.

(f) Dry thoroughly. Fix with methanol if available.

(g) The tissue biopsy (after the impression smears are made) then needs to be placed in a very small amount of ethyl alcohol (just enough to cover the specimen) in a leakproof vial (such as a “nunc” transport tube).

(h) The slides and the vial with the tissue need to be shipped per local pathology section protocol or via overnight-express to the address below. The container needs to be labeled as diagnostic specimens and no shipping permit is required.

d. Complete the Department of Defense (DOD) patient information sheet and include with the specimen for each patient biopsied. Procedural inquiries need to be made to Lieutenant Colonel Peter Weina at (301) 319-9956.

## 2. Visceral Leishmaniasis (VL)

a. Definitive diagnosis requires visualization of the amastigotic stage of *Leishmania* in smears or cultures of biopsy specimens from bone marrow, liver, enlarged lymph nodes, or spleen. Several biopsies may be required to confirm the diagnosis. Wright and Giemsa stains can be used for identification. There also are PCR and immunofluorescent tests available from military (PCR) and CDC (serum immunoflorescence assay (IFA)) research laboratories to assess biopsy material. Cultures are performed using Novy-MacNeal-Nicolle and Schneider's insect media. Antibodies to *Leishmania* may be present in patient's serum, but this finding will not confirm or exclude the diagnosis. However, antibodies to the K39 antigen, as detected with the commercially available Kala-azar Detect™(Inbios, International, Inc Seattle, WA) dipstick device are strongly predictive of VL and need to prompt an investigation to identify parasites by traditional methods.

b. Leishmania skin tests are widely used in endemic countries for both epidemiological studies and as diagnostic adjuncts for mucosal leishmaniasis and in atypical cases of CL. But there is no Food and Drug Administration (FDA)-approved, commercially available Leishmania skin test in the United States (U.S.), and skin tests are not useful in active VL. *For the U.S.-based physician evaluating a patient for any form of leishmaniasis, skin testing is currently not an available option*.

c. For diagnosis of suspected cases utilizing biopsy specimens, instructions are available upon request from the Walter Reed Army Institute of Research. The point of contact is Dr. Weina at 301-319-7155 or 301-319-9956. Samples should be returned to:

Commander, WRAIR
Attn: Leishmania Diagnostics Laboratory
Division of Experimental Therapeutics
503 Robert Grant Avenue
Silver Spring, MD 20910-7500

**ATTACHMENT B**

## TREATMENT OF LEISHMANIASIS

### 1. Cutaneous Leishmaniasis (CL)

a. The treatment of any form of leishmaniasis requires a confirmed diagnosis and usually consultation with local infectious disease consultants and recognized experts in tropical medicine. A positive scraping, positive Polymerase Chain Reaction (PCR), or positive skin biopsy establishes the diagnosis of CL. Oftentimes, treatment is not necessary because the lesions of CL heal spontaneously. Patients with small lesions (< 2 centimeter (cm) in diameter) and lesions that are few in number may warrant no therapy.

b. Even more important than lesion size or number, the primary consideration in recommending therapy is the history and appearance of the lesions themselves. The following factors need to be considered in deciding on the need for treatment: lesions greater than 1 inch in size, 3 or more lesions; sores on the face or ears; sores on the hands and feet; and sores over joints.

c. In general, patients with old lesions demonstrating epithelialization (healing) should not be treated. Conversely, patients with more recent lesions that are actively ulcerated are better candidates for active treatment. A discussion of therapeutic options with the patient always needs to include the fact that CL is self-limited, although the decision not to treat may prolong the duration of the ulcerations or result in more scarring.

d. Cryotherapy with liquid nitrogen has demonstrated efficacy in the treatment of CL, particularly in small lesions. Use of this modality requires two full 30-second freeze applications (with full thawing in between) in the same setting for efficacy. Cryotherapy needs to be used sparingly, if at all, in dark-skinned patients because cryotherapy may result in permanent depigmentation. Small lesions and lesions few in number in light-skinned patients may respond to cryotherapy. Providers with extensive experience in the use of cryotherapy (dermatologists primarily) may consider the use of cryotherapy on larger lesions.

e. Heat is the newest treatment modality for CL. Thermomed™ is the device used to apply heat. This device has been approved by the Food and Drug Administration (FDA) for a number of applications, including treatment of cutaneous leishmaniasis, and the United States (U.S.) Army has obtained a total of 14 devices from the manufacturer. While the Thermomed™ device is easy-to-use, treating one patient with Thermomed™ under the supervision of someone who has used the device before is the standard for training before independent use. Thermomed™ application produces bullous lesions in a significant number of cases. Initial use at Walter Reed Army Medical Center resulted in superficial skin infections in >20 per cent of cases and a soft tissue abscess in one patient.

f. Oral fluconazole may be an alternative to topical therapy or to the use of Pentostam, but the speed of resolution and overall success rates are not equal to those of Pentostam. In this context, the drug should only be considered in infections proven to be due to *L. major*. While easily available, the drug is not FDA-approved for this indication and there is no official recommendation for its use.

g. Antimony (Pentostam®, Sodium stibogluconate) is used in more severe cases of CL. Pentostam® is available only from the CDC and under a research protocol at Walter Reed Army Medical Center and Brooke Army Medical Center. Pentostam can be administered in the U.S. only under a FDA-approved Investigational New Drug Protocol. Before treating with Pentostam®, the diagnosis of leishmaniasis needs to be confirmed. In addition to the identification of the parasite, an attempt to culture *Leishmania* from skin lesions is important before initiating Pentostam®. Treatment for CL requires either 10 or 20 days of therapy depending on the protocol.

h. Besides the time and travel commitment involved in a full course of Pentostam®, a significant number of soldiers have elected to discontinue Pentostam® before completion of treatment. Myalgias, arthralgias, and malaise are the most frequent side effects noted by patients. Also, Pentostam® has been associated with serious toxicity and therefore, should not be used for minor skin lesions; however, it is >90 percent effective in single treatment course for cutaneous leishmaniasis.

i. The outcome of antimony treatment may not be known for 60-90 days. The appearance of new lesions or enlargement of old lesions constitutes treatment failure. Healing of old lesions and absence of new lesions in the 60-90 days after treatment defines treatment success.

**2. Visceral Leishmaniasis (VL)**

a. A confirmed case of VL usually requires treatment, which needs to be provided in consultation with a knowledgeable infectious disease expert. Liposomal amphotericin-B (AmBisome®) is the drug of choice for VL at a dose of 3 milligrams (mg) per kilogram (kg) per day on days 1-5, day 14, and day 21.

b. Pentostam® is an alternative therapy that requires 28 days of treatment.