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Mini-Review Article

Clinical and Immunopathological Aspects of Cutaneous, Mucocutaneous, Visceral, and Post-kala-azar Leishmaniasis

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Abstract

The disease Leishmaniasis is a neglected illness with two major forms clinically including cutaneous leishmaniasis and visceral leishmaniasis. From almost 100 endemic countries, an estimated one million additional records of leishmaniasis each year are documented. In the past decade, the number of confirmed cases of visceral leishmaniasis has decreased dramatically as a consequence of an improved approach to diagnosis and care and more intensive, though usual cycles may play a role in the severity of disease transmission. In the cutaneous form of leishmania disease (CL), the lesion is located in some parts like the face and arms. Whereas a visceral form of leishmania (VL) disease the parasite infects internal organs such as the liver and pancreas. Reports from the World Health Organization (WHO) record leishmaniasis as one of the ignored temperate disorders for which the improvement of novel therapies is required. Significant evidence gaps remain, and new methods are required before leishmaniasis can be definitively managed. Recent advances in our understanding of leishmaniasis and its clinical manifestations, as well as the immunological aspects of leishmaniasis, are the key objectives of this study.

Keywords: Leishmania, Sandfly, Promastigote, Kala-azar, Protozoan Infection

Introduction

Leishmania disease is a parasitic vector-borne disorder triggered by approximately 18 species of the genus Leishmania, in which a female sandfly is responsible for the transmission of the disease among mammals. Except for *Leishmania donovani* and *Leishmania tropica*, leishmaniasis is mainly zoonotic (Burza et al., 2018; Labony et al., 2014). Leishmaniasis, produced by protozoa leishmania, is one of the disorders where innate immune and adaptive immune reactions have been reviewed with the help of lab animal models (Zamora-Chimal et al., 2017). Various clinical symptoms are caused by distinct Leishmania species, varying in difficulty from cutaneous lesions cure to life-threatening visceral disease. The result is regulated by the interaction of the following parasitic features, the biology of Victor, and host circumstances, with the host factors concentrating on immune responses (Colmenares et al., 2002). The most serious, systemic type that is generally lethal unless handled is visceral leishmaniasis caused by *L donovani* in Asia and Africa and *L*

infantum in the Middle East, Central Asia, South America, and Central America. A skin form called post-kala azar dermal leishmaniasis happens following the therapy of the visceral form of leishmaniasis in otherwise healthy people (Anversa et al., 2018).

The cutaneous form of leishmaniasis is typically confined to a sore or a boil that cures itself within 4-19 months, but as impairment results, it may also cause scar formation, disfigurement, and stigmatization. Up to 15 % of cutaneous forms of leishmaniasis events proceed to further serious symptoms, depending on the parasite species. Such extreme symptoms are known as diffuse cutaneous and mucocutaneous forms of leishmaniasis, chronic forms of cutaneous leishmaniasis, and repeated leishmania infection (Limeira et al., 2019). In reality, coupled with the host's immune systems, the wide spectrum of Leishmania cases responsible for cutaneous and visceral leishmaniasis promotes the presence of numerous clinical, histopathological, and immunopathological manifestations (Anversa et al., 2018). More than 20 different species compose the genus Leishmania parasite, comprising trypanosomatid stages under the Kinetoplastida order. There is geographical variation among tropical and subtropical countries' climates in the types of species. The Leishmania parasite is divided into two subgenera based on structural alterations in sandfly intestinal development. Multi-locus enzyme electrophoresis is a conventional standardized biological technique that is generally used to differentiate among various organisms. In areas where various species coexist, molecular techniques recently developed for clinical diagnosis are particularly useful (Pace, 2014). The single vector in charge of transmission of leishmaniasis is the female sandfly, under the species Phlebotomus. Leishmaniasis spread about 800 well-known genera of sandflies (Maroli and Khoury, 2004). The Victor sandfly is a about 3 mm long arthropod with color ranges from black to white and characteristically places its wings at an angle to the abdomen, unlike other Diptera species (Killick-Kendrick, 1999). In the hot summer months in the Mediterranean region, sandflies are active (Gálvez et al., 2010). Some species bite in the daytime, a behavior that affects the insecticide spraying techniques used in their control, most sandfly species bite outdoors. Sandflies affected with Leishmania tend to be tested at many intervals on the same host, an adaptive strategy that enhances transmission (Ready, 2013). The sandfly's restricting capability to jump vertically makes it less potential for people who sleep on elevated high floors to become attacked (Pace, 2014).

This review aims to comprehensively investigate and analyze the intricate immunopathological mechanisms underlying both visceral and cutaneous leishmaniasis, aiming to enhance our understanding of disease progression, host immune responses, and potential avenues for therapeutic interventions.

Host-Parasite interaction

Throughout their life cycle, Leishmania genus alternate among two main morphological stages, promastigotes form and amastigotes form (Figure 1). The spherical or oval types of the immobile amastigote measure between 2.5-5.0µm. Kinetoplast is found near the nucleus and must replicate within the vertebrate host. Thus, through feeding in blood on a vertebrate host, phlebotomine females become infected by Leishmania amastigote types (Bates and Rogers, 2004). The amastigotes distinguished into promastigotes in the digestive tract of insects, which are characterized by their mobile and flat shape about 5-15µm in length. When its habitation digestive system of the vector, the promastigote form over many phases before they change and develop into a metacyclic form of promastigotes, which are infectious to human and vertebrate hosts (Anversa et al., 2018). Metacyclic promastigotes migrate to the mouth of the insect, which are highly adapted for effective transmission (proboscis). During a blood meal, the sandfly will inject this form of the parasite into human host circulation causing infection (Bates,

2007). The promastigotes stage then are internalized by phagocytic cells mainly macrophages once inside the vertebrate host and are transformed into amastigotes within the phagocytic vacuole, which multiplies vigorously until the parasitized cell is ruptured.

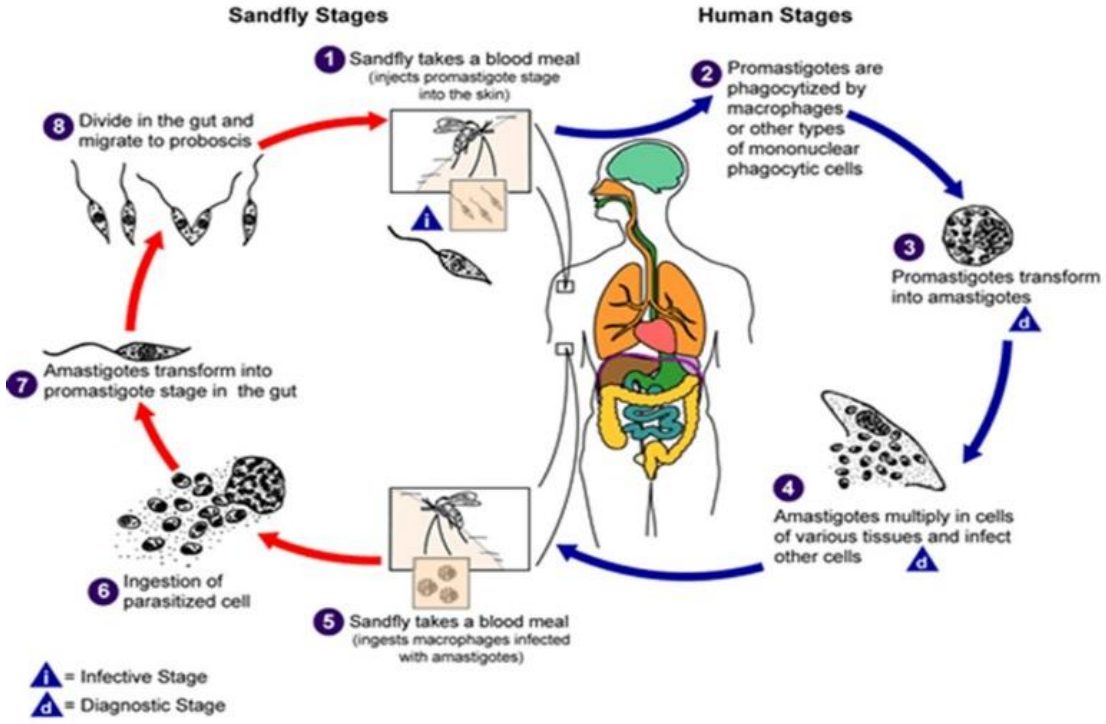

Fig. 1. Leishmania life cycle (Bates, 2007).

The amastigotes released infect other macrophages and the life cycle begins again (de Menezes et al., 2016). Parasites of the genus Leishmania have evolved many adaptation mechanisms in the various environments they encounter during their complete life cycle. In addition to resolving the violent digestive conditions found in phlebotomine sand flies, these parasites must also prevent the degradation of the vertebrate host's immune system (Cunningham, 2002; Bates, 2007). Resistance to complement-mediated lysis is conferred by molecules found in the promastigote form of the parasite. LPG blocks the C5b-9 complex from being incorporated into the membrane, and gp63 facilitates C3b cleavage on the parasite surface at C3bi, thus preventing C5 convertase from forming. Therefore, both molecules prevent the development of a complex membrane attack (Dos-Santos et al., 2016). Not only metacyclic promastigotes resistant to complement actions, but they also use it to join macrophages. Indeed, the key mode of leishmania internalization molecules such as (C3 b) and (C3 bi) that link to the parasite (Cunningham, 2002). A significant escape mechanism is the internalization of leishmania via C3 receptors, provided that the microbicidal respiratory explosion mechanism is not triggered in this process and cytokine synthesis mediated by immune cells is impaired (Dos-Santos et al., 2016). Therefore, the parasite's first defensive mechanism comprises the deferral in the development of the phagocytosis process, depending on the surface molecules of the LPG, the involvement of kinase C protein (PK-C) (Holm et al., 2003). If phagocytosis is generated, the promastigote form become amastigote form, which is much more

sensitive to the macrophage's granules' action, as they can suppress hydrolytic enzymes.

Types of Leishmaniasis

In countries with political instability, like North Africa and the Middle East, the incidence of the disease is still rising (González, 2013). Globally it has declined in the past decade half. It is crucial to highlight that in 88 countries, about two million cases of Leishmaniasis are recorded yearly (Tabbabi, 2019). Three primary human illnesses and some less prevalent clinical entities cause Leishman's disease. The consequence of each is decided by the parasite infecting organisms and host genetic predisposition (McDowell et al., 2011).

Cutaneous and Mucocutaneous Form of the Leishmania Disease

The cutaneous form of leishmania disease (CL) is the minimum dangerous type of infection triggered by many species in different regions of Central and South America, for instance, *L. major* and *L. tropica* in the Old World, and *L. mexicana, L. amazonensis*, *L. guyanensis*, *L. panamensis* and *L. braziliensis* (Goto and Lauletta Lindoso, 2012). The lesions are commonly located in exposed parts, like the face, upper arms, and legs, and grow around two weeks to even two months. In reactive dermal diseases, for example, those caused by *L. amazonensis*, variable-size noduled wounds often emit at different sites. Cutaneous lesion healing can also be accelerated by medication and wound management (David and Craft, 2009).

The cause of a mucocutaneous form of leishmania disease (MCL) is *L. Braziliensis* which may be a consequence of the expansion into the mucocutaneous tissue of regional skin disease or parasite movement from skin or cutaneous infection. mucocutaneous form of leishmania can occur in several months to even years once the primary lesion resolves. Additionally, this type leaves scars due to damage to the tissue of the oro-naso-pharynx, mouth, and nostrils causing respiratory impairment. MCL's mechanism is not well known and is possibly due to dynamic host and parasite influences (de Oliveira and Brodskyn, 2012). The condition is usually reversible by chemical therapy, and secondary super-infections and malnutrition typically cause patients to die. MCL is present in South American countries, with diseases prevalent in South America. In Ecuador, most outbreaks are found in the valleys of the Amazon, with a lower occurrence in the coastal areas between the Andes and the Pacific areas (Calvopina et al., 2004).

Visceral or kala-azar Form of the Leishmania disease

A visceral form of leishmania disease, well-known as kala-azar disease, occurs via phagocytes due to parasite and parasite-infected macrophages. *L. donovani* and *L. infantumum* are the causes of the visceral form of Leishmaniasis in the Old World (McGwire and Satoskar, 2014). VL is also induced by *L. infantum*, which is commonly found in Brazil (*L. chagasi* or *L. infantum chagasi*). Visceral disease, initiated by *L. tropica,* has been documented in the Middle East (McGwire and Satoskar, 2014), which was classically regarded as a CL agent. There is progressive hepato-splenomegaly and bone marrow suppression due to the large number of leishmania protozoa in mononuclear cells in the internal visceral organs of infected people such as in liver cells, pancreas, and bone marrow. Patients experience immunocompetent until treated and are vulnerable to another microbe (Tabbabi, 2019). Patients with visceral leishmaniasis will ultimately respond to their illness without treatment. Visceral leishmaniasis has been stated that human immunodeficiency virus (HIV) co-infected individuals are especially vulnerable to the development of atypical presentations and elevated risk of visceral leishmaniasis and the development of visceral form in HIV patients is an acquired immunodeficiency syndrome (AIDS) -defining disease (ter Horst et al., 2008). This is presumably because of the downregulation of the host's

immunity and defense mechanisms by both agents (Okwor and Uzonna, 2013; Meireles et al., 2017). kala-azar disease is a rapidly progressive and cumulative proliferation of parasites inside the skin in a group of infected people after treatment for years, leaving large papules and nodules. In people affected with *L. donovani*, this condition of kala-azar will be developed in Sudan and India (Zijlstra et al., 2003). Studies found out that Post kala-azar infection can occur in up to 55% of cases and occurs earlier (up to five months) around the world. Kala-azar disease's mechanism of action is still entirely unknown but seems to be linked to aggressive responses of the host immune system produced toward parasites driven by interferon g (Antinori et al., 2007).

Roles of the Immunity in Leishmaniasis

The interaction between Leishmaniasis and the immune response of the mammalian host commences when the parasites are recognized by elements of the innate immune system, including cells, molecules, and receptors like Toll-like receptors. (Pandey et al., 2015; Burza et al., 2018). *In vitro* experiments have already shown that 90% of the stationary-phase complement lyses leishmania promastigotes. Lymphatics drain parasite antigens into the geographic nodes after lysis (Iezzi et al., 2006). The complement fraction of C3b opsonizes the protozoan parasites that are immunized, rendering them susceptible to phagocytosis by antigen-presenting cells via complement receptor 1 and 3 (Ueno and Wilson, 2012). This form of phagocytosis is regarded as "quiet" because it does not enhance the development of oxidative bursts (Gupta et al., 2013). The modulation of T lymphocytes in the lymphoid tissues happen with pathogens draining via the lymph nodes (Hermida et al., 2014). The glycolipid lipophosphoglycan (LPG) comprises most of the glycocalyx in the parasite's promastigote process. Even during the initial stages of the immune response, this molecule is important, as it inhibits the kinase proteins activating the macrophage (Bhardwaj et al., 2010). In addition, LPG attaches to Toll-Like Receptor2, stimulating their development (Becker et al., 2003). The stimulation of LPG contributes to the development of cytokines in dendritic cells and major histocompatibility complex II (MHC II) upregulation (Argueta-Donohué et al., 2008). In addition, the initiation and differentiation of natural killer (NK) T-lymphocyte and the induction of an adaptive immune reaction. Infection with *L. major* in C57BL/6 mice Th1 immune responses has been shown to overcome the disease primarily through the development of interferon cytokines in macrophages loaded with Leishmania (Tacchini-Cottier et al., 2012). In addition, infection with *L. major* in a mouse model has shown that the T helper responses contribute to disease development, primarily due to the development of interleukin (IL) -4, that is able to eradicate the parasite (Osorio et al., 2012; Silveira, Lainson et al., 2004; Hernández-Ruiz et al., 2010). In comparison, people with leishmaniasis have low lymphocyte levels. While there is an increase in the level of secreted cytokines and chemokines mediators such as interferon-gamma (IFN-Y), IL-4, IL-5, and IL-10 (Zamora-Chimal et al., 2017).

Conclusion

In conclusion, it appears that children worldwide bear the heaviest burden of either the visceral or cutaneous forms of leishmaniasis. Detecting and treating the disease's signs and symptoms, especially in developing nations with limited travel-related data, can prove challenging for medical professionals due to the protein indicators of leishmaniasis. Travelers residing in regions where Leishmania is prevalent, such as South America, can receive guidance on preventive measures to reduce exposure. Despite the increasing attention to this neglected tropical disease, several traditional challenges persist limited treatment options, inadequate diagnostics, and insufficient community awareness, particularly for the less significant cutaneous form of leishmaniasis. Moreover, hurdles remain in the campaign to eliminate visceral leishmaniasis. Even when goals are achieved, the progress made often

regresses over time if not maintained. Although efforts have been made to advance leishmaniasis management, information gaps hinder progress, and there's a pressing need to refine control strategies. A crucial question that needs prompt attention is whether complete eradication of L. donovani transmission to humans is feasible. Despite scientific advancements and efforts reaching developing nations, leishmaniasis remains a substantial public health concern in many countries. The battle against this disease requires addressing multiple challenges, including concentrating on treatment strategies, medicines, and adaptable management that considers local environmental, social, and economic factors.

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Conflict of interest statement

The authors confirm that there is no conflict of interest.

Ethical approval

Not applicable.

References

Antinori S., Longhi E., Bestetti G., Paolini R., Acquaviva V., Foschi A., Trovati, S. Parravicini C., Corbellino M. & Meroni L. Post-kala-azar dermal leishmaniasis as an immune reconstitution inflammatory syndrome in a patient with acquired immune deficiency syndrome', *British Journal of Dermatology*, 2007, 157(5), 1032-6. doi: 10.1111/j.1365-2133.2007.08157.x

Anversa L., Tiburcio M. G. S., Richini-Pereira V. B. & Ramirez, L. E. Human leishmaniasis in Brazil: A general review', Revista da Associação Médica Brasileira, 2018, 64(3), 281-289. doi: org/10.1590/1806-9282.64.03.281

Argueta-Donohué J., Carrillo N., Valdés-Reyes L. & Zentella, A. Aguirre-García, M., Becker, I. and Gutiérrez-Kobeh, L. Leishmania mexicana: participation of NF-kappaB in the differential production of IL-12 in dendritic cells and monocytes induced by lipophosphoglycan (LPG)', *Experimental Parasitology*, 2008, 120(1), 1-9. doi: 10.1016/j.exppara.2008.04.002

Bates P. A. Transmission of Leishmania metacyclic promastigotes by phlebotomine sand flies', *International Journal of Parasitology*, 2007, 37(10), 1097-106. doi: 10.1016/j.ijpara.2007.04.003

Bates P. A. & Rogers, M. E. New insights into the developmental biology and transmission mechanisms of Leishmania', *Current Molecular Medicine*, 2004, 4(6), 601-9. doi: 10.2174/1566524043360285

Becker I., Salazar N., Aguirre M., Delgado J., Carrillo-Carrasco N., Kobeh L. G. & Ruiz, A. Cervantes R., Torres A. P., Cabrera N., González A., Maldonado C. & Isibasi, A. 'Leishmania lipophosphoglycan (LPG) activates NK cells through toll-like receptor-2', *Molecular and Biochemical Parasitology*, 2003, 130(2), 65-74. doi: 10.1016/s0166-6851(03)00160-9

Bhardwaj S., Srivastava N., Sudan R. & Saha B. 'Leishmania interferes with host cell signaling to devise a survival strategy', *Journal of Biomed Biotechnology*, 2010, 109189. doi: 10.1155/2010/109189

Burza S., Croft S. L. & Boelaert M. 'Leishmaniasis', *Lancet*, 2018, 392(10151), 951-970. doi: 10.1016/S0140-6736(18)31204-2

Calvopina M., Armijos R. X. & Hashiguchi Y. 'Epidemiology of leishmaniasis in Ecuador: current status of knowledge -- a review', Memórias do Instituto Oswaldo Cruz - Fiocruz, 2004, 99(7), 663 672. doi: 10.1590/s0074-02762004000700001.

Colmenares M., Kar S., Goldsmith-Pestana K. & McMahon-Pratt D. 'Mechanisms of pathogenesis: differences amongst Leishmania species', Transactions of the Royal Society of Tropical Medicine and Hygiene, 2002, 96 Suppl 1, S3-7. doi: 10.1016/s0035-9203(02)90044-1.

Cunningham A. C. 'Parasitic adaptive mechanisms in infection by leishmania'. *Experimental and Molecular Pathology*, 72(2), 2002, 132-41. doi: 10.1006/exmp.2002.2418

David C. V. & Craft, N. 'Cutaneous and mucocutaneous leishmaniasis'. *Dermatologic Therapy*, 2009, 22(6), pp. 491-502. doi: 10.1111/j.1529-8019.2009.01272.x

de Menezes J. P., Saraiva E. M. & da Rocha-Azevedo B. 'The site of the bite: Leishmania interaction with macrophages, neutrophils and the extracellular matrix in the dermis'. *Parasities & Vectors*, 2016, 9, 264. doi: 10.1186/s13071-016-1540-3

de Oliveira C. I. & Brodsky C. I. 'The immunobiology of Leishmania braziliensis infection'. *Frontiers in Immunology*, 2012, 3, 145. doi: org/10.3389/fimmu.2012.00145

Dos-Santos A. L., Carvalho-Kelly L. F., Dick C. F. & Meyer-Fernandes J. R. 'Innate immunomodulation to trypanosomatid parasite infections', *Experimental Parasitology,* 2012, 167, 67-75. doi: 10.1016/j.exppara.2016.05.005

González U. 'Cochrane reviews on neglected diseases: the case of cutaneous leishmaniasis'. *Cochrane Database Systematic Reviews*, 2013, (3), Ed000055. doi: 10.1002/14651858.ED000055

Goto H. & Lauletta Lindoso J. A. 'Cutaneous and mucocutaneous leishmaniasis'. *Infectious Disease Clinics of North America,* 2012, 26(2), 293-307. doi: 10.1016/j.idc.2012.03.001

Gupta G., Oghumu S. & Satoskar A. R. 'Mechanisms of immune evasion in leishmaniasis'. *Advances in Applied Microbiology*, 2013, 82, 155-84. doi:10.1016/B978-0-12-407679-2.00005-3

Gálvez R., Descalzo M. A., Miró G., Jiménez M. I., Martín O., Dos Santos-Brandao F., Guerrero I., Cubero E. & Molina R. 'Seasonal trends and spatial relations between environmental/meteorological factors and leishmaniosis sand fly vector abundances in Central Spain'. *Acta Tropica*, 2010, 115(1-2), 95-102. doi: 10.1016/j.actatropica.2010.02.009

Hermida M. D., Doria P. G., Taguchi A. M., Mengel J. O. & dos-Santos W. 'Leishmania amazonensis infection impairs dendritic cell migration from the inflammatory site to the draining lymph node'. *BMC Infectious Diseases*, 2014, 14, 450. doi: 10.1186/1471-2334-14-450

Hernández-Ruiz J., Salaiza-Suazo N., Carrada G., Escoto S., Ruiz-Remigio A., Rosenstein Y., Zentella A. & Becker, I. 'CD8 cells of patients with diffuse cutaneous leishmaniasis display functional exhaustion: the latter is reversed, in vitro, by TLR2 agonists'. *PLoS Neglected Tropical Diseases*, 2010, 4(11), e871. doi: 10.1371/journal.pntd.0000871

Holm A., Tejle K., Gunnarsson T., Magnusson K. E., Descoteaux A. & Rasmusson B. 'Role of protein kinase C alpha for uptake of unopsonized prey and phagosomal maturation in macrophages'. *Biochemical Biophysical Research Communication*, 2003, 302(4), 653-8. doi: 10.1016/s0006-291x(03)00231-6

Iezzi, G. Fröhlich A., Ernst B., Ampenberger F., Saeland S., Glaichenhaus N. & Kopf, M. 'Lymph node resident rather than skin-derived dendritic cells initiate specific T cell responses after Leishmania major infection'. *Journal of Immunology*, 2006, 177(2), 1250-6. doi: 10.4049/jimmunol.177.2.1250

Killick-Kendrick R. The biology and control of phlebotomine sand flies'. *Clinical Dermatology,* 1999, 17(3), 279-89. doi: 10.1016/s0738-081x(99)00046-2

Labony S., Begum N., Rima U., Chowdhury G., Hossain M., Habib M. & Khan M. 'Apply traditional and molecular protocols for the detection of carrier state of visceral leishmaniasis in black Bengal goat'. *IOSR Journal of Agriculture and Veterinary Science,* 2014, 7, 13-18. doi:10.9790/2380-07231318

Limeira C. H., Alves C. J., Azevedo S. S., Santos C., Melo M. A., Soares R. R., Barnabé N. & Rodrigues G. Q. 'Clinical aspects and diagnosis of leishmaniasis in equids: a systematic review and meta-analysis'. *Revista Brasileira de Parasitologia Veterinária* , 2019, 28(4), 574-581. doi:org/10.1590/S1984-29612019074

Maroli M. & Khoury C. Prevention and control of leishmaniasis vectors: current approaches, *Parassitologia,* 2004, 46(1-2), 211-215.

McDowell M. A., Rafati S., Ramalho-Ortigao M.& Ben Salah, A. 'Leishmaniasis: Middle East and North Africa research and development priorities'. *PLoS Neglected Tropical Diseases,* 2011, 5(7), e1219. doi: 10.1371/journal.pntd.0001219

McGwire B. S. & Satoskar A. R. 'Leishmaniasis: clinical syndromes and treatment'. *An International Journal of Mediciene (QJM)*, 2014, 107(1), 7-14. doi: 10.1093/qjmed/hct116

Meireles C. B., Maia L. C., Soares G. C., Teodoro I. P. P., Gadelha M., da Silva C. G. L. & de Lima M. A. P. Atypical presentations of cutaneous leishmaniasis: A systematic review'. *Acta Trop,* 2017, 172, 240-254. doi: 10.7759/cureus.22836

Okwor I. & Uzonna, J. E. 'The immunology of Leishmania/HIV co-infection'. *Immunology Research,* 2013, 56(1), 163-71. doi: 10.1007/s12026-013-8389-8

Osorio E. Y., Zhao W., Espitia C., Saldarriaga O., Hawel L., Byus C. V., Travi B. L.& Melby P. C. Progressive visceral leishmaniasis is driven by dominant parasite-induced STAT6 activation and STAT6-dependent host arginase 1 expression'. *PLoS Pathogens,* 2012, 8(1), e1002417. doi: 10.1371/journal.ppat.1002417Pace D. 'Leishmaniasis'. *Journal of Infectious,* 2014, 69 Suppl 1, S10-8. doi: 10.1016/j.jinf.2014.07.016

Pandey S. P., Doyen N., Mishra G. C., Saha B. & Chandel H. S. TLR9-deficiency reduces TLR1, TLR2 and TLR3 expressions in Leishmania major-infected macrophages'. *Journal of Experimental Parasitology*, 2015, 154, 82-6. doi: 10.1016/j.exppara.2015.04.005

Ready P. D. 'Biology of phlebotomine sand flies as vectors of disease agents'. *Annual Review of Entomology*, 2013, 58, 227-50. doi: 10.1146/annurev-ento-120811-153557

Silveira F. T., Lainson R. & Corbett C. E. Clinical and immunopathological spectrum of American cutaneous leishmaniasis with special reference to the disease in Amazonian Brazil: a review'. *Memórias do Instituto Oswaldo Cruz*, 2004, 99(3), 239-51. doi: 10.1590/s0074-02762004000300001

Tabbabi A. Review of Leishmaniasis in the Middle East and North Africa'. *African Health Sciences*, 2019, 19(1), 1329-1337. doi: 10.4314/ahs.v19i1.4

Tacchini-Cottier F., Weinkopff T. & Launois, P. 'Does T Helper Differentiation Correlate with Resistance or Susceptibility to Infection with L. major? Some Insights From the Murine Model'. *Frontiers in Immunology*, 2012 3, 32. doi: org/10.3389/fimmu.2012.00032

ter Horst R., Collin S. M., Ritmeijer K., Bogale A. & Davidson R. N. Concordant HIV infection and visceral leishmaniasis in Ethiopia: the influence of antiretroviral treatment and other factors on outcome'. *Clinivcal Infectious Diseases*, 2008, 46(11), 1702-1709. doi: 10.1086/587899

Ueno N. & Wilson M. E. Receptor-mediated phagocytosis of Leishmania: implications for intracellular survival'. *Trends in Parasitology*, 2012, 28(8), 335-44. doi: 10.1016/j.pt.2012.05.002

Zamora-Chimal J., Hernández-Ruiz J. & Becker I. NKT cells in leishmaniasis'. *Immunobiology*, 2017, 222(4), 641-646. doi: 10.1016/j.imbio.2016.11.014

Zijlstra E. E., Musa A. M., Khalil E. A., el-Hassan I. M. & el-Hassan, A. M. 'Post-kala-azar dermal leishmaniasis'. *Lancet Infectious Diseases*, 2003, 3(2), 87-98. doi: 10.1016/s1473-3099(03)00517-6