STATE-OF-THE-ART CLINICAL ARTICLE

Clinical Spectrum of Leishmaniasis

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Leishmania species, which are protozoal pathogens belonging to the order Kinetoplastida, have gained increasing notoriety over the past decade as causes of morbidity and mortality among military personnel, refugees, and tourists as well as among residents of areas where these species are endemic. They have also emerged as model systems for the study of the mononuclear cell populations and cytokines that mediate immunity to intracellular pathogens.

More than 20 *Leishmania* species have been identified (table 1) [1, 2]. In most instances they cause disease in animals, and humans become infected incidentally when they enter an area of endemicity. Numerous rodent and canine species have been incriminated as reservoirs. Sandflies are the vectors. In a few locations, humans serve as a reservoir, and the parasites are transmitted by anthropophilic sandflies. On rare occasions, transmission occurs congenitally or as a result of a blood transfusion.

The clinical manifestations of leishmaniasis depend on complex interactions between the virulence characteristics of the infecting *Leishmania* species and the immune responses of its host. The result is a spectrum of disease ranging from localized skin lesions to diffuse involvement of the reticuloendothelial system. Human disease has traditionally been divided into three major clinical syndromes: visceral, cutaneous, and mucosal leishmaniasis; however, a number of variants exist. Furthermore, a single *Leishmania* species can produce more than one clinical syndrome, and each syndrome is caused by multiple species.

The true incidence and prevalence of leishmaniasis is uncertain because many cases go undiagnosed or unreported in areas where the infection is endemic. In 1993, the World Health Organization estimated that 350 million people worldwide were at risk for infection. The incidence of cutaneous leishmaniasis has been estimated to be 1.0–1.5 million cases per year, and the incidence of visceral disease has been estimated to be 500,000 cases per year [3].

Over the past decade major epidemics of visceral leishmaniasis have been reported from eastern India and Bangladesh [4], among refugees in the Sudan [5], and in urban areas of northeastern Brazil [6]. Visceral leishmaniasis has also emerged as an opportunistic infection in patients with HIV infection or other immunocompromising conditions [7–9]. Finally, a viscerotropic syndrome that had not previously been described affected a small number of American troops during Operation Desert Storm and led to a temporary ban on blood and organ donations from veterans of the Operation [10]. Cutaneous leishmaniasis has been a recurrent problem for settlers, military personnel, and travelers in areas of Latin America and the Middle East where the infection is endemic. Mucosal leishmaniasis is an important problem in Brazil and other Latin American countries.

The Parasite and Its Life Cycle

Leishmania live as extracellular, flagellated promastigotes in the guts of female phlebotomus sandflies. They vary from rounded or stumpy forms to elongated, highly motile, metacyclic promastigotes. Most are in the range of 15–26 μm in length and 2–3 μm in width. The flagellum extends from the anterior pole. Promastigotes grow at ambient temperatures ranging from 22°C to 26°C.

Leishmania exist within the mononuclear phagocytes of mammals as oval, intracellular amastigotes that are 2–3 μm in diameter (figure 1). The amastigotes have a relatively large, eccentrically located nucleus and a bar-shaped specialized mitochondrial structure, the kinetoplast, that contains extranuclear DNA in the form of catenated mini- and maxi-circles. Amastigotes are adapted to mammalian body temperature and the acid environment of the macrophage phagolysosome where they reside.

The classification of *Leishmania* species is still undergoing refinement. The genus has been divided into two subgenera, *Viannia* and *Leishmania,* based on the site of promastigote development in the sandfly [1]. The *Viannia* species develop in the hindgut of the sandfly before migrating to the midgut and foregut (peripylaria). The subgenus *Leishmania* includes species that have lost the more primitive hindgut development

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Table 1. Clinical syndromes caused by *Leishmania* species and their geographic distribution.

Clinical syndromes	*Leishmania* species	Location
Visceral leishmaniasis		
Kala-azar: generalized involvement of the reticuloendothelial system (spleen, bone marrow, and liver)	*L. (L.) donovani*	Indian subcontinent, northern and eastern China, Pakistan, and Nepal
	L. (L.) infantum	Middle East, Mediterranean littoral, Balkans, central and southwestern Asia, northern and northwestern China, northern and sub-Saharan Africa
	L. (L.) donovani (archibaldi)	Sudan, Kenya, and Ethiopia
	L. (L.) species	Kenya, Ethiopia, and Somalia
	L. (L.) chagasi	Latin America
	L. (L.) amazonensis	Brazil (Bahia State)
	L. (L.) tropica	Israel, India, and viscerotropic disease in Saudi Arabia (U.S. troops)
Post-kala-azar dermal leishmaniasis	*L. (L.) donovani*	Indian subcontinent
	L. (L.) species	Kenya, Ethiopia, and Somalia
Old World cutaneous leishmaniasis		
Single or limited number of skin lesions	*L. (L.) major*	Middle East, northwestern China, northwestern India, Pakistan, and Africa
	L. (L.) tropica	Mediterranean littoral, Middle East, western Asiatic area, and Indian subcontinent
	L. (L.) aethiopica	Ethiopian highlands, Kenya, and Yemen
	L. (L.) infantum	Mediterranean basin
	L. (L.) donovani (archibaldi)	Sudan and East Africa
	L. (L.) species	Kenya, Ethiopia, and Somalia
Diffuse cutaneous leishmaniasis	*L. (L.) aethiopica*	Ethiopian highlands, Kenya, and Yemen
New World cutaneous leishmaniasis		
Single or limited number of skin lesions	*L. (L.) mexicana* (chiclero ulcer)	Central America, Mexico, and Texas
	L. (L.) amazonensis	Amazon basin, neighboring areas, Bahia and other states in Brazil
	L. (V.) braziliensis	Multiple areas of Central and South America
	L. (V.) guyanensis (forest yaws)	Guyana, Surinam, and northern Amazon basin
	L. (V.) peruviana (uta)	Peru (western Andes) and Argentinean highlands
	L. (V.) panamensis	Panama, Costa Rica, and Colombia
	L. (V.) pifanoi	Venezuela
	L. (V.) garnhami	Venezuela
	L. (V.) venezuelensis	Venezuela
	L. (L.) chagasi	Central and South America
Diffuse cutaneous leishmaniasis	*L. (L.) amazonensis*	Amazon basin, neighboring areas, Bahia, and other states in Brazil
	L. (V.) pifanoi	Venezuela
	L. (L.) mexicana	Mexico and Central America
	L. (L.) species	Dominican Republic
Mucosal leishmaniasis	*L. (V.) braziliensis* (espundia)	Multiple areas in Latin America

NOTE. (*L.*) = subgenus *Leishmania*; (*V.*) = subgenus *Viannia*. Data are from [1, 2].

and occupy only the midgut and foregut (suprapylaria). Identification of species within these two subgenera has been based on multiple factors other than developmental characteristics.

The *Leishmania* species responsible for human disease are shown in table 1. The subgenus distinction is provided in the table but has been omitted from the text. The majority of cases of visceral leishmaniasis are due to *L. chagasi* (in Latin America), *L. donovani* (in Africa, India, and Asia), and *L. infantum* (in the Mediterranean littoral). *L. major, L. tropica,* and *L. aethiopica* (in the Old World) and *L. mexicana, L. braziliensis,* and related species (in the Americas) typically cause cutaneous disease. *L. braziliensis* is responsible for mucosal leishmaniasis in Latin America. It has become increasingly clear that *Leishmania* species usually associated with visceral leishmaniasis can produce localized skin lesions and that species commonly found in the skin can disseminate viscerally.

Although slight ultrastructural differences exist, morphological features cannot be used to differentiate *Leishmania* species from one another. Identification of isolates is currently based on isoenzyme analysis of cultured promastigotes at World Health

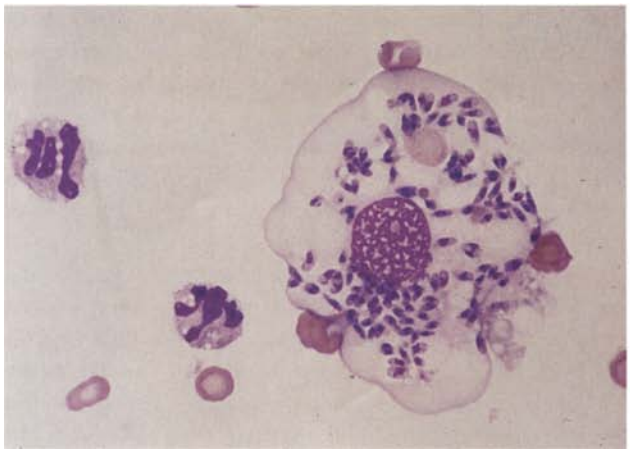

Figure 1. *Leishmania* species amastigotes, 2–3 μm in diameter, are seen within a macrophage in a cytocentrifuged preparation of pleural fluid from a patient with HIV infection and visceral leishmaniasis. (Kindly provided by David M. Markovitz, M.D., University of Michigan, Ann Arbor, Michigan, and Robert Betts, M.D., University of Rochester, Rochester, New York).

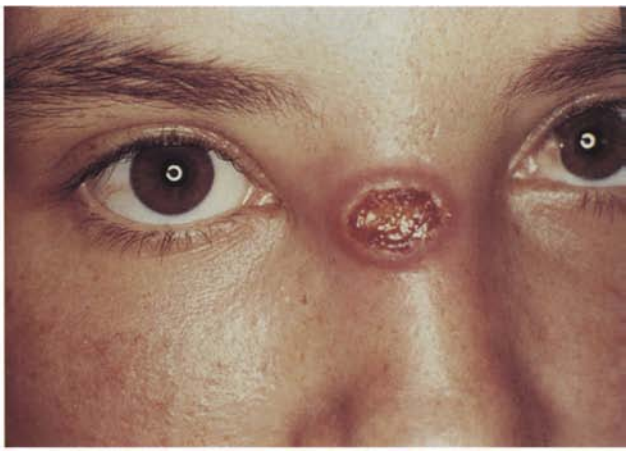

Figure 3. Patient with cutaneous leishmaniasis due to *Leishmania braziliensis* acquired in Brazil. Note the raised borders and ulcerated center of the lesion.

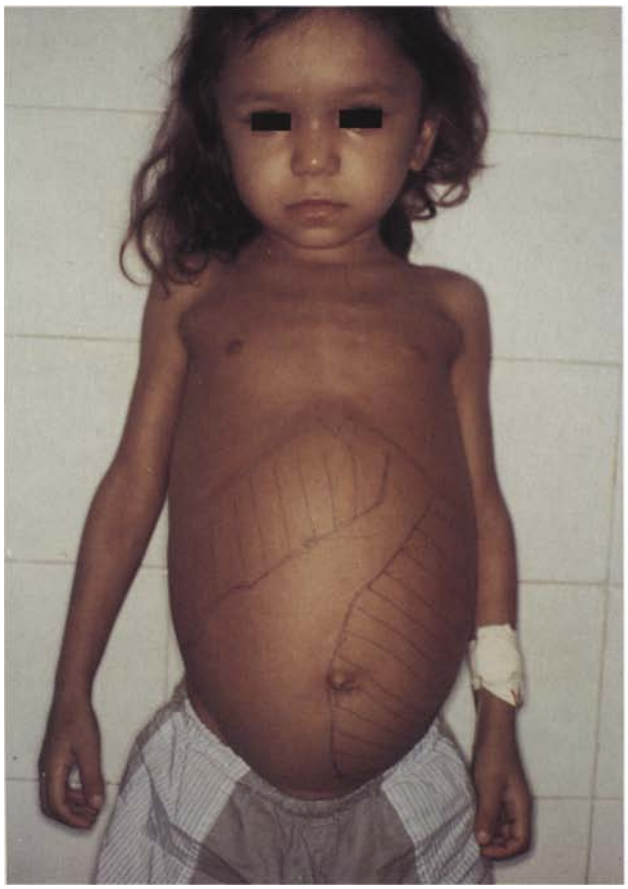

Figure 2. Brazilian patient with visceral leishmaniasis duc to *Leishmania chagasi.* Note wasting as well as hepatosplenomegaly, as outlined.

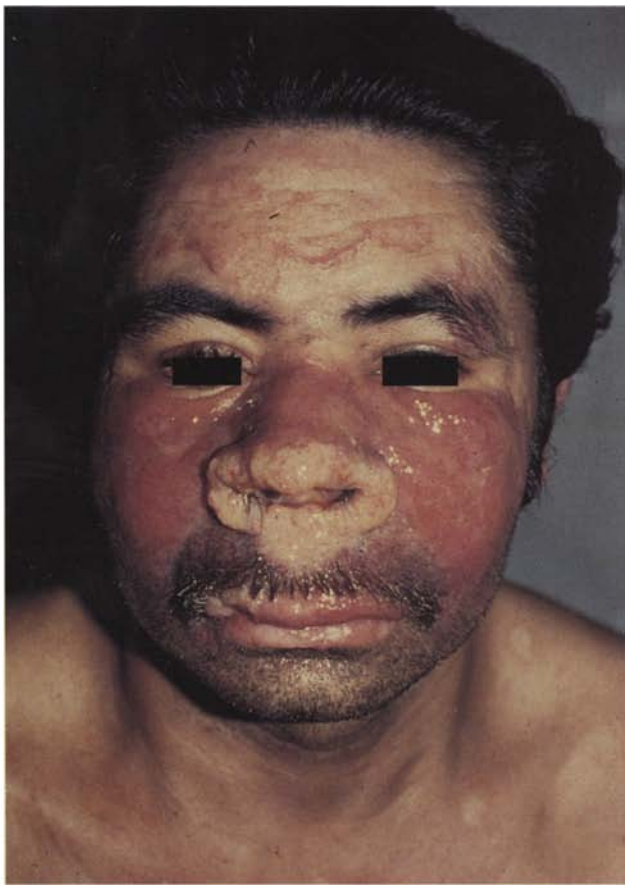

Figure 4. Brazilian patient with mucosal leishmaniasis due to *L. braziliensis.* Note the destructive involvement of the nose, nasal septum, and lips. Reprinted with permission from [31].

Organization reference laboratories. Identification of species by means of kinetoplast DNA hybridization can be done in some research laboratories. Methods based on PCR are being developed to detect species-specific DNA in cultures or directly in tissue.

Leishmania are transmitted by *Phlebotomus* species in Europe, Asia, and Africa and by *Lutzomyia* species in the Americas. Certain sandfly species are found in forests; others are endemic in desert regions; and some are peridomestic, residing in debris or rubble near houses or farm buildings.

Female sandflies, which are modified pool feeders, ingest amastigote-infected macrophages when they attempt to take a blood meal. Amastigotes transform to promastigotes, multiply, and differentiate in the sandfly gut. The life cycle is completed approximately 1 week later when infectious, metacyclic promastigotes migrate to the proboscis and are inoculated as the sandfly attempts to take its next blood meal. Factors in the saliva of the sandfly appear to enhance the infectivity of the promastigotes [11].

In humans, promastigotes attach to one or more macrophage receptors, including the complement receptor CR3, the mannosyl/fucosyl receptor, and the receptor for advanced glycosylation end products [12]. They are subsequently phagocytized by the macrophage and enveloped in a parasitophorous vacuole that fuses with lysosomes. The flagellum is lost, and the parasite shrinks as it becomes an amastigote. Amastigotes multiply and eventually break out of the vacuole to infect other mononuclear phagocytes.

Epidemiology

Visceral Leishmaniasis

Visceral leishmaniasis is typically caused by *L. donovani* in India and Africa and by two closely related species, *L. infantum* in the Mediterranean littoral and *L. chagasi* in Latin America [1]. Cases tend to occur sporadically in rural areas where the organisms are endemic [13], but large epidemics have been associated with famines, mass migration, and civil disturbances [5, 6]. Malnutrition can suppress cell-mediated immune responses and appears to predispose to the development of progressive visceral leishmaniasis in some persons.

On occasion, *Leishmania* species that are predominantly associated with cutaneous disease, such as *L. mexicana* and *L. major,* are isolated from patients with classic visceral leishmaniasis. In addition, a small group of American troops who were infected with *L. tropica* in Saudi Arabia during Operation Desert Storm developed a disseminated viscerotropic syndrome that included some, but not all, of the manifestations of classic visceral leishmaniasis [10].

Old World visceral leishmaniasis. Visceral leishmaniasis due to *L. donovani* is a major problem in eastern India, particularly in Assam and Bihār states, and in Bangladesh [4]. Major epidemics followed the cessation of DDT spraying for malaria. Humans appear to be the only reservoir of this infection. Leishmania are transmitted by *Phlebotomus argentipes,* an anthropophilic sandfly, which probably acquires amastigotes from circulating mononuclear phagocytes in the peripheral blood of persons with visceral leishmaniasis or from macrophages in skin lesions that develop in a subset of patients following chemotherapy (a condition known as post-kala-azar dermal leishmaniasis).

L. donovani is endemic in Ethiopia and the Sudan. A large epidemic of visceral leishmaniasis occurred recently among refugees in the Sudan [5]. *Phlebotomus orientalis* is a vector of the infection in this region; the reservoirs include rodents and small carnivores. Humans may serve as a reservoir during epidemics. In Kenya, *L. donovani* has been associated with termite hills that serve as a resting site for the vector, *Phlebotomus martini,* and possibly other *Phlebotomus* species. The reservoir is uncertain.

Visceral leishmaniasis due to *L. infantum* occurs sporadically in children and immunocompromised persons in southern Europe, the Middle East, and North Africa. Several *Phlebotomus* species have been implicated as vectors. Dogs are the primary reservoir, but foxes and humans have also been implicated. An increasing number of cases of visceral leishmaniasis have been diagnosed in adults with concurrent HIV infection in Spain, southern France, and Italy.

New World visceral leishmaniasis. Visceral leishmaniasis in Brazil, Venezuela, Colombia, and other areas of Latin America typically occurs in rural areas [13], but large urban outbreaks have recently been reported in northeastern Brazil [6]. The majority of cases occur in children <10 years of age. American visceral leishmaniasis is usually caused by *L. chagasi.* Domestic dogs and wild foxes are known to be reservoirs, and the clustering of cases within households suggests that humans may also be a reservoir. *Lutzomyia longipalpis* is the vector. In addition, *L. mexicana* has been isolated from a few patients with classic visceral leishmaniasis.

Visceral leishmaniasis is also endemic in areas of eastern and northeastern China, but the number of cases appears to be small. Dogs are the reservoir.

Cutaneous and Mucosal Leishmaniasis

Cutaneous leishmaniasis is typically a sporadic disease in the areas where it is endemic, but it occasionally follows an epidemic pattern, particularly when large groups of susceptible persons are exposed during military or construction operations or during settlement in the area. Cutaneous leishmaniasis is also diagnosed periodically in Americans or Europeans who have traveled or lived in areas where it is endemic.

Old World cutaneous leishmaniasis. Most cases of cutaneous leishmaniasis in the Mediterranean basin, the Middle East, southern Asia, India, and Africa are caused by three *Leishmania* species: *L. major, L. tropica,* and *L. aethiopica* [1, 14].

L. donovani and *L. infantum* are also occasionally isolated from cutaneous lesions.

L. major is endemic in rodents in rural desert areas in central Asia, the Middle East, and North Africa. It causes cutaneous lesions that tend to be exudative or "wet" and large. The reservoirs are desert rodents, including gerbils and jirds, that live in burrows with *Phlebotomus papatasi* or other *Phlebotomus* species. Infection due to *L. major* has also been reported from sub-Saharan West Africa. The epidemiology there is less clear.

L. tropica is endemic in urban areas of the Middle East, the Mediterranean littoral, India, Pakistan, and central Asia. The lesions are usually "dry," with a central crust. The primary reservoirs are dogs and humans. Sandflies such as *P. papatasi, Phlebotomus sergenti,* and *Phlebotomus chabaudi* are the vectors. A subset of American troops were infected with *L. tropica* during Operation Desert Storm.

L. aethiopica is endemic in the Ethiopian highlands and Kenya, where it causes simple cutaneous leishmaniasis as well as diffuse cutaneous leishmaniasis. Hyraxes (small mammals) serve as reservoirs; *Phlebotomus longipes* is one of the vectors.

American cutaneous and mucosal leishmaniasis. In the New World, cutaneous leishmaniasis is caused by *L. mexicana, Leishmania amazonensis, L. braziliensis, Leishmania panamensis, Leishmania guyanensis, Leishmania peruviana,* and several other species including *L. chagasi* (a species more commonly associated with visceral leishmaniasis) [1, 14, 15]. With the exception of *L. peruviana,* which is found in dogs, the reservoirs are forest rodents. The vectors are ground dwelling or arboreal *Lutzomyia* species. Humans become infected when they work or live in forested areas where the organisms are endemic or when they enter these areas for recreational or military activities.

L. mexicana is found in scattered areas throughout Latin America, extending from Argentina to Texas, where a few cases of autochthonous transmission have been reported [16, 17]. *L. mexicana* tends to produce small chronic ulcers on the face, ears, or other exposed areas. On rare occasions this species is isolated from patients with diffuse cutaneous leishmaniasis. *L. amazonensis* produces cutaneous lesions and, occasionally, diffuse cutaneous leishmaniasis. It is found in jungle areas in the Amazon basin.

L. braziliensis is endemic in many areas of Central America and South America. It is an important cause of uncomplicated cutaneous leishmaniasis, and it produces mucosal disease in a subset of persons who become infected. *L. panamensis, L. guyanensis, L. peruviana,* and several other *Leishmania* species are found in focal geographic areas. *L. panamensis* has been an important problem for American military personnel training in jungle areas of Panama.

Immunology

Leishmaniasis has emerged as a model system for the study of T-cell mediated immunity. A number of recent reviews have described this model [18–20]. The susceptibility of mice to *Leishmania* species is genetically determined; susceptibility to *L. donovani* is controlled by a single gene on chromosome 1, the *Lsh/Ity/Bcg* gene (candidate *Nramp*) [21, 22]. Susceptibility to *L. major* involves several different genes. The genetic determinants of human leishmaniasis have yet to be elucidated.

Leishmania amastigotes multiply in resting macrophages, but they are killed within macrophages activated by interferon-γ [23] or by direct contact with *Leishmania*-specific $CD4^+$ T cells [24]. After exposure to interferon-γ, intracellular killing in murine macrophages occurs by nonoxidative mechanisms through the generation of nitric oxide and its metabolites from L-arginine after induction of nitric oxide synthetase [25].

Although there are differences between mice and humans in terms of the immune response to infection with different *Leishmania* species, several important principles have emerged. Resolution of leishmanial infection and protection against reinfection in susceptible humans and mice is governed by expansion of *Leishmania*-specific helper T cells of the $CD4^+$, Th1 type that produce interferon-γ. When present, these cells activate macrophages to kill intracellular amastigotes. IL-12 appears to play an important role in promoting the development of protective Th1 responses [26]. In the murine model, interferon-γ-secreting *Leishmania*-specific $CD8^+$ cells also contribute to the resolution of *L. donovani* infection.

During progressive systemic infections in mice, there is expansion of $CD4^+$ T cells of the Th2 type that secrete IL-4, but not interferon-γ or IL-2, in response to leishmanial antigens. IL-4 suppresses the development of murine Th1 responses and the activation of macrophages by interferon-γ. In humans with visceral leishmaniasis, IL-10 rather than IL-4 is responsible for the suppression of potentially protective Th1 responses [27]. Leishmania-specific human $CD8^+$ cells have been implicated in stimulating the secretion of IL-10 by peripheral blood mononuclear cells. The chronic nature of cutaneous leishmaniasis appears to be due to the dominance of Th2-like responses at the site of infection in the skin.

The factor(s) that determine whether Th1 or Th2 $CD4^+$ cells dominate during episodes of leishmaniasis have not yet been fully defined. There are data suggesting that the initial cytokine response(s), the size of the infecting inoculum, the manner of antigen presentation by macrophages or other antigen-presenting cells within the context of Class II histocompatibility antigens, and natural killer cells are important. While the presence of IL-12 early in infection promotes the development of Th1 responses, transforming growth factor-β appears to suppress the development of Th1 cells and favors a Th2 response [28].

Clinical Manifestations

Visceral Leishmaniasis

The clinical manifestations of visceral leishmaniasis seem to be similar throughout the world. Studies in Brazil, East

Africa, and Italy indicate that in only a minority of cases do infections with *L. donovani, L. infantum,* or *L. chagasi* progress to classic visceral leishmaniasis (known locally in many areas as kala-azar) [13]. The remainder of these infections are asymptomatic or are associated with mild symptoms that eventually resolve spontaneously when protective immune responses develop [29]. In prospective studies done in areas of northeastern Brazil, where visceral leishmaniasis is hyperendemic, the ratio of *L. chagasi* infections that are progressive to those that are self-resolving among young children (the group most susceptible to visceral leishmaniasis) is ~1:6 [13]. The ratio is lower among older persons and in other areas.

The incubation period for full-blown visceral leishmaniasis is typically 3–8 months, but it has been as short as 10 days or as long as 34 months. This disease has also been diagnosed in persons who become immunocompromised years after they have moved from an area of endemicity.

Classic visceral leishmaniasis, or kala-azar, is characterized by fever, malaise, weight loss, hepatomegaly, and splenomegaly (figure 2). The onset of symptoms is usually insidious, but on occasion it is abrupt and may suggest malaria or other acute infections. The fever may be intermittent, remittent with twice-daily temperature spikes, or less commonly, continuous. Visceral leishmaniasis usually has a protracted course.

On physical examination, the spleen is firm, nontender, and frequently massively enlarged. In Sudanese and Chinese patients with visceral leishmaniasis, peripheral lymphadenopathy may also be present. Patients in India often develop hyperpigmentation—which led to the name kala-azar, meaning black fever in Hindi. Jaundice is occasionally seen. Late in the course of visceral leishmaniasis, patients may develop epistaxis, gingival bleeding, or petechiae, or they may develop edema and ascites secondary to hypoalbuminemia. Severe cachexia, apparently due to the secretion of TNF and other cytokines such as IL-1, develops over time. Measles, diarrhea, bacterial pneumonia, tuberculosis, and other secondary infections are common late in the course of visceral leishmaniasis and frequently contribute to death.

Persons with kala-azar characteristically have anemia, neutropenia, thrombocytopenia, and hypergammaglobulinemia. The anemia is normocytic and normochromic unless the person has underlying iron deficiency for other reasons. The WBC count may be as low as 1,000/mm^3. Eosinopenia is common. The levels of globulins are markedly increased, at times in the range of 9–10 g/dL, as a result of polyclonal B cell activation. Levels of liver enzymes and bilirubin are elevated in some persons.

The differential diagnosis of visceral leishmaniasis is broad. When patients present with a subacute or chronic infection, visceral leishmaniasis must be differentiated from histoplasmosis, lymphoma and other myeloproliferative disorders, miliary tuberculosis, brucellosis, hepatosplenic schistosomiasis, subacute bacterial endocarditis, infectious mononucleosis, or prolonged salmonella bacteremia. Massive splenomegaly, like that observed in patients with visceral leishmaniasis, is also seen in patients with the tropical splenomegaly syndrome that is associated with chronic malaria. Acute visceral leishmaniasis must be differentiated from malaria, typhoid fever, acute Chagas' disease, acute schistosomiasis, amebic liver abscess, and a number of bacterial and viral pathogens that cause febrile diseases.

Visceral leishmaniasis in persons with HIV infection. The majority of persons with concurrent visceral leishmaniasis and HIV infection present in a classic manner with fever, weight loss, and organomegaly, but atypical presentations are also common [7, 8]. Splenomegaly may be absent. Amastigotes have been found in macrophages in the lungs and in pleural effusions as well as in the oral mucosae, esophagus, stomach, small intestine, and skin. In several cases, amastigotes were found in the bone marrow of HIV-infected persons who presented with aplastic anemia. Asymptomatic leishmanial infections have also been reported in patients with concurrent HIV infection.

Viscerotropic leishmaniasis due to L. tropica. A small group of American military personnel who served in Operation Desert Storm developed chronic low-grade fever, malaise, fatigue, and in some instances, diarrhea due to *L. tropica;* infection with this species was previously thought to produce only cutaneous lesions [10]. Leishmania were isolated from the bone marrow specimens of these troops, who did not develop massive splenomegaly, wasting, or the progressive deterioration associated with classic kala-azar.

Post-kala-azar dermal leishmaniasis. A number of persons with visceral leishmaniasis in India and Africa develop post-kala-azar dermal leishmaniasis after treatment. The skin lesions become apparent after the manifestations of visceral disease have resolved. They vary from hyperpigmented macules to frank nodules and contain *L. donovani*–infected macrophages. The lesions develop on the face, trunk, or extremities. In Africa, post-kala-azar dermal leishmaniasis usually develops shortly after treatment and persists for several months [5]. In India, the condition can appear ≤2 years after treatment and persist for as long as 20 years. In a few cases that occurred in India, visceral leishmaniasis recurred in persons with post-kala-azar dermal leishmaniasis.

Cutaneous Leishmaniasis

Leishmania species produce a spectrum of cutaneous disease ranging from single, chronic ulcerative lesions (often referred to as "oriental sores") to disseminated, nonulcerative nodular lesions (a rare syndrome known as diffuse cutaneous leishmaniasis). The clinical characteristics of cutaneous leishmaniasis vary depending on the infecting *Leishmania* species and the host's immune responses. On occasion, a single *Leishmania*

species can even produce lesions with different characteristics in the same person.

The typical lesion first appears as an erythematous papule at the site where promastigotes are inoculated, increases slowly in size, becomes a nodule, and eventually ulcerates. The lesions are often round with raised borders (figure 3). Wet lesions are covered with an exudate and may be complicated by superficial, secondary bacterial or fungal infections. Other lesions are dry, with a central crust. On occasion, cutaneous leishmaniasis has a nodular appearance, suggesting skin cancer. In rare instances, the local lymphatics are involved, mimicking sporotrichosis. Cutaneous leishmaniasis persists for months, and in some cases years, before the lesions heal spontaneously and leave flat, hypopigmented, atrophic scars.

The differential diagnosis of cutaneous leishmaniasis includes nonspecific tropical or traumatic ulcers, venous stasis ulcers, atypical mycobacterial infections, cutaneous tuberculosis, blastomycosis, chromomycosis, sporotrichosis, leprosy, yaws, syphilis, sarcoidosis, lupus vulgaris, and neoplasms.

Persons with *L. braziliensis* infection may have regional lymphadenopathy, fever, and constitutional symptoms before the skin lesion becomes apparent [30]. Amastigotes probably disseminate to distant mucosal sites during this early phase of infection.

Diffuse cutaneous leishmaniasis. Diffuse cutaneous leishmaniasis is a rare, anergic variant of cutaneous leishmaniasis that has been associated with infection due to *L. aethiopica* in Ethiopia, *L. amazonensis* in the Amazon basin, *L. mexicana* elsewhere in Latin America, and a different *Leishmania* species in the Dominican Republic. The disease typically begins as a localized papule that does not ulcerate. Satellite lesions develop around it, and amastigotes eventually disseminate and produce multiple cutaneous nodules on the face and extremities. Diffuse cutaneous leishmaniasis progresses slowly and may persist for decades. Large numbers of amastigotes are present in macrophages throughout the skin.

Leishmaniasis recidivans. This form of the infection, which is most commonly associated with *L. tropica* in the Middle East, is a chronic syndrome in which skin lesions on the face or exposed extremities enlarge slowly, tend to heal in the center, and persist for many years. Examination of biopsy specimens reveals chronic inflammatory changes, and amastigotes are sparse in number.

Mucosal Leishmaniasis (Espundia)

A small percentage of persons infected with *L. braziliensis* in Latin America develop mucosal lesions of the nose, mouth, pharynx, or larynx months to years after the primary skin lesion heals. The disease typically begins with nasal inflammation and stuffiness. Ulceration of the nasal mucosa and perforation of the septum follow (figure 4). In some cases the lips, cheeks, soft palate, pharynx, or larynx are involved, and on rare occasions the trachea or genitalia may be affected. Tissue destruction is thought to be due to a hyperergic immune response [31]. The mortality associated with mucosal leishmaniasis is low, but the disfigurement and resulting morbidity can be substantial.

Mucosal involvement occasionally occurs as a result of infection due to other *Leishmania* species, but it is not clear that the pathophysiology in these infections is the same as that in *L. braziliensis* infection. For example, mucosal involvement secondary to contiguous spread is observed in some persons with leishmaniasis recidivans due to *L. tropica.* Amastigotes have also been found in macrophages in the mucosae of patients concurrently infected with HIV.

Diagnosis

The diagnosis of visceral or cutaneous leishmaniasis, which should be considered for persons in areas where the disease is endemic who present with the classic findings, is frequently delayed and may be missed in immigrants or returning travelers who are evaluated in the United States. The diagnosis may also be difficult to make for persons with concurrent HIV infection who present with atypical signs and symptoms [7, 8].

Leishmaniasis is confirmed by identifying amastigotes in tissue or by growing promastigotes in culture [32, 33]. Leishmania are found in the macrophages in tissue sections; they can be differentiated from intracellular *Histoplasma capsulatum,* which is similar in size, by their kinetoplasts. Amastigotes can also be identified in touch preparations in which tissue is blotted onto slides and stained with Wright's and Giemsa.

Leishmania can be grown as promastigotes in Novy, MacNeal, and Nicolle (biphasic) medium, Schneider's insect medium, or several other tissue culture media to which fetal calf serum has been added. Cultures are incubated at 24–26°C. They become positive within a few days to several weeks. The growth of promastigotes confirms the diagnosis of leishmaniasis and allows subsequent species identification by means of isoenzyme analysis, species-specific monoclonal antibodies, or DNA probes. In the future it is likely that *Leishmania* species will be identified in tissue with use of PCR and species-specific probes [34, 35].

In cases of visceral leishmaniasis, fine-needle aspiration of the spleen for culture and touch preparation is the most sensitive method, yielding a diagnosis in 96%–98% of cases [32]. The procedure is reasonably safe provided that it is done by an experienced operator and the patient has a normal coagulation profile. Examination of bone marrow aspirates results in a diagnosis in more than half of the cases. Alternative approaches include biopsy of the liver or aspiration of enlarged lymph nodes. For persons infected with *L. donovani* in India, cultures of the peripheral blood buffy coat may be positive. In patients with concurrent HIV infection, amastigotes may be found in unexpected sites such as bronchoalveolar lavage fluid or pleural

effusions or in biopsy specimens of mucosal lesions in the oropharynx, larynx, stomach, or intestine.

In cases of cutaneous leishmaniasis, a punch biopsy specimen as well as an aspirate should be obtained from the margin of the lesion after it has been meticulously cleaned. The biopsy specimen should be divided and used for culture, touch preparation, and histopathology [33].

Leishmanial antibody titers can be measured by ELISA, indirect immunofluorescence assay, a direct agglutination test, or several other assays. These antibodies are present at high titers in immunocompetent patients with visceral leishmaniasis; however, persons with concurrent HIV infection may have impaired antibody responses. Troops with viscerotropic leishmaniasis due to *L. tropica* had low or undetectable titers of antibodies. Leishmanial antibodies are measurable in some, but not all, persons with cutaneous leishmaniasis. When these antibodies are present, the titers are usually low. Finally, a positive serological test for leishmanial antibodies provides only presumptive evidence of infection because cross-reacting antibodies may be present in persons with Chagas' disease, leprosy, or other diseases.

The leishmanin test (also known as the Montenegro test), in which crude promastigote antigens are injected into the skin, will be negative in persons with visceral leishmaniasis. This test becomes positive in the majority of persons who receive successful chemotherapy and is also positive in those who have had an asymptomatic, self-resolving infection. This test is positive in persons with simple cutaneous leishmaniasis, leishmaniasis recidivans, and mucosal leishmaniasis. It is negative in persons with diffuse cutaneous leishmaniasis. The leishmania skin test antigen is not approved for use in the United States.

In chronic mucosal lesions due to *L. braziliensis,* amastigotes may be scant and touch preparations, histopathology, and cultures may be negative. A positive skin test, the presence of leishmanial antibodies, a history of exposure in an area where the disease is endemic, and evidence of a healed cutaneous leishmanial lesion allow for a presumptive diagnosis of mucosal leishmaniasis.

Therapy

The pentavalent antimony (SB^v) compounds stibogluconate sodium (Pentostam; Wellcome Foundation, London) and meglumine antimoniate (Glucantime; Rhône Poulenc, Paris) have been the mainstay of therapy for leishmaniasis, but clinical treatment failure is becoming increasingly common in many areas; in addition, these drugs are associated with important adverse effects [36, 37]. Stibogluconate sodium is available in the United States through the Drug Service of the Centers for Disease Control and Prevention in Atlanta (daytime telephone, [404]-639-3670; evenings, weekends, and holidays, [404]-639-2888). It is also used in Europe, Africa, and India. Meglumine antimoniate is available in Latin America and in Francophone countries in Africa.

Stibogluconate sodium and meglumine antimoniate are administered on the basis of their SB^v content. When properly manufactured and stored, they appear to be of comparable efficacy and toxicity. The recommended dosage of SB^v is 20 mg/(kg · d) for 20–28 days, depending on the leishmanial syndrome being treated.

Most patients tolerate SB^v therapy reasonably well, but recent studies have indicated that treatment-induced subclinical pancreatitis is common, and clinically overt pancreatitis develops in some patients [38]. Other side effects include arthralgias, myalgias, nausea, vomiting, abnormalities in liver enzyme levels, pain at the injection site when the drug is given intramuscularly, and ST-T wave changes (as evidenced on echocardiograms). Cardiac toxicity and sudden death have been reported for patients who received more than the recommended dose of SB^v (20 mg/[kg · d]).

Amphotericin B and pentamidine have been the traditional alternative drugs, but both have important side effects. Amphotericin B (0.5–1.0 mg/kg) given every other day for up to 8 weeks or for a total dose of 1.5–2.0 g, has been used successfully to treat patients in whom therapy with SB^v has failed [39]. However, amphotericin B therapy is associated with fever, nausea, vomiting, malaise, anemia, and renal toxicity. Recent studies suggest that liposomal amphotericin B, which is preferentially taken up by macrophages, is effective and may be less toxic than is the standard formulation of amphotericin B [40]. Pentamidine isethionate (2–4 mg/[kg · d]) given for 15 days or over a period of weeks is also effective, but it has significant potential side effects including hypoglycemia followed by diabetes mellitus, hypotension (if administered too rapidly), nausea, vomiting, abdominal pain, and headache.

A number of new drugs and therapeutic approaches are being studied. Although preliminary results appear promising with some, the clinical experience is still not sufficient to warrant their general use.

Visceral leishmaniasis. The response to SB^v therapy is typically not dramatic in persons with visceral leishmaniasis. There is a gradual decrease in the temperature and size of the spleen. Clinical treatment failures and relapses after administration of SB^v are well documented. In some situations therapeutic failures are due to abnormalities in the host's immune system, while in others they are attributable to SB^v resistance in the parasite. Relapses may occur up to 6 months after clinically successful therapy, and close follow-up is necessary. Therapeutic failures are particularly common in patients with concurrent HIV infection. Amphotericin B, given parenterally or experimentally in liposomes, is the principle alternative.

Recombinant interferon-γ plus SB^v has also been used successfully to treat patients with visceral leishmaniasis who failed to respond to SB^v therapy alone [41], but recombinant interferon-γ is currently available only for patients in experimental

protocols. Therapeutic successes and failures have also been reported in a few patients treated with the imidazoles ketoconazole or itraconazole, but the data are limited.

Many patients with visceral leishmaniasis are severely wasted at the time of diagnosis, and attention must be directed to correcting their nutritional deficiencies. Secondary bacterial infections are common and must be treated with appropriate antibiotics. Even with hospitalization, the mortality rate associated with visceral leishmaniasis may be as high as 9% in some areas where the disease is endemic. The prognosis for patients with concurrent HIV infection tends to be poor.

Cutaneous leishmaniasis. Cutaneous lesions that are large or located at cosmetically important sites, as well as those that are due to *L. braziliensis,* should be treated. Cutaneous lesions tend to heal slowly during therapy with SB^v. Small, inconspicuous, or healing lesions caused by *Leishmania* species that are not associated with mucosal disease can be observed expectantly.

Therapeutic failures with SB^v are common in persons with diffuse cutaneous leishmaniasis, leishmaniasis recidivans, and those infected with *L. aethiopica.* Amphotericin B and pentamidine have been the traditional therapeutic alternatives. A number of other therapeutic approaches are under study and have their proponents. Local injections of SB^v have been used successfully in some settings. Topical therapy is an attractive approach for infections due to *Leishmania* species, such as *L. major,* that do not cause mucosal leishmaniasis [42]. Cutaneously applied heat (with close monitoring) has been used effectively in the treatment of cutaneous lesions due to *L. mexicana* and *L. brasiliensis* in Guatemala [43]. Ketoconazole and itraconazole appear to have activity against some *Leishmania* species that produce human disease [44]. Oral allopurinol appeared promising in the treatment of cutaneous leishmaniasis due to *L. panamensis* in one study [45, 46]. Immunotherapy with BCG plus crude promastigote antigens has been reported to be effective in studies from Latin America, but the clinical response was slow [47]. Preliminary data suggest that recombinant interferon-γ and SB^v may be effective in the treatment of diffuse cutaneous leishmaniasis [41].

Mucosal leishmaniasis. The treatment of mucosal leishmaniasis due to *L. braziliensis* is difficult; therapeutic failures and relapses are common when SB^v is given at the recommended dose of 20 mg/kg for 28 days or longer. Patients for whom prolonged or multiple treatment courses have failed are often treated with amphotericin B or pentamidine. Plastic surgery may be necessary to repair the damage associated with mucosal leishmaniasis, but it should be delayed for at least 1 year after administration of clinically successful chemotherapy because skin grafts can be lost if a relapse occurs.

Prophylaxis

Transmission of *Leishmania* species requires the appropriate phlebotomus sandfly vector. Personal protection with insect repellents containing DEET applied to the skin and/or permethrin-treated clothing can reduce the frequency of sandfly bites among visitors to areas of endemicity. Fine mesh netting should be used for protection during sleep. Unfortunately, these measures are seldom practical for residents.

Residual DDT spraying, which was used in malaria control programs in India following World War II, resulted in a dramatic reduction in the incidence of visceral leishmaniasis, but this practice was discontinued because of the adverse environmental impact of DDT and an increase in resistance in mosquitoes. Residual insecticides have been used successfully in other areas where peridomestic transmission of leishmania occurs; however, these chemicals are relatively expensive, must be administered on a regular basis, may have harmful environmental consequences, and can select for resistant arthropods.

Reservoir control has been attempted in some areas. For example, large-scale programs to eradicate *L. chagasi*–infected domestic dogs have been carried out in northeastern Brazil. These programs appear to have lowered the number of cases of human visceral leishmaniasis, but their efficacy has not been documented in a controlled manner, and they are costly. Immunization of domestic dogs, which are a reservoir for *L. chagasi* in Latin America, has recently been proposed as a strategy [48]. Reservoir control is impossible in many areas where rodents or other wild animals are the major reservoirs.

Clinical observations as well as numerous animal studies suggest that the resolution of human leishmaniasis results in high-level, prolonged immunity against the infecting *Leishmania* species. For generations, mothers in the Middle East have exposed the buttocks of their infants to sandflies, knowing that acquisition and healing of infection in this manner could potentially protect their children against disfiguring lesions of the face and other exposed areas. Live *L. major* promastigotes have been injected at inconspicuous sites, usually the buttocks, to produce cutaneous leishmaniasis and induce immunity in troops in Israel and Russia [49]. The practice was effective, but it was discontinued because some of the ulcers were large and persistent and there was concern that viable amastigotes might remain after the lesions clinically resolved.

These observations, along with recent in vitro and in vivo studies of the immunology and molecular biology of leishmaniasis, suggest that it is only a matter of time until an effective leishmanial vaccine(s) becomes available for humans.

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Suggested Readings

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1. *Leishmania* species are transmitted by
   A. Mosquitoes
   B. Reduviid bugs
   C. Tsetse flies
   D. Sandflies
   E. Ticks
2. Resolution of leishmanial infection and protection against reinfection is mediated by
   A. T cell production of IL-10
   B. Leishmania-specific $CD4^+$ cells of the Th1 type
   C. Leishmania-specific $CD4^+$ cells of the Th2 type
   D. Leishmania-specific antibodies
   E. T cell production of IL-4
3. Which cytokine is responsible for activating macrophages to kill amastigotes?
   A. Interferon-α
   B. Transforming growth factor-β
   C. IL-10
   D. Interferon-γ
   E. IL-4
4. Which *Leishmania* species is the most common cause of mucosal leishmaniasis in Latin America?
   A. *L. chagasi*
   B. *L. mexicana*
   C. *L. tropica*
   D. *L. donovani*
   E. *L. braziliensis*
5. Which *Leishmania* species, previously associated with cutaneous lesions, produced viscerotropic leishmaniasis in American military personnel in Saudi Arabia during Operation Desert Storm?
   A. *L. aethiopica*
   B. *L. tropica*
   C. *L. infantum*
   D. *L. donovani*
   E. *L. chagasi*
6. All of the following are typical of progressive visceral leishmaniasis *except*
   A. Hepatomegaly
   B. Splenomegaly
   C. Wasting
   D. Azotemia
   E. Fever
7. The laboratory findings in a patient with progressive visceral leishmaniasis include all of the following *except*
   A. Hypergammaglobulinemia, with gamma globulin levels as high as 10 g/dL
   B. Leukopenia, with a WBC count as low as $1{,}000/mm^3$
   C. Eosinophilia
   D. Thrombocytopenia
   E. Normocytic, normochromic anemia
8. The leishmania (Montenegro) skin test is typically negative in cases of
   A. Visceral leishmaniasis
   B. Mucosal leishmaniasis
   C. Simple cutaneous leishmaniasis
   D. Leishmaniasis recidivans
   E. Asymptomatic *L. donovani* infections that have resolved
9. The most sensitive approach for the diagnosis of visceral leishmaniasis is
   A. Touch preparation, histology, and culture of a skin biopsy specimen

B. Touch preparation and culture of a bone marrow aspirate
C. Histology and culture of a liver biopsy specimen
D. Aspiration of the spleen for touch preparation and culture
E. Touch preparation, histology, and culture of a mucosal biopsy specimen

10. The treatment of choice for most leishmanial infections is
A. Pentavalent antimony (SB^v)
B. Amphotericin B
C. Pentamidine isethionate
D. Arsenic
E. Praziquantel