

Leishmania

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INTRODUCTION LEISHMANIASIS is caused by parasitic protozoa of the genus *Leishmania*. Humans are infected via the bite of phlebotomine sandflies, which breed in forest areas, caves, or the burrows of small rodents. There are four main types of the disease:

- In cutaneous forms, skin ulcers usually form on exposed areas, such as the face, arms and legs. These usually heal within a few months, leaving scars.
- Diffuse cutaneous leishmaniasis produces disseminated and chronic skin lesions resembling those of lepromatous leprosy. It is difficult to treat.
- In mucocutaneous forms, the lesions can partially or totally destroy the mucous membranes of the nose, mouth and throat cavities and surrounding tissues.
- Visceral leishmaniasis, also known as kala azar, is characterized by high fever, substantial weight loss, swelling of the spleen and liver, and anaemia. If left untreated, the disease can have a fatality rate as high as 100% within two years.

SPECIES THAT GIVE RISE TO VL

Several species of *Leishmania* are known to give rise to the visceral form of the disease. The "Old World" (Africa, Asia, Europe) species are *L. donovani* and *L. infantum* and the "New World" (South America) species is *L. chagasi*.

http://www.itg.be/itg/DistanceLearning/LectureNotesVandenEndenE/05_Leishmaniasisp10.htm - topofpage#topofpage: **CUTANEOUS LEISHMANIASIS USUALLY DIVIDED**

INTO:

- Old World leishmaniasis caused primarily by *L. tropica*, *L. major*, *L. aethiopica*, and
- New World leishmaniasis caused primarily by *L. mexicana* or *L. braziliensis*. Diffuse cutaneous leishmaniasis is caused primarily by *L. aethiopica* or *L. mexicana*.

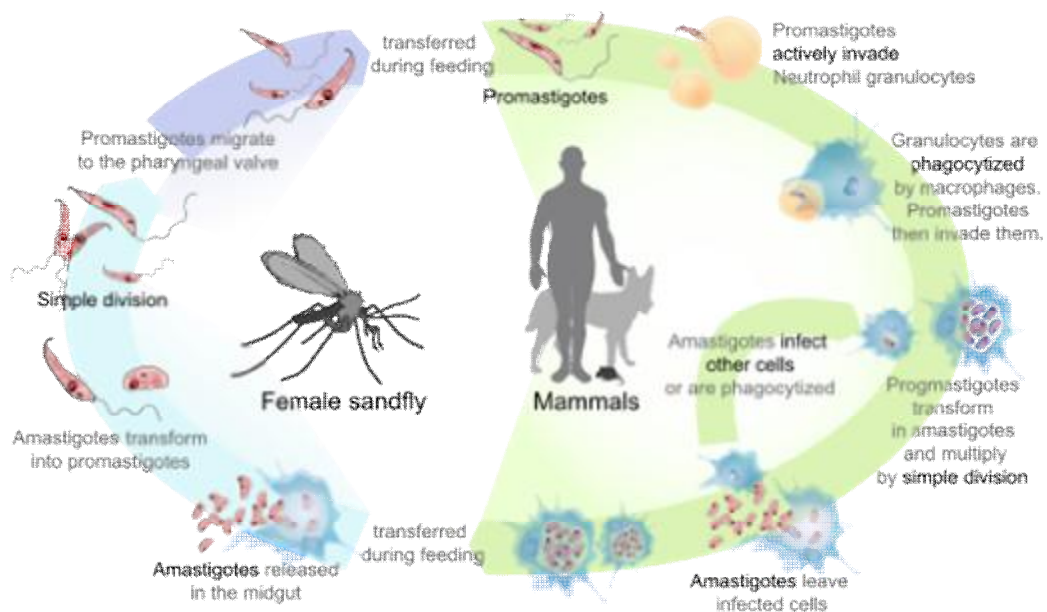
Mucocutaneous leishmaniasis (espundia) is caused primarily by *L. (viannia) braziliensis*. Altogether, there are about 21 leishmanial species that are transmitted by about 30 species of sandflies.

Incubation: Usually 2-6 months or longer. Relapse may occur as many as 10

Amastigote roundish to oval consists of a nucleus and a kinetoplast which consist of the dot like blepharoplast that attach to small axoneme and single parabasal body located adjacent to the blepharoplast

promastigote long and slender body the large single nucleus is located in or near the center the kinetoplast is located anteriorly also single free flagella extend anteriorly from the axoneme

life cycle



§

leishmania tropica

A parasitic haemoflagellate of the subgenus leishmania.
leishmania that infects man and rodents.

This taxonomic complex includes species which cause a disease
called oriental sore which is a form of cutaneous leishmaniasis of
the old world .

Cutaneous leishmaniasis

- § [Cutaneous leishmaniasis, distribution](#)
- § [Cutaneous leishmaniasis, clinical features](#)
- § [Cutaneous leishmaniasis, diagnosis](#)
- § [Cutaneous leishmaniasis, treatment](#)



distribution

Approximately 90% of all cases of cutaneous leishmaniasis now occurs in Iran, Syria, Saudi Arabia, Afghanistan, Peru and Brazil.



[clinical features]

Various forms are clinically distinguished, the most important of which are :

- § **Localised cutaneous leishmaniasis:** skin ulcers that heal very slowly or nodular lesions, limited in extent and number. These chronic sores have regional names: clou de Biskra in Algeria and Aleppo boil in Syria.
- § **Diffuse cutaneous leishmaniasis:** cutaneous nodules and plaques that do not ulcerate but can sometimes spread over the entire body.
- § **Recurrent cutaneous leishmaniasis**

"... After it is cicatrised, it leaves an ugly scar, which remains through life, and for many months has a livid colour. When they are not irritated, they seldom give much pain... It affects the natives when they are children and generally appears in the face, though they also have some on their extremities... In strangers, it commonly appears some months after their arrival. Very few escape having them, but they seldom affect the same person above more than once."



Early *Leishmania brasiliensis* infection, with lesions on the nose. This differs from *espundia*. Copyright ITM



Skin ulcer due to cutaneous leishmaniasis. Copyright ITM



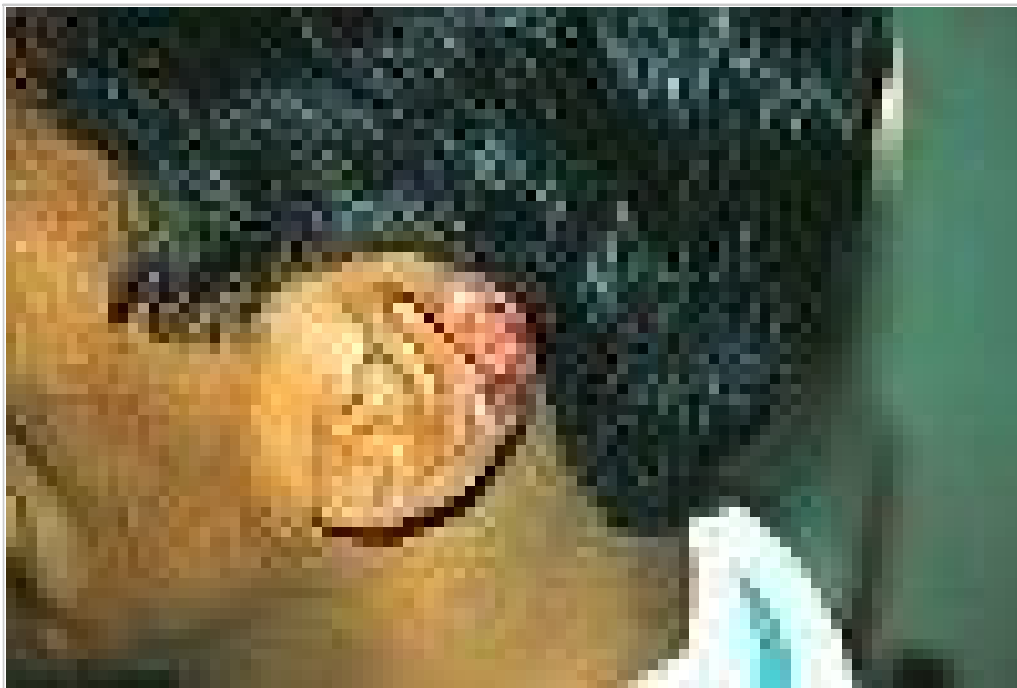
Diffuse cutaneous leishmaniasis. Infection with *Leishmania aethiopica*.
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Localised cutaneous leishmaniasis

After a bite by a sandfly infected with *L. tropica* (mainly urban infection), there is an incubation period of a few weeks or months, occasionally years. There is initially a small papula and usually only a single lesion, though sometimes there are several. This slowly spreads, can remain completely dry, become nodular or develop into a painless, sharply delineated ulcer surrounded by a purplish raised border. Satellite lesions can occur. Spontaneous healing often occurs after 6 to 12 months, resulting in a depressed scar. Recurring cutaneous lesions - possibly with severe disfigurements - occasionally occur. There is usually immunity to any subsequent infection with the same organism. In infection with *L. major* (mainly rural infections, particularly from a rodent reservoir) the lesions are usually larger and develop more quickly, hence the name. There is a greater tendency to local spreading via the lymphatics and have to be distinguished from sporotrichosis. The lesions will eventually spontaneously heal with scar forma.



Chiclero ulcer on an ear (leishmaniasis). Photo Cochabamba, Bolivia

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Diffuse cutaneous leishmaniasis

Diffuse cutaneous leishmaniasis is a diffuse affection of the skin with extensive non-ulcerative nodules and is a very chronic disease. It is sometimes followed by chronic lymphoedema of an affected part of the body. This disease is poorly understood, but is probably caused by a diminished resistance to the parasite. This immunosuppression is possibly brought about by the parasite itself. In East Africa diffuse cutaneous leishmaniasis is often caused by *L. aethiopica* and in the New World frequently by *L. mexicana*.

Due to the low resistance of the patient very numerous amastigotes are present skin smears are always positive. Treatment is difficult, as the patient's immune system itself is functioning poorly. *

Recurring cutaneous leishmaniasis

Recurring cutaneous leishmaniasis seldom occurs (Iraq, Iran). This disease, also known as leishmaniasis recidivans leads to significant tissue damage. Parasites are very difficult to detect in these very chronic lesions. Differentiation from cutaneous tuberculosis is important.

diagnosis



Leishmania mexicana, ulcer on the arm. A skin biopsy is best taken from the edge of a lesion. Copyright ITM

Attempts should be made to detect the parasite **microscopically** in a biopsy or smear from the edge of the wound. The biopsy will, if possible, be divided up for pathology (seldom available, not very sensitive, is principally used more for exclusion of another cause) and **cultures** (bacteria, mycobacteria, fungi, *Leishmania*) and an **impression**

preparation should also be made. Lesions on the face can be injected with 0.1 ml physiological saline and aspirated again while moving the small, thin needle back and forth in the skin.

Serology is usually negative.

Differential diagnosis includes ulcers due to mycobacteria, cutaneous diphtheria, tertiary syphilis, yaws, cutaneous carcinoma and deep or subcutaneous mycosis. Acid fast bacilli can be made visible using the method of **Ziehl-Neelsen**. Field sore (cutaneous diphtheria) and tropical ulcers (fusobacteria + *Borrelia*) are painful, particularly in the early phase.



9.4 Cutaneous leishmaniasis, treatment

The response to treatment varies according to the species. Drugs for systemic and topical treatment can be used. There is an urgent need for better and cheaper drugs.

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Indications for local treatment

- § lack of risk of developing mucosal lesions
- § Old World cutaneous leishmaniasis
- § small, single lesion
- § absence of lymph node metastasis

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Indications for systemic treatment

- § presence of mucosal lesion or lymph node metastasis
- § New World cutaneous leishmaniasis, except localised *Leishmania mexicana* infection
- § lesions unresponsive to local treatment

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Overview topical treatment of cutaneous leishmaniasis

- § physical methods: cryotherapy (liquid nitrogen). Blistering will occur.
- § application of local heat (e.g. infrared lamp).
- § ointment with 15% paromomycin and 12% methylbenzethonium chloride in soft white paraffin (e.g. Leishcutan® ointment). Urea can be added as a keratolytic.
- § skin infiltration with pentavalent antimony
- § imiquimod crème (Aldara®) but is best used in combination with systemic meglumine antimonate.

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Overview systemic treatment of cutaneous leishmaniasis

- § Pentavalent antimonial
- § Pentamidine.
- § Imidazoles, triazo. Ketoconazole
- § Miltefosine. Still experimental.
- § Amphotericine B
- § Allopurinol.

§ **Clinical Findings and Treatment: Visceral Leishmaniasis or Kala-Azar**

- § visceral leishmaniasis caused by *Leishmania donovani* does not appear to have an animal reservoir and is thought to be transmitted via human-sandfly-human interaction.

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- § Signs and Symptoms: Cardinal signs of visceral leishmaniasis (VL) are prolonged fever, splenomegaly, anemia, leukopenia, or hypergammaglobulinemia. A cutaneous nodule may or may not appear at the site of the bite within several days of inoculation. If present, the nodule remains, but in most cases, no other symptoms are present for at least several months. Systemic symptoms include gradual onset fever that often rises and falls

twice/day, fatigue, weight loss, dizziness, cough, and diarrhea. Visceral manifestations include pronounced splenomegaly (hard, non-tender) and to a lesser extent hepatomegaly. Other manifestations may include generalized lymphadenopathy; hyperpigmented skin of the forehead, abdomen, hands, and feet in light-skinned persons; skin lesions in dark-skinned persons; signs of bleeding (petechiae, epistaxis, bleeding gums); jaundice and ascites; and progressive wasting. Onset may also be acute, with the above manifestations appearing a few weeks after infection.

Complications: Progressive wasting or intercurrent infections (e.g., pneumonia, tuberculosis, diarrhea) may lead to death. Post kala-azar cutaneous leishmaniasis may occur as many as 10 years after the first episode. Lesions may resemble Hansen's disease and include hypopigmented macules, nodules, and erythematous patches. Leshmaniasis may occur as an opportunistic infection in immunocompromised persons. The disease may also be passed from an asymptomatic mother to her child.

- § Laboratory Findings: Leukopenia, hypergammaglobulinemia, hypoalbuminemia; thrombocytopenia with hemorrhagic fever.

Diagnosis: Presence of cardinal signs noted above, in addition to living in or visiting endemic area lead to suspicion of leishmaniasis. The organism is present in bone marrow or splenic aspirate (most sensitive), blood, and nasopharyngeal secretions. If parasites are present in sufficient concentration, light microscopy of giemsa-stained slides reveals amastigotes, the tissue form of the parasite. Direct agglutination and ELISA are positive early and the leishmanin skin test is positive only after active disease.

- § Management: antimony SP compounds ,Amphotericin B, Miltefosine
- § paromomycin

Mucocutaneous Leishmaniasis

MUCOCUTANEOUS LEISHMANIASIS, CLINICAL FEATURES

When skin and mucosae are affected the disease is known as mucocutaneous leishmaniasis. This is very rare in East Africa but frequent in South America, where it is known as "espundia". After an initial skin lesion, that slowly but spontaneously heals, chronic ulcers appear after months or years on the skin, mouth and nose, with destruction of underlying tissue (nasal cartilage, for example). Tissue destruction with disfigurement can be very severe. Parasites are usually rare in the lesions. A substantial part of the disfigurement is possibly due to immunological mechanisms. One hypothesis is a relationship between the occurrence of mucocutaneous lesions and the presence of certain alleles of polymorphic tumour

Physical

- Mucocutaneous leishmaniasis
 - The initial skin lesion is often notable for its prolonged healing time and large size. In most cases, a healed scar can be identified based on careful examination. Months to years after the initial infection, patients may have rhinorrhea, epistaxis, and nasal congestion.
 - Examination reveals excessive tissue obstructing the nares, septal granulation, and perforation. Nose cartilage may be involved, giving rise to external changes known as parrot's beak or camel's nose.
 - The palate, uvula, lips, pharynx, and larynx may exhibit granulation, erosion, and ulceration with

sparing of the bony structures. Hoarseness may be a sign of laryngeal involvement.

- Other physical signs include gingivitis, periodontitis, and localized lymphadenopathy. In time, disfiguring facial deformities may occur, requiring plastic surgery. Optical and genital mucosal involvement have been reported in severe cases.

Death occurs from suffocation secondary to airway obstruction, respiratory infection, and aspiration pneumonia

- Mucocutaneous leishmaniasis
 - Old World
 - § *L aethiopica* - Ethiopia, Kenya, Namibia
 - New World
 - § *L viannia braziliensis* - Central America, South America
 - § *L viannia panamensis* - Central America, South America
 - § *L viannia guyanensis* - Guyana, French Guyana, Surinam, Brazil
 - § Less often seen with *L leishmania mexicana* - Central America, South America, North America

Less often seen with *L leishmania amazonensis* - Brazil, Panama

History

- Mucocutaneous leishmaniasis
 - Mucocutaneous disease is most commonly caused by New World species, although Old World *L aethiopica* has been reported to cause this syndrome. Infection by *Leishmania viannia braziliensis* may lead to mucosal involvement in up to 10% of infections depending on the region in which it

was acquired. Initial infection is characterized by a persistent cutaneous lesion that eventually heals, although as many as 30% of patients report no prior evidence of leishmaniasis. Several years later, oral and respiratory mucosal involvement occurs, causing inflammation and mutilation of the nose, mouth, oropharynx, and trachea.

- Progressive disease is difficult to treat and often recurs. With prolonged infection, death occurs from respiratory compromise and malnutrition.

Mucocutaneous leishmaniasis may arise after inadequate treatment of certain *Leishmania* species.

Mortality/Morbidity

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Mucocutaneous leishmaniasis is chronic and progressive. Death can occur from secondary infection and after respiratory tract mucosal invasion. Respiratory compromise and dysphagia may lead to malnutrition and pneumonia

MUCOCUTANEOUS LEISHMANIASIS, DIAGNOSIS

The lesions often contain few parasites. Diagnosis is sometimes made solely on a clinical basis. Culture of the parasites is possible, but not really feasible in primitive rural conditions. Serology in espundia can be positive or negative (the quality of the antigen is of crucial importance). A practical problem in South America is whether a certain skin lesion with *Leishmania* amastigotes is caused by *L. braziliensis* or not. The geographical origin of the lesion or PCR and/or zymodeme analyses may give an answer here, though these laboratory techniques are not available in rural areas.

Presence of cardinal signs, positive history, and geographic risk lead to suspicion of mucocutaneous leishmaniasis. Diagnosis is difficult because amastigotes are scarce in the usual sources (scrapings, tissue aspirates, biopsy). Culture and serologic tests are usually necessary.

Signs and Symptoms: Mucocutaneous leishmaniasis (MCL) is a sequela of new world cutaneous leishmaniasis and results from direct extension or hematogenous or lymphatic metastasis to the nasal or oral mucosa. In most cases, naso-oropharyngeal symptoms appear several years after resolution of the primary lesion(s), but may also appear while the primary lesions are still present or decades later. Manifestations of mucocutaneous leishmaniasis include chronic nasal symptoms, especially of the anterior nasal septum (leading to development of the characteristic "tapir nose") and progressing to extensive naso-oropharyngeal destruction. Secondary bacterial (or fungal) infections and associated problems are common.

Complications: Mucosal leishmaniasis is, itself, a complication. Secondary infections and associated problems are common. Laboratory Findings: There are no specific laboratory findings characteristic of MCL.).



Leishmania brasiliensis ulcer on the wrist and spread via the lymphatics. Lesions occurred after a visit to rural Bolivia. Copyright ITM

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Pathogenesis:

Although the pathogenesis of visceral and cutaneous leishmaniasis are well understood, the pathogenesis of mucocutaneous leishmaniasis (MCL) is still unclear. However, it is believed that host genetic factors are important in the advancement of the disease. MCL development is similar to that of cutaneous leishmaniasis, and the two infections can occur simultaneously. MCL occurs when cutaneous lesions expand to the mucosal region or through metastasis.

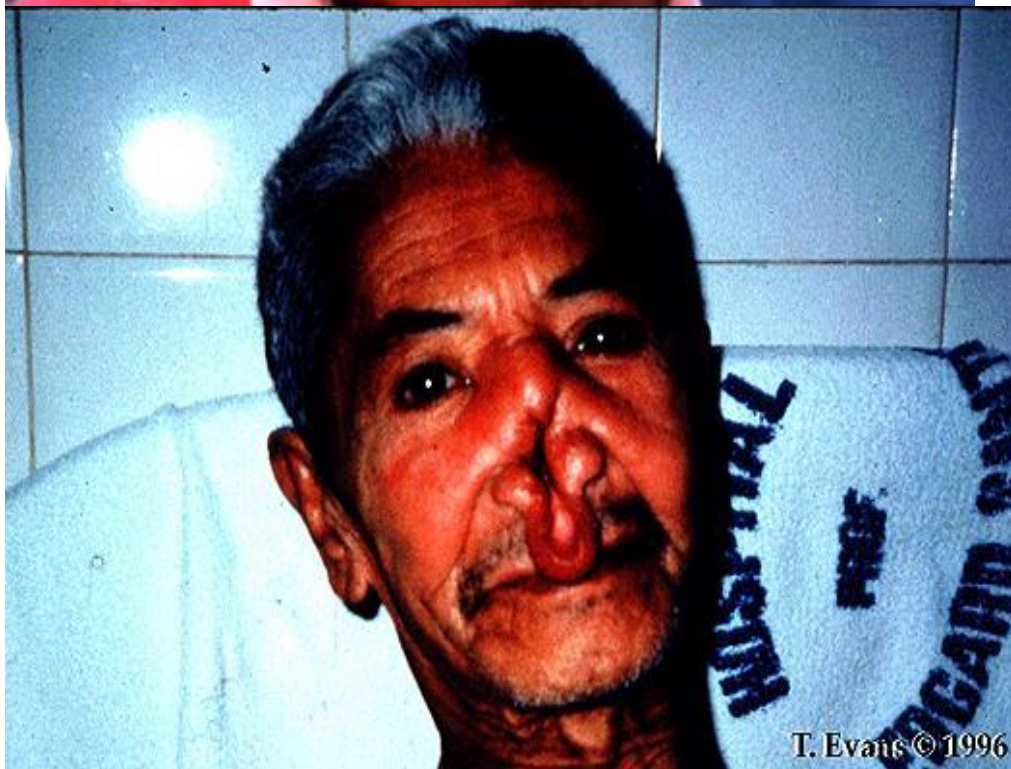
Moreover, it is not uncommon for MCL to develop many years after the recovery of an initial lesion. The result is a gradual and progressive development of destructive lesions

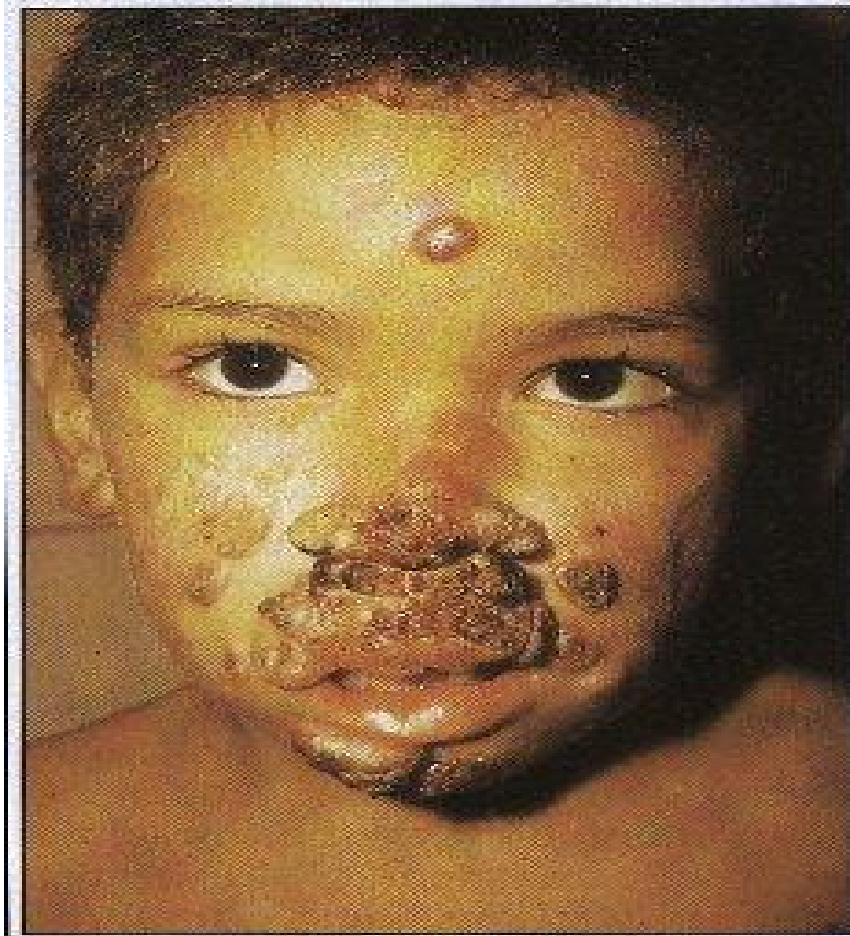
Clinical Manifestations:

- initial symptoms are similar to that of cutaneous leishmaniasis
- single or multiple lesions and ulcers develop at the mucosal regions (nose, mouth, throat cavities) and in the adjacent tissue

extensive disfiguring of the nasal septum, lips, and palate (does not include the bones) Lesions may multiply and increase in size, which can contribute to severe deformity. Because it causes major disability, those infected may be humiliated and suffer from being ostracized by their society. Respiratory tract mucosal invasion may also occur, causing numerous respiratory problems, and can result in malnutrition and pneumonia. Secondary infection is responsible for most deaths.

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Surgical Care

- Severe mucocutaneous leishmaniasis may require orofacial surgery.
- Surgical removal is not recommended for cutaneous disease because of the potential for recurrence at the excision site.
- Surgery may exacerbate quiescent disease.

Diet

- Malnutrition has been shown to increase morbidity and mortality in mucocutaneous and visceral disease. Patients should receive nutritious, well-balanced meals.

virulence factor

1-GP63 : The most abundant protein on the surface of the promastigote form of the protozoan parasites *Leishmania* spp. is gp63 or leishmanolysin. Because gp63 has been shown to possess fibronectin-like properties, we examined the interaction of gp63 with the cellular receptors for fibronectin. We measured the direct binding of *Leishmania* to human macrophages or to transfected mammalian cells expressing human fibronectin receptors. *Leishmania* expressing gp63 exhibited modest but reproducible adhesion to human macrophages and to transfected CHO cells expressing $\alpha 4/\beta 1$ fibronectin receptors. In both cases, this interaction depended on gp63. The interaction of gp63 with fibronectin receptors may also play an important role in parasite internalization by macrophages. Erythrocytes to which gp63 was cross-linked were efficiently phagocytized by macrophages, whereas control erythrocytes opsonized with complement alone bound to macrophages but remained peripherally attached to the outside of the cell. Similarly, parasites expressing wild-type gp63 were rapidly and efficiently phagocytized by resting macrophages, whereas parasites lacking gp63 were internalized more slowly. This rapid internalization of gp63-expressing parasites was dependent on the $\beta 1$ integrins, because pretreatment of macrophages with monoclonal antibodies to the $\beta 1$ integrins decreased the internalization of gp63-expressing parasites. These observations indicate that complement receptors are the primary mediators of

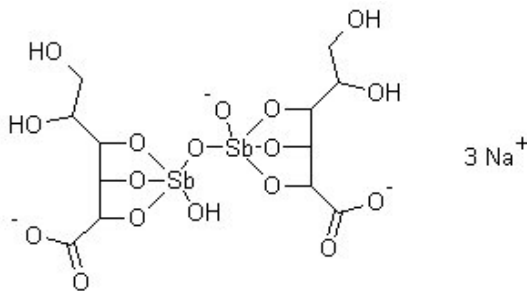
parasite adhesion; however, maximal parasite adhesion and internalization may require the participation of the $\alpha 3 \beta 1$ integrins, which recognize fibronectin-like molecules such as gp63 on the surface of the parasite.

2-lipophosphoglycan (LPG)

Cell surface lipophosphoglycan (LPG) is commonly regarded as a multifunctional *Leishmania* virulence factor required for survival and development of these parasites in mammals. In this study, the LPG biosynthesis gene *lpg1* was deleted in *Leishmania mexicana* by targeted gene replacement. The resulting mutants are deficient in LPG synthesis but still display on their surface and secrete phosphoglycan-modified molecules, most likely in the form of proteophosphoglycans, whose expression appears to be up-regulated. LPG-deficient *L. mexicana* promastigotes show no significant differences to LPG-expressing parasites with respect to attachment to, uptake into and multiplication inside macrophages. *L. mexicana* clones are at least as virulent as the parental wild-type strain and lead to lethal disseminated disease. The results demonstrate that at least *L. mexicana* does not require LPG for experimental infections of macrophages or mice. *Leishmania mexicana* LPG is therefore not a virulence factor

Treatment

Drug	mechanism of action	dosing	Therapy side effects	Results
Sodium Stibogluconate (Pentostam)	Cause parasite death by inhibiting glycolytic enzymes and fatty acid oxidation	Administered intravenously or intramuscularly	20 mg/kg body weight daily for 28 days	Coughing, headache, vomiting, Cutaneous lesions may not usually require antimonials to heal. After several weeks, the lesions tend to heal on their own.



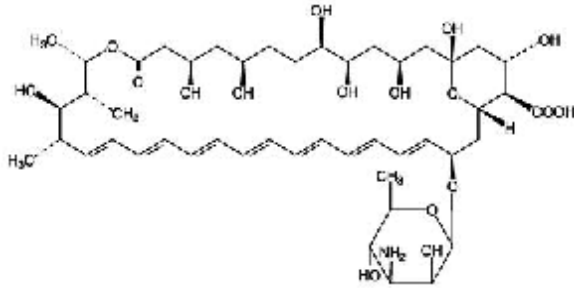
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Amphotericin B (Fungizone)

Causes parasite death

intravenously.5-1 mg/kg lb per day for up to 8 weeks

Coughing, Cutaneous headache, lesions vomiting, may not usually possible renal require damage and bone marrow depression. After several weeks, the lesions tend to heal on their own.



Cycloguanil pamoate (Camolar)

