Infection and Hyperinfection with *Strongyloides stercoralis*: Clinical Presentation, Etiology of Disease, and Treatment Options

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Abstract Human strongyloidiasis is a neglected global parasitic disease that affects large populations, especially in poorer regions of the world. Improved diagnostic tools, including serology and molecular tests, are demonstrating that the prevalence of infection is far higher than previously thought. Most complications arise as a consequence of delayed diagnosis, primarily due to physicians not considering this potentially lethal parasitic infection. The likelihood of developing mild chronic strongyloidiasis or hyperinfection syndrome depends on the status of the host defenses. The critical host responses controlling *Strongyloides stercoralis* in animal models include eosinophils, neutrophils, and antibodies. Corticosteroid treatment and human T-lymphotropic virus (HTLV)-1 infection predispose to hyperinfection in humans, but how these result in hyperinfection is poorly defined. Improved diagnostic tests and molecular epidemiology are highlighting the underappreciated burden of disease, which could be addressed with mass chemotherapy with proven effective drugs like ivermectin.

Keywords Strongyloides · Infection · Hyperinfection · Etiology · Parasitic infection · Tropical medicine

Introduction

Soil-transmitted helminths are ubiquitous in tropical and subtropical areas worldwide. Although it is estimated that one out of every four individuals is affected, 4 billion are at risk of contracting infection [1, 2].

Among soil-transmitted helminths, the prevalence of *Strongyloides stercoralis* infection is usually underestimated and its impact overlooked [3]. Previous reports from 35 years ago suggested that about 30–100 million individuals were infected worldwide [4]. However, a recent report indicates that its prevalence is about 10–40 % within tropical and subtropical countries, but can be as high as 60 % in some areas. Most of these studies have relied on insensitive diagnostic tests like single direct stool examinations [5•].

The prevalence of infection in developed countries is low, mainly because individuals have access to improved sanitation [6]. However, individuals who have temporarily lived or travelled to endemic areas, such as immigrants, tourists, and military personnel, are also at risk. Chronic asymptomatic infection may last for decades after exposure [7–9]. Treatment of these individuals with corticosteroids may lead to hyperinfection syndrome [10].

Biology

S. stercoralis is unique among helminths due to its complex life cycle. It has both a free-living stage and a parasitic cycle. During the parasitic life cycle, the filariform larvae (L3) penetrates the intact skin and travels through the venous circulation until it reaches the lungs, where it invades into the alveolar space. After molting twice, the larvae migrate up the bronchial tree and are then swallowed, reaching the gastrointestinal tract. Once in the duodenum, the larvae penetrate the mucosa, where the females lay embryonated eggs (through

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a process of parthenogenesis not requiring the male). Rhabditoid larvae (L1) hatch from these eggs within the intestinal wall, migrate into the intestinal lumen, and are either shed with the stools or mature into filariform larvae (L3), penetrate the intestinal mucosa or perianal skin and complete a new parasitic cycle. This process, known as autoinfection, is unique to *Strongyloides* among round worms. In the normal host, shedding of larvae is intermittent and the numbers small. Thus, it is difficult to diagnose by routine stool microscopy. Once in humid soil, the rhabditoid larvae mature into filariform (L3) larvae and become infective. Alternatively, they can develop into the free-living male and female adults, which reproduce sexually. This allows *S. stercoralis* to survive outside the human host for prolonged periods of time [11].

Pathology

The burden of disease and clinical manifestations of *S. stercoralis* infection are determined by the complex interaction between the host immune response and the invading pathogen. The innate immune response to parasite infections has been classically described as governed by eosinophils [12]. However, newer reports have shown that both macrophages and neutrophils can work as effector and immunomodulatory cells during *Strongyloides* infection [13•, 14].

In animal models, eosinophils are able to function as antigen-presenting cells, leading to the induction of the primary immune response [15, 16]. In addition, *S. stercoralis* antigens lead to neutrophil activation and recruitment [17]. Although the mechanisms of larval killing are not fully elucidated, both neutrophil myeloperoxidase (MPO) and eosinophil major basic protein (MBP) are required for larval killing [18]. In addition, neutrophils and eosinophils kill larvae through a mechanism dependent on complement component C3 [19]. A recent report showed that infection with *S. stercoralis* leads to the induction of alternatively activated macrophages, which in turn collaborate with neutrophils and complement to kill the parasite [14]. The link between the innate and adaptive immunity is not well defined. Eosinophils are capable of activating antigen-specific lymphocytes and assist in priming of naïve T cells to initiate type 2 T helper (Th2) cell responses against infection [12]. Th2 cells in turn produce interleukin (IL)-5, which is essential for further generation and activation of eosinophils [20]. Thus, eosinophils play a pivotal role in linking the innate and adaptive immune response.

Adaptive immunity responses involve the induction and expansion of both antigen-specific T and B cells. The expression of IL-4 and IL-5 by Th2 cells is important to generate immunoglobulin class switch to immunoglobulin (Ig)-G and IgE by B cells [21]. In mice infected with *S. venezuelensis*, IgG and IgE accelerated

expulsion of larva [22]. The importance of IL-4 was also shown by a prior report from an animal model, where the expression of IL-4R was necessary for timely elimination of larva [23]. In addition IL-13 (a Th2 cytokine) increases gut peristalsis and may help in larval expulsion [24].

Regulatory T cells (Tregs) are a unique population of cluster of differentiation (CD)-4+T cells that are able to modulate immune responses to both self-reactive lymphocytes and foreign antigens. Tregs exert their suppressive function through the production of anti-inflammatory cytokines, cell-to-cell contact, and by consumption of pro-inflammatory cytokines. By modulating the immune response, Tregs avoid collateral damage from exuberant responses. However, expansion of this population can decrease Th2 responses, rendering the host susceptible to infections [25]. There is evidence that Tregs play a role in parasitic control. Subjects infected with human T-lymphotropic virus (HTLV)-1 have increased numbers of circulating Tregs [26]. In fact, *Strongyloides* itself can also increase the number of circulating Tregs, as has been demonstrated in animal models [27•]. An increased number of Tregs could alter the immune balance necessary for efficient parasite eradication. In mice models, Tregs delay expulsion of *S. ratti* by a suppressed IL-9 response [28]. In the human counterpart, we have previously proved that the increase in the number of Tregs is inversely correlated with IL-5 levels, a key cytokine for eosinophil-mediated response to *Strongyloides* [29]. In addition, we have found an increase in the number of Tregs in intestinal tissue in patients with strongyloidiasis. This was associated with decreased IgE-expressing cells in areas adjacent to the parasite (unpublished data). Altogether, these data suggest an important role of Tregs in down-regulating an otherwise protective immune response to *Strongyloides* infection.

Clinical Manifestations

The presentation of *S. stercoralis* in immunocompetent patients is usually mild. Initial infection when noted is characterized by a cutaneous reaction as the larvae penetrate the skin, known as ground itch. Subsequently, patients may develop mild cough, wheezing, or Loeffler-like syndrome. Although the spectrum of disease is extensive, the majority of patients present with asymptomatic or mildly symptomatic chronic infections [30].

Chronic infection is characterized by mild abdominal complaints such as discomfort, bloating, nausea, vomiting, and diarrhea [11]. Eosinophilia is found in up to 90 % of the cases, with high levels of IgE in 75 % [31]. A recent report found positive serology to *S. stercoralis* in 5 % of immigrants and travelers to endemic areas [8].

In some patients, large numbers of rhabditiform larvae mature into the invasive filariform stage prior to being excreted. These infective L3 larvae can reinvade the intestinal wall or perianal area, creating cycles of auto-infection. In the absence of an effective host response, these cycles lead to massive numbers of organisms (Fig. 1). This process is known as hyperinfection syndrome [32]. Hyperinfection is typically seen in patients on high-dose or chronic corticosteroid therapy, HTLV-1 co-infection, children with malnutrition, or other defects of granulocyte function [33•]. Although HIV-infected individuals may present with decreased levels of CD4+T cells, HIV alone is not associated with hyperinfection syndrome [34].

The majority of cases of hyperinfection syndrome present with abdominal pain and diarrhea [35]. However, they may also develop constipation, ileus, intestinal obstruction, enteritis, and/or gastrointestinal bleeding [36, 37]. Extra-intestinal manifestations are varied and include pulmonary infiltrates, alveolar hemorrhage, and respiratory failure [38, 39]. In addition, the migration of the parasites through the intestinal wall into the bloodstream leads to translocation of gastrointestinal bacteria. Patients may present with bacteremia and central nervous system infections with enteric organisms including gram-negative bacteria and *Enterococcus* species [40]. The classic dermatological manifestation is a migratory, linear, and serpiginous lesions (larva currens) [41]. Unlike patients with chronic infection, patients with hyperinfection syndrome present

with large numbers of larvae but few eosinophils [32]. The case-fatality rate for hyperinfection syndrome is high (up to 85 %) [33•].

In the developed countries, corticosteroid recipients account for the majority of cases of hyperinfection syndrome [10, 42, 43]. Patients may develop hyperinfection when corticosteroids are used in treatment of autoimmune diseases, organ transplantation, or treatment of malignancies. Corticosteroids markedly suppress function of eosinophils and other granulocytes as well as aspects of cell-mediated immunity [44]. However, in resource-poor countries the main risk factors for hyperinfection include malnutrition and infection with HTLV-1 [32, 45].

Diagnosis

In contrast to other intestinal nematodes in which ova can be easily detected in stool, *S. stercoralis* is characterized by low numbers and intermittent larval shedding. A single stool exam yields positive results in, at best, 30–50 %. Examining up to three consecutive stool samples has been shown to improve sensitivity to up to 95 % [46]. Culture in an agar plate has a higher sensitivity (96 %); however, it is laborious and time consuming [47]. In the normal host, the diagnostic stage is the rhabditiform larva. In patients at risk for hyperinfection, the sensitivity of stool examination is higher due to increased parasite load in the stools. In such cases, filariform larvae are more frequently found [46].

Fig. 1 A case of severe strongyloidiasis. The *upper right* photo shows severe erosion of duodenal mucosa found in an endoscopy for a patient with intestinal sub-occlusion. The *left* photo shows H-E staining of duodenal biopsy demonstrating multiple parasites invading the intestinal wall. The *lower right* photo shows Baermann's stool sedimentation with thousands of infective stage (L3) larvae of *Strongyloides stercoralis* (Courtesy of Carlos Seas MD, UPCH, Lima, Peru)

During the past decade, multiple immunological tests have been developed. An enzyme-linked immunosorbent assay (ELISA) test for serum antibodies to multiple *S. stercoralis* antigens has a high sensitivity (83–93 %) and reported specificity (95–98 %). Comparison of the performance of several serological assays has shown that both NIE-LIPS and ELISA tests achieve close to 100 % specificity, maintain sensitivity above 75 %, and may be useful epidemiological tools [48, 49••]. Although the presence of antibodies does not distinguish between past and current infections, a recent report showed seroconversion in up to 80 % of treated patients [49••]. Other problems with conventional ELISA tests include cross-reactivity with other helminthic infections [48]. A coproantigen ELISA test has been developed with high sensitivities and no cross-reactivity to other helminthes [50]. However, the test involves the production of *S. ratti*-specific rabbit polyclonal antibodies, which are only available in research facilities.

Multiple molecular techniques are now available in research facilities. Several reverse transcription polymerase chain reaction (RT-PCR) protocols have been developed with sensitivities and specificities bordering 100 % [51]. Although expensive, these techniques have the advantage that they can be performed in samples that have been previously preserved in ethanol and stored at room temperature [52]. This allows easy transportation to facilities with real-time PCR capabilities.

Loop-mediated isothermal amplification techniques allow for rapid, highly sensitive, and specific molecular diagnosis in the field. Recently, Watts et al. [53•] described a loop-mediated isothermal amplification (LAMP) assay for *S. stercoralis* in stool [53•]. This assay represents a promising new technique for fast and reliable diagnosis in areas with few capabilities.

Treatment

S. stercoralis infection should always be considered pathological and warrants treatment, regardless of the presence or absence of symptoms. *S. stercoralis* is susceptible to ivermectin. A single oral dose of 200 mcg/kg of ivermectin is the preferred regimen [30]. Thiabendazole and albendazole are alternatives.

Multiple trials have compared the safety and efficacy of the oral medications. Ivermectin, in a single dose (200 mcg/kg) or double doses given 2 weeks apart, was superior to a 7-day course of oral albendazole 800 mg (93 %, 97 %, and 63 % success rate, respectively) [54]. Ivermectin 200 mcg/kg at a single dose was similar to twice-daily doses of thiabendazole 25 mcg/kg for 2 days, but produced fewer side effects [55]. A 7-day course of albendazole 10 mg/kg/day can be used if the other medications are unavailable, but the cure rates are significantly less (38–45 %) [54]. Both serology and eosinophil

counts improve slowly requiring 6 and 12 months to normalize. They can be used as a surrogate marker for treatment success, but are not ideal due to the delays in resolution [56•].

Whenever hyperinfection syndrome is suspected, antiparasitic therapy is required immediately. Immunosuppression should be reduced when possible. Ivermectin at a daily dose of 200 mcg/kg daily for up to 2 weeks should be given. Prolonged courses may be required if the patient continues to present signs of persistent infection. Daily stool study follow-up should be taken for at least 2 weeks to assure parasite clearance [33•].

In patients with malabsorption, unable to tolerate oral medications, or with deteriorating clinical status, daily ivermectin 200 mcg/kg can be given per rectum until able to tolerate oral administration. Other routes of administration include daily subcutaneous injections of veterinary formulations of ivermectin 200 mcg/kg for at least 2 weeks or until oral medications are tolerated [57]. Subcutaneous versus rectal administration has not been compared in clinical trials. However, rectal absorption of ivermectin is low, and serum concentrations were higher in patients with subcutaneous administration [58]. Neither rectal nor subcutaneous administrations are US Food and Drug Administration approved.

Blood culture surveillance should be taken to exclude bacteremia and meningitis. Mass drug administration for soil-transmitted helminthes has demonstrated a decrease in the prevalence of infection [59]. Most of these programs include mass chemotherapy with benzimidazole antiparasitic drugs, which have limited (albendazole) or no (mebendazole) activity against *S. stercoralis* [60]. However, little information on *S. stercoralis* impact is available, and deworming programs currently do not include additional measures to effectively target *S. stercoralis*.

Vaccines

A vaccine against *S. stercoralis* would be helpful in controlling the burden of disease, especially in areas where access to sanitation is limited. Ben Nouir et al. [61] have recently shown that the administration of *S. ratti* heat shock protein 60 conferred partial protection against challenge in mice. Recently, Abraham et al. [62] showed that the Ss-IR antigen (*S. stercoralis* immune reactive) from *S. stercoralis* is highly antigenic in humans. In addition, mice immunized with the Ss-IR antigen presented an 80 % decrease in the survival of larval parasites during the challenge infection [62].

Conclusion

S. stercoralis infection is a neglected disease that can cause chronic infection and potentially fatal hyperinfection.

Hyperinfection is most common in patients who have been treated with corticosteroids or who have HTLV-1 co-infection. Eosinophils and neutrophils are the main host cells controlling the numbers of organisms. Diagnosis is difficult in patients with low numbers of organisms, but novel assays such as real-time PCR are improving diagnosis. Treatment with ivermectin is effective. The data on the global burden of disease are limited by lack of data on prevalence of infection using sensitive diagnostic techniques. Mass chemotherapy with ivermectin could potentially have a major impact on health, but better epidemiologic data are needed to identify areas where mass chemotherapy is appropriate.

Compliance with Ethics Guidelines

Conflict of Interest Nicolas Barros and Martin Montes declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors

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