Leishmaniasis (Cutaneous and Visceral)

Kala-azar, Black Fever, Dum dum Fever, Oriental Sore, Tropical Sore, Uta, Chiclero Ulcer, Aleppo Boi, Pian Bois; Espundia, Leishmaniosis

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Importance

Leishmaniasis is an important complex of protozoal vector-borne diseases that affects both humans and animals. It can be caused by many species of Leishmania. A few of these organisms are primarily maintained in humans, but most circulate mainly in animals. Most of the latter organisms are zoonotic. Leishmaniasis is transmitted by sandflies and can be difficult to prevent, and some of the drugs used for treatment have significant side effects or limited availability outside endemic regions.

In humans, leishmaniasis has three general forms – cutaneous, mucocutaneous and visceral – and different species of Leishmania tend to cause each type. Cutaneous leishmaniasis, a form that typically remains limited to the skin, can be caused by numerous organisms. A few species of Leishmania regularly affect the mucous membranes, as well as the skin. Both cutaneous and mucocutaneous leishmaniasis may result in disfigurement, but mucosal involvement is generally more serious. Two organisms, L. donovani and L. infantum, cause most cases of visceral leishmaniasis, the most serious form. Visceral leishmaniasis is characterized by damage to the internal organs, and fully symptomatic cases are considered life-threatening.

Leishmania can also cause skin and mucosal lesions and/or visceral signs in animals. Most species of Leishmania are maintained in wildlife, often without clinical signs, but dogs are an important reservoir host for L. infantum. Dogs are also the domesticated animal most often affected by leishmaniasis. Clinical cases in this species can be life-threatening, and may be difficult to treat. Cases of leishmaniasis are also seen occasionally in guinea pigs, cats, equids, and captive or free-living wild species. Ruminant livestock are rarely affected.

Etiology

Leishmaniasis can be caused by many species of Leishmania, a protozoan parasite in the family Trypanosomatidae (order Kinetoplastida). Approximately 30 species have been described in mammals. Most of these organisms are known to affect humans and/or domesticated animals, but a few species have only been found in wild animals, to date. Additional species of Leishmania infect reptiles (lizards) or have only been detected in insects so far.

The genus Leishmania contains two subgenera, Leishmania and Viannia. The species that tend to cause human visceral leishmaniasis mostly belong to Leishmania, while organisms causing cutaneous leishmaniasis occur in both subgenera. A third subgenus, Mundinia, has been proposed for the L. enriettii complex, which seems to differ somewhat from other Leishmania in its epidemiology. The L. enriettii complex currently contains L. enriettii, L. macropodum (formerly “L. australiensis”), L. martiniquensis, “L. siamensis” (proposed name; not formally described) and an unnamed Leishmania recovered from people in Ghana. “L. siamensis” from human and animal clinical cases have mostly been reclassified as L. martiniquensis, but this organism was also identified as a distinct species in Thailand.

The classification of Leishmania is complex and, in some cases, controversial; more than one species name may be used for an organism, and some names may eventually be invalidated. Recent genetic analyses indicate that some organisms currently considered to be separate species (e.g., L. infantum and L. donovani) should be reclassified as subspecies of a single organism, and others should be renamed. Because this new system is likely to be confusing for clinicians, this factsheet continues to use the older traditional taxonomy.

Leishmania species that cause human visceral and cutaneous leishmaniasis

Human visceral leishmaniasis is mainly caused by Leishmania donovani and L. infantum. At one time, two different names were used for the latter organism - L. infantum in the “Old World” (Eastern Hemisphere) and L. chagasi in the “New World” (Western Hemisphere). However, L. chagasi is now considered to be a subspecies of L. infantum. L. donovani also contains some organisms previously given individual names, such as L. archibaldi and L. killicki. Visceral leishmaniasis is occasionally caused by other species, including organisms that are normally associated with...
cutaneous leishmaniasis (e.g., *L. tropica*, *L. braziliensis*, *L. amazonensis* and *L. martiniquensis*), as well as *L. colombiensis* and “*L. siamensis.*” Some cases caused by non-traditional organisms seem to occur when a skin-tropic *Leishmania* invades the viscera in a person who is immunosuppressed.

In the Western Hemisphere, *Leishmania* species that cause human cutaneous leishmaniasis include the members of the *L. braziliensis* complex (e.g., *L. braziliensis*, *L. panamensis*, *L. guyanensis*, *L. shawi* and *L. peruviana*), and the *L. mexicana* complex (e.g., *L. mexicana*, *L. amazonensis*, *L. venezuelensis*), as well as *L. lainsoni*, *L. naiffi* and *L. lindenbergi*. The species that cause cutaneous leishmaniasis in the Eastern Hemisphere include *L. tropica*, *L. major* and *L. aethiopica*, which are all members of the *L. tropica* complex. *L. martiniquensis*, *L. colombiensis* and an unnamed member of the *L. enriettii* complex in Ghana have been detected in a few cases. The viscerotropic organisms *L. infantum* and *L. donovani* also occur occasionally in cutaneous leishmaniasis without visceral involvement. In some cases, this seems to be caused by a specific *L. infantum* or *L. donovani* variant restricted to a localized area.

Mucocutaneous leishmaniasis in the Western Hemisphere is usually caused by *L. braziliensis*, and to a lesser extent, by *L. panamensis*, *L. guyanensis*, *L. amazonensis* and *L. peruviana*. *L. infantum*, *L. donovani*, *L. tropica*, *L. major* and *L. aethiopica* occasionally affect mucous membranes in the Eastern Hemisphere.

**Leishmaniasis in animals**

Many of the organisms that cause leishmaniasis in humans have also been found in clinical cases in animals. Two additional species, *L. macropodum* and *L. enriettii*, affect animals but have not been found, to date in humans. The distinction between cutaneous and visceral syndromes is not seen in animals, at least with *L. infantum*. Because dogs are important reservoir hosts for *L. infantum*, “canine leishmaniasis” generally refers to infections with this organism. However, dogs can also be infected by other *Leishmania* species.

**Species Affected**

With two significant exceptions (*L. donovani* and *L. tropica*), *Leishmania* are maintained primarily in animals. While infections are common, clinical cases have been reported in fewer host species. This does not imply that other species cannot be affected, particularly as the *Leishmania* found in sick animals are rarely identified to the species level.

**Reported infections and animal reservoir hosts**

Each species of *Leishmania* has one or more primary reservoir hosts, although it can also infect other animals. In sylvatic cycles, an organism may sometimes be maintained by circulating in more than one host species. Knowledge about reservoir hosts for *Leishmania* is still incomplete and sometimes speculative.

*L. infantum* is the best understood *Leishmania* in animals. Dogs are major reservoir hosts for this organism. Wildlife reservoirs also seem to be significant in some areas. Canids that may maintain *L. infantum* include red foxes (*Vulpes vulpes*) in Europe, and crab-eating foxes (*Cerdocyon thous*), bush dogs (*Speothos venaticus*) and other species in South America. Wild hares (*Lepus* spp.) may be reservoir hosts in parts of Europe and China, and rodents might maintain this organism on a Mediterranean island where dogs are absent. *L. infantum* can also infect a wide variety of other mammals, at least occasionally. Infections have been reported in domesticated cats and equids, numerous free-living or captive wild canids, various captive felids in zoos, genets (*Geneta geneta*), raccoon dogs (*Nyctereutes procyonoides*), wild rabbits (*Oryctolagus cuniculus*), opossums (e.g., white-eared opossums, *Didelphis albiventris*), Egyptian mongooses (*Herpestes ichneumon*), the lesser anteater (*Tamandua tetradactyla*), Algerian hedgehogs (*Atelerix algirus*), rodents, a seal and some species of bats. Cats might help maintain or amplify *L. infantum* in some areas, but they are thought to be incapable of maintaining it in the absence of canine reservoirs.

Known reservoir hosts for the Old World species that cause human cutaneous leishmaniasis include gerbils, jirds and other rodents for *L. major*, and members of the Hyracoidea (hyraxes) for *L. aethiopica*. *L. major* has also been found occasionally in other animals, such as dogs, a least weasel (*Mustela nivalis*), and two hedgehog species (*Atelerix algirus* and *Paraechinus aethiopicus*). The organisms that cause cutaneous leishmaniasis in the Western Hemisphere are maintained in sylvatic cycles, often among wildlife in forests. *L. braziliensis*, *L. guyanensis*, *L. panamensis*, *L. colombiensis* and *L. shawi* have been found in sloths (*Bradypus* spp. and *Choloepus* spp.), which might be reservoirs for some of these organisms. Marsupials in South America (e.g., members of the opossum genus *Didelphis*) can be infected with several New World *Leishmania* species, and are potential reservoirs for some species including *L. naiffi*. Rodents are thought to be reservoir hosts for several New World species including *L. mexicana*, *L. amazonensis*, *L. panamensis*, *L. braziliensis* and *L. lainsoni*. *L. mexicana* has also been found in opossums (*Philander opossum*) and bats in Mexico; *L. amazonensis* in various South American marsupials, bats, non-human primates, kinkajous (*Potos flavus*), skunks (*Conopatus chinga*), the lesser anteater and the crab-eating fox; and *L. braziliensis* in various wild carnivores, rodents, bats, perissodactyly and nonhuman primates, as well as dogs, cats and equids. The host range and reservoir hosts for *L. peruviana*, *L. venezuelensis*, and some members of the *L. enriettii* complex are poorly understood. *L. peruviana* has been detected in dogs, but they may have only a minor role in maintaining this organism. *L. martiniquensis* was found in black rats (*Rattus rattus*), in addition to causing a few clinical cases in livestock. There are also some reports of antibodies to
Leishmania spp. in various ruminants, and a Leishmania-infected pig was documented in South America.

*L. tropica* is primarily maintained in humans, but parasitological evidence of infection has been reported occasionally in animals such as cats, golden jackals (*Canis aureus*), foxes and rodents. The rock hyrax (*Procavia capensis*) was implicated as a potential reservoir host for *L. tropica* in Israel. *L. donovani*, likewise, primarily infects humans, but occasional serological and/or parasitological evidence suggests the possibility of infections in dogs, goats, cattle and other domestic animals, as well as wild rats and mongooses.

Little is known about the ability of mammalian Leishmania to infect other vertebrates. One study found antibodies to these organisms in geese and a pheasant (*Phasianus colchicus*), but not chickens or small numbers of Muscovy ducks and guinea fowl. Chickens were not susceptible to experimental infection. The *Leishmania* species that infect lizards seem to be distinct from those that infect mammals.

**Clinical cases in animals**

Among domesticated animals, dogs are the species affected most often by leishmaniasis. *L. infantum* is thought to be responsible for most clinical cases, but other organisms including *L. mexicana*, *L. colombiensis*, *L. amazonensis*, *L. braziliensis*, *L. panamensis*, *L. guyanensis*, *L. peruviana*, *L. major* and *L. tropica* have also been found. Some species, such as *L. major* and *L. tropica*, are detected only rarely. *L. infantum*, *L. mexicana*, *L. venezuelensis*, *L. braziliensis* and *L. amazonensis* have been found, to date, in cats with leishmaniasis. Cases of leishmaniasis are also seen occasionally in equids, with *L. infantum*, *L. braziliensis* and *L. martiniquensis* (which was originally identified as “*L. siamensis*”) reported as the causative organisms in some instances. *L. enriettii* is only known to affect guinea pigs in nature, but experimentally infected hamsters also develop mild lesions. Leishmaniasis is not a significant disease in ruminant livestock, but rare, isolated cases of cutaneous leishmaniasis have been reported in sheep, goats and cattle. The species of *Leishmania* was not identified in most of these cases, but *L. martiniquensis* (originally identified as “*L. siamensis*”) affected a cow in Europe. Sheep and pigs that were experimentally infected with *Leishmania* did not become ill.

Clinical cases are reported occasionally in free-living or captive wild animals. Illnesses have been documented in non-human primates, various canids (e.g., bush dogs, hoary zorros [*Eucalopex vetulus*], gray wolves [*Canis lupus*], maned wolves [*Chrysocyon brachyurus*]) and felids (a captive lion, *Panthera leo*, infected with *L. infantum*). Leishmaniasis was reproduced experimentally in crab-eating foxes and red foxes. *L. macropodum* causes cutaneous lesions in captive kangaroos, wallaroos and wallabies in Australia, but captive Bennett’s wallabies (*Macropus rufogriseus rufogriseus*) in some other countries were affected by *L. infantum*.

**Zoonotic potential**

Humans are affected by *L. tropica*, *L. donovani* and most species of *Leishmania* maintained in mammals, and they are the primary reservoir hosts for *L. tropica* and *L. donovani*. As of 2017, *L. enriettii* and *L. macropodum* have not been reported in people.

**Geographic Distribution**

With the exception of Antarctica, *Leishmania* spp. have been found on every continent. These organisms are most prevalent in tropical and sub-tropical regions, although they also occur in other areas. Clinical cases in people are reported mainly in Africa, parts of Asia, the Middle East, Latin America and the Mediterranean region. In Europe, leishmaniasis appears to be spreading gradually northward from its traditional foci in the south (e.g., to previously unaffected parts of northern Italy).

*L. donovani* causes visceral leishmaniasis in South Asia (the Indian subcontinent) and Africa, while *L. infantum* causes this disease in the Mediterranean, the Middle East, Latin America and parts of Asia. In the Eastern Hemisphere, cutaneous leishmaniasis is mainly caused by *L. major* in Africa, the Middle East and parts of Asia; by *L. tropica* in the Middle East, the Mediterranean and parts of Asia; and by *L. aethiopica* in parts of Africa. An unnamed member of the *L. enriettii* complex was also found in human cutaneous leishmaniasis in Africa (Ghana). In the Western Hemisphere, cutaneous leishmaniasis can be caused by many species of *Leishmania*, and is mainly seen in Mexico and Central and South America. There is also a focus of *L. mexicana* in the U.S. It affects parts of Texas, and has recently expanded to involve southern Oklahoma. *L. martiniquensis* has been reported in people in Thailand, Myanmar and the Caribbean, in a cow in Europe, and in horseshoes in Europe and North America. “*L. siamensis*” has been documented in Thailand; other cases attributed to this organism appear to be *L. martiniquensis*.

In a few locations, a *Leishmania* species causes disease in animals, but no clinical cases have been described in humans. Examples include *L. enriettii* in South America and *L. macropodum* in Australia. Likewise, canine leishmaniasis caused by *L. infantum* and occurring mainly in foxhounds has been reported in a number of U.S. states and parts of Canada. There is no evidence that humans or sandflies in the U.S. have been infected by this organism, and there are no virologically confirmed infections in wild canids. Some surveys also did not detect any seropositive wild animals. However, one group reported that wild canids rarely had low antibody titers to *Leishmania* in Pennsylvania and North Carolina.

Imported cases of leishmaniasis can be seen in areas where *Leishmania* spp. are not endemic. If appropriate insect vectors are not present, these organisms usually do
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not become established in the country. A few sporadic cases have been reported in people or animals that never left a Leishmania-free country or area, including northern France, Germany, Switzerland, Austria, Hungary, Romania, Finland, the Netherlands, the U.K., South Korea and the northern U.S. (South Dakota). Small focal populations of infected sandflies could account for some of the incidents in Europe, but other mechanisms (e.g., vertical transmission or contact with the blood of infected animals) are suspected in others.

Transmission

Vectors

The Leishmania that infect mammals are usually transmitted by phlebotomine sandflies in the genera Phlebotomus and Lutzomyia, which act as biological vectors. Each species of Leishmania is adapted to development in specific species of sandflies. Members of the L. enriettii complex might be an exception to sandfly-mediated transmission: some evidence suggests that biting midges might be the most important vectors for these organisms. For instance, L. macropodum has been found in midges of the genus Forcipomyia, but not in sandflies.

Sandfly activity mainly occurs when it is humid and there is no wind or rain. These insects are generally most active at dawn, dusk and during the night (especially early in the night), but they will bite if they are disturbed in their hiding places during the day. Common hiding places include animal burrows, holes in trees, caves, houses and other relatively cool, humid locations. Sandflies are attracted to light and may enter buildings at night. Most species do not fly long distances, but there are a few reports of sandflies traveling > 1 km. Transovarial transmission of Leishmania does not seem to occur in sandflies, but in areas with cold temperatures, the parasite can overwinter in infected mammals.

Other arthropods, including Culicoides sp., midges, ticks (e.g., Dermacentor variabilis and Rhipicephalus sanguineus), and canine fleas have been suggested as possible mechanical vectors for some Leishmania. They are probably unimportant in the epidemiology of leishmaniasis in endemic areas; however, fleas and ticks might be involved in rare dog-to-dog transmission of L. infantum where competent biological vectors are absent.

Mammals

Both symptomatic and subclinically infected mammals can infect sandflies. Whether infected animals and people can clear Leishmania completely from the body, and under what circumstances, is still under investigation. However, animals and humans can be infected asymptomatically for long periods, and they may remain chronically infected even after clinical cure. There are reports of probable transmission via blood transfusions in people and dogs, via shared needles by intravenous drug users, and by transplacental transmission in dogs (L. infantum), mice (L. mexicana) and humans (L. infantum). Human newborns can be infected whether or not the mother was symptomatic. Vertical transmission is suspected to be an important mechanism for maintaining L. infantum among foxhounds in the U.S.

Direct horizontal transmission also appears possible in some circumstances, although it is rare. In L. infantum-infected dogs, the parasites and/or their nucleic acids can sometimes be found in saliva, urine, semen and conjunctival secretions, as well as in blood and mammary glands (though they have not been detected, to date, in milk). L. infantum has occasionally been transmitted between dogs in the same household or kennel in the absence of sandflies. Case histories suggest that some of these animals might have been infected during a fight, by licking a companion’s lesions, or by ingesting blood during a hemorrhage. Venereal transmission has been reported in dogs (L. infantum) and experimentally infected mice. Venereal transmission of L. infantum was also documented in humans, but seems to be rare.

Disinfection

Leishmania spp. do not remain viable outside a host or in vitro culture. In situations where disinfection is appropriate, they can be inactivated by agents such as 1% sodium hypochlorite, 70% ethanol, 0.1% hand soap, 2% glutaraldehyde, or formaldehyde. They are also susceptible to heat of 50-60°C (122-140°F).

Infections in Animals

Incubation Period

Infected animals often remain asymptomatic for long periods or indefinitely, but these animals may develop leishmaniasis at any time. In dogs that become ill, the incubation period for L. infantum usually ranges from months to years.

Clinical Signs

Dogs

The signs of leishmaniasis in dogs are variable and can mimic other illnesses. L. infantum is the best understood species. This organism can cause cutaneous signs, visceral signs or both simultaneously. Clinical cases range from mild to severe, and many infected dogs remain asymptomatic.

Common visceral signs include lethargy, weight loss, a decreased appetite, anemia, splenomegaly and local or generalized lymphadenopathy. Fever can be intermittent, and is absent in many cases. Chronic renal disease is common in dogs infected with L. infantum; it may be the only syndrome, and it is often the cause of death. Dogs can also develop bleeding disorders, such as epistaxis, hematuria and melena. Profuse epistaxis was the only presenting sign in some cases. In addition, there may be sneezing, vomiting, intestinal signs (chronic diarrhea from small or large intestinal involvement, chronic colitis,
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chronic gastritis), chronic hepatitis, osteolytic and osteoproliferative bone lesions, orchitis, chronic prostatitis, autoimmune disorders and cardiovascular signs. Some dogs develop erosive or (more commonly) nonerosive arthritis, which can affect one to multiple joints. Chronic polyarthritis can cause progressive muscle atrophy. Neurological signs (e.g., gait abnormalities, disorientation, seizures, atypical behavior) have been reported rarely, and may be caused by meningoencephalitis, meningitis, parasite infiltration of the spinal cord, peripheral neuropathy, serum hyperviscosity-induced hypoxia and other lesions. Unusual presentations (e.g., chronic diarrhea, with or without vomiting as the primary syndrome, or nodular glossitis alone) are occasionally reported. Reproductive losses (abortions, stillbirths) have been reported in a few infected bitches, but many congenitally infected pups seem to be asymptomatic initially, and can remain so for months to years until they become immunosuppressed from another cause.

Skin lesions are common in dogs with visceral disease, but they can also occur separately. The most common cutaneous syndrome in *L. infantum*-infected dogs is a non-pruritic, exfoliative dermatitis, seen especially around the eyes and on the face, ears and/or feet. There may be areas of alopecia, especially around the eyes, and silvery white scales in these areas. Some dogs with leishmaniasis have other skin lesions, including nodules, papules, ulcers and/or scabs. A distinctive papular dermatitis, with solitary to multiple papules, has been reported in some regions. This condition seems to be mild, and does not appear to be accompanied by visceral involvement. Atypical skin lesions including sterile pustular rashes (which may be pruritic), panniculitis, depigmentation, erythema multiforme, digital and nasal hyperkeratosis, and cases that resemble alopecia areata or pemphigus foliaceus have been reported. Dogs with cutaneous signs can also have abnormally long and brittle nails. Mucosal lesions consisting of ulcers, nodules, papules or masses may also be seen, with or without skin lesions. Secondary bacterial infections are common in skin and mucosal lesions.

Ocular signs can occur with or without systemic signs, and may be seen before or after treatment. The most common abnormalities are blepharitis, conjunctivitis, keratitis and anterior uveitis. Some animals develop multiple granulomas on the eyelid margins, nictitating membrane margins, conjunctival limbus or cornea or in the anterior chamber. Sequelae may include glaucoma, keratoconjunctivitis sicca, corneal pigmentation, iris atrophy, cataracts, retinal detachment, panophthalmitis or phtisis bulbi.

Without treatment, leishmaniasis is usually slowly progressive in clinically affected dogs. One study suggested that most symptomatic dogs have only relatively subtle signs such as lymphadenopathy, thrombocytopenia and/or mild non-regenerative anemia, with or without weight loss, during the first 2 years after they are infected with *L. infantum*. Other lesions, including skin and ocular signs, were generally uncommon during this time, although a small number of dogs did become severely ill soon after exposure, with multiple signs of leishmaniasis.

Infections with other species of *Leishmania* are not as well understood, but seem to be clinically similar. Dogs infected with *L. major*, *L. braziliensis*, *L. panamensis*, *L. guyanensis* and some other species presented with skin lesions. Visceral and cutaneous signs have been reported in dogs in Texas, where *L. mexicana* is endemic, while dogs inoculated experimentally with *L. mexicana* developed cutaneous signs in the short term. *L. colombiensis* and *L. amazonensis* were found in a few cases characterized by visceral signs, and visceral, skin and mucosal involvement were reported in a few dogs infected with *L. tropica*.

**Cats**

Cats occasionally develop leishmaniasis, although most infected cats are thought to remain asymptomatic. Skin and/or mucosal lesions are described most often, with or without visceral signs. However, visceral signs can occur without cutaneous involvement.

In cats, skin lesions tend to occur on the nose, ears, eyelids or lips, but they can also be found on other sites such as the paws. Localized nodules, papules and chronic crustated or ulcerated lesions are seen most often, and may be accompanied by regional lymphadenopathy. Alopecia, scales and hemorrhagic pustules or nodules have been reported infrequently. The initial lesions are often single, but they can be multiple, and may sometimes disseminate. Oral and/or nasal lesions, and rare involvement of other mucous membranes (e.g., anal mucosa) have been described. Ocular signs, especially unilateral or bilateral uveitis (which can progress to panophthalmitis), conjunctivitis and blepharitis, can occur in some cats.

Visceral lesions and signs reported in cats include fever, hepatomegaly, jaundice, vomiting, diarrhea, lymphadenopathy, dyspnea, nasal discharge, anemia and leukopenia. Some affected cats had moderate to severe pancytopenia, but some of these animals were also infected with FIV. One cat had a history of abortion.

Both fatal cases and spontaneous cures have been reported in cats. There is also one report of recurrent skin lesions, refractory to treatment, in an otherwise healthy, *L. mexicana*-infected cat.

**Equidae**

Horses, mules and donkeys sometimes develop skin lesions, particularly on the head, neck, legs and axillary or inguinal regions. The most common lesions are solitary or multiple papules or nodules, which are often ulcerated. Disseminated skin disease has also been reported. Visceral leishmaniasis has not been documented in equids; however, parasites were found in the bone marrow of one horse in South America, and nucleic acids of *L. braziliensis* were identified in the blood of another animal.
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Other domesticated animals

Clinical cases have rarely been described in cattle or small ruminants. Skin lesions, sometimes accompanied by lymphadenopathy, were the only clinical signs reported in sheep, a goat and cattle. A pregnant cow infected with *L. martiniquensis* in Germany had multiple ulcerative or plaque-like skin lesions on several areas of the body. It recovered completely after giving birth. Experimentally infected sheep had no clinical signs except an elevated temperature. Experimentally infected pigs remained asymptomatic.

*L. enriettii* has been detected rarely in skin lesions, often on the ear, in naturally infected guinea pigs. In experimentally infected animals, the initial lesions appear as redness and swelling, but grow rapidly into large, ulcerated, tumor-like masses. Some studies found that secondary lesions developed at other sites, including the skin, lip and genitalia, but others reported that the lesions did not spread. Parasites were also detected in some internal organs. Some studies, but not others, reported spontaneous healing. Hamsters seem to be less susceptible to experimental infection with *L. enriettii*, and developed non-ulcerated nodules, which healed without treatment.

Captive wild species and wild animals

The few reported cases in free-living or captive wild canids have resembled leishmaniasis in dogs. Visceral involvement with nonspecific signs (e.g., pale mucous membranes, weight loss) was reported in some nonhuman primates. A lion had clinical signs of colitis and bloody diarrhea, epistaxis, weight loss and ulcers on the footpads. Captive Australian marsupials infected with *L. martiniquensis* have developed skin lesions consisting of focal to coalescing areas of thickened skin, or raised crusty or ulcerative pale nodules. In the wild, skin lesions have been found in some rodents infected with members of the *L. mexicana* complex. These lesions are described as swellings with hair loss or ulcers. They were reported to be most common at the base of the tail, but sometimes also occurred on the ears or toes. Subclinical infections have been reported in many species.

Post-Mortem Lesions

The gross lesions are highly variable and may be minimal in some cases. In canids, lesions may include cachexia, signs of anemia, generalized lymphadenopathy, hepatosplenomegaly, areas of alopecia with desquamation on the head and trunk, and cutaneous ulcers or nodules. Ulcers and petechiae are occasionally seen on the mucous membranes, and in some cases, hemorrhages may be evident in internal organs. Small, light colored nodular foci (granulomas) may be found in a variety of organs, including the kidney, liver and pancreas. In experimentally infected dogs, fetuses had no lesions despite the presence of parasites in their tissues.

Diagnostic Tests

*Leishmania* parasites and their nucleic acids may be found in lesions, secretions, blood and various tissue samples. Samples from the bone marrow, lymph nodes, spleen and skin, as well as conjunctival swabs, are reported to be especially sensitive for PCR testing in dogs. Other types of noninvasive samples, such as oral, nasal or vulvar swabs, have also been investigated in dogs, but their usefulness has not been extensively evaluated. Skin biopsies in uninfected dogs can sometimes contain nucleic acids transiently if the animal was bitten by an infected sandfly.

Leishmaniasis may be diagnosed by direct observation of the parasites in skin scrapings from lesions, or lymph node, spleen, and bone marrow aspirates, using Giemsa, Wright’s, Leishman’s or other stains. *Leishmania* amastigotes are round to oval parasites, with a round basophilic nucleus and a small rod-like kinetoplast. They are usually found in macrophages or freed from ruptured cells. Parasites are sometimes undetectable even in clinical cases, and they are often absent in asymptatically infected animals. Histopathology with immunohistochemistry may help detect *Leishmania* when few parasites are present.

PCR assays can detect nucleic acids in tissues. Most of these tests cannot identify *Leishmania* to the species level, and even those designed to amplify a single species, such as *L. infantum*, may also amplify others. However, PCR can be combined with other techniques, such as restriction fragment length polymorphism (RFLP) analysis or sequencing, for species identification. Improved species-specific PCR assays that do not require additional steps have also been published. Rapid point-of-care tests, such as lateral flow or loop-mediated isothermal amplification (LAMP) assays, are in development.

Leishmaniasis can be diagnosed by culturing the organism, although this is not done routinely. Some species can be difficult to isolate. Culture generally requires 5 to 30 days. Animal inoculation (hamsters) was occasionally used in the past when the parasite was difficult to find, but it has been generally been replaced by PCR.

Sick dogs with visceral involvement usually have high antibody titers to *Leishmania*; however, antibodies may be absent in some animals with only localized skin lesions. Asymptomatic dogs that were exposed, but appear to have eliminated the parasite, and subclinically infected dogs usually have only low titers. The most commonly used serological tests are the indirect fluorescent antibody test (IFA), ELISAs and rapid immunochromatographic assays (rK39 dipstick or strip-test). Other assays (e.g., direct agglutination, counterimmunoelectrophoresis, complement fixation, indirect hemagglutination, latex agglutination, immunodiffusion or immunoblotting) have more limited availability, or were used more often in the past. Cross-reactions can occur with other parasites, particularly *Trypanosoma cruzi*. Cross-reactions are more common in tests that use crude antigen preparations. Routine serological
tests cannot reliably distinguish vaccinated dogs from infected dogs, although some tests may tend to be negative in vaccinated dogs. The delayed hypersensitivity (leishmanin) test, which is used in humans, is not useful for diagnostic purposes in dogs.

Treatment

Treatment can produce clinical improvement, especially in mild to moderate cases. However, it may not eliminate the parasite and relapses are possible. Pentavalent antimonials are often used where they are available. Outside endemic regions, these drugs can sometimes be obtained from government agencies or other sources. In the U.S., they are provided through the Centers for Disease Control and Prevention (CDC). Other drugs used in humans (e.g. miltefosine, allopurinol, amphotericin B) can also be employed (provided the animal species is not unusually susceptible to the agent’s side effects). Allopurinol has been used as a maintenance drug to prevent relapses, but prolonged or indefinite treatment may be required. Drug-resistant Leishmania are common in some areas.

Immunomodulatory agents have been tried, in conjunction with anti-Leishmania drugs, but there is currently no clear evidence for their efficacy. In areas where leishmaniasis is not endemic, euthanasia may be considered to decrease the risk of transmission to humans, particularly if a competent sandfly vector is present.

Topical treatments have been uncommonly described in animals, but radio-frequency induced heat therapy was successful in two dogs with multiple localized mucocutaneous lesions on the snout. Cutaneous lesions did not return after surgical resection in some animals, including some cats and a number of horses; however, surgical resection alone was ineffective in other cases.

Control

Disease reporting

Veterinarians who encounter or suspect leishmaniasis should follow their national and/or local guidelines for disease reporting. Leishmaniasis in animals may be reportable in some states in the U.S.

Prevention

Keeping susceptible animals, indoors between dusk and dawn, especially during the warmer months, can reduce their exposure to sandflies. Insecticide-impregnated collars or topical insecticides (spot-on preparations, sprays) are reported to decrease sandfly bites in dogs. Some collars also appear to be effective in cats. Kennels and homes may be sprayed with insecticides, and insecticide-treated door and kennel nets and curtains may help keep sandflies out. These insects are tiny and can get through untreated mesh unless it is extremely fine. Because sandflies are poor fliers and are deterred by wind, fans may also be helpful. Habitat modifications to remove or dry out moist sandfly breeding areas around the home can also be considered. A Brazilian study reported that increasing the amount of sun in yards (i.e., pruning trees), together with the removal of moist piles of vegetation, appeared to be helpful.

Due to the risk that some puppies will be born infected, it is not considered advisable to breed from infected dogs, whether or not they are asymptomatic. Dogs used as blood donors in endemic areas should be tested for subclinical Leishmania infections. Canine vaccines for L. infantum are available in some countries. Some vaccines are reported to decrease the incidence of clinical cases and/or reduce the number of infections. However, protection is not absolute (dogs can sometimes become infected), and infected vaccinated dogs can transmit the organism to sandflies.

Morbidity and Mortality

When the densities of both dogs and sandflies are high, L. infantum can spread widely and rapidly. In some endemic areas, up to 63-80% of the canine population has been exposed to this organism. Studies suggest that some dogs bitten by infected sandflies can eliminate L. infantum, but others remain subclinically infected. Only a small percentage of the latter group seems to become ill. Clinical cases are particularly common in dogs that become immunosuppressed, but progression to disease is otherwise hard to predict. One study suggested that a high percentage of L. infantum–infected dogs will eventually become ill if they have “active” infections (i.e., high antibody titers + PCR evidence of infection in the bone marrow + isolation of the organism from lymph nodes). In this study, dogs with PCR evidence of organisms in the bone marrow, but negative lymph node cultures and low antibody titers, did not necessarily become symptomatic. In sick dogs, the prognosis appears to vary with the severity of the illness. A clinical staging system has been published and can assist with treatment considerations and prognosis.

Sporadic cases of leishmaniasis occur in cats, equids and other species. Because clinical cases are uncommonly reported in cats, asymptomatic Leishmania infections were also assumed to be rare. However, recent studies suggest that significant numbers of cats (up to 60%) have been exposed to Leishmania in some areas. Some cats that develop clinical leishmaniasis are co-infected with immunosuppressive viruses (e.g., FIV, FeLV) or have other debilitating conditions such as cancer or diabetes. However, this disease has also been reported in otherwise healthy cats. Relatively little is known about the prognosis for sick cats. Leishmaniasis progresses in some untreated cats; however, both untreated and treated cats have sometimes lived for years after diagnosis.

Infections in Humans

Incubation Period

People can carry some species of Leishmania asymptotically for long periods or indefinitely. The reported incubation period for cutaneous leishmaniasis ranges from 1-2 weeks to several months and occasionally...
Leishmaniasis (cutaneous and visceral)

several years. The incubation period for visceral leishmaniasis is approximately 2 weeks to several years, with many cases becoming apparent in 2-6 months.

Clinical Signs

Two forms of leishmaniasis, cutaneous and visceral, are seen in humans. Some texts also distinguish a mucocutaneous form, while others consider it to be a subset of cutaneous leishmaniasis.

Cutaneous and mucocutaneous leishmaniasis

Cutaneous leishmaniasis in humans often involves only the skin, without mucosal or visceral involvement. Initially, one to multiple erythematous papules, which may sometimes be pruritic, appear on the skin. These papules can develop into ulcers, which typically have raised, indurated margins; nodules, which may be smooth or covered in scales; flat plaques; or hyperkeratotic wart-like lesions. Except in the ear, ulcers tend to remain confined to the skin and do not affect the subcutaneous tissues. Unusual presentations that may mimic other skin diseases (e.g., erysipelas, psoriasis) can also be seen. The skin lesions of leishmaniasis are usually painless unless they become secondarily infected or an ulcer lies over a joint. L. major lesions tend to be exudative or "wet," and prone to secondary bacterial infections, while L. tropica infections tend to be "dry," with a central crust. Skin lesions may be accompanied by regional lymphadenopathy, which occasionally persists after the lesions have healed. Peripheral neuropathy has also been reported. Many cases of cutaneous leishmaniasis remain localized; however, secondary lesions sometimes appear on the skin, or occasionally the mucosa, in other parts of the body. When the parasites travel via the lymphatics rather than blood, the presentation may resemble sporotrichosis. Most cases of cutaneous leishmaniasis heal spontaneously, but this may take several months to a year or more, depending on the species of Leishmania. Some forms leave permanent scars.

Diffuse cutaneous leishmaniasis (DCL; also called anergic diffuse cutaneous leishmaniasis) is a rare form of skin disease, most commonly caused by L. amazonensis and L. mexicana. In patients with DCL, the skin lesions tend not to ulcerate, but appear as nodules, papules and tubercles that spread widely on the skin and can coalesce into large plaques. These lesions may cause damage to deep tissues, and can persist indefinitely. DCL can be incurable in some cases.

Leishmaniasis recidivans (lupoid leishmaniasis, leishmaniasis recidiva cutis) is most often caused by L. tropica, L. braziliensis, L. amazonensis, L. guyanensis and L. panamensis in Latin America, but it has also been reported from other regions (e.g., Ethiopia) where these organisms are absent. Leishmaniasis recidivans is an uncommon condition characterized by the development of new lesions, typically plaques, in and around the edges of a healed skin lesion. The mucous membranes (e.g., nose and lips) may sometimes be involved. Leishmaniasis recidivans tends to be chronic and relapsing, can be difficult to treat, and does not heal without treatment.

Classical mucocutaneous leishmaniasis (espundia) usually occurs in Latin America, where it can be caused by several organisms, but especially L. braziliensis. Mucocutaneous leishmaniasis tends to occur 1-5 years after cutaneous leishmaniasis has healed, but it can also develop while skin lesions are still present, or even in cases with no apparent cutaneous involvement. The initial signs are usually erythema and ulcerations at the nares, followed by destructive inflammation, with ulcers and nodules that can spread to involve the nasal septum, and in some cases, the oral cavity, pharynx or larynx. Frequent nosebleeds or itching in the nose can be an early sign. Lesions may eventually perforate the nasal septum, cause severe disfigurement of the face, or block the pharynx or larynx. In some cases, the genitalia may also be involved. Mucocutaneous leishmaniasis does not heal spontaneously.

Mucosal involvement, with or without concurrent or previous skin lesions, can also be caused by several species of Leishmania in the Eastern Hemisphere. There may be isolated or multiple lesions, similar to those seen in espundia, on the larynx, pharynx, oral cavity, nasal cavity or other sites. Some solitary mucosal lesions may not spread, even when they are untreated for years; others can form multiple lesions or later affect the viscera. Some treated cases may relapse.

Visceral leishmaniasis

Visceral leishmaniasis is usually an insidious, chronic disease among the inhabitants of endemic regions; however, the onset may be acute in travelers from Leishmania-free areas, and fulminant disease can occur in people who are immunosuppressed. The most common symptoms are a prolonged undulant fever, weight loss, decreased appetite, signs of anemia, and abdominal distension with splenomegaly and hepatomegaly. Particularly in Africa, a primary granuloma sometimes appears on the skin before systemic signs become evident. Thrombocytopenia may cause bleeding tendencies, including petechiae or hemorrhages on the mucous membranes, and leukopenia can result in increased susceptibility to other infections. Other reported symptoms include coughing, chronic diarrhea, darkening of the skin, lymphadenopathy, edema and in many cases, signs of chronic kidney disease. Some of these symptoms are regional or have a tendency to be associated with a particular organism. For instance, darkening of the skin is mainly reported in South Asia. CNS signs, peripheral neuropathies and ocular signs (uveitis, retinal hemorrhage) can be seen but are uncommon. People who are immunocompromised may have atypical symptoms. They are more likely to have signs associated with the respiratory tract, skin or oral cavity than immunocompetent individuals, while common signs such as fever and splenomegaly may be less prominent. Localized lymphadenopathy alone has been reported occasionally in healthy people infected with L. infantum.
Mild cases of visceral leishmaniasis with only a few symptoms (e.g., localized lymphadenopathy) may resolve spontaneously. Spontaneous remissions are generally considered unlikely in fully symptomatic cases; however, a recent report described multiple spontaneous remissions and relapses, over a 2-year-period, in a person with fully symptomatic visceral leishmaniasis caused by *L. infantum*. Unless they are treated, most fully symptomatic cases are eventually fatal, often from secondary infections and other complications. People with successfully treated infections may continue to carry the parasite, and the disease may recur if they become immunosuppressed.

Some people who recover from visceral leishmaniasis develop post-kala azar dermal leishmaniasis (PKDL). Occasionally, this syndrome has been reported in people with no apparent history of this disease. PKLD tends to be caused mainly by *L. donovani*. It is characterized by a maculopapular, macular or nodular rash that generally begins on the face (especially around the mouth), but can spread to the neck, torso and extremities. Coalescing lesions can result in enlargement of the lips and nose. Uncommonly, mucosal involvement may affect the nasal and oral cavities, eyelids and cornea. PKLD lesions do not usually ulcerate in cases reported from the Indian subcontinent; however, ulceration is reported to be more common in Africa. In Africa, PKLD is common, usually occurs within 6 months of visceral leishmaniasis (or even concurrently), and often disappears spontaneously within a year if the mucous membranes are not involved. On the Indian subcontinent, this syndrome is not very common, occurs one to many years after visceral leishmaniasis has been cured, and may require prolonged treatment to resolve. Most sources state that that PKLD does not usually regress on its own in this region; however, resolution occurred in some untreated patients in Bangladesh, with a median time of 19 months.

**Diagnostic Tests**

Cutaneous leishmaniasis can be diagnosed by direct observation of the parasites, PCR, immunohistochemistry or culture, as in animals. Amastigotes are easiest to detect visually in recent or active lesions or in cases of diffuse cutaneous leishmaniasis. A delayed hypersensitivity test, the leishmanin skin test (Montenegro skin test), may be useful in the diagnosis of cutaneous and mucocutaneous leishmaniasis, especially outside endemic areas. It is usually negative in the diffuse (anergic) cutaneous form. In endemic regions, the leishmanin skin test can indicate either current or past infections, including asymptomatic infections. Antibodies to *Leishmania* are often slow to develop and of low titer in cutaneous leishmaniasis; however, serology may be more useful in chronic conditions such as disseminated leishmaniasis, leishmaniasis recidivans and the mucocutaneous form.

Visceral leishmaniasis can also be diagnosed by parasitological techniques including direct observation of parasites and detection of nucleic acids by PCR. Amastigotes may be found in peripheral blood, or more often, in aspirates or biopsy smears from the spleen, bone marrow or lymph nodes. PCR may be particularly useful early, when parasite numbers are low. Serology can also be helpful in the visceral form. Commonly used serological tests in humans include IFA, direct agglutination, ELISA, fast agglutination-screening test (FAST), and a rapid immunochromatographic assay (K39 dipstick or strip-test). Cross-reactivity with the agents of other diseases, such as leprosy, Chagas disease, malaria and schistosomiasis, can be an issue with some serological tests. The leishmanin skin test/ Montenegro skin test is usually negative in cases of visceral leishmaniasis, but reactions can be seen once the disease is cured. A latex agglutination test to detect parasite antigens in the urine is in development, and may be particularly useful in immunosuppressed patients.

**Treatment**

Pentavalent antimonials (e.g., sodium stibogluconate, meglumine antimoniate) can be used to treat leishmaniasis where the parasites are sensitive to these drugs, but drug resistance is a major problem in some areas. Other agents such as allopurinol, liposomal amphotericin B, paromomycin and miltefosine may also be employed.

Visceral leishmaniasis is treated with systemic drugs, but drugs are sometimes given intraslesionally or topically in cutaneous leishmaniasis, depending on the infecting species and the risk of serious complications. Cryotherapy, thermotherapy, photodynamic therapy, CO₂ laser treatment or curettage have also been employed in some cases, either alone or in combination with drugs. Some cutaneous lesions that are improving may simply be observed, if they are caused by relatively benign organisms.

**Prevention**

Preventive measures against sandflies include using insect repellents such as DEET, covering exposed skin, and staying on higher floors of buildings in the evening or at night, as these insects are poor vertical fliers. Fans may be helpful, and insecticidal sprays or insecticide-impregnated materials (e.g., window curtains) may be used to help kill the insects inside houses. Insecticide-treated bed nets decrease bites from these insects at night. Untreated bed nets are not generally useful: sandflies are tiny and can pass through the mesh of most nets, while bed nets with very small holes may be too hot in warm climates. Resistance to insecticides can be an issue in some areas. Environmental modifications (see Prevention in Animals) may also be attempted.

Treating infected people can reduce the transmission of *L. donovani* and *L. tropica*. A program with the goal of eliminating *L. donovani* from India, Bangladesh and Nepal focuses on early diagnosis and treatment, together with vector control. Leukodepletion significantly reduces or eliminates *Leishmania* in blood transfusions. Decreasing the incidence of *L. infantum* in dogs (e.g., with insecticidal
collars) may help protect people from this organism. Infected dogs are also been culled in some control programs; however, these programs are controversial and their efficacy has been questioned.

Live vaccines were occasionally employed in the past, with inoculation into an inconspicuous site to prevent disfiguring facial lesions. Live vaccines are no longer available in most countries, but research into safer and more effective vaccines continues.

**Morbidity and Mortality**

Estimates vary, but approximately 1–2 million cases of cutaneous leishmaniasis and 200,000 to 500,000 cases of visceral leishmaniasis are thought to occur worldwide each year. This is probably an underestimate, as many cases are not diagnosed and leishmaniasis is not reportable in some countries. The consequences of infection seem to vary with the species of *Leishmania*, host factors (e.g., genetic susceptibility, immunity/ previous exposure, general health, age), the inoculation site, dose of the parasites, and other factors. Asymptomatic infections are common.

Localized cutaneous leishmaniasis is rarely fatal. This form often heals spontaneously, although some lesions may persist for long periods or leave scars. Other forms of cutaneous and mucosal involvement are more serious. In particular, the mucocutaneous form in South America rarely heals spontaneously, is disfiguring, and may be fatal if lesions occur in the nasopharynx. Diffuse (anergic) cutaneous leishmaniasis is difficult to cure. Immunosuppressed patients often develop skin lesions that are similar to those in immunocompetent hosts, but the risk of disseminated infections, diffuse (anergic) cutaneous leishmaniasis, mucosal or visceral involvement, and severe or atypical cases is higher.

Visceral leishmaniasis can be life-threatening. The anthropo tonic form of this syndrome, caused by *L. donovani*, tends to affect all ages. On the Indian subcontinent, the ratio of asymptomatic *L. donovani* infections to symptomatic cases is estimated to be 4-10 to 1. Some surveys suggest that, in this region, 1-23% of asymptptomatically infected people develop visceral leishmaniasis within a year, while 33-87% become seronegative and are likely to have eliminated the organism. People with high antibody titers appear more likely to become symptomatic. Healthy adults do not seem to be particularly susceptible to *L. infantum*, which causes the zoonotic form of visceral leishmaniasis. Asymptomatic infections with this organism are common, and illnesses tend to occur mainly in young children, or in people who are malnourished or immunosuppressed. Overall, the case fatality rate for untreated, symptomatic visceral leishmaniasis is estimated to be 75–95%. Cases in immunocompetent individuals can usually be cured; however, the parasites may persist and symptoms reappear if the individual later becomes immunosuppressed. Visceral leishmaniasis tends to be more severe and more difficult to treat in people who are immunocompromised. Relapse rates are higher in HIV-infected than immunocompetent patients even when they are taking highly active antiretroviral therapy (HAART). Relapse rates appear to be better for other immunosuppressive conditions, including solid organ transplants, but experience is limited.

**Internet Resources**

Centers for Disease Control and Prevention (CDC). Leishmaniasis
https://www.cdc.gov/parasites/leishmaniasis/

European Centre for Disease Prevention and Control. Leishmaniasis

LeishVet. Information for Veterinarians on Leishmaniasis
http://www.leishvet.org/

Public Health Agency of Canada. Material Safety Data Sheets

The Merck Manual
http://www.merck.com/pubs/mmanual/

The Merck Veterinary Manual
http://www.merckvetmanual.com/

World Health Organization
http://www.who.int/leishmaniasis/en/

World Organization for Animal Health (OIE)
http://www.oie.int

OIE Manual of Diagnostic Tests and Vaccines for Terrestrial Animals
http://www.oie.int/international-standard-setting/terrestrial-manual/access-online/

OIE Terrestrial Animal Health Code
http://www.oie.int/international-standard-setting/terrestrial-code/access-online/

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