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REVIEW

Leishmaniasis in travelers: A literature review

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Summary Leishmaniasis is a vector-borne protozoan infection whose clinical spectrum ranges from asymptomatic infection to fatal visceral leishmaniasis. Over the last decades, an increase in imported leishmaniasis cases in developed, non-endemic countries, have been pointed-out from a review of the international literature. Among the possible causes are increasing international tourism, influx of immigrants from endemic regions and military operations. The main area for the acquisition of cutaneous leishmaniasis, especially for adventure travelers on long-term trips in highly-endemic forested areas, is represented from South America, whereas popular Mediterranean destinations are emerging as the main areas to acquire visceral variant. Leishmaniasis should be considered in the diagnostic assessment of patients presenting with a compatible clinical syndrome and a history of travel to an endemic area, even if this occurred several months or years before. Adventure travelers, researchers, military personnel, and other groups of travelers likely to be exposed to sand flies in endemic areas, should receive counseling regarding leishmaniasis and appropriate protective measures.

1. Introduction

Leishmaniasis (or 'leishmaniosis') is a vector-borne obligate intracellular protozoan infection (Kinetoplastida, Trypanosomatidae) whose clinical spectrum, depends largely both on parasite species and host immune response. The disease ranges from asymptomatic infection to three main clinical syndromes: visceral leishmaniasis (VL) also known as 'kala-azar', cutaneous leishmaniasis (CL), and mucosal or mucocutaneous leishmaniasis (ML) also known as 'espundia'. Although the disease has been known and studied for a long time, it remains a public health problem worldwide,

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affecting approximately 12 million people in 88 countries (350 million inhabitants, mainly in remote rural areas and underserved urban areas. Based on geographical distribution, leishmaniasis is divided into 'Old World' (southern Europe, Mediterranean basin, Middle East, Asia, and Africa) and 'New World' (Latin America) leishmaniasis. The means of leishmaniasis transmission are hematophagous female sand flies (order *Diptera*, family Psychodidae, subfamily *Phlebotominae*) of the *Phlebotomus* genus in the Old World, and of the *Lutzomyia* genus in the New World. Nevertheless, fewer than 50 of the approximately 1000 species of sand flies worldwide are vectors of leishmaniasis. This could be attributable to the inability of some sand fly species to support the development of parasite infective stages in their gut, and/or a lack of ecological contact with reservoir hosts [1]. Other possible means of transmission of lesser importance are blood transfusions, or in immune-depressed intravenous-drug users, as a result of needle sharing, or following organ transplantation, or via congenital transmission, vertically or mother to child [2]. There are more than 20 *Leishmania* species known to infect humans. A female sand fly ingests *Leishmania* amastigotes while blood-feeding, and then transmits the parasite in infective stages (usually assumed to be the metacyclic promastigotes) during a subsequent blood meal. The infective promastigotes inoculated by the sand fly are phagocytosed in the mammalian host by macrophages and related cells, within those cell promastigotes transform into amastigotes and often provoke a cutaneous ulcer at the site of the bite [3].

In the last decade leishmaniasis expanded or emerged in several foci worldwide due to climate and human factors (e.g. deforestation, urbanization) [4], and some models predict that sand flies will further expand with global warming [5]. In addition, the widespread emergence of *Leishmania* species resistant to pentavalent antimonials in India, where half of VL cases occur globally, as well as the HIV co-infection (in Northwest Ethiopia up to 30% of VL cases are HIV-co-infected), leishmaniasis has become the third most frequent opportunistic parasitic disease after toxoplasmosis and cryptosporidiosis, which compromises control of the disease [6—8].

1.1. Cutaneous leishmaniasis

Of all the forms of leishmaniasis, CL is the most common. A review of international literature show that in the published cases of imported travel-related leishmaniasis over the past 25 years nearly 80% have concerned CL [9]. According to recent estimates, CL is endemic in 88 different countries, 72 of which are developing nations, placing nearly 350 million people at risk of infection and disease, 1.5 million new cases each year. More than 90% of cases occur in five countries in the Old World (Algeria, Saudi Arabia, Iran, Iraq, and Afghanistan) and two countries in the New World (Brazil and Peru) [2]. CL is more common in rural areas, in settings ranging from rainforests (jungle environments) to arid regions; however it is increasingly reported in urban and suburban areas of the Old and New World, where a number of opportunistic hosts, such as dogs and donkeys, have become the reservoirs of infection, reproducing a pattern similar to the VL caused by *Leishmania infantum* in the Mediterranean basin [10]. Main species involved in CL are: *Leishmania tropica*, *Leishmania aethiopica*, *Leishmania major*, and *L. infantum* in the Old World, and parasites belonging to the *Leishmania* (*Leishmania* [*L.*] *amazonensis*, *Leishmania* [*L.*] *mexicana*, *Leishmania* [*L.*] *venezuelensis*), and *Viannia* (the *Leishmania braziliensis* complex, with two species, *L.* [*V.*] *braziliensis* and *Leishmania* [*V.*] *peruviana*, the *Leishmania guyanensis* complex, with three species, *L.* [*V.*] *guyanensis*, *Leishmania* [*V.*] *shawi*, and *Leishmania* [*V.*] *panamensis*), the *Leishmania naiffi* complex, with one species, *L.* [V.] *naiffi*, and the *Leishmania lainsoni* complex, with one species, *L.* [*V.*] *lainsoni*) subgenus in the New World (the so-called New World or American CL, ACL). While most of the Old World species cause benign cutaneous disease, New World species cause a spectrum of disease, ranging from mild cutaneous disease to severe mucosal lesions, depending to multiple parameters, including immune status of the host and the infecting species [2]. More in details, manifestations of ACL include acute/localized cutaneous leishmaniasis (LCL), anergic diffuse cutaneous leishmaniasis (DCL), also referred to as disseminated cutaneous leishmaniasis in literature, and mucocutaneous leishmaniasis (ML, see below). In the middle of this broad clinical spectrum is LCL, the most common form of ACL. Whenever *Leishmania* infection is not controlled (i.e. inadequate treatment, poor compliance, or development of an immunosuppressive state), it can progress to one of two polar forms, either exhibiting cellular hyposensitivity, as in the cases of DCL, or cellular hypersensitivity, as in ML. Additionally, an intermediate/borderline disseminated cutaneous leishmaniasis (ICL or BDCL) pattern has recently been identified as a distinct nosological entity, representing an intermediate between LCL and either of the extreme forms, DCL and ML, similar to DCL for its chronic evolution, tendency to relapse, and partial resistance to standard antileishmanial therapy. Cell-mediated immunity, particularly T-cell-mediated one, plays an important part in the immunologic response to *Leishmania* infection. A type 1 T helper (T_H1) predominant response is related to cure, while a T_H2 predominant response or the lack of an adequate T_H1 response are both associated with worsening of disease and/or treatment failure. Individuals affected by ACL who manifest with LCL are characterized as immune responders, whereas those who manifest with disseminated disease (i.e., DCL) are described as non-responders. Those who manifest with ICL have an intermediate degree of responsiveness. Looking at the immune response, if LCL develops a T_H1 predominant response, with production of T_H1-related cytokines (mainly IFN-γ and TNF-α), DCL has a T_H2 predominant one, with production of T_H2-related cytokines (mainly IL-4 and IL-10). In contrast, as would be expected, in the ICL subset there is a mixed cytokine profile, with at least partially preserved T_H1 immune response. Any member of the subgenera *Leishmania* and *Viannia* represents the possible etiologic agents of LCL. However, *L.* [*V.*] *braziliensis* is regarded as the most important parasite associated with this form of disease in the Americas. In cases of LCL caused by *L.* [*V.*]

Table 1 Cutaneous leishmaniasis patterns, main aetiological agents, and histopathological features.

Cutaneous leishmaniasis patterns	Main aetiological agents	Histopathological features
Old world cutaneous leishmaniasis	*L. tropica*, *L. aethiopica*, *L. major*, *L. infantum*	Epithelioid granuloma
New World (or American) cutaneous leishmaniasis (ACL)		
• Acute/localized cutaneous leishmaniasis (LCL)	*L.* [*V.*] *braziliensis* *L.* [*L.*] *amazonensis*	Epithelioid granuloma Macrophagic granuloma
• Anergic diffuse cutaneous leishmaniasis (DCL)	*L.* [*L.*] *amazonensis* *L.* [*L.*] *mexicana*	Macrophagic granuloma
• Intermediate/borderline disseminated cutaneous leishmaniasis (ICL or BDCL)	*L.* [*V.*] *braziliensis*	Nodular infiltration of lymphocytes and plasma cells in the dermis, with rare macrophages and parasites
• Mucosal or Mucocutaneous leishmaniasis (ML)	*L.* [*V.*] *braziliensis* *L.* [*V.*] *guyanensis* *L.* [*V.*] *panamensis*	Tuberculoid granulomatous reaction, with abundant infiltrate of lymphocytes and plasma cells, with few histiocytes and scanty parasites

L.: *Leishmania*; *V.*: *Viannia*.

braziliensis the histopathology of the lesions proves a modest infiltration in the skin bordering the ulcerated lesion, and scanty macrophages and parasites, whereas lymphocytes and plasma cells are more frequent in the infiltrate, which has the characteristics of an epithelioid granuloma, similar to that of Old World CL. More rarely, if LCL is due to *L.* [*L.*] *amazonensis*, pathologists can highlight a large infiltration at the edge of lesion, and a dense infiltrate of vacuolated macrophages in the dermis, which are full of amastigotes and give the infiltrate the appearance of a macrophagic granuloma. In cases of DCL, *L.* [*L.*] *amazonensis* and *L.* [*L.*] *mexicana* are the main causative agents. In the dermis, the histopathological feature is a severe infiltration of macrophages containing abundant amastigotes, whereas lymphocytes and plasma cells are rare, giving also to DCL lesion the typical aspect of a macrophagic granuloma. Finally, parasites of the subgenus *Viannia*, especially *L.* [*V.*] *braziliensis*, have been identified as the major etiologic agent of ICL. The histology of this picture normally shows a nodular infiltration of lymphocytes and plasma cells in the dermis, with rare macrophages and parasites (Table 1) [11,12].

1.2. Mucosal (or mucocutaneous) leishmaniasis

Although ML develops in just a small number of patients with New World CL, its course is chronic and may be life-threatening. Mucocutaneous lesions are typically not seen in *L. Mexicana Leishmania* complex infections, except (rarely) in *L.* [*L.*] *amazonensis* infections. They are quite frequent complications of the *L. Viannia* complex infections and are seen more commonly in *L.* [*V.*] *braziliensis* than in *L.* [*V.*] *guyanensis* or *L.* [*V.*] *panamensis* infections [13]. In particular, as above-mentioned, three clinical outcomes may derive from *L.* [*V.*] *braziliensis* infection, probably due to the complex interactions with the host's imune system. In most cases a cellular immune reaction in the inoculation site could lead to the elimination of the parasites and to acquisition of immunity. Clinically, this reaction results in LCL, characterized by skin nodules, ulcers, and sometimes regional lymphadenopathy. If cellular immune response is inadequate, a cutaneous dissemination of the parasite can occur (DCL): usually these patients have lower levels of IFN-γ and TNF-α production than the ones suffering from localized forms, thereby provoking less activation of the monocyte/macrophage immune reaction. In a subset of patients, the parasites spread via hematogenous or lymphatic routes and invade the oropharyngeal mucosa, leading to ML. Here a tubercoloid granulomatous reaction, with abundant infiltrate of lymphocytes and plasma cells, with few histiocytes and scanty parasites, causes thickening of the upper airway walls, sometimes causing lumen obstruction, associated with necrosis of the cartilaginous structures (Table 1). The paucity of amastigotes in the granulomas, the strongly positive *Leishmania* test result, and the high level of circulating IFN-γ and TNF-α suggest an exaggerated hypersensitivity reaction to the parasite, largely the result of a prolonged antigen-specific T_H1 activation [14,15]. As additional pathogenic mechanism, Ronet et al. reported that metastasizing, but not non-metastatic strains of *L.* [*V.*] *guyanensis*, have high burden of non-segmented dsRNA *Leishmania* viruses (*Leishmania* RNA Viruses, LRV). These *Leishmania* viruses have been classified as Totiviridae, which includes RNA viruses detected in other protozoa, such as *Trichomonas vaginalis* and *Giardia lamblia*, and a variety of fungi, including *Saccharomyces cerevisiae*. Totiviruses have a small unsegmented dsRNA genome, between 5 and 7 kb in length, which encodes a capsid protein and a capsid-RNA dependent RNA polymerase (RDRP) fusion protein essential for their replication. Viral dsRNA is sensed by the host Toll-like Receptor 3 (TLR3), thereby inducing, via activation of the signaling TRIF (TIR-domain-containing adapter-inducing interferon-β) cascade, a pro-inflammatory response, with production of several cytokines (IL-6, TNF-α), chemokines (CCL5 and CXCL10), and NO, by iNOS activation via NFκB, then exacerbating and diffusing the disease. In addition, the authors detected an early upregulation of IFN-β, which is typically a sign of an anti-viral immune response [16].

1.3. Visceral leishmaniasis

VL is endemic in more than 60 countries in tropical and subtropical areas, as well as in Mediterranean countries. It has an annual global incidence of approximately 2 million cases, and an increase of 500,000 cases yearly, 90% of which concern six countries only — India, Nepal, Bangladesh, Ethiopia, Sudan, and Brazil [17]. *L. infantum* in the Mediterranean basin, *Leishmania donovani* in the Indian subcontinent, Asia, and eastern Africa, and *Leishmania chagasi* (*L. infantum* MON 1) in South America are the main causes of VL. Nowadays the most widespread is *L. infantum*, found from the People's Republic of China to the New World [18]. In Mediterranean countries and in South America, the disease is zoonotic and affects mainly infants and young children [19]. However, in the Mediterranean basin, an increasing rate of immune-compromised and immune-suppressed adult individuals has been noted [7,20,21], such as HIV co-infected patients and those under any immunosuppressive therapies. In these countries stray and domestic dogs and abundant sand flies are the main reservoir for infection, and the VL cycle is sustained in well-defined foci by a high prevalence (up to 25%) of canine leishmaniasis. Consequently, in these areas there is a large market for prophylactic drugs and treatment of canine leishmaniasis [22,23]. In the Indian subcontinent and Africa, VL is anthroponotic (human-to-human transmission through sand flies, without the involvement of a reservoir host) and affects both adults and children [2].

Over the last decade there has been an increase in imported cases in developed, industrialized, non-endemic countries, in association with increasing international tourism, military operations, influx of immigrants from endemic countries, and HIV-infected subjects [18,24—32]. This article reviews travel-acquired leishmaniasis with a focus on epidemiology, clinical presentation, diagnosis, and treatment. We researched the PubMed database for the period from 1980 through December 31, 2013, using the words 'leishmaniasis', 'imported', 'travelers', and 'travel-acquired'. Articles presenting original data on imported leishmaniasis cases were included in our review, and review articles were also studied. We found and examined 44 articles presenting original data on travel-acquired leishmaniasis [18,24,26—65].

2. Leishmaniasis in international travelers

The popularity of international travel is increasing so rapidly that approximately 1 billion international movements occurred by the end of 2010, and 1.6 billion will occur by 2020, most of which will take place in tropical and subtropical areas. Such intense international traffic results in greater vulnerability to the transmission of old, new and re-emerging infectious diseases, with travelers playing a leading role in disease dissemination [66—68]. More than half of international travel is for leisure or for military reasons, but an increasing number of travelers are immigrants visiting friends and relatives in tropical and subtropical areas. International travelers are increasingly involved in adventure travel and outdoor activities, which render them at increased risk of contracting leishmaniasis [18,41,69]. CL and ML are emerging among travelers involved in outdoor activities in endemic areas, and are part of the top 10 diseases causing dermatological abnormalities among tourists returning from tropical countries [25]. Furthermore, a significant number of VL cases have been reported among travelers in recent years [18,28,29,37]. In non-endemic countries the management of leishmaniasis remains a challenge for physicians, and delayed diagnosis and inappropriate treatment are frequently encountered [24,26,28,29].

2.1. Cutaneous leishmaniasis

The main clinical expression of imported leishmaniasis, involving more than 80% of cases in returning travelers, is cutaneous, and LCL is, for sure, the most common expression pattern. Cases in travelers and military personnel are almost invariably acquired in jungle environments [70]. However, limited information is available about the incidence of CL in travelers for several reasons: (1) the number of exposed people (i.e. the total number of travelers to endemic areas) is often unknown; (2) the disease is frequently misdiagnosed, given the lack of familiarity of physicians in non-endemic countries; (3) it is not a reportable disease in most industrialized countries (notification is compulsory in only 32 of the 88 countries where 350 million people are at risk); (4) spontaneous self-healing is possible. Anyhow further reports from European countries show the importance of CL among returning travelers with skin disorders. In the UK an increase in the annual number of imported *L.* [*V.*] *braziliensis* CL cases has been noted: from 4 to 18 per year between 1995 and 2003. As a possible cause of this increase, the number of UK travelers to South America, especially to highly endemic foci in Bolivia and Belize, has increased 3—5 fold [26]. In a more recent paper, Scarisbrick et al. examined, all patients with a clinical diagnosis of CL seen at the Hospital for Tropical Diseases of London, from 1997 to 2000. Forty-two patients were identified, 23 had traveled to New World countries and 19 to Old World countries. Clinical presentation typically consisted of a single nodule with ulceration. In 50% of cases infection was caused by *L.* [*V.*] *braziliensis* [45]. Similar epidemiological evidence showed that in the Netherlands the number of CL cases doubled between 1990 and 2000, with Europe, Africa, Asia, and the New World (Latin America) as the most common sources of infection [71]. More recent data showed an increase in Netherlands patients diagnosed with CL between 2005 and 2012 compared to the periods from 1979 to 1988 and 1990 to 2000 [61]. CL in Guyana (an overseas region of France) is the major source of exotic cases imported to mainland France [41]. Ehehalt et al., within the European travel medicine network (EuroTravNet), performed a retrospective analysis in travelers who acquired leishmaniasis within Europe and were diagnosed between 2000 and 2012. Thirty cases of CL (and 10 of VL) were identified; the majority was acquired in Spain, Malta and Italy, the most frequent reason for travel was tourism [72].

In the USA most civilian CL cases are acquired in Central America and Mexico; the estimated incidence is of one CL

case treated with antimonials per 1000 travelers to Suriname and one per 1 million travelers to Mexico [30]. Data from the Geosentinel database for the period 1996–2004 show that CL is among the 10 most frequent dermatologic disorders encountered in travelers, identifying South America as the main area of infection, followed by Central America [73]. It is noteworthy that few cases are acquired in countries where the vast majority of the global burden of leishmaniasis occurs – Indian subcontinent, Middle East, and East Africa. This highlights the different epidemiologic profile between imported and indigenous cases, probably due to different exposure. Imported CL is most frequently diagnosed among tourists and travelers for professional reasons (military personnel, construction workers, researchers), as well as immigrants and expatriates. Ecotourists, adventure travelers, soldiers, journalists, photographers, and researchers on long-term trips who work in forests during the night-time (e.g. geologists, veterinarians) are at high risk for acquiring CL. In a 5.3-year study of CL in US travelers, 39% occurred among tourists and 46% among scientists traveling in Central and South America. This represented one thousandth of the estimated annual cases of CL in the USA (n = 59,300) [30]. Even though long-term travels in endemic areas represent a risk factor for leishmaniasis infection, short-term travelers should not be considered immune from risk. Males account for 64–71% of all travel-acquired CL cases; this could be attributable to the overrepresentation of men in high-risk outdoor occupational activities [30,37,41,43]. Finally, CL has also been reported in patients with no history of travel to an endemic area, due to contact with sand flies imported accidentally through various means of transport, from the regions of residence of the cases [54,74]. For this reason the International Health Regulations recommend disinfection of aircraft preflight, and blocks-away spraying with pyrethroids [75].

2.2. Mucosal leishmaniasis

ML is rarely reported among western travelers returning from endemic areas, nevertheless ML is increasingly identified nowadays in travelers from South America, with the vast majority of cases acquired in rural or forest areas of the Amazon basin in Bolivia, where highly endemic foci for *L.* [*V.*] *braziliensis* exist. However, as indicated by our research, there are no published data on the risk of travelers with *L.* [*V.*] *braziliensis* CL progressing to ML [26,32,76–78].

2.3. Visceral leishmaniasis

VL is rare in travelers [73]. Imported VL cases usually concern adult male tourists, HIV-infected persons, or children. Western European travelers mostly acquire VL in the Mediterranean region, occasionally in Latin America, and rarely in the Indian continent or East Africa [18,28,29,37,43]. Imported VL cases to the UK during 1985–2004 were contracted in the countries of southern Europe (i.e. Spain, Italy, Malta, Greece, and Cyprus), and tourists accounted for 55.5% of them, while the remaining patients were immigrants; since 2000, however, no new cases of VL have been reported in immigrants, and all new patients were travelers returning from this geographical region [29]. As already reported for the UK, most cases of VL in the Netherlands were acquired in the south of Europe [79,80]. Similarly, data from the German Surveillance System for Imported Diseases collected during 2001–2004 indicate that the vast majority (81%) of VL cases were acquired in the countries of southern Europe, while almost half (48%) of CL cases were acquired in South America. Germans on holiday accounted for most imported cases in Germany. However a significant number (19%) were non-European immigrants. In this study the relative risk for acquisition of leishmaniasis by geographic area was estimated at 22.7% for South America, 5.4% for Asia, and 2.1% for Africa, compared to southern Europe [43].

3. Clinical manifestations

3.1. Cutaneous leishmaniasis

Given the broad spectrum of the disease, the published data on travelers with CL are insufficient and too heterogeneous to allow a comparison between travelers' clinical framework and patients from endemic areas. CL may manifest with one or multiple skin lesions on the areas of the body exposed to sand fly bites (single or multiple). The onset of lesions may be within a few days or several weeks after the sand fly bite. Occasionally the lesions may appear months or years later [27,30,32]. As mentioned above, ACL has variable clinical manifestations, ranging from a single ulcerative skin lesion (LCL), the most frequent, to destructive mucosal inflammation (ML), and is often accompanied by local lymphadenopathy [81], whereas Old World CL more often presents with multiple lesions [82]. Recent reports, however, indicate that some *Leishmania* spp. endemics in the Old World (Southern Europe, Africa, the Middle East and Asia) might entail mucosal involvement [83–85], with face, upper limbs, and lower limbs as the most frequently involved sites [18,30,45]. The initial CL lesion is usually a gradually enlarging, erythematous, often pruritic papule, which subsequently progresses to nodule and then to ulcer during the next 1–3 months

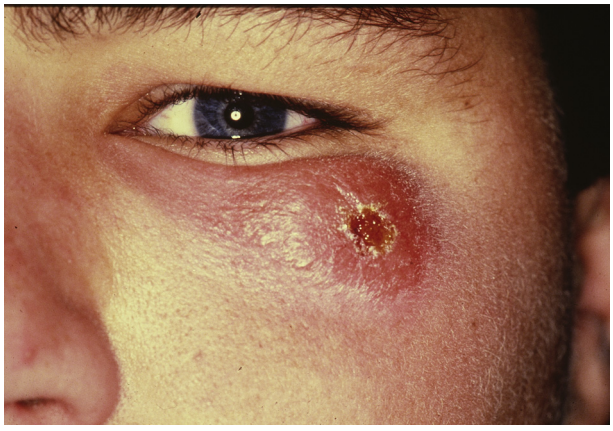

Figure 1 Ulcerated dry lesion caused by Leishmania infantum.

Table 2 New World (or American) Cutaneous Leishmaniasis (ACL) clinical manifestations.

New World (or American cutaneous leishmaniasis (ACL) patterns	First clinical manifestation	Evolution	Number of lesions
Acute/localized cutaneous leishmaniasis (LCL)	Gradually enlarging, erythematous and often pruritic papule at site of sandfly bite	Progression to nodule and then to painless ulcer during the next 1—3 months	One or few at site of sandfly bite
Anergic diffuse cutaneous leishmaniasis (DCL)	Diffuse infiltration of the skin, on which appear nodules, papules, tubercules, and infiltrated plaques, often disfiguring	Rare ulceration. Rapid spreading of initial lesions	Large number, especially in the extremities
Intermediate/borderline disseminated cutaneous leishmaniasis (ICL or BDCL)	Verrucous, zosteriform, chancriform, mycetoma-like, erysipeloid, lupoid, psoriasiform, eczematoid, sarcoidal, keloidal, paronychial, and palmoplantar lesions	Secondary infection, resulting in a purulent appearance, with crust formation, and spreading of the lesions 2—3 months following initial infection	Hundred or more, disseminated to the whole body
Mucosal or Mucocutaneous leishmaniasis (ML)	Erythema and edema of nasal and mouth mucosa, followed by ulcerations covered with a mucopurulent exudate	Ulcerative destruction of nose, mouth, pharynx, and larynx (hoarseness and dysphonia), nasal septum perforation, and facial disfigurement	Multiple lesions spreading through the airways mucosa

[24,32,36,38,39,41,50,62] (Fig. 1). Leishmanial ulcers are typically painless and grow slowly with a granulomatous or crusted base and raised inflammatory margins [86]. Painful lesions are rare, but their appearance could be a predictive sign of bacterial super-infection. Uncommon manifestations, especially in ICL, include verrucous, zosteriform, chancriform, mycetoma-like, erysipeloid, lupoid, psoriasiform, eczematoid, sarcoidal, keloidal, paronychial, and palmoplantar forms, not infrequently becoming secondarily infected, resulting in a purulent appearance, with crust formation, spreading, 2—3 months following initial infection, with the appearance of a hundred or more lesions. DCL, the more rare, anergic form of ACL, is clinically characterized by a diffuse infiltration of the skin, on which appear a large number of nodules, papules, tubercules, and infiltrated plaques, that rarely become ulcerated, and often are disfiguring, resembling lepromatous leprosy. In older cases of the disease, disseminated lesions, more rapidly than in ICL, cover much of the body, but are predominantly on the extremities [2]. Skin lesions, sometimes of several different types occurring simultaneously, may persist for months or years [87—89]. Lymphatic spread, with nodular lymphangitis (sporotrichoid distribution) and regional lymphadenopathy are commonly seen in travelers, especially the ones infected by *L.* [*V.*] *braziliensis* [38,41]. In infections caused by this parasite, lymphadenopathy may even precede the appearance of cutaneous lesions, suggesting early lymphatic spread of parasites [90]. Regional lymphadenopathy has been observed in two-thirds of Brazilian patients infected with *L.* [*V.*] *braziliensis*. In these patients, 62% of lymph node aspirate cultures yielded *Leishmania* parasites [91]. CL natural history varies depending on the species, the location of the lesion, and the immune status of the host. *L.* [*L.*] *mexicana* infections usually cause one or a few lesions that heal spontaneously within 6 months. In Mexicans infected by *L.* [*L.*] *mexicana*, lesions on the ear, called *Chiclero ulcers*, occur in 40% of patients [92]. Non-immune visitors may have a different evolution of the skin lesions and a lower responsiveness to treatment compared to adults of the local population. A study of histopathological parameters in people living in endemic areas with a history of prior CL, as evidenced by a typical scar, showed a higher frequency of giant and epithelioid cells -the hallmarks of the granulomatous response. They also had a lower number of parasites in their lesions. These findings were correlated with a lower dose of antimonials needed to achieve cure, indicating an acquired immunity in the local population with better response to treatment [93]. Despite the non-lethality of the disease and the frequent spontaneous self-healing of lesions (especially due to Old World species) over months to years, CL is often associated with significant morbidity and may affect daily activities and social life when located on the hands and face. In addition, even when cure is achieved, a psychosocial disability could persist due to disfiguration as a result of residual scarring and depigmentation [27] (Table 2).

3.2. Mucosal leishmaniasis

ML probably results from early hematogenous (especially in LCL cases) or lymphatic (especially in ICL cases) spread from cutaneous lesions to the mucosal surfaces of the nose or mouth (including tongue); this involvement might not be noticed until years (up to 35 years) after healing of the initial CL skin lesion. Generally, ML occurs in 1—10% of CL cases, 1—5 years after healing. However, in endemic regions, it is estimated that 1—10% of patients with mucosal disease report no known previous cutaneous involvement. Therefore, it is thought that a significant percentage of infections remain subclinical, so patients may be unaware of previous infection. Furthermore, given the potential for a prolonged interval between resolution of cutaneous disease and development of mucosal lesions, the remote

primary infection may simply not be recalled [18]. Risk factors for progression to ML include male sex, large (>4 cm^2) or multiple lesions, location of the lesion on the head or neck, long-standing skin lesions, for which adequate systemic treatment has not been administered, immune-suppression, malnutrition, and place of infection, for example, in the high Andean countries, notably Bolivia. In addition, it has long been suspected, but never definitely proved, that the risk of developing ML has a genetic component. Recently, an association between ML and HLA has been demonstrated, with significant decrease in the frequency of HLA-DR2 and a significant increase in HLA-DQw3 among patients compared to controls [94—97]. Alcais et al. have proved that the risk of ML ranges from three to ten times higher in migrants than in the indigenous population, indicating that tourists may also be at higher risk of developing ML than the local population [98]. Erythema and edema of the mucosa are the typical onset, and are usually followed by ulcerations covered with a mucopurulent exudate. In contrast to CL, ML is not a self-healing disease and may progress and cause permanent complications, such as ulcerative destruction of the nose, mouth, pharynx, and larynx, nasal septum perforation, and facial disfigurement resulting in social stigma. Without treatment the outcome may be fatal because of the aforementioned compromise of the airway. Patients with ML may complain of stuffiness, difficulty in breathing through their nose, and occasional bleeding as their first symptoms. Hoarseness and dysphonia may indicate laryngeal involvement including the vocal cords [26,32,38] (Table 2).

3.3. Visceral leishmaniasis

Viscerotropic *Leishmania* species infection usually results in asymptomatic or mild illness followed by spontaneous resolution. Only one out of 30—100 infected cases develop typical VL. Factors that predispose the development of typical VL include youth, malnutrition, poverty, immune deficiency, and high leishmanial load [99]. Progression time to VL is usually about 2—8 months from contact with the infectious agent, but longer periods are also reported; significantly shorter cases, up to two weeks after infection, have also been described in the literature [100]. Fever, weakness, anorexia, weight loss, pallor, hepatosplenomegaly (usually splenomegaly predominates), lymphadenopathy, and progressive deterioration of psychophysical state, may be present from the early onset of disease [19,101]. Late findings include epistaxis, gingival hemorrhage, abdominal distension, ascites, and peripheral edema [2]. Occasionally VL may manifest as acute hepatitis, cholecystitis, hemophagocytic syndrome, and Guillain-Barré syndrome [19,102]. Growth retardation may be noticed in children [103]. The natural history of VL includes a mortality rate between 75 and 95%, with delayed diagnosis increasing disease complications, particularly in patients suffering from immune-suppressive diseases. Usually exitus is caused by severe anemia, secondary infection, and hemorrhage [104—108]. Laboratory findings include normocytic normochromic anemia, neutropenia, thrombocytopenia, hypoalbuminemia, hypergammaglobulinemia, and increased transaminases [103]. HIV-infected patients usually have higher parasite loads and atypical symptoms (e.g. gastrointestinal), especially the ones with lower CD4 cell counts. In these cases VL is usually the result of relapse after years of latency or is a newly-acquired infection. This group of HIV-infected patients responds poorly to treatment and rates of relapse are high, regardless of treatment used [107,108]. American military personnel who served in the Middle East in the early 1990s developed a viscerotropic syndrome, characterized by prolonged fever, fatigue, cough, abdominal pain, and diarrhea following infection

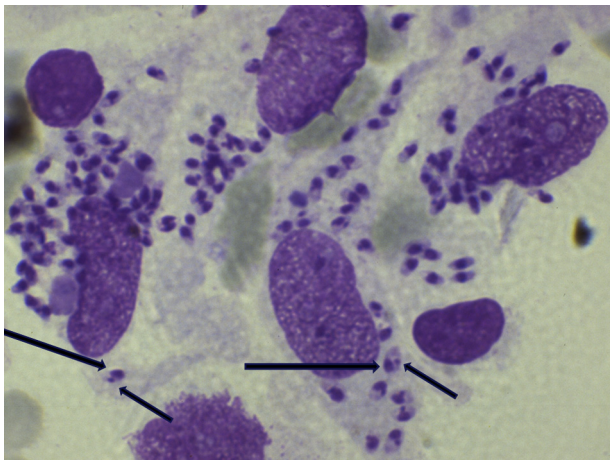

Figure 2 Giemsa-stained skin scraping of a case with cutaneous leishmaniasis at 1000× magnification showing histiocytes loaded with amastigotes. Arrows indicate the nucleus and kinetoplast, which are required to confirm that the inclusion is indeed an amastigotes.

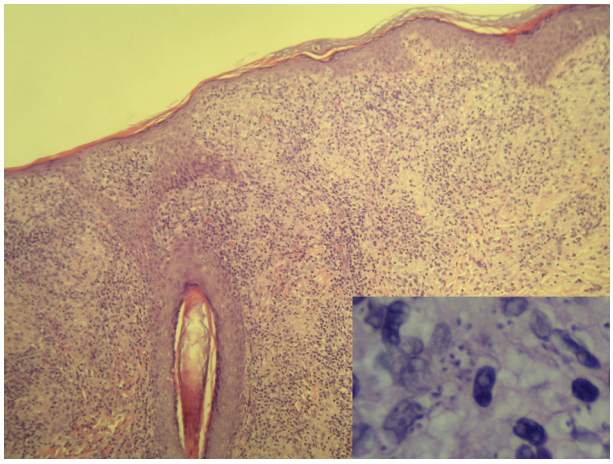

Figure 3 Skin biopsy specimen showing diffuse lymphohistiocytic dermal infiltrate with numerous poorly formed non-necrotizing epithelioid granulomas (hematoxylin-eosin, original magnification ×100) (A). Inset, histiocytes in the papillary dermis with Leishmania parasites in the cytoplasm (original magnification ×1000) (B). In sections stained with hematoxylin-eosin the parasites appear as haloed small dots and the differentiation between the nucleus and the kinetoplast cannot be made.

Table 3 Cutaneous and mucosal leishmaniasis diagnostic methods.

Diagnostic test	Expected result	Notes
Microscopic examination of Giemsa-stained skin specimens by direct light microscopy under oil immersion	Visualization of the amastigote parasite	Simple. Gives rapid results (within 20 min). Low sensitivity (about 14—18%)
Histological sections of skin lesions, stained with hematoxylin and eosin, examined under light microscopy	Detection of granulomas and amastigotes	Granulomas are characteristic of leishmaniasis, but not diagnostic (tuberculosis, sarcoidosis and fungal infections, must be excluded). Low sensitivity (33—57%)
Culture in special medium (i.e. modified Novy—Nicolle —McNeil medium, or NNN culture, at 24—25 °C for up to 3 weeks) of yield fluid from needle aspiration of the lesion's margins	Isolation of the organism and identification of the species	Low sensitivity (58—62%)
Leishmanin skin test (Montenegro test)	Assessment of delayed hypersensitivity reaction to *Leishmania* antigens	Positive in almost all patients with active CL and ML. It may be negative during the first few months. Positive for life. Not routinely available in most industrialized countries
Standard serological tests (i.e., gel diffusion, indirect hemagglutination assay, direct agglutination test, complement fixation, counter-current immune-electrophoresis, Western Blot, enzyme-linked immunosorbent assay, indirect immunofluorescence test, immunochromatographic test)	Identification of anti-*Leishmania* antibodies	Not useful for CL diagnosis. Usually positive in ML. Helpful in monitoring the response of ML to treatment. No species-specific diagnosis
Isoenzyme strains (zymodemes) or monoclonal antibody analysis on cultured *Leishmania*	Species-specific diagnosis of *Leishmania* infection	Not used as routine tests in most laboratories
Leishmania polymerase chain reaction (PCR) on skin lesion samples (punch biopsy or filter paper impressions)	Identification of parasite genoma and species-specific diagnosis	Low parasite load needed. High sensitivity (98—100%) High specificity (100%)

CL: cutaneous leishmaniasis; ML: mucosal leishmaniasis.

with *L. tropica* (generally involved only in Old World CL cases) [109].

4. Diagnosis

The diagnosis of CL or ML in travelers is frequently delayed from several months to years after symptom onset; similar delays have been reported for VL cases in non-endemic countries [26,29,37,38,41,43,45].

4.1. Cutaneous and mucosal leishmaniasis

Physicians should consider CL and ML in a differential diagnosis work-up of subjects with chronic, non-healing skin and/or mucosal lesions who have a travel history in endemic areas. Laboratory confirmation of CL is achieved by detecting *Leishmania* parasites through microscopic examination of Giemsa-stained skin specimens (Fig. 2). Direct light microscopy under oil immersion, which allows

the visualization of the amastigote parasite by using slit skin smear, obtained from the actively inflamed border of the lesion or dabs, is very useful, simple, and gives rapid results (within 20 min), and should be the first diagnostic approach, although its sensitivity is about 14–18% [110–112]. Punch biopsies with tissue-impression smears could be an equally useful diagnostic tool. Histological sections, stained with hematoxylin and eosin, are examined under light microscopy by a histopathologist to search for granulomas and amastigotes (Fig. 3). Granulomas are characteristic of leishmaniasis, but not diagnostic. Other granulomatous disease, such as tuberculosis, sarcoidosis and fungal infections, must be excluded. Needle aspiration from the margin of a lesion can yield fluid for culture in special medium (i.e. modified Novy–Nicolle–McNeil medium, or NNN culture, at 24–25 °C for up to 3 weeks) to isolate the organism and identify the species. However, all these methods suffer from low sensitivity (58–62%), and pathologists may miss the diagnosis or suggest the presence of infection from *Leishmania* spp., particularly when parasites are not visualized in the histopathological specimens. Considering both the difficulties in identification of muco-cutaneous lesions by physicians and poor sensitivity of diagnostic tools, the *Leishmania* polymerase chain reaction (PCR) analysis should be considered as a routine test in granulomatous skin disease work-up, even when a diagnosis of CL was not considered by the referring physician [113,114]. The leishmanin skin test (Montenegro test), related to delayed hypersensitivity reaction to *Leishmania* antigens, is positive in almost all patients with active CL and ML, although it may be negative during the first few months. The test is thereafter positive for life. However, it is not routinely available in most industrialized countries [26,43,71]. Standard serological tests (i.e. gel diffusion, indirect hemagglutination assay, direct agglutination test, complement fixation, counter-current immune-electrophoresis, Western Blot, enzyme-linked immunosorbent assay [ELISA], using promastigote antigen, [ELISAp], or recombinant K39 [ELISA rK39], or K26 [ELISA rK26] antigens, indirect immunofluorescence test, and immunochromatographic test, using rK39 antigen) are not useful for the diagnosis of CL, since they are often negative [115]. In contrast they usually become positive in ML. Hence serology may be helpful in monitoring the response of ML to treatment. The diagnostic methods discussed thus far are genus-specific but not species-specific. Determination of the species is clinically very important, because different species require different clinical and therapeutic approaches; in particular, species detection is of importance since there is an overlap between *Leishmania* and *Viannia* species complexes in Central and South America, and patients might have traveled through several endemic areas confounding the possible detection of species parasite through a geographical localization based approach. For example, *L. Viannia* species may cause a mucosal involvement and a systemic treatment is recommended, whereas this is not required for most cases of other CL. Unnecessary systemic therapy may be harmful, since it can be associated with toxic adverse effects [116]. Until recently the two existing methods for species-specific diagnosis of *Leishmania* infection were isoenzyme strains (or zymodemes) or monoclonal antibody analysis on cultured *Leishmania*, which are not used as routine tests in most laboratories [117]. PCR and subsequent sequencing of DNA products can permit the species identification of samples for which parasite culture remained negative or did not allow isoenzymatic characterization [118]. The multilocus sequence typing (MLST) and the Matrix-assisted laser desorption ionization time-of-flight (MALDI-TOF) mass spectrometry are promising approaches, providing rapid and accurate identification of *Leishmania* from *in vitro* culture at the species level [119,120].

PCR, especially using kinetoplast minicircle DNA or internal transcribed spacer of the multi-copy nuclear ribosomal genes, appears to be the best method for confirming a diagnosis of CL, because of the low parasite load needed, with a sensitivity of 98–100% and a specificity of 100% [118,121,122]. PCR has also proved superior to conventional methods in the diagnosis of ML, showing better sensitivity (97–100%) than the direct visualization of parasites in biopsies (hematoxylin-eosin staining) (33–57%), immunohistochemical testing of biopsy sections (69%), culture (67%), or serological testing (83%). However, leishmanial DNA may persist in the skin of patients after complete healing, resulting in possible confusion with other, unconnected mucosal diseases. In the latter case, despite high positive and negative predictive values, PCR results like those of any laboratory test should be interpreted in the light of the overall clinicopathological findings [26,123]. Two quick, in-office techniques for PCR sampling currently available to the clinician are punch biopsy and filter paper impressions. The first involves 1–2 mm biopsies of the indurate active margins of the ulcer, with part of the sample being used to make tissue impression smears and the other being exploited for PCR analysis. The second technique, which is a simpler and much less invasive procedure, entails the blotting of the lesion onto a special Whitman filter paper that is subsequently analyzed. This method has the additional advantage of allowing easy specimen transport, making it particularly appropriate to be used in areas without access to high quality laboratory equipment [124–127]. In the differential diagnosis of CL and ML, unspecific skin reactions to insect bites, bacterial skin infections (including staphylococcal infections, especially MRSA, and streptococcal pyodermas, yaws, syphilis, cutaneous tuberculosis, *Mycobacterium marinum* infections, leprosy, actinomycosis, and rhinoscleroma), mycosis (including, blastomycosis, coccidioidomycosis, paracoccidioidomycosis, histoplasmosis and sporotrichosis), cutaneous larva migrans, granulomatous disease (Wegener granulomatosis and sarcoidosis) and tumors (lymphoproliferative disease, extranodal NK-T-cell lymphoma, or midline granuloma, and nonkeratinizing squamous cell carcinomas) are the most frequent misdiagnoses. When the lesions are (1) small in number (2) located on exposed body surfaces, (3) not painful, (4) persist for several months, and (5) resist all types of administered treatment, CL should quickly ascend to the top of the differential. This profile is

Table 4 Cutaneous and mucosal leishmaniasis treatment.

Leishmaniasis patterns	Treatment
Old World CL	
• Single, stable lesion under 10 mm diameter on non-exposed areas in an immunocompetent patient • More than one lesion in exposed area • Three or more lesions larger than 4–5 cm, located in sensitive areas	• Intervention is not always necessary, as the ulcers should spontaneously regress within 2–4 months • Topical treatment with intralesional injections (see New World CL) • Systemic therapy (see ML)
New World CL	

• Skin lesion (<4 cm), exclusively when no risk for ML seems plausible
• Infection by *Viannia* complex species (especially *L.* [*V.*] *braziliensis*), multiple or large (>4 cm) lesions, established metastatic spread to lymph nodes, failure to respond to topical treatment, immune-suppressed patients
	• Local treatment:
	  • Local infiltration of pentavalent antimony (every 5–7 days, for a total of 2–5 times)
	  • Topical therapy with formulations containing 15% paromomycin, and methlybenzethonium
	  • Physical treatment (heat, cryotherapy, laser, or a combination of cryotherapy followed by intralesional pentavalent antimony)
	• Systemic therapy (see ML)

ML	
• It must always be approached with a systemic treatment	Gold standard: • Meglumine antimoniate for intramuscular administration (20 mg/kg/day without an upper limit for 20 [CL] to 28 [ML] days) • Sodium stibogluconate for intravenous administration (20 mg/kg/day without an upper limit for 20 [CL] to 28 [ML] days) • *plus* oral pentoxyfilline 3 × 400 mg/day (CL) Other approaches: • Pentamidine isethionate (300 mg once weekly for 3–5 weeks) • Miltefosine (150 mg/kg for 28 [CL] to 42 [ML] days) • Fluconazole high dos es regimen (200–400 mg/day for at least 6 weeks) • Azithromycin • Amphotericin B (20 mg/kg in 5 days for CL; 40 mg/kg in 4–8 days for ML)

CL: cutaneous leishmaniasis; ML: mucosal leishmaniasis.

especially true in Old World CL, where such characteristically chronic, ulcerative lesions are seen in 86–98% of cases [45] (Table 3).

4.2. Visceral leishmaniasis

Although very uncommon in travelers, VL should be suspected in persons with an unexplained febrile illness, especially when hepatosplenomegaly and thrombocytopenia are present, reporting a relevant travel history to an endemic area. The long incubation period of leishmaniasis, months or even years, makes it critically important for the physicians to collect a sufficiently long personal history, stressing possible travel to endemic areas. A search for risk factors for HIV infection should also be considered, including sexual encounters, intravenous drug use, and blood transfusions obtained abroad [113]. The gold standard diagnostic tool for VL is, to date, microscopic examination of bone marrow smears characterized by >90% sensitivity rates in children and 70% in adults. Higher sensitivity rates (>95%) could be obtained from analysis of spleen aspirates; however, in the context of profound thrombocytopenia, spleen sampling may trigger life-threatening hemorrhage [19,128]. Serologic testing (indirect hemagglutination assay, IHA, direct agglutination test, DAT, enzyme-linked immunosorbent assay, ELISA, and indirect immunofluorescence, IFI) shows high sensitivity and specificity rates, even though the diagnostic cut-offs depend on the area and prevalence rates of asymptomatic infection. As a rule, antibody (IgG) detection tests should complement other diagnostic tests, because they remain detectable for several years after successful treatment and do not usually distinguish between acute disease, asymptomatic infections, relapses and cured cases [2]. The complete anergy found during active disease state, limits the availability of the Montenegro test for VL in the detection of past infections [129]. The diagnosis can also be confirmed with molecular methods (i.e. PCR), using various clinical specimens (peripheral blood, bone marrow, spleen), with high sensitivity and specificity rates [128,130].

5. Treatment

Inappropriate management of leishmaniasis is common [24,26,36]. Typically one patient with New World CL

consulted six physicians, underwent two skin grafts, and paid a total of 6600 US Dollars before the correct diagnosis was considered [27]. To date an ideal anti-leishmanial agent is far from being discovered; its desirable features would be effectiveness, safety, ease of administration, and affordability. The recent paper by Hodiamont et al. demonstrates the lack of evidence in the literature for treatment of several clinical categories with different *Leishmania* species [131]. The choice of treatment is influenced by previous experience as well as availability of a particular drug within a country. Patients should be referred to specialized centers with past experience.

5.1. Cutaneous and mucosal leishmaniasis

Factors that may influence the choice of therapeutic agent include: (1) absence of evidence-based data regarding travelers; (2) possible high toxicity associated with parenteral treatment for a usually benign self-healing disease (with the exception of *Viannia* species induced New World CL, where there is a risk of mucosal dissemination); (3) lack of availability of appropriate drugs, especially pentavalent antimonial agents, in certain countries, (4) compliance of the patient [116]. Treatment is recommended to accelerate cure and avoid or reduce disfiguring scars, as well as to prevent mucosal dissemination. While a local treatment might be sufficient for the first goal, a systemic one is needed to achieve the second [116,132]. There are three basic approaches to the treatment of Old World CL, according to the specific features of lesions and patients. The first involves single, stable lesions under 10 mm diameter on non-exposed areas in an immunocompetent patient. In such cases, intervention is not always necessary ("wait and see") as the ulcers should spontaneously regress within 2—4 months. In cases with more than one lesion in an exposed area, topical treatment with intralesional injections is generally initiated so as to expedite the healing process, prevent disfiguring scarring, and reduce the likelihood of dissemination and recurrence. In cases involving three or more lesions larger than 4—5 cm, located in sensitive areas (i.e. on the face or joints), systemic therapy becomes the necessary approach. In brief, systemic treatment is indicated in cases of 1) New World CL, in which skin lesions are caused by *Viannia* complex species (especially *L.* [*V.*] *braziliensis*), 2) multiple or large (>4 cm) lesions, especially when the face or a joint are affected or lesions are present on the hands or feet, or for cosmetic reasons, 3) established metastatic spread to lymph nodes, 4) failure to respond to topical treatment, and 5) immune-suppressed patients. Several studies show how early systemic treatment may prevent mucosal lesions, which are seen more frequently in patients with incomplete or missing specific treatment [9,115,124,125,133,134] (Table 4).

5.1.1. Systemic pentavalent antimonials

The gold standard of CL and ML treatment is, to date, represented by systemic pentavalent antimonials (meglumine antimoniate for intramuscular administration, and sodium stibogluconate for intravenous use), whose biochemical basis of effectiveness is still unknown, but may involve inhibition of ATP synthesis. These agents may be also administered intralesionally [135]. However, the latter method is not approved by the US Food and Drug Administration (FDA). The recommended systemic dose is 20 mg/kg once for day without an upper limit (no higher toxicity with higher doses of the drug) for 20 days (CL suggested regimen, to decrease the risk of mucosal invasion) to 28 days (ML suggested regimen, plus oral pentoxyfilline 3 × 400 mg/day) [136]. The pentavalent antimonials show high cure rates and remain the mainstay of treatment for CL or ML, providing cure with a low rate of recurrence [116,132,137]. A recent meta-analysis concluded that meglumine antimoniate is the drug of choice for ML with 88% cure rates compared to 51% cure rates for stibogluconate [138—146]. However, pentavalent antimonials are far from being ideal drugs because of their difficult administration and toxicity. Fatigue, musculoskeletal pain, and gastrointestinal symptoms (anorexia and nausea) are the most common adverse effects. Occurrence of acute pancreatitis during treatment among immune-suppressed patients is noteworthy (e.g. patients co-infected with HIV or those on immune-suppressive therapy following renal transplant). Laboratory abnormalities are very common and include higher levels of liver and pancreatic enzymes, and hematological findings such as leucopenia and thrombocytopenia. Reversible ECG alterations (T wave changes) are seen in 30—60% of cases and may occur without evidence of myocardial damage. However, cardiac toxicity and potentially lethal ventricular tachyarrhythmias, associated with prolongation of the QT interval, have been documented and increase with total drug accumulation. In addition, patients with preexisting cardiovascular morbidity and hypokalaemia are at particular risk and should be closely monitored. It is therefore desirable that they be administered by experienced personnel and only when medically justified [139—146].

5.1.2. Pentamidine

A useful alternative to antimonials is pentamidine isethionate, an aromatic diamidine, toxic for a number of protozoa and fungi, including *Leishmania*, *Pneumocystis carinii* and African trypanosomes, whose mechanism of action has not been established. Due to long experience in terms of efficacy and safety it is considered the first-line agent for *L.* [*V.*] *guyanensis* in French Guiana, Suriname, and Brazil. The drug is less efficient against *L.* [*L.*] *braziliensis* infections [147,148]. The drug is administered at a dose of 300 mg once weekly for 3—5 weeks [132]. In an open-label study of 11 cases of imported Old World CL with large and chronic lesions, a first line treatment consisting of three intramuscular injections of 4 mg/kg pentamidine base every 48 h yielded a success rate of 73% [149]. Elevation of creatinine kinase has been noticed with much higher doses, thus creatinine kinase and kidney function have to be checked before each injection [132,150]. Glucose serum levels should also be checked, since one case of hyperglycemia and glucosuria has been described after one 200 mg dose of pentamidine [150].

5.1.3. Miltefosine

Miltefosine, a phosphocholine analog, is the first oral anti-leishmanial drug. Preliminary studies show promising results with the use of the drug in New World CL and ML at a

dosage of 150 mg/day (in 2—3 doses) for 28 days (prolonged in ML, e.g., to 42 days). Oral miltefosine is effective against *L. major* CL in Iran and *L.* [*V.*] *braziliensis* CL in Bolivia with 92.9% and 88% cure rates, respectively. Nevertheless the same drug was found to be less effective in cases caused by the same species in Guatemala, so a longer follow-up is needed to evaluate the relapse rate [151]. However, miltefosine has not proven useful to treat DCL [152].

The most notable side effects include nausea, vomiting, diarrhea, motion sickness, and headache. An increase of transaminases and creatinine kinase has also been reported [132,151,153,154].

5.1.4. The imidazoles

The imidazoles and the structurally-related triazoles (fluconazole, itraconazole, and ketoconazole), originally used as antifungal drugs, have also demonstrated anti-leishmanial activity. They can be administered orally and have a good safety profile [132]. However, they are only effective against a limited number of *Leishmania* species. A 6-week course of oral fluconazole was shown to be safe and effective over *L. major* CL in Iran, with cure rates of 36% and 88% after 50 days and 90 days, respectively [155]. A more recent randomized clinical trial in Iran showed that a high dose fluconazole regimen (400 mg/day) had better outcomes than the low-dose regimen (200 mg/day) [156]. Nevertheless, the effect of fluconazole has been questioned. In a recent study conducted among travelers with imported *L. major* CL, a cure rate of 44.4% at day 50 was recorded, comparable to published rates of spontaneous healing [27].

5.1.5. Azithromycin

Azithromycin exhibits anti-leishmanial activity *in vitro* and has also been used for the treatment of CL and ML. However, its use is limited to patients with treatment failure or contraindications for all other options, such as young children, pregnant women, or patients with a severe underlying disease [157,158].

5.1.6. Amphotericin B

The first use of amphotericin B for the treatment of CL was reported in the early 1960s when it was proved that the main sterol in cellular membrane of *Leishmania* was ergosterol [159]. Amphotericin B desoxycholate is active against *Leishmania* species, but has the disadvantage of a high incidence of adverse reactions (i.e. hyperpyrexia, severe malaise, hypotension, thrombophlebitis, hepatitis, hyperazotemia, renal tubular damage, hypokalemia, and anemia). Several other amphotericin B lipid formulations with much lower toxicity have been developed, proving useful in the treatment of VL (see below). Based on currently available data, liposomal amphotericin B has been insufficiently studied, with regard to formulation and dosage, to assess its efficacy in CL and ML. Despite this, liposomal amphotericin B is being successfully used in travelers as a first-line treatment in CL and ML, as a second-line treatment after relapse, or in HIV-co-infected patients (total dose of 20 mg/kg, in 5 days for CL; total dose of 40 mg/kg in 4—8 days for ML) [48,132].

5.1.7. Local treatment

Local treatment is used exclusively when no risk for ML seems plausible. It is mainly relevant in treating *Leishmania* complex infections. Local treatment may be useful as an adjuvant to systemic treatment to accelerate healing. Local treatment may also be considered in patients for whom systemic treatment is contraindicated, such as pregnant women or subjects suffering from cardiac problems [132,160]. Drugs in topical formulations offer significant advantages over systemic therapy, such as ease of administration, fewer adverse effects and positive cost-effectiveness ratio. However, the intact skin hampers percutaneous absorption, mainly the stratum corneum. Therefore, topical formulations may be applied to open lesions that have lost their stratum corneum barrier property, but are less successful in lesions where absorption is hindered by epithelial thickening. Local infiltration of pentavalent antimony maximizes the concentration within lesions and has few systemic adverse effects; however, it does not reach metastatic lesions. Intralesional infiltrations are also painful and require some experience. The basic aim of local treatment with pentavalent antimonials is to fill the infected part of the dermis. The drug must not be injected into the subcutaneous tissue, where it is rapidly absorbed and does not reach the site of infection. However, injection into the dermis is difficult, since the tissue space is small. This means carefully infiltrating the area around the lesion, including its base. A 25-fine gauge needle is used to inject the drug under pressure as the needle advances. Treatment should be given every 5—7 days, for a total of two to five times. If the lesion is not healing after five treatments, it should be re-examined in 1 month, when a decision about switching to systemic treatment should be made. When such injections are preceded by cryotherapy, which involves bleaching of the lesion for $\geq$10 s, the result is more efficacious than their individual use [161,162]. The above-mentioned advantages of topical therapy are easily obtained by formulations containing 15% paromomycin, an aminoglycoside antibiotic, with methlybenzethonium in white soft paraffin or urea and white soft paraffin, or with 0.5% gentamicin. The combination of paromomycin with methylbenzethonium appears to be more effective than the combination with urea, but it causes the strongest local inflammatory reactions [132,163]. In *L.* [*V.*] *braziliensis* or *L.* [*V.*] *peruviana* CL the efficacy of pentavalent antimonials (also in terms of faster healing) seems to be improved by the association of topical immune-modulators (e.g. imiquimod cream) [132]. The combination of oral pentoxyfilline 3 $\times$ 400 mg/day with antimonials for 28 days has proved to have the same beneficial effects [160]. Physical treatment for CL, such as heat, cryotherapy, laser, or a combination of cryotherapy with intralesional meglumine antimoniate has been successfully applied in endemic countries [164—167]. In particular, cryotherapy consists of repeated topical applications of liquid nitrogen with a cotton-tipped applicator or a cotton swab with moderate pressure to the lesion, up to 2 mm outside the lesion margin. The freezing time per application is 15—20 s. The procedure must be repeated two or three times at short intervals (1—2 days), resulting in a total time of 30—120 s.

Whitening of the skin at 2–3 mm outside the margins of the lesion reflects an adequate application. The usual post-freeze pattern is some edema and blistering of the lesion itself for 2–3 days, followed by crusting and formation of an eschar [166,168].

5.2. Visceral leishmaniasis

Treatment for VL should be started as soon as the diagnosis is established.

5.2.1. Systemic pentavalent antimonials

The pentavalent antimonials meglumine antimoniate and sodium stibogluconate remain the standard anti-leishmanial treatment for VL in developing endemic areas with the exception of India, where their use has been abandoned due to the occurrence of a widespread anti-monial resistance, and they have been replaced with conventional amphotericin B [132,169]. Experience with antimonials for almost 70 years indicates efficacy rates of >90–95% and low fatality and relapse rates [107,135,170,171]. One advantage is their low cost; the main disadvantages include intramuscular route of administration, prolonged (20 mg/kg once for day for 21–30 days) schedules, and transient but occasionally life-threatening side effects, such as increased serum hepatic transaminases, pancreatitis, and cardiac arrhythmias [103].

5.2.2. Amphotericin B

Conventional amphotericin B has excellent anti-leishmanial activity. A 15-day regimen at a dose of 0.75 mg/kg, seems to result in cure rates over 90% in Indian VL [172]. Excluding HIV-infected patients, relapses are rare. Even considering its effectiveness, amphotericin B does not offer any advantage over pentavalent antimonials for use outside India, because of several disadvantages, including prolonged hospitalization and administration, and frequent side effects (infusion-related fever and chills, nephrotoxicity, and hypokalemia) [135]. Lipid formulations of amphotericin B (i.e. liposomal amphotericin B, amphotericin B lipid complex, and amphotericin B colloidal dispersion) are selectively picked up by the reticulo-endothelial system of the host, where parasites replicate, offering the advantage of a highly localized and increased efficacy with limited systemic toxicity. Contrary to what was said for the conventional formulation, liposomal amphotericin B is the first-line drug for VL in Europe, USA, and other industrialized countries nowadays, offering great advantages compared to pentavalent antimonials, because of its rapid cure rates up to 100%, with a total dose of 20 mg/kg in 2–7 days, preferably 10 mg/kg once per day, on 2 consecutive days, or a total dose of 40 mg/kg, administered over 4–8 days, for immunodeficient patients, improved compliance of the patient, and reduced health care costs [173]. In HIV co-infected patients, liposomal amphotericin B is also the drug of choice both for treatment and for secondary prophylaxis, because of its efficacy and safety profile [108], while antimonials and conventional amphotericin B should be avoided due to serious toxicity and intolerance [174]. However, in poorly resourced endemic countries even short courses of liposomal amphotericin B are unaffordable, but nowadays the formulation is available at reduced price in endemic countries, and for free for selected poor countries [175]. In a recent study in India, injectable paromomycin was shown not to be inferior to amphotericin B for the treatment of VL [176].

5.2.3. Miltefosine

In a phase 4 trial of treatment with miltefosine in 1132 VL adults and children in India, 95% cure rates were noted, while adverse effects, including gastrointestinal toxicity and increased hepatic transaminases and creatinine levels, were noted in 3% of patients [177]. Currently, miltefosine is licensed in India, Colombia, and Germany. It is administered at a dose of 150 mg (in 2–3 doses) for 28 days in adults >50 kg (50 mg/day in adults weighting <50 kg, 2.5 mg/kg/day in children), and 150 mg/day (in 2–3 doses) for 6 weeks in immunodeficient patients [178]. Due to the possible teratogenicity, miltefosine should not be administered to women who may become pregnant within 2 months after drug discontinuation.

6. Prevention

International travelers are frequently uninformed about leishmaniasis and the appropriate protective measures. A survey conducted among 373 travelers in Manu National Park, Peru, revealed that only 6% of them had heard of leishmaniasis, although 96.5% of the latter had received pre-travel advice and 97.5% used protective measures [179]. In another survey conducted among 58 American travelers with New World CL, 53% reported that they have heard about leishmaniasis, however only 29% were aware of protective measures. Of note, 63% of the travelers who reported not to have ever heard about leishmaniasis (47% of the total) had received some pre-travel advice [30].

To date, no vaccine against human leishmaniasis is available. Research and development of vaccines against canine leishmaniasis have been stimulated by the economic importance of dogs and their role as reservoirs of human leishmaniasis caused by *L. infantum* in the Mediterranean region and the Americas. Leishmune®, containing the fucose-mannose ligand antigen of *L. donovani*, is the first licensed vaccine against canine leishmaniasis, with a reported efficacy of 76–80% [180]. Travelers to endemic areas should be advised that the only preventive measures are to avoid sand fly bites, such as: 1) avoiding outdoor activities, in particular from dusk to dawn when sand flies are most active; 2) wear protective clothes (i.e. long-sleeved shirts); 3) apply DEET (N,N-diethyl-meta-toluamide)-containing repellents to exposed skin; 4) use of permethrin-treated clothing, as shown in a study of Colombian military personnel, in which soldiers wearing permethrin-treated uniforms in an endemic area acquired the disease significantly less often than those without permethrin-treated clothing [180]. In addition, sand flies are weak fliers and therefore their movement may be inhibited by fans or ventilators. Sleeping in air-conditioned or well-screened areas is also advisable, as well as indoor spraying. Sand flies are smaller than mosquitoes and they

can pass through the holes of ordinary bed-nets (use only fine-mesh bed netting). The treatment of bed-nets with a pyrethroid-containing insecticide (permethrin or deltamethrin) may protect against indoor transmission [181]. A randomized study in Venezuela evaluated the implementation of pyrethroid-treated curtains in an urban area with a 4% incidence of CL. A total of 2913 inhabitants from 569 homes were enrolled. The use of pyrethroid-treated curtains reduced the sand fly population, and 12 months later the incidence of CL was eliminated to 0% [181].

7. Conclusions

Among international travelers, imported leishmaniasis is an uncommon but emerging infectious disease, whose management in developed, non-endemic countries is still a challenge due to the unfamiliarity of physicians with its wide clinical spectrum, diagnostic modalities, and available treatment options. Leishmaniasis should be considered in the diagnostic assessment of patients presenting with a compatible clinical syndrome and a history of travel to an endemic area, even if this occurred several months or years before. Adventure travelers, researchers, military personnel, and other groups of travelers likely to be exposed to sand flies in endemic areas, should receive counseling regarding leishmaniasis and appropriate protective measures.

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Conflict of interest

None.

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