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Leishmaniasis in Iraq: A Comprehensive Review of Species Diversity, Epidemiological Trends, and Regional Challenges

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Abstract **Review Article**

Leishmaniasis is a parasitic infection caused by intracellular protozoa, primarily spread to humans via the bite of phlebotomine sand flies. The disease exhibits diverse clinical formand epidemiological patterns, making it a significant global public health concern. The disease varies in severity, from localized cutaneous lesions to visceral forms that can be life-threatening, particularly in regions with limited healthcare resources in tropical and subtropical climates. Effective clinical management relies heavily on prompt and accurate diagnosis. However, the diversity of Leishmania species and the variable sensitivity of diagnostic methods often complicate detection and treatment. Leishmaniasis appears in three main clinical forms: visceral (VL), cutaneous (CL), and mucocutaneous (ML). Visceral leishmaniasis tends to occur more frequently in rural and peri-urban regions of lower-income countries such as India, Bangladesh, Ethiopia, Sudan, South Sudan, and Brazil. In contrast, cutaneous leishmaniasis is more widespread worldwide, with about 75% of cases reported in countries like Afghanistan, Algeria, Iran, Peru, Costa Rica, Brazil, Ethiopia, Sudan. ML tends to occur in regions like Bolivia, Brazil, Peru, Ethiopia, and Thailand. This review aims to shed light on the fundamental aspects of Leishmania parasites, including their scientific taxonomy, hierarchical classification, life cycle, and associated epidemiological patterns.

Keywords: Leishmaniasis, Sand flies, Protozoa, Visceral leishmaniasis, Cutaneous leishmaniasis.

INTRODUCTION

Leishmaniasis is a parasitic disease predominantly endemic to tropical and subtropical regions, caused by intracellular protozoan parasites of the family Trypanosomatidae. These organisms exhibit a complex life cycle involving both vertebrate hosts and insect vectors. Once introduced into the human body, the parasite replicates within macrophages, eventually destroying the host cells and spreading to neighboring intact macrophages. Transmission typically occurs through the bite of infected sand flies—Phlebotomus species (such as *Phlebotomus papatasi*) in the Old World, and Lutzomyia species in the New World [1]. The parasite undergoes morphological transformation and proliferation within its hosts. Although infrequent, transmission of leishmaniasis through accidental exposure in laboratory environments has been documented. The World Health Organization (WHO) identifies leishmaniasis as one of the seven most critical tropical diseases worldwide [2,3]. It poses a serious public health challenge due to its wide spectrum of clinical manifestations, which can lead to severe or even fatal outcomes. Leishmaniasis is endemic in multiple geographic regions spanning several continents, including northeastern Africa, southern Europe, the Middle East, southeastern Mexico, as well as parts of Central and South America. The clinical manifestations of the disease differ depending on the specific Leishmania species involved and the immune response of the host. [1,4] Sand flies are widespread, and in tropical climates, certain species can complete their life cycle year-round. In contrast, in subtropical areas, their activity and reproduction are usually limited to warmer seasons. These flies are nocturnal, silent, and often go unnoticed by their hosts [5,6]. To date, over 23 species of Leishmania have been identified, most of which are zoonotic. Among the most significant is *Leishmania infantum*, a major cause of visceral leishmaniasis in domestic animals and young children, especially under the age of five in Iraq. In Latin America, this species is also referred to as *L. chagasi*, which affects humans of all ages but more frequently children. Dogs and foxes serve as key reservoir hosts for transmission to humans. Another important species, *Leishmania donovani*, is

responsible for visceral leishmaniasis (also known as black fever or kala-azar) in both humans and canines, with endemic presence in countries such as Iraq, India, Kenya, Sudan, and China. This systemic infection can be deadly if left untreated.

In dogs, the disease often affects both internal organs and the skin, a condition known as viscerocutaneous or canine leishmaniosis. While cats, horses, and other mammals can also contract the infection, it is much rarer in these species. In felines, it may present in either cutaneous or visceral forms. *Leishmania braziliensis,* which causes tegumentary leishmaniosis in dogs, is commonly Canine leishmaniosis is a significant zoonotic disease, reported in over 89 countries. It is prevalent across Europe, Africa, Asia, and found throughout South America and may coexist geographically with *L. chagasi.* both Central and South America. Notably, vertical transmission between dogs has also been documented in the United States. In non-endemic regions, the disease still poses a concern due to imported cases, representing a potential threat to both veterinary and public health sectors [6]. Cutaneous leishmaniasis is the most prevalent form of leishmaniasis in humans. It is a parasitic skin disease caused by unicellular protozoa transmitted through the bite of female phlebotomine sand flies. Approximately 30 different Leishmania species are known to be responsible for this condition. While most cases are zoonotic meaning they are naturally transmitted from animals to humans—Leishmania tropica is an exception, often classified as anthroponotic, where transmission occurs from human to animal hosts [5,7].

Both L. tropica and L. major are primary causes of cutaneous leishmaniasis. *L. tropica* typically leads to the formation of dry lesions, commonly known as “dry oriental sore” or “Baghdad boil” in Iraq.

This variant is often associated with urban settings and is also found in the Mediterranean region, as well as parts of central and northern India. In contrast, L. major is associated with “moist oriental sore,” which appears more frequently in rural areas of the Middle East and India.

Another complex species group *is L. mexicana*, which includes four major species*: L. Mexicana*, *L. amazonensis, L. venezuelensis*, and *L. aethiopica*. In dogs, cutaneous leishmaniasis usually manifests as superficial ulcers on areas like the lips or eyelids and often resolves without intervention. However, the visceral form is more common in canines. In these cases, dogs may first exhibit hair loss around the eyes giving the appearance of “spectacles”—followed by generalized alopecia and skin inflammation. The affected skin often harbors high concentrations of the parasite. Additional symptoms may include recurring fever, anemia, severe weight loss (cachexia), and widespread enlargement of lymph nodes. It is also common for dogs to experience long symptom-free intervals followed by recurrence of clinical signs [44].

Taxonomy and Classification of Leishmania Spp

The causative agents of leishmaniasis are protozoan parasites of the genus Leishmania, which are classified under the family Trypanosomatidae, within the class Kinetoplastida, and the phylum Euglenozoa. These flagellated protozoa are primarily transmitted to humans through the bite of infected female phlebotomine sand flies. [39]

Kingdom: Protistta
Phylum: Protozoa
Subphylum: Sarcomastigophora
Class: Zoomastigophora
Order Kinetoplastidea
Family: Trypanosomatidae
Genus: Leishmania

Life Cycle

The life cycle of Leishmania involves two hosts: a vertebrate host (typically mammals, including humans) and an insect vector (the sandfly). The cycle consists of several stages its Infective Stage (Promastigote)which Leishmania is transmitted to humans through the bite of an infected sandfly.

The sandfly injects the infective form of the parasite, the promastigote, into the skin and Infection of Macrophages Once inside the vertebrate host, the promastigote is engulfed by macrophages (immune cells). Inside these cells, the parasite transforms into an amastigote, the non-motile, intracellular form of Leishmania. The third stag is Amastigote Stage the amastigotes multiply within the macrophages, leading to the rupture of the host cell and the release of new amastigotes, which can infect neighboring macrophages. This stage is responsible for the tissue damage obser

The female phlebotomine sand fly, predominantly nocturnal in behavior and most active between dusk and dawn, serves as the biological vector for the transmission of Leishmania parasites to mammalian hosts, including both humans and a range of animal reservoirs. Within its digenetic life cycle [7,9].

During a blood meal, promastigotes are injected into the dermis of the mammalian host, where they are phagocytosed by mononuclear phagocytic cells. Within these cells, they differentiate into amastigotes — commonly referred to as *Leishman Donovan* bodies — and multiply within the phagolysosomal compartments of cells in the reticuloendothelial system, including macrophages of the liver, spleen, bone marrow, and lymph nodes. The ensuing pathology varies from asymptomatic colonization to severe clinical disease, influenced by both the Leishmania species involved and the host’s immunogenetic back ground [7]

Dissemination of amastigotes via hematogenous and lymphatic routes may lead to mucosal and visceral involvement, particularly in infections caused by species of the Viannia subgenus. Recent studies have illuminated the role of Leishmania RNA Virus 1 (LRV1), an endosymbiotic virus identified in L. (V.) guyanensis and *L. braziliensis*, which exacerbates host immune responses through Toll-like receptor activation, contributing to mucocutaneous damage and increased metastatic potential [10-12].

Transmission dynamics differ geographically and ecologically. In anthroponotic cycles, humans act as the sole reservoir, as is the case with *L. tropica* (cutaneous leishmaniasis in the New World) and *L. donovani* (visceral leishmaniasis in the Indian subcontinent). In contrast, zoonotic transmission involves a variety of mammalian hosts such as canines, rodents, marsupials, primates, and edentates with dogs being the principal reservoir for *L. infantum* in endemic areas of the Mediterranean basin and Latin America [13-15].

While vector-borne transmission remains predominant, alternative non-vectorial transmission routes, though rare, have been documented. These include vertical (congenital) transmission, blood transfusion, organ transplantation, and parenteral exposure through intravenous drug use, all of which carry implications for disease surveillance and control in non-endemic settings [14,16].

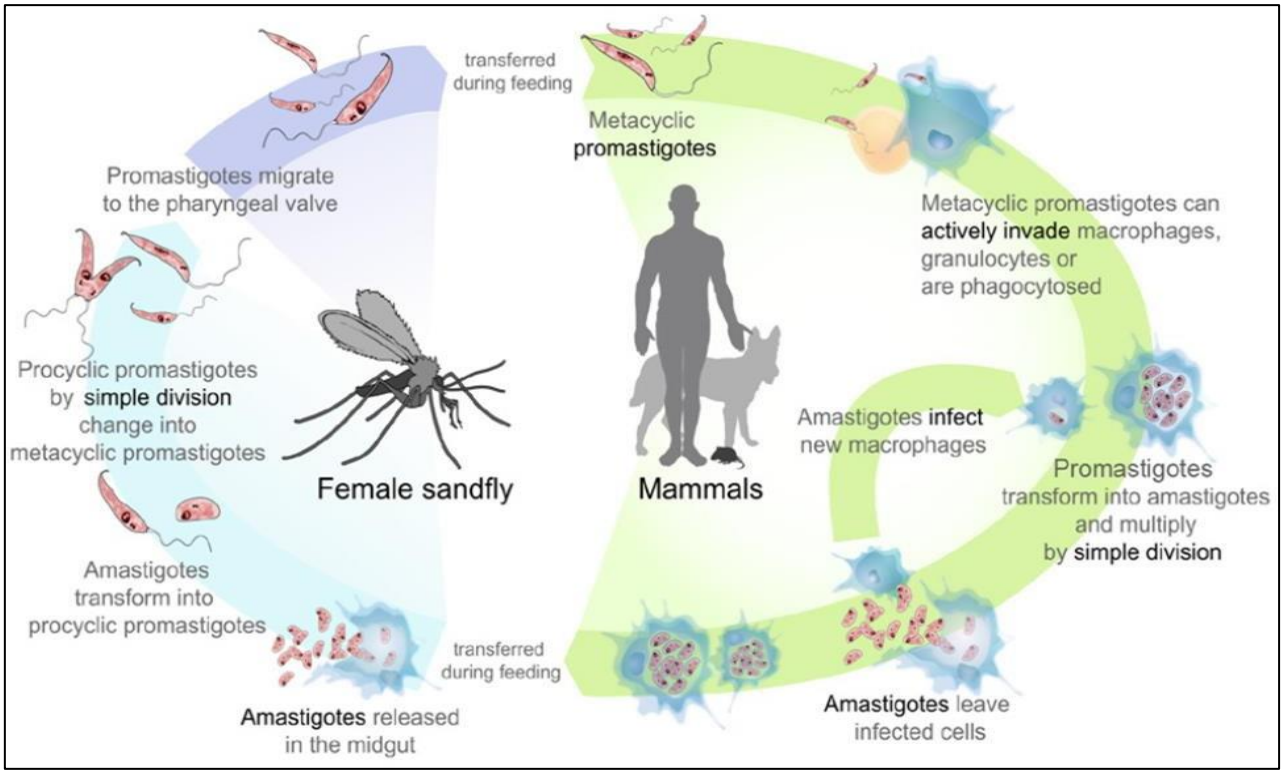

Figure 1: Life cycle of Leishmania parasites, the causative agents of leishmaniasis. [43]

Species and Clinical Signes

Leishmaniasis is classified among the neglected tropical diseases (NTDs) and encompasses a wide spectrum of clinical manifestations. Visceral leishmaniasis (VL) represents the most severe form, with potentially fatal outcomes. It ranks as the second leading cause of mortality and seventh in disability-adjusted life years (DALYs) lost among tropical infectious diseases. Canine visceral leishmaniasis (CVL) affects both humans and canines and is transmitted primarily by phlebotomine sand flies. The species *Leishmania infantum* is the etiological agent responsible for Mediterranean visceral leishmaniasis, with domestic dogs serving as the principal reservoir hosts.

Asymptomatic dogs infected with L. infantum can harbor the parasite for extended periods, sometimes for their entire lifespan, without displaying overt clinical signs. If untreated, VL is potentially fatal and characterized by marked splenomegaly, which may render the spleen palpable and, in severe cases, even larger than the liver upon abdominal examination. Hepatomegaly, intermittent (undulating) fever, weight loss, edema, bleeding tendencies primarily due to thrombocytopenia affecting mucosal sites such as the nose and intestines and anemia (including neutropenia, thrombocytopenia, and monocytosis) are commonly observed clinical features [17,18].

This epidemiological distribution underscores the critical importance of species-specific diagnosis to enable clinicians to promptly identify cases with visceral involvement and to initiate appropriate treatment regimens.

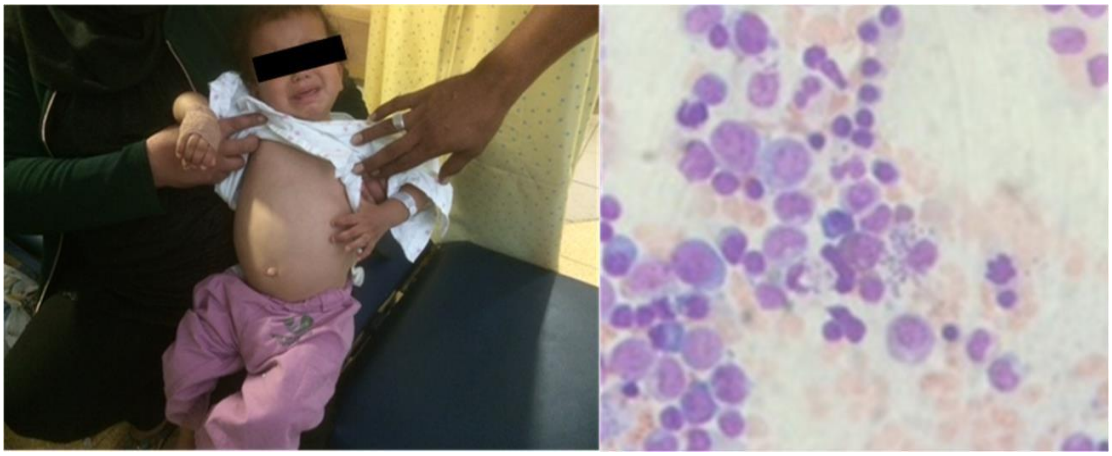

Figure 2: Clinical presentation of visceral leishmaniasis in a 4-year-old patient, demonstrating hepatosplenomegaly (left panel) and the presence of amastigotes within a bone marrow biopsy specimen (right panel) [41].

Mucocutaneous leishmaniasis (MCL) is a chronic inflammatory condition affecting the mucous membranes of the nose, pharynx, and larynx, and may result in severe tissue destruction [19,20] Continuous monitoring is essential due to the potential for complications, particularly as the disease progresses. MCL poses a significant threat to life and therefore necessitates systemic therapy. This form of leishmaniasis typically arises following infection with Leishmania species belonging to the Viannia subgenus, which are commonly found in the Americas—including *L. braziliensis, L. amazonensis, L. panamensis, and L. guyanensis* [21,22]. The progression to mucosal involvement is influenced by both host cell-mediated immune responses and the virulence of the parasite [23]. Among individuals initially presenting with cutaneous leishmaniasis, approximately 1–10% develop mucosal disease [19,20,24]. As the condition advances, ulcers may appear around the nasal openings and lips, which can be misdiagnosed as impetigo contagiosa. This underscores the importance of clinician awareness of local epidemiology and the specific Leishmania species involved [25].

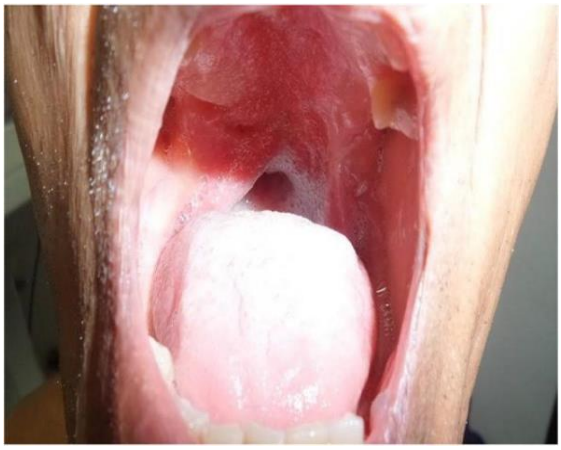

Fig. 3: Mucocutaneous leishmaniasis in a patient with *L.Panamesis* [42]

Cutaneous leishmaniasis (CL) represents the most common clinical manifestation of leishmaniasis, with an estimated annual incidence ranging from 600,000 to 1 million new cases worldwide. Remarkably, nearly 90% of these cases are concentrated in just many countries [26]. The clinical manifestation of CL varies and is largely influenced by the specific Leishmania species involved [16]. Lesions caused by *L. tropica* and *L. major* typically undergo spontaneous healing within a year, though they often leave permanent scarring. Conversely, infections with *L. aethiopica* may persist for several years and can progress into more severe forms, such as oral–nasal mucocutaneous leishmaniasis (MCL) or diffuse cutaneous leishmaniasis [17]. While CL is not typically life-threatening, it warrants clinical attention due to its potential to cause lasting disfigurement.

Permanent scarring associated with CL may lead to cosmetic concerns, reduced quality of life, and profound psychological distress. [24] These factors underscore the importance of timely diagnosis and effective management. The variability in clinical progression and species-specific responses presents significant challenges for healthcare providers aiming to achieve definitive cures [27].

The initial indication of localized CL commonly appears as a papule at the site of the sandfly bite, which gradually enlarges and may ulcerate over time, evolving into the characteristic skin lesion.

The cutaneous form of leishmaniasis typically begins with the appearance of an erythematous macule at the site of a sandfly bite, following an incubation period that ranges from two weeks to three months. This initial lesion gradually develops into a papule, which subsequently ulcerates over a period ranging from two weeks to six months. The classic presentation is a painless, round or oval-shaped ulcer located on exposed areas of the skin. Although spontaneous healing may occur within several months to a year, the resulting scar is often cosmetically unappealing. Importantly, this cutaneous form has the potential to progress into one of the more severe clinical variants of the disease. Diffuse cutaneous leishmaniasis (DCL) is characterized by widespread cutaneous lesions that closely resemble those seen in leprosy and poses significant therapeutic challenges. Eradication of the parasite alone does not guarantee a satisfactory cosmetic outcome, which is often subjectively assessed by the patient. The resulting scarring is influenced by a complex interplay of various factors, including the timing of diagnosis, the host's individual immune response, and the virulence characteristics of the infecting parasite [19,23]. *Leishmania tropica*, although commonly associated with cutaneous leishmaniasis in many endemic areas, has been rarely documented to cause visceral leishmaniasis [28].

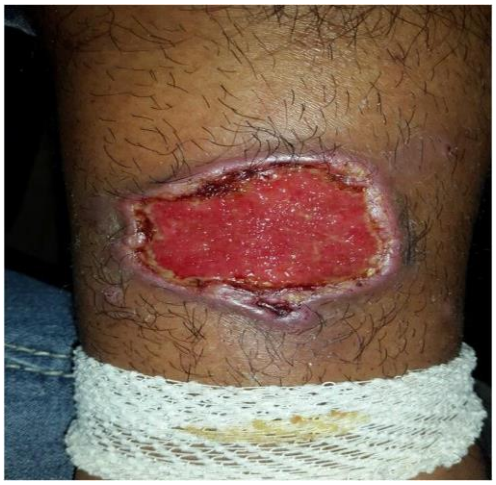

Fig. 4 Cutaneous leishmaniasis presenting as a typical ulcerative lesion on the arm of a patient infected with Leishmania panamensis. [42]

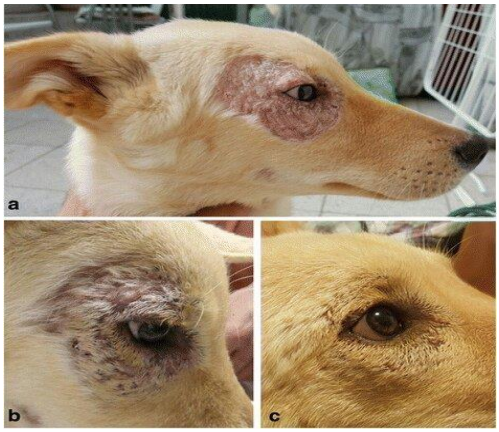

Figure 5: Cutaneous periocular lesion caused by Leishmania major in a canine showing progression over time:
a) at initial diagnosis at 6 months of age;
b) at 7 months of age on the day of follow-up;
c) evidence of partial healing and hair regrowth following treatment. [45]

Transmission

The transmission cycles of leishmaniasis exhibit substantial geographic variability, reflecting intricate ecological relationships among various Leishmania species, phlebotomine sand fly vectors (invertebrate hosts), and a wide range of vertebrate reservoir hosts. To date, more than 50 Leishmania species have been identified worldwide, with at least 21 classified as medically important due to their capacity to cause disease in humans. [29,30]. A broad range of mammals serve as reservoir hosts for various Leishmania species, including rodents, canines, marsupials, edentates, carnivores, primates, and humans [29].

Leishmaniasis is primarily transmitted through the bite of infected female phlebotomine sand flies, which are classified under the order Diptera, family Psychodidae, and subfamily Phlebotominae. In the Old World, vectors primarily belong to the genus Phlebotomus, whereas in the New World, transmission is mainly attributed to species of the genus Lutzomyia. To date, approximately 700 phlebotomine species have been formally described, with over 40 additional species suspected to play a role as potential vectors in leishmaniasis transmission cycles. [31]

Transmission occurs during the blood-feeding (hematophagy) process when the infected sand fly bites the host. Although rare, non-vectorial transmission can also occur—for instance, through laboratory accidents. In cases of visceral leishmaniasis (VL), additional modes of transmission have been reported, including congenital transmission, blood transfusion, and the sharing of needles among intravenous drug users. [29]

Pathogenesis of Leishmana

The pathogenesis of leishmaniasis is primarily mediated by the host's immune response to the Leishmania parasite. The clinical manifestations of the disease are influenced by the Leishmania species involved, the host's immune status, and the nature of the infection. A critical determinant of disease outcome is the balance between the different arms of the immune response. Following the entry of promastigotes into the host, they are phagocytosed by macrophages, prompting the activation of a T-helper type 1 (Th1) immune response. This Th1 response enhances macrophage activity, facilitating intracellular killing of the parasites and limiting disease severity in immunocompetent individuals.

In contrast, a weakened or dysregulated immune response often marked by a dominant Th2 profile fails to effectively control the infection, allowing the parasites to persist and proliferate within macrophages. This persistence leads to progressive disease and associated tissue damage (40). The primary mechanism of tissue injury involves the intracellular replication of Leishmania amastigotes, which causes macrophage lysis and triggers a local inflammatory response. This results in the hallmark clinical features of leishmaniasis, such as skin lesions and, in more severe cases, visceral organ damage.

Leishmaniasis may become chronic in certain cases, particularly in visceral leishmaniasis, where parasites can persist in deep tissues such as the liver and spleen. This persistence contributes to disease relapse, even following initial treatment

Diagnosis

The diagnosis of leishmaniasis requires a comprehensive approach that integrates clinical presentation, epidemiological context, and laboratory findings. The choice and sensitivity of diagnostic methods vary depending on the clinical form of the disease, the duration of lesion development, and the specific Leishmania species involved [29]. The detection of the parasite through direct microscopic observation remains the "gold standard" for diagnosis due to its high specificity.

In cases of cutaneous leishmaniasis (CL), parasitological confirmation is typically achieved through techniques such as lesion scarification, biopsy, imprint smears, or fine-needle aspiration—usually performed at the active margin of the lesion. These methods are rapid and cost-effective but have reduced sensitivity in chronic lesions.

For visceral leishmaniasis (VL), parasite detection in tissue samples often necessitates invasive procedures, which limits their routine use. Bone marrow aspiration is the most commonly employed technique, with a sensitivity ranging from 60% to 85%. Although splenic aspiration offers a higher sensitivity (over 95%), it is infrequently performed due to the significant risk of hemorrhage. Less invasive procedures, such as liver or lymph node aspiration, present lower sensitivities—approximately 45%.

In vitro culture of clinical specimens or inoculation into laboratory animals can enhance diagnostic accuracy and increase positivity rates. However, these approaches are rarely utilized in clinical settings due to their technical complexity, time requirements, and limited practicality [30] Polymerase chain reaction (PCR) has demonstrated considerable promise in the diagnosis of leishmaniasis. In addition to its high sensitivity, PCR can be applied to a variety of clinical specimens, including peripheral blood samples in cases of visceral leishmaniasis (VL). Moreover, certain PCR techniques allow for species-level identification of Leishmania, which is crucial for guiding appropriate treatment strategies. However, despite its advantages and widespread use in research settings, PCR is not routinely implemented in clinical diagnostics. This is largely due to its high cost, the need for technical standardization, specialized laboratory infrastructure, and the requirement for trained personnel [29]

Serological methods—such as indirect immunofluorescence antibody test (IFAT), direct agglutination test (DAT), and enzyme-linked immunosorbent assay (ELISA)—are well-established tools for detecting anti-Leishmania antibodies and are primarily used in the diagnosis of VL. These techniques are particularly effective in VL due to the strong humoral immune response typically observed in affected individuals. In contrast, serological tests are less reliable in diagnosing cutaneous leishmaniasis (CL), particularly localized CL (LCL)[32]. owing to variable sensitivity and specificity and generally low antibody titers.

To overcome some of these limitations, immunochromatographic assays have been evaluated in various endemic regions for their potential application in field-based diagnosis of VL, offering a more accessible and rapid diagnostic alternative in resource-limited settings.

Epidemiology

Leishmaniasis is a parasitic disease endemic to tropical, subtropical, and temperate regions, with transmission occurring through the bite of infected sandflies. Various species of Leishmania are responsible for different clinical forms of the disease. The infection has been reported in approximately 89 countries [33, 34] In the Americas, leishmaniasis is primarily a sylvatic zoonosis—although transmission can also occur in semi-arid and cooler environments—mainly via sandflies of the genera Phlebotomus and Lutzomyia. It is distributed widely from the southern United States to northern Argentina, with a reported seroprevalence of 0.17% for cutaneous leishmaniasis (CL) [35] excluding countries such as Chile, Uruguay, and El Salvador. [34].

In 2012 the World Health Organization (WHO) undertook a comprehensive assessment of the global burden and distribution of leishmaniasis across 102 countries, territories, and regions. Based on data collected up to 2010, approximately 90% of all visceral leishmaniasis (VL) cases were reported from Bangladesh, Brazil, Ethiopia, India, South Sudan, and Sudan. Similarly, nearly 70% of all CL cases originated from Afghanistan, Algeria, Brazil, Colombia, Costa Rica, Ethiopia, Iran, Sudan, and the Syrian Arab Republic. [36]

TREATMENT

Treatment varies based on the form of leishmaniasis (cutaneous, visceral, or mucocutaneous) and the severity of the disease. Cutaneous Leishmaniasis (CL) it Localized Disease Often heals without treatment, but treatment can speed healing and reduce scarring. Treatment Options Topical treatments like paromomycin ointment. Oral treatments like miltefosine. Visceral Leishmaniasis (VL) first-line treatments Amphotericin B (IV) is highly effective. Miltefosine (oral) as an alternative. Other options Sodium Stibogluconate (antimony-based), Paromomycin (injectable antibiotic). Mucocutaneous Leishmaniasis (MCL) it Treatment Systemic Antimonials (e.g., Sodium Stibogluconate). Amphotericin B for severe cases. Miltefosine for resistant cases. Post- Kala-Azar Dermal Leishmaniasis (PKDL)Treated similarly to VL, using amphotericin B, miltefosine, or antimonials. Drug Resistance and Challenges: Resistance to antimonials is increasing, leading to the use of alternatives. Side effects and high costs of treatment, especially for amphotericin B, are challenges. Supportive Care Management of symptoms like fever and nutritional support, particularly for VL. Wound care for CL lesions to avoid secondary infections.

Prompt initiation of treatment is critical to preventing severe complications and limiting disease progression. The success of therapy depends on a combination of factors, [37] including host-related elements such as genetic background, immune response, and the clinical manifestation of the disease. Treatment-related factors such as drug quality, appropriate dosage, duration, and adherence to therapy also play a vital role. Additionally, characteristics of the parasite, including its inherent drug susceptibility and absence of resistance mechanisms, significantly influence treatment outcomes. Currently, pentavalent antimonial compounds remain the first-line pharmacological agents for the treatment of all clinical forms of leishmaniasis [38].

CONCLUSION

Leishmaniasis is a potentially fatal protozoan disease caused by intracellular parasites of the genera Leishmania and Endotrypanum. It is endemic to tropical and subtropical regions but has expanded geographically due to environmental and anthropogenic factors. increased global travel has contributed to its emergence as a global public health concern. The disease presents in three major clinical forms: cutaneous, mucocutaneous, and visceral leishmaniasis. Rapid and accurate diagnosis, including species-level identification, is essential for effective management and reduction of morbidity. Non-invasive serologic methods, such as rapid antigen tests, are valuable tools for diagnosing visceral leishmaniasis (VL) and initiating timely treatment. However, despite progress in molecular diagnostics, the diagnosis of cutaneous leishmaniasis (CL) still often relies on microscopic examination and correlation with clinical and epidemiological data. In cases of CL, it is critical to identify and exclude species associated with mucocutaneous leishmaniasis (ML), to ensure appropriate treatment and follow-up. Traditional species identification via isoenzyme analysis is time-consuming and requires parasite culturing. In contrast, modern molecular techniques allow for faster, more specific diagnosis directly from clinical samples.

Recommendations

1. Prompt diagnosis and treatment of infected individuals to reduce transmission and complications.
2. Implementation of vector control strategies, including the use of insecticides to eliminate sand flies.
3. Management of animal reservoirs through the control of stray dogs and rodents.

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