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Editorial

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Cutaneous leishmaniasis and the vicious cycle of neglect

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Leishmaniasis is a neglected tropical disease caused by a protozoan parasite transmitted by the bite of female sandflies. Close to 20 species are involved in cutaneous, mucocutaneous and mucosal leishmaniasis (CL, MCL and ML, respectively). As a group of disease, they are referred to tegumentary leishmaniasis and distributed in the Old World (Mediterranean basin, the Middle East, the Horn of Africa and South and Central Asia) and the New World (Mexico, Central and South America). It is estimated that up to one million new cases of CL occur annually with 87 countries being endemic.[1] The WHO road map for neglected tropical diseases 2021–2030 targeted CL for control and has set milestones for the next 10 years. By 2030, it is expected that 85% of all cases will be detected and reported in all endemic countries and that 95% of reported cases will be treated.[1] Education, access to diagnostic resources, access to treatment and strong evidence-based recommendations for management are essential in the pursuit of the 2030 targets.

Cutaneous leishmaniasis is linked to poverty and is associated with poor sanitation, population displacement, environmental changes, host immune response and malnutrition.[1] Violent conflict in endemic countries resulting in population displacement, resettlement in refugee camps, poor shelter and sanitation, disruption of control programs and healthcare systems appear associated with increases in cases and sustained transmission.[1] In Syria, affected by war since 2011, the number of CL cases increased from 42 221 in 2010 to 82 275 in 2018.[2] Several countries welcoming Syrian refugees witnessed an increased number of cases of CL.[3,4] A recent case series in this journal described the gravity of CL among Syrian refugees, with 85% having complex lesions and half of the cases presenting with a disease duration of more than 1 year. Despite previous treatment in Syria, 45% presented with recurrences, worsening of lesions or pronounced scarring.[4] The combination of host factors (malnutrition, concurrent infections, stress, immunosuppression), socioeconomic and environmental factors lead this vulnerable population into a downward spiral of disease chronicity, complications and impaired quality of life.[5]

In non-endemic countries, the lack of awareness of CL among returned travellers and migrants by primary care physicians may result in delayed diagnosis, increased morbidity, and impairment of quality of life.[6] There are few data on the impact of CL on health-related quality of life (HRQoL) in returned travellers. Peleva *et al.*[7] in this journal reported a moderate or high impact on the HRQoL in 63% of returning travellers with a confirmed diagnosis of CL, which is comparable to reports from endemic areas. With increased travel and migration, clinicians in non-endemic countries may encounter an increasing number of cases and play an important role in early recognition and reporting in order to decrease physical and psychological morbidity.[8]

Treatment of cutaneous leishmaniasis is challenging, there is no universally applicable therapeutic approach and individualized management is required for each case. Host characteristics, clinical presentation and infecting species are important considerations when determining optimal management.[9] Virulence factors and modulation of the host immune response by the parasite, differential response to treatment even within a single species and emergence of drug resistance add to the complexity of management.[10] Available treatment can be intra-lesional, topical or systemic. Systemic treatments available for CL include amphotericin B, pentavalent antimonials (SB^v), pentamidine isethionate (PI), miltefosine and in some cases the antifungal azoles. For most of those agents, we have only descriptive and observational studies, or relatively poor-quality comparative studies to guide our decisions. As a result, most recommendations are supported by low- or very-low-quality evidence. The lack of human and financial resources and the lack of standardization contribute to the poor evidence base.[11]

In a systematic review published in this edition of *JTM*, Piccica *et al.*[12] summarized the available evidence on safety and efficacy of PI for the treatment of tegumentary and visceral leishmaniasis. PI has mostly been used for the treatment of *L. V. guyanensis* complex CL. It is classified as a 'lesser alternative' for ML and VL because of its reported toxicity and lower efficacy. Given the limited choices, it is essential to better characterize the optimal niche of the available drugs. For tegumentary leishmaniasis, 54 studies were included for a total of 2082 patients amongst which, 1945 patients were from observational and interventional studies (27 articles) and 137 patients (27 articles)

from case series and case reports. The definitions of clinical cure were heterogeneous. Close to 20% of the 27 observational/interventional studies did not report data on the timing of follow-up which is essential for evaluating clinical cure. Only 3 patients among the total of 1045 patients were immunocompromised, which limits the generalizability of the data to this vulnerable population. The causative species is not reported in nearly a third of the clinical trials comprising almost half of all, further limiting the interpretation of the data. The treatment doses ranged from 2 to 7 mg/kg/day and the treatment duration ranged from one to 84 days. Similarly, in case reports and cases series, there was an important heterogeneity in whether the treatment was given as first line, second line or in combination, the treatment dose, duration, frequency, route of administration and follow-up. The pooled cure rate efficacy was 78.8% (CI 95%: 76.9–80.6) in clinical trials and 92.7% (CI 95%: 88.3–97.1) in case reports and case series. Side effects were in general poorly reported; the most common were subjective complaints, renal toxicity, reversible hyperglycemia, irreversible diabetes and mild cardiac toxicity. The authors conclude that PI is associated with cure rate probably comparable to recognized first-line drugs in CL, although most of the evidence is available only for New World CL. The authors suggest a role when the first-line treatment fails or is contraindicated given the reported efficacy, the low cost and the availability. However, as well illustrated here, systematic reviews have mostly shed light on the need for high-quality clinical trials. The heterogeneity and incomplete descriptions of the population studied, the infecting species, the exact treatment regimen, the outcome definitions and the follow-up severely limit the interpretation of the cure rates and the generalizability.

In 2013, Olliaro *et al.*[11] published methodologic recommendations to provide clinical investigators with guidance for the design, conduct, analysis and reporting of clinical trials meant to assess the efficacy and safety of treatments for CL. This is an important step in improving the quality of the trials. There is a clear need for more human and financial resources to support the capacity to conduct those trials in endemic countries. Increasing awareness among clinicians and affected populations is also important to control this neglected tropical disease. Endemic areas need better diagnostic capacity, speciation methodology and a better understanding of the roles of virulence factors, modulation of host immunity and mechanisms of resistance. Coordinated efforts and collaborative research are needed to reach the 2030 milestone and break the vicious cycle of neglect.

Authors' contributions

Sapha Barkati designed the work and drafted the manuscript. Michael Libman contributed to the drafting and revision of the manuscript. All the authors revised the manuscript critically for important intellectual content, gave final approval of the version to be published and agreed to be accountable for all aspects of the work.

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References

1. *Ending the neglect to attain the sustainable development goals: a road map for neglected tropical diseases 2021–2030*. Geneva: World Health Organization, 2020, Licence: CC BY-NC-SA 3.0 IGO.
2. Muhjazi G, Gabrielli AF, Ruiz-Postigo JA *et al.* Cutaneous leishmaniasis in Syria: a review of available data during the war years: 2011-2018. *PLoS Negl Trop Dis* 2019; **13**:e0007827.
3. Sobirk SK, Inghammar M, Collin M, Davidsson L. Imported leishmaniasis in Sweden 1993-2016. *Epidemiol Infect* 2018; **146**:1267–74.
4. Lindner AK, Richter J, Gertler M *et al.* Cutaneous leishmaniasis in refugees from Syria: complex cases in Berlin 2015-2020. *J Travel Med* 2020; **27**:1–8. doi: 10.1093/jtm/taaa161.
5. Pires M, Wright B, Kaye PM, da Conceicao V, Churchill RC. The impact of leishmaniasis on mental health and psychosocial well-being: a systematic review. *PLoS One* 2019; **14**: e0223313.
6. El Hajj L, Thellier M, Carriere J, Bricaire F, Danis M, Caumes E. Localized cutaneous leishmaniasis imported into Paris: a review of 39 cases. *Int J Dermatol* 2004; **43**:120–5.
7. Peleva E, Walker SL. Cutaneous leishmaniasis and health-related quality of life in returning travellers to the UK. *J Travel Med* 2020; **27**:1–2. doi: 10.1093/jtm/taaa188.
8. Boggild AK, Caumes E, Grobusch MP *et al.* Cutaneous and mucocutaneous leishmaniasis in travellers and migrants: a 20-year GeoSentinel Surveillance Network analysis. *J Travel Med* 2019; **26**. doi: 10.1093/jtm/taz055.
9. Aronson N, Herwaldt BL, Libman M *et al.* Diagnosis and treatment of leishmaniasis: Clinical Practice Guidelines by the Infectious Diseases Society of America (IDSA) and the American Society of Tropical Medicine and Hygiene (ASTMH). *Clin Infect Dis* 2016; **63**:e202–64.
10. Barkati S, Ndao M, Libman M. Cutaneous leishmaniasis in the 21st century: from the laboratory to the bedside. *Curr Opin Infect Dis* 2019; **32**:419–25.
11. Olliaro P, Vaillant M, Arana B *et al.* Methodology of clinical trials aimed at assessing interventions for cutaneous leishmaniasis. *PLoS Negl Trop Dis* 2013; **7**:e2130.
12. Piccica M, Lagi F, Bartoloni A, Zammarchi L. Efficacy and safety of Pentamidine isethionate for tegumentary and visceral human leishmaniasis: a systematic review. *J Travel Med* 2021;1–13. doi: 10.1093/jtm/taab065.