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Strongyloides stercoralis in Immunosuppressed Patients

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Abstract

Context: *Strongyloides stercoralis* is a nematode parasite, which is endemic in tropical and subtropical regions. Infection usually remains asymptomatic, but in immunocompromised hosts, hyperinfection syndrome (HS) and disseminated disease (DD) can occur and can be related to a high mortality rate.

Evidence Acquisition: An exhaustive bibliographic research was performed in the main biomedical databases, including PubMed, Scopus, Index Copernicus, DOAJ, EBSCO, Iranmedex, Scielo, and Google Scholar. Articles written in English, Spanish, and Portuguese were considered. Narrative and systematical reviews, case-control studies, observational studies, and remarkable case reports (due to atypical presentation) were included in the revision. Duplicated articles, abstracts only, and grey literature were not considered for revision. A narrative review of the included article was done. The databases were searched to identify review articles, original manuscripts, and case reports about strongyloidiasis in immunocompromised patients. Terms used in the search were the following: *Strongyloides stercoralis*, hyperinfection syndrome, immunosuppressed patients, AIDS, HIV, HTLV-1, transplant recipients, corticosteroid therapy, immunosuppressive drugs, síndrome de hiperinfestación, pacientes inmunocomprometidos, SIDA, VIH, receptors de trasplantes, tratamiento con corticoides, e inmunosupresores.

Results: *S. stercoralis* is an intestinal nematode that can survive in asymptomatic form in its human host for decades after the initial infection. However, this geohelmintic parasite can lead to a disseminated and fulminant hyperinfection syndrome in severely immunocompromised patients, or patients with HIV or HTLV-1 retroviral infections, especially those treated with high doses of corticosteroid therapy.

Conclusions: Clinical features of strongyloidiasis are nonspecific, and a high index of suspicion is necessary for early diagnosis and to improve the poor prognosis of patients with hyperinfection syndrome due to *S. stercoralis*.

Keywords: Strongyloides stercoralis, Nematode Infection Treatment, Epidemiology, Diagnosis, Hosts, Immunocompromised

1. Context

S. stercoralis is an intestinal nematode with a wide spectrum of clinical manifestations in human beings. Clinical syndromes associated with *S. stercoralis* infection include the five following pictures: 1) asymptomatic intestinal infection; 2) acute infection with cutaneous and Loeffler's syndrome; 3) chronic intestinal disease characterized by chronic anemia, peripheral eosinophilia, malabsortion syndrome, and chronic diarrhea; 4) hyperinfection syndrome (HS); and 5) disseminated disease (DD). The last clinical pictures (4 and 5) are strongly associated with immunodepression (1).

Strongyloides stercoralis HS has been described with increasing frequency since 1966 as a result of the wide use of immunosuppressive therapies in organ transplant recipients, cancer, autoimmune diseases, and AIDS.

Clinical presentation and outcomes depend on the interaction between the parasite and the host's immune response, especially the Th-2 cell-mediated immunity. Some clinical conditions associated with defects in cell-mediated immunity can modify an asymptomatic intestinal carriage into a fulminant and frequently fatal disease.

The centers for disease control and prevention (CDC) included extraintestinal strongyloidiasis in the original classification of AIDS-defining opportunistic infections. However, this was later deleted because of the relative infrequency of DD due to *S. stercoralis* in AIDS patients with few cases being reported in the medical literature (2).

2. Evidence Acquisition

An exhaustive bibliographic research was performed in the main biomedical databases, including PubMed, Scopus, Index Copernicus, DOAJ, EBSCO, Iranmedex, Scielo, and Google Scholar. Articles written in English, Spanish, and Portuguese were considered. Narrative and systematical reviews, case-control studies, observational studies and remarkable case reports (due to atypical presentation) were included in the revision. Additional references were obtained from the articles' references. Duplicated articles, abstracts only, and grey literature were not considered for revision. A narrative review of the included

articles was performed. The databases were searched to identify review articles, original manuscripts, and case reports about strongyloidiasis in immunocompromised patients. Terms used in the search were the following: *Strongyloides stercoralis*, hyperinfection syndrome, immunosuppressed patients, AIDS, HIV, HTLV-1, transplant recipients, corticosteroid therapy, immunosuppressive drugs, sindrome de hiperinfestación, pacientes inmunocomprometidos, SIDA, VIH, receptores de trasplantes, tratamiento con corticoides, e inmunosupresores.

3. Results

3.1. Epidemiology of Strongyloides stercoralis Infection

Several parasites are responsible for life-threatening infections in immunocompromised patients. They occur in patients with a profound immunodeficiency affecting the T cell-mediated immunity. Approximately 70 million people worldwide are infected with *S. stercoralis*; the majority of them are living in tropical and subtropical tropical regions and unaware of their condition (3). It is endemic in the tropical and subtropical countries of Southeast Asia, Sub-Saharan Africa, South America, and Eastern Europe. Most infected individuals present with the chronic and asymptomatic form of the parasitic disease (60%) or with minor and unspecific gastrointestinal manifestations (4). However, in the last years the incidence of strongyloidiasis has increased in many developing countries relative to immigration, international travel, and the increasing number of immunocompromised clinical conditions (3, 5).

3.2. The Importance of Knowing the Life Cycle of Strongyloides stercoralis

The unusual life cycle of *S. stercoralis* has important clinical implications. The female worm can generate progeny without copulation with the male worm in a process known as parthenogenesis. The ability of *S. stercoralis* to produce a severe disease is due to the fact that the non-invasive and non-infectious rhabditiform larvae can mature into invasive filariform larvae in the small bowel of humans. This process is called autoinfection, and it eliminates the need for further exposure to exogenous, infective larvae. Consequentially, the infection can persist in the host many years after the host leaves an endemic area. This cycle of autoinfection represents a form of endogenous reinfection that is unique to *S. stercoralis* (6). One of the most important characteristics of the life cycle of *S. stercoralis* within the human body is the ability to transform rhabditiform larvae into invasive filariform larvae in the gut. This distinctive characteristic of *S. stercoralis* gives the nematode the ability to survive and replicate inside the human host (autoinfection cycle) (7).

Free-living and infective *S. stercoralis* filariform larvae penetrate through the skin and initiate the parasitic life cycle with a mode of transmission similar to other geohelmints (8). Female parasites, which are parthenogenetic, mature into adult organisms in the upper small intestine. Egg deposition begins approximately 28 days after the initial infection. The majority of eggs are excreted in the stools; the male parasites do not invade the tissue and also are eliminated with the stools (9). The larvae invade and colonize the small intestinal mucosae (especially the duodenal and the jejunal); there, they develop into the adult forms of the worm. Adult female worms usually relocate to the submucosae, and there they shed their eggs. Fertilized eggs produce the rhabditiform larvae that migrate into the intestinal cavity and are excreted with the feces. Also, the parasitic cycle of *S. stercoralis* includes a cycle of autoinfection that is extremely frequent and significant in immunosuppressed or immunocompromised hosts when considered with the possibility of autoreinfection. This type of autoinfection is characterized by direct, indirect, or exo-autoinfection during which the rhabditiform larvae can circulate to other organs and tissues through the circulatory system and cause the most severe forms of the disease, HS, and DD (5). In disseminated cases, the nematode can affect every organ.

The autoinfection cycle during this hemintiasis explains why the parasitic infection can be perpetuated without further exposure to exogenous infective larvae.

Presentation and evolution of this parasitic infection are determined by the interaction between the host and the helmint. Abnormalities in Th-2 cell-mediated immune response, as well as humoral or mucosal immunity, may facilitate the transformation from rhabditiform to filariform larvae, which is followed by the replication of a large number of parasites and their migration from the small bowel to the lungs or other sites in the gastrointestinal tract (stomach and colon), configuring HS or DD in other organs (1).

3.3. Cutaneous Manifestations of S. stercoralis Infection

Common skin manifestations of strongyloidiasis include a migratory, pruritic, raised, linear rash called "creeping eruption" or "larva currens," and urticarial eruptions that appear to be manifestations of immediate hypersensitivity reactions to the migrating worms (10).

3.4. Intestinal Strongyloidiasis

The presence of *S. stercoralis* in gastroduodenal mucosae can be asymptomatic or associated with some gastrointestinal syndromes, including epigastric pain mimicking a peptic ulcer, chronic or acute watery diarrhea, malabsorption syndrome with weight loss, and, occasionally, gastrointestinal bleeding with chronic anemia and small bowel obstruction. In the pre-highly active antiretroviral therapy (HAART) era, Manatsathit et al. (11) reported an incidence of 4.4% of *S. stercoralis* as the cause of chronic di-

arrhea in AIDS patients in Thailand. More recently, and in the post-HAART era, Silva et al. (12) detected an incidence of 12% *S. stercoralis* in a series that included 100 HIV/AIDS patients. In Peru, Garcia et al. (13) detected *S. stercoralis* in 7% of the patients with AIDS who also had diarrhea for two or more weeks. *S. stercoralis* should be included in the differential diagnosis of chronic diarrhea in immunocompromised patients. Gastric and intestinal findings include an intense inflammatory infiltration and diffuse ulcerative mucosae lesions. The most intense infiltration and edema, and a large number of ulcers, predominate in the duodenum and jejuno-ileum, where it is possible to see numerous eggs and larvae in the blood vessels and the duodenal glands.

3.5. Pulmonary Strongyloidiasis

Lung involvement in patients with strongyloidiasis can be seen either during the lymphohematic migration of the parasite in its life cycle (passing through the right side of the heart and penetrating the capillary walls and moving into the alveoli) or in the context of HS or DD. The diagnosis of pulmonary strongylodiasis is often delayed due to nonspecific clinical signs, symptoms, and radiological findings (14). Clinical manifestations range from a dry cough, bronchospasm (Loeffler's syndrome), chest pain, dyspnea, and hemoptysis to the most severe form of adult respiratory distress syndrome (ARDS) (15). ARDS is most common in patients with chronic lung diseases and in subjects with altered cellular immunity response or who have undergone prolonged corticosteroid therapy. Furthermore, pulmonary compromise with *S. stercoralis* may be evidence of underlying gram-negative bacteria sepsis (due to bacterial translocation through the bowel wall or the adherence of bacteria to the external surface of the parasite) or bacterial or fungal pneumonia in patients with an occult parasite infection.

The concomitant presence of filariform larvae in stool smears in patients with pulmonary symptoms should alert clinicians to analyze sputum samples for the detection of *Strongyloides stercoralis* larvae. In patients with chronic underlying pulmonary disease, the clinical manifestations of pulmonary strongyloidiasis are usually interpreted as an exacerbation of a pre-existing condition. Some patients are treated with high doses of corticosteroids and can potentially develop HS (16). Also, screening for *S. stercoralis* infection may be performed in patients with severe bronchial asthma or chronic obstructive pulmonary disease who require frequent, recurrent courses of corticosteroid therapy. A combination of chronic lung disease with unexplained lung infiltrates, with or without gastrointestinal symptoms, may be suggestive of pulmonary strongyloidiasis (6, 17). Peripheral blood eosinophilia in association with pneumonia or bronchospasm is also suggestive of strongyloidiasis in patients who have lived in or traveled to endemic areas. Eosinophilia of more than 5% has been reported in 65% to 90% of these patients (14, 16, 18, 19).

Radiological findings include alveolar, unilateral, or bilateral infiltrates, lobar infiltrates, pleural effusion, and infiltrates that progress to ARDS. Although normal chest radiographs have been reported in patients with pulmonary strongyloidiasis, most patients have abnormal findings. During the initial phases of the infection, the chest radiograph and CT-scan can show fine miliary nodules or diffuse reticular infiltrates. As the infection progresses, patchy and diffuse lobar infiltrates can develop. In patients with pre-existing lung disease and in those with hyperinfection syndrome, massive larval migration through the lungs can lead to extensive lung infiltration and the development of ARDS (14, 15).

Woodring et al. (15), in a study that included 20 patients with pulmonary strongyloidiasis, detected 9 (45%) who had developed ARDS. Eight of these nine (89%) had secondary bacterial or fungal pulmonary infections (pneumonia or abscesses). Another interesting finding of this study was that 95% of the patients had abnormal and unspecific radiographic findings, including alveolar interstitial or lobar infiltrates and pleural effusion. Eosinophilic pleural effusion, defined as the presence of more than 10% of eosinophils in the pleural fluid, has been associated with parasitic infections like paragonimiasis, ascariasis, ancylostomiasis, and strongyloidiasis. In patients with strongyloidiasis, the eosinophilic pleural effusion, with or without larvae in the pleural fluid, is probably a consequence of filariform larvae in the lungs during the migratory phase of the life cycle. In the presence of eosinophilic effusion with peripheral eosinophilia, the presence of helmintic parasitic infections like strongyloidiasis should be considered, especially in individuals from endemic areas (20). Finally, strongyloidiasis should be included in the differential diagnosis of pulmonary involvement or ARDS in immunocompromised hosts (21).

Histopathological findings on HS pulmonary involvement include hemorrhages, perivascular granulomas with macrophages, the presence of larvae within the alveoli, lymphatics, and bronchial tree lumen, and interlobular septa thickening. Larvae are more difficult to identify in the lungs than in the gastrointestinal tract.

In patients with bronchoalveolar lavage or sputum positive to larvae, a repeat bronchoscopy 7 - 10 days after treatment is recommended to verify the total eradication of the parasites (21).

3.6. Risk Factors in the Development of Severe Clinical Syndromes Associated With S. stercoralis Infection

The most common immunocompromised conditions associated with the severe forms of *S. stercoralis* infection, HS, and DD are treated with prolonged therapy with high or low doses of corticoids (22, 23); cyclosporine therapy to prevent the rejection of transplanted organs, especially in renal transplant recipients; and other immunosuppressive drugs, such as chemotherapy and antineoplastic

drugs (24, 25). In HS, parasites are found in the proximal small bowel, stomach, colon, and lungs all the sites in which *S. stercoralis* is located during its life cycle. Conversely, DD occurs when the filariform larvae spread to other organs not usually involved in their life cycles.

Of all the immunosuppressive drugs, glucocorticoids are the most frequently used and the most commonly associated with the transformation of chronic strongyloidiasis into HS or DD (4). Corticosteroid therapy is associated with a two- to three-fold increase in the risk of severe forms of clinical disease due to *S. stercoralis* (17, 26, 27). Some explanations for the ability of glucocorticoids to induce HS include the acute suppression of the eosinophilia response, lymphocyte activation, and the direct effect on the parasites, accelerating the transformation of rhabditiform to the invasive filariform larvae (4, 28).

Corticosteroids may reduce local inflammation, thus impairing the ability of the gut to contain the parasites. With increased numbers of larvae completing the autoinfection cycle, large numbers of worms can enter systemic circulation producing a hyperinfection syndrome associated with sepsis or meningitis, with enteric organisms causing significant morbidity and mortality in immunocompromised patients (19). Since disseminated strongyloidiasis is fatal in 80% of its cases, it is recommended to diagnose and treat the asymptomatic infection due to *S. stercoralis* before long-term corticotherapy.

Immunosuppression is a risk factor for severe strongyloidiasis; patients with hematologic malignancies are especially at risk because they are immunosuppressed due to their underlying disease and also because of the treatment. Schaffel et al. (29) evaluated 164 patients with hematological malignancies which were tested for IgG antibodies against *S. stercoralis* by enzyme-Linked immunosorbent assay. The prevalence of strongyloidiasis was 13%. The underlying diseases were acute leukemia in 21% and lymphoma in 52% of the patients. The majority of patients were receiving chemotherapy (93%) and steroids (76%). Leukemia and lymphoma account for up to 90% of the cases of malignancy-associated severe strongyloidiasis (17, 19, 30-32). Therapy with monoclonal antibodies such as rituximab for treatment of non-Hodgkin lymphomas with CD20 expression has been associated with the development of HS (33).

S. stercoralis HS has been reported in recipients of solid organs and stem cell transplantations. In all of these patients, HS was associated with high mortality rates. In renal transplant recipients, HS typically occurs within the first 3 months after transplantation and in patients with a history of living in endemic areas of *S. stercoralis* infection (34). In stem cell transplantation, the risk is increased in allogenic transplants in comparison with the autologous hematopoietic stem cell transplantation. In these patients, HS appears earlier, in the immediate post-transplantation period, because that is the period of most intensive immunosuppressive therapy (34). Screening for latent *S. stercoralis* infection should be included as a part of the evaluation for patients with a history of living in endemic areas before chemotherapy regimens for bone marrow or stem cell transplantation (26).

On the other hand, the immunosuppressive clinical conditions associated with the high risk of HS and DD include the human T-lymphotropic virus type-1 (HTLV-1) infection and the human immunodeficiency virus (HIV) infection. Infection with HTLV-1 is associated with an increased prevalence of *S. stercoralis* infection (35, 36); a low response to antihelmintic therapy, including ivermectin, thyabendazole and albendazole; and a high risk of HS. One reason is that HTLV-1 infection is associated with a high Th-1 response related to high levels of gamma-interpheron and a low Th-2 response associated with low levels of interleukins 4 and 5, IgE, and eosinophilia (35-37).

Co-infection by HTLV-1/2 and HIV is associated with an increased risk of strongyloidiasis for HIV patients, with a significantly higher frequency of *S. stercoralis* among co-infected patients (38).

HS due to *S. stercoralis* is strongly associated with acquired immunodeficiency syndrome due to HIV infection (39). Clinically, HS is often complicated with the development of ARDS and the presence of filariform larvae in sputum, bronchial washing, or lung biopsy smears (40, 41). Most of these patients receive steroid therapy due to *Pneumocysitis jirovecii* pneumonia (41) and *Toxoplasma gondii* encephalitis, as a part of the chemotherapy regimen for non-Hodgkin lymphoma or Hodgkin's disease (42).

In a recent, retrospective study, Corti et al. (43) analyzed 30 patients with *S. stercoralis* infections. HIV co-infection was present in 21 patients (70%) with a median of $CD4^+$ T-cell counts of 50 cells/μL. In this series, overall mortality was 20%. A significant inverse correlation between the survival rate and the $CD4^+$ T-cell counts, as well as peripheral aneosinophilia, was observed. In this study, there was also a significant correlation between HIV co-infection and mortality. HS in AIDS patients can also occur in what is called "post-treatment HS." One possible explanation for this is that antihelmintic therapy induces parasite migration (44). Post-treatment HS has also been described in renal transplant recipients treated with cyclosporine (45). Immune reconstitution inflammatory syndrome (IRIS) in AIDS patients is commonly associated with mycobacterial, viral, or invasive fungal infections. The spectrum of infections associated with IRIS is expanding and includes a number of parasitic infections (protozoal and helmintic) (46). In HIV infection, IRIS related with HAART may trigger the development of HS (47).

Patients with AIDS present a variety of abnormalities in the regulation of cytokine expression, including an increase in Th-2 cytokines and a decrease in the Th-1 cytokines (48). However, in AIDS patients, the predominant Th-2 pattern appears to favor coccidian infection as cryptosporidiosis rather than helmintic infection (49).

Glucocorticoid treatment and AIDS and human T-lymphotropic virus type 1 (HTLV-1) infections are the two conditions most specifically associated with HS (19, 50).

Different and unusual clinical presentations have been

described in immunosuppressed patients with strongyloidiasis. Several clinical pictures have been reported, including cutaneous involvement with extensive purpura eruption described in a patient treated with chronic corticosteroid therapy due to myasthenia gravis (51).

Also, nephrotic syndrome secondary to parasitic infections has been described in association with malaria, schistosomiasis, and filariasis. However, cases due to strongyloidiasis have rarely been described. In these cases, clinical and laboratory abnormalities associated with nephritic syndrome improve after the treatment for *S. stercoralis* infection (52).

Finally, acute and fulminant gastrointestinal bleeding associated with many gastric and duodenal ulcers with *S. stercoralis* filariform larvae in the microscopic examination of the biopsy mucosal smears was also described in association with HS (2).

Additionally, HS due to strongyloidiasis has been associated with a high incidence of severe bacterial or yeast infections. Meningoencephalitis, pneumonia with ARDS, and sepsis due to gram-negative bacilli are severe complications that can reveal the presence of an underlying occulted *S. stercoralis* infection (19, 53, 54). An important clinical feature of HS is that 30% to 45% of the cases develop gram-negative sepsis caused by the colonic flora that penetrate the colonic mucosae.

In conclusion, patients on corticosteroid therapy; patients receiving hepatic transplantation or renal transplants; patients with renal deficiency; patients with systemic lupus erythematosus, asthma, chronic dermatosis, chronic infections (lepromatous leprosy, tuberculoid leprosy, and tuberculosis); as well as those with neoplastic conditions (lymphoma, leukemia, and solid tumors), protein-calorie malnutrition, chronic alcoholism, AIDS, HTLV-1 infection and achlorhydria—all are at higher risk for DD or HS (19, 50, 55).

3.7. Immunological Response to S. stercoralis Infection

In both immunocompetent and immunocompromised patients with chronic active infection, high immunoglobulin (Ig) G serum antibodies to Strongyloides filariform larvae antigens have been demonstrated (20, 21). Most patients also have specific serum IgA responses against filariform larvae antigens. Immediate hypersensitivity is a prominent component of the immune response to Strongyloides infection and may play a role in the pathogenesis of disease as well as in protection (56-58).

3.8. Diagnosis of Strongyloides stercoralis Infection

Diagnosis of strongyloidiasis is one of the most frequent problems in clinical practice because at least 25% of the examinations of stool smears can also be false negative (Table 1).

The first step in diagnosis is the screening of high-risk populations. In addition, peripheral eosinophilia, chronic diarrhea, malabsortion syndrome, and chronic anemia are unspecific indications of *S. stercoralis* infection and should alert clinicians. Peripheral blood eosinophilia correlates with recurrent larvae migration, but may be absent in patients with HS, and, in these cases, it is considered a poor prognosis finding (57). The severity of strongyloidiasis is strongly related to peripheral eosinophilic levels. In symptomatic patients or those with large numbers of larvae present, peripheral hypereosinophilia is a good prognosis laboratory finding. On the other hand, the absence of an eosinophilic response is associated with a poor prognosis and a high mortality rate. Peripheral eosinophilia may be absent in patients with HS, most likely due to the suppression of eosinophilic exposure by corticosteroid therapy or in association with bacterial sobreinfection (56, 57).

The screening of high risk individuals is based on the detection of specific serum antibodies or by the detection of larvae in stool samples. The diagnosis of strongyloidiasis relies on the identification of the parasite in stool samples or, rarely, in sputum and biopsies. The Baermann-Moraes method and fecal culture in agar are the most sensitive and specific methods used to detect the larvae of the parasite (58, 59). However, a single stool sample may be negative in up to 70% of cases. Examination of at least 3 samples improves larvae detection and is recommended (40, 60). Unfortunately, false negative results are frequent; the main causes are the variable amounts of larvae in the stool collected at different periods, the necessity of analyzing at least three stool samples, and the difficulty in performing the tests (61, 62). Also, *S. stercoralis* infection may elevate the IgE levels in the infected patients (5).

Table 1. Diagnosis of *Strongyloides stercoralis* hyperinfection Syndrome (Modified From Roxby et al. (24))

Method	Outcome
Direct examination of fresh fecal material or after stool concentration techniques	Larvae is frequently seen
Peripheral hypereosinophilia	Generally not detected. Aneosinophilia is frequent and is associated with a poor prognosis and elevated mortality rate.
Gastric and duodenal aspirates or biopsy specimens	Highly sensitive
Body fluid direct examination (sputum, bronchoalveolar lavage)	Frequently positive
Cerebrospinal, peritoneal, and pleural fluids or urine	Occasionally positive

Detection of parasite-specific antibodies by the indirect immunofluorescence antibody test (IFAT) and the enzyme-linked immunosorbent assay (ELISA) may be useful as a complementary method to the parasitological diagnosis of strongyloidiasis, but such tests show cross-reactivity with filaria, schistosomes, hookworm, *Ascaris lumbricoides*, *Trichuris trichiura*, and *Echinococcus*. The knowledge that specific antibodies against antigens of the filariform larvae of *S. stercoralis* are synthetized by the immune system after the infection has led to the development of an immunodiagnostic test to detect *S. stercolaris*-specific IgG antibody (28, 63-65).

The ELISA for the detection of anti-*S. stercoralis* antibodies in serum is associated with a high sensitivity, ranging from 83% to 93%, and a high specificity of 95% to 97% (66). Immunocompromised patients may have an altered immune response to *S. stercoralis*. The sensitivity of the ELISA in immunosuppressed patients was only 10% in one study and 80% in another (67, 68). Schaffel et al. (29) evaluated 164 patients with hematological malignancies, which were tested for IgG antibodies against *S. stercoralis* by the ELISA. The prevalence of strongyloidiasis was 13%. The sensitivity, specificity, and positive and negative predictive values were 68%, 89%, 48%, and 95%, respectively. The authors conclude that the ELISA may be an excellent assay to rule out the diagnosis of strongyloidiasis in patients with hematological malignancies.

There is a significant association between a positive serology by the ELISA and the diagnosis of active strongyloidiasis (69). The detection of specific IgE and IgG1 and 4 antibody subclasses by the ELISA may improve the serological diagnosis of human *S. stercoralis* infection (70). The ELISA does not discriminate between recent or past infections and can produce cross-reactions with other helmintic infections (71). The ELISA reversion to a negative serological status was demonstrated after ivermectin therapy in treated persons. In addition, there have been few reports about the molecular methods for the amplification of the DNA of the parasite. Finally, antigenic components of *S. stercoralis* can be recognized by serum IgG antibodies in Western blotting (WB) assay using *S. ratti* larvae antigenic extract for the diagnosis of human strongyloidiasis. Pereira Silva et al. (72) compared the IFAT, ELISA, and WB for the diagnosis of human strongyloidiasis. The authors demonstrated a positive concordance for the three tests in 87.5% of the cases of strongyloidiasis. The negative concordance in the three tests was 94% and 97.5% in patients with other intestinal parasitoses and healthy individuals, respectively. In cases of positive ELISA and negative IFAT results, diagnosis could be confirmed by WB. The authors conclude that WB can be used to define the diagnosis of strongyloidiasis in patients with discordant serological results.

3.9. Diagnosis of Strongyloides stercoralis HS

The named HS refers to the cycle of autoinfection characterized by a high number of worms in the gastrointestinal tract and lungs (25). Parasitological diagnosis of HS in immunocompromised patients is generally simple and based on the high number of larvae (high worm burden) present in stools, sputum smears, and the immunologic status of the host (4). HS is characterized by the high migration of the larvae into the body, with the possible invasion of the liver, brain, lungs, and kidneys and the eventual progression to multiple organ failure and death (Box 1).

In immunosuppressed patients, severe strongyloidiasis can be diagnosed by the identification of filariform or rhabditiform larvae in stool samples by various techniques (74). Multiple direct examinations of the stool smears are associated with an increased rate of larvae visualization in feces (69, 70). In our experience, the examination of at least 3 stool samples with the use of direct and Baerman-Moraes methods generally improve the diagnosis. In addition, the larvae may also be identified in duodenal aspirate, sputum, or bronchoalveolar lavage fluid. The histolological examination of gastric and duodenal biopsy smears showed inflammatory infiltrates in the lamina propria of the gastric crypts and the duodenal glands, including mononuclear and lymphocytes, as well as neutrophils and eosinophils. Eosinophilic infiltration is increased in patients with HS and a high number of parasites in the digestive tract. Edema, erosions, and ulcers of the mucosae also have been observed. *S. stercoralis* can be seen in the histological sections of the gastric and/or duodenal crypts, generally in many sections, as eggs, rhabditoid and filariform larvae, and adult female parasites. Gastric location is always associated with the duodenal presence of parasites, and achlorhydria appears to be the cause that permitted the colonization of the stomach crypts by the parasites. Histopathological diagnosis is based on the small size of the parasite, the size of the eggs that generally appear to be embryonated, and the frequent presence of both larvae and adult parasites with eggs (27, 75, 76).

S. stercoralis larvae can be detected in respiratory secretions by direct examination, as in stools smears, or by Papanicolau stain or fluorescent microscopy of the sputum (77).

Box 1. Risk Factors for Autoinfection and Hyperinfection With *Strongyloides stercoralis* (modified from Mokhlesi et al. (73))

Risk Factors
Prolonged high doses of corticosteroid therapy
Immunosuppressive drug therapy
Chronic lung disease
HIV/AIDS
HTLV-1 infection
Chronic renal failure
Systemic collagen disease
Solid tumor
Hematologic malignancy (leukemia and lymphoma)
Malnutrition
Achlorhydria
H2 blockers and antacids
Decreased gut motility

Table 2. Sensitivity of Diagnostic Tests for Strongyloidiasis (Modified From Mokhlesi et al. (73)[a]

	Intestinal Strongyloidiasis	Hyperinfection Syndrome
Eosinophilia	60 - 90	< 20
Stool ova and parasitesSingle stool exam	20 - 30	> 30
≥ 3 stool exam	60 - 70	> 80
7 stool exam	> 95	95 - 100
Duodenal aspirates	40 - 90	Moderate to high
Sputum/BAL	Low	Moderate to high
Serologic testsELISA (IgG to *S. stercoralis* antigen)	80 - 90	NA

Abbreviation: NA, not available.
[a]Data are presented as percentage.

Occasionally, *S. stercoralis* has also been detected from urine, pleural, peritoneal, or cerebrospinal fluid examination or in biopsy samples of the gastric or intestinal mucosae (25, 27, 76) (Table 2).

3.10. Treatment

HS is associated with a high rate of mortality which ranges from 15% to 87% (1). Early diagnosis related to a high index of suspicion, followed by specific anti-parasite therapy, may improve the poor prognosis of these patients.

In immunocompromised patients, ivermectin in doses of 200 μg/kg/day taken orally for 2 days, every 2 weeks and repeated 3 times is the treatment of choice for strongyloidiasis, with a cure rate > 90% in patients with HS (78-80).

Torres et al. (78) suggested the efficacy of multiple doses of ivermectin in strongyloidiasis associated with HIV infection, especially in patients with HS or DD. A single dose of ivermectin may be useful for the treatment of uncomplicated strongyloidiasis in immunocompromised individuals (81).

As an alternative, thiabendazole in regimens of 400 to 800 mg (25 mg/kg) taken orally twice daily, with a maximum dose of 3,000 mg/day, for 3 to 10 days is also associated with good cure rates that ranged from 67% to 81% for chronic strongyloidiasis (82-84).

Thiabendazole has been replaced by ivermectin as the treatment of choice due to a better tolerance. These antihelmintics drugs can be used to treat HS or DD alone, or in combination.

Albendazole at doses of 400 mg orally twice daily for 3 days is associated with a cure rate of 38% to 45%. Albendazole can be used as an alternative to ivermectin in HS (84).

Ivermectin is much better tolerated when compared with azoles, thiabendazole, and albendazole, and it is the treatment of choice and the first alternative therapy for patients with HS (9, 43, 78, 85, 86).

The prognosis of patients with HS is poor with a 50% mortality rate despite their having had adequate therapy (85, 86).

Treatment refractory infections are frequent in immunosuppressed patients. Therapy should be continued until the resolution of the clinical syndrome and until there are no longer any larvae detectable in stool smears. Due to the autoinfective cycle, at least 2 weeks of treatment and recorded negative fecal studies are required for complete treatment (9).

Some authors suggest that suppressive therapy may be required in treating immunosuppressed patients, especially those with AIDS in which secondary prophylaxis with a dose of 200 μg/kg/orally of ivermectin every 2 weeks has been recommended until the immune reconstitution associated with HAART occurs (24, 82, 86).

4. Conclusions

Strongyloidiasis is a worldwide parasitic infection that affects approximately 70 million people, especially in areas characterized by high temperatures and humidity and accompanied by poor hygiene conditions. Strongyloidiasis infection can be totally asymptomatic or associated with a wide spectrum of clinical manifestations, including HS and DD, and it is strongly related to the immunological status of the affected hosts. This helmintic parasite is a unique geohelmint that can cause HS and DD many years after exposure. *Strongyloides stercoralis* is characterized by the unusual capacity of a life cycle that includes replication within the bowel of the human host. This characteristic permits cycles of autoinfection due to intestinal production of infective larvae and a large number of invasive Strongyloides filariform larvae that can disseminate to all the organs and systems, especially in severe immunosuppressed patients. The presence of larvae of *S. stercoralis* in the sputum specimens and the observation of a large number of larvae in the feces, defined the HS. In DD, the larvae not only may invade the lungs and the gastrointestinal tract as in HS, but it can also invade the central nervous system, liver, peritoneum, and kidneys. Gram-negative sepsis pneumonia or meningitis can complicate the clinical course of this parasitic infection. Although HS is frequently associated with both HIV and HTLV-1 infections, DD is uncommon in these clinical conditions. Even the asymptomatic form of the disease

should be treated because it has the potential to develop the most severe clinical forms, HS and DD, in a variety of immunosuppressed associated conditions.

We recommend that all physicians develop a high level of clinical suspicion, especially regarding patients with unspecific gastrointestinal symptoms, prior to chemotherapy or steroid therapy, or with retroviral infections (HIV and HTLV 1) to rule out the presence of *Strongyloides stercoralis* larvae in stool samples. Stool examination and eosinophilic counts are necessary to monitoring the results of the treatment.

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