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Strongyloides Stercoralis Infection: to what Extent can we use Antibody Screening as the Definitive Diagnosis?

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ABSTRACT

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Introduction

Strongyloides stercoralis is an intestinal nematode transmitted by skin penetration of the infective larvae (L3) present in contaminated soil. It infects around 370 millions people worldwide, especially in tropical countries, where poor socio-economic and sanitary conditions combined with a suitable environment contribute to the maintenance of its transmission [1]. However, in spite of being a neglected tropical disease (NTD), human strongyloidiasis is an increasing problem in developed countries, where travelers and immigrants from tropical areas are the most commonly affected individuals [2]. Usually, this parasite develops a chronical and asymptomatic infection and the host can remain infected and undiagnosed for decades, despite the life spam **of** *Strongyloides stercoralis* parthenogenic female be around five years. This occurs because this parasite has an unusual characteristic: the ability of produce an autoinfective cycle [3].

In this way, the parasite can reproduce within the host and produce new generations, leading to a lifelong infection. However, when an alteration in the immune system occurs, the parasite-host balance can be broken and it results in life-threatening conditions such as hyperinfection syndrome and disseminated strongyloidiasis. Factors predisposing to severe strongyloidiasis include corticosteroid therapy, Human T-cell lymphotropic virus type I (HTLV-1) infection and chronic use of alcohol [4-6]. Therefore, an effective diagnosis combined with an adequate treatment are essential for the severe strongyloidiasis prevention. Currently, *S. stercoralis* infection diagnosis is still performed through parasitological methods, by the finding of larvae in feces. The most used technique is Baermann-Moraes, which is based in the positive larval thermo-hydrotropism. However, studies have shown that Agar Plate Culture (APC) is more sensitive, yet it is underused due to the more complex methodology and higher cost [7]. Nonetheless, independent on the technique used, all parasitological methods are limited by the parasite load and larvae output intermittence, which requires the analysis of, at least, three fecal samples collected on alternate days. Besides, other factors also influence in the parasitological diagnosis efficacy, such as the amount, preservation and processing of stool samples and the experience of the microscopist in the identification of larva. Immunological methods represent an alternative for ***S.*** *stercoralis* diagnosis. Few studies have evaluated coproantigen diagnostic tests, which use has been limited by the difficulty in producing monoclonal or polyclonal antibodies to *S. stercoralis* antigens and the low specificity of developed tests [8,9].

Most works have evaluated immunoassays for antibodies detection. Although different biological materials, such as urine [10], saliva [11] and breast milk [12], can be suitable for this purpose, the most common are serum samples. The first articles, to our knowledge, on this matter were published in 1981 by

groups from United States of America (USA) and Australia using *S. stercoralis* **and** *S. ratti* antigen to detect IgG anti-*S. stercoralis* by enzyme-linked immunosorbent assay (ELISA) and indirect immunofluorescent assay (IFA) [13,14]. Since then, several improvements have been made trying to increase the sensitivity and specificity of diagnostic methods based on antibody detection. The sensitivity and specificity of various reported serological tests ranged from 56 to 100% and 29–100%, respectively, depending on the type of assay, antigen, antibody-isotype, cut-off, study population and reference method used [15]. Several techniques, such as the luciferase immunoprecipitation system (LIPS) [16], immunoblotting [17] and fluorescent bead (Luminex) [18] have been studied, but their use is usually restricted to research centers or reference laboratories.

The most commonly used method is still ELISA. As matter of fact, there are three commercial assays available, the Bordier-ELISA (Bordier Affinity Products SA, Switzerland) and IVD-ELISA (Scimedx Corporation, USA) using *Strongyloides ratti* and *S. stercoralis* crude antigens, respectively, and one with a recombinant antigen (NIE-ELISA, NovaLisa; NovaTec Immunodiagnostica, Dietzenbach, Germany). However, two major limitations hamper the use of antibodies detection as a routine technique: false-positive results and the antigen production. False-positive results are common in an indirect diagnosis and can be caused by remaining antibodies after the parasitological cure (immunological memory) or by cross-reactivity with other parasites [19].These problems can be reduced by the use of different antibodies classes and subclasses. Patients with strongyloidiasis have been reported to produce different isotypes of immunoglobulins against the parasite, i.e. immunoglobulin A (IgA), E (IgE), M (IgM), and G (IgG), and the subclasses of IgG antibody (i.e IgG1, IgG2, IgG3 and IgG4).

However, current serological tests detect mainly specific IgG and, to a lesser extent, IgG4 [15]. Some authors have suggested that IgE is a better marker for recent infections [20,21] and that IgG4 provides the highest sensitivity and specificity for *S. stercoralis* diagnosis [18]. Indeed, an increased specificity, of around 13%, was observed when IgG was changed by IgG4 as the secondary antibody in a *Strongyloides*-ELISA test (22). Concerning to the antigen production, the limitation comes from the difficulties in produce either homologous or heterologous antigens, once both depend on infected hosts. Recombinant antigens are a good alternative to substitute crude antigens and overcome those difficulties. Three recombinant antigens to *S. stercoralis* diagnosis are described in the literature: NIE, who is already commercially available as an ELISA test, and has been tested in other techniques, such as Luciferase Immunoprecipitation Systems Assay (NIE-LIPS) [16] and Luminex [18]; Ss-IR, who was used as a diagnostic tool and tested as a vaccine candidate in mice [23-25] and a recent discovered S. stercoralis recombinant protein named as rSs1a, used in an IgG4-ELISA [26]. A study comparing the sensitivity and specificity of Bordier-ELISA and NIE-ELISA found that despite the NIE-ELISA be more specific than the Bordier-ELISA, its low sensitivity limits its use in *S. stercoralis* screening [27]. Furthermore, more studies are needed to evaluate these antigens for *S. stercoralis* diagnosis in different endemic areas, where cross-reactions with other parasites may occur.

Thus, *S. stercoralis* diagnosis still remains a challenge since there is not a gold-standard method. Larvae absence in feces cannot be used as definitive non-infection evidence, pointing out serological methods as an alternative. However, they also have limitations for *S. stercoralis* diagnosis. Despite this, its use is extremely important, especially in patients in risk to develop severe strongyloidiasis. In these cases, a high specific antibodies level can justify the treatment for strongyloidiasis to prevent a life-threatening infection [28]. While there are limited studies on the use of serological follow-up for monitoring seroreversion in patients after treatment, negativization or even the decrease in antibody reactivity are strong indicators of a successful treatment [29]. In our research group, in two different patients with strongyloidiasis, one with Hansen's diseases and under corticosteroid chronic use [5] and one with HTLV-1 [4], it was possible to observe a negativization to IgG-ELISA after a successful treatment. In this way, studies that pursue the improvement of immunoassays to *S. stercoralis* infection diagnosis are extremely needed. Meanwhile, physicians should be aware of the antibody detection usefulness as a diagnostic tool in patients at risk of developing severe strongyloidiasis.

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