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Strongyloidiasis: a neglected Neglected Tropical Disease (NTD)

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Abstract

The majority of the 30–100 million people infected with *Strongyloides stercoralis*, a soil transmitted intestinal nematode, have subclinical (or asymptomatic) infections. These infections are commonly chronic and longstanding because of the parasite's unique life cycle that allows for autoinfection. A change in immune status can increase parasite numbers, leading to hyperinfection syndrome, dissemination, and death if unrecognized. The use of corticosteroids and HTLV-1 infection are most commonly associated with the hyperinfection syndrome. *Strongyloides* adult parasites reside in the small intestine and induce immune responses both local and systemic that are like other nematodes. Definitive diagnosis of *S. stercoralis* infection is based on stool examinations for larvae, but newer diagnostics – including new immunoassays and molecular tests – will assume primacy in the next few years. Although good treatment options exist for infection and control of this infection, *S. stercoralis* remains largely neglected.

Keywords

Strongyloidiasis; Strongyloides; autoinfection; hyperinfection; anthelmintic therapy; corticosteroids

Introduction

The *Strongyloides* group of parasites includes over 50 different species, each of them naturally infecting a very limited number of mammalian species[1]. Strongyloidiasis, the human disease caused by infection with *Strongyloides stercoralis*, and in rare instances in restricted geographic locations (Papua New Guinea, Thailand and Philippines) with *Strongyloides fuelleborni fuelleborni* or with *S. fuelleborni kelleyi*[1–3], is a soil-transmitted helminthiasis (STH) with an global prevalence estimated to be between 30–100 million[4,5].

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Infections range from asymptomatic (or subclinical) infections to symptomatic strongyloidiasis and to the potentially life-threatening hyperinfection syndrome in immunocompromised patients[6,7]. The parasite is largely confined to the tropics and subtropics, although foci of infection occur in any place where poor sanitation or other factors facilitate its transmission through fecal contamination[5,8]. The medical importance of strongyloidiasis resides in its capacity to remain clinically asymptomatic and chronically unnoticed until the host suffers alterations in its immune equilibrium that allow for accelerated larval reproduction that can lead to dissemination[9]. Infections caused by *S. stercoralis* in humans must be analyzed through a wide lens that incorporates all of the complexities associated with the two -way interaction between humans and helminths. Superimposed on this complex interrelationship is the chronicity of *Strongyloides* spp infection that can have profound parasite antigen-induced consequences to its human host that are, in turn, linked to behavioral and socioeconomic causes.

From a public health perspective, the estimated size of the population affected and “at risk “and its relationship to poverty and lack of adequate water and sanitation, puts strongyloidiasis squarely in the Neglected Tropical Disease (NTD) camp, although it is not currently incorporated in the World Health Organization’s (WHO) strategy against STH[10] despite the growing recognition of strongyloidiasis as a disease of great public health significance[11,12].

Epidemiology

Life cycle

The unique life cycle of *S. stercoralis* is determinant for the clinical presentations in infected individuals. The alternative pathways between and within the host and the environment encompass both free-living and parasitic stages. *S. stercoralis* is unique among nematodes infectious for humans in that larvae in the feces can give rise to a free-living generation of worms which, in turn, give rise to infective larvae. This so-called heterogonic development process serves as an amplification mechanism that allows for increased numbers of infective larvae in the external environment. The infective larvae are active skin penetrators; oral infection, while possible, is probably of limited importance[13]. Adult female worms nested in the small intestine, most commonly in the duodenum in humans, lay eggs in the mucosa that hatch into rhabditiform larvae, which are shed in the stool. Because the parasitic female’s eggs hatch often within the gastrointestinal tract, the potential for autoinfection exists when precociously developing larvae attain infectivity (filariform larvae) while still in the host or through the perianal skin. When the rate of autoinfection escapes control by the host, massive re-penetration and larval migration may result, triggering what is clinically defined as hyperinfection syndrome.

In the environment, under warm moist conditions, rhabditiform larvae can either molt into infective filariform larvae or develop through succeeding rhabditiform stages into free-living adults. Sexual reproduction occurs exclusively in the free-living stage. After dermal penetration, the filariform larvae migrate to the small intestine. The most clinically relevant, though perhaps not the predominant migration is the classic pulmonary route, in which organisms enter the bloodstream and are carried to the lungs[14,15], ascending the

tracheobronchial tree to enter the gastrointestinal tract. Only female adults are detectable in humans and subsequent reproduction occurs asexually through parthenogenesis[16]. Unique among nematodes infecting humans, along with *Capillaria spp*, rhabditiform larvae of S. *stercoralis* can transform into invasive filariform larvae before being excreted and re-infect the host by invading the intestinal wall or the perianal skin[9]. With an alteration in host immune responsiveness, even one adult female can multiply rapidly by parthenogenesis, leading to accelerated autoinfection and/or dissemination.

Transmission

The exposure of filariform larvae to the transcutaneous route is the most common route of infection for *S. stercoralis*[17]. The oral route is also considered as a possible route, supported by the observation of a higher prevalence of *Strongyloides* infection in patients with *Blastocystis hominis*, a protozoan acquired by the fecal oral route[18]. Transmission of *S. stercoralis* infection after transplantation of solid organs has been suggested by several reports where only donors had a history of exposure and the disease developed in the recipient[19,20].

As for all STH, risk factors for the acquisition of the infection are linked to exposure to a combination of 3 elements: 1) soil contamination with human feces: 2) environmental conditions that allow survival (and for the particular case of *S. stercoralis*, reproduction); and 3) contact of human skin with contaminated soil. In epidemiologic studies, lack of adequate sanitation facilities within the household (but not lack of adequate water supply) was identified as a risk factor[8], as were farming activities, walking barefoot and living in areas with high humidity[21,22]. Latrine availability at home was found to carry a lower risk than using shared latrines[23]. The correlation between hookworms and *S. stercoralis* has been examined and confirmed by 2 recent epidemiologic studies, highlighting the common infectious route of these species that access the human host through larval penetration of intact skin[7,8].

The relationship between age and intensity of prevalence demonstrates for *S. stercoralis* an age distribution similar to hookworms[24], with prevalence rising rapidly during the first 20 years with a slower but continued increase in prevalence through adult life[5,25–27]. Other risk factors, initially considered to be associated with an increased risk for clinically severe disease, such as HIV or HTLV-1 infection and alcoholism have also been found to be more frequently associated with acquisition of infection[28,29], although in the case of alcohol abuse, the risk might be linked to malnutrition rather than pure toxicity due to ethanol itself[30].

The concept of strongyloidiasis as a zoonotic infection is becoming a subject of renewed interest where evidence from DNA sequence polymorphism analysis revealed humans and dogs from the same community sharing a *S. stercoralis* strain that suggests a potential role for dogs in transmission[31]. This raises the possibility that dogs should also be targeted for treatment in the setting of human deworming campaigns[32]

Global distribution

As in most chronic infections, distribution maps highlight not just the areas where transmission occurs but also those areas where populations movement are most significant due to the influx of immigrants and refugees[5]. Although *Strongyloides* is endemic to the tropics and subtropics, clinical suspicion should be present in all those with a present or past, even remote, exposure in endemic areas, including temperate regions such as Japan, Italy, Spain, Australia and the countries of North America[5,33].

CLINICAL MANIFESTATIONS

In uncomplicated strongyloidiasis, many patients are asymptomatic or have mild cutaneous and/or abdominal symptoms.

Acute Strongyloidiasis

The clinical manifestations of acute strongyloidiasis are related to the path of larval migration from the site of infection to the location, most frequently the small intestine, where new adults will develop and start producing larvae. These clinical manifestations are associated with the prepatent period, defined as the time from penetration of infective larvae to production of new larvae by a mature female adult[17]. Infected individuals frequently experience irritation at the site of skin penetration that appears immediately followed occasionally by localized edema or urticaria that can last up to 3 weeks. Within a week following infection, a dry cough may occur. Gastrointestinal symptoms such as diarrhea, constipation, abdominal pain or anorexia can occur following the establishment of the infection in the small intestine as early as the 3rd week of infection[9,17]. Once larval production by the newly established adults starts (~1 month following initiation of infection) new cycles of infection can be initiated through autoinfection (whether within the intestinal mucosa or in the perianal skin) that often presents as a non-specific urticarial rash or pathognomonic *larva currens*[1,34].

Chronic Strongyloidiasis

The chronic stage of *S. stercoralis* infections is most frequently asymptomatic or mildly symptomatic. The gastrointestinal tract and skin are the main systems affected by the manifestations. Symptomatic individuals may complain of diarrhea, constipation, intermittent vomiting or borborygmus. Since most of these symptoms are non-specific and most frequently of mild or moderate intensity, it is difficult to suspect strongyloidiasis unless other signs or symptoms are present; despite the non-specificity of the symptoms. Grove demonstrated in a controlled analysis with infected and un-infected individuals, among ex-prisoners-of-war from Australia who had been in southeast Asia, a significant increase in the presence of indigestion, diarrhea, constipation, anal pruritus and weight loss among gastrointestinal symptoms and urticaria and *larva currens* among dermatologic complaints[35].

Larva currens is defined as pruritic linear streaks along the lower trunk, thighs and buttocks resulting from migrating larvae through the subcutaneous tissues. As the larvae moves it leaves behind a thin red line that gradually fades to brown and disappears within 48 hours. Compared to the cutaneous larva migrans secondary to *Ancylostoma braziliensis*, which is

most frequently localized in the big toe, *larva currens* due to *S. stercoralis* can progress much faster with a speed of 2 to 4 inches (5 to 10 cm) an hour[1].

Unusual manifestations of chronic strongyloidiasis in other organs have been reported but without significantly higher prevalence in controlled studies; they include reports of; nephrotic syndrome[36], massive upper gastrointestinal bleed[37], ascitis[38], chronic malabsorption[39], hepatic lesions[40], arthritis in an HLA-B27 positive individual[41] and asthma[42].

Severe manifestations

In contrast to the mild clinical course of chronic strongyloidiasis that frequently goes unnoticed in the large majority of the cases, severe manifestations including the hyperinfection syndrome and disseminated strongyloidiasis occur in a minority of individuals who suffer florid clinical manifestations with potentially life threatening consequences and a mortality rate of up to 85 to 100%[6]. Hyperinfection describes the syndrome of accelerated autoinfection due to an alteration in the immune mechanisms of the host[9]; although cases in immunocompetent individuals have been reported[43]. The concepts of autoinfection and hyperinfection are somewhat overlapping; therefore, hyperinfection syndrome denotes the presence of signs and symptoms attributable to increased larval migration due to autoinfection with the development or exacerbation of gastrointestinal and pulmonary symptoms; this is accompanied by the detection of increased numbers of larvae in stool and/or sputum and defines hyperinfection. Larvae in non-disseminated hyperinfection are increased in numbers but confined to the organs normally involved in the autoinfective cycle that occurs chronically at low scale (i.e. gastrointestinal tract, peritoneum and lungs) although enteric bacteria and yeast, that can be carried by the filariform larvae or gain systemic access through intestinal ulcers, may affect any organ system[44]. Although the migratory route that allows the perpetuation of the cycle is through the GI- pulmonary-GI route, extra-pulmonary migration of larvae has been shown to occur routinely during the course of chronic *S. stercoralis* infections in experimental dogs[14]. Notably, many cases of hyperinfection are fatal without having larvae being detected outside the GI/pulmonary systems.

The clinical manifestations of hyperinfection vary widely, since the onset and course of the syndrome can be related to the *S. stercoralis* itself, the bacteria that disseminate with the *S. stercoralis* larvae or both; therefore, the presence of fever or other signs of progressive disease should trigger a search for enteric bacteria in other organ systems.. The presence of eosinophilia is only seen in a minority of cases during hyperinfection; more often there is a suppression of peripheral eosinophil levels, sometimes related to corticosteroid therapy[13,45]. The presence of peripheral eosinophilia during hyperinfection appears to predict a better prognosis[46].

Gastrointestinal symptoms are frequent but non-specific and directly related to the presence of large quantities of larvae in the intestinal lumen. The symptom relate to the invasion of the GI tract that leads to inflammation, bleeding and ulceration. Abdominal pain (often described as crampy or bloating in nature), watery diarrhea, constipation anorexia, weight loss, difficulty swallowing, nausea, vomiting and small bowel obstruction may result, with

diffuse abdominal tenderness and hypoactive bowel sounds. Protein-losing enteropathy or ascites might appear as well, as are electrolyte abnormalities that reflect these gastrointestinal disturbances. Occult or gross blood is a common finding, resulting from colitis and proctitis[1,44]. Paralytic ileus with dilated and thickened loops without evidence of mechanical obstruction can be found on abdominal imaging or surgical exploration. These radiographic findings, like small bowel distension with air-fluid levels should prompt suspicion and the search for larvae in stools when accompanied with fever, tachycardia and hypotension.

Involvement of the respiratory system is the rule, although pulmonary symptoms occasionally are lacking. Most often symptoms related to the passage of larvae and the irritative responses are seen in disseminated infections and include: dyspnea, cough, wheezing, choking, hoarseness, chest pain, hemoptysis or palpitations. Rare findings of filariform or rhabditiform larvae and even, occasionally, S. stercoralis eggs support the hypothesis of adult parasites actually developing in lung tissue[47]. Chest imaging most frequently show bilateral or focal interstitial infiltrates that represent alveolar hemorrhage. Dermatologic findings include *larva currens* in the lower trunk, thighs and buttocks. Petechial and purpuric rashes of these same areas, in which larvae have been demonstrated on skin biopsy, is common, including the thumbprint sign of periumbilical purpura, that radiates from the umbilical area and resembles thumbprints[48]. Vasculitis and disseminated intravascular coagulation seen associated with sepsis may also signal hyperinfection. Meningeal signs and symptoms are the most common manifestation of neurologic involvement in hyperinfection syndrome. In patients with meningitis, spinal fluid may show parameters of aseptic or alternatively demonstrate characteristics of a gram-negative bacterial infection. Bacterial meningitis unrelated to neurosurgical procedures with spinal fluid or blood cultures identifying enteric flora, including polymicrobial infections, is a manifestation of hyperinfection; as is sepsis, which is caused by gut flora that gain access to extraintestinal sites, presumably through ulcers induced by the filariform larvae or by virtue of being carried on the surface or in the intestinal tract of larvae themselves[44,49]. Reports identifying organs to which larvae have disseminated include mesenteric lymph nodes, gallbladder, liver, diaphragm, heart, pancreas, skeletal muscle, kidneys, ovaries and brain based largely on autopsy studies[9].

Predisposing conditions

A variety of drug exposures and clinical conditions that impair immune responses have been reported to predispose to hyperinfection (Table 1). Among the conditions associated with hyperinfection syndrome and dissemination, corticosteroids are the most frequently encountered. Beyond their known immunomodulating effects, it has been postulated that corticosteroids have a direct effect on the *S. stercoralis* parasites[50]. Hyperinfection syndrome has been described regardless of dose, duration or route of administration of corticosteroids. Even short courses (6–17 days) of corticosteroids in immunocompetent patients without underlying immunosuppressive conditions have even been associated with hyperinfection syndrome and death[51].

Human T-cell lymphotropic virus type 1 (HTLV-1) represents a significant risk factor for the development of hyperinfection syndrome or disseminated strongyloidiasis[52,53]; the underlying mechanism appears to be associated to alterations in regulatory T-cell counts and reduced antigen driven IL-5 production, which is expressed by low total IgE levels[54,55]. There is also an impact of *S. stercoralis* infection on the natural history of HTLV-1 and has been considered a co-factor in the development of HTLV-1-associated diseases[56,57]. In contrast, HIV infections were once considered an AIDS-defining illness although there is no evidence of a relationship between HIV status and severe strongyloidiasis and corticosteroids have been implicated in several cases of hyperinfection occurring in HIV infected individuals[9].

S. stercoralis infections in the transplanted population, both in solid organ and hematologic transplants, is linked to the immunosuppression used as part of post-transplant regimens or for the treatment of conditions such as graft vs host disease (GVHD) and has been primarily linked to tacrolimus use[58]. *Strongyloides* infection acquisition through a cadaveric kidney has also been reported[59].

Diagnosis

The major obstacle for understanding the distribution, burden and clinical characterization of chronic (often asymptomatic) *S. stercoralis* infection lies in the poor sensitivity of the available diagnostic methods[11,60] and in the biology of *Strongyloides*, where the adult female releases eggs/larvae intermittently. Diagnosis of hyperinfection syndrome/ disseminated *S. stercoralis* infection is much less difficult given the florid clinical presentation and the large numbers of larvae often seen in the stool or other bodily fluids including cerebrospinal (CSF) and bronchoalveolar lavage fluid.

Although classic parasitological methods looking for the identification of larvae through either culture or direct methods are still used in many laboratories, their complexity in terms of labor and their relatively low sensitivity, is giving way to the incorporation of new immunological- and nucleic acid amplification (NAAT)-based methods for both the clinical and public health approaches to strongyloidiasis[60,61]. Nevertheless the lack of an acceptable gold standard for diagnosis makes it difficult to assess the accuracy of new methods[62].

Parasitological methods

Definitive diagnosis relies on detection of larvae in the stool rendering the more standard STH-egg focused techniques such as Kato-Katz, McMaster`s and FLOTAC relatively useless for *S. stercoralis*. As mentioned above, intermittent and scanty excretion of larvae also limits the utility of standard stool studies. Among these techniques, the formalin ethyl acetate concentration technique appears as the method that is most frequently used in routine stool examination and is also a method that can be completed and yield results rapidly. Indeed, this method had a sensitivity that, in some studies, was the superior among parasitological methods[63]. The collection of stools without preservatives improves sensitivity by maintaining larvae alive thus allowing easier detection of moving larvae under the microscope. In the Baermann concentration method, stool is placed on coarse fabric or paper overlying a mesh screen in a funnel that is filled with warm water and connected to a

clamped tube; after incubation, larvae migrate into the water and are collected by sedimentation in the water through centrifugation; this method can be further improved if the stools are previously cultured for 24 hours with charcoal. Despite its superior efficacy in diagnosing infections in different studies, this technique is cumbersome and laborious[61,64] and other techniques such as the Harada-Mori filter paper culture or nutrient agar plate cultures are also methods with a sensitivity higher than direct smears (but require longer incubation times[65,66]). Sensitivity improves with larger numbers of sequentially collected samples reaching almost 100% when seven stool samples were studied[64,67]. Invasive methods to retrieve larvae from the duodenum, where adults are most frequently found, such as duodenal aspiration and the string test are not currently part of routine practice. Duodenal biopsy, when performed, can demonstrate parasites nested in the gastric crypts or duodenal glands, as well as eosinophil infiltration of the lamina propria[68] although this depends on finding the correct anatomical niche.

Nucleic Acid Amplification Tests (NAAT)

Consistent with the trend in diagnostics, NAAT using standard (and/or nested) PCR, qPCR or loop mediated isothermal amplification (LAMP) assays – have been increasingly gaining traction for use in the diagnosis of *S. stercoralis* infections[69–73]. Indeed, the improved specificity relies on the specific DNA targets used (18S rRNA, IST1, cytochrome c oxidase subunit 1 or the highly repetitive interspersed repeat sequence[74]) and improved methods for DNA extraction in stool[70,72]. As a public health tool as well as a multitarget clinical tool, the integration of *S. stercoralis* qPCR in platforms that are bundled with other intestinal parasites in multiplex and multi-parallel forms allows integration and screening in a standard, simplified way[70,71,75]. Although a recent systematic review warned about the limitations of these NAATs, which in this analysis was found to have an overall sensitivity of 71.8%, specificity in the other hand was interpreted to be at least 93%[76]. Sub-optimal sensitivity has been hypothesized to be secondary to intermittent larval production (or at least lower than the threshold of detection by the particular method) and to the presence of PCR inhibitors in stools[77] though most of these theoretical concerns have been overcome with better technological approaches. NAAT methods have been explored in extra-intestinal samples in just a few studies in urine samples in a rodent model and in a clinical study in endemic communities[78,79].

In the setting of clinical trials to evaluate the efficacy of interventions to treat infection, proper interpretation of results also suffers from the limitations of current diagnostic methods. In a very well-designed experiment, Dreyer *et al* demonstrated using the Baermann concentration technique in samples from military recruits in Brazil, that with 8 samples the cumulative sensitivity climbed from 32% with 1 sample to 67% with 8. Because of the intermittent positivity throughout the 8 separate collections from a single individual, in the setting of a clinical trial results would be mistakenly interpreted as cure when the first but not the subsequent samples are positive[67]. Serology offers a solution as a more reliable test of cure (see below) since it relies on the human immune system that does not depend on intermittent larval detection in stools[80,81].

Immunological methods

Several immunoassays for antibody detection, most notably enzyme-linked immunosorbent assays (ELISAs), have been increasingly used to overcome the limitations of parasitological methods to increase diagnostic sensitivity and to simplify processing. Almost all of these tests (both in commercial and government-run laboratories) rely on measuring an IgG response to a crude soluble extract of larvae obtained from experimentally *S. stercoralis*-infected animals or from related *Strongyloides* species (e.g. *S. ratti*). Despite their utility, these antibody-based immunoassays have several limitations including: 1) cross reactivity in patients with active filarial or other STH infections; 2) lower sensitivity in patients with hematologic malignancies or HTLV-1 infection; and 3) the inability to distinguish between current and past infection.

To overcome some of these diagnostic obstacles, *S. stercoralis*- specific recombinant antigens, such as NIE[82] and SsIR[83] have been used in a number of formats including ELISA[63], luciferase immunoprecipitation systems[63,81] and diffraction-based biosensors[84]. The use of recombinant NIE and/or SsIR has improved greatly the diagnostic accuracy and utility of these antibody-based assays[60]. The high negative predictive value of these immunoassays can be particularly useful in excluding *S. stercoralis* infection as part of the differential diagnosis[80,85].

In a blinded comparative multicenter assessment that included 399 samples, specificities above 90% were achieved with the LIPS-NIE being the most specific[85] and most assays demonstrating sensitivities above 80–85 %. In another trial with 101 samples, 2 commercially available ELISA kits (InBios Strongy Detects IgG ELISA - InBios International, Inc., Seattle, WA and the SciMedx Strongyloides serology microwell ELISA - SciMedx Corporation, Denville, NJ), were compared to an in-house LIPS using the recombinant antigens NIE and SsIR[86]. Although there was only a 65% agreement among the 3 assays, the lack of stool microscopy (or qPCR) data makes the study uninterpretable with regards to sensitivity and specificity for *S. stercoralis*[86].

Direct antigen detection assays have been evaluated in the form of capture ELISA assays developed for *S. stercoralis* coproantigen detection, but their utility awaits further testing and availability[87].

Indirect markers

The diagnosis of strongyloidiasis can occasionally be inferred indirectly based on elevated eosinophil or serum IgE levels in concert with appropriate clinical and epidemiologic settings. Eosinophil counts have been the most studied as strongyloidiasis is often included in the differential diagnosis when eosinophilia is encountered either as an incidental finding or as part of the evaluation of special populations such as migrants, refugees or returning travelers with fever[88,89]. In a recently published report in refugees from Southeast Asia to the US, eosinophilia (>400 cells/μL) was significantly associated with a diagnosis of strongyloidiasis[90]; noteworthy, eosinophilia was not a very sensitive indicator of strongyloidiasis in that study, since 27% of those positive for *S. stercoralis* by qPCR were not eosinophilic. Similar findings were reached in another study with mostly African

refugees that found that eosinophilia was absent in 33% of those definitively diagnosed with strongyloidiasis[91]. Since a significant number of individuals may have eosinophilia, strongyloidiasis should be considered in the differential diagnosis of eosinophilia in travelers or expatriates from endemic areas, particularly when accompanied by infiltrates in chest images and/or abdominal symptoms[90,92];

Elevated serum IgE levels are another frequent finding in strongyloidiasis and present in 39 to 58% of the cases[61]. This association between elevated serum IgE levels and strongyloidiasis is rarely observed in HTLV-1 co-infected individuals[54], a finding that may be linked to the inability of HTLV-I positive patients to clear *S. stercoralis*.

Treatment

Specific antiparasitic treatment with anthelmintic drugs is indicated in all infections with *S. stercoralis* regardless of the presence of symptoms or the immune status of the host. Treatment aims for resolution of symptoms and infection in symptomatic individuals and cure in asymptomatic individuals to prevent potential lethal complications in individuals harboring infections chronically. In contrast to the goals of drug treatments for other STH, which in the context of public health interventions, target the control of these endemicities in affected communities by eliminating high and moderate intensity infections without curative goals[93], the case of *S. stercoralis* with its capacity for internal reproduction through autoinfection has a curative goal in all instances, so that the organisms are cleared completely, thereby eliminating the possibility of autoinfection.

Ivermectin is currently the drug of choice for all type of treatments. The regimen of 200 μg/kg/day for 2 days remains the treatment for uncomplicated *S. stercoralis* infections as it targets both adults and larvae[6,94]. Thiabendazole (25 mg/kg/day) for 3 days is an alternative treatment, but drug availability and gastrointestinal side effects have limited the use of this drug as ivermectin became more widely available. Albendazole at 400 mg twice a day for 3–7 days has been shown to be less effective than ivermectin for the treatment of uncomplicated *S. stercoralis*[94,95] and is an alternative therapy (Table 2). A recent Cochrane Collaboration Review concluded that ivermectin has superior efficacy than albendazole and is statistically equal to thiabendazole, but the latter has more adverse events than ivermectin[94] (Table 3). In this review[94] the cure rates for ivermectin, albendazole and thiabendazole were 74 to 84%, 48% and 69% respectively. A recent report from a non-endemic area warned of the failure of ivermectin to achieve parasitologic cure in a small group of individuals followed for up to 4 years[96]. From a public health perspective, data from different latitudes agree on the efficacy of mass drug administration with ivermectin in lowering the prevalence of *S. stercoralis* infections, in some cases even years after treatment is stopped[97–99]. Hyperinfection syndrome, as a medical emergency, should prompt initiation of treatment with ivermectin immediately if this diagnosis is being considered. The regimen for severe disease is for a minimum of 2 weeks (and often until there has been evidence of two full weeks of negative stool examination), although the lack of clinical trials precludes the recommendation of evidence-based guidelines. Reduction of immunosuppressive therapy should also be an important part of treatment when this is feasible.

Unorthodox methods of ivermectin administration may have to be used when patients are unable to take or absorb oral medication (even through a nasogastric tube) because of severe systemic illness or paralytic ileus. These include per rectal and parenteral formulations that come from veterinary formulations[100].

Closing remarks

Human strongyloidiasis is a cosmopolitan public health infectious disease problem that is unique compared to other STH. These unique features must be addressed and incorporated in public health strategies for diagnosis and treatment and for individual case management. In view of growing awareness and advocacy of the importance of *S. stercoralis* infection as a significant medical problem and the lack of a public health strategy[11], new insights into the true global prevalence and the most adequate diagnostic, therapeutic and overall public health approach for disease control are likely to change our understanding of human strongyloidiasis in the near future.

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Key Points

- *Strongyloides stercoralis* is a unique soil transmitted helminth which through autoinfection can sustain chronic asymptomatic infections for decades.
- New diagnostic approaches through serology and nucleic acid amplification tests (NAAT) with superior sensitivity compared to stool microscopy are becoming more available for case management.
- In transplant candidates and subjects receiving immunosuppressive drugs (mainly corticosteroids), strongyloidiasis should be considered and treated promptly
- Hyperinfection is a medical emergency with high mortality that requires prompt treatment initiation.
- Ivermectin is the treatment of choice for all clinical forms of strongyloidiasis, which should be treated even in asymptomatic cases.

Table 1 -

Conditions associated with hyperinfection syndrome

Drugs/Biologies	
Immunosuppressives	Corticosteroids
	Azathioprine
	Cyclophosphamide
	Methotrexate
	Tacrolimus
	6-mercaptopurine
Anti-neoplastic agents	Adriamycin
	Bleomycin
	Carmustine
	Chlorambucil
	Doxorubicin
	Daunorubicin
	Ifosfamide
	Melphalan
	Mitoxantrone
	VP16
	Vinca Alkaloids
Biologies	Etanercept
	Infliximab
	Rituximab
	Antithymocyte globulin
	Muromonab-CD3 (OKT3)
	Mycophenolate mofetil
Total body irradiation	
Diseases/Syndromes	HTLV1
	Hypogammaglobulinemia (nephrotic syndrome and multiple myeloma)
	Hematologic malignancies and myelodysplastic syndromes
	Solid Organ Transplantation
	Hematopoietic Stem Cell Transplantation
	HIV/Immune Reconstitution Inflammatory Syndrome (IRIS)
	Malnutrition
	Alcoholism

Table 2.

Treatment for strongyloidiasis

Clinical syndrome	Treatment of choice	Alternative treatment
Asymptomatic, acute and chronic non-complicated	Ivermectin 200μg/Kg/day orally for 2 days	Albendazole 400 mg, orally twice a day for 3–7 days Thiabendazole, 25 mg/kg orally twice a day for 3 days.
Hyperinfection	Ivermectin 200μg/Kg/day orally for at least 2 weeks after stool negative for larvae	Subcutaneous ivermectin: 200 mg/kg, daily, divided doses, each arm, until negative stool exam persists for 2 weeks or until patient can tolerate dosing by mouth or per rectum * Rectal ivermectin, 200mg/kg, daily, until negative stool exam persists for 2 weeks * Albendazole 400 mg orally twice a day (in addition to ivermectin)

*: not FDA approved

Table 3.

Drugs used for strongyloidiasis

Drug	Formulation	Most relevant adverse events	Contraindications and warnings
Ivermectin	3 and 6mg tablets	Encephalopathy in those with high levels (>20000/ml) of *Loa loa* microfilariae (mf)	Confirmed high levels of *Loa loa* mf < 15kg body weight Pregnancy Lactating women on 1st wk of puerperium
Albendazole	200 and 400mg tablets	Choking in infants	1st trimester pregnancy Effective contraception is recommended during therapy and for 1 month after the last dose
Thiabendazole	Tablets, 500 mg Suspension, 500 mg/5 mL	*Gastrointestinal:* anorexia, nausea, vomiting, diarrhea, abdominal pain, jaundice, parenchymal liver damage. *Central Nervous System:* dizziness, weariness, drowsiness, headache, hyperirritability, seizures, tinnitus	Activities requiring mental alertness should be avoided.