TITLE: EVIDENCE-BASED GUIDELINES FOR SCREENING AND MANAGEMENT OF STRONGYLOIDIASIS IN NON-ENDEMIC COUNTRIES.

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Key words: strongyloidiasis, screening, recommendations, Strongyloides, ivermectin, migrant

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ABSTRACT

Strongyloidiasis is an intestinal parasitic infection becoming increasingly important outside endemic areas, not only because of the high prevalence found in migrant populations, but also because immunosuppressed patients may suffer a potentially fatal disseminated disease. The aim of these guidelines is to provide evidence-based guidance for screening and treatment of strongyloidiasis in non-endemic areas. A panel of experts focused on three main clinical questions (who should be screened and how, how to treat), and reviewed pertinent literature available in international databases of medical literature and in documents released by relevant organizations/societies. A consensus of the experts' opinion was sought when specific issues were not covered by evidence. In particular, six systematic reviews were retrieved and constituted the main support for this work. The evidence and consensus gathered led to recommendations addressing various aspects of the main questions. Grading of evidence and strength of recommendation were attributed to resume the quality of supporting evidence.

The screening of individuals at risk of the infection should be performed before they develop any clinical complication. Moreover, in immunosuppressed patients, the screening should be mandatory. The screening is based on a simple and widely accessible technology and there is now a universally accepted treatment with a high efficacy rate. Therefore, the screening could be implemented as part of a screening program for migrants although further cost-effectiveness studies are required to better evaluate this strategy from a public health point of view

INTRODUCTION

Strongyloidiasis is a parasitic disease widely distributed in tropical and subtropical regions[1], with over 350 million people estimated to be infected worldwide.[2] Migrant populations living in European countries present a high risk of having strongyloidiasis,[3,4] and it has been reported that the prevalence in immigrants may range from 2 to 46%,[5] but few studies have assessed the burden and risk factors of imported strongyloidiasis[3,6].

The infection has three peculiar characteristics that are of importance from the clinical and public health point of view: Firstly, more than half of infected subjects are asymptomatic or have mild, not specific complains,[6] and eosinophilia is often the only finding.[4] Therefore they are usually unaware that they might harbour an infection[7]. Secondly, *S.stercoralis* has the ability to replicate indefinitely inside the host (autoinfective cycle) without any further exposure to an infected site, thus causing a lifelong infection if left untreated.[8,9] Thirdly, immunosuppressed patients can develop the hyperinfection syndrome or the disseminated disease, which has a fatality rate of 60-70%.[10] The most frequent trigger of this complication is a chronic therapy with steroids, but solid organ or bone-marrow transplant recipients, patients with malignancies, or those under therapy with immunosuppressive drugs are also at risk.[11] Human T-Cell Lymphotropic virus 1 (HTLV-1) is also a risk factor for severe disease and treatment failure.[12,13]

. The rationale for a screening of *S. stercoralis* in non-endemic countries is based on the high estimated prevalence of the infection among migrants, the availability of a sensitive method for detection, and the potential to prevent fatal complications through early case detection. Currently, a few societies/organizations recommend screening for

S.stercoralis in specific fields, like solid organ transplantation[14] since it has been recognised that strongyloidiasis can be acquired from an infected donor.[15–17]

Different screening strategies include universal screening (when all individuals in a certain category are tested,[18]) and case finding (when only a well-defined group with risk factors are candidates for screening.[19]).

OBJECTIVES

These guidelines are aimed to provide evidence-based guidance and, when not available, consensus opinion from a group of experts to address the screening and treatment of strongyloidiasis in non-endemic areas.

The following definitions were used in these guidelines:

1. Individuals with high risk of exposure to *S. stercoralis*: immigrants coming from endemic areas (Africa, Latin-America, Asia and Oceania), adopted children who have been living for at least one year in highly endemic area, expatriates (i) undertaking long trips (more than one year) to endemic countries and (ii) with exposure to rural areas.
2. Individuals with intermediate - low risk of exposure to *S. stercoralis*: short-term (less than one year) travellers to highly endemic areas; elderly patients living in countries where transmission was occurring in the past, which include Northern Italy[20] and the Spanish Region of Valencia.[21]
3. Immunosuppressed: patients in chronic treatment with corticosteroids, chemotherapy, immunosuppressant and immunomodulator agents, transplant recipients, patients with AIDS or HTLV-1 infection or any immunosuppression condition.

4. Candidates to immunosuppression: candidates to immunosuppressant therapies (see above), candidates to solid or bone marrow transplant. Patients with well-controlled HIV infection should be managed like non-immunosuppressed individuals.

5. Disseminated strongyloidiasis: severe infection with presence of parasites outside the classical life cycle (ie, in organs other than the skin, gastrointestinal tract, lungs).

6. *Strongyloides* hyperinfection: increase in the number of larvae in the stools and/or sputum along with clinical manifestations limited to the respiratory and gastrointestinal systems, and peritoneum.

2.METHODS

Panel composition

We convened a panel of six experts, all of them specialists in migrant health and imported diseases, with a particular experience in strongyloidiasis.

The panel addressed the following 3 clinical questions:

(i) Who should be screened?

(ii) How to screen strongyloidiasis

(iii) How to treat strongyloidiasis

Literature review and analysis

Panel members thoroughly reviewed the literature pertinent to each of the question using Pubmed /Medline, and Cochrane library.

They particularly evaluated the results of four recent systematic reviews (SRs) about strongyloidiasis published by the COHEMI-project. All these SRs had been undertaken

by five members of the panel. The COHEMI project comprehensively reviewed different aspects of strongyloidiasis and the final results were four SRs published in peer-reviewed journals[3,7,10,22] and another study that evaluated the accuracy of five different serological assays for the screening, diagnosis and follow up of *S.stercoralis* infection.[23,24]

Moreover, other SRs on strongyloidiasis have been additionally included for the guidelines development. For this purpose, panel members thoroughly reviewed the literature pertinent to each of the question using Pubmed/Medline, Embase, CINAHL, Cochrane CENTRAL, as well as grey literature for other relevant documents as well as published guidelines and reports on screening for strongyloidiasis in relevant organizations (e.g., ECDC, WHO) databases.

Process overview

In creating the guidelines, the panel applied the same principles as the Agency for Healthcare Research and Quality (AHRQ)[25].

This included the available evidence based on the SRs and the grading of the recommendations. The panel members reviewed each recommendation, their strengths and the quality of evidence. Discrepancies were discussed and resolved, in order to achieve a consensus for each recommendation. The strength assigned to a recommendation reflects the panel's confidence that the benefits of following the recommendation are likely to outweigh potential harms.

Grading of evidence

- Ia: systematic review or meta-analysis of randomized controlled trials (RCTs).
- Ib: at least one RCT.

- IIa: at least one well-designed controlled study without randomization.
- IIb: at least one well-designed quasi-experimental study, such as a cohort study.
- III: well-designed non-experimental descriptive studies, such as comparative studies, correlation studies, case-control studies and case series.
- IV: expert committee reports, opinions and/or clinical experience of respected authorities.

Grading of recommendations

- A: based on hierarchy I evidence.
- B: based on hierarchy II evidence or extrapolated from hierarchy I evidence.
- C: based on hierarchy II evidence or extrapolated from hierarchy I or II evidence.
- D: directly based on hierarchy IV evidence or extrapolated from hierarchy I, II or III evidence

3. RESULTS

Six systematic reviews have been finally included (see table 1)

(i)Who should be screened?

First, epidemiological data are important to identify patients at risk of exposure to *S.stercoralis*. However, there is limited evidence in the literature providing prevalence data of strongyloidiasis. In one systematic review about imported strongyloidiasis, prevalence ranged from 0.4-46%, which varied depending on the diagnostic technique used and the targeted population (migrant and/or refugees)[26]. Another systematic review suggests that *S.stercoralis* affects between 10 and 40% of the population in most tropical and subtropical countries[5]; this study also estimates high infection rates in

refugees and migrants living in non-endemic areas, reaching prevalences up to 75%.[5]. However, infection rates varied substantially depending on the refugees' country of origin and the studies analyzed suggest that the infection may be underreported, especially in Sub-Saharan Africa and South-East Asia[5].

Second, we should differentiate between (i) patients with high risk of exposure to *S.stercoralis* and (ii) patients with intermediate-low risk of exposure, as defined previously.

Moreover, the risk of developing a severe disease is not the same in all patients harbouring the infection. Most infected subjects will never incur in the complicated form throughout their life,[8] while immunocompromised patients are at risk of developing a severe, life-threatening disease.[10]

Therefore, when considering the screening for *S.stercoralis*, we should differentiate two clinical situations. **Immunocompetent patients.**

The economic benefits of soil-transmitted infections screening in asymptomatic immunocompetent individuals, both in cost per hospitalization averted and disability-adjusted life years (DALYs), have been evaluated through cost-effectiveness studies conducted in the United States.[27,28]

The results of these economic analyses showed that universal screening and presumptive antiparasitic treatment were more cost-effective strategies to control soil-transmitted helminths in immigrants entering United States, compared to a "watchful waiting" strategy.[27] However, these studies did not consider serology as a screening method, nor new data about the efficacy of ivermectin for the treatment of strongyloidiasis.[29]

Testing for *S.stercoralis* has been suggested only for patients with eosinophilia (>500 eosinophils-per-microliter of blood) returning from the tropics.[30] Eosinophilia is a frequent (48-78%) finding in patients with strongyloidiasis, [31–33] but clearly, its absence does not exclude the infection.[22] It is a too weak predictor of strongyloidiasis in migrants.[22,34,35]

Hence, strongyloidiasis should be ruled out in any individual at risk of the infection and with eosinophilia as part of the differential diagnosis of eosinophilia. However, a two-steps screening strategy (blood count and serological-test if eosinophilia is present) is not recommended considering a) the need of two accesses of the patient to the lab; b) the insufficient sensitivity of eosinophilia.

Recommendations. **Immunocompetent patients who present high risk of exposure to *S. stercoralis* infection should be routinely screened for strongyloidiasis.**

Grading of evidence: III

Grading of recommendations: D.

Immunosuppressed patients/ candidates to immunosuppression (see "Definitions").

People exposed to immunosuppressant conditions should be particularly targeted due to the increased risk of developing severe disease which has a high mortality rate.[10,36] A study which evaluated the risk factors for developing strongyloidiasis hyperinfection, concluded that all patients with severe disease were immunocompromised.[37] As it has already been mentioned, a wide variety of predisposing factors has been described: hematologic malignancies, transplantation, immunosuppressant drugs. Steroids remain the most frequent risk factor for developing severe disease, which has been reported even during short steroid courses.[37,38] It is difficult to quantify the risk of developing hyperinfection or disseminated disease in case of immunosuppression and also the amount of risk of complication involved in each particular type of immunosuppression

is unknown. To sum up, immunosuppression poses the patients at risk of developing the severe disease, then it has been recommended to screen the patients for *S.stercoralis* before administering immunosuppressant therapy, as well as before transplantation or other immunosuppressant conditions.[10]

Finally, and considering the high efficacy and tolerability of ivermectin, it might be probably worth treating high – risk patients pre-emptively in case an appropriate test (stool culture or serology) is not available.[10]

Recommendations. **Immunosuppressed patients and candidates to immunosuppression should be routinely screened for strongyloidiasis if they have high or intermediate risk of exposure to *S.stercoralis*.**

If an appropriate diagnostic test is not available, specific treatment with ivermectin should be pre-emptively provided.

Grading of evidence: Ia

Grading of recommendations: B

(ii) How to screen?

The diagnosis of *S. stercoralis* infection is hampered by the low sensitivity of fecal-based tests and the suboptimal specificity of most serological test.[22]

Direct methods (parasitological-based methods)

A single stool examination fails to detect *S. stercoralis* larvae in up to 70% of cases. Repeated examinations of stool specimens improve the chances of finding parasites; in some studies, diagnostic sensitivity increases to 50% with 3 stool examinations.[39,40]

A recent meta-analysis on the evaluation of conventional parasitological methods found the highest sensitivity (89%) for agar plate culture, followed by the Baermann technique

(72%), FECT (48%), and direct wet smear (21%).[41] In most of the diagnostic studies on strongyloidiasis, the reference standard used was based on faecal methods.[22] However, the sensitivity of any faecal-based reference standard may be sub-optimal, especially in chronic infections where larval output is often very low.

Indirect methods (serology)

Serological methods are the most sensitive available diagnostic tools. There are several serologic tests that demonstrated better sensitivity compared to stool methods.[42–49] However, false negative results occur, especially in acute infections[50] and in immunosuppressed patients[22,33,51,52] and false positive can occur due to other helminthic infection, especially nematodes.[23]

A diagnostic accuracy trial has evaluated five different serological tests for *S.stercoralis*, including the two commercially available Bordier-ELISA and IVD-ELISA.[23] The two latter tests showed a high sensitivity andspecificity: 91.2% and 99.1% for IVD-ELISA, 89.5% and 98.3% for Bordier ELISA.

Recommendation

Screening should be performed with a highly sensitive serological test. If not available, improved faecal techniques could also be used (Baerman or APC).

Grading of evidence: Ia

Grading of recommendations: B

Recommendation

In immunosuppressed patients, a combination of serological and parasitological methods (see above) is mandatory, and screening should be performed before the immunosuppression if possible; first to avoid the risk of severe disease and second

because serology is less sensitive once immunosuppression has already been established.

Grading of evidence: III

Grading of recommendations: D

COHEMI recommendations for screening are resumed in figure 1.

(iii) How to treat?

A recent Cochrane systematic review has reported a higher cure rate of strongyloidiasis with ivermectin compared with albendazole and a better tolerance. Similar cure rates were observed when ivermectin was compared with thiabendazole but more adverse events were reported with the second drug[53].

Most trials were relatively small, with less than 100 patients per arm. All trials but one exclusively relied on faecal diagnostic methods for the assessment of cure.

The main findings of the trials are summarized in Table 2 (that includes also trials not considered in the Cochrane review). The number needed to treat (NNT) was also calculated for each trial.

Albendazole versus placebo. A double blind, placebo controlled trial evaluated the efficacy of albendazole for several intestinal helminths, including *S.stercoralis* at the dose of 400 mg daily for three consecutive days, and showing a cure rate of 48%.[54]

Albendazole at high dosage. A randomized controlled trial comparing two different, high dosage schedules of albendazole, showed an efficacy of 87.9% for albendazole (800 mg twice-daily three days) and 89.5% for albendazole (800 mg twice-daily five days) no significant difference).[55]

Albendazole versus ivermectin. Six RCT were carried out from 1994 to 2011, on ivermectin single standard dose for one or two days, versus albendazole at different dose schedules, including high dosage. All invariably showed a superiority of ivermectin, with cure rates ranging from 83-100% for the latter, and from 38-79% for albendazole.[56–60]

Albendazole versus thiabendazole. We retrieved a single RCT[61] reporting a similar high cure rate for albendazole at high dose (800 mg daily for 5 consecutive days, with cure rate 95%) and thiabendazole (1g twice daily for 5 days, with cure rate 100%). The sample size of this study was particularly small, with 35 patients enrolled overall and a short duration of follow up (21 days).

Thiabendazole versus ivermectin. Three RCT compared the two drugs,[62–64] all demonstrating equivalent efficacy and a much higher incidence of untoward effects for thiabendazole.

Recommendations.

Chronic (uncomplicated) strongyloidiasis should be treated with ivermectin.

Grading of evidence: Ia

Grading of recommendations: A

At the moment, the recommended dosage is a stat dose of 200 µg/kg (as reported in the patient information leaflet), although some authors suggest that multiple doses might increase the efficacy.[65] The World Health Organization (WHO) model drug formulary[66] gives both options: one day versus two consecutive days, single dose. Two trials compared the two different regimens of ivermectin, the first one published in 1994[62] and with small numbers reported a cure rate of 100% with both schemes, while the second and more recent one,[60] reported a slightly higher cure rate (not statistically significant) for the single dose (97% versus 93%). A multicentre RCT is currently

underway (including serology for assessment of cure), comparing single to multiple doses of ivermectin.[67].

Empiric treatment.

In case adequate laboratories facilities are not available, and the infection cannot be excluded, empiric treatment might be worth, in consideration of the good tolerability of the drug and the potential harm caused by a missed diagnosis.[65] This is particularly advised for patients who are candidate to be immunosuppressed, such as, but not limited to, transplant recipients.[68]

Recommendation. **Empiric treatment of patients at risk of immunosuppression, if past exposure cannot be excluded, is indicated without testing in case of lack of adequate diagnostic facilities (see the section "How to screen").**

Grading of evidence: IV

Grading of recommendations: D

Follow up after treatment

Evidence summary

A post-treatment evaluation with parasitological methods does not reliably exclude the infection, as the sensitivity of these methods is low. Several studies have reported that the serologic titer usually tends to decrease after treatment,[48,64,69–71] but uniform criteria to define cure have not been established.[22,42] Recently, it has been shown that, for all of the five tests analyzed by a diagnostic study (three ELISA tests, one LIPS and one IFAT), the OD/luminescence/titre consistently showed a diminishing trend with time, tending to negativization, for the cases treated successfully, although the time required may be as long as 12 months or more.[24] Failure to achieve a significant reduction in titer or OD (to 50% or less of the OD prior to treatment, or at least two IFAT dilutions)

should be considered as a potential treatment failure, even if faecal-based tests are negative.

Recommendations. **Post treatment follow up should be performed with the most sensitive technique available. Serology should be done at baseline and repeated after 6 and 12 months after treatment to monitor the decrease in OD/titer or negativization.**

Grading of evidence: IIb

Grading of evidence: C

DISCUSSION

The rationale for the implementation of a screening programme should be based on the classical 10 principles of Wilson and Jungner[72]. There are several reasons that justify the screening in asymptomatic people.

In the first place, an early detection of the infection in individuals at risk, before they develop any clinical complication, is in itself a sufficient argument to propose a screening. Moreover, in immunosuppressed patients, the screening should be mandatory. Secondly, there is a drug, ivermectin, which is now the universally accepted treatment with a high efficacy rate and a low rate of adverse effects. Thirdly, the screening is based on a simple and widely accessible technology, including commercially available tests which are highly sensitive. The screening could be implemented as part of a screening program for migrants, although further cost-effectiveness studies are required to better evaluate this strategy from a public health point of view.

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720 Table 1. systematic reviews finally included

Title	Author	Year	Topic on strongyloides	Reference
Imported strongyloidiasis: epidemiology, presentations, and treatment	Buonfrate D	2012	Prevalence	[26]
Prevalence of strongyloidiasis in Latin America: a systematic review of the literature	Buonfrate D	2015	Prevalence	[7]
Strongyloides stercoralis: Global Distribution and Risk Factors.	Schar	2013	Prevalence	[5]
The laboratory diagnosis and follow up of strongyloidiasis: a systematic review	Requena-Méndez, A	2013	Diagnosis	[22]
Severe strongyloidiasis: a systematic review of case reports	Buonfrate, D	2013	Clinical presentations	[10]
Ivermectin versus albendazole or thiabendazole for Strongyloides stercoralis infection.	Henriquez-Camacho	2016	Treatment	[53]

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Table 2. **Summary of published trials of strongyloidiasis treatment**

Author	Drug(s), dose	Diagnostic methods	Cured (%)	NTT	p-value	Ref
Pene	Placebo	Harada-Mori	0/31(0%)		NS	[54]
	Albendazole 400 mg/d x 3 d		12/25 (48%)	2.08		
Singthong	Albendazole 800 mg bid for 3 d repeated after 1 w	Agar Plate Culture (APC)	51/57 (87.9%)	64.8	NS	[55]
	Albendazole 800 mg bid for 5 d repeated after 1 w		51/58 (89.5%)			
Datry	Albendazole 400 mg/d x 3 d	Fecal smear, Kato, FECT / Baermann	9/24 (38%)		<0.01	[56]
	Ivermectin 150-200 µg/kg single dose		24/29 (83%)	2.2		
Marti	Albendazole 400 mg/d x 3 d	Baermann method / Kato-Katz	67/149 (45%)		<0.01	[57]
	Ivermectin 200 µg/kg single dose		126/152 (83%)	2.6		
Toma	Albendazole 800 mg bid for 3 d	Harada-Mori APC	65/84 (77.4%)	1.35(iv vs pyr) 5.1 (iv vs alb) ---	<0.01	[58]
	Ivermectin 6 mg single dose		65/67 (97.0%)			
	Pyrvinium pamoate 5 mg/kg for 3 d		14/60 (23.3%)			
Nontasut	Albendazole 400 mg bid for 5 d	Kato-Katz culture, APC	26/33 (78.8%)	5	<0.01	[59]
	Ivermectin 200 µg/kg single dose		77/78 (98-7%)			
Suputtamongkol	Albendazole 800 mg/d x 7 d	FECT	8/21 (38.1%)	2.625	0.029	[73]
	Ivermectin 200 µg/kg single dose		16/21 (76.2%)			
Suputtamongkol	Ivermectin 200 µg/kg single dose	Fecal smear, FECT, APC	30/31 (96.8%)	3	NS	[60]
	Ivermectin 200 µg/kg single dose for 2 d		27/29 (93.1%)	3.6		
	Albendazole 800 mg/d x 7 d		19/30 (63.3%)	---	<0.01	
	Albendazole 400 mg bid for 5 d	Fecal smear, Harada-Mori, larva count (Stool and Sasa method)	22/23 (95%)	23		
	Thiabendazole 1 g bid for 5 d		12/12 (100%)			
Gann	Ivermectin 200 µg/kg single dose	Baermann	16/16 (100%)	19	NS	[62]
	Ivermectin 200 µg/kg single dose for 2 d		18/18 (100%)	19		
	Thiabendazole 25 mg/kg bid for 3 d		18/19 (94.7%)	---		
Adenusi	Ivermectin 200 µg/kg single dose	Baermann	95/113 (84.1%)	18.4	NS	[63]
	Thiabendazole 25 mg/kg bid for 3 d		81/103 (78.6%)			
Bisoffi	Ivermectin 200 µg/kg single dose	APC, serology (IFAT)	32/47 (68.1%)		NS	[29]
	Thiabendazole 25 mg/kg bid for 3 d		31/45 (68.9%)	124.411		

FIGURE LEGENDS

Figure 1. Algorithm diagnosis of screening

* Serology is preferable but if not available, improved faecal techniques could also be used (Baerman or APC).

** When serology or more sensitive stool techniques (Baermann or stool culture) is not available, consider empiric treatment with ivermectin

Con formato: Fuente: Calibri, 11 pto, Sin Negrita