BMJ Best Practice

Leishmaniasis

Straight to the point of care

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Summary

Leishmaniasis has a range of clinical presentations; cutaneous leishmaniasis is more common, but visceral leishmaniasis is more serious and can be fatal if left untreated.

Diagnosis is confirmed by various tests, including microscopic exam, culture, or molecular testing, depending on the type of leishmaniasis and test availability.

Possible treatments depend on clinical presentations, parasite species and strain, and the country in which infection was acquired.

Treatment is less effective and sometimes more toxic in people who are immunocompromised than in those who are immunocompetent.

Definition

The leishmaniases are a group of protozoan diseases infecting humans and other animals, causing either skin lesions; mucosal involvement; or infiltration of the spleen, liver, and bone marrow.[1] [2] They are caused by obligate intracellular (macrophage) protozoa of the genus *Leishmania* , and the main route of transmission is via the bite of an infected phlebotomine sand fly. Occasionally, infection occurs congenitally, through a blood transfusion or organ/tissue transplantation, or by laboratory infection.[3] [4] [5]

The leishmaniases can be broadly classified into two major clinicopathologic presentations: cutaneous leishmaniasis (CL) and visceral leishmaniasis (VL).[1] [2] CL is the more common form and may be subclassified into a range of different presentations, such as localized CL, diffuse CL, leishmaniasis recidivans, disseminated leishmaniasis, and mucosal leishmaniasis (ML); ML is sometimes classified as a separate subtype on its own. VL occurs when parasites disseminate through the reticuloendothelial system. It is potentially life-threatening without treatment. Post-kala-azar dermal leishmaniasis may present months or years following treatment of VL.[6] This condition exhibits a macular, maculopapular, or nodular rash.[7]

[CDC: parasites – leishmaniasis] (https://www.cdc.gov/parasites/leishmaniasis/index.html)

[WHO: leishmaniasis] (https://www.who.int/leishmaniasis/en)

Epidemiology

According to the Global Burden of Disease Study from 2019, between 498,000 and 862,000 new cases of all forms of leishmaniasis are estimated to occur annually, resulting in up to 18,700 deaths and up to 1.6 million disability-adjusted life years lost.[14]

The leishmaniases are endemic in more than 90 countries in the tropics, neotropics, and southern Europe. An estimated 0.7 to 1 million cases are diagnosed each year.[15] According to the World Health Organization, over 1 billion people living in endemic areas are at risk of infection.[16]

Cutaneous leishmaniasis (CL) is the most common leishmanial syndrome worldwide, and is the form most likely to be seen in the US. About 85% of global CL cases occur in Afghanistan, Algeria, Brazil, Colombia, Islamic Republic of Iran, Iraq, Pakistan, Peru, and the Syrian Arab Republic.[17] An incidence of 18.4 cases per 100,000 population was reported in transmission areas of the Americas in 2020.[18] The global number of cases has been increasing, due to the adaptation of transmission cycles to peridomestic environments; the spread to previously nonendemic areas due to urbanization and deforestation; limited or nonexistent vector or reservoir control programs; improved diagnosis and case notification; increased detection of leishmaniasis associated with opportunistic infections (e.g., HIV/AIDS); and the emergence of antileishmanial drug resistance.[19] [20] In the US and the UK, CL has also been reported in increasing numbers, most likely due to increased travel to CL-endemic areas as a result of tourism, military duty, or professional work.[21] [22] [23] [24] Additionally, the incidence in the Americas decreased by 2% in 2020 compared with the previous year; El Salvador, Colombia, Guyana, and Mexico all reported decreases, whereas Guatemala, Peru, Costa Rica, and Paraguay reported an increase in cases.[18] [25] Large outbreaks (i.e., >200,000 cases) of CL have been associated with sustained periods of conflict and the resulting collapse of health services (e.g., in Afghanistan and Syria).[26]

Visceral leishmaniasis (VL) is the most serious form of the disease and is fatal in over 95% of cases if left untreated. An estimated 50,000 to 90,000 new cases of VL occur globally each year.[15] About 97% of VL cases are reported from Brazil, Ethiopia, Eritrea, Kenya, India, Nepal, Somalia, South Sudan, Uganda, and Yemen.[17] An outbreak in Kenya was reported in early 2017.[27] In these countries, VL affects mainly poor people in rural areas. Several reports have documented the expansion of VL to urban areas (e.g., in Brazil).[28] In the US, symptomatic VL is a rare disease found in returning US military service members from Iraq or Afghanistan, or in migrants or visitors from endemic areas.[29] [30] [31] However, surveillance for asymptomatic *Leishmania infantum* (synonym: *Leishmania chagasi*) infection among Iraq-deployed US service members identified a 19.5% infection rate.[32] Foxhounds have been found to be infected by *L infantum* (synonym: *L chagasi*) in eastern states, but autochthonous transmission to humans has yet to be described in the US.[33]

[WHO: leishmaniasis country profile] (https://www.irycis.org/en/leishmaniasiscc-spain-leishmaniasis)

Etiology

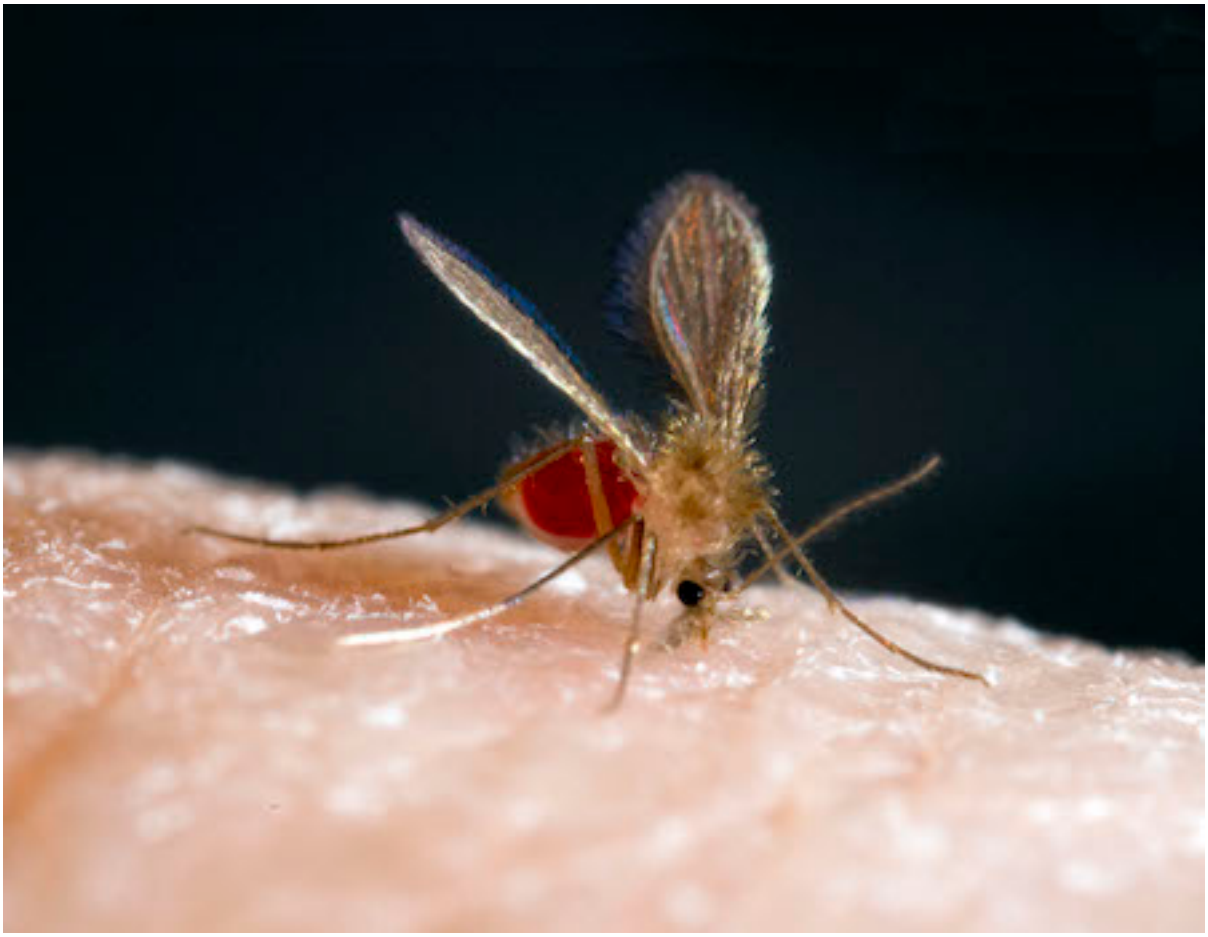
Leishmaniasis is a localized or systemic infectious disease, caused by the obligate intracellular (macrophage) protozoa of the genus *Leishmania* and transmitted to humans by the bite of infected female phlebotomine sand flies.[1] [2] There are more than 20 *Leishmania* species, including *Leishmania tropica*, *Leishmania major*, *Leishmania aethiopica*, *Leishmania infantum* (synonym: *Leishmania chagasi*), *Leishmania donovani*, *Leishmania mexicana*, *Leishmania amazonensis*, and *Leishmania venezuelensis*, as well as the *Viannia* subgenus that includes *Leishmania braziliensis*, *Leishmania guyanensis*,

Leishmania panamensis , and *Leishmania peruviana* .[1] A new subgenus, *Mundinia* , is associated with *Leishmania martiniquensis* , *Leishmania orientalis* , *Leishmania enrietti* .[34]

Transmission is either anthroponotic or zoonotic, depending on whether human or nonhuman mammals are reservoirs of the disease. Many sand fly and mammalian species have been implicated as leishmaniasis vectors and reservoir hosts, respectively.[1] [2] Other modes of transmission (e.g., congenital, blood transfusion, organ/tissue transplantation, needle sharing, laboratory infection) occur, but are comparatively rare.[4] [5]

Multiple *Leishmania* species can cause cutaneous leishmaniasis (CL).[1] Visceral leishmaniasis (VL) is caused by *L donovani* in East Africa and South Asia, or by *L infantum* (synonym: *L chagasi*) in Latin America, Europe, North Africa, and parts of Asia, with emerging foci of VL due to *Leishmania martiniquensis* in Thailand, French West Indies, and Guyana.[2] [35] [36] [37] Most metastatic mucosal leishmaniasis (ML) cases are due to *L braziliensis* , but can also be caused by *L guyanensis* , *L panamensis* , *L amazonensis* , *L aethiopica* , and, in patients who are immunosuppressed, *L infantum* (synonym: *L chagasi*).[1] Post-kala-azar dermal leishmaniasis is due mostly to *L donovani* rather than *L infantum* (synonym: *L chagasi*).[6] Some CL species (e.g., *L major*) are known to cause more benign, self-healing lesions than other species (e.g., *L braziliensis* and *L tropica*).

Comparative studies focusing on different ethnic groups, natives, migrants, or family clustering have shown that human genetic components control CL susceptibility and resistance.[38] Thus, studies indicate a role of human leukocyte antigen (HLA) molecules in localized CL and ML leishmaniasis, and the role of tumor necrosis factor (TNF)-alpha in developing ML. Similarly, studies have demonstrated a genetic basis for VL susceptibility.[39] [40]



Female Phlebotomus papatasi sand fly

With kind permission from EdRowtonPhotography.com

Pathophysiology

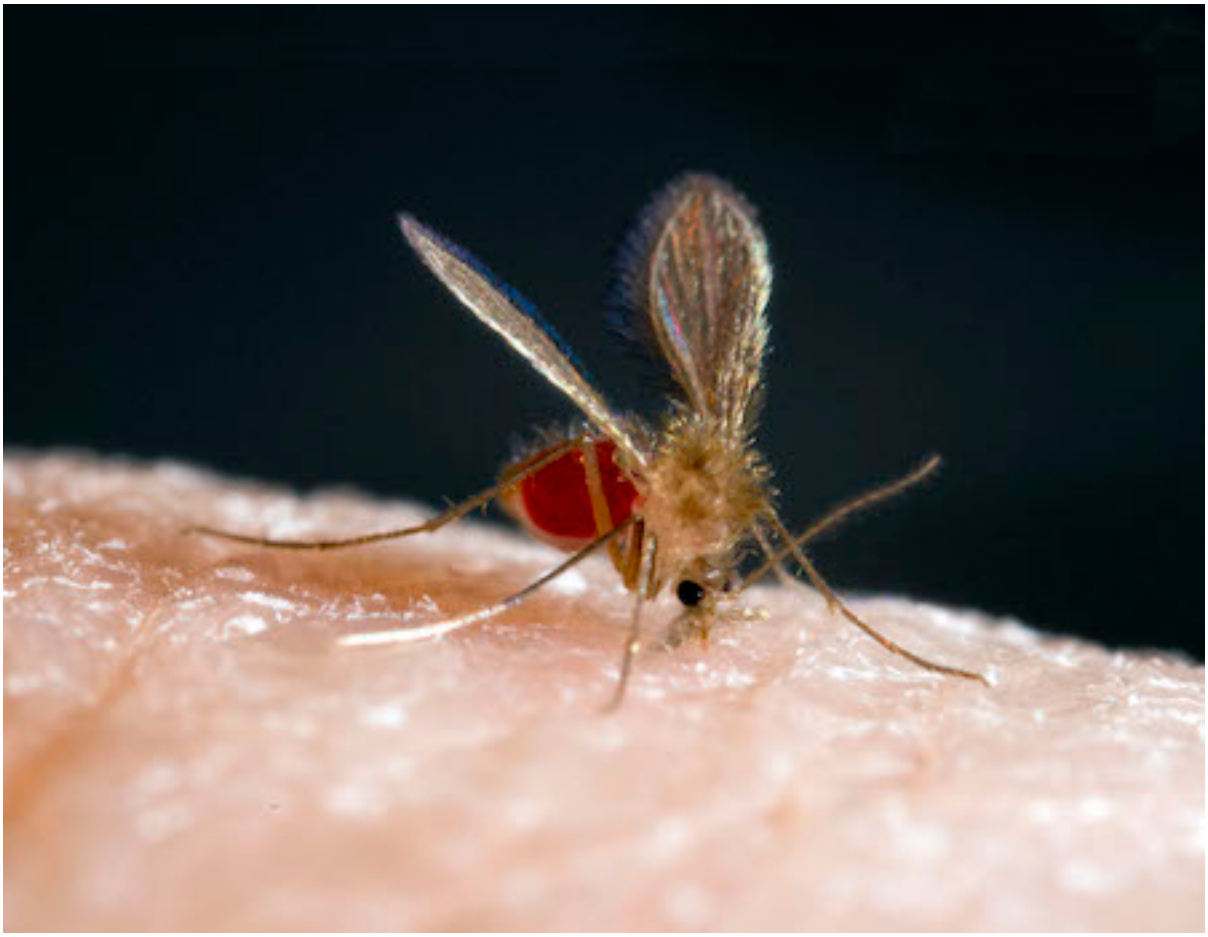
When biting their hosts to obtain a blood meal, infected female sand flies regurgitate the flagellated *Leishmania* promastigotes into the skin, which then invade or are phagocytosed by local or recruited host cells, primarily macrophages.[3] [41] [42]

Experimental studies have shown that sand fly saliva is vasodilatory, anticoagulatory, and immunogenic: this enhances erythema and increases parasite burden, lesion size, and parasite persistence, probably by shifting the immune response from a T helper 1-type to a T helper 2-type cell-mediated response.[43] [44] Some limited data available in natural setting show that variation in sand fly saliva can determine clinical outcome of *Leishmania infantum* (synonym: *Leishmania chagasi*) infections.[45]

Within the phagolysosomes of resident macrophages, promastigotes become nonflagellated amastigotes.[46] This amastigote tissue form is found during human infection. Amastigotes replicate, and may then infect additional macrophages, either locally (e.g., in localized cutaneous leishmaniasis [CL]) or in distant tissues after dissemination (e.g., visceral leishmaniasis [VL] or mucosal leishmaniasis). It is unclear why some *Leishmania* species remain localized while others disseminate.[1] [2] [47] [48] Dissemination from the dermis through the lymphatic and vascular systems leads to infection of other monocytes and macrophages. This results in infiltration of bone marrow, hepatosplenomegaly, and sometimes lymphadenopathy.

In advanced VL, bone marrow and spleen infiltration results in decreased production and increased consumption of blood cells (hypersplenism). Thus, anemia, leukopenia, and/or thrombocytopenia ensue. As the reticuloendothelial system is invaded, the monocytic cell line becomes increasingly susceptible to other infectious agents, as shown by the high frequency of superimposed bacterial infections (e.g., pneumonia, diarrhea, or tuberculosis).

Most human *Leishmania* infections remain asymptomatic.[1] [2] The ratio of asymptomatic to symptomatic infections depends on the type of infecting *Leishmania* species and strain, host, and sand fly factors, and other noncharacterized factors. For example, this ratio is generally higher in *L infantum* (synonym: *L chagasi*) than in *Leishmania donovani* areas, reflecting the higher virulence of the latter. Other factors (e.g., malnutrition) influence infection and disease as highlighted by the observations that the ratio of asymptomatic to symptomatic *L infantum* (synonym: *L chagasi*) infections is different in Latin America than in Europe.[2] People with defective cell-mediated immunity, such as patients infected by HIV or with severe malnutrition, are at higher risk of developing the disease, sometimes years or decades after infection.[19] [49] [50] Other host determinants such as genetic factors may play an important role in the adaptive immune response.[38] The incubation period can be variable and depends on parasite species.[1] [2] This typically is 1 to 3 months for CL, although longer periods are seen.



Female Phlebotomus papatasi sand fly

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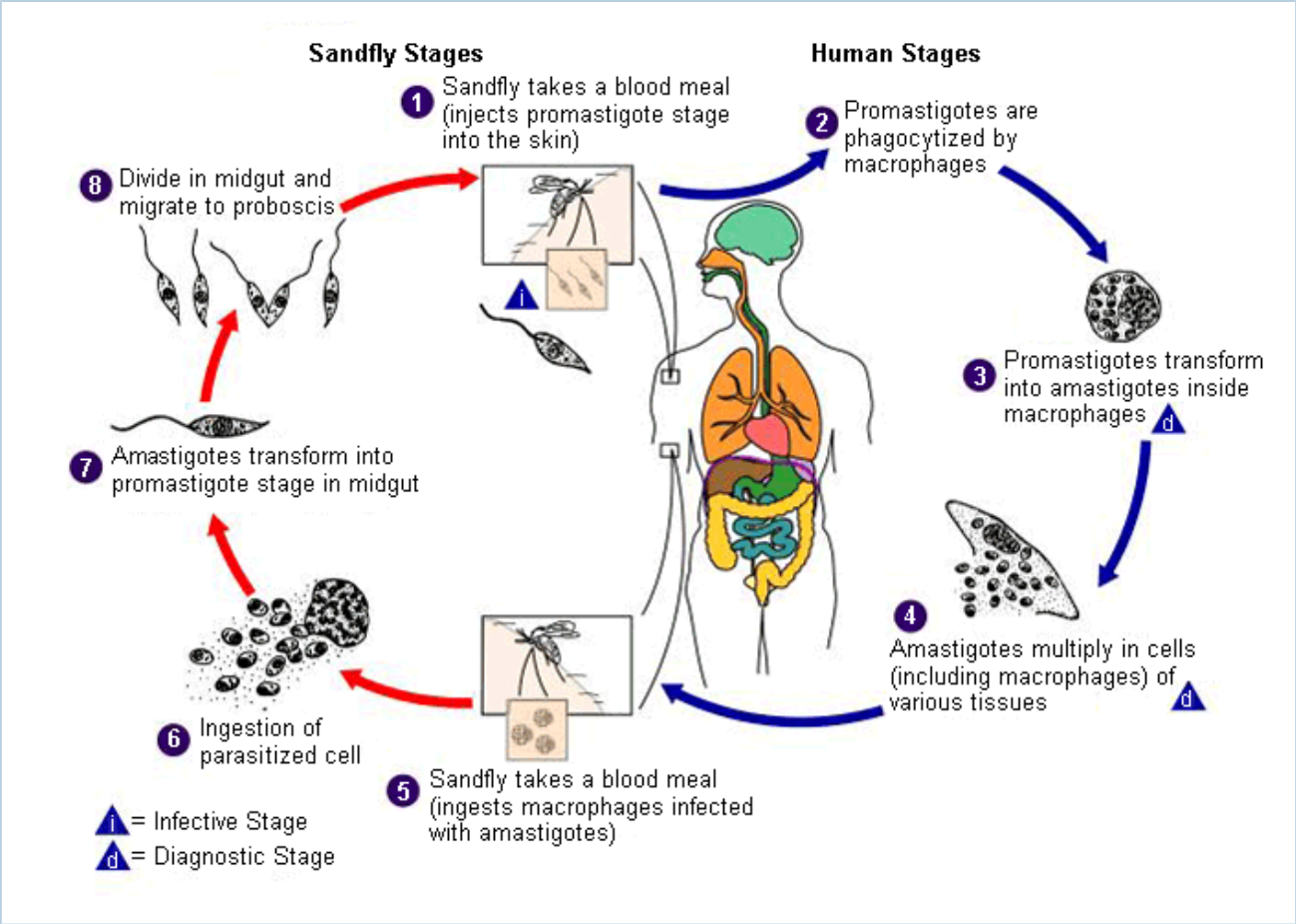
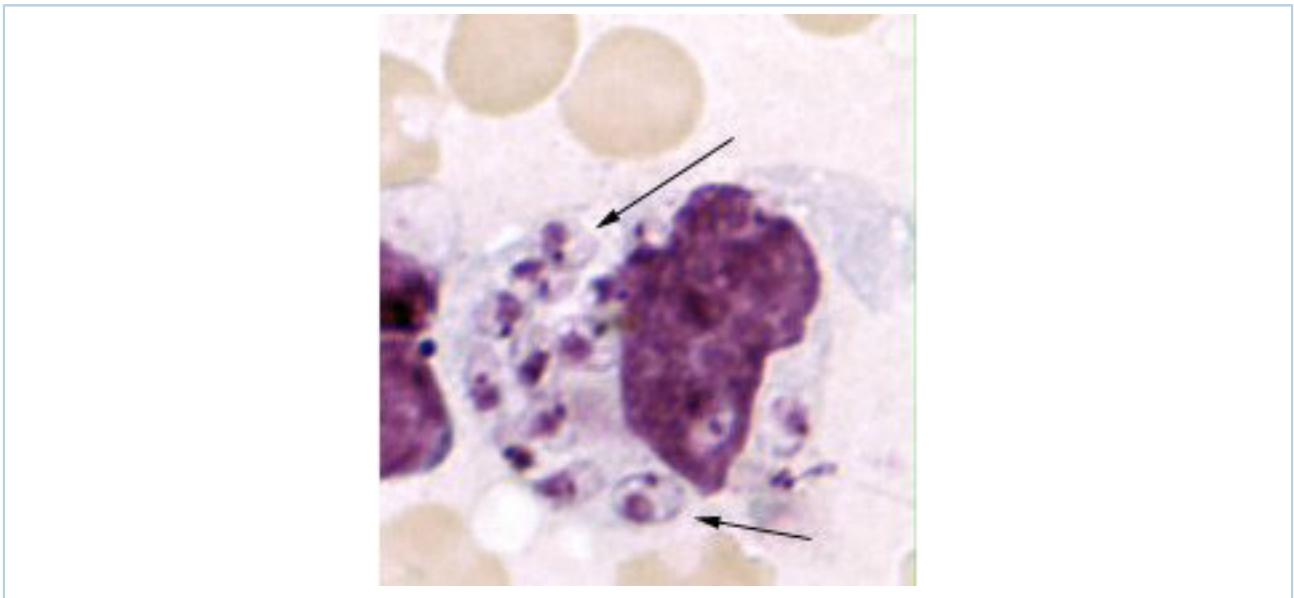


Life cycle of Leishmania species, the causal agents of leishmaniasis

Image courtesy of CDC; A.J. da Silva, PhD; M. Moser



Skin touch preparation showing Leishmania tropica amastigotes. Intact macrophage is practically filled with amastigotes, several of which have a clearly visible nucleus and kinetoplast (arrows)

Image courtesy of CDC; NCID; DPDx

Classification

Leishmaniasis subtypes

Cutaneous

- Localized cutaneous leishmaniasis
- Diffuse cutaneous leishmaniasis
- Disseminated leishmaniasis
- Leishmaniasis recidivans
- Mucosal leishmaniasis (sometimes classified as a separate subtype on its own)

Visceral

- Visceral leishmaniasis (also known as kala-azar, mainly when associated with *Leishmania donovani*)
- Post-kala-azar dermal leishmaniasis

Cutaneous leishmaniasis is sometimes categorized by geographic occurrence:[1]

- Old World: caused by *Leishmania* species found in the Eastern hemisphere, including Africa, Southwest Asia, the Middle East, and the Mediterranean (e.g., *Leishmania tropica* , *Leishmania major* , *Leishmania aethiopica* , *Leishmania infantum* [synonym: *Leishmania chagasi*], and *Leishmania donovani*)
- New World: caused by *Leishmania* species found in the Western hemisphere, including South and Central America (e.g., *Viannia* subgenus, including *Leishmania braziliensis* , *Leishmania guyanensis* , *Leishmania panamensis* , and *Leishmania peruviana* ; as well as *Leishmania mexicana* , *Leishmania amazonensis* , *Leishmania venezuelensis* , and *L infantum* [synonym: *L chagasi*]; listing not exhaustive).

Clinical classification

The appropriate management is individualized for each CL patient. The Infectious Diseases Society of America (IDSA)/American Society of Tropical Medicine and Hygiene (ASTMH) guidelines classify cutaneous leishmaniasis as either simple or complex.[8]

- Simple CL:
  - No mucosal involvement and parasite species not associated with ML
  - ≤4 lesions <1 cm
  - Location feasible for local therapy and/or nonexposed skin (not cosmetically important)
  - Immunocompetent host
  - Lesions resolving without therapy.
- Complex CL:
  - Parasite species caused by species associated with ML
  - Local subcutaneous nodules
  - Large regional adenopathy
  - >4 lesions generally >1 cm
  - Individual lesion ≥5 cm

- Size or location makes local therapy infeasible and/or lesion of the face, fingers, toes, joints, or genitalia
- Immunocompromised host
- Failure of local therapy
- Unusual syndromes (leishmaniasis recidivans, diffuse cutaneous leishmaniasis, or disseminated leishmaniasis).

Case history

Case history #1

A 20-year-old US college student has recently returned from a 2-month training session in an Amazon rainforest diversity station in Peru. She reports a 2-month history of painless open sores on her leg. Other students in her group have similar skin findings. She also reports intermittent use of personal protective measures and having slept in open-air housing with evening exposure to insect bites. Physical exam reveals two nontender 3 × 3 cm skin ulcerations with indurated rims on her left leg and an enlarged femoral lymph node. No other symptoms are reported.

Case history #2

An 8-year-old boy from the province of Bihar, India is visiting his uncle in Chicago. He reports a 3-month history of intermittent fever, weight loss, fatigue, epistaxis, and abdominal distension. Physical exam reveals pallor, emaciation, and a grossly enlarged spleen.

Other presentations

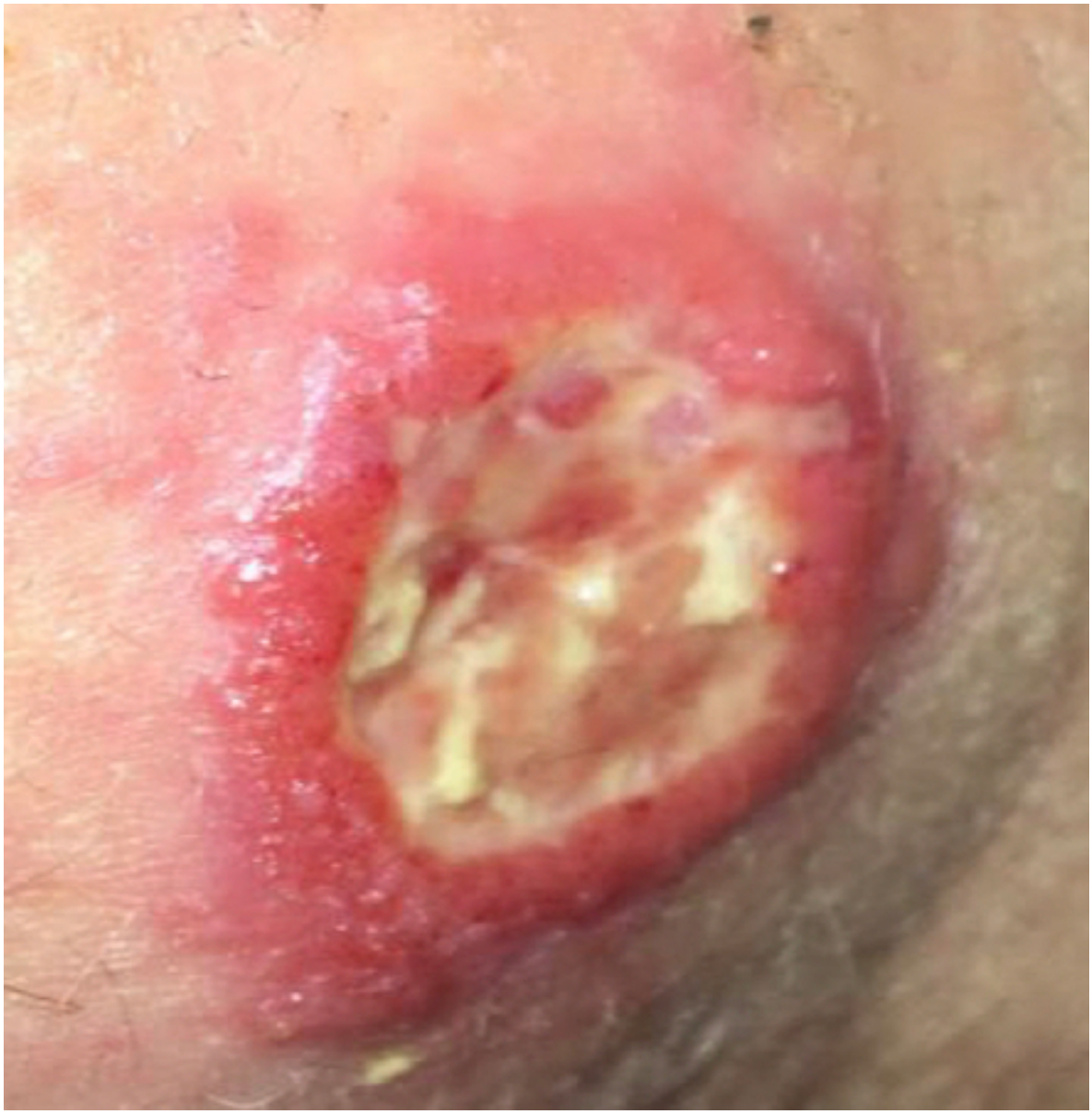
Localized cutaneous leishmaniasis (CL) tends to affect skin areas readily exposed to sand fly bites (i.e., face, arms, and lower limbs). Occasionally, lesions are reported on atypical areas (e.g., sexual organs).[9] An auricular manifestation of CL is a single ulcerative lesion, typically involving the ear pinna (known as "chiclero's" ulcer in southeast Mexico and Latin America when caused by *Leishmania mexicana*).[10] Lesions may develop at sites distant from the sand fly bite, such as sites of minor trauma (e.g., bee sting, new tattoo, surgical incision), or may be disseminated in immunocompromised hosts.[11] Skin lesions are chronic, usually painless, and can have various appearances, but cutaneous induration is present. There may be multiple or single lesions. Small subcutaneous nodules may be palpated (nodular lymphangitis) often in a sporotrichoid pattern, and regional lymphadenopathy may be present in some cases.

Mucosal leishmaniasis (also known as espundia) may occur concurrently with localized CL or years later after the skin lesion has healed. It is restricted to the mucosa (generally nasal, oropharyngeal, or laryngeal) with patients complaining of nasal congestion, discharge, epistaxis, throat irritation, or, most concerningly, changes in their voice. Physical exam usually reveals inflammation of the anterior nasal septum (sometimes with perforation), hypertrophy of the tissue of the upper lip and mucosa, or granulomatous tissue on the pharynx/larynx that may ulcerate. A hypopigmented atrophic scar may be noted, indicative of a prior infection.[12] [13]

Visceral leishmaniasis (VL) is characterized by a spectrum of clinical presentations from asymptomatic, to paucisymptomatic, to symptomatic (characterized by fever, weight loss, organomegaly, cytopenias, and hypergammaglobulinemia).

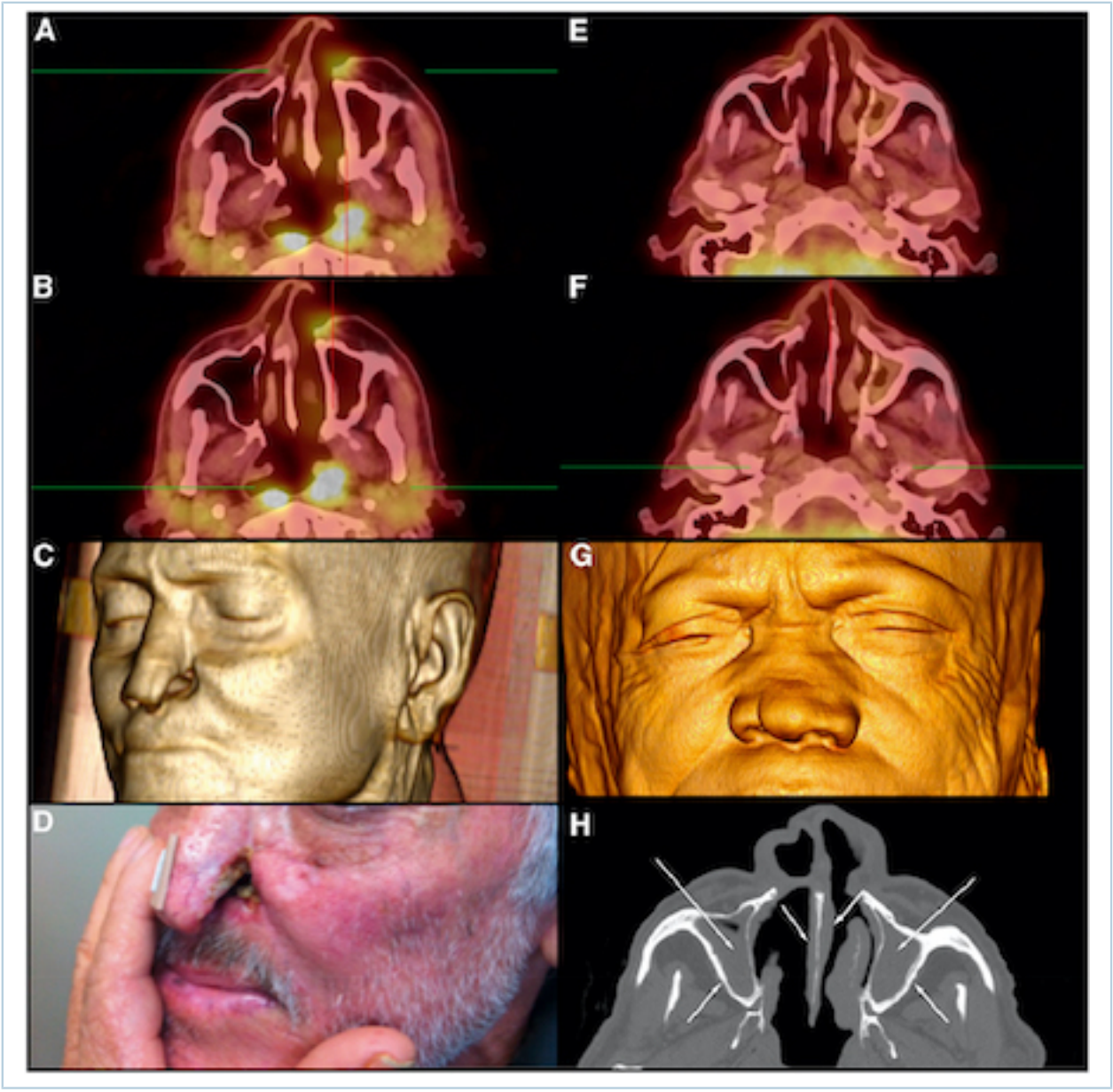
Skin darkening of the hands, feet, forehead, or abdomen, which led to the name of kala-azar ("black fever" in Hindi), is sometimes present in patients with VL from South Asia. Enlarged lymph nodes are observed frequently in Sudanese patients with VL, but rarely in patients from other areas. Concomitant bacterial infections (e.g., pneumonia, diarrhea, or tuberculosis) may confuse the initial clinical presentation. Digestive (e.g., persistent diarrhea, dysphagia) or respiratory symptoms may be presenting symptoms in patients with severe cell-mediated immunosuppression.

Post-kala-azar dermal leishmaniasis (PKDL) may occur months or years after treatment of VL.[6] Characterized by a macular, maculopapular, or nodular rash, PKDL is mainly found in East African, particularly Sudanese, and also Bangladeshi patients; less frequently it is found in patients from other *Leishmania donovani* -endemic countries (i.e., India); and, rarely, in *Leishmania infantum* (synonym: *Leishmania chagasi*)-infected patients with immunosuppression. [CDC: parasites – leishmaniasis] (https://www.cdc.gov/parasites/leishmaniasis/index.html) [WHO: leishmaniasis] (https://www.who.int/leishmaniasis/en)

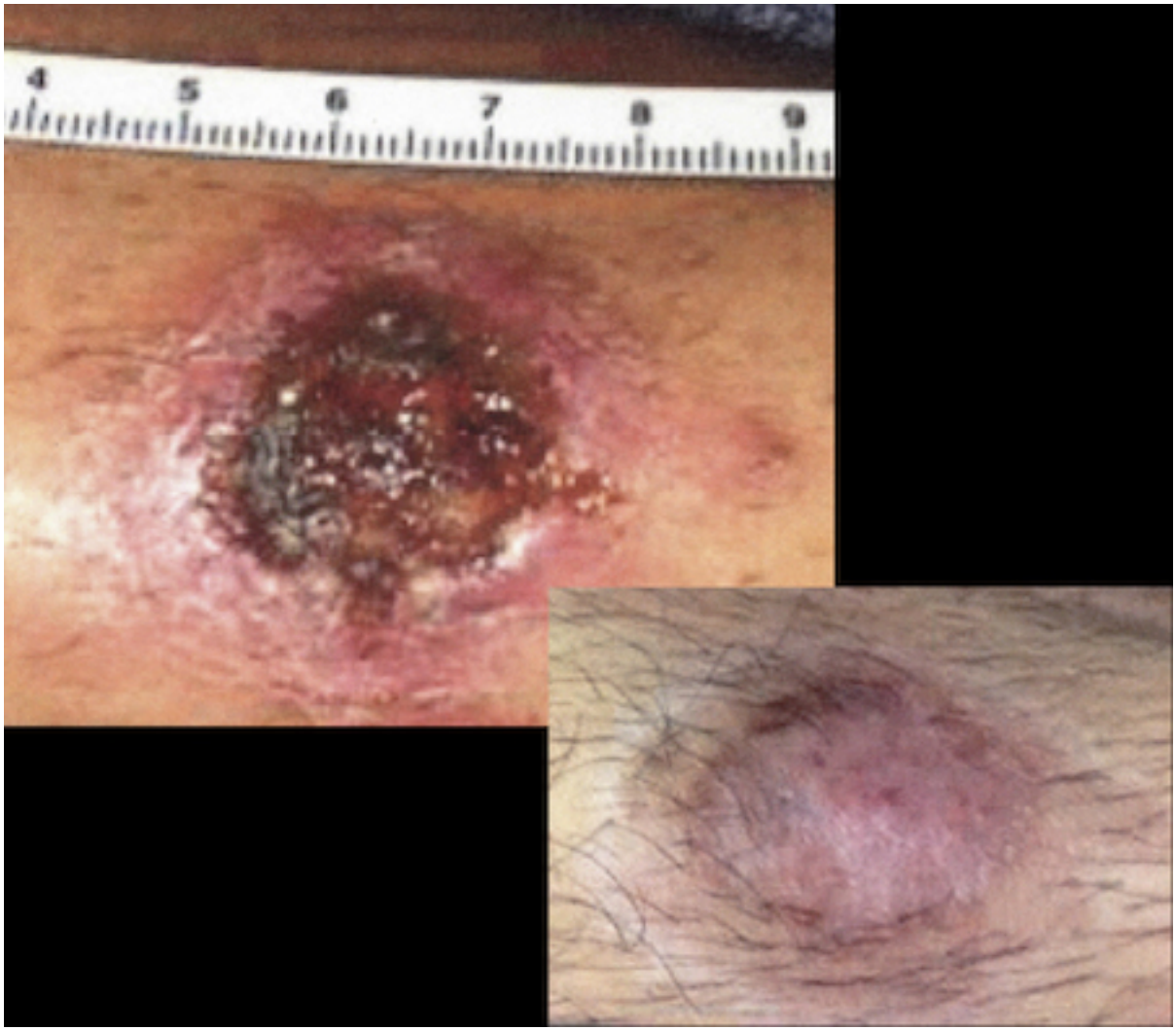


Ulcerative Leishmania braziliensis lesion from a student who traveled to Peru

From the collection of Dr N. Aronson; used with permission



Mucosal leishmaniasis in 2 Brazilian patients. A-D: patient 1 with positron emission tomography/computed tomography (PET/CT) images showing enhancement and subcutaneous thickening adjacent to erosion of the left nasal wing and obliteration of the posterolateral recess (A and B), 3D volume-rendered image of multislice CT data (3D CT) and picture with erosion of the left nasal wing (C and D). F-H: patient 2 with PET/CT images showing preserved glycolytic metabolism of facial structures (E and F), 3D CT with collapse of the nasal pyramids (G), and bone window CT with diffuse thickening of nasal wings and collapse of the nasal pyramid (H)



Ulcerative Leishmania mexicana lesion, pre- and post-treatment

From the collection of Dr N. Aronson; used with permission

Hepatosplenomegaly in an Ethiopian patient with visceral leishmaniasis

Image courtesy of the World Health Organization

Nodular post-kala-azar dermal leishmaniasis in an Ethiopian patient

Image courtesy of the World Health Organization

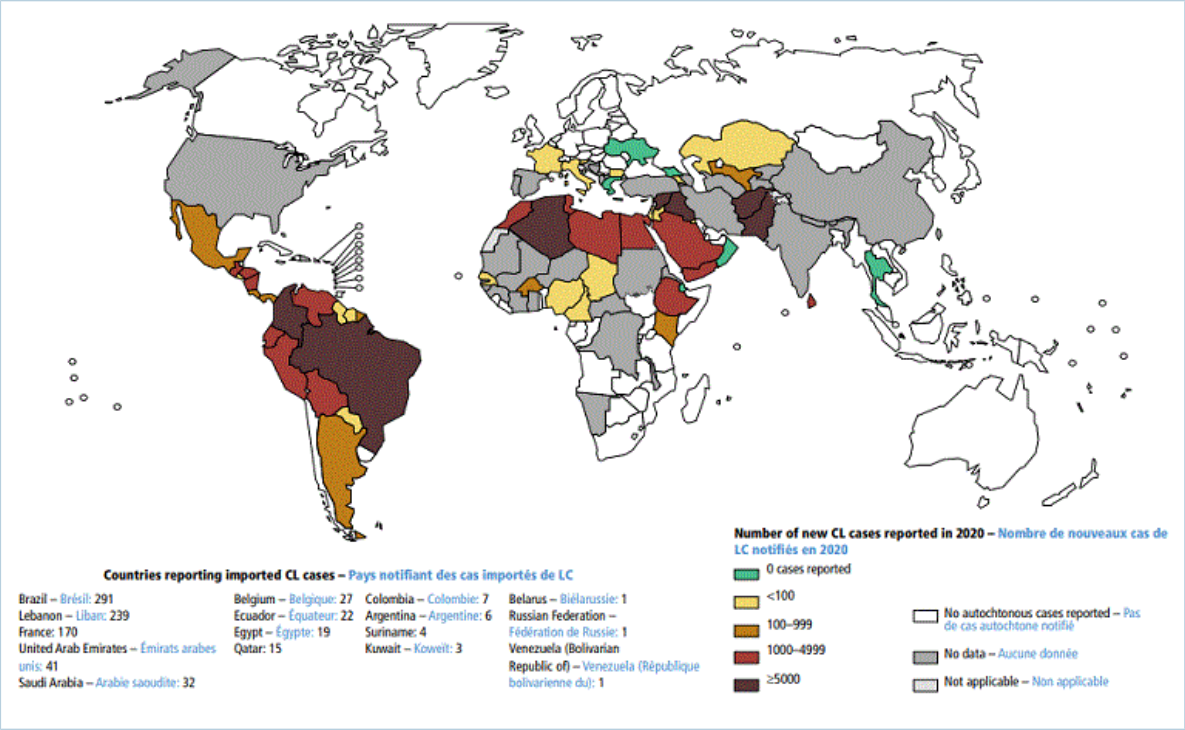
Approach

Prominent risk factors for infection include exposure to sand fly bites, poor disease awareness, malnutrition, immunosuppression, and in some cases proximity to infected patients. History taking and physical exam are crucial to determine the degree of clinical suspicion for both cutaneous leishmaniasis (CL) and visceral leishmaniasis (VL). Laboratory confirmation is mandatory, as other illnesses can present with a similar clinical picture.

History

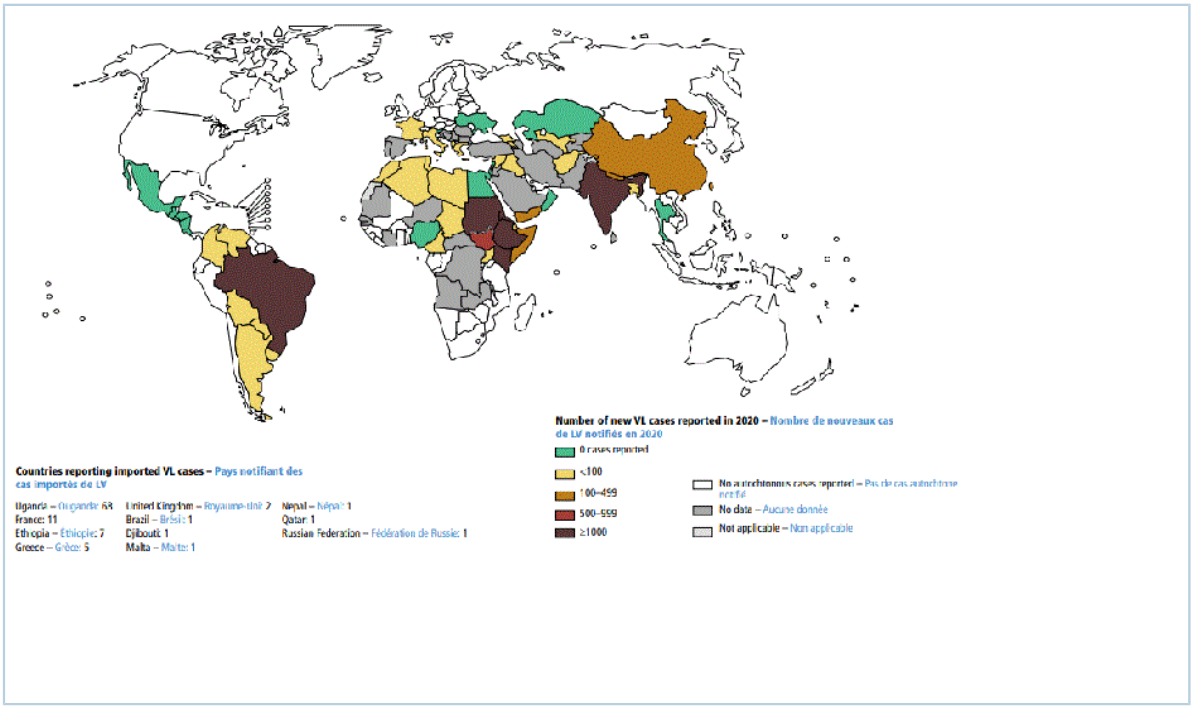
In both VL and CL, the patient may present with a history of:

- A previous stay in an endemic area



Status of endemicity of cutaneous leishmaniasis (CL) worldwide, 2020

Global leishmaniasis surveillance: 2019–2020, a baseline for the 2030 roadmap: World Health Organization; 2021. Licence: CC BY-NC-SA 3.0 IGO (https://creativecommons.org/licenses/by-nc-sa/3.0/igo/)



Status of endemicity of visceral leishmaniasis (VL) worldwide, 2020

Global leishmaniasis surveillance: 2019–2020, a baseline for the 2030 roadmap: World Health Organization; 2021. Licence: CC BY-NC-SA 3.0 IGO (https://creativecommons.org/licenses/by-nc-sa/3.0/igo/)

- Cell-mediated-type immunosuppression, including the less mature immune system
- Previous antileishmanial treatment (raises suspicion of relapse).

Presenting symptoms in VL include:

- Prolonged fever
- Fatigue
- Anorexia
- Weight loss
- Abdominal distention.

DIAGNOSIS

Hepatosplenomegaly in an Ethiopian patient with visceral leishmaniasis

Image courtesy of the World Health Organization

Less common symptoms in VL include:

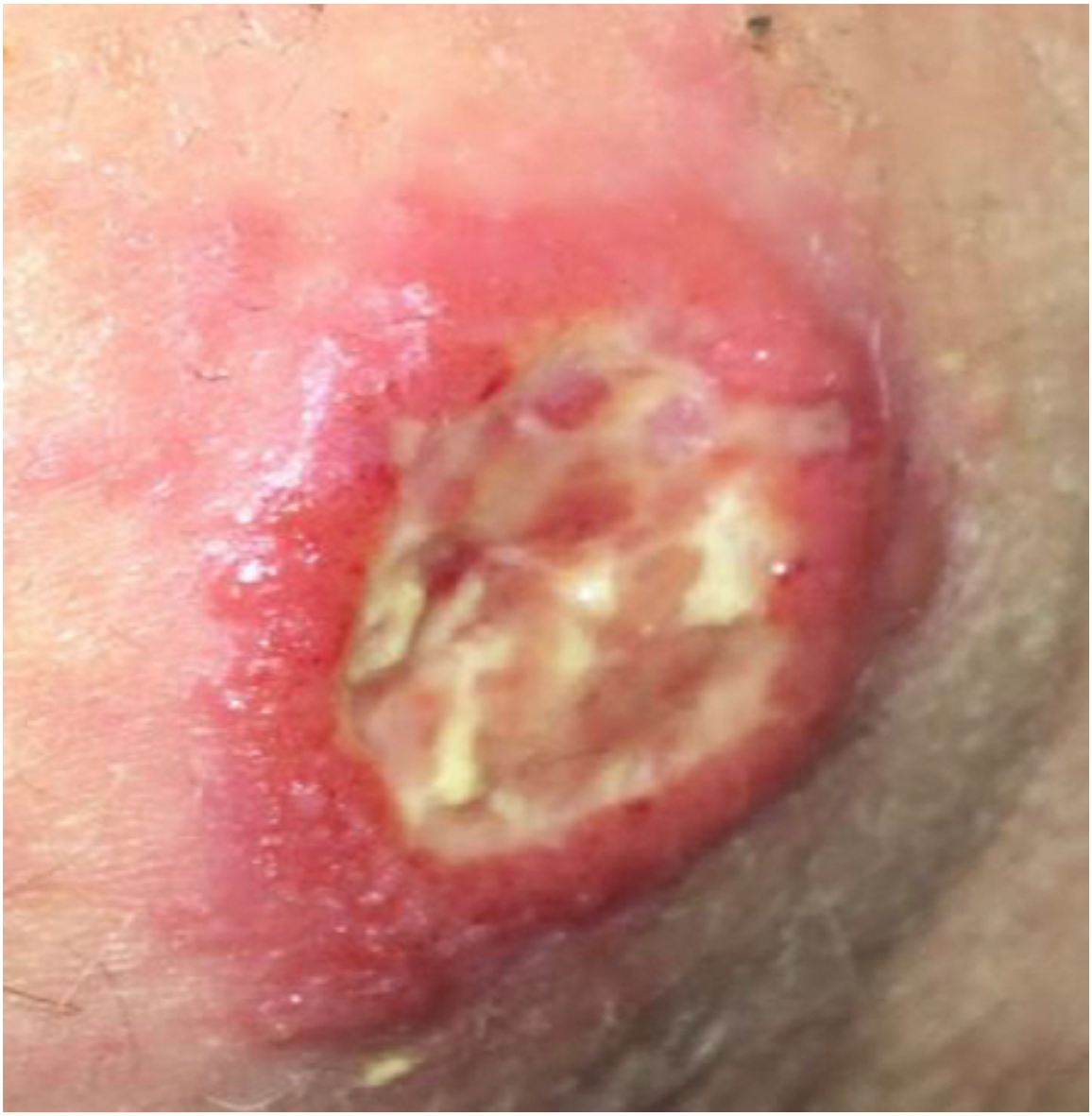
- Cough
- Diarrhea
- Rigors
- Bleeding, including epistaxis.

Clinical exam

Presenting signs in CL include:

- Ulcerative, nodular, plaque-like, or verrucous skin lesions at the bite site (localized CL). Lesions typically affect readily exposed skin, including the face, arms and lower limbs. A single ulcerative lesion involving the ear pinna is known as "chiclero's" ulcer in southeast Mexico and Latin America, when caused by *Leishmania mexicana* .[10]
- Lesions at sites distant from the sand fly bite, such as areas of minor trauma.
- Multiple nonulcerative skin nodules (diffuse cutaneous leishmaniasis).
- Many ulcerative and papulonodular skin lesions (disseminated leishmaniasis).
- Nodulo-ulcerative lesions surrounding a healed leishmanial scar (leishmaniasis recidivans).
- Small subcutaneous nodules (nodular lymphangitis) often in a sporotrichoid pattern, as well as regional lymphadenopathy in some cases.

- Granulomatous, ulcerating, and/or destructive mucosal inflammation most commonly in the nose, but may also involve the oropharynx or larynx (mucosal leishmaniasis [ML]).



Ulcerative Leishmania braziliensis lesion from a student who traveled to Peru

From the collection of Dr N. Aronson; used with permission

Intralesional injection for the treatment of cutaneous leishmaniasis

Image courtesy of the World Health Organization

In VL, the following can be detected:

- Wasting
- Lymphadenopathy (common in Sudan, uncommon elsewhere)
- Splenomegaly
- Hepatomegaly
- Hyperpigmentation (in South Asia).

In the majority of cases, the clinical presentation of VL in immunosuppressed patients is similar to that of immunocompetent patients. However, a minority of immunosuppressed patients present with atypical features (e.g., signs of digestive or respiratory tract involvement, lack of splenomegaly).

Investigations

A complete blood count is recommended in VL to identify and monitor anemia, leukopenia, and thrombocytopenia. Certain medications used in the treatment of leishmaniasis (e.g., paromomycin, pentavalent antimonial drugs, amphotericin-B, and miltefosine) may cause hepatic or renal dysfunction, necessitating measurement of liver function tests and blood urea nitrogen at baseline. A human chorionic gonadotropin (hCG) pregnancy test is essential prior to choosing treatment options as various medications are toxic to the fetus. An ECG prior to using pentavalent antimonial drugs or pentamidine to assess the baseline QT interval is prudent.

Diagnosis is confirmed by microscopic exam of relevant specimens (histopathology), parasite isolation by blood or tissue culture, and molecular detection of parasite DNA by polymerase chain reaction (PCR); supplemental tests include serologic testing in VL.[76] [77] [78] The choice of test depends on the type of

leishmaniasis and test availability. Multiple tests are recommended, if possible, in order to maximize the likelihood of a positive result.[8]

[CDC: practical guide for leishmaniasis] (https://www.cdc.gov/parasites/leishmaniasis/resources/pdf/cdc_diagnosis_guide_leishmaniasis_2016.pdf)

Laboratory evaluation in cutaneous leishmaniasis

The skin lesion should be clean or debrided, if needed, prior to collection of a sample. If possible, multiple types of testing should be done to maximize the diagnostic yield.[79]

If available, molecular parasitologic diagnosis (i.e., PCR-based assays) should be performed if CL is suspected. Such an approach is particularly useful in samples with a low parasite load (e.g., from patients with ML).[78] Molecular parasitologic diagnosis is done using tissue samples obtained via skin scrapings (collecting tissue about the size of a rice grain), swabs of ulcers, aspirates, or slit smears. Skin punch or shave biopsies may actually have a lower yield as higher parasite burden is found in the epidermis and superior dermis.[80] Molecular methods are also used to determine the *Leishmania* species.

If molecular parasitologic diagnosis is not available, use a microscopic exam of biopsy aspirates, smears, scrapings, or skin slit smears, staining with Giemsa or hematoxylin-eosin.[77] Microscopic exam is probably the most common diagnostic approach used in CL-endemic countries. A rod-shaped kinetoplast must be visualized.[1] The parasite is best seen using oil immersion microscopy, at a magnification of 100.

Parasite isolation by culture of tissue or biopsy samples may be useful, and is approximately 95% specific; however, this approach is not very sensitive (typically <50%), is labor intensive, and requires specialized laboratories. Species determination can be done biochemically (with isoenzyme electrophoresis), by mass spectroscopy (MALDI), or by using nucleic acid amplification. A knowledge of the *Leishmania* species responsible for infection helps direct therapy, especially when multiple species are circulating in a given area, and helps determine whether systemic treatment might be necessary (e.g., infection acquired in the Amazon region where the risk of ML is greater).[8]

Serology is not used in the diagnosis of CL due to poor sensitivity and an inability to distinguish between present and past infections.

Laboratory evaluation of visceral leishmaniasis in immunocompetent patients

VL can be suggested by one of several highly sensitive and specific serologic tests (enzyme-linked immunosorbent assay [ELISA], indirect fluorescent antibody test, Western blot, direct agglutination test, rK39 antigen-based dipstick). The choice of test mainly depends on availability and laboratory expertise.[2] However, the sensitivity and specificity of these immunologic assays may vary with geography, host immune response, and type of test. Furthermore, a positive result can persist for years after treatment.

In patients with a typical clinical presentation and positive VL serology, parasitologic confirmation is advised, as the finding and quantification of parasites confirms the diagnosis and may help in assessing response to treatment. In patients with positive serology but atypical clinical disease, parasitologic diagnosis is required. Parasitologic specimens can be obtained by aspiration of splenic tissue, although this carries a risk of fatal hemorrhage; the bone marrow, which is the preferred method; the liver; or the lymph nodes. The sensitivity of a microscopic exam of bone marrow or lymph node tissue can be <50%;

therefore, a negative result does not rule out leishmaniasis infection. A sample of aspirate should be sent for culture and/or PCR, which are more sensitive than smear microscopy.[78]

In patients with negative serology, an alternative diagnosis should be sought.[2] However, if the clinical suspicion of VL remains high, parasitologic tests are recommended.

Laboratory evaluation of visceral leishmaniasis in immunosuppressed patients

Parasitologic diagnosis is the first-line approach in immunosuppressed patients, because serology is less sensitive in this cohort. Additionally, parasitologic diagnosis is typically more sensitive because immunosuppressed patients have a higher parasite load in blood and tissues. An exam of peripheral blood smear or buffy coat by direct microscopy, culture, or PCR (the most sensitive method) is a noninvasive first-line test. If results are negative, the same procedures should be applied on a bone marrow aspirate. Depending on the clinical presentation, lesions in other body sites (e.g., digestive tract, skin) may be sampled.

Serologic diagnosis is an adjunctive measure because of the variable, typically lower sensitivity of this testing method in immunosuppressed patients. Furthermore, a delay in the diagnosis and subsequent treatment has the potential to cause greater harm in this vulnerable patient group.[19] [81]

Diagnosis of visceral leishmaniasis relapse

Patients with VL relapse usually have the same clinical presentation as the initial episode. Relapse should be parasitologically confirmed. Parasitologic diagnosis by direct exam or tissue culture is preferred. The diagnostic value of PCR is uncertain, as PCR can remain positive in patients with clinical cure; however, quantitative PCR may show rising levels of DNA in relapse.[8] [82] The diagnosis of relapse cannot be based on serologic tests, as antibodies against *Leishmania donovani* or *Leishmania infantum* (synonym: *Leishmania chagasi*) usually remain detectable for years after initial diagnosis.[83] [84]

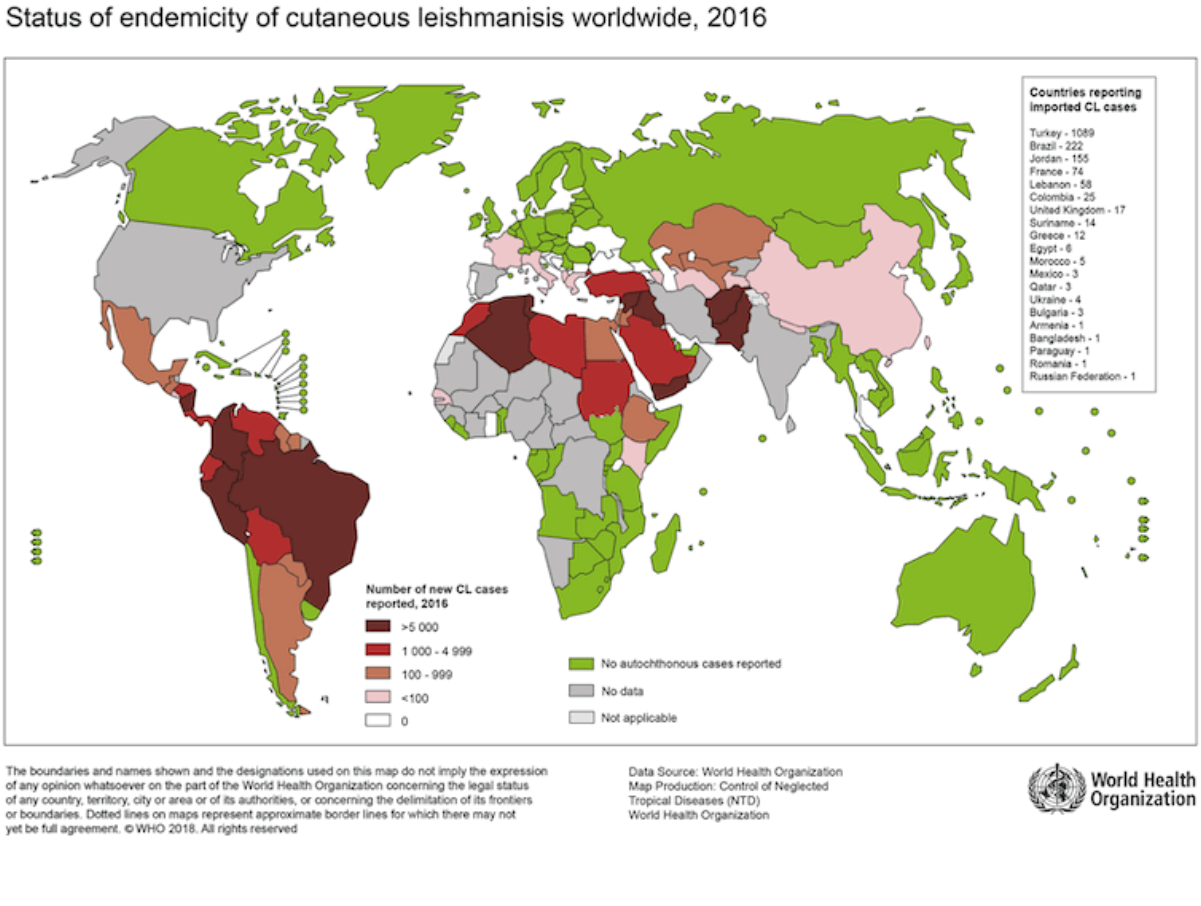
Post-kala-azar dermal leishmaniasis

History-taking (present or past treatment of VL) and clinical exam (presence of macular, maculopapular, or nodular lesions at typical locations) are sufficient to initiate treatment for post-kala-azar dermal leishmaniasis. The diagnosis may be confirmed by direct exam, culture, or PCR of biopsies from skin lesions. The sensitivity of parasitologic diagnosis is improved if large or nodular lesions are sampled.[6] Serologic diagnosis is unhelpful, as specific antibodies against *L donovani* usually remain detectable for years after treatment of VL.[83] [84]

History and exam

Key diagnostic factors

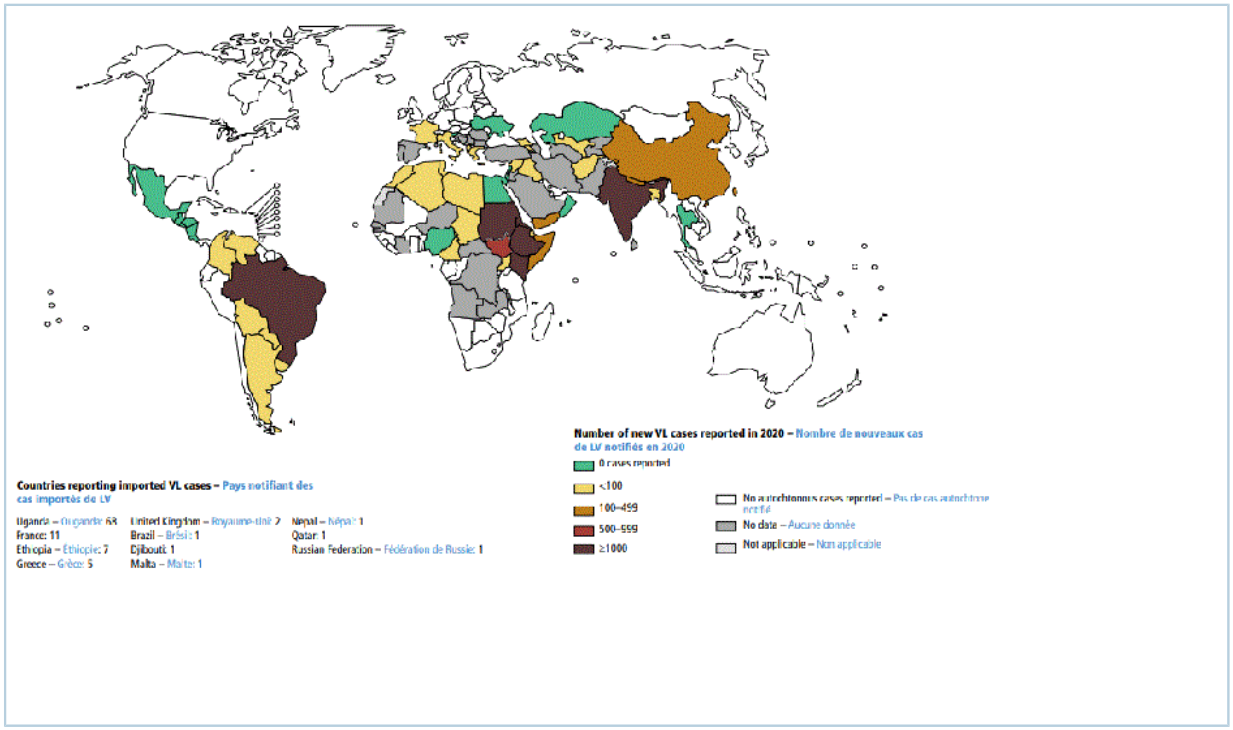
previous stay in endemic area (common)

- Feature of cutaneous leishmaniasis (CL) and visceral leishmaniasis (VL).
- A complete history of travel is necessary to identify previous exposure in CL- and VL-endemic areas: parts of Latin America, Mediterranean basin, Middle East, Central Asia, sub-Saharan Africa (in particular East Africa), northern India, southern Nepal, or northwest Bangladesh.
- Incubation period can be variable and depends on parasite species.[1] [2]
- 

Status of the endemicity of cutaneous leishmaniasis worldwide, 2016

Image courtesy of the World Health Organization

DIAGNOSIS



Status of endemicity of visceral leishmaniasis (VL) worldwide, 2020

Global leishmaniasis surveillance: 2019–2020, a baseline for the 2030 roadmap: World Health Organization; 2021. Licence: CC BY-NC-SA 3.0 IGO (https://creativecommons.org/licenses/by-nc-sa/3.0/igo/)

immunosuppression (common)

- Feature of visceral leishmaniasis.
- Cell-mediated immunosuppression.

prolonged fever (common)

- Feature of visceral leishmaniasis.
- Prolonged (weeks or months) and may be intermittent.[2] Classically described as double quotidian (two episodes of fever occur daily).

weight loss (common)

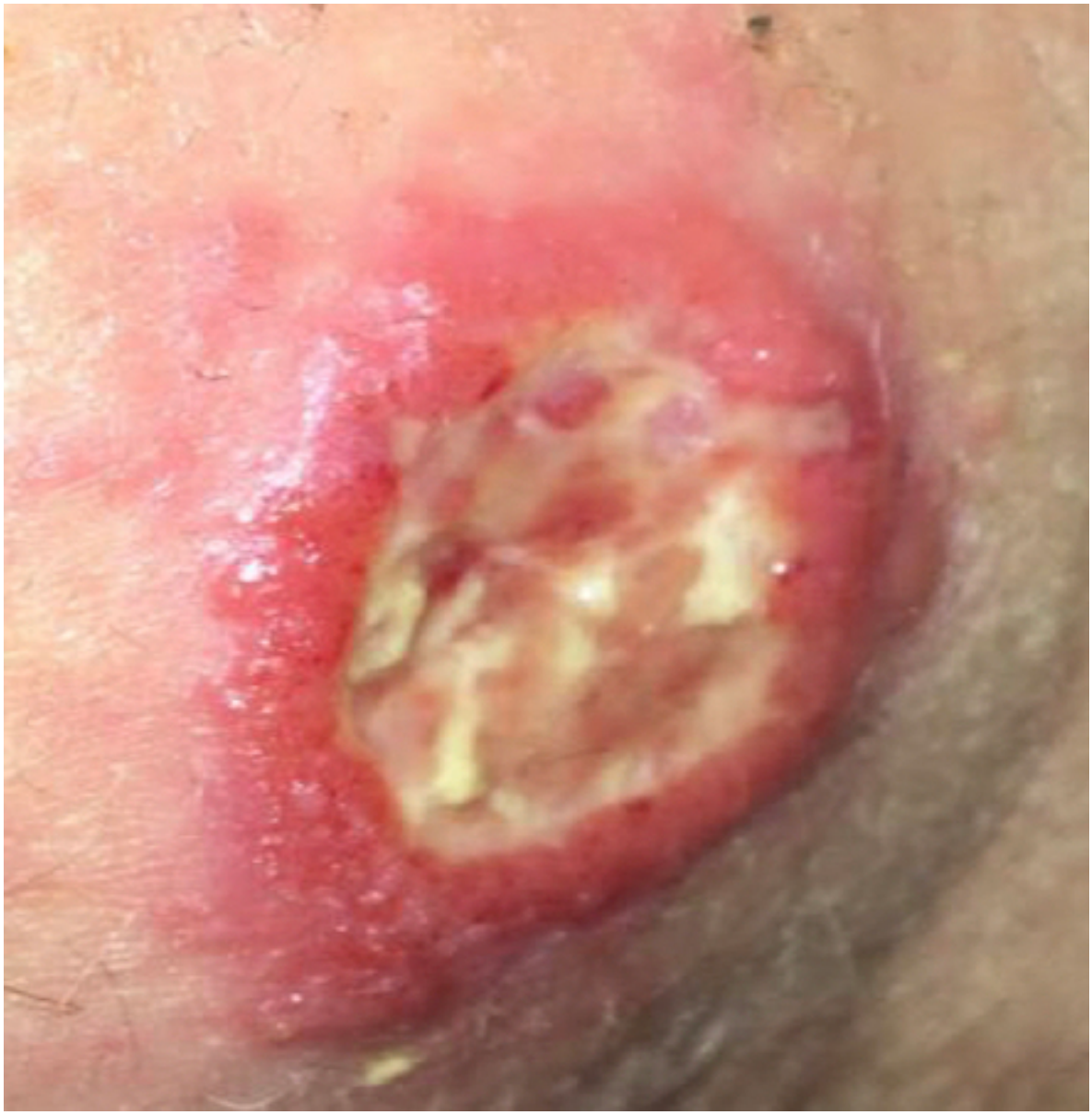
- Feature of visceral leishmaniasis.
- Weight loss is due to anorexia and persistent inflammatory state.
- Concomitant infections (e.g., HIV, tuberculosis, diarrhea) may be aggravating factors.[2]

ulcerative skin lesions (common)

- Characteristic clinical sign of cutaneous leishmaniasis (CL).
- Sometimes occurs in visceral leishmaniasis (e.g., immunocompromised patients).
- Single or multiple lesions, often painless and persistent. Lesions can vary in appearance, although the classic localized CL lesions are characterized by a volcano-like appearance (i.e., raised, indurated borders with depressed, ulcerative lesion center) at the bite site.
- Tends to affect skin that is readily exposed to sand fly bites (i.e., face, arms, and lower limbs). May develop at distant sites, such as areas of minor trauma (e.g., bee sting, new tattoo, surgical incision),

or may be disseminated in immunocompromised hosts.[11] Lesions are occasionally reported on atypical areas (e.g., sexual organs).[9]

- An auricular manifestation of CL is a single ulcerative lesion, typically involving the ear pinna (known as 'chiclero's' ulcer in southeast Mexico and Latin America when caused by *Leishmania mexicana*).[10]
- The Old World CL ulcer often has a dry crust covering it.[1]



Ulcerative Leishmania braziliensis lesion from a student who traveled to Peru

From the collection of Dr N. Aronson; used with permission

Intralesional injection for the treatment of cutaneous leishmaniasis

Image courtesy of the World Health Organization

multiple nonulcerative skin nodules (common)

- Characteristic of diffuse cutaneous leishmaniasis.

destructive mucosal inflammation (common)

- Characteristic of mucosal leishmaniasis.

splenomegaly (common)

- Associated with visceral leishmaniasis.
- Can be massive and symptomatic.
- Palpation of the spleen is usually painless.[2] [54]

skin darkening (uncommon)

- Feature of visceral leishmaniasis.
- Generally observed by the patient or family.
- Described in South Asia (kala-azar).

Other diagnostic factors

fatigue (common)

- Feature of visceral leishmaniasis.
- Pronounced, due to the persistent inflammatory state, weight loss, and anemia.[2]

cough (common)

- Feature of visceral leishmaniasis.

headache (common)

- Feature of visceral leishmaniasis.

wasting (common)

- Characteristic of visceral leishmaniasis.

enlarged lymph nodes (common)

- Commonly associated with cutaneous leishmaniasis (CL); less commonly associated with visceral leishmaniasis (VL).
- Enlarged lymph nodes in CL are in the local and regional lymphatic drainage distribution, sometimes leading to a sporotrichoid appearance.
- In Sudan, it is common for CL and VL.
- Often generalized in VL, if present.
- Lymph nodes are firm, mobile, and painless.[1] [2]

hepatomegaly (common)

- Associated with visceral leishmaniasis.
- Less massive than splenomegaly.
- Liver palpation is usually painless.[2]

previous antileishmanial treatment (uncommon)

- Feature of cutaneous leishmaniasis (CL) and visceral leishmaniasis (VL).
- Raises suspicion of relapse in case of recurrent symptoms of CL or VL, or post-kala-azar dermal leishmaniasis if consistent skin signs are present.

epistaxis (uncommon)

- Feature of visceral leishmaniasis.
- The etiology of epistaxis is poorly understood.
- Thrombocytopenia is likely a risk factor.[2]

abdominal pain (uncommon)

- Atypical feature found in patients with immunosuppression.

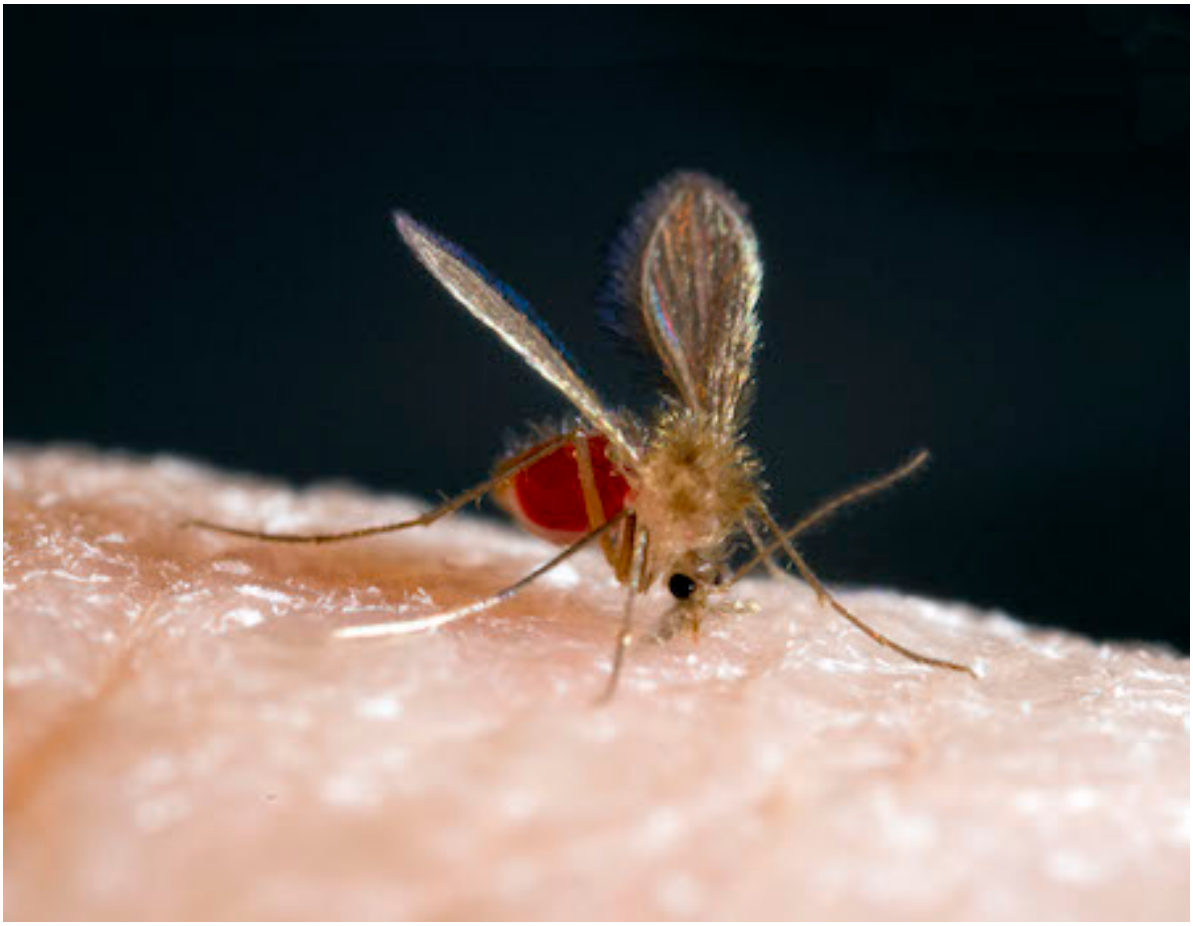
Risk factors

Strong

high exposure to sand fly bites

- A prolonged stay in zones of intense *Leishmania* transmission, such as rural areas of Afghanistan, Iraq, the State of Bihar in India, or eastern Sudan, increases risk. Use of personal protective measures including applying diethyltoluamide (DEET) to exposed skin, wearing permethrin-treated clothing that covers skin at night, and sleeping in permethrin-treated bed nets are advised to reduce the risk of sand fly bites. Risk is particularly from dusk to dawn.

- Bed net use and spraying of the home with insecticides have been shown to protect against infection and/or disease caused by some sand fly species.[51] [52] [53]



Female Phlebotomus papatasi sand fly

With kind permission from EdRowtonPhotography.com

poverty

- Poverty increases the risk of leishmaniasis. Poor housing and sanitary conditions may increase sand fly breeding sites and vector access to humans. Additionally, malnutrition contributes to a poor immune response to the parasite.

proximity to a patient with a history of infection

- Only a risk in anthroponotic disease (humans are the major or sole infection reservoir). This applies to *Leishmania tropica* for cutaneous leishmaniasis and *Leishmania donovani* for visceral leishmaniasis.

ownership of domestic animals

- A complex relationship; may be a risk factor or protective, depending on ecology.[28] [51] [54] Domestic dogs and cats have been associated with an increased risk of visceral leishmaniasis.[55] [56] [57] [58]

immunosuppression

- Coinfection with HIV, use of immunosuppressive drugs (e.g., post-transplantation, biologic modifying agents such as tumor necrosis factor [TNF]-alpha antagonists), severe malnutrition, and

immunosuppression associated with malignancy all increase the risk of developing active cutaneous leishmaniasis and visceral leishmaniasis (VL).[5] [19] [49] [50] [59] [60] [61]

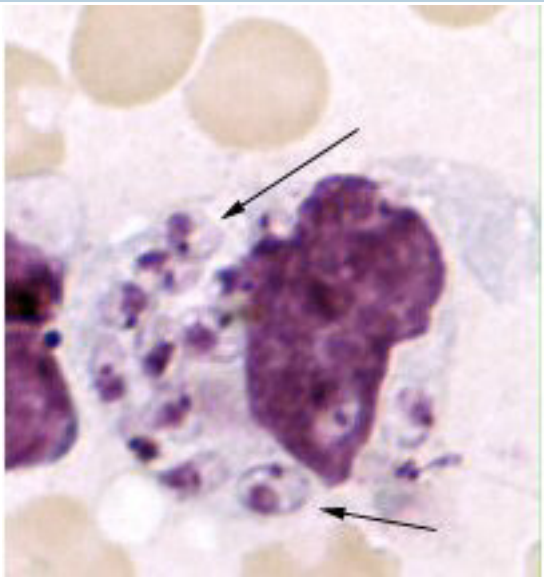
- CD4 counts <200 cells/microliter and failure to take antiretroviral therapy (ART) are strong risk factors for VL in HIV-infected patients.
- The widespread use of ART had a strong impact in decreasing the number of diagnosed HIV-VL coinfections in Europe; however, coinfection in developing countries continues to be increasingly reported.[19] [62]

Investigations

1st test to order

Test	Result
CBC • Should be ordered in patients with visceral leishmaniasis. • Anemia is the most common finding, followed by leukopenia and thrombocytopenia. • Pancytopenia was found in only 16% of patients in Nepal, but specificity was high (98%).[85] Pancytopenia is more frequent in HIV-coinfected patients.[86]	**anemia, leukopenia, thrombocytopenia**
liver function tests and BUN • Treatment with paromomycin, pentavalent antimonial compounds, amphotericin-B, or miltefosine requires monitoring of liver and renal function; therefore, baseline liver function tests and BUN should be ordered.	**variable; may be elevated in visceral leishmaniasis, particularly alkaline phosphatase**
serum human chorionic gonadotropin (hCG) • Pregnancy status determines treatment choices and later in pregnancy the immunologic response, so all women of childbearing age should be tested prior to treatment.	**may be positive or negative**

Other tests to consider

Test	Result
microscopic exam of relevant specimen • Recommended to confirm diagnosis of suspected cutaneous leishmaniasis (CL) or visceral leishmaniasis (VL). Probably the most common confirmatory test used in CL-endemic countries.[1] • CL: biopsy aspirates, smears, scrapings, and skin slit smears are used.[77] Sensitivity is variable and depends on sampling technique, duration of lesions, presence/absence of ulceration, and presence of superinfection. Sensitivity is poor (<50%) in mucosal leishmaniasis.[1] [87] • VL: specimen can be obtained by aspiration of splenic tissue (discouraged due to risk of fatal hemorrhage), bone marrow, liver, or lymph nodes. Microscopic exam of splenic aspirates is the most sensitive technique (>95%), but carries a 1:1000 risk of major bleeding; considerable technical expertise is required.[88] Exam of bone marrow aspirate or lymph node fluid is safer, but is of lower sensitivity (70% to 90% and 58%, respectively). The sensitivity of a bone marrow exam is increased to 85% in patients with immunosuppression.[89] [90] In people with HIV infection who are immunocompromised, tissue biopsy of gastrointestinal mucosa or buffy coat smears may be diagnostic. • May also be used to confirm diagnosis of post-kala-azar dermal leishmaniasis (PKDL). Sensitivity is improved if large or nodular skin lesions are sampled in PKDL.[6]  *Skin touch preparation showing Leishmania tropica amastigotes. Intact macrophage is practically filled with amastigotes, several of which have a clearly visible nucleus and kinetoplast (arrows)* *Image courtesy of CDC; NCID; DPDx*	**amastigote form of the *Leishmania* species in macrophages or monocytes**

Test	Result
blood (buffy coat) or tissue culture • Recommended to confirm diagnosis of suspected cutaneous or visceral leishmaniasis, and is especially useful when the goal is to characterize infecting parasite species. • Novy-Nicolle-McNeal medium or other biphasic-type media are often used, although modified Schneider medium is often sufficient.[91] • While 100% specific, sensitivity is variable (typically <50%), and depends on sampling technique and quality of culture media, sample processing and laboratory infrastructure, duration of lesions, and presence of superinfection. Culture with isoenzyme characterization permits species identification. • May also be used to confirm diagnosis of post-kala-azar dermal leishmaniasis (PKDL). Sensitivity is improved if large or nodular skin lesions are sampled in PKDL.[6]	**promastigote forms of the *Leishmania* species in culture media**
polymerase chain reaction (PCR) • Recommended to confirm diagnosis of suspected cutaneous leishmaniasis (CL) or visceral leishmaniasis (VL), if available. More sensitive than microscopic exam or parasite culture for the diagnosis of suspected CL and VL.[8] • Sensitivity estimates range from 70% to 100% when using tissue biopsies for CL diagnosis and when using peripheral blood for VL diagnosis.[78] [82] [92] [93] • Particularly useful in cases with a low parasite load (e.g., mucosal leishmaniasis [ML]).[78] • May also be used to confirm diagnosis of post-kala-azar dermal leishmaniasis. Sensitivity is improved if large or nodular lesions are sampled.[6] • Recommended when species characterization is needed (e.g., to determine whether a patient may be at risk of ML in the future because of *Leishmania [Viannia]* species infection). There is no clinically available PCR on offer at a species level of determination; many are genus only. • The diagnostic value of PCR in patients with relapsed VL is uncertain, as PCR can remain positive in patients with clinical cure; however, quantitative PCR may show rising levels of DNA in relapse.[82]	***Leishmania* DNA**
serology • Recommended to support diagnosis of suspected visceral leishmaniasis (VL).[8] • A useful test in immunocompetent patients with suspected VL, but less sensitive in patients who are immunosuppressed. However, it may be used in patients who are immunosuppressed if parasitologic diagnosis is not feasible.[19] [81] • Various highly sensitive and specific tests are available, and the choice depends mainly on availability and laboratory expertise.[2] • Direct agglutination test: one meta-analysis of 30 studies showed 94.8% sensitivity and 97.1% specificity.[94] • rK39 dipstick: rapid diagnostic test that takes 10 to 20 minutes. One meta-analysis of 18 studies showed 91.9% sensitivity and	**positive for *Leishmania* antibodies, or antibody titer above locally validated threshold**

Test	Result
92.4% specificity.[95] Less sensitive in East Africa than on the Indian subcontinent and in Latin America.[65] [95] [96] [97] • Indirect fluorescent antibody test: moderate to high sensitivity (>85%) and high specificity (>90%) have been reported.[98] [99] • Enzyme-linked immunosorbent assay (ELISA): highly sensitive and specific. Crude soluble *Leishmania* antigen or various recombinant proteins (including rK39) can be used; use of recombinant antigen may increase sensitivity.[2] • Western blot: promising test but experience is restricted to a few laboratories.[100] • Diagnosis of relapse cannot be based on serologic tests, as antibodies against *Leishmania donovani* or *Leishmania infantum* (synonym: *Leishmania chagasi*) usually remain detectable for years after initial diagnosis.[83] [84]	
serum HIV testing • Visceral leishmaniasis is an opportunistic infection in patients with HIV/AIDS. Newly diagnosed patients should be evaluated for HIV/AIDS.	**may be positive or negative**

Differentials

Condition	Differentiating signs / symptoms	Differentiating tests
Hyperreactive malarial splenomegaly (HMS)	• Differential for visceral leishmaniasis (VL). • Formerly called tropical splenomegaly syndrome. • The clinical presentation can mimic VL but fever is a less consistent feature.[101] • A clinical response to antimalarials also helps distinguish the diagnoses.	• Major criteria for HMS diagnosis are splenomegaly >10 cm on CT scan, high titers of antimalarial antibodies, and IgM titers >2 standard deviations above the mean of the local population. • *Plasmodium* species in the peripheral blood smear are typically not found. • In practice, VL must be ruled out by specific serologic or parasitologic tests.[101]
Malaria infection	• Differential for visceral leishmaniasis (VL). • As malaria is more acute than VL, patients present with fever of shorter duration and mild or absent splenomegaly. • Recurrent malaria can be more difficult to distinguish from VL, as fever can be longer lasting and intermittent, and the spleen markedly enlarged. • Patients unresponsive to effective antimalarials should be investigated for VL, as dual infection is common in endemic areas.	• Malaria can be diagnosed by microscopic exam of a stained, thin, and thick smear of peripheral blood or by a rapid diagnostic test detecting circulating antigens specific to *P falciparum* or other species.[102]
Schistosomiasis	• Differential for visceral leishmaniasis. • Splenomegaly, secondary to portal hypertension, can be massive. • Chronic schistosomiasis does not cause fever but the patient may present with concomitant infection such as malaria, typhoid fever, or tuberculosis.[103]	• Chronic *Schistosoma mansoni* infection is diagnosed by the presence of characteristic eggs in the stools or by antibody-based assays. • Abdominal ultrasound, CT scan, or MRI show the typical features of hepatic schistosomiasis and signs of portal hypertension.[103]
Leprosy	• Differential for disseminated cutaneous leishmaniasis. • Residence in/travel to an endemic area. • Absence of ulcerative lesions.	• Histopathology: positive for acid-fast bacilli.

Condition	Differentiating signs / symptoms	Differentiating tests
	• Presence of neuropathy.	
Paracoccidioidomycosis	• Differential for mucosal leishmaniasis. • Residence in/travel to an endemic area. • Skin lesions often involve the face: for example, the nasal and oral mucocutaneous borders.	• Histopathology: large yeasts that form multiple buds (sometimes called a pilot wheel or Mickey Mouse ears).
Blastomycosis	• Differential for cutaneous leishmaniasis. • Residence in/travel to an endemic area. • Fungal skin lesions can appear nodular, ulcerated, or verrucous, and typically have a raised, irregular border.	• Histopathology: acute inflammation with or without necrosis, granuloma formation, and multinucleated giant cells. Large yeasts that characteristically form a single broad-based bud (may be described as having a 'footprint' morphology).
Disseminated histoplasmosis	• Differential for visceral leishmaniasis. • Residence in/travel to an endemic area. • Skin lesions are uncommon but may occur in disseminated histoplasmosis. • Fever, splenomegaly, and pancytopenia may be found.	• Histopathology: visualization of *Histoplasma capsulatum* ; this looks very similar to an amastigote but without a rod-shaped kinetoplast.
Sarcoidosis	• Differential for cutaneous leishmaniasis. • Tender erythematous nodules on lower extremities. • The granulomatous lesion of leishmaniasis recidivans can mimic sarcoidosis.	• Skin biopsy: noncaseating granulomas.
Cutaneous tuberculosis	• Differential for cutaneous leishmaniasis. • Cutaneous tuberculosis may present with similar skin lesions; however, they are uncommon in tuberculosis.	• Biopsy, histopathology, culture, and/or polymerase chain reaction of lesions distinguish tuberculosis.
Squamous cell carcinoma of the skin	• Differential for cutaneous leishmaniasis. • History of skin cancer or sun damage to skin. • Appears as erythematous papules or plaques that often have a scale or hemorrhagic crust, or as a nodule. May	• Biopsy: keratinocyte atypia.

Condition	Differentiating signs / symptoms	Differentiating tests
	bleed easily, ulcerate, or exhibit rapid growth.	
Basal cell carcinoma	• Differential for cutaneous leishmaniasis. • History of skin cancer or sun damage to skin. • Presents as pearly papules or plaques with rolled borders, telangiectasia, and ulceration when tumors become larger.	• Biopsy: tumor nests with basaloid differentiation, with large nuclei and scant cytoplasm.

Screening

Screening asymptomatic people for *Leishmania* infection is only relevant for research purposes (e.g., epidemiologic or vaccine studies).

High-risk population screening

There is no clinically validated screening test for asymptomatic cutaneous leishmaniasis or visceral leishmaniasis. For epidemiologic purposes, groups at increased risk in the population tested can be identified. Diagnostic testing is recommended in this same group of asymptomatic people one year later. Identifying those patients who seroconvert or whose interferon-gamma release assay becomes positive allows measurement of the incidence of new infections.[104] [105]

Considering the high risk of developing or reactivating the disease during cell-mediated immunosuppression, providers might consider screening patients at risk for previous *Leishmania* infection (i.e., history of prolonged stay in an endemic area) if a validated screening test becomes available.[5] [106]

Blood/organ/tissue donors or recipients

There are no international guidelines to screen for *Leishmania* infection in donors or recipients of blood, organs, or tissues, or in patients with immunosuppression. In the US, soldiers who were deployed to Afghanistan are ineligible to be blood donors for 12 months. Because of the possibility of infection following blood transfusion or organ/tissue donation, it is recommended that people with a history of leishmaniasis (particularly visceral leishmaniasis) do not donate blood, and if organ/tissue donation is contemplated (pre- or postmortem), the donor's history of leishmaniasis should be considered.

Approach

The treatment of leishmaniasis is complex and, after discussing the primary drug options more generally, discussion is grouped by major clinical syndromes. It is important to recognize that the available literature on treatment varies in methodology with relatively few well-controlled clinical trials and a diversity of treatment end points.

For all types of leishmaniasis, parasite and host factors can influence treatment outcomes. Not only can treatment outcomes vary by species but there can be differences seen within a single species from different geographic regions. For example, the response to treatment of visceral leishmaniasis (VL) caused by *Leishmania donovani* varies significantly between South Asia and East Africa, with liposomal amphotericin-B being preferred in the former and pentavalent antimonial compounds retaining higher efficacy in the latter.[113] Host factors that influence the response to treatment include nutritional status and the presence of immunocompromise, such as HIV/AIDS.

In addition to treating the parasite, consideration has to be given to managing coinfections and/or supportive care, particularly in VL. The goal of therapy in all forms of leishmaniasis is clinical cure, recognizing that *Leishmania* parasites likely persist after treatment.[114] [115]

General considerations for choosing therapy include regional efficacy, safety, availability, and cost, with the latter two often driving management decisions in low-resource settings.

Antileishmanial drugs

Amphotericin-B

- Liposomal amphotericin-B is the preferred formulation for the treatment of leishmaniasis, when available. Its use is limited by cost, availability, and the requirement of a cold chain. It is approved in the US for VL; use in other types of leishmaniasis is off-label. Liposomal amphotericin-B is generally well tolerated with adverse effects including infusion-related reactions (e.g., chills, fever), nausea, vomiting, hypokalemia, and renal insufficiency.[116] [117] [118]
- Amphotericin deoxycholate is an option if the liposomal formulation is not available; adverse effects are similar but more frequent and severe, and administration is more complicated.[119] [120]
- Other lipid formulations of amphotericin-B, if available, have been less rigorously studied and appear to be inferior to liposomal amphotericin-B.[121]
- Amphotericin-B is the only antileishmanial with safety data in pregnancy.

Miltefosine

- Miltefosine is the only oral antileishmanial available.
- Use of miltefosine is limited by:
    - High risk for teratogenicity in pregnancy. Women require a negative pregnancy test and effective contraception during treatment and for at least 5 months after completion of treatment
    - Significant gastrointestinal adverse effects including nausea, vomiting, and abdominal pain
    - Natural or emerging resistance in some regions.[122] [123]
- Miltefosine is approved in the US for use in:

- VL caused by *Leishmania donovani*
- Cutaneous leishmaniasis (CL) due to *Leishmania braziliensis*, *Leishmania guyanensis*, and *Leishmania panamensis*
- Mucosal leishmaniasis (ML) due to *Leishmania braziliensis*.

Pentavalent antimonial compounds

- Antimonials are the oldest available medications for the treatment of leishmaniasis. However, the adverse-effect profile with the high doses required makes their use less appealing.
    - Adverse effects are common and include decreased appetite, nausea, vomiting, abdominal pain, myalgias, arthralgias, headache, generalized weakness, and malaise. Laboratory abnormalities include cytopenias, elevated aminotransferases, and elevated amylase and lipase.
    - Severe adverse effects include pancreatitis, QT prolongation (potentially leading to cardiac arrhythmias including torsades de pointe), and sudden death.
    - Pentavalent antimonial compounds have been shown to be embryotoxic in rats and associated with a high rate of spontaneous abortions in humans.[124] [125] [126]
- Specific drugs include sodium stibogluconate and meglumine antimoniate. Branded products are generally preferred due to more reliable content and less toxicity.[127]
- In the US, there are no Food and Drug Administration (FDA)-approved pentavalent antimonial compounds currently available. In Europe, sodium stibogluconate is licensed for use in all major forms of leishmaniasis.
- Significant regional differences in efficacy have been seen, with a high level of resistance in South Asia.[128]

Paromomycin

- Paromomycin is an aminoglycoside that can be administered topically in CL or intramuscularly in VL, and is often used in combination with another agent.
- Neither intramuscular nor topical preparations of paromomycin are approved for use in the US. Oral preparations in the US are approved for other indications and can be used to compound topical ointments, but this use is off-label.
- When used topically, paromomycin can cause mild to moderate local-site reactions including redness, pain, swelling, burning, and itching. Adverse effects with systemic paromomycin include significant injection-site pain, elevated aminotransferases, renal insufficiency, and reversible ototoxicity.
- Safety data are lacking for paromomycin in pregnancy.

Pentamidine

- Use is generally limited to specific situations in CL and secondary prophylaxis among immunocompromised patients.
- Pentamidine is available in the US, but use is off-label in leishmaniasis. It is approved in Europe for the treatment of CL.

- Adverse effects are significant and include diabetes mellitus, pancreatitis, gastrointestinal symptoms, hypotension, QT prolongation, electrolyte disturbances, nephrotoxicity, hepatotoxicity, cytopenias, and rhabdomyolysis. These effects are mitigated when drug is administered intralesionally for cutaneous leishmaniasis.
- There are no data on the safety of pentamidine in pregnancy.

Other drugs such as azole antifungals may have a role in some specific situations.

Cutaneous leishmaniasis: general principles

The appropriate management is individualized for each CL patient. The Infectious Diseases Society of America (IDSA)/American Society of Tropical Medicine and Hygiene (ASTMH) guidelines classify cutaneous leishmaniasis as either simple or complex.[8]

- Simple CL:
    - No mucosal involvement and parasite species not associated with ML
    - ≤4 lesions <1 cm
    - Location feasible for local therapy and/or nonexposed skin (not cosmetically important)
    - Immunocompetent host
    - Lesions resolving without therapy.
- Complex CL:
    - Parasite species caused by species associated with ML
    - Local subcutaneous nodules
    - Large regional adenopathy
    - >4 lesions generally >1 cm
    - Individual lesion ≥5 cm
    - Size or location makes local therapy infeasible and/or lesion of the face, fingers, toes, joints, or genitalia
    - Immunocompromised host
    - Failure of local therapy
    - Unusual syndromes (leishmaniasis recidivans, diffuse cutaneous leishmaniasis, or disseminated leishmaniasis).

In high-resource settings, parasitologic diagnosis with species-level identification is optimal to guide management and should be obtained. In low-resource settings, attempt should still be made to confirm the diagnosis to the extent possible due to the significant adverse effects associated with treatment.[129] [130] [131] In cases where the species cannot be determined, knowledge of regional (old world versus new world) and local prevalence patterns may help in guiding therapy. For example, a patient with CL from the "mucosal belt" of Bolivia, Brazil, and Peru may be at higher risk of mucosal spread and so consideration might be given to monitoring patients without a clear species-specific diagnosis for the development of mucosal disease after management of the primary skin lesion(s).

Simple CL may require only watchful waiting or, to accelerate cure, can be managed with local therapies or potentially azole antifungals. Complex CL generally requires systemic therapy to prevent disability and social stigma, and/or to prevent parasite dissemination (e.g., mucosal leishmaniasis [ML]) or relapse.

For all cases of ulcerative CL, care should be taken to ensure proper wound management including washing of ulcer(s) and applying barrier ointment. The presence of warmth, redness, pain, and/or purulent

discharge should prompt for the evaluation and management of a secondary bacterial infection. Evidence of healing often begins with flattening, and large ulcers may not be completely healed by the end of therapy. [CDC: parasites – leishmaniasis] (https://www.cdc.gov/parasites/leishmaniasis/index.html)

Treatment recommendations for specific situations are given below; however, most trials on the treatment of CL have been poorly designed and reported, resulting in a lack of clear evidence for potentially beneficial treatments. There is a need for large, well-conducted studies that evaluate long-term effects of current therapies, and evaluate recurrence rates of cutaneous leishmaniasis and its progression to mucosal disease.[132] [133]

Cutaneous leishmaniasis: specific treatment

Simple cutaneous leishmaniasis

For simple CL, options include watchful waiting, local therapies, or less toxic systemic medications.

Most cases of CL, particularly among Old World species, will resolve spontaneously within 18 months; therefore, it is important to decide whether or not treatment is truly indicated.[113] [134] This decision must be individualized considering factors such as whether healing has already begun, impairments of wound healing, risk of secondary infections, patient preference, whether there is evidence of impaired cell-mediated immunity, and availability/expertise in treatment.

Among those who undergo treatment, options for local therapy include cryotherapy, thermotherapy, and topical or intralesional medications. Before any local therapy is started, any crust should be removed, if present.[8]

- Cryotherapy: involves freezing the lesion and surrounding 1 to 2 mm of healthy skin with liquid nitrogen until it is white in appearance, allowing the area to thaw, and freezing again. The IDSA/ASTMH guidelines recommend a cryotherapy session every 3 weeks up to three times total.[8] The per lesion efficacy of cryotherapy is 67% across all regions, and is statistically the same as intralesional antimonial compounds.[135] Adverse effects include transient pain and redness as well as hypopigmentation.
- Thermotherapy: utilizes heat administered to the lesion(s), often in a single treatment, resulting in a second-degree burn and requiring local anesthesia. A meta-analysis showed 73% efficacy across all regions, equivalent to systemic antimonial therapy but with fewer adverse effects.[136] Efficacy may be even higher in the Old World, with cure rates as high as 94% in *Leishmania tropica* .[113] Adverse effects include cellulitis, redness, and pain at the treatment site, and US guidelines recommend utilizing topical antibiotics post-procedurally for several days.[8] This treatment modality requires the use of special equipment and operator training on this equipment, which limits its broad applicability.
- Topical paromomycin: the best studied topical medication for the treatment of CL. The efficacy varies in the literature with the precise formulation; therefore, commercial and compounded versions may not be equivalent to what is reported. Paromomycin may be used alone or in combination with methylbenzethonium chloride, urea, or gentamicin.[132]
    - In the Old World disease with ulcerative *Leishmania major* an overall cure rate of approximately 80% was seen (with or without the addition of gentamicin) compared with 57% in the vehicle only arm.[137]

- In two studies in the New World among lesions caused by *L panamensis* , *L guyanensis* , or *L braziliensis* , similar paromomycin products had cure rates of 77% to 79%.[138] [139]
- Older studies in the New World have shown lower rates of efficacy (approximately 50%) with various different paromomycin formulations; however, the cure rates with systemic pentavalent antimonial compounds in these studies were similar (74%) to topical paromomycin in newer studies.[140]
- In Panama, 3% of patients treated with topical paromomycin developed mucosal disease that required systemic treatment.[138] The risk of mucosal disease among patients with *Viannia* subgenus parasites remains a significant concern warranting close monitoring if topical treatment is chosen versus opting for systemic therapy initially.

- Intralesional therapy: involves injecting lesions with an antileishmanial drug, most commonly pentavalent antimonial compounds. Pain with injection can be significant. In the Old World, the best results are seen by combining intralesional sodium stibogluconate with cryotherapy, with cure rates of 89% to 91% reported.[113] While the evidence in the New World is less robust and concerns for ML remain, a meta-analysis showed pooled efficacy of 75%, but with a preference for meglumine antimoniate (efficacy 82%) rather than sodium stibogluconate, which is preferred in the Old World.[141] Sodium stibogluconate is available for intralesional use in Europe, but is not available in the US. Pentamidine can also be used intralesionally.[142]
- Other methodologies such as photodynamic therapy or CO_2 laser therapy are potential alternative local therapies, but limited evidence prevents making recommendations regarding their use.

Intralesional injection for the treatment of cutaneous leishmaniasis

Image courtesy of the World Health Organization

Generally, systemic therapy is reserved for complex disease, but azole antifungal therapy may be an option in simple CL.

- Fluconazole, itraconazole, and ketoconazole have been evaluated and are available globally, although use in CL is off-label in both the US and Europe.
- All have gastrointestinal adverse effects and a risk of hepatotoxicity, but ketoconazole carries a warning related to the risk of life-threatening hepatotoxicity and QT prolongation that could lead to fatal arrhythmias.
- A systematic review did not find enough evidence to recommend any of the azole antifungals routinely, but in the New World pooled efficacy for ketoconazole in the treatment of *Leishmania mexicana* was as high as 89%, suggesting this as a potential option in Mexico and parts of Central America with appropriate monitoring of adverse effects.[143]

Complex cutaneous leishmaniasis

In complex CL, systemic therapy is preferred due to the extent or location of the lesion(s), prior failure of local therapy, and/or the risk of dissemination.

- Miltefosine: a more recent option for CL. It is approved for *Viannia* subgenus parasites in the New World, but even in that context there is variability regionally. Cure rates in Brazil, Bolivia, and Colombia range from 71% to 91% for *Viannia* species, but in Guatemala the cure rate was only 33% for *L braziliensis* .[144]
- Pentavalent antimonial compounds (sodium stibogluconate, meglumine antimoniate): generally effective but less favorable due to the associated toxicity and duration of treatment. In Old World disease, cure rates range as high as 98% for *L major* and as low as 41% for *L tropica* . In the New World, efficacy ranges from 77% to 90%, but significant levels of treatment failure are seen among parasites of the *Viannia* subgenus, especially *L braziliensis* , and also in certain geographic regions such as *L mexicana* in Guatemala, or among *Leishmania* species in the southern jungle regions of Peru bordering with Bolivia.[144]
- Liposomal amphotericin-B: likely effective for complex CL, but data are limited to observational studies and several small trials. Retrospective data from various regions range from 46% to 84% cured, but small trials in Bolivia had rates of 85% to 100%.[144]
- Pentamidine: has a limited role in treating CL in the New World caused by *L guyanensis* in French Guiana and Suriname with cure rates generally of 84% to 90% reported.[145] [146] Intravenous injection is preferred over intramuscular injection as increased efficacy is seen with intravenous administration (85% cure with intravenous versus 51% with intramuscular).[147] Another potential use is intralesional pentamidine in Bolivia with a reported efficacy of 73%, but this may not impact the risk of mucosal spread.[142] However, combination of this same regimen with 28 days of miltefosine resulted in 92% cure rates and has the advantage of systemic treatment, albeit with increased duration and cost.[148] In other settings, the adverse effects and relatively lower efficacy of pentamidine typically preclude its use. This may be due in part to underdosing based on the salt (isethionate) versus the base.[149]

The treatment of other complex forms of CL including disseminated leishmaniasis, diffuse cutaneous leishmaniasis, and leishmaniasis recidivans should be guided by experts as treatment can be challenging and data are limited.

- Liposomal amphotericin-B has been used with reasonable success in disseminated leishmaniasis (cure rate of 75%).[150]
- For diffuse cutaneous leishmaniasis, the Pan American Health Organization recommends treatment in a referral center and lists pentavalent antimonial compounds, pentamidine, or

miltefosine as potential options.[151] However, cure in these patients can be challenging to achieve.

- Leishmaniasis recidivans can be frustrating to treat.[8] One potential regimen combines a pentavalent antimonial compound with allopurinol for 30 days.[152] Liposomal amphotericin and miltefosine are often used.

Pregnant patients

- Treatment of simple and complex cutaneous disease in pregnant patients is highly individualized. If possible, treatment should be deferred until after pregnancy, even exophytic lesions; however, there may be an increased risk of preterm birth and stillbirth in untreated CL patients.[153]
- Theoretical concerns for transplacental transmission of CL exist based on studies in mice, but this has not been reported in humans.[154]
- Local therapies are generally preferred to systemic therapies if possible, noting that intralesional therapies can lead to systemic absorption.
- Amphotericin-B is the preferred agent if systemic therapy is required due to its relative safety compared with other options.
- Pentavalent antimonial compounds have increased risks of miscarriage and early delivery, generally precluding their use during pregnancy.

Mucosal leishmaniasis

Patients with ML should always receive treatment with systemic therapy. Robust data are limited and treatment efficacy varies, requiring an individualized approach to therapy. Options for therapy include pentavalent antimonial compounds, amphotericin-B formulations, miltefosine, and pentamidine. The Pan American Health Organization classifies the evidence of all options as low or very low, but gives its strongest recommendation to pentavalent antimonial compounds.[110] [151] The US guidelines do not stratify among the alternatives other than classifying pentamidine as a lesser alternative.[8]

- Pentavalent antimonial compounds are a reasonable first choice in patients able to tolerate the course. Efficacy varies from 58% with sodium stibogluconate to 88% with meglumine antimoniate. Some studies have added adjuncts such as pentoxifylline or interferon-gamma, but evidence for this is weak.[130]
- Amphotericin-B formulations are an alternative, particularly for treatment failure, relapse, or intolerance of pentavalent antimonial compounds. Liposomal amphotericin-B has less data, but is preferred when available in light of better safety and tolerability.[8] In a retrospective series from Brazil, the cure rate was 93% for patients treated with liposomal amphotericin-B.[155]
- If this treatment fails, miltefosine can be used, but cure rates are low apart from in clinically mild disease.[156]

Pregnant patients

- Amphotericin-B is preferred due to the better safety profile.

Visceral leishmaniasis: general principles

The main objective of treatment is prevention of death and achievement of long-term clinical cure. Eradication of parasites is unlikely in most patients, as evidenced by disease reactivation years after initial clinical cure and by the post-treatment persistence of parasites in a significant proportion of patients when highly sensitive detection methods (e.g., polymerase chain reaction) are used.[82] [157]

As in CL, there are parasite factors (often corresponding to species and/or geographic region) and host factors that should be considered when determining a treatment course for an individual. All patients with symptomatic disease should be treated. It is unknown whether the treatment of latent VL infection would prevent the development of symptomatic disease and it is not recommended, especially in light of the toxicities of available treatments.

In addition to the treatment of *Leishmania*, management must address frequent complications such as volume depletion, malnutrition, anemia, and concomitant bacterial infections (e.g., pneumonia) or parasitic infections (e.g., malaria).

Visceral leishmaniasis: treatment in immunocompetent patients

Amphotericin-B formulations

- Outside of East Africa, liposomal amphotericin-B is the treatment of choice, with clinical cure in >90% with varying regimens.[8] [113] [144]
- For *L donovani* in India, liposomal amphotericin-B was demonstrated to be reasonably safe and had a 96% cure rate in clinical trials.[158] Multiple subsequent studies including over 2500 patients treated with liposomal amphotericin-B across South Asia have shown similar or higher efficacy.[159] [160] [161] [162] [163]
- In East Africa, higher doses of liposomal amphotericin-B are required to treat *L donovani* and have achieved a clinical cure in >90% despite most of these patients being complex (e.g., pregnancy, relapse, advanced disease, or extremes of age).[164] [165]
- *Leishmania infantum* (also known as *Leishmania chagasi*) is also preferentially treated with liposomal amphotericin-B.[144] Most efficacy data are from the Mediterranean region, but a study in Brazil supports the use of liposomal amphotericin-B over pentavalent antimonial compounds and modeling demonstrates the cost-effectiveness of this approach.[166] [167]

Combination therapy

- The combination of pentavalent antimonial compounds with paromomycin is highly effective for the treatment of VL due to *L donovani* in East Africa, with cure rates of 90% to 95%.[165] [168] This drug combination should not be used in patients >50 years of age or those with HIV due to decreased cure rates of 81% and 56%, respectively.[168] As parenteral paromomycin is not available in the US or Europe, it is unusual to see this regimen used outside of East Africa.
- In South Asia, the combinations of liposomal amphotericin-B with short courses of miltefosine or paromomycin, or miltefosine with paromomycin, are highly effective alternatives to amphotericin-B.[162] [163] [169]

Other monotherapy options

- Miltefosine monotherapy is an alternative option. In South Asia, initial results were excellent, but after 10 years of use a decline in efficacy was observed and now use is generally as an alternative or in combination with other drugs. Effectiveness of monotherapy in East Africa and South America is also suboptimal.[144]
- Pentavalent antimonial compounds can be used for *L donovani* in East Africa, or in *L infantum* with decent efficacy, but they are considered second-line when other options are not available. Drug resistance in South Asia precludes their use in the subcontinent.[113]
- While paromomycin monotherapy has been demonstrated as 95% to 98% effective when compared with amphotericin-B or as a single arm in South Asia in limited studies, other safer and

equally efficacious options make this a lower-tier option even in areas where it is available.[170] [171]

Patients who do not respond to, or who relapse after, initial therapy should receive full treatment with an antileishmanial drug (or a combination of antileishmanial drugs) from a different class. However, if the initial treatment was with liposomal amphotericin-B, retreatment with amphotericin-B, potentially at higher total doses, is appropriate.[8] [113]

Pregnant patients

- Treatment is essential because untreated VL can be fatal to both mother and fetus.
- Limited data suggest that liposomal amphotericin-B is a safe and effective treatment option.[8] [125]
- Use of pentavalent antimonial compounds in pregnancy should generally be avoided due to an increased risk of miscarriage or preterm delivery, and there are no safety data on paromomycin in pregnancy.[8] However, if no other options are available, treatment with these medications (alone or in combination) may be an option under expert guidance only.
- Miltefosine must be avoided due to fetal risk.

Visceral leishmaniasis: treatment in immunocompromised patients

Immunocompromise among VL patients is most commonly due to HIV coinfection followed by iatrogenic immunosuppression (e.g., solid organ transplant recipients). Immunocompromising conditions not only increase the risk of developing symptomatic disease but also decrease the chance of initial cure while increasing the risk of relapse.[172] [173] A comprehensive approach of treating the parasite, managing immunosuppression, monitoring for relapse, and, potentially, administering secondary prophylaxis is essential.

HIV/AIDS

- Lifelong antiretroviral therapy should be initiated or continued in all patients with HIV infection according to current local guidelines.
- Liposomal amphotericin-B is generally regarded as the best option for patients with VL and HIV infection.[8] [111][174] A higher total dose is used in patients who are immunocompromised. However, even with higher doses, treatment can be unsatisfactory and relapse is common. A published trial in East Africa showed only a 55% efficacy for liposomal amphotericin-B monotherapy among patients with a median CD4 count of 69 cells/microliter.[175]
- Combination therapy should be considered in this context. In the trial of liposomal amphotericin-B in East Africa discussed above, the second arm showed 88% efficacy with the combination of liposomal amphotericin-B and miltefosine among patients with a median CD4 count of 54 cells/microliter.[175] In India, the combination of miltefosine and liposomal amphotericin-B was associated with 96% efficacy compared to miltefosine monotherapy at 85%.[176] The combination of sodium stibogluconate and paromomycin, highly effective in non-HIV-coinfected East Africans, had only a 56% cure rate and probably should be avoided unless it is the only option.[168] The World Health Organization (WHO) suggests liposomal amphotericin-B plus miltefosine over liposomal amphotericin-B monotherapy in people with HIV coinfection in East Africa and South East Asia.[62]

- Pentavalent antimonial compounds are an alternative in patients with HIV infection; however, increased mortality has been observed when compared with amphotericin-B, and higher rates of severe adverse reactions have been observed.[177] [178] [179]

Secondary prophylaxis in HIV/AIDS

- Secondary prophylaxis with antileishmanial drugs should be given to all patients with a CD4 count <200 to 350 cells/microliter (the higher CD4 cut-off is recommended by the Pan American Health Organization) due to the high risk of relapse.[8] [111][151] [174] There is no consensus on the best regimen, but guidelines do recommend various options.
- A prospective study of pentamidine prophylaxis in East Africa had a 46% relapse rate at 1 year among those with CD4 counts <200 cells/microliter compared with an historically observed relapse rate of 60% to 70% when prophylaxis was not used.[180]
- It is unclear when secondary prophylaxis should end. Some guidelines suggest stopping after CD4 counts reach >200 to 350 cells/microliter, whereas others recommend indefinite therapy as the risk for relapse continues. Regardless, careful monitoring for relapse is essential in all patients with HIV infection.[8] [111]
- In East Africa, relapse rates have been shown to be high even among those with CD4 counts >200 cells/microliter, with history of prior relapse being a significant predictor of future relapse or death.[180]
- In East Africa, a 37% relapse rate was observed over a 2 year follow-up after 12-18 months of pentamidine prophylaxis, mainly in those with a low basilar CD4 count.[181]

Other forms of immunosuppression

- Includes solid organ transplant patients, lymphatic or hematologic malignancy, or treatment with immunosuppressants for other indications.
- If patients are on immunosuppressants for other indications, consider decreasing the dose or stopping these medications, if possible, although this is based on expert opinion and not on strong data.[173]
- Treatment has been accomplished with multiple regimens, but liposomal amphotericin-B is recommended, particularly in solid organ transplant patients.[8] [151]
- While relapse is common, particularly among solid organ transplant patients (approximately 25%), data are not clear on the role of secondary prophylaxis. The IDSA/ASTMH guidelines recommend against secondary prophylaxis among those without a prior relapse, but in a small retrospective case-control study, risk of relapse decreased by 27% among those on secondary prophylaxis.[8] [182] Consider secondary prophylaxis on an individual basis, especially among patients with a history of prior relapse for whom the immunosuppressive condition is ongoing.

Among all immunosuppressed patients who relapse, treatment with liposomal amphotericin-B is reasonable, even among those who received this as primary therapy, because failure in this setting is thought to be immunologic rather than a result of drug resistance. Alternatively, other options or combination therapies can be tried.[8]

Pregnant patients

- Treatment is essential because untreated visceral leishmaniasis can be fatal to both mother and fetus.
- Limited data suggest that liposomal amphotericin-B is a safe and effective treatment option.[8] [125] The other forms of amphotericin may be used if liposomal amphotericin is unavailable.

Post-kala-azar dermal leishmaniasis

There are few controlled studies on the management of post-kala-azar dermal leishmaniasis. Mild-to-moderate post-kala-azar dermal leishmaniasis (PKDL) self-heals in the majority of patients of East African descent within 3 to 12 months. Treatment is indicated for East African patients with severe or non-self-healing PKDL, in Indian PKDL, and in patients who are immunocompromised.[6]

- In South Asia, miltefosine is the recommended first-line treatment for PKDL.[174] A meta-analysis demonstrated concern for declining efficacy, which is being observed even at 12 weeks of therapy, and concerns for safety (e.g., ocular disorders including blindness, ulcerative keratitis, blurred vision, photophobia) with longer courses of treatment.[183] [184]
- Amphotericin-B is considered second-line in South Asia.[174] Liposomal amphotericin-B has shown some efficacy in limited studies in the region.[185] [186] However, molecular analysis demonstrated resurgence of parasites 6 months after treatment with liposomal amphotericin-B, but not with miltefosine.[187]
- In India, combination liposomal amphotericin-B and 45 days of miltefosine therapy showed 100% efficacy versus 90 days of miltefosine monotherapy (75% efficacy).[188]
- When treatment is required in East Africa, pentavalent antimonial compounds are still being used commonly.

Pregnant patients

- Liposomal amphotericin-B is preferred due to safety concerns, particularly with miltefosine and pentavalent antimonial compounds.

Treatment algorithm overview

Please note that formulations/routes and doses may differ between drug names and brands, drug formularies, or locations. Treatment recommendations are specific to patient groups: see disclaimer

Acute (summary)

cutaneous leishmaniasis (CL)			
	simple: nonpregnant	**1st**	**watchful waiting**
		plus	**wound management**
		1st	**local therapy**
		plus	**wound management**
		2nd	**azole antifungal**
		plus	**wound management**
	complex: nonpregnant	**1st**	**systemic antileishmanial therapy**
		plus	**wound management**
	disseminated/diffuse disease or leishmaniasis recidivans: nonpregnant	**1st**	**expert consultation**
	pregnant	**1st**	**deferred treatment or local therapy**
		plus	**wound management**
		2nd	**amphotericin-B**
		plus	**wound management**
mucosal leishmaniasis (ML)			
	nonpregnant	**1st**	**systemic antileishmanial therapy**
	pregnant	**1st**	**amphotericin-B**
visceral leishmaniasis (VL)			
	immunocompetent: nonpregnant	**1st**	**amphotericin-B**
		plus	**supportive care**
		1st	**combination antileishmanial therapy**
		plus	**supportive care**
		2nd	**miltefosine**
		plus	**supportive care**
		2nd	**pentavalent antimonial compound or paromomycin**

MANAGEMENT

Acute (summary)

	plus	supportive care
immunocompetent: pregnant	1st	amphotericin-B
	plus	supportive care
	2nd	pentavalent antimonial compound or paromomycin
	plus	supportive care
immunocompromised (HIV/AIDS): nonpregnant	1st	amphotericin-B
	plus	start or continue antiretroviral therapy
	plus	supportive care
	adjunct	secondary prophylaxis
	2nd	combination antileishmanial therapy
	plus	start or continue antiretroviral therapy
	plus	supportive care
	adjunct	secondary prophylaxis
	3rd	pentavalent antimonial compound
	plus	start or continue antiretroviral therapy
	plus	supportive care
	adjunct	secondary prophylaxis
immunocompromised (other): nonpregnant	1st	amphotericin-B
	plus	supportive care
	adjunct	discontinue immunosuppressant or decrease dose
	adjunct	secondary prophylaxis
immunocompromised: pregnant	1st	amphotericin-B
	plus	supportive care
	plus	start or continue antiretroviral therapy
	adjunct	discontinue immunosuppressant or decrease dose
	adjunct	secondary prophylaxis

Ongoing		(summary)
post-kala-azar dermal leishmaniasis (PKDL)		
nonpregnant	**1st**	**systemic antileishmanial therapy**
pregnant	**1st**	**amphotericin-B**
relapse		
	1st	**retreatment**

Treatment algorithm

Please note that formulations/routes and doses may differ between drug names and brands, drug formularies, or locations. Treatment recommendations are specific to patient groups: see disclaimer

Acute

cutaneous leishmaniasis (CL)

simple: nonpregnant

1st **watchful waiting**

» Simple CL is defined as: no mucosal involvement and parasite species not associated with mucosal leishmaniasis; 4 or fewer lesions <1 cm; location feasible for local therapy and/or nonexposed skin (not cosmetically important); immunocompetent host; lesions resolving without therapy.[8]

» Most cases of CL, particularly among Old World species, will resolve spontaneously within 18 months; therefore, it is important to decide whether or not treatment is truly indicated.[113] [134] This decision must be individualized considering factors such as whether healing has already begun, impairments of wound healing, risk of secondary infections, patient preference, whether there is evidence of impaired cell-mediated immunity, and availability/expertise in treatment.

plus **wound management**

Treatment recommended for ALL patients in selected patient group

» Care should be taken to ensure proper wound management including washing the ulcer(s) and applying barrier ointment. The presence of warmth, redness, pain, and/or purulent discharge should prompt for the evaluation and management of a secondary bacterial infection. Evidence of healing often begins with flattening, and large ulcers may not be completely healed by the end of therapy. [CDC: parasites – leishmaniasis] (https://www.cdc.gov/parasites/leishmaniasis/index.html)

1st **local therapy**

» Simple CL is defined as: no mucosal involvement and parasite species not associated with mucosal leishmaniasis; 4 or fewer lesions <1 cm; location feasible for local therapy and/or nonexposed skin (not cosmetically important); immunocompetent host; lesions resolving without therapy.[8]

Acute

» Local therapies may be used when watchful waiting is not recommended, or to accelerate cure. Any crust should be removed, if present, before local therapy is started.[8]

» Cryotherapy: an option across all regions. Simple to administer: involves freezing the lesion and surrounding 1 to 2 mm of healthy skin with liquid nitrogen until it is white in appearance, allowing the area to thaw, and freezing again. Sessions are recommended every 3 weeks for up to three treatments. Adverse effects include transient pain and redness as well as hypopigmentation.[8]

» Thermotherapy: an option across all regions. Size, location, and number of lesions influence the efficacy and efficiency of this modality. Highly effective against *Leishmania tropica* .[113] Local anesthesia and topical antibiotics are recommended post-procedurally. A single treatment is often sufficient, and a specialized device is required. Adverse effects include cellulitis, redness, and pain at the treatment site.[8]

» Topical paromomycin (15% in a complex base): effective for Old World disease, particularly *Leishmania major* , and New World disease caused by *Viannia* species.[137] [138] [139] Use in *Viannia* species may not be appropriate due to the risk for mucosal disease.[138] Local irritation is expected and is greater with some formulations. Commercial or compounded formulations may not be equivalent. A reasonable regimen is applying topically daily for 20 days. It may be used alone or in combination with methylbenzethonium chloride, urea, or gentamicin.[132]

» Intralesional therapy: pentavalent antimonial compounds are most commonly used, when available. The combination of intralesional sodium stibogluconate and cryotherapy is very effective in Old World disease.[113] Meglumine antimoniate is preferred in the New World.[141] Treatment can be administered one to five times every 3 to 7 days. Sodium stibogluconate is available for intralesional use in Europe, but is not available in the US. Pentamidine can also be used intralesionally.[142] Pain with injection can be significant.[8]

plus **wound management**

Treatment recommended for ALL patients in selected patient group

MANAGEMENT

Acute

» Care should be taken to ensure proper wound management including washing the ulcer(s) and applying barrier ointment. The presence of warmth, redness, pain, and/or purulent discharge should prompt for the evaluation and management of a secondary bacterial infection. Evidence of healing often begins with flattening, and large ulcers may not be completely healed by the end of therapy. [CDC: parasites – leishmaniasis] (https://www.cdc.gov/parasites/leishmaniasis/index.html)

2nd **azole antifungal**

Primary options

» fluconazole: consult specialist for guidance on dose

OR

» itraconazole: consult specialist for guidance on dose

Secondary options

» ketoconazole: consult specialist for guidance on dose

» Fluconazole, ketoconazole, and itraconazole are options where local therapies are not available but treatment (rather than watchful waiting) is preferred. All have gastrointestinal adverse effects and a risk of hepatotoxicity, but ketoconazole carries a warning related to the risk of life-threatening hepatotoxicity and QT prolongation that could lead to fatal arrhythmias.

» A systematic review did not find enough evidence to recommend any of the azole antifungals routinely, but in the New World pooled efficacy for ketoconazole in the treatment of *Leishmania mexicana* was as high as 89%, suggesting this as a potential option in Mexico and parts of Central America with appropriate monitoring of adverse effects.[143]

» Use of azole antifungals is off-label for this indication in the US and Europe.

plus **wound management**

Treatment recommended for ALL patients in selected patient group

» Care should be taken to ensure proper wound management including washing the ulcer(s) and applying barrier ointment. The presence of warmth, redness, pain, and/or purulent discharge should prompt for the evaluation

Acute

and management of a secondary bacterial infection. Evidence of healing often begins with flattening, and large ulcers may not be completely healed by the end of therapy. [CDC: parasites – leishmaniasis] (https://www.cdc.gov/parasites/leishmaniasis/index.html)

complex: nonpregnant **1st** **systemic antileishmanial therapy**

Primary options

» miltefosine: consult specialist for guidance on dose

OR

» sodium stibogluconate: consult specialist for guidance on dose

OR

» meglumine antimoniate: consult specialist for guidance on dose

OR

» amphotericin B liposomal: consult specialist for guidance on dose

OR

» amphotericin B deoxycholate: consult specialist for guidance on dose

Secondary options

» pentamidine: consult specialist for guidance on dose

» Complex CL is defined as: parasite species caused by species associated with mucosal leishmaniasis; local subcutaneous nodules; large regional adenopathy; >4 lesions generally >1 cm; individual lesion ≥5 cm; size or location makes local therapy infeasible and/or lesion of the face, fingers, toes, joints, or genitalia; immunocompromised host; failure of local therapy.[8]

» Systemic therapy is preferred due to the extent or location of the lesion(s), prior failure of local therapy, and/or the risk of dissemination.

» Miltefosine: the only oral antileishmanial. Effective in New World disease caused by *Viannia* species, although lower efficacy is seen in Guatemala.[144] Significant adverse effects

Acute

such as nausea, vomiting, and abdominal pain are frequent.

» Pentavalent antimonial compounds (sodium stibogluconate, meglumine antimoniate): highly effective in Old World *Leishmania major* and widely used in the New World, when available, though may be less effective against *Leishmania braziliensis* and *Leishmania mexicana* in Guatemala.[144] Serious adverse effects can occur (e.g., pancreatitis, QT prolongation) and patients should be carefully monitored. Pentavalent antimonial compounds are not available in the US. Sodium stibogluconate is commercially available in Europe.

» Amphotericin-B: less robust data, but likely useful globally. Higher efficacy seen in New World disease in Bolivia.[144] Liposomal amphotericin-B is the preferred formulation with improved safety, but expense and cold chain may limit availability globally and so amphotericin-B deoxycholate is an alternative. Generally well tolerated; however, patients require monitoring for nephrotoxicity, electrolyte disturbances, and anemia.

» Pentamidine: highly effective against *Leishmania guyanensis* in French Guiana and Suriname.[145] [146] Intravenous administration is more effective than intramuscular.[147] In other settings, the adverse effects and relatively lower efficacy of pentamidine typically preclude its use. This may be due in part to underdosing based on the salt (isethionate) versus the base.[149] Serious adverse effects can occur (e.g., diabetes mellitus, pancreatitis, gastrointestinal symptoms, hypotension, QT prolongation, electrolyte disturbances, nephrotoxicity, hepatotoxicity, cytopenias, and rhabdomyolysis) and patients should be carefully monitored. These are mitigated with intralesional use.

» Dose depends on organism and geographic location; consult local guidance for drug selection and dose information.

plus **wound management**

Treatment recommended for ALL patients in selected patient group

» Care should be taken to ensure proper wound management including washing the ulcer(s) and applying barrier ointment. The presence of warmth, redness, pain, and/or purulent discharge should prompt for the evaluation

Acute

and management of a secondary bacterial infection. Evidence of healing often begins with flattening, and large ulcers may not be completely healed by the end of therapy. [CDC: parasites – leishmaniasis] (https://www.cdc.gov/parasites/leishmaniasis/index.html)

disseminated/diffuse disease or leishmaniasis recidivans: nonpregnant

1st **expert consultation**

» Treatment of complex forms of CL including disseminated leishmaniasis, diffuse cutaneous leishmaniasis, and leishmaniasis recidivans should be guided by experts as treatment can be challenging and data are limited.

» Disseminated leishmaniasis: liposomal amphotericin-B has been used with success (75% cure rate).[150]

» Diffuse cutaneous leishmaniasis: can be treated with pentavalent antimonial compounds (when available), amphotericin-B, miltefosine, or pentamidine, but outcomes are frequently unsatisfactory.[151]

» Leishmaniasis recidivans: can be frustrating to treat.[8] One potential regimen combines a pentavalent antimonial compound with allopurinol for 30 days.[152] Liposomal amphotericin-B and miltefosine are often used.

pregnant

1st **deferred treatment or local therapy**

» Treatment of simple and complex cutaneous disease in pregnant patients is highly individualized.

» If possible, treatment should be deferred until after pregnancy, even exophytic lesions; however, there may be an increased risk of preterm birth and stillbirth in untreated CL patients.[153]

» Local therapy options such as cryotherapy, thermotherapy, and topical paromomycin are often preferred to systemic therapies; however, there may be an increased risk of preterm delivery and stillbirth. Intralesional therapies can lead to systemic absorption and so are not recommended in pregnant women.

» Treatment of complex forms of CL including disseminated leishmaniasis, diffuse cutaneous leishmaniasis, and leishmaniasis recidivans should be guided by experts as treatment can be challenging and data are limited.

plus **wound management**

Acute

Treatment recommended for ALL patients in selected patient group

» Care should be taken to ensure proper wound management including washing the ulcer(s) and applying barrier ointment. The presence of warmth, redness, pain, and/or purulent discharge should prompt for the evaluation and management of a secondary bacterial infection. Evidence of healing often begins with flattening, and large ulcers may not be completely healed by the end of therapy. [CDC: parasites – leishmaniasis] (https://www.cdc.gov/parasites/leishmaniasis/index.html)

2nd **amphotericin-B**

Primary options

» amphotericin B liposomal: consult specialist for guidance on dose

OR

» amphotericin B deoxycholate: consult specialist for guidance on dose

» Liposomal amphotericin-B has the best overall safety data and has demonstrated safety in pregnancy. Expense and cold chain may limit availability globally and so amphotericin-B deoxycholate is an alternative.

» Generally well tolerated; however, patients require monitoring for nephrotoxicity, electrolyte disturbances, and anemia.

» Dose depends on organism and geographic location; consult local guidance for drug selection and dose information.

» Treatment of complex forms of CL including disseminated leishmaniasis, diffuse cutaneous leishmaniasis, and leishmaniasis recidivans should be guided by experts as treatment can be challenging and data are limited.

plus **wound management**

Treatment recommended for ALL patients in selected patient group

» Care should be taken to ensure proper wound management including washing the ulcer(s) and applying barrier ointment. The presence of warmth, redness, pain, and/or purulent discharge should prompt for the evaluation and management of a secondary bacterial infection. Evidence of healing often begins with flattening, and large ulcers may not be

Acute

completely healed by the end of therapy. [CDC: parasites – leishmaniasis] (https://www.cdc.gov/parasites/leishmaniasis/index.html)

mucosal leishmaniasis (ML)

nonpregnant — **1st** — **systemic antileishmanial therapy**

Primary options

» sodium stibogluconate: consult specialist for guidance on dose

OR

» meglumine antimoniate: consult specialist for guidance on dose

OR

» amphotericin B liposomal: consult specialist for guidance on dose

OR

» amphotericin B deoxycholate: consult specialist for guidance on dose

OR

» miltefosine: consult specialist for guidance on dose

Secondary options

» pentamidine: consult specialist for guidance on dose

» Patients with ML should always receive treatment with systemic therapy. Robust data are limited and treatment efficacy varies requiring an individualized approach to therapy.

» Pentavalent antimonial compounds (sodium stibogluconate, meglumine antimoniate): reasonable first choice, when available, in patients able to tolerate the course with up to 88% efficacy seen with meglumine antimoniate (lower with sodium stibogluconate). Some studies have added adjuncts such as pentoxifylline or interferon-gamma, but evidence for this is weak.[130] Serious adverse effects can occur (e.g., pancreatitis, QT prolongation) and patients should be carefully monitored. These are mitigated with intralesional use. Pentavalent antimonial compounds are not

Acute

available in the US. Sodium stibogluconate is commercially available in Europe.

» Amphotericin-B: data are limited compared with data for pentavalent antimonial compounds, but it has a better safety profile. It is an alternative, particularly for treatment failure, relapse, or intolerance of pentavalent antimonial compounds.[8] Retrospective data from Brazil show a 93% cure rate.[155] Liposomal amphotericin-B is the preferred formulation with improved safety, but expense and cold chain may limit availability globally and so amphotericin-B deoxycholate is an alternative. Generally well tolerated; however, patients require monitoring for nephrotoxicity, electrolyte disturbances, and anemia.

» Miltefosine: a potential option, but data are less robust and cure rates are low apart from clinically mild disease.[156] It is the only oral antileishmanial drug. Significant adverse effects such as nausea, vomiting, and abdominal pain are frequent.

» Pentamidine: pentamidine is considered a lesser alternative.[8]

» Dose depends on organism and geographic location; consult local guidance for drug selection and dose information.

pregnant **1st** **amphotericin-B**

Primary options

» amphotericin B liposomal: consult specialist for guidance on dose

OR

» amphotericin B deoxycholate: consult specialist for guidance on dose

» Treatment of ML should not be deferred in pregnant women.

» Liposomal amphotericin-B has the best overall safety data and has demonstrated safety in pregnancy. Expense and cold chain may limit availability globally and so amphotericin-B deoxycholate is an alternative.

» Generally well tolerated; however, patients require monitoring for nephrotoxicity, electrolyte disturbances, and anemia.

Acute

» Dose depends on organism and geographic location; consult local guidance for drug selection and dose information.

visceral leishmaniasis (VL)

immunocompetent: nonpregnant

1st **amphotericin-B**

Primary options

» amphotericin B liposomal: consult specialist for guidance on dose

OR

» amphotericin B deoxycholate: consult specialist for guidance on dose

» Liposomal amphotericin-B is highly effective for *Leishmania donovani* in South Asia and *Leishmania infantum* (also known as *Leishmania chagasi*).[8] [113] [144]

» Higher doses are required for *L donovani* in East Africa; therefore, this is a less preferred option in this region.[164] [165]

» Expense and cold chain may limit availability globally and so amphotericin-B deoxycholate is an alternative.

» Generally well tolerated; however, patients require monitoring for nephrotoxicity, electrolyte disturbances, and anemia.

» Dose depends on organism and geographic location; consult local guidance for drug selection and dose information.

plus **supportive care**

Treatment recommended for ALL patients in selected patient group

» Management must address frequent complications such as volume depletion, malnutrition, anemia, and concomitant bacterial infections (e.g., pneumonia) or parasitic infections (e.g., malaria).

1st **combination antileishmanial therapy**

Primary options

» sodium stibogluconate: consult specialist for guidance on dose
-or-
» meglumine antimoniate: consult specialist for guidance on dose

--AND--

MANAGEMENT

Acute

» paromomycin: consult specialist for guidance on dose

OR

» amphotericin B liposomal: consult specialist for guidance on dose

--AND--

» miltefosine: consult specialist for guidance on dose
-or-
» paromomycin: consult specialist for guidance on dose

OR

» miltefosine: consult specialist for guidance on dose
-and-
» paromomycin: consult specialist for guidance on dose

» In East Africa, the combination of a pentavalent antimonial compound with paromomycin is highly effective for VL due to *Leishmania donovani* with cure rates of 90% to 95%.[165] [168] This regimen is the preferred treatment in East Africa (over amphotericin-B) due to cost, availability, and regional efficacy. It should not be used in patients >50 years of age or those with HIV due to decreased cure rates in these patients.[168] This combination is not recommended in South Asia.

» In South Asia, the combination of liposomal amphotericin-B with short courses of miltefosine or paromomycin, or miltefosine with paromomycin, are highly effective alternatives to amphotericin-B.[162] [163] [169]

» Dose depends on organism and geographic location; consult local guidance for drug selection and dose information.

plus **supportive care**

Treatment recommended for ALL patients in selected patient group

» Management must address frequent complications such as volume depletion, malnutrition, anemia, and concomitant bacterial infections (e.g., pneumonia) or parasitic infections (e.g., malaria).

2nd **miltefosine**

Primary options

Acute

» miltefosine: consult specialist for guidance on dose

» An alternative option for *Leishmania donovani* in South Asia, but emerging resistance has led to a decline in use. Efficacy in other regions is suboptimal for monotherapy.[144]

» Significant adverse effects such as nausea, vomiting, and abdominal pain are frequent.

» Dose depends on organism and geographic location; consult local guidance for drug selection and dose information.

plus **supportive care**

Treatment recommended for ALL patients in selected patient group

» Management must address frequent complications such as volume depletion, malnutrition, anemia, and concomitant bacterial infections (e.g., pneumonia) or parasitic infections (e.g., malaria).

2nd **pentavalent antimonial compound or paromomycin**

Primary options

» sodium stibogluconate: consult specialist for guidance on dose

OR

» meglumine antimoniate: consult specialist for guidance on dose

OR

» paromomycin: consult specialist for guidance on dose

» Pentavalent antimonial compounds (sodium stibogluconate, meglumine antimoniate): can be used for *Leishmania donovani* in East Africa, or in *Leishmania infantum* with decent efficacy, but they are considered second-line when other options are not available. Drug resistance in South Asia precludes their use in the subcontinent.[113] Serious adverse effects can occur (e.g., pancreatitis, QT prolongation) and patients should be carefully monitored. Pentavalent antimonial compounds are not available in the US. Sodium stibogluconate is commercially available in Europe.

» Paromomycin: safety and efficacy for monotherapy have been demonstrated in

Acute

Leishmania donovani in South Asia, but other safer options with equal or greater efficacy are available.[170] [171] Patients should be monitored for nephrotoxicity and ototoxicity. Systemic formulations of paromomycin are not available in the US.

» Dose depends on organism and geographic location; consult local guidance for drug selection and dose information.

plus **supportive care**

Treatment recommended for ALL patients in selected patient group

» Management must address frequent complications such as volume depletion, malnutrition, anemia, and concomitant bacterial infections (e.g., pneumonia) or parasitic infections (e.g., malaria).

immunocompetent: pregnant **1st** **amphotericin-B**

Primary options

» amphotericin B liposomal: consult specialist for guidance on dose

OR

» amphotericin B deoxycholate: consult specialist for guidance on dose

» Treatment is essential because untreated VL can be fatal to both the mother and the fetus.

» Limited data suggest that liposomal amphotericin-B is a safe and effective treatment option.[8] [125]

» Expense and cold chain may limit availability globally and so amphotericin-B deoxycholate is an alternative.

» Generally well tolerated; however, patients require monitoring for nephrotoxicity, electrolyte disturbances, and anemia.

» Dose depends on organism and geographic location; consult local guidance for drug selection and dose information. Higher doses are required for *Leishmania donovani* in East Africa.[164] [165]

plus **supportive care**

Treatment recommended for ALL patients in selected patient group

Acute

» Management must address frequent complications such as volume depletion, malnutrition, anemia, and concomitant bacterial infections (e.g., pneumonia) or parasitic infections (e.g., malaria).

2nd **pentavalent antimonial compound or paromomycin**

» Use of pentavalent antimonial compounds in pregnancy should generally be avoided due to an increased risk of miscarriage or preterm delivery, and there is no safety data on paromomycin in pregnancy.[8] However, if no other options are available, treatment with these medications (alone or in combination), when available, may be an option under expert guidance only.

plus **supportive care**

Treatment recommended for ALL patients in selected patient group

» Management must address frequent complications such as volume depletion, malnutrition, anemia, and concomitant bacterial infections (e.g., pneumonia) or parasitic infections (e.g., malaria).

immunocompromised (HIV/AIDS): nonpregnant

1st **amphotericin-B**

Primary options

» amphotericin B liposomal: consult specialist for guidance on dose

OR

» amphotericin B deoxycholate: consult specialist for guidance on dose

» Liposomal amphotericin-B is generally regarded as the best option for patients with VL and HIV infection.[8] [111][174]

» A higher total dose is used in immunocompromised patients. However, even with higher doses, treatment can be unsatisfactory and relapse is common. A published trial in East Africa showed only a 55% efficacy for liposomal amphotericin-B monotherapy among patients with a median CD4 count of 69 cells/microliter.[175]

» Expense and cold chain may limit availability globally and so amphotericin-B deoxycholate is an alternative.

Acute

» Generally well tolerated; however, patients require monitoring for nephrotoxicity, electrolyte disturbances, and anemia.

» Dose depends on organism and geographic location; consult local guidance for drug selection and dose information.

plus **start or continue antiretroviral therapy**

Treatment recommended for ALL patients in selected patient group

» Lifelong antiretroviral therapy should be initiated (or continued in patients already on it) in all patients with HIV infection according to current local guidelines. An improvement in immune function is essential to the treatment of VL. See HIV infection .

plus **supportive care**

Treatment recommended for ALL patients in selected patient group

» Management must address frequent complications such as volume depletion, malnutrition, anemia, and concomitant bacterial infections (e.g., pneumonia) or parasitic infections (e.g., malaria).

adjunct **secondary prophylaxis**

Treatment recommended for SOME patients in selected patient group

» Secondary prophylaxis with an appropriate antileishmanial drug should be given to all patients with CD4 count <200 to 350 cells/microliter (the higher CD4 cut-off is recommended by the Pan American Health Organization) due to the high risk of relapse.[8] [111][151] [174]

» There is no consensus on the best regimen, but guidelines do recommend various options.[111] Consult local guidelines for further guidance.

» It is unclear when secondary prophylaxis should end. Some guidelines suggest stopping after CD4 counts reach >200 to 350 cells/microliter, whereas others recommend indefinite therapy as the risk for relapse continues. Regardless, careful monitoring for relapse is essential in all patients with HIV infection.[8] [111]

2nd **combination antileishmanial therapy**

Primary options

Acute

» amphotericin B liposomal: consult specialist for guidance on dose
-and-
» miltefosine: consult specialist for guidance on dose

» Combination therapy should be considered in this context. A combination of liposomal amphotericin-B and miltefosine showed an efficacy rate of 88% in East Africa among patients with a median CD4 count of 54 cells/microliter.[175] In India, the combination of miltefosine and liposomal amphotericin-B was associated with 96% efficacy compared to miltefosine monotherapy at 85%.[176]

» The World Health Organization (WHO) suggests liposomal amphotericin-B plus miltefosine over liposomal amphotericin-B monotherapy in people with HIV coinfection in East Africa and South East Asia.[62]

» Dose depends on organism and geographic location; consult local guidance for drug selection and dose information.

plus **start or continue antiretroviral therapy**

Treatment recommended for ALL patients in selected patient group

» Lifelong antiretroviral therapy should be initiated (or continued in patients already on it) in all patients with HIV infection according to current local guidelines. An improvement in immune function is essential to the treatment of VL. See HIV infection .

plus **supportive care**

Treatment recommended for ALL patients in selected patient group

» Management must address frequent complications such as volume depletion, malnutrition, anemia, and concomitant bacterial infections (e.g., pneumonia) or parasitic infections (e.g., malaria).

adjunct **secondary prophylaxis**

Treatment recommended for SOME patients in selected patient group

» Secondary prophylaxis with an appropriate antileishmanial drug should be given to all patients with CD4 count <200 to 350 cells/microliter (the higher CD4 cut-off is recommended by the Pan American Health Organization) due to the high risk of relapse.[8] [111][151] [174]

Acute

» There is no consensus on the best regimen, but guidelines do recommend various options.[111] Consult local guidelines for further guidance.

» It is unclear when secondary prophylaxis should end. Some guidelines suggest stopping after CD4 counts reach >200 to 350 cells/microliter, whereas others recommend indefinite therapy as the risk for relapse continues. Regardless, careful monitoring for relapse is essential in all patients with HIV infection.[8] [111]

3rd **pentavalent antimonial compound**

Primary options

» sodium stibogluconate: consult specialist for guidance on dose

OR

» meglumine antimoniate: consult specialist for guidance on dose

» Use in HIV coinfection has been associated with higher mortality and higher rates of severe adverse reactions and so other options should be used if possible.[177] [178] [179]

» Serious adverse effects can occur (e.g., pancreatitis, QT prolongation) and patients should be carefully monitored.

» Pentavalent antimonial compounds are not available in the US. Sodium stibogluconate is commercially available in Europe.

» Dose depends on organism and geographic location; consult local guidance for drug selection and dose information.

plus **start or continue antiretroviral therapy**

Treatment recommended for ALL patients in selected patient group

» Lifelong antiretroviral therapy should be initiated (or continued in patients already on it) in all patients with HIV infection according to current local guidelines. An improvement in immune function is essential to the treatment of VL. See HIV infection .

plus **supportive care**

Treatment recommended for ALL patients in selected patient group

Acute

» Management must address frequent complications such as volume depletion, malnutrition, anemia, and concomitant bacterial infections (e.g., pneumonia) or parasitic infections (e.g., malaria).

adjunct **secondary prophylaxis**

Treatment recommended for SOME patients in selected patient group

» Secondary prophylaxis with an appropriate antileishmanial drug should be given to all patients with CD4 count <200 to 350 cells/microliter (the higher CD4 cut-off is recommended by the Pan American Health Organization) due to the high risk of relapse.[8] [111][151] [174]

» There is no consensus on the best regimen, but guidelines do recommend various options.[111]

» It is unclear when secondary prophylaxis should end. Some guidelines suggest stopping after CD4 counts reach >200 to 350 cells/microliter, whereas others recommend indefinite therapy as the risk for relapse continues. Regardless, careful monitoring for relapse is essential in all patients with HIV infection.[8] [111]

immunocompromised (other): nonpregnant **1st** **amphotericin-B**

Primary options

» amphotericin B liposomal: consult specialist for guidance on dose

OR

» amphotericin B deoxycholate: consult specialist for guidance on dose

» Other forms of immunosuppression include solid organ transplant, lymphatic or hematologic malignancy, or treatment with immunosuppressants for other indications.

» Treatment has been accomplished with multiple regimens, but liposomal amphotericin-B is recommended, particularly in solid organ transplant patients.[8] [151] [173]

» Expense and cold chain may limit availability globally and so amphotericin-B deoxycholate is an alternative.

Acute

» Generally well tolerated; however, patients require monitoring for nephrotoxicity, electrolyte disturbances, and anemia.

» Dose depends on organism and geographic location; consult local guidance for drug selection and dose information.

plus **supportive care**

Treatment recommended for ALL patients in selected patient group

» Management must address frequent complications such as volume depletion, malnutrition, anemia, and concomitant bacterial infections (e.g., pneumonia) or parasitic infections (e.g., malaria).

adjunct **discontinue immunosuppressant or decrease dose**

Treatment recommended for SOME patients in selected patient group

» If patients are on immunosuppressants for other indications, consider decreasing the dose or stopping these medications, if possible, although this is based on expert opinion and not on strong data.[173] An improvement in immune function is essential to the treatment of VL.

adjunct **secondary prophylaxis**

Treatment recommended for SOME patients in selected patient group

» Consider secondary prophylaxis on an individual basis, especially among patients with a history of prior relapse for whom the immunosuppressive condition is ongoing. While relapse is common, particularly among solid organ transplant patients (approximately 25%), data are not clear on the role of secondary prophylaxis. The Infectious Diseases Society of America/American Society of Tropical Medicine and Hygiene guidelines recommend against secondary prophylaxis among those without a prior relapse, but in a small retrospective case-control study, risk of relapse decreased by 27% among those on secondary prophylaxis.[8] [182]

immunocompromised: pregnant

1st **amphotericin-B**

Primary options

» amphotericin B liposomal: consult specialist for guidance on dose

OR

Acute

» amphotericin B deoxycholate: consult specialist for guidance on dose

» Treatment is essential because untreated VL can be fatal to both the mother and the fetus.

» Limited data suggest that liposomal amphotericin-B is a safe and effective treatment option.[8] [125]

» Expense and cold chain may limit availability globally and so amphotericin-B deoxycholate is an alternative.

» Generally well tolerated; however, patients require monitoring for nephrotoxicity, electrolyte disturbances, and anemia.

» Dose depends on organism and geographic location; consult local guidance for drug selection and dose information.

plus **supportive care**

Treatment recommended for ALL patients in selected patient group

» Management must address frequent complications such as volume depletion, malnutrition, anemia, and concomitant bacterial infections (e.g., pneumonia) or parasitic infections (e.g., malaria).

plus **start or continue antiretroviral therapy**

Treatment recommended for ALL patients in selected patient group

» Lifelong antiretroviral therapy should be initiated (or continued in patients already on it) in all patients with HIV infection according to current local guidelines. A specific regimen recommended for pregnant women should be used. An improvement in immune function is essential to the treatment of VL. See HIV infection in pregnancy .

adjunct **discontinue immunosuppressant or decrease dose**

Treatment recommended for SOME patients in selected patient group

» If patients are on immunosuppressants for other indications, consider decreasing the dose or stopping these medications, if possible, although this is based on expert opinion and not on strong data.[173] An improvement in immune function is essential to the treatment of VL.

adjunct **secondary prophylaxis**

Acute

Treatment recommended for SOME patients in selected patient group

» Secondary prophylaxis with an appropriate antileishmanial drug should be given to patients with HIV infection and a CD4 count <200 to 350 cells/microliter (the higher CD4 cut-off is recommended by the Pan American Health Organization) due to the high risk of relapse.[8] [111][151] [174]

» In patients with other forms of immunosuppression, consider secondary prophylaxis on an individual basis, especially among patients with a history of prior relapse for whom an immunosuppressive condition is ongoing.

Ongoing

post-kala-azar dermal leishmaniasis (PKDL)

nonpregnant **1st** **systemic antileishmanial therapy**

Primary options

» miltefosine: consult specialist for guidance on dose

OR

» sodium stibogluconate: consult specialist for guidance on dose

OR

» sodium stibogluconate: consult specialist for guidance on dose

--AND--

» paromomycin: consult specialist for guidance on dose

Secondary options

» amphotericin B liposomal: consult specialist for guidance on dose

OR

» amphotericin B deoxycholate: consult specialist for guidance on dose

» Treatment is indicated in East African patients with severe or non-self-healing PKDL, in Indian PKDL, and in immunocompromised patients.[6]

» Miltefosine: recommended first-line treatment in South Asia.[174] It is the only oral antileishmanial drug. Significant adverse effects such as nausea, vomiting, and abdominal pain are frequent. Combination therapy with liposomal amphotericin-B and miltefosine was associated with 100% efficacy in South Asia.[188]

» Amphotericin-B: considered a second-line option in South Asia.[174] Liposomal amphotericin-B has shown some efficacy in limited studies in the region.[185] [186] Expense and cold chain may limit availability globally and so amphotericin-B deoxycholate is an alternative. Generally well tolerated; however, patients require monitoring for nephrotoxicity, electrolyte disturbances, and anemia.

Ongoing

» Pentavalent antimonial compounds: commonly used in East Africa for severe or persistent disease.[189] Serious adverse effects can occur (e.g., pancreatitis, QT prolongation) and patients should be carefully monitored. Pentavalent antimonial compounds are not available in the US. Sodium stibogluconate is commercially available in Europe.

» Dose depends on organism and geographic location; consult local guidance for drug selection and dose information.

pregnant — **1st** — **amphotericin-B**

Primary options

» amphotericin B liposomal: consult specialist for guidance on dose

OR

» amphotericin B deoxycholate: consult specialist for guidance on dose

» Limited data in this setting, but the recommendation is guided by relative safety and the contraindication of miltefosine in pregnancy.

» Liposomal amphotericin-B has the best overall safety data and has demonstrated safety in pregnancy.

» Expense and cold chain may limit availability globally and so amphotericin-B deoxycholate is an alternative.

» Generally well tolerated; however, patients require monitoring for nephrotoxicity, electrolyte disturbances, and anemia.

» Dose depends on organism and geographic location; consult local guidance for drug selection and dose information.

relapse

1st — **retreatment**

» Relapses are uncommon with appropriate treatment in immunocompetent hosts. Patients should be monitored for signs of relapse, particularly patients with HIV/AIDS or who are immunocompromised.

» An expert should be consulted to determine the best regimen for retreatment if necessary.

Ongoing

» Amphotericin-B formulations are an option in mucosal leishmaniasis, particularly for treatment failure or relapse.[8]

» Immunocompetent patients with visceral leishmaniasis (VL) who do not respond to, or who relapse after, initial therapy should receive full treatment with an antileishmanial drug (or a combination of antileishmanial drugs) from a different class. However, if the initial treatment was with liposomal amphotericin-B, retreatment with amphotericin-B, potentially at higher total doses, is appropriate.[8] [113]

» Among immunocompromised patients with VL who relapse, treatment with liposomal amphotericin-B is reasonable, even among those who received it as primary therapy as failure in this setting is thought to be immunologic rather than a result of drug resistance. Alternatively, other options or combination therapies can be tried.[8]

Emerging

Nitroimidazoles

Fexinidazole is a nitroimidazole used to treat African trypanosomiasis that has shown potent activity against *Leishmania donovani* . Unfortunately, in a phase 2 study in Sudan, despite initial clearance in most patients, only 21% were cured at 6 months. It is possible that future studies looking at a combination of fexinidazole and miltefosine may be done.[190] Other nitroimidazoles (e.g., DNDi-0690, pretomanid, delamanid) show in vitro and/or in vivo activity against *Leishmania* parasites, and DNDi-0690 has been tested in a phase 1 trial.[191] [192]

Novel drug candidates

In addition to DNDi-0690, the Drugs for Neglected Diseases initiative (DNDi) is moving other novel drug candidates into early clinical development.[193] GSK3186899 is a novel compound that DNDi is supporting in ongoing phase 1 studies in the UK.[194] DNDi-6148 is an oxaborole compound (chosen from among three similar compounds) that is planned to progress into phase 1 studies. LXE408 is a proteasome inhibitor planned for a phase 2 trial in India.[195] [196] CpG-D35 is an immunomodulator theorized to stimulate an innate immune response, as an adjuvant to treatment with antimonials in cutaneous leishmaniasis.

Primary prevention

Primary prevention depends on the sleeping habits of people in endemic areas; sand fly abundance, distribution, and diversity; and the type of transmission (anthroponotic versus zoonotic).[1] [2] Prevention of infection and disease is based on controlling the human or nonhuman reservoir.[63] This entails early detection and treatment of patients for anthroponotic transmission cycles; destruction of rodent burrows, or collaring of dogs, for zoonotic transmission cycles; vector control (e.g., indoor spraying of households with insecticide for some sand fly species); or methods of personal protection (e.g., use of topical repellent to exposed skin, covering with clothing, and insecticide-treated bed nets, curtains, or blankets).[1] [2] [64] [65]

There is limited evidence to show that a prevention and control approach can consistently result in reduced disease incidence.[66] Therefore, it is inconclusive whether large-scale distribution of long-lasting insecticidal bed nets can provide additional protection compared with existing visceral leishmaniasis (VL) control measures in India and Nepal.[67] [68] Dog culling for controlling zoonotic VL is unproven as a control measure.[69] [70]

While controlled *Leishmania major* infection (leishmanization) protects from homologous infection, an effective human leishmaniasis vaccine does not yet exist.[71] However, a third-generation vaccine for human VL and post-kala-azar dermal leishmaniasis has undergone investigation in a phase 1 clinical trial.[72] Additionally, a phase 2 safety and immunogenicity trial in Sudan evaluated a chimpanzee adenovirus-based (ChAd63-KH) vaccine, where 7/23 patients (30.4%) showed >90% clinical improvement and minimal adverse reactions were reported.[73] [74] [75] A randomized controlled trial is underway.[73]

Secondary prevention

Secondary prophylaxis with an appropriate antileishmanial drug should be given to patients with HIV infection and a CD4 count <200 to 350 cells/microliter (the higher CD4 cut-off is recommended by the Pan American Health Organization) due to the high risk of relapse.[8] [111][151] [174] In patients with other forms of immunosuppression, consider secondary prophylaxis on an individual basis, especially among patients with a history of prior relapse for whom an immunosuppressive condition is ongoing. See Management approach .

Patient discussions

During treatment, the patient should be told to report the following to the physician:

- Palpitations
- Shortness of breath
- Abdominal pain
- Vomiting
- Any new symptoms.

After treatment, the physician should be contacted in case of:

- Recurrence of skin lesions (in cutaneous leishmaniasis) or mucosal lesions (in mucosal leishmaniasis)
- Persistent fever (in visceral leishmaniasis)
- Other symptom(s) similar to the initial episode
- Appearance of a skin rash (e.g., maculopapular or nodular).

[WHO: fact sheet - leishmaniasis] (http://www.who.int/mediacentre/factsheets/fs375/en)

FOLLOW UP

Monitoring

Monitoring

During treatment

- Pentavalent antimonial compounds: clinical evaluation daily; ECG weekly or every 2 to 3 days if increased risk of cardiotoxicity; CBC, liver function tests (LFTs), renal function tests, blood potassium, and amylase/lipase tested weekly or on request.
- Amphotericin-B formulations: CBC, renal function tests, and blood electrolytes tested once or twice weekly.
- Miltefosine and paromomycin: renal function tests and LFTs taken weekly. With miltefosine use, monitor platelets and, in female patients, ensure a pregnancy test is negative and effective contraception is used at treatment initiation through 5 months after treatment.
- Pentamidine: ECG, CBC, LFTs, renal function tests, blood electrolytes, fasting blood glucose, and urinalysis before each dose.

After treatment

- Follow-up evaluation (clinical evaluation; additionally, in visceral leishmaniasis, check CBC and other laboratory tests as needed) at months 0, 1, 3, and 6 after treatment.
- Further follow-up evaluations every 3 to 6 months in immunosuppressed patients.
- Parasitologic testing (e.g., smear, polymerase chain reaction) only if suspicion of nonresponse or relapse.
- Pentamidine: fasting blood glucose and urinalysis at 3 weeks and 2 to 3 months post treatment.

FOLLOW UP

Complications

Complications	Timeframe	Likelihood
pentavalent antimonial-induced acute pancreatitis	**short term**	**high**
Elevation of amylase and lipase occurs in almost all patients but does not require treatment interruption in most asymptomatic patients. In contrast, acute clinical pancreatitis can be potentially lethal and necessitates transient or definitive interruption of treatment. HIV-coinfected patients are at particular risk.		
cutaneous leishmaniasis-related bacterial superinfection	**short term**	**high**
Bacterial superinfection is possible in cutaneous leishmaniasis, especially if lesions are ulcerative or open to the air (e.g., feet, hands) and in environments of poor hygiene. Infection can also occur when lesions are treated with thermotherapy due to the localized second-degree burn. Superinfection can delay treatment response. Topical or systemic antibiotic treatment should be applied in cases of bacterial superinfection. Topical antibiotics can be given after application of thermotherapy to prevent superinfection.		
visceral leishmaniasis-related bacterial superinfection	**short term**	**high**
The immunosuppression induced by visceral leishmaniasis favors potentially lethal bacterial infections such as dysentery, pneumonia, and sepsis. Patients must have a careful physical exam performed before and during treatment. Suspected or proven bacterial infections must be treated early with appropriate antibiotics.		
pentavalent antimonial-induced cardiotoxicity	**short term**	**medium**
More frequently reported during treatment of visceral leishmaniasis than cutaneous leishmaniasis. Can be fatal. Patients with HIV coinfection, underlying cardiopathy, or electrolyte disorders are at particular risk. ECG monitoring is recommended during treatment. Treatment should be transiently or definitely interrupted if ominous signs develop (e.g., marked ST-T wave changes or prolonged corrected QT interval >0.5 second).		
amphotericin-B-induced nephrotoxicity	**short term**	**medium**
Frequent and potentially lethal adverse effect of amphotericin-B deoxycholate.		

Complications	Timeframe	Likelihood
Monitoring of blood potassium and creatinine necessary. If monitoring not possible, treatment on alternate days is preferable. Risk reduced by administration of supplemental sodium chloride and electrolytes and by avoidance of dehydration. Nephrotoxicity is less commonly reported with liposomal amphotericin-B, but remains a significant concern.		
bleeding	**short term**	**medium**
Epistaxis occurs commonly in visceral leishmaniasis (VL) and is typically benign. On occasion, severe intestinal bleeding can occur in VL, leading to shock or worsening of preexisting anemia. Disease-related thrombocytopenia is likely to be the main cause of the bleeding tendency. Vital signs must be closely monitored during treatment, and blood should be transfused in case of severe bleeding or severe anemia.		

Prognosis

The syndromes caused by *Leishmania* are diverse in appearance and outcome. Cutaneous leishmaniasis (CL), apart from species associated with mucosal leishmaniasis, tends to impact quality of life and is generally not life-threatening. However, the importance of the stigma and morbidity related to chronic persistent lesions and permanent scarring should not be underestimated. Some patients with *Viannia* species parasites develop mucosal leishmaniasis. The ensuing disease can produce significant mutilation and patients can die from aspiration pneumonia or airway obstruction. The majority of visceral leishmaniasis (VL) infections remain latent, but infection that becomes symptomatic is typically fatal without treatment. The primary goal of therapy is to decrease or prevent mortality, though the treatments themselves are not without risk. Death during treatment of both CL and VL can be due to a complication of the disease (e.g., bacterial superinfection) or can be drug-related (e.g., cardiac arrest with antimonial compounds). Mortality is low among VL patients treated with liposomal amphotericin-B and miltefosine.[199] Mortality with pentavalent antimonial compounds is increased in patients older than 45 years, those who are severely malnourished, and those with signs of long-lasting illness or coinfection with HIV.[200] [201] Mortality with amphotericin-B deoxycholate appears similar to pentavalent antimonial compounds in both immunocompetent and HIV-coinfected patients.[178] [202] In general, death is more likely among immunosuppressed patients, even with appropriate treatment.

Clinical cure

Initial cure at the end of treatment is assessed clinically (flattening of cutaneous lesions or healing of ulcers in CL; disappearance of fever, improvement of general condition, and decrease in splenic size in VL) and by laboratory tests in VL (improvement of anemia, normalization of inflammation markers). Definite clinical cure in immunocompetent patients is declared 6 months after initial cure if clinical exam and laboratory tests have normalized. Parasitologic methods to assess cure are generally not helpful, because parasitologic cure does not occur in many cases; however, these methods can be used to assess for relapse.

Immunosuppressed patients are at higher risk of nonresponse than immunocompetent patients, independent of the antileishmanial drug given.

Relapse

Relapses are uncommon with appropriate treatment in immunocompetent hosts. In contrast, relapse within 3 to 6 months after initial therapy occurs in most HIV-coinfected patients, who generally experience multiple subsequent relapses. Risk factors for relapse in HIV-VL coinfection are: absence of an increase in CD4+ cells at follow-up; lack of secondary prophylaxis; previous history of VL relapse; and CD4+ counts <100 cells/mL at the time of primary VL diagnosis.[203] Relapse is also common among other immunosuppressed patients, such as recipients of solid organ transplants.

Diagnostic guidelines

International

CDC Yellow Book: health information for international travel - cutaneous leishmaniasis (https://wwwnc.cdc.gov/travel/page/yellowbook-home) [107]

Published by: Centers for Disease Control and Prevention **Last published:** 2023

CDC Yellow Book: health information for international travel - visceral leishmaniasis (https://wwwnc.cdc.gov/travel/page/yellowbook-home) [108]

Published by: Centers for Disease Control and Prevention **Last published:** 2023

Parasites - leishmaniasis. Resources for health professionals (https://www.cdc.gov/parasites/leishmaniasis/health_professionals/index.html) [109]

Published by: Centers for Disease Control and Prevention **Last published:** 2023

Diagnosis and treatment of leishmaniasis (https://www.idsociety.org/practice-guideline/alphabetical-guidelines) [8]

Published by: Infectious Diseases Society of America; American Society of Tropical Medicine and Hygiene **Last published:** 2016

Position statement on leishmaniosis (https://worldvet.org/policies/wva-position-statement-on-leishmaniosis) [58]

Published by: World Veterinary Association **Last published:** 2021

Manual of procedures for leishmaniases surveillance and control in the Americas (https://iris.paho.org/handle/10665.2/51838) [110]

Published by: Pan American Health Organization **Last published:** 2019

Guidelines for the prevention and treatment of opportunistic infections in HIV-infected adults and adolescents - leishmaniasis (https://clinicalinfo.hiv.gov/en/guidelines/hiv-clinical-guidelines-adult-and-adolescent-opportunistic-infections/whats-new) [111]

Published by: Centers for Disease Control and Prevention; National Institutes of Health; HIV Medicine Association of the Infectious Diseases Society of America **Last published:** 2017

Diagnosis and treatment of leishmaniasis (https://www.idsociety.org/practice-guideline/practice-guidelines/#/+/0/date_na_dt/desc) [8]

Published by: Infectious Diseases Society of America; American Society of Tropical Medicine and Hygiene **Last published:** 2016

Manual on case management and surveillance of the leishmaniases in the WHO European region (https://www.who.int/publications/i/item/9789289052511) [112]

Published by: World Health Organization, Regional Office for Europe **Last published:** 2017

International

Canine leishmaniosis (https://www.gov.uk/government/publications/hairs-risk-assessment-canine-leishmaniosis) [57]

Published by: Human Animal Infections and Risk Surveillance **Last published:** 2022

Treatment guidelines

International

CDC Yellow Book: health information for international travel - cutaneous leishmaniasis (https://wwwnc.cdc.gov/travel/page/yellowbook-home) [107]

Published by: Centers for Disease Control and Prevention **Last published:** 2023

CDC Yellow Book: health information for international travel - visceral leishmaniasis (https://wwwnc.cdc.gov/travel/page/yellowbook-home) [108]

Published by: Centers for Disease Control and Prevention **Last published:** 2023

Guidelines for the prevention and treatment of opportunistic infections in HIV-infected adults and adolescents - leishmaniasis (https://clinicalinfo.hiv.gov/en/guidelines/hiv-clinical-guidelines-adult-and-adolescent-opportunistic-infections/whats-new) [111]

Published by: Centers for Disease Control and Prevention; National Institutes of Health; HIV Medicine Association of the Infectious Diseases Society of America **Last published:** 2017

Diagnosis and treatment of leishmaniasis (https://www.idsociety.org/practice-guideline/practice-guidelines/#/+/0/date_na_dt/desc) [8]

Published by: Infectious Diseases Society of America; American Society of Tropical Medicine and Hygiene **Last published:** 2016

Guideline for the treatment of leishmaniasis in the Americas (https://iris.paho.org/handle/10665.2/56120) [151]

Published by: Pan American Health Organization; World Health Organization **Last published:** 2022

Guideline for the treatment of visceral leishmaniasis in HIV co-infected patients in East Africa and South-East Asia (https://www.who.int/publications/i/item/9789240048294) [62]

Published by: World Health Organization **Last published:** 2022

Manual on case management and surveillance of the leishmaniases in the WHO European region (https://www.who.int/publications/i/item/9789289052511) [112]

Published by: World Health Organization, Regional Office for Europe **Last published:** 2017

WHO technical report series 949: control of the leishmaniases (https://www.who.int/publications/i/item/WHO-TRS-949) [174]

Published by: World Health Organization **Last published:** 2010

Therapy of leishmaniasis in France: consensus on proposed guidelines (https://www.ncbi.nlm.nih.gov/pubmed/21106333) [197]

Published by: Société de Pathologie Exotique (France) **Last published:** 2011

International

Clinical guidelines for the management of cutaneous leishmaniasis in British military personnel (https://militaryhealth.bmj.com/content/151/2/73.long) [198]

Published by: Royal Army Medical Corps (UK) **Last published:** 2005

Online resources

1. CDC: parasites – leishmaniasis (https://www.cdc.gov/parasites/leishmaniasis/index.html) *(external link)*
2. WHO: leishmaniasis (https://www.who.int/leishmaniasis/en) *(external link)*
3. WHO: leishmaniasis country profile (https://www.irycis.org/en/leishmaniasiscc-spain-leishmaniasis) *(external link)*
4. CDC: practical guide for leishmaniasis (https://www.cdc.gov/parasites/leishmaniasis/resources/pdf/cdc_diagnosis_guide_leishmaniasis_2016.pdf) *(external link)*
5. WHO: fact sheet - leishmaniasis (http://www.who.int/mediacentre/factsheets/fs375/en) *(external link)*

Key articles

- Aronson N, Herwaldt BL, Libman M, et al. Diagnosis and treatment of leishmaniasis: clinical practice guidelines by the Infectious Diseases Society of America (IDSA) and the American Society of Tropical Medicine and Hygiene (ASTMH). Clin Infect Dis. 2016 Dec 15;63(12):1539-57. Full text (https://academic.oup.com/cid/article/63/12/1539/2645617) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/27941143?tool=bestpractice.bmj.com)
- Aronson NE, Joya CA. Cutaneous leishmaniasis: updates in diagnosis and management. Infect Dis Clin North Am. 2019 Mar;33(1):101-17. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/30712756?tool=bestpractice.bmj.com)
- National Institutes of Health, Centers for Disease Control and Prevention, HIV Medicine Association, and Infectious Diseases Society of America. Panel on Guidelines for the Prevention and Treatment of Opportunistic Infections in Adults and Adolescents with HIV. Guidelines for the prevention and treatment of opportunistic infections in adults and adolescents with HIV: Leishmaniasis. 2017 [internet publication]. Full text (https://clinicalinfo.hiv.gov/en/guidelines/hiv-clinical-guidelines-adult-and-adolescent-opportunistic-infections/leishmaniasis)
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- Burza S, Croft SL, Boelaert M. Leishmaniasis. Lancet. 2018 Sep 15;392(10151):951-70. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/30126638?tool=bestpractice.bmj.com)
- Chakravarty J, Sundar S. Current and emerging medications for the treatment of leishmaniasis. Expert Opin Pharmacother. 2019 Jul;20(10):1251-65. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/31063412?tool=bestpractice.bmj.com)
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2. Chappuis F, Sundar S, Hailu A, et al. Visceral leishmaniasis: what are the needs for diagnosis, treatment and control? Nat Rev Microbiol. 2007 Nov;5(11):873-82. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/17938629?tool=bestpractice.bmj.com)
3. Killick-Kendrick R. The biology and control of phlebotomine sand flies. Clin Dermatol. 1999 May-Jun;17(3):279-89. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/10384867?tool=bestpractice.bmj.com)

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Images

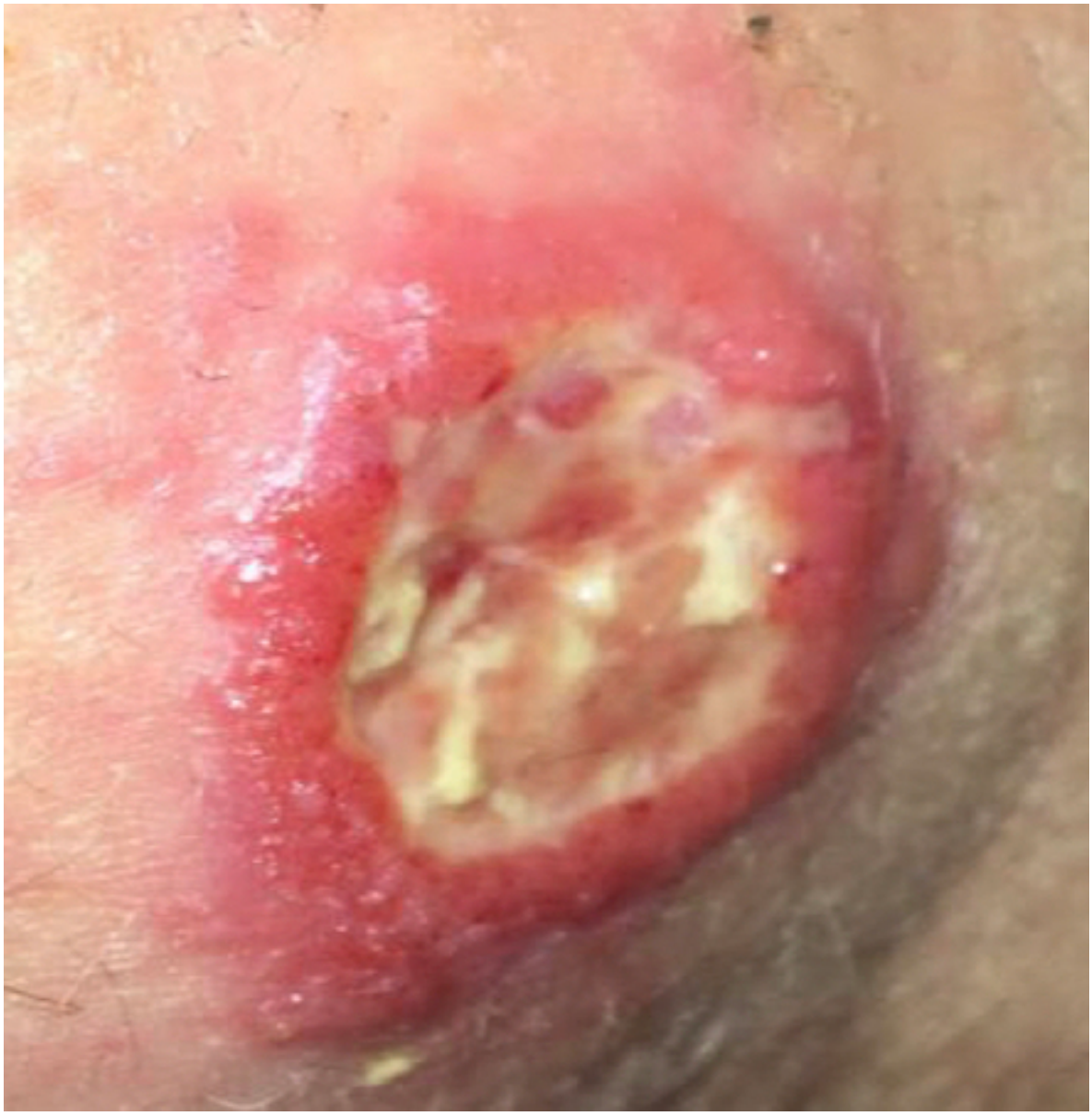

Figure 1: Ulcerative Leishmania braziliensis lesion from a student who traveled to Peru

From the collection of Dr N. Aronson; used with permission

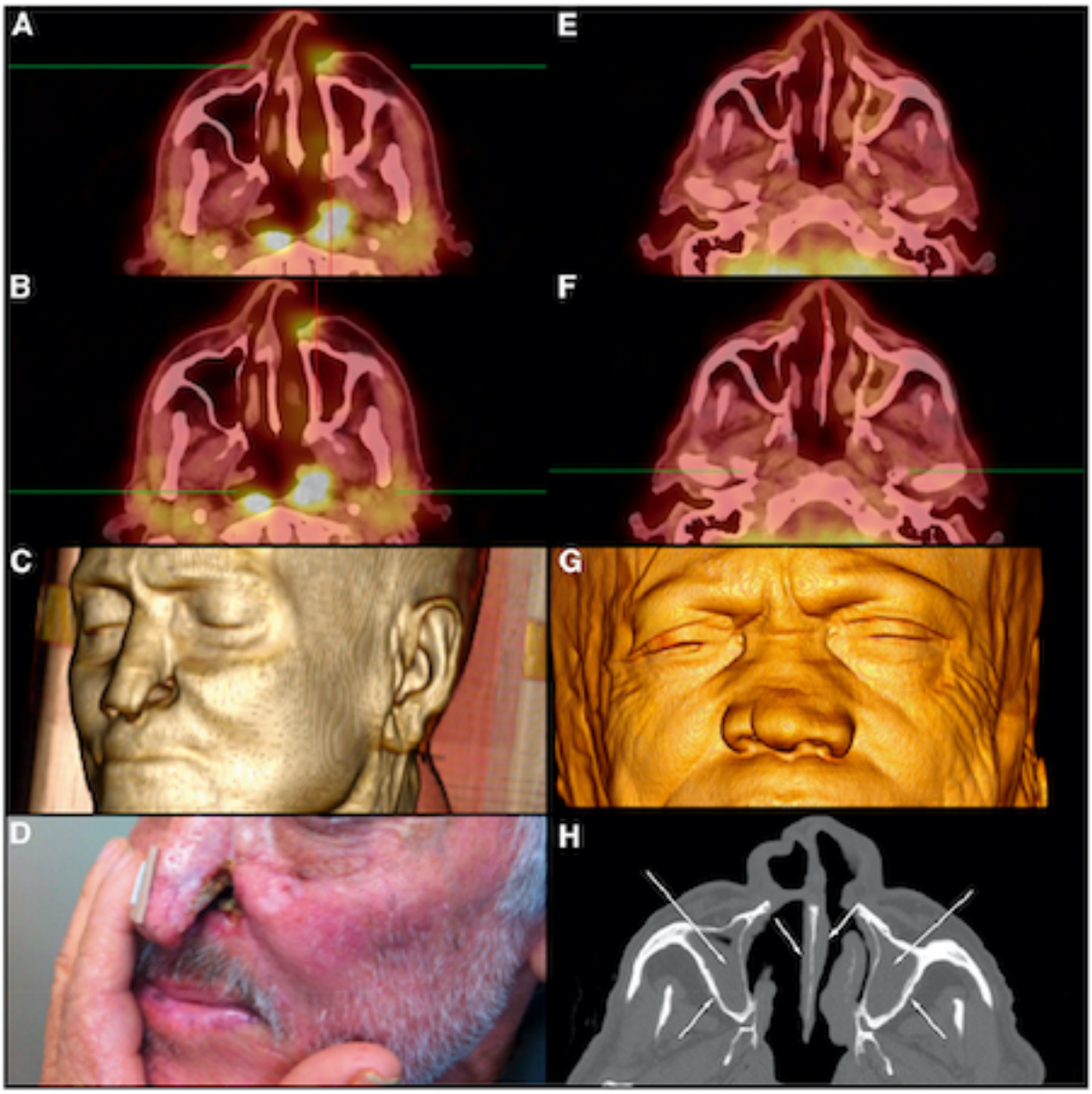

Figure 2: Mucosal leishmaniasis in 2 Brazilian patients. A-D: patient 1 with positron emission tomography/computed tomography (PET/CT) images showing enhancement and subcutaneous thickening adjacent to erosion of the left nasal wing and obliteration of the posterolateral recess (A and B), 3D volume-rendered image of multislice CT data (3D CT) and picture with erosion of the left nasal wing (C and D). F-H: patient 2 with PET/CT images showing preserved glycolytic metabolism of facial structures (E and F), 3D CT with collapse of the nasal pyramids (G), and bone window CT with diffuse thickening of nasal wings and collapse of the nasal pyramid (H)

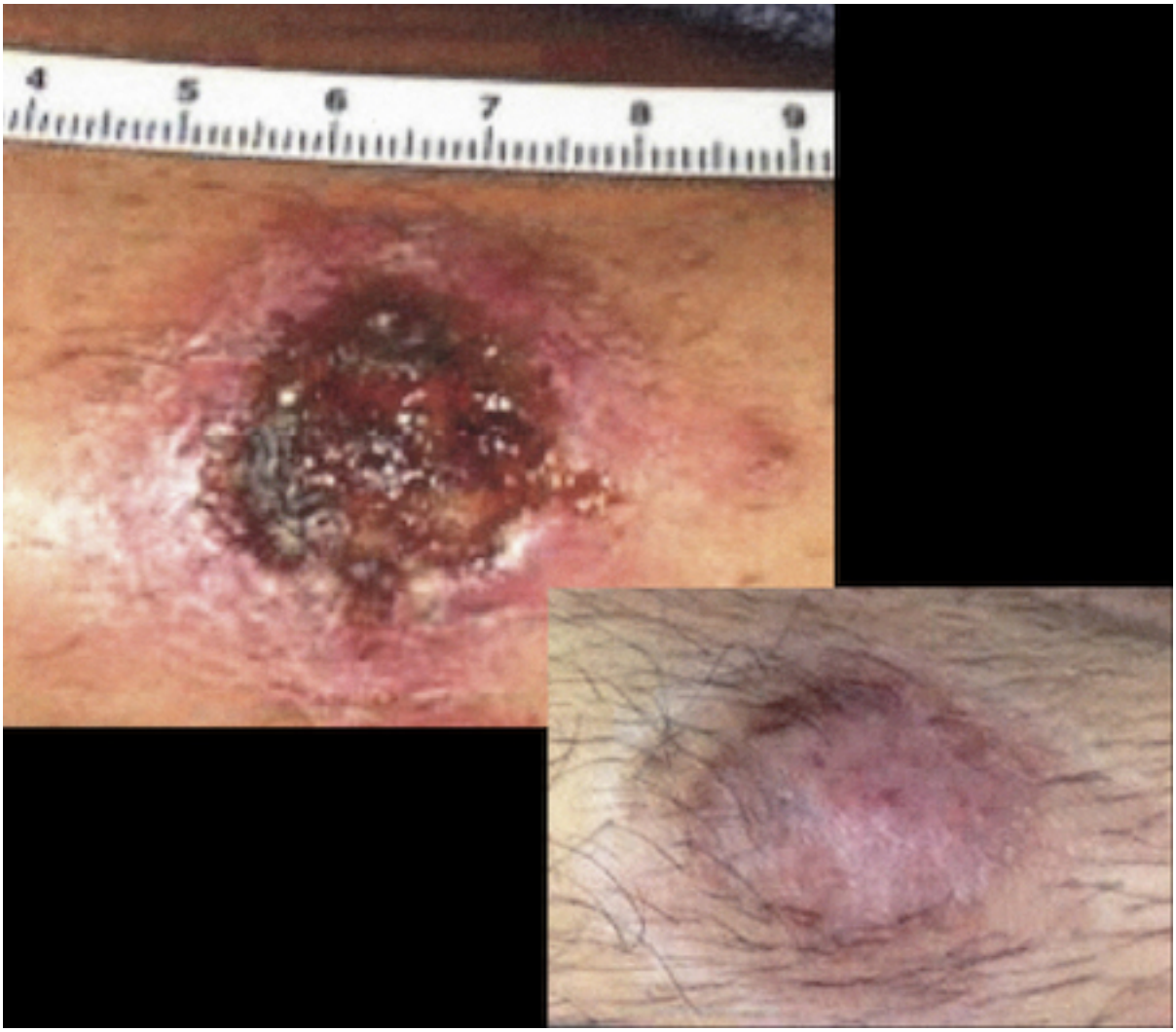

Figure 3: Ulcerative Leishmania mexicana lesion, pre- and post-treatment

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Figure 4: Hepatosplenomegaly in an Ethiopian patient with visceral leishmaniasis

Image courtesy of the World Health Organization

Figure 5: Nodular post-kala-azar dermal leishmaniasis in an Ethiopian patient

Image courtesy of the World Health Organization

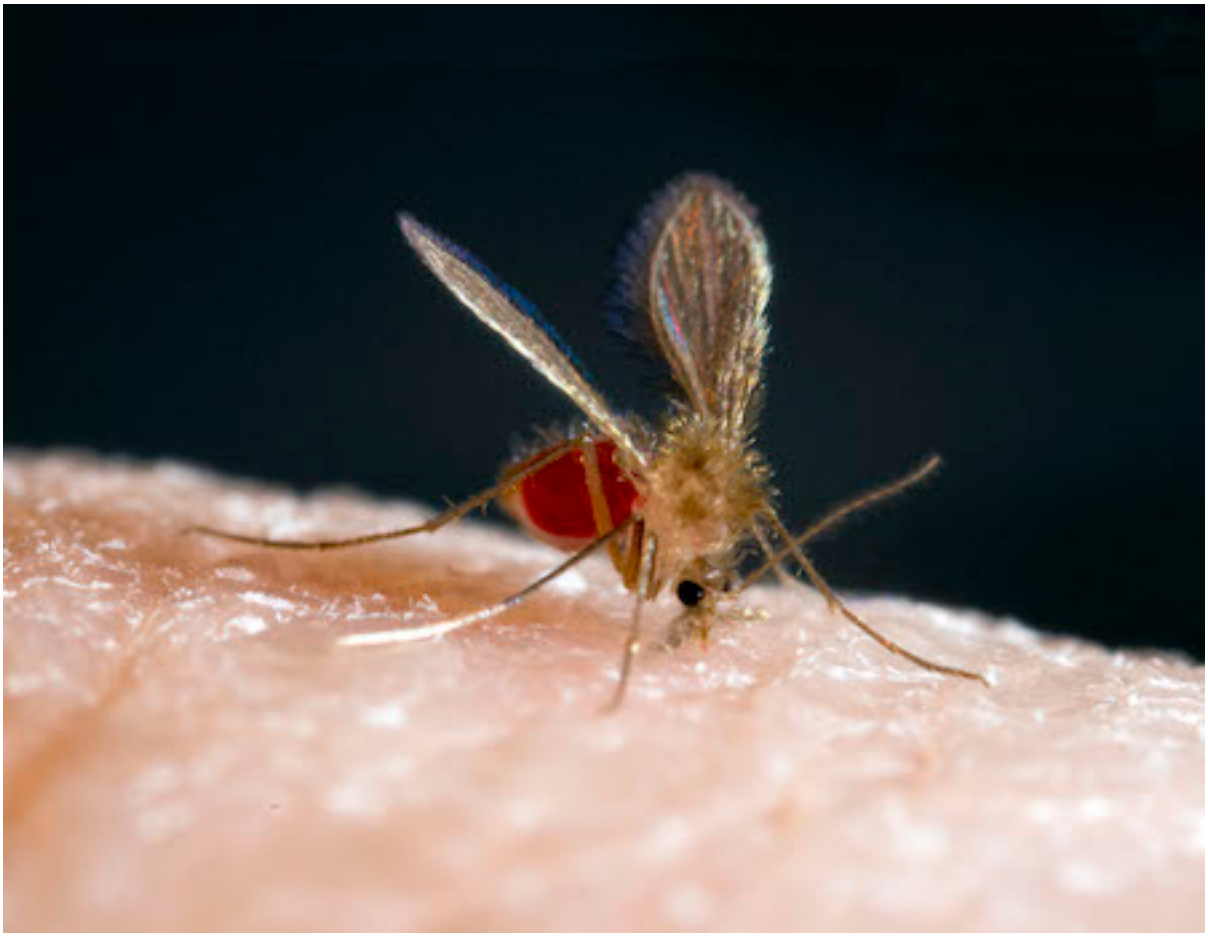

Figure 6: Female Phlebotomus papatasi sand fly

With kind permission from EdRowtonPhotography.com

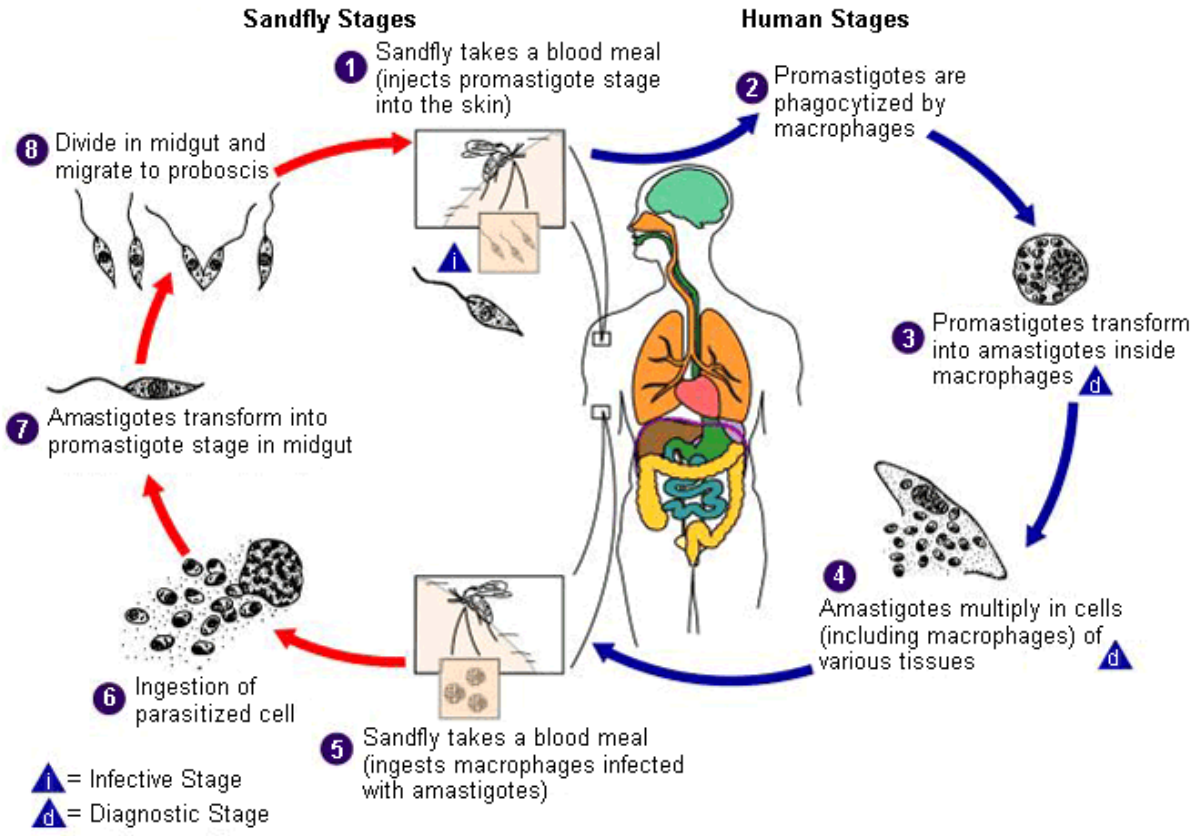

Figure 7: Life cycle of Leishmania species, the causal agents of leishmaniasis

Image courtesy of CDC; A.J. da Silva, PhD; M. Moser

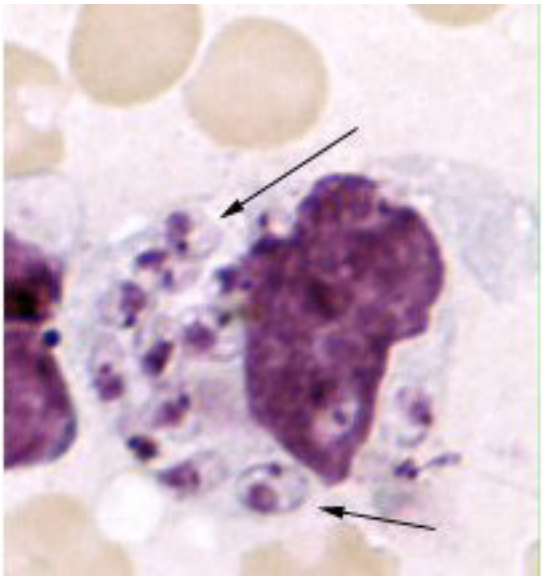

Figure 8: Skin touch preparation showing Leishmania tropica amastigotes. Intact macrophage is practically filled with amastigotes, several of which have a clearly visible nucleus and kinetoplast (arrows)

Image courtesy of CDC; NCID; DPDx

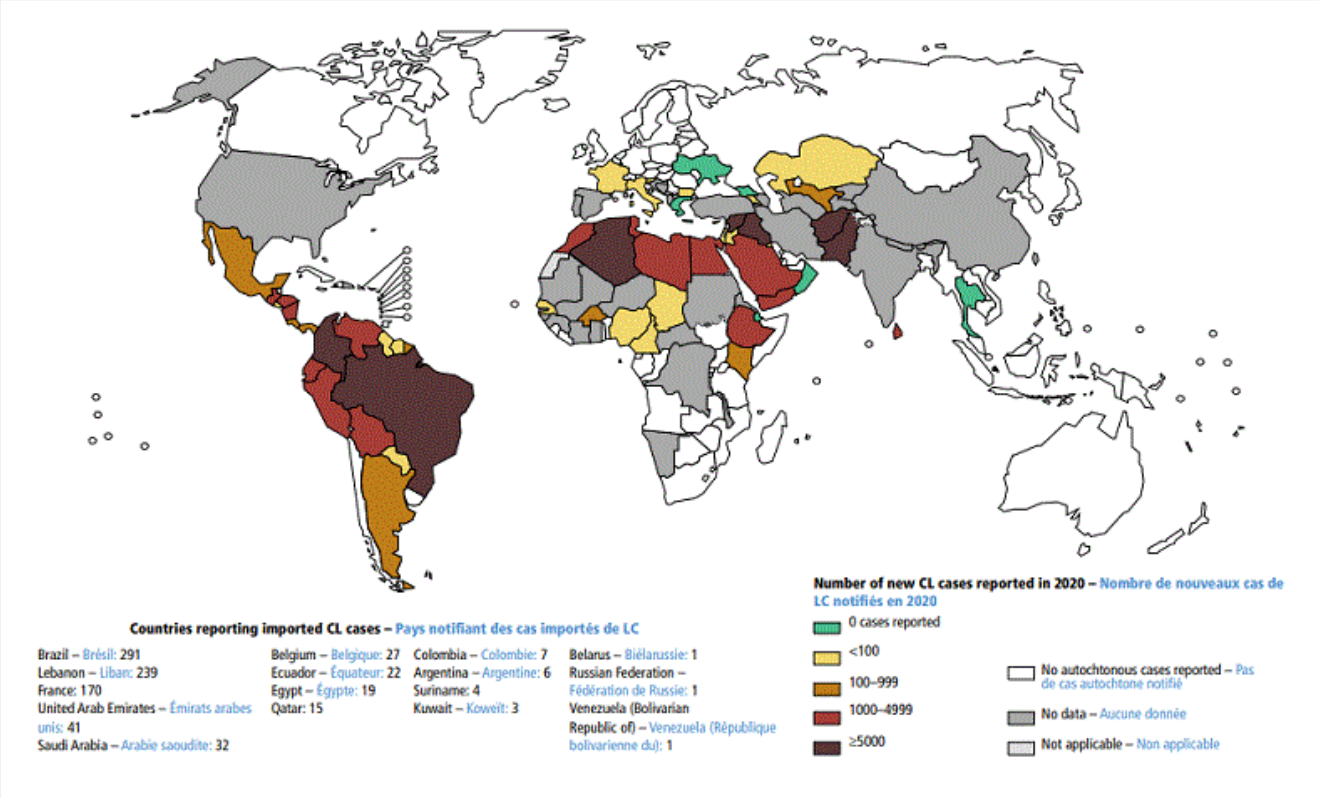

Figure 9: Status of endemicity of cutaneous leishmaniasis (CL) worldwide, 2020

Global leishmaniasis surveillance: 2019–2020, a baseline for the 2030 roadmap: World Health Organization; 2021. Licence: CC BY-NC-SA 3.0 IGO (https://creativecommons.org/licenses/by-nc-sa/3.0/igo/)

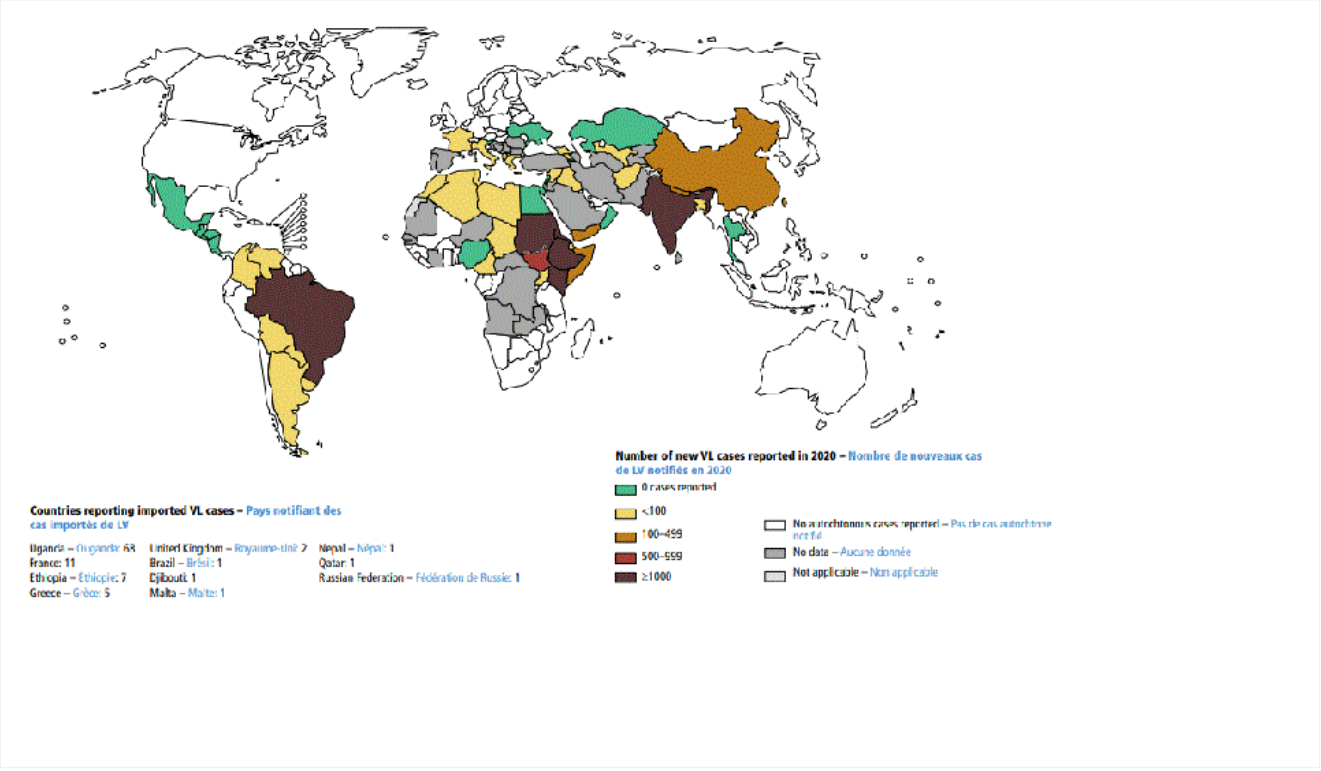

Figure 10: Status of endemicity of visceral leishmaniasis (VL) worldwide, 2020

Global leishmaniasis surveillance: 2019–2020, a baseline for the 2030 roadmap: World Health Organization; 2021. Licence: CC BY-NC-SA 3.0 IGO (https://creativecommons.org/licenses/by-nc-sa/3.0/igo/)

IMAGES

Figure 11: Intralesional injection for the treatment of cutaneous leishmaniasis

Image courtesy of the World Health Organization

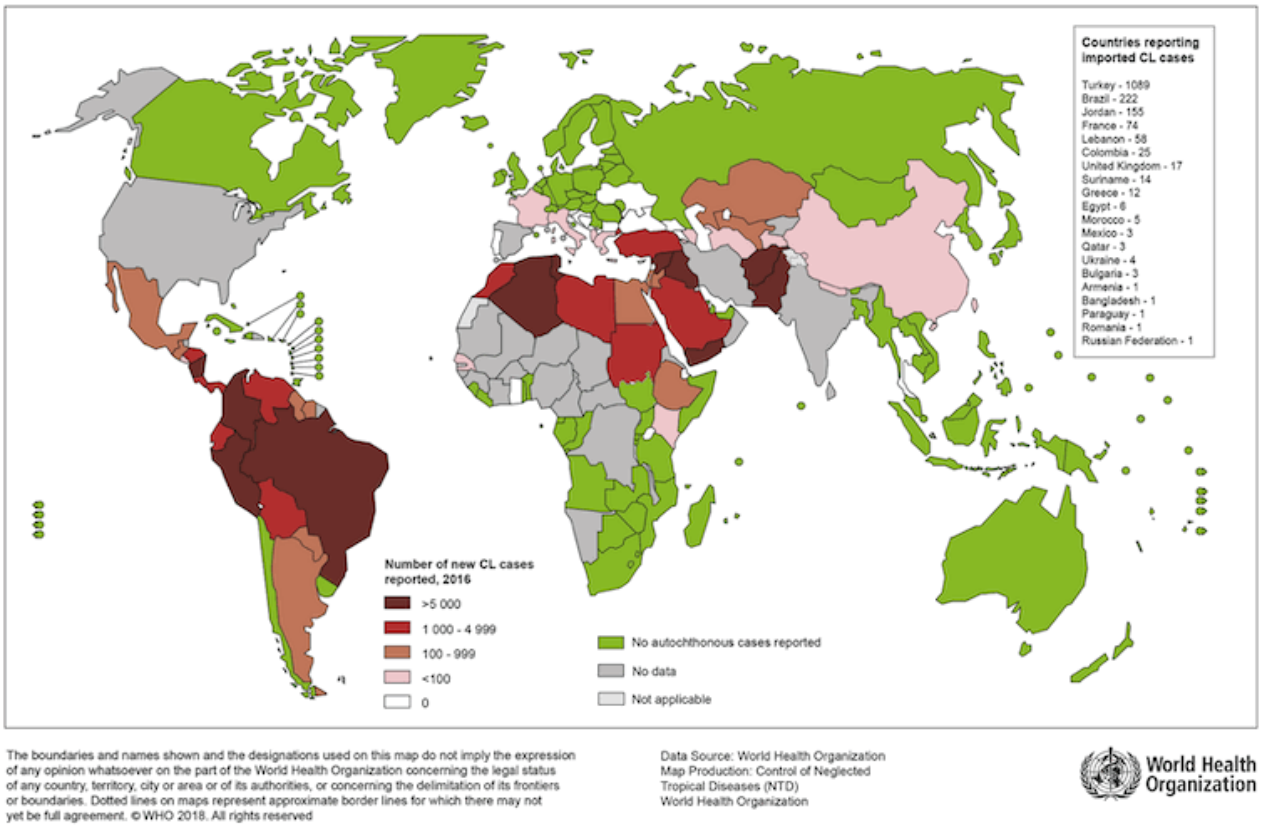

Figure 12: Status of the endemicity of cutaneous leishmaniasis worldwide, 2016

Image courtesy of the World Health Organization

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Please note that recommended formulations and doses may differ between drug databases drug names and brands, drug formularies, or locations. A local drug formulary should always be consulted for full prescribing information.

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This approach is in line with the guidance of the International Bureau of Weights and Measures Service.

Figure 1 – BMJ Best Practice Numeral Style

5-digit numerals: 10,000

4-digit numerals: 1000

numerals < 1: 0.25

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Contact us

+ 44 (0) 207 111 1105
support@bmj.com

BMJ
BMA House
Tavistock Square
London
WC1H 9JR
UK

Contributors:

// Authors:

Naomi E. Aronson, MD

Professor of Medicine
Director, Infectious Diseases Division, Uniformed Services University of the Health Sciences, Bethesda, MD
DISCLOSURES: NEA receives federal grants to study leishmaniasis (received by NEA's institution USU), has given lectures on the topic of leishmaniasis at national and international meetings, and has a patent on biomarkers for leishmaniasis. NEA has received honoraria from the Welcome Trust. NEA's institution USU has received royalties for her writing and editorial work for UpToDate. NEA is an author of a number of references cited in this topic. The views expressed in this topic are those of the authors and do not reflect the official policy of the Department of Army/Navy/Air Force, the Department of Defense, or the US Government.

Nathanial K. Copeland, MD, MTM&H

Assistant Professor of Medicine
Uniformed Services University of the Health Sciences, Bethesda, MD
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// Peer Reviewers:

Roberto Arenas, MD

Chief of the Mycology Section
Dr. Manuel Gea Gonzalez General Hospital, Mexico
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