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Cutaneous Leishmaniasis an Updating Review of Epidemiology, Diagnosis and Control: Leishmaniasis Kulit: Tinjauan Terkini tentang Epidemiologi, Diagnosis, dan Pengendalian

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Abstract

General Background: Cutaneous leishmaniasis is a neglected tropical disease caused by dermotropic Leishmania species transmitted by sand flies, with a significant global burden.**Specific Background:** The disease shows diverse clinical manifestations and complex transmission patterns influenced by ecological, immunological, and socioeconomic factors. **Knowledge Gap:** Despite advances in understanding parasitebiology and diagnostic tools, challenges remain in earlydetection, treatment variability, and access to healthcare in endemic regions. **Aims:** This review summarizes epidemiology, pathogenesis, diagnosis, treatment, and control strategies of cutaneous leishmaniasis while highlighting key gaps. **Results:** Findings indicate that disease distribution is shaped by environmental changes, host immune responses determine clinical outcomes, and molecular diagnostics such as PCR provide high sensitivity. Treatment remains limited by toxicity, resistance, and accessibility issues. **Novelty:** The article integrates multiple dimensions of the disease and emphasizes the relevance of a One Health approach linking human, animal, and environmental health. **Implications:** Strengthening diagnostic capacity, improving therapeutic strategies, and implementing integrated control measures are essential to reduce disease burden and improve patient outcomes.

Keywords: Cutaneous Leishmaniasis, Epidemiology, Diagnosis, Treatment, Vector Control

Key Findings Highlights

Global transmission patterns are shaped by ecological and socio-environmental changes
Immune response dynamics determine disease progression and lesion outcomes
Diagnostic and therapeutic limitations remain major barriers in endemic regions

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Introduction

One of the most common neglected tropical diseases around the world is cutaneous leishmaniasis (CL) which is caused by the dermotropic protozoa of the genus Leishmania and is transmitted by the bite of infected female phlebotomus and Lutzomyia sand flies (Rafique et al., 2023). Over one billion people are at risk of getting infected and up to half a million and even one million new cases are expected to be registered every year but it is estimated that at least the same amount of people is getting the illness unnoticed by the system due to the lack of proper surveillance and unreported cases in the conflict-stricken areas (De Vries & Schallig, 2022). CL is still endemic in over 90 countries in the Middle East, North Africa, South America, the Indian subcontinent and some parts of Central Asia where environmental and socio-political factors are strongly involved in the transmission of the virus (Karami et al., 2022).The clinical presentation of CL is wide and includes localized and self-limiting ulcers and chronic and disfigurement lesions with significant psychological and social consequences. Such heterogeneity indicates how complicated the interaction between the species of parasites, and the distribution of vectors is, together with host immunity and ecological determinants (Parkash, 2025). Over the past decades, climate change, urbanization, ecological degradation, population migration, and the introduction of competent vectors of the sand fly into new ecological niches have all transformed global trends in CL (Trájer & Grmasha, 2023). Iraq is among the most burdened Middle East countries with CL cases reported in almost all governorates. It can be noted that the disease has a significant seasonal and geographic concentration, particularly in central and southern areas where populations of Phlebotomus sand flies thrive due to the ecological favorability (Kyari, 2024). The presence of environmental disturbances and ineffective waste management, the high density of rodents, and unplanned rapid urbanization have played a major role in supporting active foci of transmission and frequent outbreaks (Cosma et al., 2024). Even though CL is classified as a non-fatal condition, this disease poses a significant burden on a population because of the extended lesion time, possible secondary bacterial infections, permanent scars, and social stigma (Bautista-Gomez et al., 2022). In most of the endemic areas, access to timely diagnosis and treatment is still low. Traditional parasitological techniques are not sensitive, whereas molecular diagnostic procedures like PCR are not available in the low-resource areas (Candia-Puma et al., 2025). The existing treatments, such as pentavalent antimonials, amphotericin B, miltefosine, cryotherapy, and thermotherapy, are associated with the issues of drug toxicity, increased resistance, treatment failures, and variable drug availability (Sundar et al., 2024). The more recent scientific developments argue that more work should be done on translational research, especially on creating topical and locally targeting therapies with a lower systemic toxicity and increased access by the affected populations (Altamura et al., 2020). The one health approach is needed to develop the sustainable CL control plans which combine the human, veterinary, and environmental health sectors because of the zoonotic nature of most Leishmania species and the involvement of animal reservoirs in the disease transmission (rodents and dogs) (Filho et al., 2025). The review is expected to offer a brief summary of cutaneous leishmaniasis, its epidemiology, pathogenesis, diagnosis and the existing treatment options, highlight critical areas of knowledge gaps and the relevance of a One Health approach.

1. Global Epidemiology of Cutaneous Leishmaniasis

The distribution of cutaneous leishmaniasis (CL) has a very focal and widespread global trend, with the greatest resolutions being centralized in few endemic areas (De Vries & Schallig, 2022). Despite over 90 countries reporting transmission, most of all confirmed cases are a result of a few high-incidence centers that spread throughout the Middle East, North Africa, and even into parts of Latin America (Al-Ashwal, 2024). Other countries, including Afghanistan, Syria, Iran, Saudi Arabia and Iraq, regularly record some of the most significant numbers of Old World cases(Rahimi et al., 2025). These areas are characterized by high changes in intensity of transmission associated with ecological appropriateness of sand fly vectors and

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existence of established foci of zoonotic reserves (Al-Ashwal, 2024). Epidemiological records indicate that the CL occurrence in different years has fluctuated significantly due to the difference in land use, the density of rodent population and the change in climatic conditions that affected the seasonality of sand flies (jamali& Bokaie, 2024). Also the coincidence between Leishmania major and Leishmania tropica leads to heterogeneous transmission cycles, the zoonotic and anthroponotic patterns exist simultaneously (Saik et al., 2022). South-to-north expansion of sand fly habitats has been witnessed in many countries and an extension of the transmission season following the increase in warmer temperatures over extended periods of the year (Maia, 2024). forced displacement and population movement have reshaped reservoir-vector-human contact patterns in place, as well as introducing infection into new settlements, and changing the epidemiological situation in such places as Syria or Yemen. In Brazil, Peru, Colombia, and Bolivia, high transmission has been sustained in the New World where the rate of environmental erosion and intrusion in forest margins have increased human contact(Karimi et al., 2021). In all the impacted areas climate change is becoming one of the strongest causes of CL epidemiology. The modeling studies are forecasting major growth of the zones that are conducive to the vectors and this might lead to incidence in areas that had reported the least transmission(Amro et al., 2022). Poor infrastructure, social economic vulnerability, and access to diagnostic and treatment services also contribute to the disease burden of most endemic countries (Dires et al., 2022).

2. Etiology and Parasite Biology

Leishmania protozoan parasites of the genus Leishmania cause cutaneous leishmaniasis (CL), which is a dermotropic protozoan disease (Balahbib et al., 2023). The organisms have a digenetic life cycle between a mammalian host and a phlebotomine sand fly vector. The parasite has two primary forms of development intracellular amastigote in the macrophage of the vertebrate host and extracellular promastigote in the gut of the sand fly (Cecílio et al., 2022). (Fig. 1)

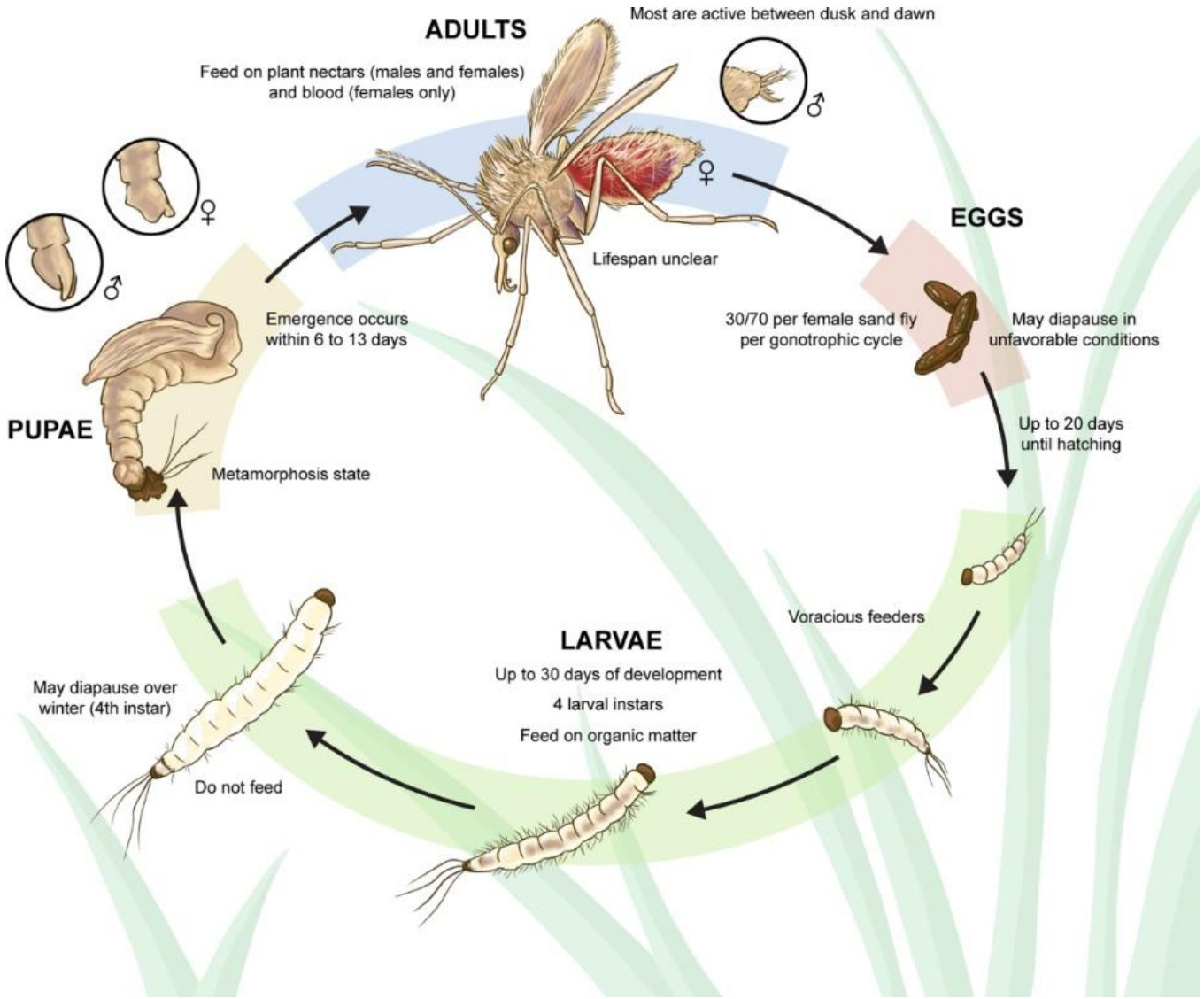

Fig. 1 : Schematic representation of the sand flies life cycle.

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Leishmania in the mammalian host remains as amastigotes, which are small, non-flagellated, and they survive and reproduce in parasitophorous vacuoles of the host macrophages (Yasmin et al., 2022). These cells create a safe habitat that helps the parasite to escape immune-mediated destruction and facilitates uninterrupted multiplication within the cell (Barrie, 2022). The parasite alters the macrophage signaling and inhibits the production of major cytokines including IL-12, hence promoting a microenvironment which facilitates its survival (Saha et al., 2022). By feeding on a female sand fly, infected macrophages are consumed and amastigotes develop into promastigotes in the midgut of the vector (Cecílio et al., 2022). These promastigotes develop in procyclic, nectomonad and leptomonad stages and finally in metacyclic stages- the most infective form adapted to be transmitted (Tao & Jia, 2024). Sand fly saliva is essential in the inoculation process; it has strong immunomodulatory molecules that help the parasite to establish itself by suppressing neutrophil premature responses and biasing local immunity (Tom et al., 2023). Differences between species affect tissue tropism, virulence and disease phenotype. L. major is mostly responsible of rapid lesions that are ulcerative with a high inflammatory response, and L. tropica is responsible of more chronic and dry lesions that take a long time to heal (Yadav et al., 2023). Species of the New World, especially the L. braziliensis complex, have a special ability to spread metastatically to mucosal tissues resulting in mucocutaneous leishmaniasis (Reimann et al., 2022).

3. Pathogenesis and Immunological Response

The pathogenesis of cutaneous leishmaniasis (CL) is governed by the complex interplay between *Leishmania* parasites and the host immune system (Costa-Da-Silva et al., 2022). Clinical outcome is determined not only by parasite species and virulence factors but also by the nature, timing, and magnitude of the host immune response .Fig. 2 (Scott & Novais, 2016).

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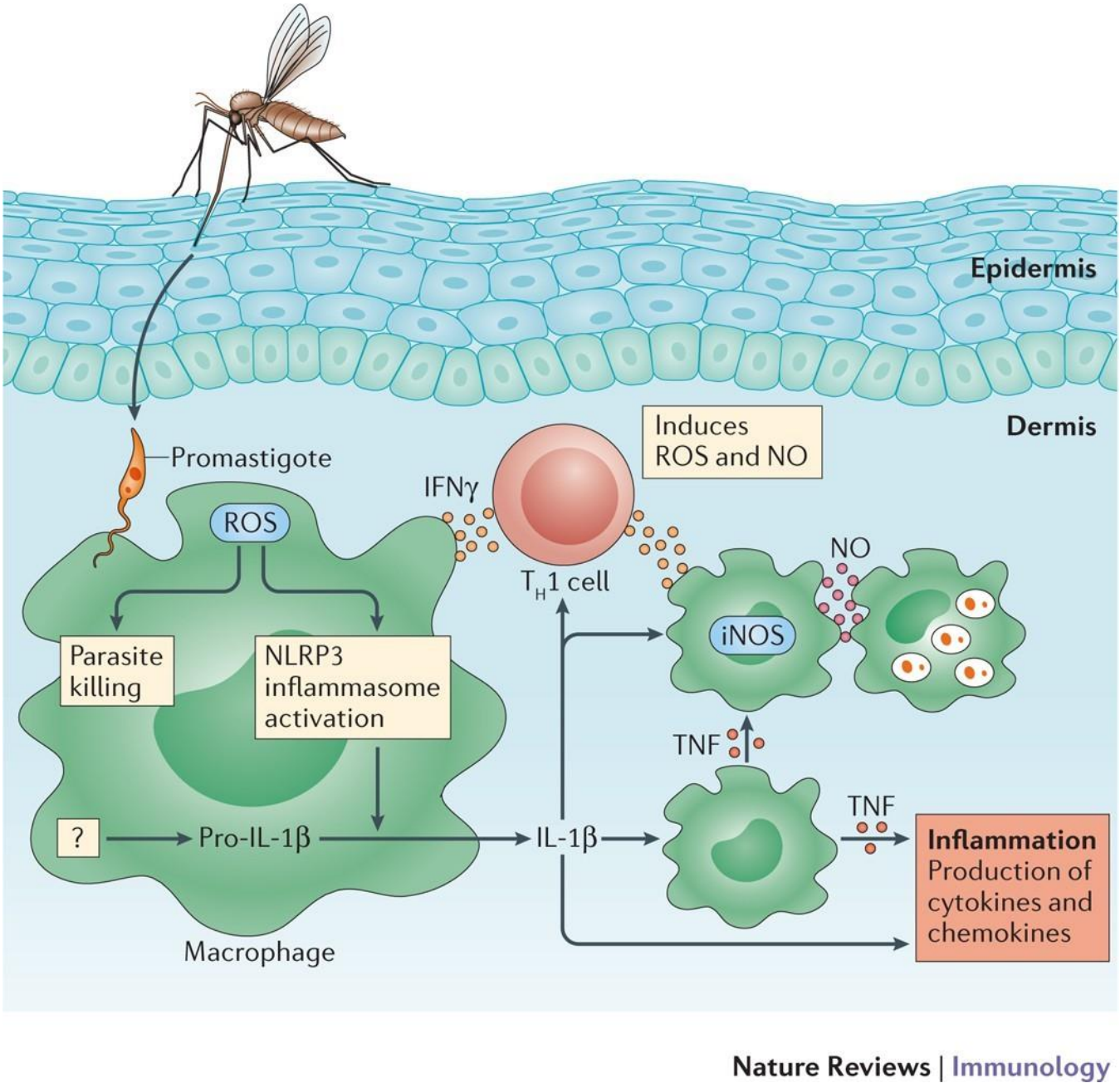

Fig.2: Immunological pathways activated during cutaneous leishmaniasis, showing macrophage responses, TH1 activation, and production of reactive oxygen and nitrogen species.

Following metacyclic promastigotes inoculation in the dermis, sand fly saliva promotes early parasite survival by suppressing neutrophil activation, as well as regulating local inflammatory mediators (Yasmin et al., 2022). The initial cells to come into contact with the parasite are neutral blood cells known as neutrophils and the initial cells to serve as temporary carriers of the Trojan horse, which enables Leishmania to find its way into the macrophages undetected (Uribe-Querol & Rosales, 2024). The infection process is successful when the promastigotes change into intracellular amastigotes in the macrophages (Clos et al., 2022). Leishmania is able to modulate so many signaling pathways to avoid the activation of macrophages, inhibit oxidative and nitrosative killing as well as the synthesis of IL-12 which is a key cytokine needed to generate protective cellular immunity (Saha et al., 2022). Th1-mediated and Th2-mediated immunological reactions represent a vital factor in the development or control of a disease (Bamigbola & Ali, 2022). Th1-dominant response which is favoring production of IFN-s, IL-12 and TNF-s facilitates classical activation of macrophages and activation of nitric oxide in causing parasite killing (Paton et al., 2025). Localized and self-limiting lesions and presence of parasite replication are generally linked to this profile. Conversely, a Th2-biased reaction, characterized by IL-4, IL-10, and TGF-B prevents the microbicidal activity in macrophages and promotes parasite survival, which leads to chronic or non-healing disease (Guglielmo et al., 2024). It is especially IL-10 that is central to the inhibition of antigen presentation and cytotoxic T-cell

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effector functions, allowing further intracellular survival to occur. Other immune components besides Th1/ Th2 paradigm have a role to regulate disease outcome(Costa-Da-Silva et al., 2022). Regulatory T cells (Tregs) restrain excessive inflammation, but instead there may be the encouragement of chronic infection through inhibitor effector responses (Zayats, 2023). Early immune evasion has also been attributed to neutrophil extracellular traps (NETs) dysfunction, dendritic cell dysfunction, and antigen presentation defects (Costa-Madeira et al., 2022). In addition, species variations in parasites lead to diverse immunopathological responses: L. major has been shown to trigger intense inflammatory reactions with rapid ulceration, and L. tropica has been shown to trigger slower, chronic inflammatory reactions and slow development of lesions (De Vries & Schallig, 2022). The species included in L. braziliensis complex induce excessive levels of cytotoxicity which may cause mucosal destruction and extreme tissue damage (Carvalho et al., 2022). The persistence of parasites and the efforts to combat them both result in the chronic inflammation observed in CL lesions in a dynamic balance, The continuing amastigotes ensure an inflammatory microclimate, which favors the establishment of granuloma and remodelling of the tissue (Balahbib et al., 2023) .The major protective and pathological immune mechanisms involved in cutaneous leishmaniasis are summarized in Table 1.

Table 1 : Immunopathological Mechanisms in Cutaneous Leishmaniasis

Immune Component	Protective Role	Pathological Role	Key Cytokines / Pathways	Supporting References
Th1 Response	Parasite clearance	—	IFN-γ, IL-12	Scott & Novais, 2016
Th2 Response	—	Disease progression	IL-4, IL-10	Yasmin et al., 2022
Neutrophils	Early parasite control	Trojan horse effect	NETs, ROS	Uribe-Querol & Rosales, 2024
Macrophages	Killing via NO production	Intracellular parasite survival	iNOS, ERK1/2	Barrie, 2022
T cell exhaustion	—	Chronic infection	PD-1 pathway	Costa-Madeira et al., 2022

4. Clinical Manifestations

The clinical manifestation of cutaneous leishmaniasis (CL) is considerably diverse with respect to the infecting species of Leishmania, geographical area, immune response of the host, as well as the length of infection (Saidi et al., 2023). In spite of this variability, the majority of cases start at the locale of the sand fly bite in the form of a small erythematous papule which continues to increase in size over weeks and results in a nodule or plaque, which finally evolves into a well-defined ulcer with raised indurated sides and centrally situated necrotic base (Yizengaw et al., 2024). These ulcers are typically painless unless secondarily infected, and they may appear singly or as multiple lesions depending on the number of bites or dissemination patterns (De Souza et al., 2025).

4.1. Localized Cutaneous Leishmaniasis (LCL)

The most common form, often caused by *L. major*, *L. tropica*, or *L. mexicana*. Lesions often appear in exposed regions of the face, arms and legs and L. major infections often ulcerate very quickly with severe inflammation but L. tropica lesions are more persistent and chronic, which can last months or years before healed (LaRocque et al., 2024).

4. 2. Diffuse Cutaneous Leishmaniasis (DCL)

A serious variant, which is rare and usually caused by L. amazonensis or L. aethiopica. It is found in people who are unable to honor cellular immunity against Leishmania causing the extensive nodules non-ulcerative on the skin. These lesions are full of amastigotes and have poor response to the conventional therapy (Kumar et al., 2023).

4. 3. Mucocutaneous Leishmaniasis (MCL)

L. braziliensis and its associated species are the major causes of this in Latin America. The lesions can start as normal cutaneous ulcers and then progress to mucosal lesions of the nose, mouth and pharynx(ElShewy, 2024). The effects of MCL are progressive damage of tissue, perforation of the nasal septum and severe disfigurement in case of untreated MCL. Pathogenesis is characterized by overreaction of cytotoxic immunity and not heavy loads of parasites (Ibrahim et al., 2023).

4. 4. Leishmania Recidivans (LR)

Also known as L. tropica, it is a chronic relapsing disease which manifests as gradually growing papular lesions around the periphery of a healed scar. Completely inadequate clearance of the parasites and low-grade focal inflammatory response may result in LR taking years to resolve (Gavazzoni Dias et al., 2023).

4. 5. Post–Kala-Azar Dermal Leishmaniasis (PKDL)

Even though mainly associated with L. donovani infection following visceral leishmaniasis, PKDL is sometimes overlapping with CL within endemic areas. It manifests as Macules, papules, or nodules on the face and the trunk and is a cause of persistent transmission in some geographical locations.Fig3. (Karunaweera et al., 2019).

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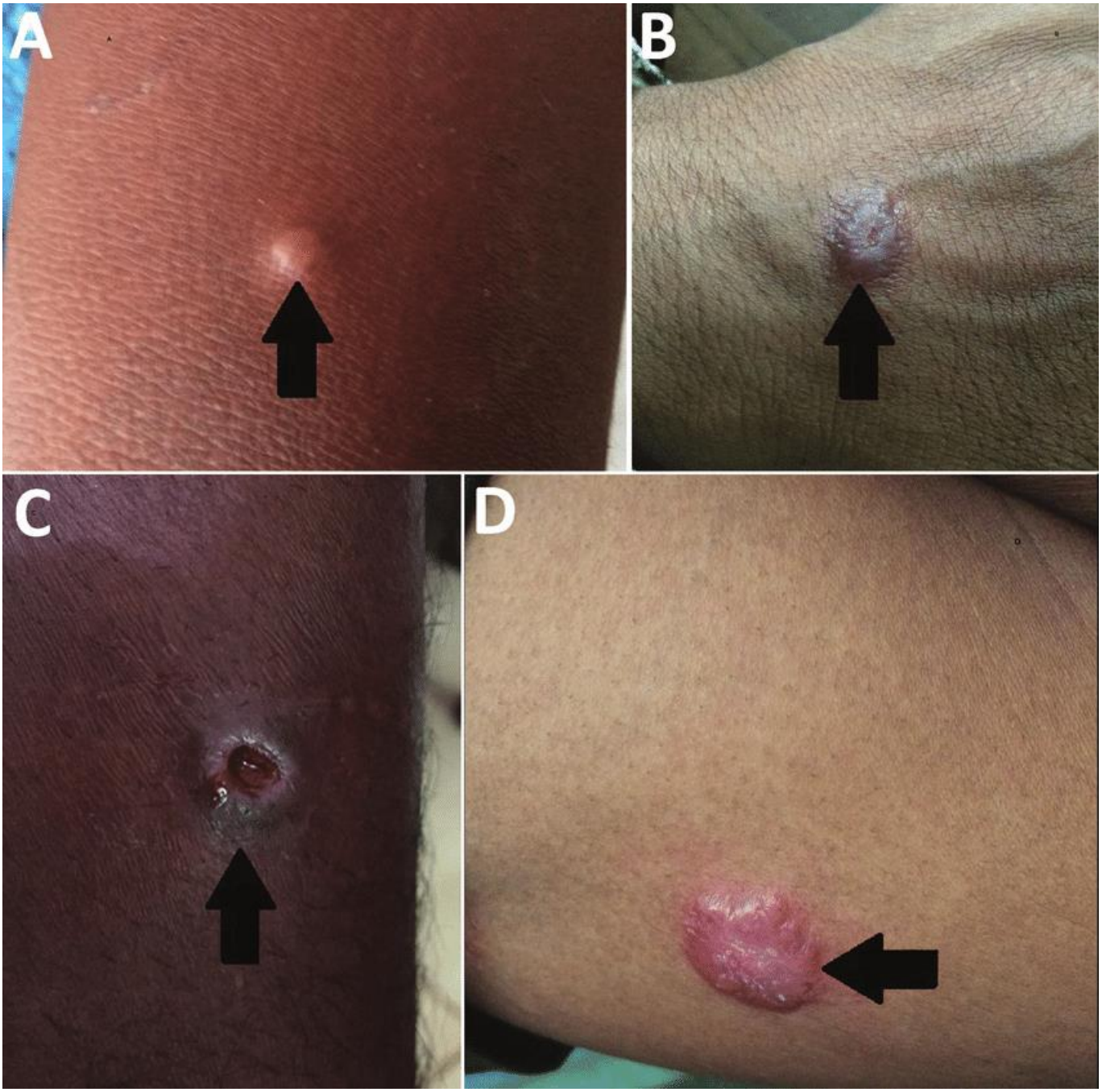

Fig. 3. Representative clinical forms of cutaneous leishmaniasis. A) papule; B) nodule; C) ulcer; D) plaque. (Karunaweera et al., 2019).

5. Diagnosis of CL

Cutaneous leishmaniasis (CL) is a condition whose diagnosis is based on both clinical assessment, parasitological diagnosis, molecular diagnosis, and immunological or serological diagnosis (De Vries & Schallig, 2022). Clinical presentation gives initial suspicion but diagnostic confirmation is necessary because the problem has a wide differential diagnosis of bacterial, fungal and mycobacterial infections and other ulcerative dermatoses. Species identification is important in the treatment guideline, clinical outcomes and epidemiology (Balahbib et al., 2023).

5. 1. Clinical Diagnosis

Clinicians generally identify CL according to morphology of the lesions which may be papules, nodules, plaques, or ulcerative forms with elevated borders (Alasswad et al., 2024). Nevertheless, the identification of clinical features is not

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enough to make the final diagnosis because there are several dermatological conditions that can resemble CL. Epidemiological context, such as residence or travel to endemic areas, strengthens diagnostic suspicion (Al-Dabbagh & Ismail, 2024).

5. 2. Parasitological Diagnosis (Microscopy and Culture)

Direct microscopic detection of amastigotes in Giemsa-stained smears from lesion scrapings, aspirates, or biopsies remains the most widely used diagnostic method in endemic settings (Saïdi et al., 2022). The sensitivity is 50-90 percent with regard to parasite burden and quality of the sample (Palma et al., 2024). Culture in Novy-MacNeal-Nicolle (NNN) media or Schneiders medium is more diagnostic but lacks special facilities, it also takes a long incubation period and it is also likely to be contaminated (De Oliveira Filho et al., 2024).

5. 3. Molecular Diagnosis (PCR-Based Methods)

The most sensitive and specific technique of detecting CL and species identification has been polymerase chain reaction (PCR) (Van Henten et al., 2022). Low parasite loads, and differentiation between L. major, L. tropica, L. infantum and New World species can be detected by conventional PCR, nested PCR, real-time PCR, and kDNA-targeted PCR.Molecular tools are particularly valuable in chronic lesions, atypical presentations, or cases with negative microscopy (Grogl et al., 2023).

5. 4. Loop-Mediated Isothermal Amplification (LAMP)

LAMP represents an emerging, field-friendly diagnostic approach requiring minimal equipment and providing rapid results. It has proven to be highly sensitive just like PCR and it is usable even at point-of-care locations hence it is ideal when in remote or resource-limited regions (Nzelu et al., 2019).

5. 5. Histopathology

Histopathological examination of a skin biopsy indicates the presence of granulomatous inflammation, amastigote-filled macrophages, and the levels of necrosis (Sánchez-Romero et al., 2019). In chronic lesions or in the healing lesions, amastigotes are usually limited; nevertheless, histopathology is also applicable to eliminate the presence of alternative diagnoses like cutaneous tuberculosis, deep fungal or lesions of neoplasms (Al-Dabbagh & Ismail, 2024).

5. 6. Serological and Immunological Tests

In CL, serology is not as useful as it would be because the systemic response to antibodies is low. ELISA, IFAT and DAT are the tests applicable to visceral leishmaniasis. But, intradermal Leishmanin Skin Test (LST or Montenegro test) is useful in epidemiological survey and in the detection of the delayed-type hypersensitivity, but not in the confirmation of the acute disease (Deepachandi et al., 2022).Table 2

Table 2 . Comparative Diagnostic Performance and Evidence-Based Evaluation of Methods for Cutaneous Leishmaniasis

Method	Sensitivity (Reported Range)	Specificity	Species Identification	Field Applicability	Supporting Evidence
Microscopy	50–90%	High	No	High	Widely used first-line tool; operator dependent
Culture	Moderate	High	Limited	Low	Time-consuming; low field feasibility
PCR	>95%	Very High	Yes	Moderate	High accuracy (AUC ≈ 0.91) (Candia-Puma 2025)
LAMP	High	High	Yes	High	Suitable for point-of-care settings (Nzelu 2019)
CL Detect Rapid Test	64–83% (modified sampling)	Moderate	No	High	Variable sensitivity across regions (Van Henten 2022; Grogl 2023)
Histopathology	Variable	Moderate	No	Moderate	Useful for differential diagnosis

6. Treatment and Therapeutic Challenges

The treatment of cutaneous leishmaniasis (CL) varies by species, geography, lesion severity, and host immune status, the availability of multiple therapeutic options, no single regimen is universally effective, and treatment is often complicated by toxicity, resistance, and limited access to species identification (Madusanka et al., 2022).

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6. 1. Pentavalent Antimonials

Sodium stibogluconate and meglumine antimoniate remain first-line therapies in many endemic countries, they are effective against *L. major*, but resistance and toxicityincluding cardiac, hepatic, and pancreatic effects limit their use in some regions (Solomon et al., 2024).

6. 2. Miltefosine

The only widely used oral drug for CL. It shows good efficacy against several New World species but variable results for *L. tropica*. Gastrointestinal side effects, teratogenicity, and emerging resistance restrict its long-term applicability (López et al., 2022).

6. 3. Amphotericin B (including Liposomal Form)

Effective for complicated, chronic, or mucocutaneous disease. Liposomal formulations are safer but costly and often unavailable in low resource settings,Nephrotoxicity remains a concern (Carrer et al., 2026).

6. 4. Local Therapies

Cryotherapy, thermotherapy, and intralesional antimonials are effective for uncomplicated lesions and offer lower systemic toxicity, they remain practical options for first-line management in many endemic regions (Pradhan et al., 2021).

6. 5. Alternative and Emerging Options

Azole antifungals (e.g., fluconazole, ketoconazole) show modest success for some species. New approachessuch as topical paromomycin, immunomodulators, nanocarriers, and photodynamic therapy are under investigation to improve safety and efficacy (Isern et al., 2025).Table 3

Table 3 . Current Therapies and Reported Drug Resistance in Cutaneous Leishmaniasis

Treatment	Main Use	Advantages	Limitations	Reported Resistance / Reduced Response	Key References
Pentavalent Antimonials	First-line in many endemic regions	Effective for *L. major*	Toxicity; parenteral administration	Increasing treatment failure in *L. tropica* endemic areas	Madusanka 2022; Sundar 2024
Miltefosine	Oral alternative for several species	Easy dosing	GI effects; teratogenicity	Reduced cure rates in New World CL; emerging resistance	De Souza 2025; López 2022
Amphotericin B (liposomal)	Complicated/refractory cases	High efficacy	High cost; nephrotoxicity	Limited resistance reported; cost limits access	Sundar 2024
Local Therapies (Cryo/Thermotherapy)	Uncomplicated single lesions	Low systemic toxicity	Variable efficacy	Combination therapy improves outcomes	López 2022
Azoles	Secondary option	Safe; inexpensive	Inconsistent cure rates	Variable species-dependent response	Madusanka 2022
Topical Paromomycin	Selected species	Non-invasive	Limited availability	Resistance less documented; variable response	Carrer 2026

7. Control of Cutaneous Leishmaniasis (CL)

Cutaneous leishmaniasis can only be controlled through a combination of measures that focus on the parasite, the sand fly vector, and the animal reservoir hosts coupled with the focus on environmental and socioeconomic conditions that perpetuate conditions of transmission (Cosma et al., 2024).

7. 1. Vector Control

Reducing sand fly populations is central to CL prevention. Effective methods include:

- Indoor and outdoor residual insecticide spraying.
- Use of insecticide-treated bed nets and curtains in high-risk areas.
- Environmental modifications such as removing organic debris and improving waste management to reduce breeding sites.
- Personal protection measures, including repellents and protective clothing during sand fly activity periods (Kumari et al., 2025).

7. 2. Reservoir Host Management

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For zoonotic species (*L. major*, *L. mexicana*, *L. braziliensis*), controlling reservoir hosts helps disrupt the transmission cycle. Strategies include:

- Rodent control in peri-urban and agricultural areas.
- Reducing food waste and improving sanitation to limit rodent populations.
- Monitoring and managing infections in domestic animals when relevant (Blaizot et al., 2024).

7. 3. Case Detection and Treatment

Diagnosis and prompt treatment decrease the infectivity period and minimize the spreading. It is important to make diagnostic capacity in primary healthcare centers stronger, especially in endemic rural areas (Madusanka et al., 2022).

7. 4. Community Education and Behavioral Measures

Community participation in prevention can be enhanced by creation of awareness regarding sand fly avoidance, optimal times of day when sand flies bite, and the hygiene of the areas. Long-term sustainable control is made by educating populations at risk (Berhe et al., 2022).

7. 5. Environmental and Urban Planning Interventions

The expansion of cities into the natural habitats enhances the human-vector-reservoir interaction. Planned housing, effective waste disposal and vegetation management minimize the sand fly density and human contact (Khosravi et al., 2025).

7. 6. Integrated Control Programs

Combining the best interventions with the use of vectors control, environmental control, reservoir control, and enhanced clinical care is the most successful. It takes coordination between the authorities in the public health, veterinary services, and local communities to have lasting impact (Bamorovat et al., 2023).

Conclusion

Cutaneous leishmaniasis remains a significant public health concern shaped by complex interactions between parasite biology, vector ecology, and host immune responses. There has been significant advancement in the epidemiology, clinical manifestation, diagnosis, treatment, and control of its epidemiology. Nevertheless, there are still obstacles because of species-related differences, lack of diagnostic access in the endemic regions and inconsistent efficacy of known treatments. Enhancing early diagnosis, administering proper treatment regimens, and initiating a combination of both, with regards to the use of vectors and reservoirs, is critical in the efforts to decrease disease burden and enhance disease outcomes in the concerned populations.

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