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Leishmaniasis in immunosuppressed individuals

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Abstract

Leishmaniasis is a vector-born chronic infectious disease caused by a group of protozoan parasites of the genus *Leishmania*. Whereas most immunocompetent individuals will not develop disease after *Leishmania* infection, immunosuppression is a well-established risk factor for disease. The most severe form is visceral leishmaniasis (VL), which is typically fatal if untreated. Whereas human immunodeficiency virus (HIV) co-infection (VL–HIV) was initially mainly reported from southern Europe, it is now emerging in other regions, including East Africa, India, and Brazil. VL has also been found in a wide range of non-HIV-related immunosuppressive states, mainly falling under the realm of transplantation medicine, rheumatology, haematology, and oncology. Clinical presentation can be atypical in immunosuppressed individuals, being easily misdiagnosed or mistaken as a flare-up of the underlying disease. The best diagnostic approach is the combination of parasitological and serological or molecular methods. Liposomal amphotericin B is the drug of choice. Treatment failure and relapse rates are particularly high in cases of HIV co-infection, despite initiation of antiretroviral treatment. Primary prophylaxis is not recommended, but secondary prophylaxis is recommended when the patient is immunosuppressed. Cutaneous leishmaniasis can have a number of particular features in individuals with immunosuppression, especially if severe, including parasite dissemination, clinical polymorphism with atypical and often more severe clinical forms, and even visceralization. Mucosal leishmaniasis is more common. Treatment of cutaneous and mucosal leishmaniasis can be challenging, and systemic treatment is more often indicated. With globally increased travel and access to advanced medical care in developing countries, the leishmaniasis burden in immunosuppressed individuals will probably continue to rise, warranting increased awareness and enhanced surveillance systems.

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Introduction

Leishmaniasis is a chronic infectious disease caused by a group of protozoan parasites of the genus *Leishmania*. The parasites are transmitted to humans via the bite of phlebotome sandflies, and predominantly target reticuloendothelial cells. Leishmaniasis can present with a spectrum of clinical manifestations (Table 1) [1]. Visceral leishmaniasis (VL; kala azar) is a potentially fatal condition characterized by hepatosplenomegaly, chronic fever, weight loss, and pancytopenia [2]. Typically, VL is classified as zoonotic, caused by *Leishmania infantum* (syn. *Leishmania chagasi* in South America), with the dog as the main reservoir, or anthroponotic, caused by *Leishmania donovani*, mainly found in East Africa and the Indian subcontinent [1–3]. Cutaneous leishmaniasis (CL) is more widely distributed [3,4]. Ulcerative skin lesions occurring at the site of the bite of the sandfly constitute the most common cutaneous manifestation (localized CL). Although it often heals spontaneously, CL typically leaves scars and can be disfiguring and stigmatizing. There are several more rare forms, such as diffuse CL, which is often difficult to treat. Mucosal leishmaniasis (ML) or mucocutaneous leishmaniasis (MCL) refers to an often destructive form with mucosal inflammation, which has been mainly reported in association with *Leishmania brazilienzis* [4,5], but also in the Old World [6]. The most recent global estimates suggest

TABLE 1. Aetiology, burden, clinical forms and treatment of leishmaniasis

Aetiology/main geography[a]	High-burden countries	Clinical presentation/forms	Main treatment options
VL *Leishmania infantum* (syn. *Leishmania chagasi*): Mediterrean basin, Latin America, Middle East, Asia (China) (zoonotic transmission) *Leishmania donovani*: Indian subcontinent (anthroponotic), East Africa (mainly anthroponotic; possibly zoonotic transmission)	Top six countries (90% of global burden): India, Nepal, Bangladesh, Brazil, South Sudan, Ethiopia	Persistent fever, (hepato)splenomegaly and weight loss Pancytopenia, hyperglobulinaemia	Antimonials Conventional amphoterin B Liposomal amphoterin B Miltefosine[b] Paromomycin[b]
CL and ML New World CL: (South and Central America) *Leishmania braziliensis*, *Leishmania panamensis*, *Leishmania peruviana*, *Leishmania guyanensis*, *Leishmania colombiensis*, *Leishmania amazonensis*, *Leishmania mexicana*, *Leishmania venezuelensis* Old World CL: *Leishmania major* (north-eastern Africa, Middle East, Asia); *Leishmania tropica* (Asia, North Africa, Middle East); *Leishmania aethiopica* (Ethiopia); *L. infantum* (see above)	Top 10 countries (70–75% of global burden): Afghanistan, Iran, Syria, Algeria, Ethiopia, North Sudan, Colombia, Brazil, Costa Rica, Peru	Localized CL rare forms: Diffuse CL, Disseminated CL, Leishmaniasis recidivans cutis ML	Local treatment: Intralesional antimonials, Topical paromomycin, Cryotherapy/thermotherapy Systemic treatment: Antimonials, Conventional and liposomal amphoterin B, Miltefosine[b], Paromomycin[b], Ketoconazole/fluconazole, Pentamidine

CL, cutaneous leishmaniasis; ML, mucosal leishmaniasis; VL, visceral leishmaniasis.
[a]Some more exceptional species (e.g. *Leishmania killicki*, *Leishmania pifanoi*, and *Leishmania garnhami*) are not included.
[b]Difficult to obtain/limited availability in most Western countries.

approximately 0.2–0.4 million annual cases of VL and approximately 1 million cases of CL [3].

Whereas autochthonous leishmaniasis remains relatively rare in Europe, being mainly confined to southern Europe (estimated annual VL incidence of 340–510 cases), imported leishmaniasis is now being increasingly reported [7–12]. As demonstrated by the spread of *L. infantum* in Italy and the recent outbreak in Madrid [13], leishmaniasis has the potential to further emerge or re-emerge within Europe, through spread of the current species (*L. infantum* and *Leishmania tropica*) because of climate change, the introduction of exotic *Leishmania* species because of international travel and immigration, and the increased number of immunosuppressed people [14,15]. Immunosuppression is one of the strongest risk factors for overt clinical disease, and can also alter disease presentation and treatment response. Although immunosuppression has historically been mainly observed in human immunodeficiency virus (HIV)-infected patients, non-HIV-related immunosuppressive conditions are becoming increasingly prevalent globally, mainly because of better medical care of patients with chronic illnesses and the therapeutic use of immunosuppressive drugs. In this review, we focus on the challenges in terms of diagnosis, prevention and treatment of leishmaniasis in immunosuppressed individuals. Given its life-threatening potential and the strong interaction with immunosuppression, the main focus will be on VL.

Epidemiology and Risk Factors

The epidemiological and clinical impact of immunosuppression on VL was most strikingly illustrated by the effect of the HIV epidemic in VL-endemic countries in southern Europe, with HIV contributing to the re-emergence of VL. By early 2000, almost 2000 cases of VL–HIV (predominantly in intravenous drug users) had been notified, with 50–60% of all VL cases being HIV-co-infected at some point [16]. It is of interest that an anthroponotic transmission cycle for *L. infantum* could be demonstrated, whereby parasites were transmitted among intravenous drug users via the shared use of needles and syringes [17]. Moreover, some studies demonstrated that *L. infantum* could be more readily detected in peripheral blood in HIV-infected patients, suggesting increased infectivity, and possibly also indicating an overall higher parasite load. Fortunately, with the wide-scale introduction of highly active antiretroviral therapy (HAART), a gradual decline in VL incidence has been observed over the last decade [18,19]. Currently, the burden of VL–HIV co-infection is most pronounced in some regions in East Africa, such as north-western Ethiopia, where between 20–40% of individuals with VL are co-infected with HIV [18]. The problem also seems to be emerging in India and Brazil [18,20–23].

In Europe, where individuals with VL–HIV co-infection are often intravenous drug users, parasites causing VL in HIV-infected individuals have been found to be more diverse, with higher enzymatic polymorphism, than those in the general population [16]. In some HIV-co-infected cases, non-human pathogenic trypanosomatids have been isolated [24,25]. The extent and significance of these observations at the global level are currently not well defined. It is of interest that a recent study from Italy suggested an apparent reversal of the initial increase in zymodeme diversity concurrent with HAART introduction [26].