

## Review Article

# Cutaneous leishmaniasis: an overview of parasitology and host-parasite-vector inter relationship

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**Abstract** Cutaneous leishmaniasis is expressed as a myriad of disease manifestations which depend upon parasite species, host responses, and poorly understood host-parasite-vector interactions. Several species of *Leishmania* are capable of infecting humans and causing disease. This article is mainly focused on describing detailed characteristics of *Leishmania* parasite and vector (*sandfly*) transmitting the parasite to humans. Host-parasite-vector inter-relationship is also briefly touched in the article.

**Key words**

Leishmaniasis, *Leishmania* spp., sandfly.

## Introduction

The protozoan *Leishmania* is an obligatory intracellular parasite which exists in two distinctive forms. In man and other hosts it occurs as a non-flagellar amastigote form, while in culture and gut of sandflies the flagellar or the promastigote form is seen. They are neither found in the peripheral blood nor in any visceral organ.<sup>1</sup> Classification and taxonomy of *Leishmania* parasite, along with geographical distribution is tabulated in **Table 1, 2 and 3.**<sup>2</sup>

## Morphology of *leishmania* parasite

The amastigote are small, round to oval, bodies which measure about 2-5µm and found only in the macrophages of infected vertebrate hosts (**Figures 1 and 2**). They are colourless, have a homogenous cytoplasm and are surrounded by a pellicle. The nucleus is centrally located, anterior to which is the kinetoplast. The kinetoplast is a section of the mitochondrion in which the mitochondrial DNA is arranged in regular arrays of fine fibrils.<sup>1</sup> The nucleus and a kinetoplast are easily visible in routine hematoxylin-eosin staining and rarely a short intracytoplasmic portion of the flagellum is also visible. The flagellar or the promastigote forms are seen in the culture media and in the gut of the sandfly, mosquitoes and bugs but it is only in the

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**Table 1** Taxonomy of *Leishmania* parasite [2].

|            |   |
|------------|---|
| Kingdom    | <i>Protozoa</i>   |
| Subkingdom | <i>Protista</i>   |
| Phylum     | <i>Sarcomastigophora</i>  |
| Sub-phylum | <i>Mastigophora</i>   |
| Class      | <i>Zoomastigophora</i>  |
| Order      | <i>Kinetoplastida</i>   |
| Suborder   | <i>Trypanosomatina</i>  |
| Genus      | <i>Leishmania</i>   |
| Species    | <i>L. tropica</i> complex<br><i>L. donovani</i> complex<br><i>L. mexicana</i> complex<br><i>L. braziliensis</i> complex |

**Table 2** *Leishmania* species causing human diseases [2].

| Complexes                              | Species                      | Diseases            |
|--|------------------------------|---------------------|
| <i>Leishmania donovani</i> complex     | <i>L.d. donovani</i>         | Visceral (kalaazar) |
|  | <i>L.d. infantum</i>         | Infantile visceral  |
|  | <i>L.d. chagasi</i>          | Cutaneous           |
| <i>Leishmania tropica</i> complex      | <i>L. major</i>              | Cutaneous           |
|  | <i>L. tropica</i>            | Cutaneous           |
| <i>Leishmania mexicana</i> complex     | <i>Leishmania aethiopica</i> | Diffuse cutaneous   |
|  | <i>L. m. amazonensis</i>     | Cutaneous           |
|  | <i>L.m. pifanoi</i>          | Cutaneous           |
|  | <i>L.m. garnhami</i>         | Cutaneous           |
|  | <i>L.m. venezuelensis</i>    | Cutaneous           |
| <i>Leishmania braziliensis</i> complex | <i>L.b. braziliensis</i>     | Mucocutaneous       |
|  | <i>L.b. guyanensis</i>       | Cutaneous           |
|  | <i>L.b. panamensis</i>       | Cutaneous           |
|  | <i>L. peruvianis</i>         | Cutaneous           |

sandfly that the parasite reaches the buccal cavity which becomes the insect vector of the parasite. They are motile, slender, organisms measuring 10-15 um in length with a single anterior flagellum (**Figure 2**). Rosette or clusters of promastigotes may also be seen. The electron microscopic

**Table 3** *Leishmania* species causing cutaneous disease in the Old World.

| Parasite species               | Geographic distribution   |
|--------------------------------|---|
| <i>L. major</i>                | Middle East, Indo-Pak subcontinent, Mediterranean region, Western Asiatic areas, Central Asia, Central and North Africa, Northwestern China |
| <i>L. tropica</i>              | Middle East, Indo-Pak subcontinent, Mediterranean region, Western Asiatic areas, Central Asia, Central and North Africa                     |
| <i>L. aethiopica</i>           | East Africa, Yemen  |
| <i>L. infantum</i>             | Mediterranean basin   |
| <i>L. donovani</i>             | Sudan, East Africa  |
| <i>L. mexicana</i> complex     | Mexico, Honduras, Guatemala, the Amazon basin and Venezuela   |
| <i>L. braziliensis</i> complex | Brazil, East Andes, Guyana, Venezuela, Panama, Columbia and Peru  |
| <i>L. chagasi</i>              | Brazil, Venezuela and Colombia. Isolated cases throughout S. and Central America  |

pictures (**Figure 3**) show that amastigotes have a double membrane supported by a layer of subpellicular fibrils. They run a spiral course from the region of the flagellar base towards the posterior apical end. One of the membranes is lost when the transformation of the amastigotes takes place, the fibrils are however retained. Amastigotes lack the flagellum but a short flagellum may be seen arising from the kinetosome. This has a 9x2 fibril configuration and extends beyond the flagellar pocket. Mitochondria are rare in an amastigote. The kinetoplast represents the sole mitochondria of the organism.<sup>1-5</sup>

### Vector

*Leishmania* parasites are transmitted by phlebotomine sandflies. These sandflies are

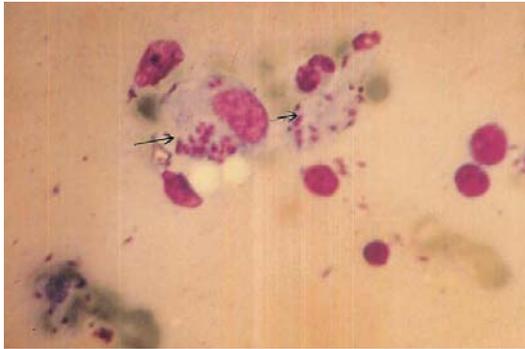


Figure 1 Intracellular *Leishmania* amastigotes seen in skin slit smear preparation.

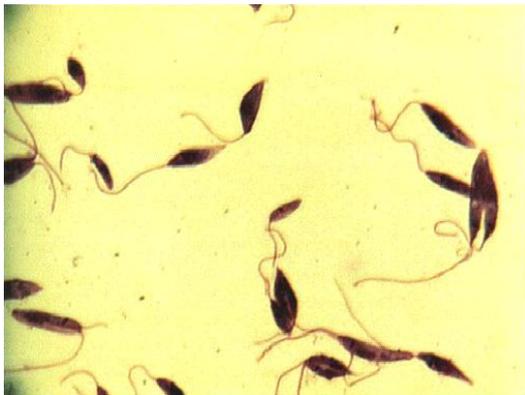


Figure 2 Promastigotes (Flagellated *Leishmania* parasites).



Figure 3 Electron microscopic picture of leishmania amastigote.

widely distributed in the tropics and other warm mainland areas and extend northwards to latitudes in the region of 50° N.<sup>6</sup> There are some 600 species in five genera within the subfamily *Phlebotominae*. Species in three genera, *Phlebotomus*, *Lutzomyia* and *Sergentomyia*, suck blood from vertebrates,



Figure 4 Vector sandfly (*Phlebotomus*).

only the former two transmit disease to man. There are over 50 species of genus *Phlebotomus* in the Old World and genus *Lutzomyia* in the New World, that transmit disease to man.<sup>7</sup> In addition some authorities regard the subgenus *Psychodopygus* of the genus *Lutzomyia* as sufficiently distinct to warrant a separate generic rank.<sup>8</sup> Generally speaking the species biting man in the Old World will be *Phlebotomus* and in the new world *Lutzomyia*. The phlebotomine sandfly vectors for cutaneous leishmaniasis in Pakistan are *P. papatasi*, *P. sergenti* and *P. salehi*.<sup>9-11</sup> Adult phlebotomine sandflies can be readily recognized by their minute size (2-5 mm in length), their hairy appearance, relatively large eyes and their relatively long and stilt like legs. Sandflies live in rodent burrows, crevices, holes in river banks, trees and houses in the Old World while in the New World sandflies also dwell in the tree canopies and forest litter.<sup>12</sup> Sandflies are small brownish hairy flies that are identified by the presence of erect narrow wings covered with hair (**Figure 4**).<sup>6</sup> Sandflies show nocturnal activity and have a characteristic hopping type of flights. Adults are weak fliers and do not usually disperse more than a few hundred meters from their

breeding places. They breed in a confined microclimate that may be provided by the wild reservoir itself. Subsoil water also contributes to breeding, a high water table level is suitable for the development of the larvae of the sandfly and the gerbils and increase in the two results in the increased incidence of the disease. Both sexes feed on plant sugar. The females, in addition, suck blood from a variety of hosts. Sandfly can bite a variety of animals and gets infected from an infected animal. The infection in the sandfly is in the midgut and moves out anteriorly towards the mouth parts.<sup>13,14</sup> In temperate areas of the Old World, sandflies are seasonal in their appearance. There are two peaks in the density curve of most species, one in June or July and the other in August or September.<sup>15</sup>

In Pakistan, *P. sergenti* was first found to be the vector in 1935 as described by Shortt.<sup>16</sup> The endemic areas of pre-partition India were Indus valley region and this was bounded on the east by a line joining Bombay and Delhi. This line also marks eastern limits of the distribution of *P. sergenti* in the Indo-Pak sub-continent and was described by Sinton in 1924.<sup>4</sup> *P. papatasi*, *P. punjabensis*, *P. argentipes* are also found in Pakistan.<sup>16</sup> *P. papatasi* and *P. chinensis* are found in Gilgit in the north.<sup>17</sup>

### Reservoir hosts

Vertebrate animals, other than man, act as animal reservoirs. The infection is, therefore, mostly zoonotic, where man is an accidental host. There are, however, situations where man may be the reservoir and the cycle then is anthroponotic. Each species of *Leishmania* favours one or more

animal reservoir, except *L. donovani* and *L. tropica*, which are thought to be mainly, if not exclusively, anthroponotic. The parasite is hosted by a large number of animals called the wild reservoir or the animal hosts, the vector sandfly is the intermediate host and domestic dogs and man are domestic or accidental hosts. Identification and control of reservoir host has an immense influence on the epidemiology of the disease.<sup>18</sup> In anthroponotic (urban or dry type) cutaneous leishmaniasis, caused by *L. tropica*, the transmission is generally man-sandfly-man, although in some countries dogs and rats have been found to be infected with this parasite and these may be serving as the reservoir host. In zoonotic cutaneous leishmaniasis (rural, wet type) caused by *L. major*, the transmission of infection i.e. rodent-sandfly-rodent cycle is maintained in wild rodent/gerbil colonies as sandflies breed in abundance in the cool and shady burrows.<sup>9,11</sup> *Rhombomys opimus*, *Meriones* spp. and *Psammomys obesus* are the three major reservoir species of the rodents that maintain infection in most of Central Asia, Middle East and North Africa.<sup>9</sup> Others that are implicated in various parts of the world include dogs, cats, jackals, carnivores, fox, wolves, rats etc.<sup>19</sup> A number of rodent species have been implicated as being the animal reservoir hosts in Pakistan, these include, *Meriones hurriane* or other species of gerbils, *Rhombomys opimus* and *Tatera indica*.<sup>9,10,20</sup> Other rodents that might be important in this respect include, *Meriones persicus*, *M. crassus*, *M. lybicus erythrorus* and *Mus musculus*.<sup>21,22</sup>

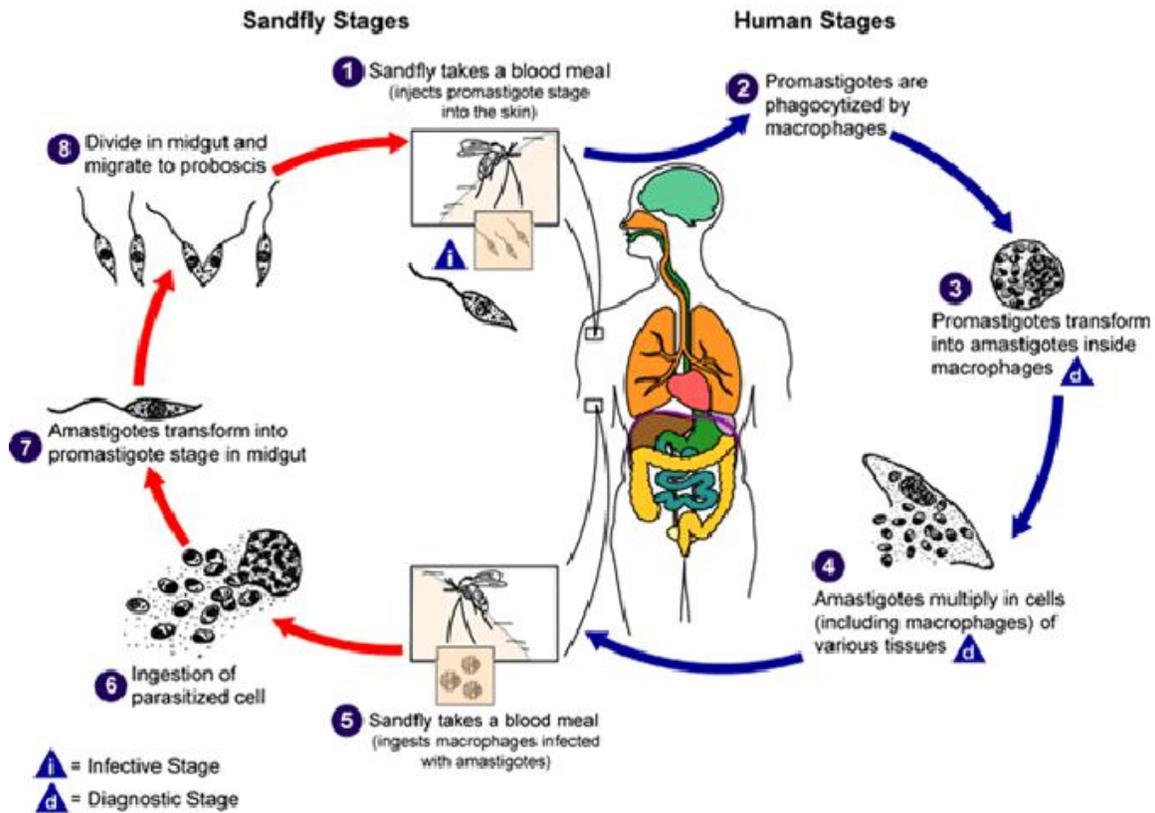


Figure 5 Life cycle of human cutaneous leishmaniasis.

**Life cycle (Host-parasite-vector interrelationship) [Figure 5]**

After ingestion in the sandfly the parasite turns into a promastigote, in the gut of the sandfly. A flagellum appears which is 1 µm in size to begin with and then grows to a full length in 4 hours. It helps in the movement as well as attachment of the organism to the gut. The parasites multiply and move towards the anterior portion of the gut and finally come to lie in the mouth and block it. The fly takes a bite to the nearest host available to get rid of these and thus manages to inject the parasites into the host. In man the dermal histiocytes take up the promastigotes and turn them into amastigotes. These again divide by binary fission. The kinetoplast being the first one to

divide followed by nucleus and later the outer membrane splits forming two parasites. The host cell when filled, ruptures and the Leishman-Donovan bodies are picked up by other macrophages or by the bite of the sandfly and the cycle continues.<sup>20</sup> Human beings are usually accidental hosts of leishmaniasis, because they live in endemic zones and are thereby exposed to infected sandflies. Transmission of leishmania infection occurs almost exclusively through the bite of an infected sandfly; however, other possible modes of transmission reported are the direct transmission via skin contact of cutaneous leishmaniasis and congenital transmission in visceral leishmaniasis. The exact mode of transmission of parasite from the vectors mouth to man is not very clear because the

sandfly may bite many times but may not always transmit the disease even though it may be heavily infected.<sup>23,24</sup> In a successful bite, between 10-200 promastigotes enter the dermis during each feeding by an infected sandfly.<sup>18</sup> Parasites on entering the body through the bite of the sandfly are introduced into the blood stream. There they encounter complement, antibodies, and phagocytic cells. All of these can kill the promastigotes. Almost 80% of these are killed one way or the other. Survivors are found in the phagocytic cells, both in neutrophils and mononuclear phagocytic cells. Different factors contribute to the attachment and uptake of parasites into the host cells, long-term survival is possible only in the macrophages. For the disease to be initiated the promastigote must enter the mononuclear phagocyte evading the various potentially lethal cells and humoral factors. Since the macrophage is equipped with mechanisms that are destructive for the parasite, therefore the parasite must possess factors that reduce the impact of macrophage destructive mechanism. The initial interaction with the macrophage membrane may influence the fate of the parasites once they are taken in the cells.<sup>25</sup>

Considering the complex interplay between various factors, cutaneous leishmaniasis may well be regarded as a disease, which in addition to parasite species and host responses, also depends upon poorly understood host-parasite-vector interactions.

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