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REVIEW

Loa loa and *Mansonella perstans* infections in non-endemic countries: a narrative review

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Abstract

Purpose of Review Loiasis and mansonellosis are filarial infections potentially causing a relevant impact on morbidity and mortality. In non-endemic countries, there is poor awareness on these conditions, and clinical management is not standardized. Aim of this work is to review current evidence on cases diagnosed in non-endemic areas, in order to guide clinical management.

Recent Findings In non-endemic areas, a wider range of symptoms and signs have been reported for both infections, compared to endemic areas. Diagnostic tools include parasitological tests, serology and molecular methods, each one potentially playing a different role (i.e. for screening, determination of microfilarial load, etc). Treatment is not standardized, and first-line drugs might not be available everywhere.

Summary Loiasis and mansonellosis can be diagnosed in non-endemic countries; here we comment on strategies for screening, diagnosis, treatment and follow-up in clinical practice.

Keywords *Loa loa* · Loiasis · *Mansonella perstans* · Mansonellosis · Filaria · Filariosis

Introduction

Loiasis and mansonellosis are filarial infections caused respectively by the filarial nematodes *Loa loa* and *Mansonella* spp, with *M. perstans* being the most frequent cause of human mansonellosis.

The geographical distribution of these infections mirrors the presence of the vector in the area. *L. loa* infection occurs in limited forested areas of West and Central Africa, including northern Angola, southeastern Benin, Cameroon, Central African Republic, Chad, Congo, Equatorial Guinea, Gabon, Nigeria, Sudan, the Democratic Republic of Congo, and Uganda [1], where the "Mango fly" or "deer fly" of the genus *Chrysops* breeds. More than 13 million people are estimated to be infected with *L. loa* [2].

Mansonella perstans, affecting more than 114 million people, is transmitted by *Culicoides* biting midges diffused mostly in sub-Saharan Africa, from Senegal to Uganda and Zimbabwe, and in Central and South America, from Panama to Argentina. Smaller foci of transmission are reported for *Mansonella ozzardi* (Central and South America and the Caribbean islands) and for *Mansonella streptocerca* (tropical rain forests of western and central Africa). A fourth species has been described lately in Gabon, *Mansonella* sp. DEUX, whose clinical relevance remains uncertain [3].

Long considered as indolent conditions, they were subjects of relatively few studies. Since individuals with high levels of circulating *L. loa* microfilariae (mf) in the blood (>10000mf/ml) have an increased risk of potentially life-threatening encephalopathy after antifilaricidal treatment with diethylcarbamazine (DEC) or ivermectin [4, 5], loiasis has often been studied only as an impediment to mass-drug administration (MDA) based interventions to eliminate onchocerciasis and lymphatic filariasis in co-endemic areas in Central Africa.

Recent evidence shed light on the clinical relevance of these infections *per se*, with increased mortality associated with high *L. loa* microfilariaemia (>30000 microfilariae/ml of blood [6]), and relevant signs/symptoms due

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to mansonellosis. For the latter conditions, observational studies from non-endemic countries were the main source of novel information [6, 7].

Indeed, with the increase of migratory flows and international travels in the last decades, these infections are increasingly diagnosed non-endemic countries, sometimes with different clinical presentations compared to the classical features described in literature.

Due to the high complexity of realizing randomized controlled trials on imported cases, there is lack of robust evidence guiding diagnosis and treatment of loiasis and mansonellosis in non-endemic areas; hence, clinical management greatly varies among different countries, and is based mostly on expert consensus.

In this work, we comprehensively review the clinical presentation, diagnosis and treatment of loiasis and mansonellosis in the non-endemic setting, discussing future perspectives to improve their clinical management in non-endemic countries.

Epidemiology in Non-endemic Areas

Loiasis and mansonellosis are presumably underdiagnosed and underreported, due to variable, sometimes unapparent clinical presentation, and low awareness of health professionals. Moreover, co-infections with other parasites causing similar symptoms can be present, further confounding the path to diagnosis. Therefore, the prevalence of these infections among migrants and travelers is uncertain.

In a report by the GeoSentinel Surveillance Network from 1997 to 2004, filarial infections comprised 0.62% (n=271) of all medical conditions (43,722) reported to the GeoSentinel Network from migrants and travelers; 25% of these cases were infected with *L. loa* [8]. Another GeoSentinel survey reported 113 cases of filarial infection diagnosed from 2007 to 2011 out of 42,173 travelers (0.3%), but without species identification [9].

In a 2017 cross-sectional study from Italy, seroprevalence of filariasis was 9.35% in migrants from sub-Saharan Africa; however, there are no data on what proportion of these cases were attributable to *L. loa* or *Mansonella spp* [10]. In reports from Spanish tropical disease hospitals, *M. perstans* was reported in 3.9-10.9% patients from sub-Saharan Africa having undergone specific parasitological tests to detect microfilariae [11–13].

Pathogenesis

L. loa life cycle starts once the *Chrysops* fly takes a blood meal ingesting microfilariae. Once in the fly's midgut, microfilariae develop into L3 larvae. The fly then takes another blood meal, and *L. loa* L3 larvae enter the human body. L3 molt into adult worms while migrating in subcutaneous tissue and intermuscular fascial layers. There, they mate and the adult female produces sheathed microfilariae, which circulate in the blood with diurnal periodicity, corresponding to the biting habits of the *Chrysops* fly. The symptoms are mostly due to the migrating adults. Microfilariae are found in peripheral blood during daytime according to the biting habits of the *Chrysops* fly, while they accumulate in the pulmonary blood vessels during night-time, to avoid to be cleaned up by the spleen [1]. Microfilariae have also been detected in spinal fluid, urine, sputum, and in the lungs, and can live up to one year, while adult worms can live up to twenty years [1].

The patent period, indicating the time from infection by L3 larvae to the first clinical symptoms, is around 3-6 months [14]; the time between infection and appearance of microfilariae in peripheral blood is usually longer than 1 year, up to 15 years [5].

Mansonella larvae are transmitted to humans through the bite of flies of the genus *Culicoides* [15]. *M. perstans* larvae transform into adults, which live in body cavities, most commonly the pleural and peritoneal cavities; *M. streptocerca* adults live in the dermis and *M. ozzardi* adults live in subcutaneous tissue or body cavities [16]. Adults produce microfilariae, which are released into peripheral blood (or also skin for *M. streptocerca*) 9-12 months after infection without circadian periodicity [17, 18].

Clinical Manifestations

Loiasis

Clinical manifestations are caused by the migration of the adult worm in subcutaneous tissues and serous body cavities, the presence of microfilariae in peripheral blood and tissues, and the immune response of the host.

Loiasis classic features of infection are Calabar swelling, a transient angioedema of allergic nature to substances released by the adult worms migrating in the subcutaneous tissues, and the so-called "eyeworm", caused by the migration of the adult worm under the bulbar conjunctiva, which can cause pain, hyperemia and conjunctival chemosis, and foreign body sensation. Both these clinical features are pathognomonic of the infection; they are transient, lasting from a few hours up to 7 days, and leave no sequalae [1, 5, 14].

In endemic areas, Calabar swelling and eyeworm confirm the most frequent clinical presentation [19–21]. Cases of loiasis in non-endemic countries outline a wider spectrum of clinical presentations, ranging from benign to more

Table 1 Main clinical characteristics reported in studies of imported cases of loiasis and mansonellosis

	Loa loa					*Mansonella perstans*			
	Gobbi, F *et al* 2014 [19]	Gobbi, F *et al* 2018 [22]	Puente, S *et al* 2020 [21]	Bouchaud, O *et al*, 2022 [20]	Bottieau, E *et al*, 2022 [23]	Gobbi, F *et al*, 2017 [18]	Puente, S *et al* 2020 [24]	Tamarozzi, F *et al* 2022 [25]	Bottieau, E *et al*, 2022 [23]
Population (n)	100	238	131	167	150	74	503	281	123
Calabar swelling n (%)	77 (77)	106 (45.3)	30 (22.9)	54 (32.3)	86 (57)		18 (3.6)		10 (8)
Eyeworm n (%)	25 (25)	57 (24.2)	19 (14.5)	39 (23.3)	30 (20)				
Spleen nodules n (%)	8 (8)								
Neurologic involvement n (%)	2 (2)								
Headache n (%)						11 (15)			
Subcutaneous oedema n (%)			3 (2.3)	29 (17.3)		11 (14.9)			
Abdominal pain n (%)			4 (3.1)			17 (23)	15 (3)	67 (23.8)	
Itching n (%)	34 (34)		57 (43.5)	74 (44.3)	46 (30)	25 (33.8)	190 (37.8)	56 (20)	25 (19)
Lymphadenopathy n (%)	6 (6)				1 (1)				
Artralgias n (%)	11 (11)		12 (9.2)			10 (13.5)	50 (9.9)		
Pleural effusion/respiratory symptoms n (%)	1 (1)				6 (4)			9 (3.2)	8 (6)
Other systemic symptoms n (%)					10 (7)			24 (8.5)	3 (2)
Urticaria, rash n (%)	8 (8)					9 (12.2)		15 (5.3)	

severe conditions. Table 1 resumes the clinical manifestations reported in non-endemic countries.

The presence of splenomegaly and granulomatous splenic nodules has been seldom described in *L. loa* infection both in case series and case reports [26, 27], but is worth of note. On histopathological examination, microfilariae within these lesions were either intact or in various degree of degeneration, both inside and outside blood vessels. Considered the rarity of these findings in routine autopsies of people living in endemic areas, it has been hypothesized that the process can clear spontaneously. It is not yet clear whether splenic nodules indicate a temporary, self-resolving response to degenerating microfilariae or an impaired immunologic mechanism. Awareness on possible presence of transient spleen nodules due to *L. loa* is important in clinical practice, since misdiagnosis can expose patients to unnecessary treatment and even splenectomy [27].

Peripheral neuropathies represent another unusual presentation of loiasis described in case reports from Italy, with palsies and sensory deficit especially of the ulnar nerve, resolved after antifilarial treatment [19, 26].

Severe, chronic, and intermittent headache that resolved with antifilarial therapy has also been reported in patients with loiasis in France [28].

Less frequent symptoms that have been reported in non-endemic areas are: i) the superficial migration of the worm in the dermis or infrequently in the eyelid, typically leading to non-inflammatory, transient skin tracks, from which the adult worm can be extracted directly [29, 30]; ii) cardiovascular symptoms, namely heart failure and endomyocardial fibrosis [31].

Mansonellosis

Mansonellosis, when symptomatic, can present with non-specific manifestations common to loiasis and other parasites, such as localized and generalized chronic pruritus, urticaria and rashes, transient oedemas at varying body sites, headache, arthralgia and lymphadenopathy [23, 24, 32].

Other features of *M. perstans* infection that have been described in non-endemic areas are abdominal pain, asthma-like presentation, fever, myalgia, skin eruption, pericarditis, pleuritis and inflammatory granulomatous nodules surrounding dead adult worms [16, 18, 24] (Table 1).

In recent case reports of infection by *M. perstans* from France, the US and Japan, lymphadenopathy [33], fatigue and abdominal bloating [34], fever and itching [35] were reported, respectively.

A large 2022 case series reporting cases from five TropNet centers across Europe, described 392 cases of mansonellosis [25] diagnosed in migrants, expatriates and travelers by direct detection of *M. perstans* microfilariae

in peripheral blood. Little more than half of the patients were symptomatic, with abdominal pain and itching as the two most frequent symptoms [25].

A case series from Italy reported 74 patients with *M. perstans* infection [18], 89.2% of whom were symptomatic, with abdominal pain and itching being the most frequently reported symptoms. A study from a Spanish reference center describing the characteristics [24] of 503 cases of migrants from tropical and subtropical areas with *M. perstans* infection found that 45.3% were symptomatic, with pruritus and arthralgia being the most common features.

Laboratory Findings

Observational studies from non-endemic areas permitted to highlight the high frequency of eosinophilia (generally defined as an eosinophil count ≥ 500 eosinophils/µl blood) and hyper-IgE (generally defined as an IgE level>100 UI/ml). Despite being unspecific laboratory parameters, they can be helpful in raising the index of suspicion for filarial (or at least, helminth) infection in the absence of specific symptoms.

In the analysis of 100 cases of loiasis diagnosed in Italy, eosinophilia was found in 80% of patients, and 74% of patients had hyper-IgE [19]. In a large, retrospective analysis of *L. loa* cases diagnosed in a 25 year-timespan, eosinophilia and hyper-IgE were found respectively in 90% and 76% patients. Eosinophilia was also found in all patients included in a large study (n=167 cases) of loiasis cases in France [20] and a smaller study (n=16 cases) from Italy [36].

In a large case series of travel-related *M. perstans* infection across different hospitals in Europe, eosinophilia was present in more than 50% of cases [25]. This finding was confirmed by another cohort study of *Mansonella* infection in Spain, in which absolute eosinophilia was detected in 67.6% of cases. Moreover, in the latter study, hyper-IgE was observed in 90% of patients [24].

In another case series from Italy, hypereosinophilia (defined as eosinophils count>1000/µl) was found in 43.8% of the *Mansonella* cases, while IgE level was elevated in 83.3% of cases [18]. It should be noted that in this case series, eosinophilia might have been caused by other co-infections, which were frequently found.

Diagnosis

For *L. loa*, eyeworm detection is sufficient for diagnosis, while for *Mansonella spp* no patognomonic clinical sign exists.

Parasitological Diagnosis

Parasitological diagnosis of *L. loa* and *Mansonella* spp infection relies on microscopy examination of blood smears, where circulating microfilariae can be observed (Fig. 1).

Sensitivity of this method can be improved using Knott's concentration or Nucleopore filtration. For *L. loa*, peripheral blood must be obtained around midday, since microfilaraemia peaks accordingly to the biting habits of the *Chrysops* fly [37, 38].

Length of *L. loa* adult worms range from 2.0 to 3.5 cm for males, and from 5 to 7 cm for females; microfilariae are sheathed, with a tapered tail and with nuclei extending to the tip of the tail. Microfilariae measure 230 to 250 µm long in stained blood smears.

Between 30 and 60% of patients with *L. loa* infection do not develop microfilaraemia, either due to single-worm infection, single-sex infection, efficient immunological control, or genetic predisposition [5, 39, 40].

Mansonella adult worms range in length from 3.5 to 4.5 cm for males, and from 5 to 8 cm for females. Microfilariae of *M. perstans* are unsheathed, with a blunted tail and a round terminal nucleus at the tip of it. *M. perstans* is most similar to *M. ozzardi*, which has a tapered, anucleate tail. When observed in stained blood smears, they typically measure between 190 to 200 µm in length. Microfilariae of *M. streptocerca* are detected in skin snips and are unsheathed, typically ranging from 180 to 240 µm in length. Their nuclei extend to the tail tip, often curved into a hook-like shape [41]. *Mansonella* parasites in the skin cannot be reliably identified using light microscopy because *M. perstans* and *O. volvulus* cannot be morphologically distinguished from one another and because both are commonly confused with *M. ozzardi, M. streptocerca,* and *L. loa* [16, 42].

Serology

There are serology kits, mostly ELISAs, available on the market. They are pan-filarial tests, detecting target antigens present in all filarial species. Sensitivity varies depending on the assay, ranging from 55% of one assay tested in amicrofilariemic patients to 95% estimated for an ELISA based on *Achantocheilonema vitae*. In an Italian study, 1170 patients coming from endemic areas were screened for antifilarial antibodies using the latter kit: 149 (12.7%) had a positive result; of these, 93 were tested with modified Knott test and mf were found in 29 (n=24 *M. perstans*, n=4 *L. loa*, n=1 mixed *M. perstans* + *L. loa*). A decrease in antibody titer/seroreversion was observed after treatment: this result suggests that a positive ELISA test is an index of active infection, and serology might be used for post-treatment monitoring [43].

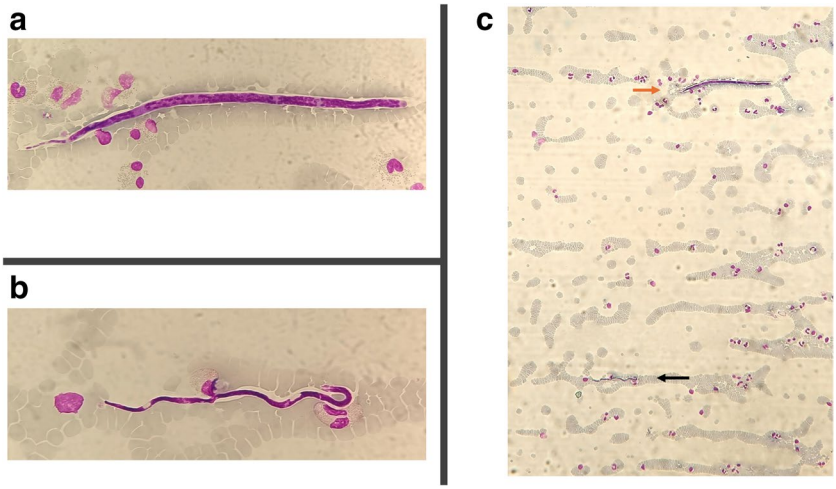

Fig. 1 **A**) *L. loa* microfilariae (230-250 µm x 6.5–8.5µm) in a Giemsa-stained peripheral blood smear. Image captured at 63x magnification using oil immersion. Notable features include the short head space and the tail with nuclei irregularly spaced to the tip, while the presence of the sheath is imperceptible; **B**) *M. perstans* microfilariae (190–200µm x 4.5-6.5µm) in Giemsa-stained peripheral blood smear. Image taken at 63x magnification with oil. The microfilariae shows a blunt tail, with nuclei extending to its tip; **C**) *L. loa* (orange arrow) and *M. perstans* (black arrow) microfilariae in a blood smear stained with Giemsa stain (arrows) captured by the Knotts concentration technique (40× power magnification)

A rapid lateral flow assay has also been developed, and is currently available as research-use-only. It demonstrated a 94% sensitivity for the diagnosis of loiasis and a 100% specificity for filarial infections in endemic areas [44]. In a study carried out in a non-endemic setting, the rapid test demonstrated excellent sensitivity (100% positive in case of confirmed diagnosis, that is microfilaremia or eyeworm) [45] and specificity around 92%, showing cross-reactions mostly with *M. perstans*. However, the test is not commercially available, and a positive test would not refrain from microfilariae detection.

Molecular Methods

Molecular methods, such as polymerase chain reaction (PCR) or loop mediated isothermal amplification (LAMP) have been developed for *L. loa* and *Mansonella* [46–49]. The main advantage of PCR over parasitological examination is that it is less time consuming; moreover, the test is virtually 100% specific and does not require microscopy skills. However, validated commercial assays are not yet on the market, so in-house methods are available only in referral centers.

Diagnostic Workup for Filaria in the Non-endemic Setting

In case of individuals without pathognomonic signs/symptoms, screening might entail the use of serology as first step, as this is a very sensitive test that can indicate presence of filarial infection. Second step would be species identification either with PCR or microscopy examination (depending on local expertise/suitability) for those resulting serological- positive. It should then be considered that, in case of *L. loa* infection, quantitative microfilaremia should be assessed to guide treatment, as described in the treatment paragraph.

Differences between Infections in Travelers, Expatriates, and Migrants

Some observational studies reported different clinical presentations and laboratory findings between migrants born in endemic countries (endemic population) and expatriates born in a non-endemic country (but with a long-term stay in the endemic country) or short-term travelers (non-endemic population). Regarding loiasis, two large case series published in the 1990's reported that Calabar swelling and eosinophilia were significantly more frequent in expatriates/travelers, while "eyeworm" was seen in a higher proportion of migrants [14, 50]. These findings were confirmed in more recent studies [19, 44, 51, 52].

The levels of *L. loa* microfilaraemia were also reported to be significantly different between migrants and expatriates/travelers: the latter group (including expatriates with a long time of residency in endemic countries) were found to be significantly more likely to be amicrofilaraemic and to present eosinophilia compared to migrants [19, 53]. No

significant differences were demonstrated in the IgE levels among the two groups [19].

Discrepant data concern the results of serology, which has been found to be more sensitive in expatriates/travelers in some studies [14, 20], but not in others [19].

These data suggest that the responsiveness to *L. loa* infection does not depend merely on the duration of exposure, yet from a combination of factors, including genetic differences, chronic polyparasitism, or prenatal sensitizations [50].

Regarding mansonellosis, no difference between migrants and expatriates or travelers has been described in median eosinophil count and microfilaremia [18, 23, 24].

Treatment

Loiasis

Given the scarcity of evidence-based data, there are no guidelines on the treatment of *L. loa* and *Mansonella* infections in non-endemic countries.

Regarding *L. loa*, three drugs are currently used for treatment: DEC, ivermectin (IVM) and albendazole (ALB). Main characteristics of these drugs are reported in Table 2.

In individuals with elevated microfilariaemia there is a significant risk of life threatening encephalopathy in case of administration of either DEC or IVM, probably due to the rapid destruction of microfilariae [4, 5]. Since the severity and frequency of treatment-related side effects are directly related to blood microfilarial count [4, 54], it is crucial to assess blood microfilariae levels before starting treatment. DEC is the only drug with activity both against microfilariae and adult worms, and is therefore the gold standard treatment against *L. loa*. In patients with low microfilarial count, it is given 9mg/kg/day in 3 weekly doses. In patients with high microfilarial count, it is recommended to administer ALB first, followed by DEC at a starting dose of 1mg/kg/day and increasing over 3 days to 9 mg/kg/day daily for three weeks. Main limitation of the use of DEC in the non-endemic setting is the unavailability of the drug in the market.

IVM has a strong and durable microfilaricidal effect, but it is ineffective on adult worms. It is given 150-200µg/kg as a single or multiple dose.

ALB is given 200-400mg bid for 21-28 days, and its activity is supposed to be predominantly macrofilaricidal with an embryotoxic effect on the developing microfilariae rather than microfilaricidal. Because of its slow and progressive effect, it is the drug of choice to reduce microfilaraemia in patients with a high microfilarial burden.

Nevertheless, albendazole-induced encephalopathy has been reported in case reports [46, 55] also in patients without predisposing conditions, so caution is always warranted. Treatment should be administered in a hospital environment during the first days.

Given the risk of serious adverse events, the following treatment scheme has been proposed by Boussinesq et al.: ALB when microfilarial load is higher than 8000/ml, followed by IVM for microfilaraemia between 2000 and 8000, and DEC when microfilarial density is below 2000/ml [56].

Data From the Non-endemic Setting

In the non-endemic setting, DEC monotherapy has been reported to have a worse outcome when compared to combination therapies (IVM+DEC, DEC+ALB, ALB+IVM), with a parasitological cure rate of 38-51% [22, 57].

Table 2 Main characteristics of the drugs recommended for Loa loa infection

	Diethylcarbamazine	Ivermectin	Albendazole
Mechanism of action	Micro and macrofilaricidal	Microfilaricidal	Macrofilaricidal (embryotoxic effect), slow effect
Recommended use	Mf count <2000mf/ml	Mf count between 2000/ml and 8000/ml	Mf count above 8000/ml
Dose	1mg/kg/day, increasing over 3 days to 9mg/kg/day for 3 weeks	150-200µg/kg, single or multiple dose	200-400mg bid for 21-28 days
Advantages	Rapid macrofilaricidal effect	Rapid microfilaricidal effect, high efficacy in combination with ALB	Fewer adverse events, high efficacy in combination with IVM
Limitations	Risk of encephalopathy Unavailability on the market Lower efficacy both alone and in combination with other anthelmintics; Contraindicated in patients with onchocerciasis	Risk of encephalopathy Not active against adult worms	Not active against microfilariae

In a large retrospective study comparing drug regimens in different reference centers for tropical medicine across Europe [22], reporting data of 238 cases of loiasis, DEC was administered in the majority of cases (45.1%), followed by IVM (25%) and ALB (3.7%). Combination therapies were also administered: ALB + IVM in 11.6% of cases, IVM + DEC in 9.7% of cases and ALB + DEC in 4.9% of cases. In this study, the highest proportion of parasitological cure (defined as negativization of microfilariaemia and normal eosinophil count) and clearance of symptoms was reached with the combination of ALB + IVM , while only 50% of patients treated with DEC alone achieved a parasitological cure.

Combination therapy was confirmed to achieve higher cure rates than mono-therapy also in a study from Spain, namely considering DEC or IVM + other anthelmintics [21], and in a study from 167 cases from France in which the combination IVM+DEC was used [20].

These data suggest that, regardless of the microfilarial level, a combination therapy of two antihemintics rather than a course of a single drug might be the best option to treat loiasis. Worth of note, the combination ALB + IVM demonstrated good efficacy, and may be preferred also in light of the unavailability of DEC in most non-endemic countries, and the need of multiple treatment courses to achieve cure with this drug [36].

Mansonellosis

Relating to *M. perstans* infection, poor responses have been reported to standard antifilarial drugs including DEC, ivermectin, albendazole and mebendazole [58].

M. perstans from Mali, Cameroon and Ghana has been found to harbor the intracellular endosymbiont *Wolbachia*; given the dependence of the parasite from the bacterium, the administration of doxycycline can be useful in the treatment of mansonellosis from these geographic regions [59, 60]. Cases from Uganda and Gabon, not harboring Wolbachia, do not respond to doxycycline.

Data from the Non-endemic Setting

A large case series from Italy reported that 83% of patients given mebendazole and/or doxycycline became amicrofilaremic after one or more treatment courses [25], and 50% of patients treated with mebendazole followed by 6 weeks of doxycycline became amicrofilaremic after a single course of treatment, while the other half needed two or more courses to completely clear microfilaraemia [43].

In a retrospective cohort study of *M perstans* infections diagnosed in Spain, 66.8% of the treated patients were given one drug only: mebendazole, IVM or ALB. 28.8% were treated with combined therapy, mainly IVM + mebendazole, and a significant decrease in eosinophilia was detected before and after treatment with all regimens [24].

Post-treatment Monitoring

Outcome is measured as a combination of laboratory paramethers (negativization of microfilaraemia, decrease in the antibody titer and normalization of eosinophil and IgE count) and clearance of symptoms.

Evidence on imported cases [18, 23, 51, 58] suggests periodical (every two to three months) evaluation of microfilariaemia, until complete clearance. Also, clearance of eosinophilia and symptoms should be evaluated if present at baseline, in order to decide about a possible further treatment course.

Conclusions

Loiasis and mansonellosis, despite being rare as imported infections and asymptomatic in most cases, remain important tropical diseases to consider in the differential diagnosis of patients coming from endemic countries, also due to the fact that currently no control programs are recommended for these filarial infections in endemic areas. Due to the poor feasibility of randomized trials in non-endemic countries and the consequent lack of robust clinical evidence, recommendations for clinical management are usually based on expert opinion, thus can vary between different countries. However, observational studies and case series from non-endemic areas are important to add up useful information for the clinical management of these conditions, as we review here.

Although *L. loa* can manifest with pathognomonic symptoms/signs, it might also present with a wide range of symptoms that can sometimes mimic other conditions. The clinical presentation of mansonellosis is less studied than that of loiasis; the clinical relevance of this infection has also been questioned, so diagnostic workup and treatment is not universally recommended. However, we believe that the emerging evidence is enough to warrant treatment.

Both for *L. loa* and *M. perstans* infections, screening might be decided based on epidemiological basis only or in presence of clinical or laboratory signs and symptoms which could raise the index of suspicion for filarial infection. A highly sensitive test (serology) might be used for screening, with a more specific test carried out in serology-positive individuals. For loiasis, microfilarial level on peripheral blood should always be assessed before treatment, to reduce the risk of iatrogenic encephalopathy. For loiasis, DEC, IVM and ALB are recommended for treatment, in different order and combination, based on the level of microfilaremia. For

mansonellosis, treatment might target the endosymbiont *Wolbachia* (for which doxycycline is recommended), when present; in the other cases, anthelminthic drugs including mebendazole, IVM, ALB, DEC can be used, though response is less defined.

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Data Availability No datasets were generated or analysed during the current study.

Declarations

Conflict of Interest The authors declare no competing interests.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- • Of importance
- •• Of major importance

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