Leishmaniasis: An Arabic Middle Eastern Glimpse

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Leishmaniasis is a neglected, chronic vector-borne disease caused by an obligatory intracellular protozoan. Although the number of cases is not rising worldwide, it is geographically widespread. It is endemic in most Arabic countries. Human leishmaniasis is caused by approximately 30 different parasite species. Leishmaniasis is transmitted to man by inoculation of the infective stage "promastigote" during the bite of the female sandfly. Disease development and severity are regulated by the equilibrium between TH1 and TH2 immune responses. The common types are cutaneous leishmaniasis (CL), mucocutaneous leishmaniasis (MCL), and visceral leishmaniasis (VL). Early diagnosis and proper treatment are crucial in the prognosis of the disease. Diagnosis can be achieved through stained blood smear examination, culture, serological assays, and molecular diagnostics. Treatment options include drug chemotherapy, local therapy, or a combination of them, depending on the case. Many generations of vaccines have been developed, but there is no conclusive one. Many challenges face the control of leishmaniasis in the Middle East and North Africa (MENA) regions.

INTRODUCTION

Leishmaniasis is a parasitic illness spread by the bite of a female phlebotomine sandfly that affects many animal species, including humans. It is a parasitic disease transmitted by vectors that is often under-reported. They continue to be an important health issue in many developing nations [1]. About 30 distinct species make up the genus *Leishmania*, the majority of which often infect people and cause a variety of diseases, including mucocutaneous, cutaneous, and visceral leishmaniases. The variety of the *Leishmania* species and the immunological reaction of the infected people both contribute to the heterogeneity of the clinical characteristics [1].

METHODOLOGY

This review information is collected mostly from recent WHO endemicity reports, Manson`s Tropical Diseases, the 23rd and 24th editions, and from meticulous literature searches on NCBI PubMed or Google Scholar. Searching process was done using the terms "global distribution", "incidence", "diagnosis", "prevention and control of leishmaniasis", "Leishmaniasis North Africa", and "Leishmaniasis Middle East".

Parasite classification

The protozoans of the genus *Leishmania* are members of the Kinetoplastida order and the Trypanosomatidae family, which also contains other parasites that affect humans and other animals (genus *Trypanosoma*), plants (*Phytomonas*), and insects (*Leptomonas*, *Crithidia*, etc.). Approximately 70 distinct varieties of sand flies (named *Phlebotomus* in the Old World and *Lutzomyia* in the New World) are known to transmit more than twenty species of *Leishmania*. The writers who put the greatest effort into categorization and made it evolutionary were Lainson and Shaw [2]. *Leishmania sensu stricto* is prevalent in the Old and New Worlds. *Leishmania viannia* is only prevalent in the New World. They were separated into two subgenera in their most recent classification of the genus *Leishmania* [2]. There were several species complexes within these two subgenera. Most of the taxonomic categories formerly defined by the Linnean classifications, especially those of Lainson and Shaw **[2]**, were confirmed by the phenetic and especially the cladistic classifications.

Epidemiology

Geographical distribution

Leishmaniasis is a worldwide illness, although the location of the vector has an impact on where it occurs. Latitudes 32° south and 45° north serve as the extension limitations. 350 million people in 90 nations are at risk from the leishmaniases. Between 1.5 and 2 million new instances are thought to occur annually. There are 47 nations where the disease is present, and its mean yearly incidence is thought to be approximately 500,000 new cases. From east to west, the main historical centers of endemicity are Brazil, China, India, East Africa, Central Asia, and the Mediterranean region. The anthroponotic species *Leishmania donovani* is geographically limited to regions such as China, India, and East Africa, whereas the zoonotic species *L. infantum* is prevalent across China and East Africa. Ninety percent of all VL cases globally are in Bangladesh, India, Nepal, Sudan, and Brazil [1]. The bulk of Old-World CL is attributed to the two species *L. major* and *L. tropica*, and it comes from the Near and Middle East, including Afghanistan, Iran, Saudi Arabia, and Syria. The zoonotic CL-causing species, *L. major*, has a wide geographic range that includes West, North, and East Africa, the Near and Middle East, and Central Asia. The anthroponotic species *L. tropica* is widespread in the Near and Middle East, as well as Tunisia and Morocco, where some foci may have an animal reservoir. Other species have restricted geographic ranges: *L. aethiopica* to Kenya and Ethiopia, *L. arabica* to Saudi Arabia, and *L. killicki* to Tunisia and Algeria **[1]**. Figure 1 and Table 1 show roughly the 21 nations that make up the Arabic Middle East and the status of endemicity, including Mauritania, Morocco, Algeria, Tunisia, Libya, Egypt, Yemen, United Arab Emirates, Syria, Saudi Arabia, Qatar, Palestinian territory, Oman, Lebanon, Kuwait, Jordan, Israel, Iraq, Iran, Djibouti, and Bahrain. In these places, factors including poverty and a lack of veterinary and public health services contribute to the spread of leishmaniasis **[3,4]**. *L. braziliensis* has the broadest geographic range in the New World. It reaches north of Argentina and south of Mexico. Although *L. amazonensis* is widely distributed across South America, the incidence of human infection is still uncommon.

Vector

Sandflies, the vectors of *Leishmania* species, belong to the Phlebotominae subfamily of the Psychodidae family. There are over eight hundred known sandfly species, divided between the New World and the Old World. There are ٢ distinguished biological phases in their life cycle: the flying adult and the developmental stages **[5]**. The adults are little flying insects with yellowish fuzzy bodies that measure between 2-4 mm in length. They snooze during the day in protected, dark areas (resting spots). They are active in the evening and at night. Both sexes consume plants, but before females can produce eggs, they also require a blood meal. Potential hosts include mammals, birds, amphibians, and reptiles. The kind of sandfly and the characteristics of the host determine the species' feeding behavior. The first larval stage will hatch from 50–100 eggs laid by an engorged mother. The black head larvae have a cylindrical, filthy white body with long caudal setae. Depending on the species, the climate, and the availability of food, larval development may take place from 30 to 60 days.

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They reproduce by breaking down organic molecules in the soil. The accurate location for sandfly breeding is still unclear for most species, which makes it difficult to control sandflies. The 4th stage larva clings to the substrate to produce the pupa, which turns into an adult in 7–8 days **[2]**.

Fig. 1: Middle East and North Africa Arabic countries endemicity map **[6]**

Table 1. 2022 WHO updated report for the endemicity of CL and VL in the Arabic Middle Eastern region **[٧]**.

Country	2021 (CL and VL endemicity)
Mauritania	Endemic
Morocco	Endemic
Algeria	Endemic
Tunisia	Endemic
Libya	Endemic
Egypt	Endemic
Palestinian Territory	Endemic
Jordan	Endemic
Israel	Endemic
Lebanon	Endemic
Syria	Endemic
Kuwait*	Endemic
Iraq	Endemic
Iran	Endemic
United Arab Emirates	Nil
Qatar	Nil
Bahrain	Nil
Oman	Endemic

Saudi Arabia	Endemic
Yemen	Endemic
Djibouti	Endemic

*Kuwait is recorded as endemic for CL only.

Reservoir

The reservoir hosts for the majority of leishmaniases are different kinds of animals. Both wild and domestic mammals can serve as reservoirs, or in some instances, even humans, depending on the focus. These several reservoir types in the instance of visceral leishmaniasis illustrate various evolutionary stages taken in the direction of anthropizing a wild zoonosis. One significant exception is the dog, which frequently gets a widespread and lethal illness because it is well-accommodative to *Leishmania* and only develops minor infections that may last for several years. The reservoirs are found in 7 families of mammals, including edentates, rodents, carnivores, hyraxes, marsupials, primates, and perissodactyls **[^]**.

Life cycle (Fig. 2)

Man, or other animal reservoirs, get the infection through bites of the female phlebotomine sand fly, mostly at night ("from dusk till morning"). The promastigote and amastigote are two distinct phases in the life cycle of *Leishmania* sp. The promastigote has a flagellum that aids in motility in the gut of the sandfly **[9, 10]**. The promastigote forms, also known as the Leishman-Donovan bodies, are transformed into the amastigote forms inside the mammalian host. This occurs when the promastigote form is inoculated into the mammalian host and phagocytosed by mononuclear cells. The amastigotes multiply and expand inside the host's reticuloendothelial system, producing either the asymptomatic or symptomatic forms of the disease, depending on the underlying host and parasite species' characteristics. To generate mucosal and visceral illness, the amastigotes can move hematogenously and lymphatically **[9]**. According to recent research, the *Leishmania* RNA Virus (LRV1) infects both the *L. Viannia (V.) guyanensis* and *L.V. braziliensis* species. This virus causes a hyperimmune reaction by toll-like receptors, which leads to damage of the mucosa and widespread infection. Despite the discovery of LRV2 (a non-Viannia subspecies of LRV) in *L. major*, there is no evidence linking severity to clinical phenotype **[8]**. The main way that *Leishmania* sp. spreads is through the inoculation of metacyclic promastigotes, which are typically transmitted through sandfly bites. There have been a few documented cases of blood-borne spread of visceral leishmaniasis (VL) and congenital transmission. Direct sexual contact transmission has been documented **[11]**. Syringe exchange has been implicated in the large number of *HIV/L. infantum* co-infections among intravenous addicts in southern Europe. In CL, contacting the active lesion is not harmful; however, the infection necessitates injecting extracts from active lesions. This was previously done in the past in endemic locations as a rudimentary type of immunization **[12]**.

Pathogenesis

Leishmaniasis is traditionally understood to result from an imbalance between TH1 and TH2 cells. Primary TH1 responders have good parasite control and minimal parasitemia, but because of their hyperactive cellular immunity and cellular degeneration, they are susceptible to MCL **[13, 14]**. People with a predominated TH2 showed a higher parasite burden because antibody production can’t control the intracellular infection. Patients with predominant TH2 activity have a higher risk of developing disseminated sickness, which can manifest as VL or, in the New World, disseminated cutaneous leishmaniasis (DCL). Numerous lesions throughout the body clinically suggest DCL **[13]**.

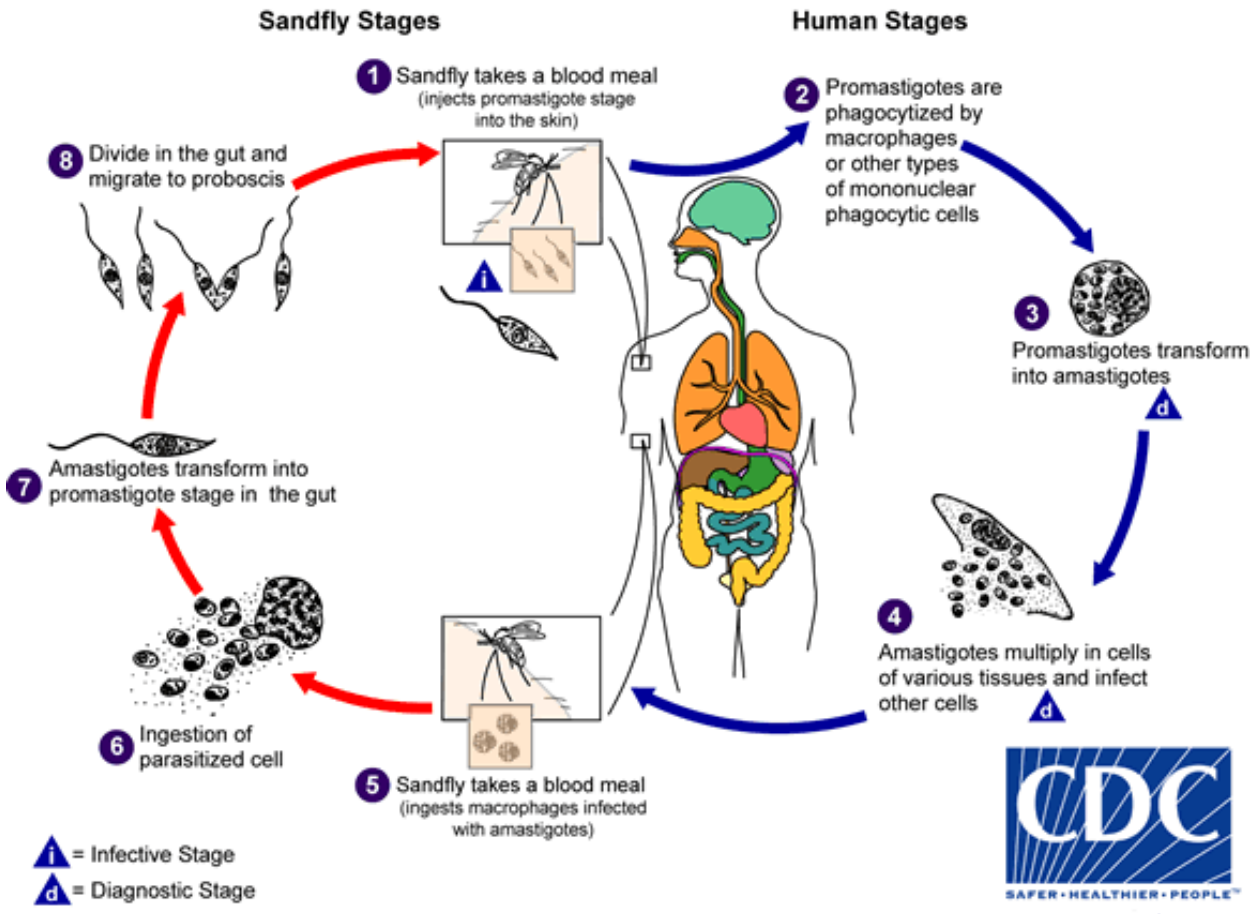

Fig. 2. The life cycle of Genus *Leishmania* **[10].**

Virulence factors

Lipophosphoglycan:

Procyclic and metacyclic promastigotes have different thicknesses of their surface glycocalyx, with lipophosphoglycans (LPGs) being the dominant structure. LPGs are synthesized in promastigotes and have varying side chain structures and core locations. They are essential during the parasite's entrance and the sequelae of infection. The earlier defense against *Leishmania* is by the polymorphonuclear cells (PMNs), which transfer promastigotes safely into macrophages in a process called the "Trojan Horse." The leishmanial virulence factor LPG prevents phagosome and lysosome fusion, allowing the parasite to change from pH-sensitive promastigotes into pH-resistant amastigotes. It chelates calcium ions and inhibits diacyl glycerol (DAG)/ protein kinase c (PKC) signaling, blocking PKCα signaling in macrophages. LPG postpones the emergence of the tardy endosomal markers Rab7 and LAMP-1 on the buildup of F-actin and parasitophorous vacuoles. Additionally, it shields parasites from lysosomal enzyme-mediated destruction and reactive oxygen intermediates. Additionally, LPG inhibits the assembly of NADPH oxidase in phagosomes, which impacts the stimulation of the host's innate immune reaction **[14, 15]**.

GRP94

A distinct truncated type of LPG called LPG3 could be identified as the Genetic complementation of LPG-defective *L. donovani*. The LPG3 shares structural similarity with mammalian endoplasmic reticulum chaperone GRP94. The LPG3/GRP94 regulates chaperone-like functions in the parasite and is highly immunogenic. It plays a distinct function in parasite metabolism concerning its mammalian homolog **[15]**.

Proteases

Proteases are a group of enzymes that are capable of digesting the target proteins. They can be classified by the amino acid present in the active sites, playing crucial roles in an organism's life cycle. Aspartyl-, serine-, metallo-, and

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cysteine proteases are reported as important virulent factors for *Leishmania* parasites. Aspartyl protease expression is essential for parasite proliferation.

GP63 is a leishmanial protease with a large scale of substrate specificity, including gelatin, casein, hemoglobin, albumin, and fibrinogen. It belongs to the metzincin class and is inactive after translation **[16]**. GP63 is a Zn-dependent metalloprotease and is processed in the endoplasmic reticulum. It can be excreted by vesicles or constantly, depending on the autoproteolytic breakdown of the inactivation peptide. GP63 is a key factor in *Leishmania* virulence, cleaving C3b into C3bi, which aids in the attraction of the complement lysis mechanism and safe internalization of parasites. It also supports parasite adherence to macrophages through fibronectin receptors, which helps the penetration and spread of *L. mexicana*. GP63 suppresses macrophage immune signaling and aids in infection persistence. It can break down the SNARE-Vamp8 protein, inhibiting the maturation of phagosomes and antigen cross-presentation to cytotoxic T cells. Additionally, MARCKS-regulated proteins (MRP), which are important PKC substrates, are deactivated by GP63. Lacking LPG, mastigotes defend against reactive oxygen intermediates (ROI) mediated harm by preventing PKC activation through GP63 **[17]**.

Cysteine proteases (CPs) in *Leishmania* sp. exhibit similar modes of action to papain proteases, with 3 variants: CPA, CPB, and CPC. A single-nucleotide polymorphism in CP genes determines dermatotropic or viscerotropic parasite infection [18]. CPs' expression level correlates with parasite virulence and may have the potential as drug targets and vaccine candidates. Oligopeptidase B (OPB), which is a serine protease, has a significant role during the amastigote stage differentiation. It covers amastigotes with enolase and plasminogen for protection. OPB-deficient *L. donovani* parasites induce global gene dysregulation in host macrophages, affecting 495 genes **[18]**.

Arginase

A metalloenzyme called arginase is essential to *Leishmania*'s virulence and persistence. To protect amastigotes, the parasite arginase transforms host *L-arginine* into *L-ornithine*, avoiding the L-arginine pool. When the host arginase pool is depleted, it is transported into the host and is mostly found in the glycosomes of both promastigotes and amastigotes **[19]**.

EF1α

The discovery of elongation factor 1α, an essential virulence factor in *Leishmania*, has opened new avenues for structure-based drug targeting. EF1α, a GTP-dependent transcription factor, catalyzes amino-acyl tRNA attachment with ribosomes. It is exported from parasites and attaches to host SHP-1 phosphatase, resulting in macrophage suppression. The leishmanial secretome contains EF1α, which aids in the exosomal export of more leishmanial antigens **[20]**.

Heat shock protein (HSPs)

During propagation among the vector and the host, the parasite needs to perform some modifications to the host's temperature and pH. The parasite produces a huge amount of leishmanial heat shock proteins (HSPs) to overcome this obstacle, protecting the parasite proteins from heat-related damage. Therefore, *Leishmania* HSPs play a crucial role in *Leishmania* sp. growth at the mammalian stage. HSP100, a casinolytic protease B protein, plays another role in leishmanial virulence. It is generated from the parasite's flagellar pockets through temperature-enhanced exosomal release, contributing to the virulence of *Leishmania* sp., by influencing the exosomal trafficking pathway **[15]**. HSP78, an ATP-dependent protein, aids in managing heat and pH stress in amastigote-specific *L. donovani* parasites. It inhibits pro-inflammatory reaction, including nitric oxide, and has been identified as a potential chemotherapeutic target by ATP analogue, Ap5A **[21]**.

Small molecular weight HSPs (sHSPs) are highly divergent and bind to a wide range of target proteins, assisting ATP-dependent chaperones like HSP100. HSP90, P23, and HSP23 are well-characterized from *Leishmania* sp., with HSP20 playing an essential role as an immunogenic antigen during canine leishmaniasis. HSP23 is a heat-inducible chaperone essential for amastigote stage differentiation and defense against trivalent antimony Sb (III) and metalloid-based drugs **[22]**.

A2

Leishmania infection is a process where parasites transition from promastigote to amastigote,

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which is essential for their survival. Amastigotes possess virulence factors that distinguish them from the promastigote form. A2 is a protein found in *L. donovani*, which is mostly expressed in parasites causing VL but not CL. A2 gene is expressed abundantly in amastigote-like conditions, and its amino acid sequence shares similarities with the S antigen of *Plasmodium falciparum* V1. Persistence and pathogenicity of amastigotes inside macrophages and BALB/c mice are significantly impacted by A2 absence. Additionally, in an experimental animal model, *L. donovani* and *L. major* with overexpressed A2 genes showed increased organ parasite load. Mice immunized with a DNA vaccine or recombinant A2 protein exhibited a strong protective immunological response against *L. donovani* **[23]**.

Clinical, pathological, and immunological data

A variety of clinical, histological, and immunopathological manifestations of CL and VL are made possible by the large variety of parasites and the host immune reaction **(Fig. 3)**. Localized cutaneous leishmaniasis (LCL), diffuse cutaneous leishmaniasis (DCL), and MCL are further classifications of CL that take into account the host's immune reaction, the position of the lesions after the vector bite, and the clinical progression **[24]**. The most frequent symptom of LCL is the occurrence of a skin lesion just at the site of the insect bite, often on bare skin areas, including the face, hands, and legs. The lesion starts red and swollen and gets bigger following a varied incubation time, which lasts between 10 days and 3 months. Then, it turns into a classic ulcer with an erythematous foundation and a rounded or oval form. It has high borders, a solid consistency, a reddish backdrop with coarse graduations, and is penetrated. It is also well-defined. Although the lesion is often harmless, if a bacterial infection is present, local discomfort and the generation of seropurulent exudate may occur **[25]**. Generally, there aren't many parasites in LCL ulcers, and the patient's cellular immunity is still intact. This includes a robust T-cell reaction with a preponderance of Th1 cytokines (IFN- and IL-12) **[13]**. The lesion usually heals on its own over a few months to a few years if left untreated, but it may potentially continue to be active for an exceptionally long time, depending on the *Leishmania* sp. and the host's immunological reaction **[24]**. DL, the disseminated form of CL, is an uncommon manifestation that most likely results from hematogenous, or lymphatic parasite spread. In these situations, cutaneous lesions are numerous, often tiny and ulcerated, and dispersed over various body parts. There are very few or no parasites in lesions, and the immune response varies widely. T cell inhibition seems to be insufficient, yet the Th1 response triumphs over the Th2 response. MCL is often diagnosed after LCL with chronic evolution and is manifested by severe upper airways mucosal insults, which may be caused by the transfer of parasites to these regions as a result of insufficient or nonexistent therapy. Nasal obstruction, hyperemia, and epistaxis are the primary common clinical symptoms. The mucosa of the nasal septum, lateral walls, vestibule, and head of the inferior turbinate are the areas that are most commonly affected, with secondary effects on the palate, lips, tongue, throat, and larynx. The nose's volume may gradually expand, the cartilage in the nasal septum may be destroyed, the tip of the nose may collapse, the nose and its surroundings may be destroyed (including swallowing and speech problems), and the face may be severely mutilated. Complications from secondary infections may result in death **[25]**. From an immunological standpoint, MCL is distinguished by strong Th1 and Th2 responses **[26]**. The prolonged and severe tissue degradation, as well as the death of parasites in the lesions, are explained by the elevated levels of proinflammatory mediators (TNF- and IFN-) and IL-4 in these instances, and the low levels of IL-10 and TGF **[27]**. Mucosal lesions are often progressive if left untreated, and even when they are, they may have side effects such as uvula destruction, septum or palate perforation, and retraction of the nasal pyramid **[24]**. An uncommon and severe clinical variant of CL known as DCL develops in people who are considered anergic and have a deficit in their cells' ability to respond to leishmanial antigens. It starts as a single lesion and develops into several nodules without ulceration over massive epidermal extensions as well as infiltrating plaques throughout time. The patients' cytokine profiles are mainly of the Th2-type, with little IFN release and elevated levels of IL-4 and IL-10, with a high number of parasites frequently

present inside the lesions. Usually, nodular lesions are resistant to existing treatments and are not cured on their own **[28]**. Kala-azar, another name for VL, is a chronic, systemic disease that mostly affects the liver, spleen, lymph nodes, and bone marrow. Less commonly, it also affects the skin, lungs, kidneys, and stomach Peyer's patches. The most obvious or conspicuous clinical manifestations of the disease include fever, diarrhea, pallor in the mucous membranes and the skin, hepatomegaly, and splenomegaly. From ten days to 2 years (with a mean of 2 to 6 months), the illness's incubation time varies greatly. Complementary testing frequently reveals varying degrees of leukopenia, hypoalbuminemia, hypergammaglobulinemia, anemia, thrombocytopenia, and lymphomonocyte predominance **[29]**. The immunological elements of VL have not yet been characterized with precision. Given that large quantities of certain antibodies are also seen in this type of illness, the Th1-resistance and Th2-susceptibility model may be a reflection of a much more complicated series of responses under these circumstances **[30]**. Even when treated, VL can have fatal case rates of 10–20%, with bleeding and/or bacterial infections frequently being the cause of death. Left untreated, VL nearly invariably proceeds to death **[31]**.

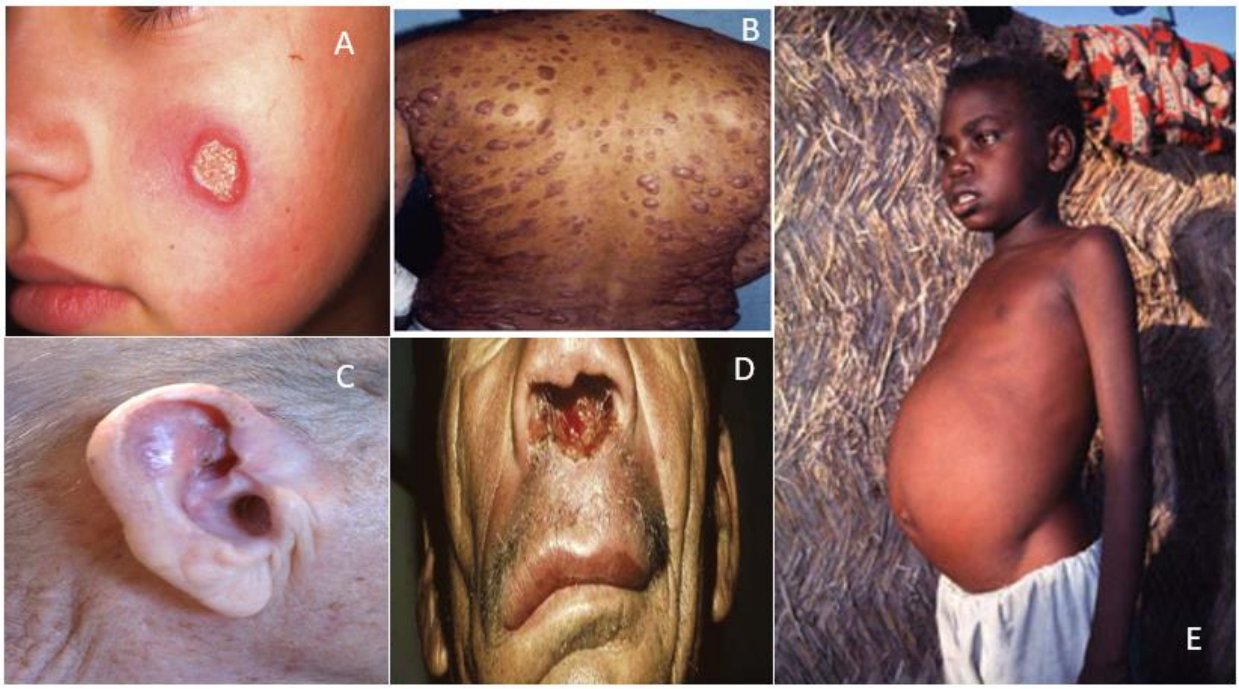

Fig. 3: Clinical forms of leishmaniasis in the old and new worlds;
A: Localized cutaneous leishmaniasis **[32],** B: Diffuse cutaneous leishmaniasis **[33],** C: Chiclero ulcer **[34],** D: Muco-cutaneous leishmaniasis **[35],** E: Visceral leishmaniasis **[36].**

Leishmania and HIV

The first evidence for this phenomenon came from intravenous drug users in Southern Europe who shared syringes, which resulted in a reduction in the count of CD4 T-cells; in most of them, the infection described reactivation of a sub-clinical or latent infection of VL. The result of this immunological deficit is a reduced response to therapy and recurrent recurrence. Following the CD4 T-cell number rises with the extremely successful anti-retroviral therapy, there are currently no clear guidelines for stopping anti-parasite medications **[37]**. Given that a shift to a Th2 reaction was noted with pregnancy, pregnant women can be considered a unique population with a condition prone to

Leishmania reactivation and immune response alterations **[38]**. This is how HIV-infected individuals might be thought of as a special population.

Diagnosis

The clinical and relevant epidemiological context forms the basis for the diagnosis. *Leishmania* species identification and laboratory confirmation are crucial. Both non-ulcerated lesions and cutaneous or mucosal ulcerations that have been scraped (particularly the margins) have been reported to contain the protozoan. Another diagnostic technique is a biopsy, which should be taken from the lesion's active border. The parasites may be seen in a smear as free parasites, in macrophages, or, less commonly, inside PMNs, which can contain 2 to 20 parasites per cell. The parasite is oval or piriform and has an oval or rounded nucleus, with a size between 2 and 5 µm long and 1 to 2 µm broad **[39]**.

Histopathology

Localized necrotic areas, atrophy or hyperplasia of epidermis, and an inflammatory infiltration of macrophages, lymphocytes, and plasma cells are visible in hematoxylin and eosin sections of LCL patients. In the later phases of the infection, there are fewer infected macrophages, fewer amastigotes, and some lympho-histiocytic infiltrates, which may indicate the presence of a tuberculoid granuloma. Histiocytes' cytoplasmic vacuoles may contain parasites in the initial phases of the infection (Leishman bodies). Granuloma development occurs in three stages: cell maturation into an epithelioid granuloma, cellular assembly into a disordered granuloma, and the establishment of a mononuclear phagocytic infiltrate. The histopathological patterns were categorized as follows: Type I exudative-cellular reaction, Type II exudative-necrotic reaction, Type III exudative and necrotic-granulomatous reaction, Type IV exudative granulomatous reaction, Type V exudative tuberculoid reaction **[40]**.

Culture

Through the inoculation of the sampled tissue in a certain medium, the culture is carried out. *Leishmania* is grown on Novy-McNeal-Nicolle (N-N-N) medium or an Evans biphasic medium. The cultures should be incubated at 24–26°C. Forms without flagella are nearly invariably produced in the initial culture, but after the 1st re-seeding, flagellated forms with lengths up to 50 µm start to develop. The sensitivity of both methods (microscopic examination and culture) is 85% **[39]**.

Molecular and immunity tests

The cellular immune response could be tested by the *Leishmania* skin test (LST) or the Montenegro skin test (MST). It is positive for localized types but negative with anergic types; a positive result increases the susceptibility of infection but does not rule it out (particularly if the patient does not reside in an infected region). Even in the absence of lesions, this allergy indicator helps determine if prior contact with the parasite has occurred. After 72 hours, a skin test is reported positive if the response is > 5 mm. The US Food and Drug Administration, however, has not authorized the intradermal injection of *Leishmania* antigen **[41]**. The most popular and effective diagnostic technique, according to research, involves seeing the parasites using Giemsa or Wright stains. When dealing with VL, the identification of infection is made by seeing the tissue protozoan stages under the microscope that have been aspirated from the lymph node, spleen, or bone marrow with a sensitivity of 95%, 55-97%, or 60%, respectively **[39]**. Serum anti-*Leishmania* IgG and anti-K39 antibody measurements are also utilized, with a high sensitivity and varied specificity depending on the location. A novel diagnostic strategy is the urinary detection of *Leishmania* antigens **[42]**. Direct agglutination, direct immunofluorescence, and enzyme-linked immunosorbent assays employing rK39 or heat shock protein (HSP83) antigens are other methods for detecting antibodies. However, due to their limited availability, these serological tests are rarely advised in CL **[41]**. A qualitative membrane-based immunoassay called the Rapid Test for *Leishmania* was made available to detect all significant *Leishmania* species causing CL. It added value to the clinical management of CL despite having a limited sensitivity. Lesions that test positive on a rapid test should receive treatment like CL **[43]**.

When compared to traditional parasitological diagnosis, molecular assays have been successfully used in the diagnosis of VL and CL. It has a greater sensitivity than classical methods of diagnosis, like culture. PCR has reported an enhanced sensitivity and specificity; it may also be employed in instances of mucosal leishmaniasis. Unfortunately, only specialist

laboratories or travelers' clinics provide this method **[44]**. Many real-time PCR (qPCR) methods, depending on coding and/or non-coding sections of the *Leishmania* genome, have been described for the identification of leishmaniasis. The parasite species contains 34–36 chromosomes and a distinct genomic structure wherein genes that code for proteins are arranged in polycistronic units without introns. Kinetoplast DNA (KDNA), the mitochondrial genome of *Leishmania* parasites, is arranged in a concatenated network comprising many dozen maxicircles (about 23 Kb each) and thousands of minicircles (0.8–1.0 Kb each) **[45]**. Regarding non-protein-coding regions, about 95% of kDNA is composed of minicircles, which are perfect targets for the identification of *Leishmania* due to their good sensitivity. Minicircles consist of a variable region and a conserved region, with various classes depending on the strain. *Leishmania* parasites are typically identified at the genus or subgenus level using assays on minicircles' conserved areas. Ribosomal DNA (rDNA) is also used as a target on chromosomal DNA. The 18S rRNA gene, followed by the 5.8S and LSU genes, is frequently used for *Leishmania* spp. identification because of its conservation. Two internal transcribed spacer regions, ITS1 and ITS2, are situated between the 18S and 5.8S genes and between the 5.8S and LSUα genes, respectively. ITS sections offer species-level typing, and qPCR tests based on minicircles' conserved kDNA sections provide the highest detection limit **[46]**. In 2016, by utilizing ITS1-PCR applied to 41 skin scraps on glass slides, *Leishmania* were detected correctly with species identification **[47]** in Jordan by Hijjawi and his colleagues. The PCR-RFLP test enabled species identification for 28 *L. major* and two additional *L. tropica* strains in 30 samples. However, Jordanian medical labs still do not have access to it **[47]**. Also, qPCR techniques use protein-coding genes like tryparedoxin peroxidase, glucose-6-phosphate dehydrogenase (G6PD), glucose phosphate isomerase (GPI), mannose phosphate isomerase (MPI), 6-phosphogluconate dehydrogenase (6PGD), DNA polymerase, and HSP70 for parasite detection and quantification. These targets have lower sensitivity but higher specificity. HSP70 is an exception, with a limit of detection of 0.1 parasites/ml **[45]**. The majority of the time, RFLP analysis followed by molecular amplification of the hsp70 gene fragment (PCR-hsp70) is a useful method for the diagnosis of the parasite in clinical specimens, as was proved in Colombia by Montalvo *et al*. **[48]**. Regarding genotyping, real-time PCR techniques should be developed to get data on *Leishmania* subgenus, complex, or species level. ITS region, SSU, HSP70, G6PD, 6PGD, MPI, cysteine protease B (cpB), kDNA minicircle, and other targets have all been assessed for this purpose **[49]**. In recent the years, several qPCR-based typing techniques have been reported. For example, to differentiate the *L. infantum* genotypes prevalent in Greece, a retrospective analysis carried out between 2005 and 2020 examined serum samples taken from 3661 probable VL patients. *Leishmania*-positive PCR samples were genotyped depending on polymorphisms in 12 microsatellite loci of the internal transcribed spacers (ITSs) 1 and 2. Results revealed that all VL cases are associated with *L. infantum* ITS type A **[50]**. In another study from Italy, the multilocus sequence typing was used for species identification of *Leishmania* parasites. Two polymorphisms were identified by the MLST analysis with the aid of sequences from GenBank. Seven genotypes were found by the quick screening of these polymorphisms in 73 isolates using two high-resolution melt (HRM) based tests. The majority of *L. infantum* zymodemes (MON-1, MON-72) were connected with genotype 1, which was also the most prevalent in the entire collection **[51]**.

Prophylaxis

Wearing thick clothing with long sleeves, such as shirts and long trousers, can help protect against insect bites. Additionally, it's advisable to avoid walking in forests at night. To effectively control insect vectors, consider using insecticides, removing stagnant water, applying insect repellents, and following prophylactic measures.**[52]**. The widespread endemicity of the disease, particularly in some areas like Brazil and India, as well as the toxicity of second-line medications and the rise in resistance to first-line medications, all contribute to the production of an effective vaccine. Additionally, because vaccines have extended action and may be used in both prophylactic and treatment purposes without causing resistance, they are superior to chemotherapy **[53]**. There were many challenges

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to the introduction of an efficient vaccine. In addition to neglect and financial issues, the studies reported a variety of obstacles. Antigen presentation is ineffective when the entire parasite is used **[54]**. The fact that Old World *L. major* and New World *L. mexicana/L. amazonensis*, respectively, differ in certain virulence factors and the immunological responses they elicit, which is one of the main issues with the vaccine against CL **[55]**. Therefore, a vaccine against *L. major* that causes CL may not always be effective against the range of illnesses found in the New World, including diffuse cutaneous and mucocutaneous variants. Even if the vaccine is effective against different types of CL, it still faces the difficulty of protecting against VL. The first method of immunization, produced in 1940 and used by many nations over the years, was called "leishmanization". It depends on the injection of live *L. major* promastigotes intradermally over the deltoid muscle. Ulceration appears and then resolves without any treatment, thus resulting in persisting immunity against leishmaniasis for a long time **[56]**. Following leishmanization, first-generation vaccines appeared. They included killed, live attenuated, and fractionated vaccines. The best mixture in the killed one was the use of killed promastigotes with the addition of Bacillus Calmette-Guerin (BCG) as an adjuvant, nevertheless, more studies have to be done to pave the way for efficient vaccines **[54]**. The current gold standard for utilization is live attenuated nonpathogenic strains. *In vitro* cultivation for a long time, temperature sensitivity, γ radiation, chemical-induced mutagenesis, and gentamicin culture are some methods for attenuation **[57]**. Some fractionated vaccines are also used, like the A2 membrane protein, soluble parasite fractions (enolase, aldolase, and P45), and some polyproteins as Q-protein and Leish 111f **[58]**. Introduction of the second-generation vaccines depends on the use of genetically modified strains or microorganisms and some recombinant subunits. For example, the use of *L. tarentolae*-PpSP15 in conjunction with CpG as a primary boost gives strong resistance against *L. major* infection **[59]** and also testing the *Lactococcus lactis (L. lactis)* as a tool for vaccination by carrying certain proteins. In 2020, *Davarpanah* and his team showed that *L. lactis* expressing the PpSP15 salivary protein of the sand fly could protect against *L. major* infection.

In the 21st century, the application of DNA vaccines delivers the third generation. Injecting these DNA plasmids carrying certain proteins will lead to the production of endogenous ones that can provoke a specific immune response (humoral and cellular) against the parasite **[60]**. *Leishmania's* hemoglobin receptor (HbR) is a protein that is preserved among different *Leishmania* strains. HbR-DNA immunization produced multitask CD4 and CD8 T cells. They offer hamsters and mice complete protection against *L. donovani* infection **[61]**. DNA vaccines can also be made with fused targets, and the HisAK70 DNA vaccine encodes seven *Leishmania* genes (H2A, H2B, H3, H4, A2, KMP11, and HSP70). In the CL model, HisAK70-immunized mice showed no parasite dissemination to the viscera, whereas in the VL model, they displayed several sterile granulomas in the liver linked to marked reduction of hepatic parasite loads **[62]**. DNA vaccines have the following benefits: (a) they can be produced quickly, easily, and affordably on a large scale; (b) they don't require storage, transportation, or low temperatures; and (c) they can offer long-term protection against a variety of *Leishmania* strains. The primary risk associated with these third-generation DNA vaccines is the potential for eukaryotic genome modification to cause cancer or autoimmune illness **[63]**.

Controlled human infection models

Both cutaneous and visceral manifestations of illness have been studied using a variety of animal mammalian models. Nevertheless, there was a questionable correlation between these models' forecasting ability and human reaction. The most widely used experimental model is the mouse. Their unique immune responses to *Leishmania* infection may be challenging to translate into clinical settings, signifying the importance of human research **[12]**. Studies known as controlled human infection models (CHIMs) intentionally expose human subjects to infections, usually to evaluate the effectiveness of potential vaccines or better comprehend the etiology of diseases. When combined with conventional vaccine trials and immunological analysis, CHIM studies offer several benefits for assessing the effectiveness of early interventions. While testing the recent vaccines, more precise

results can be translated to clinical practice than animal research **[63]**. To produce a novel CHIM, it is essential to ensure its effectiveness, reliability, and safety for participants.

RNA Technology in *Leishmania* Vaccines

Vaccines, depending on RNA-based technology, emerged during the COVID-19 pandemic. Using the same technique with *Leishmania*, several antigens that have been shown to provide at least partial defense in animal models can be evaluated and used in response to clinical information. The possibility for low-cost and somewhat generic production is also suggested by the relative simplicity of designing and producing vaccines based on nucleic acids **[64]**. Since in vitro transcription can produce the RNA in a cell-free environment, RNA-based vaccines have a significant logistical advantage over most other platforms. Simple downstream purification may be carried out in this manner to enable quicker and more economical manufacturing for both mRNA as well as self-amplifying replicon RNA (repRNA) complexes. Furthermore, the composition of T-cell reactions produced by various vaccination platforms varies qualitatively: MHC I presentation and the production of related CD8+ T cell reactions are made possible by the intracellular localization of RNA vaccines, which is not often noted because of subunit vaccines. The new study denotes that the production of longer-lasting T cell responses gives a persistent advantage, even though the efficacy of this is debatable **[65]**. The best profile for defending against long-term illnesses like leishmaniasis may be the production of both helper and cytotoxic cell responses **[66]**.

Gene editing by CRISPR-Cas9

CRISPR-Cas9 (*Streptococcus pyogenes* Clustered Regularly Interspaced Short Palindromic Repeats) is an RNA-guided endonuclease used for gene editing in various organisms **(Fig. 4)**. It requires a Cas9 nuclease (CRISPR-associated protein 9) and a guide RNA (gRNA) to form an RNA-protein complex. The gRNA consists of a 20-nt guide sequence and an 82-nt chimeric sequence. The Cas9 nuclease breaks down the target DNA to produce a double-stranded break (DSB), which can be repaired by mutation-prone repair pathways like microhomology-mediated end-joining (MMEJ), single-strand annealing (SSA), or homology-directed repair (HDR). The Cas9 nuclease can be programmed to focus on new sites by changing the gRNA's guide sequence **[67]**. Recently, CRISPR technology for *Leishmania* has greatly enhanced the efficiency of gene editing. CRISPR is simpler and more effective than the traditional gene targeting method; it has been used to tag endogenous genes with or without the use of a selection marker, create gene deletion and disruption mutants, and show the importance of several parasite genes. Deletion of multicopy family genes has been done successfully. This was frequently not possible with the traditional technique, and to produce targeted chromosomal translocations, which will encourage research on pathogenesis and polycistronic transcription control in leishmaniasis **[68]**. CRISPR family members now consist of CAS9, CAS12, and CAS13.

Treatment

Leishmaniasis therapy can be quite difficult, much like leishmaniasis diagnosis. Overall, leishmaniasis therapy should depend on the patient, the kind of leishmaniasis, the parasite subspecies, and other factors. Patients with CL who may be susceptible to MCL benefit most from the use of the PCR technique for species determination to decide the best course of treatment. Treatment for cutaneous leishmaniasis **(Table 2)** depends on the species, host, and clinical presentation. CL brought on by *L. mexicana* and *L. major* in an immunocompetent person who shows no signs of mucosal illness does not need to be treated since it often goes away on its own **[8]**.

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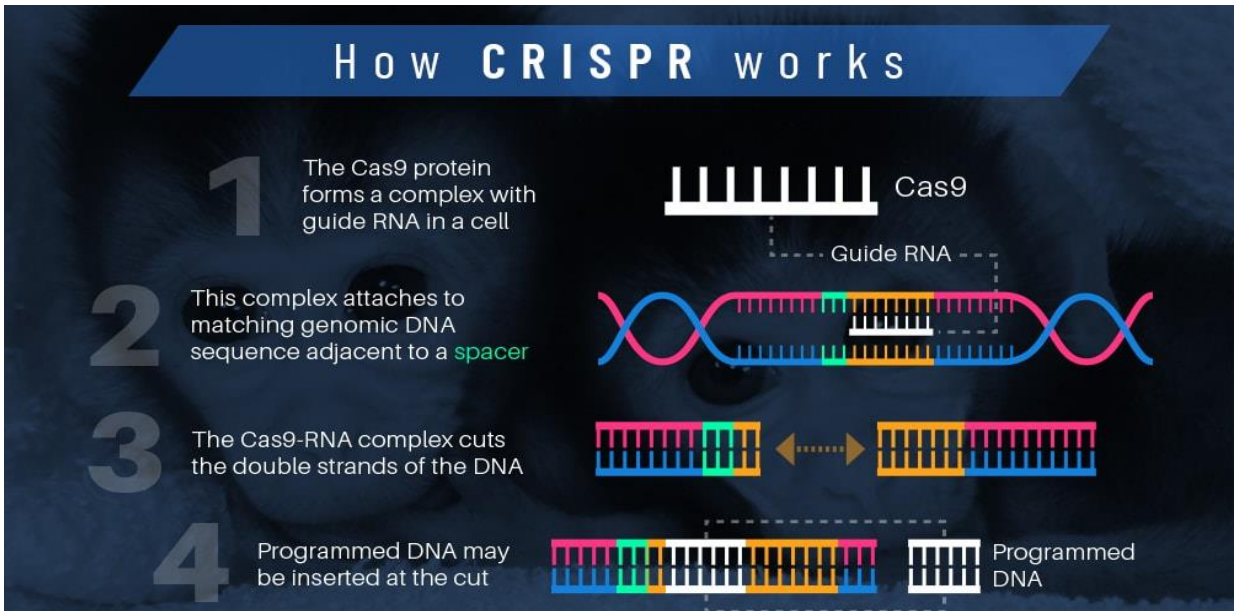

Fig. 4: How CRISPR works **[69].**

The urge to start treatment is for the immunosuppressed patient, with the number of lesions exceeding 3, lesions > 2.5 cm, or on the joints, face, hands, or feet **[70]**. However, systemic therapy is advised for complex CL, whereas in situ treatment is advised for simple lesions that do not cure independently **(Table 3)**. Complex CL is indicated by more than 5 lesions, an area > 5 cm, lesions on the face, hands, feet, or genitalia, regional adenopathy, > six months, DCL, and an immunosuppressed host **[52]**. Treatment in these situations can stop mucosal illness, morbidity, and recurrence. There are several systemic treatments available **(Table 3)**, including oral treatments like fluconazole and miltefosine, pentavalent antimonials like meglumine antimoniate and sodium stibogluconate, amphotericin (deoxycholate and liposomal formulation), and pentamidine. In Latin America, pentavalent antimonials are regarded as a standard of care for treating CL systemically **[71]**. Thermotherapy, local paromomycin, in situ injections of antimonials, light or laser therapy, and thermotherapy are all advised for clinically straightforward lesions that are not at danger of becoming ML **[52]**. In South America, the use of thermotherapy is on the rise and is linked to clinical cure and a reduction in lesion size **[71]**. While there is no perfect course of treatment, medical professionals advise personalized therapy for each patient based on their immunological state, co-morbid illnesses, plans for pregnancy, adverse pharmaceutical effects, and related studies on the effectiveness of therapy depending on species and area distribution **(Table 2)**. Collagenase ointment has been used to accelerate healing and lessen fibrous scarring **[72]**. Unfortunately, the available CL therapies have adverse effects **[73]**, are expensive **[74]**, and are not fully effective. Meglumine antimoniate, glucantime, sodium stibogluconate, and pentostam are the only pentavalent antimonials utilized in treating and managing CL **[75]**. Regrettably, after prolonged use, patients have experienced resistance, and adverse effects include joint and muscle pains, pancreatitis, hepatic illness, low white blood cell count, and cardiac troubles **[76]**. Several studies have shown that in vitro antimonial sensitivity may be connected to the patient and *the Leishmania* parasite and is not always connected to therapeutic success **[76, 77]**. Although not fully effective, amphotericin B, liposomal amphotericin B, paromomycin, and miltefosine are also in use. Discovering new pharmacological treatments for leishmaniasis is increasingly crucial **[78]**. Moreover, medicinal plants could serve as an important substitution.

Safe natural ingredients can be utilized to create novel treatments that address unmet medical needs across various illnesses, including CL. For instance, medicinal plants have been employed to remedy a range of ailments for millennia. They have been used in the sectors of medicine, makeup, dietary science, chemistry, food, drugs, and industry **[79]**. Methanol extract from

eighteen plants found in the Yucatan Peninsula effectively controlled *Leishmania Mexicana*, including "leaves of *Aphelandra scabra*, bark of *Byrsonima bucidaefolia*, bark of *Byrsonima crassifolia*, leaves of *Clusia flava*, bark of *Cupania dentata*, leaves of *Diphysa carthagenensis*, whole plant of *Dorstenia contrajerva*, roots of *Milleria quinqueflora*, whole plant of *Tridax procumbens*, and bark of *Vitex gaumeri*" **[80]**. A pure fraction of ginger is a viable therapeutic option for treating diseases caused by *L. amazonensis*, whether alone or in combination with other medications **[81]**. The use of medicinal herbs for treating CL has made no exception. Some of the most popular botanicals used in Iran for leishmaniasis treatment include *Lawsonia inermis, Lavandula spica, Camellia sinensis, Mimosa tenuiflora, Echinacea purpurea, Arnebia euchroma, Achillea millefolium, Vinca major, Artemisia sieberi, Scrophularia striata, Rumex spp., Medicago lupulina,* and *Portucala oleracea* **[82]**. Microbes, invertebrates, and plants are among the marine creatures that provide marine natural products (MNPs), which are bioactive metabolites. The vast reservoir of varied chemical structures found in MNPs from marine environments will continue to provide new treatments, either in their natural state or after being optimised by synthetic medicinal chemistry **[83, 84]**. Numerous biological properties, including antibacterial, antifungal, anti-cancer, antiviral, anti-inflammatory, neuroprotective, and antiparasitic properties, have been identified for these MNPs **[83, 85, 86]**. MNPs feature unique molecular patterns, don't cytotoxically affect host cells, and are less likely to cause drug resistance **[87]**. It has been discovered that the imidazole alkaloid paenidigyamycin A **[88]** and its derivative paenidigyamycin G **[89]** consistently exhibit significant antitrypanosomal activity, strong leishmanicidal activity, and comparatively moderate cytotoxicity. The Irish brown alga Bifurcaria bifurcate yielded a novel linear diterpene, bifurcatriol (1), along with two previously identified chemicals, elegandiol (2) and bifurcane (3). The chemical (1) suppressed drug-resistant *P. falciparum* K1 at low concentrations and showed moderate in vitro antiprotozoal efficacy against *L. donovani*, *T. brucei rhodesiense*, and *T. cruzi* **[90]**.

Mucosal leishmaniasis, in contrast to CL, cannot resolve on its own and can result in increasing damage, deformity, and even death (through aspiration pneumonia or pulmonary obstruction). Consequently, following a comprehensive naso-oro-pharyngeal examination, systemic treatment should start immediately. For patients at potential risk of respiratory occlusion, who could get worse if anti-leishmaniasis medication is started, the IDSA advises hospital admission with good surveillance and administration of steroids. People with MCL should undergo personalized systemic treatment (using the systemic medicines formerly specified for CL), much as people with complicated CL.

Individuals with symptoms and a proven diagnosis of VL necessitate prompt systemic treatment due to its aggressiveness. Pentavalent antimonials were originally thought to be the gold standard of treatment, however, resistance in different parasite species remains a worry. The IDSA advises liposomal amphotericin B for the treatment of VL in immunocompetent patients, with miltefosine being taken into account in non-breastfeeding, non-pregnant people. In places with established low drug resistance patterns, pentavalent antimonials can be utilized as an option for leishmaniasis patients unable to take liposomal amphotericin B or miltefosine. Liposomal amphotericin B should preferably be administered to immunocompromised patients (such as HIV or transplant recipients); nevertheless, miltefosine combination treatment can also be taken into account. Antiretroviral treatment (ART) with secondary prophylactic drugs attacking the particular parasite are indicated for HIV patients but not for transplant recipients. All clinical types of leishmaniasis patients who successfully complete therapy should be checked for relapses. Patients who have recurrence are encouraged to undergo repeat therapy for a long time **[52]**. Regrettably, diagnosis of drug resistance is commercially unavailable, however, it is generally not advised to perform repeat biopsies or serological examinations. Local treatments have been generated for localized CL to avoid the dangerous side effects of systemically administered drugs **(Table 2)**. Photo-Dynamic therapy includes the use of aminolaevulinic acid (ALA) or methyl-amino-levulinate topical

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application to the skin, with subsequent irradiation with laser or intense pulsed light. Intracellular and extracellular ice-crystal formation and alteration in cell membranes with cryotherapy substantially result in the destruction of the infected cells and damage to amastigotes at temperatures below freezing. Cryo-necrosis leads to the release of antigenic products that stimulate an immune reaction and lead to the resolution of other lesions. The *Leishmania* species causing CL are heat-sensitive and unable to grow in temperatures exceeding 39°C **[91]**. Therefore, thermotherapy has been contemplated as a CL lesion treatment choice. Radiofrequency (RF) therapy, a type of thermotherapy, has been tested in patients with CL. A study from Brazil reported a success rate of 85.7 % in patients with CL **[71]**.

Table 2. Localized treatment for CL **[92]**.

Type	Mechanism	Advantage
PDT	Local ALA/MAL, followed by laser or IPL, destroys infected cells and thus kills parasites	Prompt local control of the lesion
Cryotherapy	Decreases local tissue temperature, causing cryonecrosis	Short treatment regimen, good compliance
Thermotherapy	Elevates local tissue temperature using baths, infrared light, and laser. Destroy temperature-sensitive parasites	Safe and effective

ALA, aminolevulinic acid; IPL, intense pulsed light; MAL, methyl aminolevulinate; PDT, photodynamic therapy.

Table 3. Chemotherapeutic agents for leishmaniasis **[92]**.

Drug	Route	Dose	Adverse effects	Advantages	Disadvantages
Pentavalent antimonial	IV, IM, and IL	20 mg/kg/day for 28–30 days	Toxicity to organs, e.g., heart, pancreas, kidney, and liver.	Cheap	Long treatment regimen, annoying injections.
Amphotericin B	IV	0.75–1 mg/kg/day for 15–20 days, daily or alternate daily	Toxicity to kidneys, hypersensitivity reactions, and lower potassium levels in the blood	Drug resistance is not frequently noted	Hospital admission is advised.
Liposomal amphotericin B	IV	10–30 mg/kg total dose (single dose; 3–5 mg/ kg/dose)	Chills and rigors with administration, mild toxicity to the kidneys.	Elevated efficacy; mild toxicity	Expensive
Miltefosine	Oral	100–150 mg/day for 28 days	GI AEs: hepatorenal toxicity, teratogenic potential	Good efficacy	Expensive, and potential teratogenicity
Paromomycin	IM or topical	15 mg/day for 21 days or 20 mg/kg for 17 days	Renal, ear, and liver toxicity Aural and hepatorenal toxicity	Good efficacy, non-expensive	Variable effectiveness according to geographical area; potential for resistance
Pentamidine	IM	3 mg/kg/day IM alternate daily for 4 injections	Elevated blood glucose and heart rate, decreased blood pressure, ECG changes	Short treatment regimen	Variable effectiveness according to the *Leishmania* species

AD, adverse effect; CL, cutaneous leishmaniasis; GI, gastrointestinal; IL, intralesional; IM, intramuscular; IV, intravenous; VL, visceral leishmaniasis

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Strategic framework for leishmaniasis in the Arabic MENA

Reducing the prevalence of the disease is the primary objective of the World Health Organization network for leishmaniasis surveillance and control. Each nation should incorporate these surveillance and control measures into its health development efforts to accomplish this goal. The global goals of this network include early diagnosis and treatment, vector control, reservoir control, particularly for zoonotic types, health education and training, and intersectoral collaboration **[93]**. The following will provide more information on the network's various objectives: The first step in every nation's health development effort should be to apply health education, community involvement, risk assessment, considering program management, case identification, management, and disease surveillance. Second, finding new emerging foci is crucial to properly conducting preventive measures. Data collection should be done by professional staff. Thirdly, each nation's health promotion initiative should establish a local geographical network to exchange knowledge and insights, provide access to medications for more people in need, and broaden sub-regional cooperation. Finally, to make the nation ready for upcoming and global public health concerns, each nation's health development efforts should promote and foster cross-border cooperation, multisectoral cooperation, and intersectoral collaboration. Since leishmaniasis has long been a serious public health issue in the MENA, significant scientific resources and infrastructure have been devoted to eradicating this serious yet unaddressed illness. A recent worldwide research plan for leishmaniasis in the MENA was proposed in 2011 **[4]**. In reality, the year 2009 saw an improvement in the relationship between the USA and many MENA nations. The three key themes—*Leishmania* genetics, host immunological response, and vector transmission—all call for further study, according to various participants. The dynamic interaction between these elements, according to experts, will ensure that important findings are presented in this context **[94]**. Indeed, employing *Leishmania* genetics and evolvability, the first topic (*Leishmania* genetics) can produce new vaccine candidates and therapeutic targets against CL. The creation of new biomarkers for vaccine generation and immunotherapy that clarify the host immune response to illnesses can be stimulated by the second theme (host immune response). In activities devoted to vector biology and transmission dynamics, the third theme (vector transmission) can lead to new understanding of entomological risk assessment, vector management, and risk anticipation. However, this collaboration will place a high priority on national and worldwide health education and training. Such efforts are made more difficult because leishmaniasis is still common in many places of extreme poverty and conflict **[95]**. Nevertheless, research into leishmaniasis therapy and possible leishmaniasis vaccines is ongoing.

Off course the bad political circumstances like wars and civil wars provide an ideal ground for infectious disease outbreaks. One example in MENA is the revolutions of the arabian spring that affected many countries like Syria, Libya and Yemen. A surge of CL patients with very abnormal and unique clinical symptoms was reported in all provinces following the start of the Syrian war, particularly in Aleppo **[96]**. In secure governorates like Latakia, where the number of cases peaked in 2013 (about 2400), the incidence rate increased dramatically as a result of the altered population distribution brought about by the low stability in some areas and the migration of people to safe places. Many research, including the 2020 study **[97]** by *Ayham A. Alnukari*, attempted to track any changes in the kinds of *Leishmania* that caused CL in Lattakia city during the crisis. These studies clarified that *L.tropica* was the cause of all positive CL patients included in the analysis.

The majority (57.1%) had the lesion from the nearby provinces of Edlib and Aleppo, primarily from Edlib, whereas just 28.6% had it initially from Lattakia, despite the fact that all of the cases were identified there.

Conclusion

As one of the neglected tropical diseases, leishmaniasis remains a big public health problem in the tropics and subtropics with

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significant morbidity and mortality. Understanding the virulence factors, immune response, and immune evasion strategies of the parasite has helped the emergence of new diagnostic tools, drug therapies, and control measures, including a soon-to-be futuristic production of effective vaccines. This still needs more research emerging from the endemic areas under the supervision of the WHO and the specific research institutes all over the world.

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HIGHLIGHTS

- Early diagnosis and proper treatment of Leishmaniasis are crucial in the prognosis of the disease.
- Diagnosis can be achieved through stained blood smear examination, culture, serological assays, and molecular diagnostics.
- Treatment options include drug chemotherapy, local therapy, or a combination of them, depending on the case.

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