Clinical criteria for Mucosal Leishmaniasis diagnosis in rural South America: A systematic literature review

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Abstract

Background

Mucosal Leishmaniasis (ML), a neglected tropical disease caused by Leishmania parasites, impairs the quality of life of under-resourced populations in South America. If not treated promptly, this disease progresses to facial deformities and death. The low sensitivity of microscopy results and the unavailability of other accurate tests hamper the diagnosis. As clinical criteria are readily available in any setting, these may be combined in a syndromic algorithm, which in turn can be used as a diagnostic tool. We explore potential clinical criteria for a syndromic diagnostic algorithm for ML in rural healthcare settings in South America.

Methodology/Principal findings

The protocol for this systematic review was pre-registered in PROSPERO with the number: CRD42017074148. In patients with ML, described in case series identified through a systematic retrieval process, we explored the cumulative ML detection rates of clinical criteria. Participants: all patients with active mucosal disease from an endemic area in South America. Any original, non-treatment study was eligible, and case reports were excluded. PUBMED, EMBASE, Web of Science, SCIELO, and LILACS databases were searched without restrictions. The risk of bias was assessed with the JBI checklist for case series. We included 10 full texts describing 192 ML patients. Male gender had the highest detection rate (88%), followed by ulcer of the nasal mucosa (77%), age >15 (69%), and symptom duration >4 months (63%).
Significance
Within this selection of patients, we found that the male gender, ulcer of the nasal mucosa, age >15, and symptom duration >4 months lead to the highest detection rates. However, higher detection comes -naturally- with a higher rate of false positives as well. As we only included ML patients, this could not be verified. Therefore, the criteria that we found to be most promising should be validated in a well-designed prospective study.

Author summary
Mucosal leishmaniasis, a disease caused by *Leishmania* parasites, is transmitted from animals to humans by sandflies. It is a forgotten disease that affects under-resourced populations in South America. Without treatment, this disease mutilates the face and can even be fatal. Diagnosing mucosal leishmaniasis is challenging. The only available testing in rural areas is the use of either a lesion smear or biopsy for light microscopy, however, this is unreliable. Many patients suffer for years before receiving treatment. Syndromic algorithms use patient characteristics, such as age, gender, and symptoms to identify patients for treatment. This method has been promoted to manage infectious diseases, such as tuberculosis and sexually transmitted diseases, in low resource settings. We explore clinical criteria for a new algorithm to diagnose mucosal leishmaniasis in patients described in the medical literature. We searched the literature for reports written in any language and identified 10 studies describing 192 patients with mucosal leishmaniasis. We found that male gender, ulcer of the nasal mucosa, age >15, and symptom duration >4 months lead to acceptable detection rates. Therefore, diagnostic algorithms might improve the detection of patients with mucosal leishmaniasis but need prospective studies in clinical practice to prove their true potential.

Introduction
Background
Mucosal leishmaniasis (ML), a disease caused by the *Leishmania* parasites, is a Neglected Tropical Disease (NTD) that affects under-resourced populations mainly in remote, rural areas of the South American continent [1, 2]. In most cases, ML is caused by *Leishmania braziliensis* and, less commonly by *L. guyanensis*, *L. panamensis*, or *L. amazonensis*. The parasites are transmitted through the bite of an infected female sandfly (genus *Lutzomyia*). Following a bite, most patients develop cutaneous ulcers or nodules, referred to as cutaneous leishmaniasis (CL). ML can develop simultaneously with CL or start months to decades after a healed skin lesion. ML is caused by the dissemination of parasites to the oral, nasal, pharyngeal, and laryngeal mucosa. However, not all new ML patients report a history of CL [3, 4]. Unfortunately, the spontaneous cure of ML is rare. Furthermore, if untreated, ML may progress to nasal septum perforation and destruction, severe facial deformities, airway obstruction, and ultimately, death [5–7]. Antimonials and amphotericin-B are the recommended treatments for ML but both are associated with severe side effects and have to be injected [8–10]. Miltefosine is an expensive systemic agent for oral administration, but has limited efficacy, potentially severe side effects, and is not universally available [9, 11]. Therefore, accurate diagnosis is essential to justify ML treatment. However, diagnosing ML is challenging on clinical grounds alone, as there is a significant number of differential diagnoses such as common rhinitis, chronic...
sinusitis, banal nasal septum perforation, midline lymphoma, paracoccidioidomycosis, tuberculosis, rhinosporidiosis, nasal scleroma, Wegener’s granulomatosis, histoplasmosis, sporotrichosis, Hansen’s disease, squamous cell carcinoma, and chronic nasal cocaine use, among others [12, 13]. Given the significant harms of not treating ML, a high index of suspicion is warranted in all patients from endemic areas with chronic nasal, oropharyngeal, or laryngeal symptoms. Additionally, serology and the Montenegro skin test can indirectly support the diagnosis of ML, but these are neither sensitive nor specific and often unavailable in rural settings [2, 6, 14, 15]. Therefore, mucosal tissue smear slide or histopathology is recommended for a more precise diagnosis. However, the diagnostic accuracy of both these testing methods is extremely variable but usually low, even when performed in specialized centers, due to the paucity of amastigotes in the mucosal tissue [7, 16, 17]. In addition, even molecular diagnostics, such as polymerase chain reaction techniques, fail to confirm the diagnosis in more than a quarter of patients and are usually unavailable in resource-limited endemic areas [18, 19]. Syndromic algorithms for the diagnosis of infectious diseases have shown effectiveness, and are often the only option in resource-limited settings [20–22]. To the best of our knowledge, little evidence exists on the application of syndromic algorithms for ML diagnosis. However, it could increase access to therapy in resource-limited populations. This study explores clinical criteria for syndromic ML diagnosis in low-resource settings in South America. Before designing a prospective diagnostic accuracy study to evaluate a syndromic algorithm, we planned to assess the accuracy of a syndromic algorithm in the existing literature. However, this requires meticulous reporting of patient characteristics and test results, as done in case series and diagnostic accuracy studies (containing patients with and without ML). As no diagnostic accuracy studies of any syndromic algorithm for ML diagnosis were available, we aimed to investigate the ML detection rates of predefined clinical characteristics and test results. Hereeto, case series of ML patients were retrieved through a systematic literature review and the presence of predefined characteristics and test results in these case series were recorded.

Objective
Objective: To explore the ML detection rates of clinical criteria in participants from endemic areas in South America.

Methods
Protocol
The protocol for this systematic review was pre-registered on August 10, 2017, in the PROSPERO International prospective register of systematic reviews with registration number: CRD42017074148, 2017 [23] and is available from; https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42017074148. This systematic review followed the Preferred Reporting Items for a Systematic Review and Meta-analysis (PRISMA) guideline [24].

General study eligibility criteria
Study eligibility criteria for inclusion in this systematic review are described in Table 1. Case series were included without date or language limitations. Treatment studies and studies reporting on less than five ML patients were excluded to avoid selection bias.

General study identification
PUBMED, EMBASE, Web of Science, SCIELO, and LILACS databases were searched without restrictions, with the last search on the 14th of April 2022. The following search string was
applied in PUBMED: “human AND (mucocutan* OR mucos* OR mucous OR tegument* OR nasal) AND (leishmanias* OR leishmanios*)”. The annotation of the search string was adjusted for each literature database. In addition, reference lists of studies included for full-text analysis were searched for additional papers.

Study selection
Title and abstract screening were performed using the Rayyan QCR software [25]. Full texts of included studies were either retrieved electronically or requested manually by the medical library of the University of Amsterdam. Full texts were assessed using a predefined checklist (S1 Table) and included if they matched the eligibility criteria (Table 1). Each step of the study selection was done independently by JB and either KM or CN. Differences were resolved through consensus, or with help of HdV or HS.

General data collection
All steps in data collection were individually performed by JB and either KM or CN. Disputes were resolved through consensus. Using a pre-defined form, the following information was extracted from individual patients in the included papers: identifiers of the patient, presence of concomitant CL, diagnostic method(s) used, HIV status, other concomitant illnesses, results of histopathology, and smear slide microscopy (both defined as positive exclusively in case of amastigote visualization), causing Leishmania species, medications used before diagnosis, stage of disease according to Lessa et al. [6], presenting symptoms; epistaxis, dysphagia or odynophagia, voice changes, CL-scar, ulceration of the nasal mucosa, nasal deformation, oropharyngeal lesions, and symptom duration.

Risk of bias assessment
Risk of bias assessment was done with the JBI checklist for case series [26]. Because this study retrieved data at the individual patient level, the question on the appropriateness of the statistical analysis was obviated from the JBI checklist. The following question was added to assess the possible risk of bias through the inclusion of a specific patient population: ‘Did the case series avoid exclusion based on clinical characteristics?’ Risk of bias assessment was individually performed by JB and KM. Disputes were resolved through discussion.

Table 1. General study eligibility criteria for inclusion in this systematic review.

| Inclusion criteria                                                                 |
|------------------------------------------------------------------------------------|
| 1. Case series with any publication date or language                               |
| 2. Report on patients with a history of a stay in an ML epidemic area of South America |
| 3. Report on patients with active nose, throat, or oral disease (e.g. obstruction, hyperemia, erosion, ulceration, or granulomatus lesions) |
| 4. Present clinical information at individual patient level.                       |

| Exclusion criteria:                                                             |
|--------------------------------------------------------------------------------|
| 1. Narrative reviews                                                             |
| 2. Studies reporting on <5 ML patients                                            |
| 3. Treatment studies                                                             |
| 4. Duplicate publication on the same individual patient or patient group         |
| 5. Patients without a history of a visit to South America                        |

ML: Mucosal Leishmaniasis
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Table 2. Twelve rurally available clinical criteria assessed for diagnostic accuracy in this study.

| Criterion                          | Reason                                      |
|-----------------------------------|---------------------------------------------|
| Male                              | Risk factor for ML [28]                     |
| Age >15 years                     | Risk factor for ML [28, 29]                 |
| Symptom duration >4 months        | Differentiation from acute viral syndromes [30] |
| Ulcer of the nasal mucosa         | Present from stage 2 of the disease [6]     |
| Epistaxis                         | Present from stage 2 of the disease [6]     |
| Oropharyngeal lesion              | Worse prognosis of the disease[31]          |
| Dysphagia or odynophagia          | Sign of severe disease [6]                  |
| Nasal deformation                 | Sign of severe disease [6]                  |
| CL scar                           | Risk factor for ML [4, 7]                   |
| Concomitant CL                    | Risk factor for ML [4, 32]                  |
| Histopathology                    | Current confirmative test [33]              |
| Smear slide microscopy            | Current confirmative test [14]              |

Data analysis

All included studies were investigated for 12 predefined binary clinical criteria that are frequently mentioned in the literature and are easily available in clinical practice in rural settings, as our ultimate goal is to develop an algorithm for syndromic management (See Table 2). Cumulative detection rates were calculated per patient with Microsoft Excel 2018 software [27]. For cumulative detection rate calculation, the criteria were arranged from the highest absolute number of patients positive to the lowest. Non-reported criteria were interpreted as negative. Cumulative detection rates were calculated separately for males and females to avoid gender-based selection of patients by a diagnostic algorithm. Because of the low quality of the included studies and the exploratory nature of this paper, a meta-analysis was not done.

Results

Study selection and data obtained

After the removal of duplicates, 4377 reports were retrieved through the searches in different databases. Of these, 10 were included that reported on a total of 192 ML patients [5, 6, 16, 34–40]. 160 full texts were excluded because they reported on less than five ML patients and seven because they presented no data at the individual patient level. The reasons for full text exclusions are summarized in Fig 1.

General study characteristics

This review included 10 case series that were all published between 1968 and 2019. Most studies reported on patients diagnosed in Brazil (n = 6), followed by Peru (n = 2). The median number of reported ML cases per publication was 13, ranging from 5 to 50. Most patients were diagnosed with several methods, including PCR, Montenegro skin test, culture, and histopathology. *L. braziliensis* was reported as the most common species in ML lesions. However, the species was unknown in two (20%) of the included studies (Tables 3 and S1).

Risk of bias assessment

Assessment of the risk of bias in the 10 case series included in this systematic review, using the modified JBI checklist for case series, revealed a high risk of bias in all the included studies. Six studies lacked clear inclusion criteria and three studies included patients on the basis of clinical
characteristics: Boaventura et al. included patients if they had concomitant CL and Falcao et al. and Motta et al. included patients if they had oral lesions. Four studies did not describe ML diagnostic methods clearly. Six studies applied indirect methods (skin test, serology, or cure on antimonial treatment) for ML diagnosis. Only two studies included patients consecutively and completely. Patient demographics (age, gender, and duration of symptoms) were unclearly described by one study. No study reported completely on the clinical criteria explored for ML detection rates. Follow-up was unclear in two studies and demographic data of the study site was unclear in three. Results of the risk of bias assessment are summarized in Fig 2.

Findings
All of the study participants’ genders were known, with 88% of them being male. Information was incomplete for the other criteria. The male gender resulted in the highest number of patients positive, followed by ulcer of the nasal mucosa, age >15, and symptom duration >4 months. Results of histopathology and smear slide microscopy were unknown for the majority of patients and were positive in 55 and 41% of reported patients respectively (Table 4).

The cumulative detection rates of clinical criteria for males and females are shown in Tables 5 and 6. Two or more positives out of the three criteria ‘ulcer of the nasal mucosa’, ‘age >15’, and ‘symptom duration >4 months’ had a cumulative detection rate of 84% in males and 79%
in females. Three or more positives out of the six criteria 'ulcer of the nasal mucosa', 'age $>$15', 'symptom duration $>$4 months', 'oropharyngeal lesion', 'epistaxis', and 'histopathology positive' had a cumulative detection rate of 75% in males and 54% in females.

Table 3. Characteristics of the 10 case series reporting on 192 ML patients included in the systematic review.

| Study characteristic                      | Year published (median, range) | Number of ML patients (median, range) | Country of diagnosis | Number of studies | Number of patients (%) |
|------------------------------------------|--------------------------------|---------------------------------------|----------------------|-------------------|-----------------------|
| Year published (median, range)           | 2007                           | 13                                    | Brazil               | 6                 | 101 (53)              |
| Number of ML patients (median, range)     | 1968–2019                      | 5–50                                  | Peru                 | 2                 | 73 (38)               |
| Country of diagnosis                     |                                |                                       | Ecuador              | 1                 | 13 (7)                |
|                                           |                                |                                       | United Kingdom       | 1                 | 5 (3)                 |

Diagnostic method for inclusion in study

| Diagnostic method for inclusion in studya | Number of studies | Number of patients (%) |
|------------------------------------------|-------------------|-----------------------|
| PCR                                      | 7                 | 64 (33)               |
| Montenegro skin test                     | 8                 | 115 (60)              |
| Culture                                  | 4                 | 22 (11)               |
| Histopathology                           | 9                 | 51 (27)               |
| Serology                                 | 3                 | 27 (14)               |
| Smear slide microscopy                   | 1                 | 13 (7)                |
| Cure with antimonial treatment            | 2                 | 6 (3)                 |

Reported causative Leishmania speciesb

| Reported causative Leishmania speciesb   | Number of studies | Number of patients (%) |
|-----------------------------------------|-------------------|-----------------------|
| L. braziliensis                          | 8                 | 70 (36)               |
| L. amazonensis                          | 2                 | 6 (3)                 |
| L. viannia complex                      | 2                 | 12 (6)                |
| Unknown                                  | 2                 | 104 (54)              |

aThe majority of studies applied several diagnostic methods to every patient
bSeveral studies reported mixed causative species and the species was unknown in a part of the patients.

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in females. Three or more positives out of the six criteria 'ulcer of the nasal mucosa', 'age $>$15', 'symptom duration $>$4 months', 'oropharyngeal lesion', 'epistaxis', and 'histopathology positive' had a cumulative detection rate of 75% in males and 54% in females.
Table 4. Arrangement of the clinical criteria from the highest absolute number of patients positive to the lowest.

| Nr. | Criterion                        | Reported in N patients (%) | N positive (% of reported) | Detection rate |
|-----|----------------------------------|----------------------------|---------------------------|---------------|
| 1   | Male                             | 192 (100)                  | 168 (88)                  | 0.88          |
| 2   | Ulcer of the nasal mucosa        | 159 (83)                   | 147 (92)                  | 0.77          |
| 3   | Age >15                          | 141 (73)                   | 133 (94)                  | 0.69          |
| 4   | Symptom duration >4 months       | 148 (77)                   | 121 (82)                  | 0.63          |
| 5   | Oropharyngeal lesion             | 155 (81)                   | 88 (57)                   | 0.46          |
| 6   | Epistaxis                        | 63 (33)                    | 58 (92)                   | 0.30          |
| 7   | Histopathology                   | 93 (48)                    | 51 (55)                   | 0.27          |
| 8   | Dysphagia or odynophagia         | 42 (22)                    | 40 (95)                   | 0.21          |
| 9   | CL scar                          | 57 (30)                    | 36 (63)                   | 0.19          |
| 10  | Concomitant CL                   | 68 (35)                    | 31 (46)                   | 0.16          |
| 11  | Nasal deformation                | 86 (45)                    | 30 (34)                   | 0.16          |
| 12  | Smear slide microscopy           | 32 (17)                    | 13 (41)                   | 0.07          |

N = Number

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Table 5. Cumulative detection rates of clinical criteria in 168 male Mucosal Leishmaniasis (ML) patients.

| Nr. | Criterion                        | Cumulative detection rates at individual patient level | Cut-off score |
|-----|----------------------------------|-------------------------------------------------------|---------------|
|     |                                  |                                                       | ≥1    | ≥2    | ≥3    | ≥4    |
| 2   | Ulcer of the nasal mucosa (%)    |                                                       | 139 (83) | 0 (0) | 0 (0) | 0 (0) |
| 3   | Age >15 (%)                      |                                                       | 160 (95) | 141 (84) | 42 (25) | 0 (0) |
| 4   | Symptom duration >4 months (%)   |                                                       | 168 (100) | 162 (96) | 88 (52) | 14 (8) |
| 5   | Oropharyngeal lesion (%)         |                                                       | 168 (100) | 163 (97) | 104 (62) | 40 (24) |
| 6   | Epistaxis (%)                    |                                                       | 168 (100) | 163 (97) | 126 (75) | 60 (36) |
| 7   | Histopathology positive (%)      |                                                       | 168 (100) | 163 (97) | 130 (77) | 75 (45) |
| 8   | Dysphagia or odynophagia (%)     |                                                       | 168 (100) | 163 (97) | 144 (86) | 82 (49) |
| 9   | CL scar (%)                      |                                                       | 168 (100) | 164 (98) | 153 (91) | 99 (59) |
| 10  | Concomitant CL (%)               |                                                       | 168 (100) | 165 (98) | 153 (91) | 102 (61) |
| 11  | Nasal deformation (%)            |                                                       | 168 (100) | 165 (98) | 20 (25) | 11 (46) |
| 12  | Smear slide microscopy positive (%)|                                               | 168 (100) | 165 (98) | 20 (25) | 11 (46) |

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Table 6. Cumulative detection rates of clinical criteria in 24 female Mucosal Leishmaniasis (ML) patients.

| Nr. | Criterion                        | Cumulative detection rates at individual patient level | Cut-off score |
|-----|----------------------------------|-------------------------------------------------------|---------------|
|     |                                  |                                                       | ≥1    | ≥2    | ≥3    | ≥4    |
| 2   | Ulcer of the nasal mucosa (%)    |                                                       | 18 (75) | 0 (0) | 0 (0) | 0 (0) |
| 3   | Age >15 (%)                      |                                                       | 24 (100) | 16 (67) | 0 (0) | 0 (0) |
| 4   | Symptom duration >4 months (%)   |                                                       | 24 (100) | 19 (79) | 7 (29) | 0 (0) |
| 5   | Oropharyngeal lesion (%)         |                                                       | 24 (100) | 22 (92) | 8 (33) | 3 (13) |
| 6   | Epistaxis (%)                    |                                                       | 24 (100) | 23 (96) | 9 (38) | 6 (25) |
| 7   | Histopathology positive (%)      |                                                       | 24 (100) | 23 (96) | 13 (54) | 6 (25) |
| 8   | Dysphagia or odynophagia (%)     |                                                       | 24 (100) | 23 (96) | 14 (58) | 7 (29) |
| 9   | CL scar (%)                      |                                                       | 24 (100) | 23 (96) | 18 (75) | 7 (29) |
| 10  | Concomitant CL (%)               |                                                       | 24 (100) | 23 (96) | 20 (83) | 11 (46) |
| 11  | Nasal deformation (%)            |                                                       | 24 (100) | 23 (96) | 20 (83) | 11 (46) |
| 12  | Smear slide microscopy positive (%)|                                               | 24 (100) | 23 (96) | 20 (83) | 11 (46) |

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Discussion

The objective of this study was to explore the ML detection rates of clinical criteria combinations. In our systematic review, we included 10 case series reporting on more than 190 ML patients in South America.

Our main finding is the acceptable ML detection rate of clinical criteria and promising combinations for ML diagnostic algorithms. As accurate reference tests are often unavailable in lower resource settings, such as many centers in South America [14, 15], algorithms for syndromic diagnosis for ML would be highly desirable to select patients for the, often toxic, treatment.

Adverse effects, such as musculoskeletal pain and gastrointestinal disturbances, are very common after administration of antimonials and severe complications such as arrhythmias, leucopenia, hepatitis, and pancreatitis occur in up to 14% of treated patients. Occasionally, even deaths are reported from patients under antimonial treatment [8]. To avoid drug toxicities in patients who do not have ML, it is at least as important to know the proportion of false positive results as the proportion of true positives. However, the proportion of false positives (one minus the specificity) requires a study sample including participants without ML and these were not included in this study. Therefore, we have no estimates of the specificity of clinical criteria combinations and we cannot rule out that the proportion of false positive results of syndromic algorithms may be too high.

The absence of an established universal reference test for ML diagnosis limits the current study. We included ML patients diagnosed with any of the currently applied tests in South America, including the Montenegro skin test, serology, and cure with antimonial treatment. This results in the possible inclusion of non-ML patients in this study and the overestimation of detection rates.

Risk of bias evaluation revealed significant flaws in all the studies leading to a high risk of bias. The incomplete reporting of clinical criteria limits this study and leads to a possible underestimation of the detection rates as non-reported criteria were interpreted as negative. The selection of concomitant CL or oral ML patients by three studies possibly leads to an overestimation of the detection rates of concomitant CL and oropharyngeal lesions.

Former studies have reported that the male gender is a risk factor for leishmaniasis in its cutaneous (CL), mucosal (ML), and visceral expressions [28, 41]. The underlying processes could be sex-specific biological, differences in vector exposure, variances in health-seeking behavior, and marginalization of female patients in health care and publications [42–44]. Therefore, it is not unexpected that the majority of the patients in this study are men. As the methodological quality of the included studies is low, we cannot exclude that the gender difference was at least partially caused by biased patient inclusion or publication. That also applies to the criterion ‘age >15’. We emphasize that the clinical criteria combinations shown in this paper have to be adapted according to the results of a well-designed prospective study (including non-ML patients) that should avoid the exclusion of patients based on gender, age, ethnicity, and other personal identifiers and include an evaluation of health-seeking behavior in its protocol.

The ML detection rates of clinical criteria combinations explored in this review reached levels comparable to the performance of the Montenegro skin test [7, 45]. Their application would be rapid, cheap, and feasible in any rural clinical setting located in endemic regions and thus of potential clinical value.

Conclusion

We present an exploration of the detection rates of clinical criteria in 192 ML patients reported in case series. Within this selection of patients, we found that male gender, ulcer of the nasal
mucosa, age >15, and symptom duration >4 months lead to the highest detection rates. They
could improve diagnosis and hence prompt treatment of ML in vulnerable groups in resource-
limited settings where diagnostic confirmation cannot be obtained. Therefore, the criteria that
we found to be most promising, should be validated in a well-designed prospective study.

Supporting information

S1 Appendix. PRISMA 2020 abstract checklist for systematic reviews.
(DOCX)

S2 Appendix. PRISMA 2020 checklist for systematic reviews.
(DOCX)

S1 Table. Characteristics of included studies.
(XLSX)

S2 Table. Characteristics of 192 individually assessed patients.
(XLSX)

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References

1. WHO. Investing to Overcome the Global Impact of Neglected Tropical Diseases: Third WHO Report on
Neglected Tropical Diseases 2015. Geneva: World Health Organization; 2015.

2. WHO. Control of the leishmaniases: report of a meeting of the WHO Expert Commitee on the Control of
Leishmaniases, Geneva, 22–26 March 2010. Geneva: World Health Organization; 2010. Contract No.: 949.

3. Bennett JE, Dolin R, Blaser MJ. Principles and Practice of Infectious Diseases. Philadelphia: Elsevier
Health Sciences; 2019.

4. Cincura C, De Lima CMF, Machado PRL, Oliveira-Filho J, Glesby MJ, Lessa MM, et al. Mucosal leish-
maniasis: A retrospective study of 327 cases from an endemic area of Leishmania (Viannia)
braziliensis. American Journal of Tropical Medicine and Hygiene. 2017; 97(3):761–6. https://doi.org/10.4269/ajtmh.16-0349 PMID: 28722607
5. Calvopina M, Angel G, Armijos R, Gomez E, Mimori T, Cooper P, et al. Clinical features of mucocutaneous leishmaniasis in the Amazonian region of Ecuador. Res Rep Ser. 2005; 6:82–9.
6. Lessa HA, Lessa MM, Guimaraes LH, Lima CM, Arruda SMachado PR, et al. A proposed new clinical staging system for patients with mucosal leishmaniasis. Transactions of the Royal Society of Tropical Medicine and Hygiene. 2012; 106(6):376–81. https://doi.org/10.1016/j.trstmh.2012.03.007 PMID: 22578516
7. Amato VS, Tuon FF, Imamura R, de Camargo RA, Duarte MI, Neto VA. Mucosal leishmaniasis: description of case management approaches and analysis of risk factors for treatment failure in a cohort of 140 patients in Brazil. Journal of the European Academy of Dermatology and Venereology. 2009; 23(9):1026–34. https://doi.org/10.1111/j.1468-3083.2009.03238.x PMID: 19453817
8. Oliveira LF, Schubach AO, Martins MM, Passos SL, Oliveira RV, Marzochi MC, et al. Systematic review of the adverse effects of cutaneous leishmaniasis treatment in the New World. Acta tropical. 2011; 118(2):87–96. https://doi.org/10.1016/j.actatropica.2011.02.007 PMID: 21420925
9. Pinart M, Rueda JR, Romero GA, Pinzón-Flórez CE, Osorio-Arango K, Silveira Maia-Elkhoury AN, et al. Interventions for American cutaneous and mucocutaneous leishmaniasis. The Cochrane database of systematic reviews. 2020; 8:Cd004834. https://doi.org/10.1002/14651858.CD004834.pub3 PMID: 32853410
10. Santos CR, Tuon FF, Cieslinski J, de Souza RM, Imamura R, Amato VS. Comparative study on liposomal amphotericin B and other therapies in the treatment of mucosal leishmaniasis: A 15-year retrospective cohort study. PloS one. 2019; 14(6):e0218786. https://doi.org/10.1371/journal.pone.0218786 PMID: 31242231
11. Sunyoto T, Potet J, Boelaert M. Why miltefosine— a life-saving drug for leishmaniasis—is unavailable to people who need it the most. BMJ global health. 2018; 3(3):e000709. https://doi.org/10.1136/bmjgh-2018-000709 PMID: 29736277
12. Rodríguez G, Sarmiento L, Hernández CA. Leishmaniasis mucosa y otras lesiones destructivas centrafaciales. Biomedica. 1994; 14(4):215–29.
13. Agnihotri NT, McGrath KG. Allergic and nonallergic rhinitis. Allergy and asthma proceedings. 2019; 40(6):376–9. https://doi.org/10.2500/aa p.2019.40.4251 PMID: 31690374
14. Hashiguchi Y, Velez LN, Villegas NV, Mimori T, Gomez EAL, Kato H. Leishmaniasis in Ecuador: Comprehensive review and current status. Acta tropical. 2017; 166:299–315. https://doi.org/10.1016/j.actatropica.2016.11.039 PMID: 27919688
15. Braz LMA. Tegumentary leishmaniasis diagnosis: what happened with MST (Montenegro Skin Test) in Brazil? Revista do Instituto de Medicina Tropical de Sao Paulo. 2019; 61:e17. https://doi.org/10.1590/S1678-9946201961017 PMID: 30864622
16. Boggild AK, Valencia BM, Veland N, Ramos AP, Calderon F, Arevalo J, et al. Non-invasive cytology brush pcr diagnostic testing in mucosal leishmaniasis: Superior performance to conventional biopsy with histopathology. PloS one. 2011; 6(10) (no pagination) (e26395). https://doi.org/10.1371/journal.pone.0026395 PMID: 22046280
17. Zajtchuk JT, Casler JD, Netto EM, Grogl M, Neafie RC, Hessel CR, et al. Mucosal leishmaniasis in Brazil. The Laryngoscope. 1989; 99(9):925–39. https://doi.org/10.1288/00005537-198909000-00006 PMID: 2671555
18. Gomes CM, Mazin SC, Santos ER, Cesetti MV, Bächtold GA, Cordeiro JH, et al. Accuracy of mucocutaneous leishmaniasis diagnosis using polymerase chain reaction: systematic literature review and meta-analysis. Memorias do Instituto Oswaldo Cruz. 2015; 110(2):157–65. https://doi.org/10.1590/0074-02769140280 PMID: 25946238
19. Calvopina M, Armijos RX, Hashiguchi Y. Epidemiology of leishmaniasis in Ecuador: current status of knowledge—a review. Memorias do Instituto Oswaldo Cruz. 2004; 99(7):663–72. https://doi.org/10.1590/s0074-02769140230 PMID: 15654419
20. Banda H, Robinson R, Thomson R, Squire SB, Mortimer K. The ‘Practical Approach to Lung Health’ in sub-Saharan Africa: a systematic review. The international journal of tuberculosis and lung disease: the official journal of the International Union against Tuberculosis and Lung Disease. 2016; 20(4):552–9. https://doi.org/10.5588/ijtld.15.0613 PMID: 26970167
21. Marais BJ, Gie RR, Hesseling AC, Schaal HS, Lombard C, Enarson DA, et al. A refined symptom-based approach to diagnose pulmonary tuberculosis in children. Pediatrics. 2006; 118(5):e1350–9. https://doi.org/10.1542/peds.2006-0519 PMID: 17079536
22. WHO. Sexually transmitted and other reproductive tract infections: a guide to essential practice: World Health Organization; 2005.
23. Bezemer J, Meesters K, Calvopina M, Machado P, de Vries H, Schallig H. Syndromic management of mucosal leishmaniasis in south america: a systematic review and meta-analysis. PROSPERO. 2017: CRD42017074148.

24. Page MJ, Moher D, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. PRISMA 2020 explanation and elaboration: updated guidance and exemplars for reporting systematic reviews. Bmj. 2021;372. https://doi.org/10.1136/bmj.n160 PMID: 33781993

25. Ouzzani M, Hammady H, Fedorowicz Z, Elmagarmid A. Rayyan-a web and mobile app for systematic reviews. Systematic reviews. 2016; 5(1):210. https://doi.org/10.1186/s13643-016-0384-4 PMID: 27919275

26. Munn Z, Barker TH, Moons L, Tufanaru C, McArthur A, et al. Methodological quality of case series studies: an introduction to the JBI critical appraisal tool. JBI evidence synthesis. 2020; 18(10):2127–33. https://doi.org/10.11124/JBISRIR-D-19-00099 PMID: 33038125

27. Microsoft Excel. Internet: Microsoft Corporation; 2018.

28. Machado-Coelho GL, Caiaffa WT, Genaro O, Magalhaes PA, Mayrink W. Risk factors for mucosal manifestation of American cutaneous leishmaniasis. Transactions of the Royal Society of Tropical Medicine and Hygiene. 2005; 99(1):55–61. https://doi.org/10.1016/j.trstmh.2003.08.001 PMID: 15550262

29. Ampuero J, Macedo V, Marsden P. Clinical findings of tegumentary leishmaniasis in children under five years of age in an endemic area of Leishmania (Viannia) braziliensis. [Portuguese]. Revista da Sociedade Brasileira de Medicina Tropical. 2006; 39(1):22–6. https://doi.org/10.1590/s0037-8682200600100004 PMID: 16501761

30. Jaume F, Valls-Mateus M, Mullol J. Common Cold and Acute Rhinosinusitis: Up-to-Date Management in 2020. Curr Allergy Asthma Rep. 2020; 20(7):28. https://doi.org/10.1007/s11882-020-00917-5 PMID: 32495003

31. Costa DCSD Palmeiro MR, Moreira JS Martins ACDC, Da Silva AF, De Fatima Madeira M, et al. Oral manifestations in the American tegumentary leishmaniasis. PloS one. 2014; 9 (11) (no pagination) (e109790). https://doi.org/10.1371/journal.pone.0109790 PMID: 25386857

32. Canário A, Queiroz M, Cunha G, Cavalcante T, Riesz V, Sharma R, et al. Presence of parasite DNA in clinically unaffected nasal mucosa during cutaneous leishmaniasis caused by Leishmania (Viannia) braziliensis. Clinical Microbiology and Infection. 2019; 25(4):515.e5–e7. https://doi.org/10.1016/j.cmi.2018.12.027 PMID: 30616010

33. Cantanhede LM, Mattos CB, Cruz AK, Ikenohuchi YJ, Fernandes FG, Medeiros E, et al. Overcoming the Negligence in Laboratory Diagnosis of Mucosal Leishmaniasis. Pathogens. 2021; 10(9). https://doi.org/10.3390/pathogens10091116 PMID: 34578149

34. Lawn SD, Whetham J, Chiodini PL, Kanagalingam J, Watson J, Behrens RH, et al. New world mucosal and cutaneous leishmaniasis: an emerging health problem among British travellers. QJM: monthly journal of the Association of Physicians. 2004; 97(12):781–8. https://doi.org/10.1093/qjmed/hch127 PMID: 15569809

35. Boaventura VS, Cafe V, Costa J, Oliveira F, Bafica A, Rosato A, et al. Short report: Concomitant early mucosal and cutaneous leishmaniasis in Brazil. American Journal of Tropical Medicine and Hygiene. 2006; 75(2):267–9.

36. Falcão G, Lins-Kusterer L, Leite-Ribeiro PM, Sarmento VA. Orofacial manifestations of mucocutaneous leishmaniasis: a case series from Brazil. F1000Research. 2019; 8:756. https://doi.org/10.12688/ f1000research.19056.4 PMID: 33042516

37. Motta ACF, Lopes MA, Ito FA, Carlos-Bregni R, De Almeida OP, Roselino AM. Oral leishmaniasis: A clinicopathological study of 11 cases. Oral Diseases. 2007; 13(3):335–40. https://doi.org/10.1111/j.1601-0825.2006.01296.x PMID: 17448219

38. Barral A, Pedral-Sampaio D, Grimaldi G Jr, Momen H, McMahon-Pratt D, Ribeiro De Jesus A, et al. Leishmaniasis in Bahia, Brazil: Evidence that Leishmania amazonensis produces a wide spectrum of clinical disease. American Journal of Tropical Medicine and Hygiene. 1991; 44(5):536–46. https://doi.org/10.4269/ajtmh.1991.44.536 PMID: 2063957

39. de Almeida OP, Sanchez-Romero C, Junior HM, Matta VLRd, Soares CdM, Mariano F, et al. Immunohistochemical and Molecular Diagnosis of Mucocutaneous and Mucosal Leishmaniasis. International journal of surgical pathology. 2018. https://doi.org/10.1177/1066896918876706 PMID: 31566041

40. Reyes Aragon J. [Skin leishmaniasis. II. Otorhinolaryngologic lesions]. Acta otorino-laringologica ibero-americana. 1968; 19(2):97–121 contd. PMID: 5721523

41. Valero NNH, Uriarte M. Environmental and socioeconomic risk factors associated with visceral and cutaneous leishmaniasis: a systematic review. Parasitology research. 2020; 119(2):365–84. https://doi.org/10.1007/s00436-019-06575-5 PMID: 31897789
42. Cloots K, Burza S, Malaviya P, Hasker E, Kansal S, Mollett G, et al. Male predominance in reported Visceral Leishmaniasis cases: Nature or nurture? A comparison of population-based with health facility-reported data. PLoS neglected tropical diseases. 2020; 14(1):e0007995. https://doi.org/10.1371/journal.pntd.0007995 PMID: 31995564

43. Lockard RD, Wilson ME, Rodríguez NE. Sex-Related Differences in Immune Response and Symptomatic Manifestations to Infection with Leishmania Species. Journal of immunology research. 2019; 2019:4103819. https://doi.org/10.1155/2019/4103819 PMID: 30756088

44. Dahal P, Singh-Phulgenda S, Olliaro PL, Guerin PJ. Gender disparity in cases enrolled in clinical trials of visceral leishmaniasis: A systematic review and meta-analysis. PLoS neglected tropical diseases. 2021; 15(3):e0009204. https://doi.org/10.1371/journal.pntd.0009204 PMID: 33725005

45. Weigle KA, De Davalos M, Heredia P. Diagnosis of cutaneous and mucocutaneous leishmaniasis in Colombia: A comparison of seven methods. American Journal of Tropical Medicine and Hygiene. 1987; 36(3):489–96. https://doi.org/10.4269/ajtmh.1987.36.489 PMID: 2437815