New World and Old World Leishmania Infections
A Practical Review

Ines Kevric, MD[a], Mark A. Cappel, MD[a], James H. Keeling, MD[b,*]

KEYWORDS

• Leishmania infection • Leishmaniasis • Cutaneous leishmaniasis • Mucocutaneous leishmaniasis

KEY POINTS

- Leishmaniasis is a parasitic infection transmitted by the bite of a sandfly, which is endemic to tropical and subtropical regions.
- The incidence of cases is rising with increased travel to these areas.
- Polymerase chain reaction is emerging as the diagnostic test of choice, because it quickly and accurately identifies the infecting species.
- Treatment recommendations vary, but pentavalent antimonials remain the preferred choice in most centers.
- Travelers to endemic countries should be counseled appropriately, because there is no vaccine to prevent this infection.

INTRODUCTION/OVERVIEW

Leishmaniasis is a tropical disease caused by an intracellular parasite of the genus *Leishmania*. The vector of transmission is the sandfly, which deposits one of the 20 disease-causing protozoan species during a blood meal. Clinical presentation depends on the complex interplay between the host cell-mediated immune response, and the specific protozoa and vector species. There are four generally accepted classifications of clinical disease: (1) cutaneous leishmaniasis (CL), (2) diffuse CL (DCL), (3) mucocutaneous leishmaniasis (ML), and (4) visceral leishmaniasis (VL). This disease is also often classified according to the world regions in which it occurs. Old World (OW) leishmaniasis exists in the Eastern Hemisphere and is endemic in Asia, Africa, and southern Europe. New World (NW) leishmaniasis is endemic to the Western Hemisphere, extending from south-central Texas to Central and South America (except Chile and Uruguay). The disease is not found in Australia, Antarctica, or the Pacific islands.

It is difficult to obtain accurate numbers on disease incidence. It is believed to be underreported because it can be subclinical and is a disease primarily affecting the impoverished parts of the world. Estimates suggest that there are 12 million people infected, with 2 million new cases annually, most of which are cutaneous and mucocutaneous infections.[1–3] Leishmaniasis is the second leading cause of parasite-related death (after malaria) causing 20,000 to 30,000 deaths annually.[2]

Although this disease historically is limited to the tropics and subtropics, there are several factors contributing to its dissemination to new areas. These include climate change, urbanization, deforestation, increased travel for tourist and work-related reasons, immigration from endemic countries, and military operations.[4–8] In the United States, leishmaniasis is typically

[a] Department of Mayo Clinic, 4500 San Pablo Rd, Jacksonville, FL 32224, USA; [b] Department of Dermatology, Mayo Clinic, 4500 San Pablo Road South, Jacksonville, FL 32224, USA
* Corresponding author.
E-mail address: Keeling.James@mayo.edu

Dermatol Clin 33 (2015) 579–593
http://dx.doi.org/10.1016/j.det.2015.03.018

diagnosed among travelers to endemic areas, military personnel, and immigrants. However, CL acquired in Texas and Oklahoma has been reported.[3,9] Long-term stay in endemic countries is a risk factor, but travelers may become infected in 12 hours in an endemic area.[10] The lack of familiarity with this disease in nonendemic countries leads to delays in its diagnosis and selection of proper treatment.[6–8,11]

ETIOPATHOGENESIS

Leishmania infection is acquired through the bite of the female sandfly of the genera *Phlebotomus* (OW) and *Lutzomyia* (NW). At the time of the blood meal, the flagellated motile promastigote form of leishmania is deposited and quickly phagocytosed by macrophages, dendritic cells, and neutrophils. Inside the host cells, the promastigote transforms into the aflagellate amastigote form. It then multiplies by binary fission and proceeds to infect other cells. The cycle is completed when the sandfly feeds again consuming the amastigotes, which transform back into the promastigote form in the gut of the sandfly. The promastigotes then migrate to the proboscis of the sandfly and are ready to repeat the cycle with the subsequent bite.

The major reservoirs of this disease are animals, such as dogs and rodents. The female sandfly is most active from dusk to dawn, and bites typically occur on the exposed skin of the arms, legs, neck, and face. The sandfly is smaller than a mosquito, has a painless bite, and does not make an audible noise. Infection also can be transmitted through needle sharing, blood transfusion with infected blood products,[12] or transplacentally.[13]

The major infecting species of OW and NW leishmaniasis and the associated clinical disease classification are included in **Table 1**.[2,3,14–17] It is generally regarded that OW species cause self-limiting disease and may not require treatment, whereas some NW species have a propensity to affect mucosal surfaces and thus necessitate more aggressive parenteral treatment (**Fig. 1**).[18,19]

IMMUNOLOGY

The health status of the individual, the species of *Leishmania*, and the vector of transmission are thought to be factors in determining the clinical presentation resulting from infection. It is the interplay of these elements that fashions the individual immunologic response and generates the clinical picture. The current understanding of the complex overlapping immunologic regulatory pathways is imperfect but is growing and is the subject of more detailed reviews.[16,20–22] This article provides a limited overview of key factors involved in the immunologic response.

A classic simple T-helper (Th) cell type 1/2 model has been used for years to explain the disease. Promastigotes transmitted by the sandfly bite are processed by dendritic cells and presented to naive T-cells, which in turn produce a pattern of cytokines resulting in the formation of differentiated and expanded T-cell populations: Th1, Th2, and T-reg cells. Th1 $CD4^+$ cells are activated and produce interleukin-2, interferon-γ, and tumor necrosis factor. Interferon-γ activates macrophages, which then engulf and kill the protozoa. T-reg cells then are activated and modulate the ongoing antimicrobial response thereby limiting damage to the host. However, should the Th2 $CD4^+$ response predominate, Th1 response would be inhibited and infection would persist and spread.

Table 1
Leishmania taxonomy

Region	Complex	Species	Clinical Manifestation
Old World	*Leishmania donovani*	*L donovani*	CL, VL, PKLD, ML (rare)
		L infantum	CL, VL (children), PKLD, ML (rare)
		L chagasi	CL, VL (children), PKLD, ML (rare)
	Leishmania tropica	*L tropica*	CL, ML (rare), VL (rare)
		L major	CL, ML (rare)
		L aethiopica	CL, DCL
New World	*Leishmania mexicana*	*L mexicana*	CL, DCL (rare)
		L amazonensis	CL, DCL, ML, VL (rare), PKLD (rare)
		L venezuelensis	CL, DCL (rare)
	Leishmania (Viannia) braziliensis	*L braziliensis*	CL, ML, VL
		L guyanensis	CL, ML
		L panamensis	CL, ML
		L peruviana	CL

Abbreviation: PKLD, post–kala-azar dermal leishmaniasis.