# Leishmaniasis (Leishmania)

The leishmaniases are a diverse group of diseases caused by intracellular protozoan parasites of the genus Leishmania, which are transmitted by phlebotomine sand flies. Multiple species of Leishmania are known to cause human disease involving the skin and mucosal surfaces and the visceral reticuloendothelial organs. Cutaneous disease is generally mild but may cause cosmetic disfigurement. Mucosal and visceral leishmaniasis is associated with significant morbidity and mortality.

## ***ETIOLOGY***

The parasite is dimorphic, existing as a flagellate promastigotein the insect vector and as an aflagellate amastigote that resides and replicates within mononuclear phagocytes of the vertebrate host.

## ***EPIDEMIOLOGY***

**Localized cutaneous leishmaniasis (LCL)** in the Old World is caused by *L. (Leishmania) major* and *L. (L.) tropica* in North Africa, the Middle East, central Asia, and the Indian subcontinent. *L. (L.) aethiopica* is a cause of LCL and diffuse cutaneous leishmaniasis (DCL)in Kenya and Ethiopia. **Visceral leishmaniasis (VL)** in the Old Worldis caused by *L. (L.) donovani* in Kenya, Sudan, India, Pakistan, and China and by *L. (L.) infantum* in the Mediterranean basin, Middle East, and central Asia. Members of the *Viannia* subgenus also cause **mucosal leishmaniasis(ML)** in a similar geographic distribution

## ***PATHOLOGY***

Histopathologic analysis of the LCL lesion shows intense chronic granulomatous inflammation involving the epidermis and dermis. ML is characterized by an intense granulomatous reaction with prominent tissue necrosis, which may include adjacent cartilage or bone. In VL there is prominent reticuloendothelial cell hyperplasia in the liver, spleen, bone marrow, and lymph nodes.

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## ***CLINICAL MANIFESTATIONS***

There are 4 clinical types of Leishmaniases:-

1. **Localized Cutaneous Leishmaniasis *(Oriental sore)*:-**

It is mainly affect children & usually caused by ***Leishmania major, L. tropica, & L. Mexicana***. It result in chronic granulomatous inflammation of epidermis and dermis → papular, nodular, plaquelike, or ulcerative lesions that are usually located on exposed skin (at site of sandfly bite). They usually not tender & heal spontaneously within 3-6 mo leaving a scar. ***L. Viannia*** may cause palpable subcutaneous nodules with regional LAP +/_ lymphatic cords.

**2. Diffuse Cutaneous Leishmaniasis:-**

It is rare but severe form of Localized Cutaneous L.; it occurs over several years & usually occurs in those with immune defects.DCL manifests as large nonulcerating macules, papules, nodules, or plaques that often involve large areas of skin and may resemble lepromatous leprosy. The face and extremities are most commonly involved.

**3. Mucosal Leishmaniasis *(Espundia)*:-**

It is uncommon but serious disease that mainly caused by ***L. Viannia*** **complex** after hematogenous metastases from a cutaneous lesions to the nasal or oropharyngeal mucosa resulting in nasal congestion, discharge, and recurrent epistaxis. Oropharyngeal and laryngeal involvement is less common but associated with severe morbidity. Marked soft tissue, cartilage, and even bone destruction occurs late in the course of disease and may lead to visible deformity of the nose or mouth, nasal septal perforation, and tracheal narrowing with airway obstruction.

**Visceral Leishmaniasis *(Kala-Azar)*:-**

It is the most important & common form of L. that mainly caused by ***L. donovani*** (Africa and Asia), ***L. chagasi*** (New World), and ***L. infantum*** (Mediterranean region). After inoculation of these organisms into the skin by sandfly, the child may become completely asymptomatic, oligosymptomatic, or symptomatic.

**Oligosymptomatic** illness involve; intermittent fever, malaise, fatigue, intermittent diarrhea, and mild hepatomegaly.

Children who are oligosymptomatic most of these children the illness will resolve without therapy, but in approximately 25% it will evolve to active kalaazar within

2-8 mo. During the first few wk to months of disease evolution the fever is intermittent, there is weakness and loss of energy, and the spleen begins to enlarge. ***The classic clinical features of high fever, marked splenomegaly, hepatomegaly, and severe cachexia typically develop approximately 6 mo after the onset of the illness***.At the terminal stages of kala-azar the hepatosplenomegaly is massive, there is gross wasting, the pancytopenia is profound, and jaundice, edema, and ascites may be present. Anemia may be severe enough to precipitate heart failure. Bleeding episodes, especially epistaxis, are frequent. The late stage of the illness is often complicated by secondary bacterial infections, which frequently are a cause of death. A younger age at the time of infection and underlying malnutrition may be risk factors for the development and more rapid evolution of active VL. ***Death occurs in more than 90% of patients without specific antileishmanial treatment***.

A small percentage of patients previously treated for VL develop diffuse skin lesions, a condition known as **post–kala-azar dermal leishmaniasis.** These lesions may appear during or shortly after therapy or up to several years later. The lesions of post–kalaazar dermal leishmaniasis are hypopigmented, erythematous, or nodular and commonly involve the face and torso.

## ***LABORATORY FINDINGS***

***Montenegro skin test***, people in the endemic areas who have had a subclinical infection can be identified by a positive delayed-type hypersensitivity skin response to leishmanial antigens (similar to TST); or by antigen-induced production of interferon-γ in a whole blood assay.

***Cutaneous & Mucosal*** Leishmaniasis are mainly diagnosed **clinically** (especially in endemic area) or by **culture** because direct microscopy can identify amastigotes in only ≈ half of cases of Cutaneous L. & rarely from lesions of Mucosal L.; whereas serologic tests often have low sensitivity and specificity.

***Visceral*** Leishmaniasis tests include:-

1. **Laboratory findings** associated with classic kala-azar include anemia (hemoglobin 5-8 mg/dL), thrombocytopenia, leukopenia (2,000-3,000 cells/μL), elevated hepatic transaminase levels, and hyperglobulinemia (>5 g/dL) that is mostly immunoglobulin G.

2.**Serology**; EIA, indirect fluorescence assay, direct agglutination, or immunochromatographic strip test when used with recombinant antigen (K39), result in high sensitivity and specificity due to very high level of antileishmanial antibodies.

3.**Definitive Dx** of Leishmaniasis is established by either demonstration of amastigotes in tissue specimens by **direct microscopy** by Giemsa staine or through isolation of the organism by **culture** using (NNN) biphasic blood agar; the culture specimen is taken from tissues of RES, especially spleen, BM, or LN. **In experienced hands, splenic aspiration has a higher Dx sensitivity, but it is rarely performed because of the risk for bleeding complications**

## ***DIFFERENTIAL DIAGNOSIS***

***DDX*** of Visceral Leishmaniasis include: malaria, typhoid fever, miliary tuberculosis, schistosomiasis, brucellosis, amebic liver abscess, infectious mononucleosis, lymphoma, and leukemia.

## ***Treatment***

Anti-leishmanial therapy include:-

 **Pentavalent antimonies** include: **Sodium stibogluconate (Pentostam) & Meglumine antimoniate**, both in dose 20 mg/kg IV or IM for 20 days in LCL & DCL or for 28 days in ML & VL. Repeated courses may be necessary in severe or resistant cases. Adverse effects of antimony therapy are dose and duration dependent and commonly include fatigue, arthralgias andmyalgias (50%), abdominal discomfort (30%), elevated hepatic transaminase level (30-80%), elevated amylase and lipase levels (almost 100%), mild hematologic changes (slightly decreased leukocyte count, hemoglobin level, and platelet count) (10-30%), and nonspecific T-wave changes on electrocardiography (30%). Sudden ***death from cardiac toxicity has rarely been reported with use of very high doses .***

***Note:*** *Some patients with Visceral L. may develop diffuse skin lesions after therapy called " post-kala-azar dermal leishmaniasis".*

 **Amphotericin B** is also very effective in Rx of VL, 0.5–1.0 mg/kg every day or every other day for 14–20 doses. Liposomal amphotericin B is less nephrotoxic, 3 mg/kg on days 1–5, and again on day 10.

 **Other drugs** which also effective in the Rx of VL include: Paromomycin, Recombinant human interferon-γ (as an adjunctive Rx), and oral Miltefosine(**a membrane-activating alkylphospholipid, has been recently developed as the 1st oral treatment for VL & has a cure rate of 95% in Indian patients with VL when administered orally at 50–100 mg/day for 28 days).**

 **Uncomplicated LCL can be observed only without Rx** because it may heal spontaneously within few months. However, complicated LCL & DL can be treated with oral antifungals e.g. Ketoconazole or Fluconazole. Topical agents include: paromomycin plus methylbenzethonium chloride ointment.

## ***PREVENTION***

Personal protective measures should include avoidance of exposure to

the nocturnal sandflies and, when necessary, the use of insect repellent

and permethrin-impregnated mosquito netting.