An Overview of the Clinical and Laboratory Diagnosis and Pharmacological Treatment of Leishmaniasis

**Mutlaq Fahad Aldajani1, Thamer Salem Aldajani2, Bahni Mohammed Alsahabi3, Baraa Talal Melibari4, Mohamad Abdullah M Alharazi5, Thamer Husaen A Alwaal6, Saeed Ahmad Alshaikhi7, Fars Adnan Althgafi7, Entesar Ibrahem M Alsolemani8, Saeef Ali B Alnofaie9, Raed Mohammed Alrajhi9, Ahmad Sair Aldagani10, Faisal Khalid Alghamdi11, Ahmad Nassar Alghamdi12, Sami Ali Mohammed12**

1. King Faisal General Hospital, Internal medicine &Infectious disease, consultant
2. King Faisal General Hospital, Internal Medicine & Pulmonary consultant
3. Alnoor specialist hospital, Senior medical registrar
4. Alnoor specialist hospital, Senior medical registrar, Infectious disease fellow at national guard hospital
5. Alnoor Specialist Hospital, General physician
6. Lab technician, Al iskan phcc
7. Laboratory tech, King Abdullah Medical city
8. Lab technician, Iskan Phcc
9. King Abdullah Medical City, Pharmacist
10. King Abdullah Medical city, Pharamcy
11. Pharmacist Technician, Aljumom health sector Ministry of Health, Makkah, Saudi Arabia
12. Pharmacy technician, Hera General Hospital

**ABSTRACT**

Leishmaniasis is a neglected tropical disease caused by protozoa of the genus Leishmania, transmitted by the bite of infected female phlebotomine sandflies. The disease manifests in three primary forms: cutaneous (CL), mucocutaneous (MCL), and visceral leishmaniasis (VL or kala-azar), each with unique clinical and pathological features. Accurate diagnosis and effective treatment are crucial to reduce morbidity and mortality. This review explores the clinical and laboratory diagnosis of leishmaniasis and evaluates pharmacological treatments, focusing on efficacy, challenges, and future prospects.

**KEYWORDS:** diagnosis, leishmaniasis, tropical disease.

**1. Introduction**

Leishmaniasis is a complex and diverse vector-borne disease caused by protozoan parasites of the genus Leishmania. It is transmitted through the bite of infected female phlebotomine sandflies, with over 90 sandfly species serving as potential vectors. The disease is endemic in more than 90 countries, primarily in tropical and subtropical regions, and disproportionately affects resource-limited settings. Globally, leishmaniasis accounts for an estimated 700,000–1 million new cases annually, with more than 20,000 deaths, although these figures are likely underreported due to limited diagnostic and surveillance infrastructure [1].

The clinical manifestations of leishmaniasis are highly variable and depend on the infecting Leishmania species, host immune response, and geographic factors. It is classified into three primary forms:

1. Cutaneous Leishmaniasis (CL): The most common form, presenting as localized or disseminated skin lesions that may progress to chronic ulcers or plaques.
2. Mucocutaneous Leishmaniasis (MCL): A disfiguring form involving mucosal tissues, particularly of the nose, throat, and mouth, often developing from untreated CL.
3. Visceral Leishmaniasis (VL): Also known as kala-azar, this is the most severe form, characterized by systemic involvement of internal organs such as the spleen, liver, and bone marrow. Without treatment, VL is almost universally fatal.

The epidemiology of leishmaniasis is closely linked to environmental, socio-economic, and immunological factors. Rural and peri-urban populations in endemic areas are most at risk, particularly those living in conditions conducive to sandfly breeding, such as poorly ventilated housing and proximity to livestock. Malnutrition, HIV coinfection, and other forms of immune suppression further increase susceptibility to severe disease [2,3].

Despite being one of the most neglected tropical diseases, leishmaniasis poses a substantial health and economic burden. The World Health Organization (WHO) classifies leishmaniasis as a neglected tropical disease (NTD), emphasizing the urgent need for improved diagnostic, therapeutic, and preventive strategies. Diagnosis of leishmaniasis relies on a combination of clinical evaluation and laboratory techniques, ranging from direct microscopy to advanced molecular diagnostics. Treatment options are highly specific to the disease form and geographic region, and they include pentavalent antimonials, amphotericin B, miltefosine, and paromomycin [1].

The management of leishmaniasis faces numerous challenges, including drug resistance, treatment toxicity, high costs, and limited access to healthcare in endemic regions. In addition, the disease disproportionately affects impoverished populations, who often lack access to timely diagnosis and effective treatment. These challenges highlight the importance of public health interventions, such as vector control, health education, and improved healthcare infrastructure [4].

This review aims to provide a detailed examination of the clinical and laboratory diagnostic approaches for leishmaniasis and to critically evaluate the pharmacological treatments available. By synthesizing current evidence.

1. Clinical Diagnosis

Leishmaniasis manifests in a variety of forms, ranging from self-limiting cutaneous lesions to fatal visceral disease. The clinical diagnosis is often the first step and relies heavily on recognizing the characteristic features of the disease in its different presentations.

1.1. Cutaneous Leishmaniasis (CL)

CL is characterized by painless skin lesions that begin as papules and progress to ulcers with raised borders and a necrotic base. Lesions may occur as single or multiple, depending on the causative species. Lesions are typically found on exposed areas such as the face, arms, and legs, correlating with sandfly bite sites [5].

* Regional Variations:

In the Old World (Middle East, North Africa, and Central Asia), Leishmania major and L. tropica are the predominant causative species. In the New World (South and Central America), L. mexicana and L. braziliensis are more common [6].

* Differential Diagnosis:
  + Includes tropical ulcers, fungal infections, tuberculosis of the skin, and syphilis.

1.2. Mucocutaneous Leishmaniasis (MCL)

MCL usually develops months to years after a cutaneous lesion has healed, especially in cases caused by L. braziliensis. Symptoms include mucosal ulcers, nasal obstruction, epistaxis, and eventually severe tissue destruction and disfigurement [7]. MCL results from the parasite's spread to the mucosa, often triggered by an overactive immune response rather than parasite load alone.

1.3. Visceral Leishmaniasis (VL)

VL, also known as kala-azar, is the most severe form and is caused by L. donovani and L. infantum. Symptoms include intermittent fever, hepatosplenomegaly, pancytopenia, weight loss, and darkening of the skin (hence the term “kala-azar” or “black fever”).

Secondary bacterial infections, bleeding tendencies, and post-kala-azar dermal leishmaniasis (PKDL) are significant complications [8].

* Geographic Variations:

Endemic in South Asia, East Africa, and parts of Latin America.

2. Laboratory Diagnosis

2.1. Microscopy

* Methodology:

Direct visualization of Leishmania amastigotes (intracellular forms) in Giemsa-stained smears from skin scrapings (CL) or aspirates (VL). Sensitivity depends on the type of sample, with splenic aspirates having the highest yield in VL (>95%) [9].

* Advantages:
  + Simple and cost-effective.
* Limitations:
  + Requires trained personnel, and sensitivity decreases in cases with low parasite load.

2.2. Culture

Parasite isolation in specific mediums like Novy-MacNeal-Nicolle (NNN) or Schneider’s medium. Confirms the diagnosis and allows species identification for tailored therapy. Time-consuming and requires laboratory infrastructure.

2.3. Molecular Diagnostics

* PCR:

Polymerase chain reaction (PCR) is highly sensitive and specific, detecting Leishmania DNA in clinical samples like blood, tissue, or aspirates [10]. Particularly valuable for diagnosing VL in patients with low parasite loads.

* Species Identification:

PCR allows differentiation between species, which is crucial for determining the treatment protocol.

2.4. Serological Tests

* rK39 Antigen Test:
  + A rapid diagnostic test (RDT) for VL, detecting antibodies against the rK39 antigen.
  + Sensitivity: 95% in endemic areas, though specificity can vary due to cross-reactivity.
* DAT (Direct Agglutination Test):
  + Highly effective for VL diagnosis in field settings, with long-term stability and low cost.
* Limitations:
  + Serology has limited utility in CL and MCL due to low antibody titers.

2.5. Histopathology

* Biopsy Analysis:
  + Skin or mucosal biopsies reveal granulomatous inflammation and Leishmania amastigotes.
* Use in MCL:
  + Often required to differentiate from malignancies or fungal infections.

2.6. Imaging and Hematological Parameters

* Ultrasound/CT:
  + Useful in VL to assess hepatosplenomegaly and guide splenic aspiration.
* CBC:
  + Pancytopenia, anemia, and thrombocytopenia are common findings in VL.

3. Pharmacological Treatment

The choice of treatment depends on the type of leishmaniasis, species, geographical region, and patient-specific factors such as age, pregnancy, and immune status.

3.1. Cutaneous Leishmaniasis (CL)

* Pentavalent Antimonials (SbV):
  + Sodium Stibogluconate:
    - Administered intralesionally or systemically.
    - Effective for L. major and L. tropica.
    - Side Effects: Cardiotoxicity, hepatotoxicity [11].
* Miltefosine:

An oral drug effective against L. braziliensis and L. guyanensis.

* + Side Effects: Gastrointestinal upset, teratogenicity.
* Topical Treatments:

Paromomycin-based ointments for localized lesions.

3.2. Mucocutaneous Leishmaniasis (MCL)

* Systemic Antimonials:

Higher doses are required compared to CL. Often effective but associated with higher toxicity.

* Liposomal Amphotericin B:

Effective in refractory cases or where antimonials fail [12].

* Adjunctive Therapies:

Surgical debridement for severe mucosal damage.

3.3. Visceral Leishmaniasis (VL)

* Liposomal Amphotericin B:

WHO-recommended first-line treatment. Single-dose regimens (10 mg/kg) are increasingly preferred due to high efficacy (>95%) and reduced toxicity.

* Combination Therapy:

Amphotericin B with miltefosine or paromomycin reduces resistance risk and treatment duration [13].

* Miltefosine:

Oral agent with high efficacy; limited by teratogenicity and side effects.

* Pentavalent Antimonials:

Used in certain endemic areas but limited by resistance, particularly in India.

3.4. Special Populations

* HIV Coinfection:

Liposomal amphotericin B is preferred due to its safety and efficacy. Relapse prevention requires secondary prophylaxis [14].

* Pregnancy:
  + Amphotericin B is safe and effective during pregnancy.

4. Challenges in Leishmaniasis Management

1. Drug Resistance:

Resistance to pentavalent antimonials is widespread, especially in VL-endemic regions like India and Sudan.

1. Toxicity:

Systemic treatments, including amphotericin B and antimonials, are associated with severe side effects.

1. Access and Cost:

High cost of liposomal amphotericin B and limited availability of miltefosine in low-resource settings.

1. Relapse and Refractory Cases:

Immunocompromised individuals and those with HIV are at higher risk of relapse.

**2. Conclusion**

Advances in diagnostic techniques have significantly enhanced the ability to detect and manage leishmaniasis. Traditional methods such as microscopy and culture, while valuable, are increasingly supplemented by molecular diagnostics like PCR and serological tests such as the rK39 antigen-based assays. These advancements offer higher sensitivity and specificity, enabling earlier detection and improved species differentiation, which is critical for tailoring treatment regimens. However, the lack of widespread access to advanced diagnostic tools in endemic regions remains a critical barrier, highlighting the need for cost-effective, point-of-care solutions.

The pharmacological treatment of leishmaniasis has evolved substantially over the past decades, with drugs such as liposomal amphotericin B and miltefosine transforming outcomes for visceral and cutaneous forms of the disease. Liposomal amphotericin B, in particular, is the gold standard for visceral leishmaniasis due to its efficacy and safety profile, especially in vulnerable populations such as pregnant women and immunocompromised individuals. Despite these advances, significant challenges persist, including drug resistance to pentavalent antimonials, the high cost of newer therapies, and the teratogenic risks associated with miltefosine. Furthermore, the discontinuation of treatment often leads to disease relapse, particularly in immunosuppressed patients such as those co-infected with HIV.

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