

***Strongyloides stercoralis*, the hidden worm. Epidemiological and clinical characteristics of 70 cases diagnosed in the North Metropolitan Area of Barcelona, Spain, 2003–2012**

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Background: The nematode *Strongyloides stercoralis* has a very particular autoinfection life-cycle which leads to chronic infections remaining undetected for decades. However, hyperinfection can occur in patients receiving immunotherapy resulting in high mortality rates. The main objective of this study was to assess the results of a 10-year multicenter surveillance program performed in an area with dense immigration in Barcelona, Spain.

Methods: From January 2003 to December 2012, all individuals with *Strongyloides stercoralis* infection attending the four centers with diagnostic capability in the North Metropolitan area of Barcelona were recorded.

Results: The annual detection rate was 0.2 new diagnosed cases x10 000 inhabitants/year and 1 case x10 000 immigrants/year. Many patients were immigrants (63; 90.0%), asymptomatic (45; 64.3%) and with a high eosinophil count (63; 90.0%). Immunosuppression was present in 11 (15.7%) patients, among whom two (2.8%) cases of disseminated hyperinfection were recorded. Ivermectin was prescribed in 45 (76.3%) and albendazole in 14 (23.7%). Following treatment seven patients (11.9%) receiving albendazole presented relapse, that is, albendazole failed to clear the parasite in 50% of these drug-treated patients ($p < 0.001$).

Conclusions: During the study period, 90% of the cases of *Strongyloides stercoralis* diagnosed could be considered as imported by immigrants, most being asymptomatic and with eosinophilia. The infection is probably largely underestimated and population-based studies are needed to determine its true prevalence. Meanwhile, diagnosis must be based on active investigation of the helminth (serology and feces culture), especially in immunocompromised patients. The implementation of pre-immunosuppression protocols with the aim of identifying *Strongyloides stercoralis* is encouraged with empirical treatment with ivermectin being recommended in sites without diagnostic facilities.

Keywords: *Strongyloides stercoralis*, Intestinal parasites, Immigrants, Eosinophilia, Immune suppression, Ivermectin

Introduction

Strongyloides stercoralis is an intestinal nematode parasite found in many rural flooded environments. While present in some restricted areas of the European Union (EU) such as northern Italy, rural Romania or southeastern Spain,¹ the helminth is frequently recorded in extensive endemic areas of tropical and sub-

tropical regions and affects anywhere from 30–100 million people worldwide.^{2,3} Thus, the steady immigrant influx to the EU has inevitably increased the number of infected carriers.⁴

The diagnosis of *S. stercoralis* is often delayed due to three major concurrent factors:⁵ the presence of subclinical or poorly-symptomatic cases, the usually low parasite load and irregular larvae output and the lack of a gold standard diagnostic test.

This situation is compounded by the fact that *S. stercoralis* females reproducing parthenogenetically can undergo autoinfection leading to lifelong, chronic, infections. In a complicated, unique and fascinating life-cycle completed in human hosts, repeated generations of filariform and rhabditiform larvae successively develop within the small intestinal wall without the need for any vector or the soil maturation period usually required by other worms.⁶

Altogether, these facts lead to a scenario characterized by a large number of underestimated infections. Few European studies have provided data on the prevalence, diagnosis and treatment of infections by *S. stercoralis*. Unfortunately, there are far more records available on the well-known hyperinfection form, an often lethal parasite dissemination that may occur in immunocompromised patients. Since many current treatments include anti-CD monoclonal or anti-TNF antibodies the relevance of *S. stercoralis* as a public health challenge increases every year. Furthermore, Spain has a very particular situation since the presence of subclinical infections among recent immigrants could be compounded by the existence of autochthonous cases.⁷

The main objective of this study was to describe the cases of *S. stercoralis* infection reported over a 10-year period in the North Metropolitan area of Barcelona (Catalonia, Spain).

Materials and methods

From January 2003 to December 2012, sentinel clinicians from the North Metropolitan Working Group on Imported Diseases voluntarily recorded all consecutive individuals diagnosed with *S. stercoralis* infection in the four centers with diagnostic capability attending the North Metropolitan area of Barcelona. These centers were one International Health Unit (Unitat de Salut Internacional Metropolitana Nord; Santa Coloma de Gramenet), two second-level hospitals (Hospital Municipal de Badalona; Badalona and Hospital de l'Esperit Sant; Santa Coloma de Gramenet) and a tertiary care hospital (Hospital Universitari Germans Trias i Pujol; Badalona), serving a population of 406 000 inhabitants, 61 300 (15.1%) of whom are immigrants from endemic countries.⁸ These centers belong to the Catalan Health Service and, therefore, the medical visits are easily accessible and free of charge. Most patients were referred by family practitioners while others were derived from the implementation of a screening protocol applied to immunocompromised or pre-immunosuppression patients shared by the participating centers.

Individuals were considered as infected when one of the following diagnostic tests was positive: larvae or adult worms were visualized in the three initial feces smears; one commercial ELISA-based serological test (Strongyloides ELISA kit, Diagnostic Automation Inc, Calabasas, CA, USA) against crude antigens of *S. stercoralis* was positive; filariform larvae were seen in feces culture (by means of a Harada-Mori filter paper strip culture incubated at 37°C); and filariform or rhabditiform larvae were determined in sputum smears. According to the protocol, on a diagnostic suspicion, a feces culture was performed; if negative, a subsequent ELISA serology was requested. In spite of this, 17 individuals were only tested with serology due to the lack of larvae culture facilities in the two district hospitals.

There was a consensus of criteria on the taxonomic identification of larvae in cultures according to caudal pole shape (notched tails), buccal cavity size and structure and localization of the genital primordium. Patients residing outside the Barcelona North Metropolitan area were excluded from the study.

The following variables were assessed and recorded by means of a specific questionnaire: age, sex, immigrant (yes/no), length of residence in the EU (years), biogeographical origin, initial reason for consultation, presence of symptoms attributable to *S. stercoralis* infection, type of disease, diagnostic test used, baseline eosinophil count (cells/ μ L), other concurrent parasitic diagnoses, immunocompromised at diagnosis (yes/no) and treatment.

An individual was considered as an immigrant when born in any endemic *S. stercoralis* country and had migrated to the EU. European-born patients with a history of antecedents of expatriation or trips abroad were considered as imported cases, while those with no record of visiting endemic areas out of Spain were considered as autochthonous cases. The variable length of residence was expressed as the time (years) between the arrival of an immigrant to the EU and diagnosis or, with respect to travelers, from their last trip to endemic countries. Hence, this variable was not evaluated among autochthonous cases. The variable presence of symptoms attributable to *S. stercoralis* infection was categorized in five items (asymptomatic, digestive, dermatologic, neurologic, other).

The eosinophil count was divided into three categories according to the WHO recommendations:⁹ normal count (≤ 500 cells/ μ L), mild eosinophilia (501–1500 cells/ μ L) and hypereosinophilia (≥ 1500 cells/ μ L). An individual was considered as immunocompromised when they had HIV infection with a CD4 count < 500 cells/ μ L and were taking either corticoids > 0.5 mg/kg or another immunomodulatory drug.

The treatment prescribed was ivermectin 200 μ g/kg once in two courses given 15 days apart. From 2003 to June 2006 ivermectin was achieved only after a very arduous process and much paper work, and thus some early patients received albendazole 400 mg bid for 5 days. All patients were followed up 3–6 months after treatment. The persistence of symptoms, eosinophilia or larvae in feces were considered as indicators of parasite survival and were treated again with ivermectin.

The relative frequency of the variables and their association with socio-demographic (age, sex, immigrant, length of residence and biogeographical origin) and clinical (reason for consultation, symptoms attributable, type of disease, diagnostic test and immunosuppression) characteristics were analyzed using SPSS 12.0 software (SPSS Inc, Chicago, IL, USA). The χ^2 test with Fisher correction was applied to compare the outcomes of the treatments prescribed. Since the variable eosinophil count did not approach a normal distribution in either immunocompetent or in immunocompromised patients, the Mann–Whitney U test was used for comparison. An ANOVA tendency test was performed comparing the length of residence and the median annual eosinophil count. Statistical significance was considered with a p value of $< 5\%$.

Results

During the study period, 75 individuals were diagnosed with *S. stercoralis* infection. Five were excluded from the study because they lived outside the study area. Seventy patients began the study but 11 (16%) dropped out before receiving treatment, representing a detection rate of 0.2 newly diagnosed cases x10 000 inhabitants/year and 1 case x10 000 immigrants/year. The median age of the patients was 35.7 (SD = 5.9) years, 41 were male and most were from Southern America. The socio-demographic and clinical characteristics of the study participants are shown in Tables 1 and 2 and the detection capabilities of the tests are shown in Table 3. Two

Table 1. Socio-demographic and clinical characteristics of *Strongyloides stercoralis* cases (n = 70)

Variable	n (%)
Age, years; mean (SD)	35.9 (5.9)
Sex	
Male	41 (59)
Female	29 (41)
Immigrant	
Yes	63 (90)
No	7 (10)
Traveller	5 (7)
Autochthonous	2 (3)
Length of residence, n = 52; median (range)	4 (5m–31y)
Biogeographical origin	
SubSaharan Africa	18 (26)
Indostan + SE Asia	9 (13)
Maghreb + Nearest Orient	0
South America + Caribbean	41 (59)
Spanish autochthonous	2 (3)
Initial consultation reason	
High eosinophil count	32 (46)
Digestive symptoms	9 (13)
Dermatologic symptoms	8 (11)
Neurologic symptoms	1 (1)
Screening	5 (7)
Other	14 (20)
Symptoms attributable to <i>S. stercoralis</i>	
Infection	
Presence	25 (36)
Absence	45 (64)
Type of disease	
Chronic infection	68 (97)
Disseminated hyperinfection	2 (3)
Diagnostic test	
ELISA serology	33 (47)
Feces larvae culture	33 (47)
Sputum smear	1 (1)
Stool smears ^a	3 (4)
Eosinophil count	
Median (range)	1340 (20–11190)
<500	7 (10)
500–1500	44 (63)
>1500	19 (27)
Immunosuppressed	
Yes ^b	11 (16)
No	59 (84)

^aBy microscopic visualization of rhabditiform larvae (3) in stool;^bSix patients HIV-infected (8.6%; 55% of overall immunosuppressed)

cases of hyperinfection (HIV-infected patients with CD4 counts of 20 and 110 cells/ μ L respectively) were recorded; both patients remained alive.

Eosinophilia was detected in 63 (90%) patients. The median (range) count among immunocompetent patients was 1340

Table 2. Type of digestive, dermatologic and neurologic symptoms attributable to *S. stercoralis* infection, n = 25

Variable	n (%)
Digestive symptoms	16 (64)
Upper digestive tract	10
Episodic diarrhoea	5
Malabsorption	1
Two symptoms	3
Three symptoms	1
Dermatologic symptoms	8 (32)
Episodic urticaria	5
Larva currens	5
Neurologic symptoms	1 (4)
Transverse neuritis	1

(110–11 190) cells/ μ L, being 950 cells/ μ L (20–3000) among immunocompromised patients ($p = 0.12$). There was no significant decrease in the eosinophil count in comparison with the length of residence (ANOVA p value = 0.88 in the tendency test) as shown in Figures 1 and 2. The simultaneous presence of another parasite was determined in 29 (41%) patients, with *Trypanosoma cruzi* accounting for 11 cases (15.7% of all cases; 37.9% of the 29 polyparasitic cases) as shown in Table 4.

Ivermectin was prescribed in 45 (76%) of the 59 patients treated and albendazole in 14 (24%), with no side-effects being recorded. After treatment, seven (12%) albendazole-treated patients presented relapse ($p < 0.001$), three by persistence of larvae in feces and four by maintained high eosinophil count. No case of relapse was recorded among the ivermectin treated group.

Discussion

Although not a population-based study, these data may provide an approach to the epidemiologic situation of *S. stercoralis*, the worm often described as 'there but not seen'.¹⁰ During the study period, up to 26 cases of hyperinfection from the EU countries were recorded in the PubMed database (half being from the UK, Spain and France).¹¹ This number is comparable with the number of articles published in relation to chronic infection and reflects its growing relevance, particularly among immunocompromised patients.

To our knowledge, no European-wide population-based study has been reported. However, a number of seroepidemiologic papers have been reported, usually describing well-defined communities of refugees, immigrants or farmworkers living in endemic autochthonous areas.¹² The situation is compounded by the lack of a gold standard diagnostic test.¹³ Larvae stool cultures using Harada-Mori liquid media or agar plates have recorded sensitivities of around 40–50%, clearly superior to the 27.7% found in our study, a difference which may indicate the need for improvement in the standardization procedures of what are, in fact, home-made cultures, or even the use of the Baermann method instead. Serology would be much simpler and accessible, but it is also far from ideal. Its usual constraints include possible cross-reaction with other anti-helminthic antibodies (thus being scarcely

Table 3. Detection capability of *Strongyloides stercoralis* and other geohelminths using feces larvae culture or ELISA serology

Geohelminth	Feces larvae culture Positive/Performed	ELISA serology after a negative feces culture Positive/Performed	Direct ELISA serology Positive/Performed	Total detection rate Positive/Performed
<i>S. stercoralis</i>	33/190 (17.7%)	23/54 (43%) ^a	10/17 (59%)	66/261 (26.7%)
<i>Ancylostoma duodenale</i> or <i>Necator americanus</i>	19/190 (10.0%)	NA	NA	19/190 (10.0%)
Any geohelminth	52/190 (27.7%)	23/54 (43%) ^a	10/17 (59%)	85/261 (32.7%)

^a42 patients were lost after the negative feces culture
NA: Not available

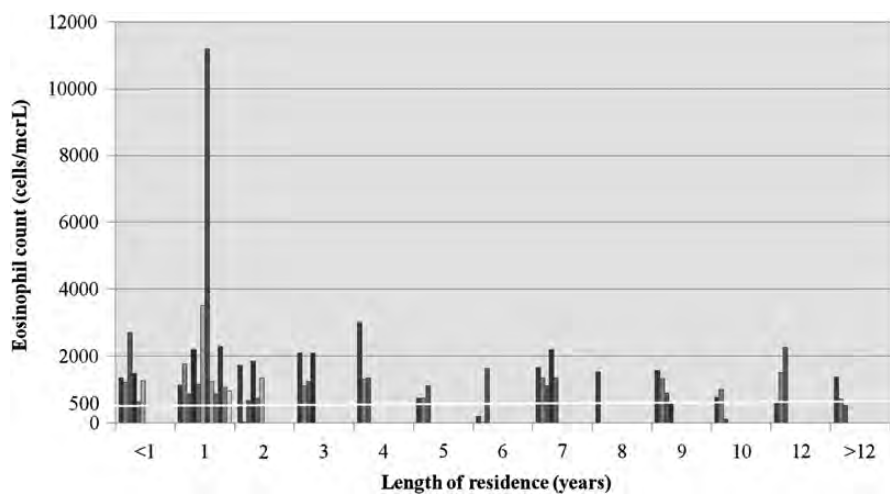


Figure 1. Length of residence in the EU and eosinophil count at the time of diagnosis of *Strongyloides stercoralis* infection

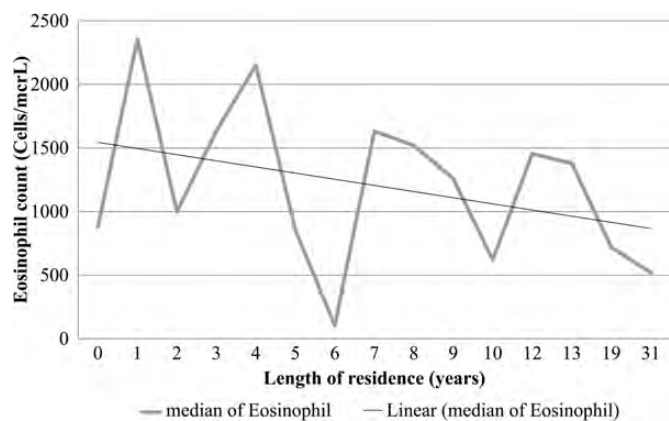


Figure 2. Median of eosinophil count (cells/mcL)/length of residence (years) in the EU at the time of *Strongyloides stercoralis* infection diagnosis (n = 52). ANOVA p-value = 0.88

useful among recently-arrived immigrants) and the common false negative results among immunocompromised patients.¹⁴ Furthermore, crude antigens-based ELISA tests require a constant supply of the very similar *S. ratti* filariform larvae from a

cycle maintained in rats, thereby making the test impractical with limited availability.¹⁵ New real-time PCR¹⁶ or luciferase immunoprecipitation assay (LIPS)¹⁷ based tests may play a prominent role in the coming years.¹⁸

Considering all the data available, this infection is clearly underestimated.¹⁹ Even in an area with an ongoing surveillance program within a free-of-charge Public Health System such as that of the North Metropolitan area of Barcelona, the median time from the arrival in Spain and diagnosis was 4 years with a maximum of 31 years.

Only a small number of cases were considered autochthonous or were imported by travelers.²⁰ Immigrants accounted for up to 90% of the diagnoses and, therefore, surveillance systems and diagnostic programs should be focused on that population.

Most of the patients remained asymptomatic and were generally referred for the presence of unexplained eosinophilia.^{21,22} After a clinical examination, only 25 (36%) reported symptoms attributable to *S. stercoralis* infection, otherwise usually being nonspecific with the exception of the five patients reporting *Larva currens*. Clinical examination and interrogation does not, therefore, seem to be a key aspect of the diagnostic process in *S. stercoralis* infection.²³

The eosinophil count was abnormally high in 90% of cases. These data do not concur with the few screening-based studies

Table 4. Other parasites identified in 70 patients infected with *Strongyloides stercoralis*

Parasite	n
Intestinal protozoa	
<i>Entamoeba histolytica</i>	1
<i>Entamoeba hartmanni</i>	1
<i>Dientamoeba fragilis</i>	2
<i>Blastocystis hominis</i>	3
<i>Giardia lamblia</i>	1
Tissue protozoa	
<i>Trypanosoma cruzi</i>	11
Intestinal helminths	
<i>Ascaris lumbricoides</i>	3
<i>Hymenolepis nana</i>	1
Tissue helminths	
<i>Mansonella perstans</i>	2
<i>Schistosoma haematobium</i>	2
<i>Schistosoma mansoni</i>	1
<i>Loa loa</i>	1
Total individuals with some additional parasite	29 (41%)
Two parasites detected	4 (6%)

described among immigrants in which the medians of cell counts and the proportion of eosinophils reported are usually lower.²⁴ This result may be overestimated since the study includes many cases referred by the Primary Care Centers for the presence of eosinophilia. Consequently, the detection rate of 0.2 cases x 10 000 inhabitants/year found can be considered as, at best, indicative and is probably underestimated considering that not all *S. stercoralis* infections show eosinophilia. Despite such a low rate, it may be reasonable to search for the presence of *S. stercoralis* in immigrants with unexplained eosinophilia, accordingly to the recommendations of the Consensus of The British Infection Society in 2010.²⁵

Despite a lack of statistical differences regarding eosinophil cell counts between immunocompetent and immunocompromised patients, clinicians should note that eosinophil cell counts in the latter are generally lower than those displayed by the former owing to the profound impairment in immune response which may involve eosinophils.^{26,27}

Polyparasitism is expected in a study with a large number of relatively newly-arrived immigrants similar to that reported in other studies.²⁸ The frequency of Chagas co-infection may be explained by the rural origin of the large Bolivian community established within the study area. Indeed, the main cause of eosinophilia in the whole of the Chagas-infected immigrant population in the North Metropolitan area was the presence of *S. stercoralis*. To date, this high prevalence of *S. stercoralis*–*Trypanosoma cruzi* co-infection lacks an explanation beyond the epidemiologic relationship. In a recent communication from Barcelona, similar results were described (44% co-infection), with the authors recommending the screening of *S. stercoralis* in Chagas-infected Latin American immigrants.²⁹

The proportion of immunocompromised patients found is similar to that described in other studies.³⁰ The association

between HIV and HTLV-1 viruses and *S. stercoralis* is common, through a disruption in Th2 immunity.³¹ Consequently, all new individuals from endemic areas and diagnosed with HIV or in a pre-immunosuppression program³² (especially chemotherapy, immunotherapy and transplantation programs) should be screened for *S. stercoralis*, by both feces larvae culture and serology if an acceptable immune function is maintained. If no diagnostic facilities are available, empirical treatment with ivermectin should be given regardless of the eosinophil counts.³³ Every effort should be made to improve the implementation of screening protocols.

Ivermectin must be considered as the first choice drug in the treatment of *S. stercoralis*, as it is far more effective than albendazole.³⁴ Two doses of ivermectin given 14 days apart should be considered as a reasonable treatment schedule while awaiting new research.^{35,36} In the early stages of the study, however, some patients received albendazole due to the lack of availability of ivermectin. Rapid and simpler procedures are recommended in order to treat disseminated cases.

In conclusion, strongyloidiasis may be an underestimated major global health challenge in a study area that may reflect many parallel situations in densely immigrant-populated districts of the EU. The study has limitations and could be considered as a starting point for designing a survey on the prevalence of *S. stercoralis* in Spain or the EU carried out with standard diagnostic methods. Meanwhile, active surveillance of *S. stercoralis* should be emphasized among newly arrived immigrants, especially those displaying eosinophilia. Every immigrant, former traveler or even autochthonous subjects from endemic EU areas included in pre-immunosuppression programs should be screened for the presence of *S. stercoralis*. In centers without diagnostic facilities, empiric treatment with ivermectin is strongly recommended.

Authors' contributions: LV, SR conceived the study and methodology. LV wrote the first draft. LV, SR, GFR, OMC, ALB and XR participated in the surveillance program, reported data, revised the study design and interpreted the outcomes. LB performed the statistical analyses. Every author has carefully reviewed the manuscript and takes full responsibility for it.

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