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Review Article

REQUENA-MÉNDEZ AND OTHERS

SCREENING OF STRONGYLOIDIASIS

Evidence-Based Guidelines for Screening and Management of Strongyloidiasis in Non-Endemic Countries

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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 assess 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. First, more than half of infected subjects are asymptomatic or have mild, not specific complaints,⁶ and eosinophilia is often the only finding.⁴ Therefore, they are usually unaware that they might harbor an infection.⁷ Second, *Strongyloides 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} Third, 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, such as solid organ transplantation,¹⁴ since it has been recognized 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 1 year in highly endemic area, expatriates 1) undertaking long trips (more than 1 year) to endemic countries and 2) with exposure to rural areas.
2. Individuals with intermediate to low risk of exposure to *S. stercoralis*: short-term (less than 1 year) travelers to highly endemic areas; elderly patients living in countries where transmission was occurring in the past, which include Northern Italy²⁰ and the Spanish Region of Valencia.²¹
3. Immunosuppressed: patients in chronic treatment with corticosteroids, chemotherapy, immunosuppressant and immunomodulator agents, transplant recipients, patients with acquired immune deficiency syndrome or HTLV-1 infection or any immunosuppression condition.
4. Candidates for immunosuppression: candidates for immunosuppressant therapies (see above), candidates for solid or bone-marrow transplant. Patients with well-controlled human immunodeficiency virus infection should be managed like non-immunosuppressed individuals.
5. Disseminated strongyloidiasis: severe infection with presence of parasites outside the classical life cycle (i.e., 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.

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 three clinical questions:

1. Who should be screened?

2. How to screen strongyloidiasis?
3. 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., European Centre for Disease Prevention and Control, World Health Organization [WHO]) databases.

Process overview.

In creating the guidelines, the panel applied the same principles as the Agency for Healthcare Research and Quality.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, 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: SR 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 nonexperimental 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.

RESULTS

Six SRs have been finally included in Table 1.

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 SR about imported strongyloidiasis, prevalence ranged from 0.4 to 46%, which varied depending on the diagnostic technique used and the targeted population (migrant and/or refugees).²⁶ Another SR suggests that *S. stercoralis* affects between 10% and 40% of the population in most tropical and subtropical countries⁵; 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 southeast Asia.⁵

Second, we should differentiate between 1) patients with high risk of exposure to *S. stercoralis* and 2) 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 harboring the infection. Most infected subjects will never incur in the complicated form throughout their life,⁸ whereas 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, 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 with 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-step screening strategy (blood count and serological test if eosinophilia is present) is not recommended considering 1) the need of two accesses of the patient to the laboratory and 2) 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 for immunosuppression (see “Definitions”).

People exposed to immunosuppressant conditions should be particularly targeted due to the increased risk of developing severe disease that has a high mortality rate.^{10,36} A study that 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; 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 preemptively in case an appropriate test (stool culture or serology) is not available.¹⁰

Recommendations.

“Immunosuppressed patients and candidates for 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 preemptively provided.”

Grading of evidence: Ia

Grading of recommendations: B

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 three 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 fecal methods.²² However, the sensitivity of any fecal-based reference standard may be suboptimal, 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 with stool methods.^{42–49} However, false-negative results occur, especially in acute infections⁵⁰ and in immunosuppressed patients^{22,33,51,52} and false-positive results can occur because of 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 (enzyme-linked immunosorbent assay) and IVD-ELISA.²³ The two latter tests showed a high sensitivity and specificity: 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 fecal techniques could also be used (Baermann or agar plate culture).”

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.

How to treat?

A recent Cochrane SR 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 fecal 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 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 3 consecutive days, and showing a cure rate of 48%.⁵⁴

Albendazole at high dosage.

An RCT comparing two different, high dosage schedules of albendazole showed an efficacy of 87.9% for albendazole (800 mg twice daily for 3 days) and 89.5% for albendazole (800 mg twice daily for 5 days) with no significant difference.⁵⁵

Albendazole versus ivermectin.

Six RCTs were carried out from 1994 to 2011, on ivermectin single standard dose for 1 or 2 days, versus albendazole at different dose schedules, including high dosage. All invariably showed a superiority of ivermectin, with cure rates ranging from 83% to 100% for the latter, and from 38% to 79% for albendazole.^{56–60}

Albendazole versus thiabendazole.

We retrieved a single RCT⁶¹ reporting a similar high cure rate for albendazole at high dose (800 mg daily for 5 consecutive days, with cure rate 95%) and thiabendazole (1 g 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 RCTs 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 WHO model drug formulary⁶⁶ gives both options: 1 day versus 2 consecutive days, single dose. Two trials compared the two different regimens of ivermectin, the first one published in 1994⁶² and with small numbers reported a cure rate of 100% with both schemes, whereas the second and more recent one⁶⁰ reported a slightly higher cure rate (not statistically significant) for the single dose (97% versus 93%). A multicenter RCT is currently underway (including serology for assessment of cure), comparing single to multiple doses of ivermectin.⁶⁷

Empiric treatment.

In case adequate laboratory 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 posttreatment 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/titer 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 fecal-based tests are negative.

Recommendations.

“Posttreatment 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

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. Second, there is a drug, ivermectin, which is now the universally accepted treatment with a high efficacy rate and a low rate of adverse effects. Third, the screening is based on a simple and widely accessible technology, including commercially available tests that 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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FIGURE 1. Algorithm diagnosis of screening. * When serology or more sensitive stool techniques (Baermann or stool culture) are not available, consider empiric treatment with ivermectin. This figure appears in color at www.ajtmh.org.

TABLE 1

Systematic reviews finally included

Title	Author	Year	Topic on <i>Strongyloides</i>	Reference
Imported strongyloidiasis: epidemiology, presentations, and treatment	Buonfrate and others	2012	Prevalence	²⁶
Prevalence of strongyloidiasis in Latin America: a systematic review of the literature	Buonfrate and others	2015	Prevalence	⁷
<i>Strongyloides stercoralis</i> : global distribution and risk factors.	Schär and others	2013	Prevalence	⁵
The laboratory diagnosis and follow-up of strongyloidiasis: a systematic review	Requena-Méndez and others	2013	Diagnosis	²²
Severe strongyloidiasis: a systematic review of case reports	Buonfrate and others	2013	Clinical presentations	¹⁰
Ivermectin vs. albendazole or thiabendazole for <i>S. stercoralis</i> infection	Henriquez-Camacho and others	2016	Treatment	⁵³

TABLE 2

Summary of published trials of strongyloidiasis treatment

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

Figure 1

