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Update on Strongyloidiasis in the Immunocompromised Host

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Abstract Immunocompromised persons are the most vulnerable population at risk for developing life-threatening clinical syndromes associated with strongyloidiasis, such as hyperinfection syndrome (HS) or dissemination. This review focuses on describing *Strongyloides* infection in the immunocompromised host, including immune response against this infection, analyzing the cases with HS published during the past 4 years in the United States, and describing the most sensitive diagnostic tools and the most effective treatment for each clinical syndrome. Strongyloidiasis is becoming an important parasitic disease in the United States, especially in the immunocompromised immigrant population. Because the transplant population is particularly at risk for developing HS, both recipients and donors should be screened for *Strongyloides*. Clinicians should also be aware that the development of HS can follow unexpectedly a few days after appropriate anthelminthic therapy. Highly sensitive screening tests are still not available in the major tertiary medical centers. Parenteral ivermectin has been used in some severe cases. Further therapy developments and improving diagnostic tools are warranted.

Keywords *Strongyloides stercoralis* · Strongyloidiasis · Immunocompromised host · Hyperinfection syndrome · Dissemination · Autoinfection · Transplant population · Immigrant · Agar plate · Anthelminthic · Ivermectin · Parenteral · USA

Introduction

Strongyloides stercoralis and *Strongyloides fuelleborni* (genus: *Strongyloides*) are two intestinal nematodes that cause the disease strongyloidiasis, which affects an estimates 30–100 million people around the world [1]. An increased number of cases seen in developed countries are related to the increased numbers of immigrants, refugees, and travelers. Without an adequate control program, this infection might be a potential emerging global infectious disease [2•]. The unique life cycle in *Strongyloides* has severe clinical consequences in humans. Both the free-living cycle (environment) and the parasitic cycle (in humans) can develop adult worms. The adult worms can survive in humans permanently for years, in a process better known as autoinfection. Nonetheless, a dysregulation of the host's immune response during this latent infection may be lethal, because multiple infective larvae can develop and invade other organs than the intestines, causing sepsis and death. This increase in the number of larvae with invasion to other organs is called hyperinfection syndrome (HS) with dissemination [3].

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Strongyloidiasis is highly prevalent in some developing countries. However, it has been seen more frequently in developed countries, especially where immigrants are present. A recent study reported 347 deaths related to strongyloidiasis (0.79 per 10 million deaths, 14–29 deaths per year) from 1991 to 2006 in the United States [4••]. Lack of strategic control programs, the increased number of infected humans' deaths reported in developed countries, and the lack of readily available treatment are some of the major issues related to this neglected disease. This review describes the immunology interaction between *Strongyloides* and some immunodeficient conditions; collects the available US cases of disseminated strongyloidiasis reported between 2006 and 2010; and updates the most available and sensitive diagnostic tests and treatment of strongyloidiasis described in the literature.

Overview of the Pathogenesis and Immune Response of *Strongyloides* Infection

A fine balance between the T helper 1 (Th1) and 2 (Th2) response plays a key role in the host's response against *Strongyloides* infection (Fig. 1). CD4/T cells are composed of Th1 and Th2 subpopulations based on the type of cytokine secretion. In general, the cytokine production of the Th1-type T-cell subpopulation can down-regulate the Th2-type cytokines profile, and vice versa. In the Th1 response, there is production of interferon (IFN)-γ, activation of macrophages, $CD8^+$ cytotoxic T cells, and generation of IgG2a; whereas in the Th2 response, interleukin (IL)-4, IL-5, IL-10, and IL-13, and IgA, IgE, and IgG1 are produced [5]. Immune responses elicited by nematode infections in normal subjects are Th2 type, characterized by production of high levels of IL-3, IL-4, IL-5, and IL-13, and eosinophils and specific IgA [6, 7].

During *Strongyloides* infection, two Th2-dependent mechanisms have been proposed for killing the penetrating infective larvae: mast cell degranulation and direct killing of the parasite by eosinophils. Mast cells are activated by IL-4 and their degranulation depends on the presence of IgE against parasite antigens. The IgE, IgG1, and IL-4 cytokines are elicited by *Strongyloides* infection [8]. At an intestinal level, a strong Th2 response is present by intense mast cell activation through IL-3 pathway, and eosinophil production against the parasite [9–11]. Expansion and activation of eosinophils for parasite killing depends on IL-5; when IL-5 suppressors are used (decreasing Th-2 response), levels of larva killing decreased significantly [12]. Likewise, corticosteroids suppress Th2 response directly by binding the glucocorticoid receptors of the $CD4^+$ Th_2 cell membrane, causing apoptosis and T-cell dysfunction. Corticosteroids may also increase ecdysteroid-like substances, which act as molting signals for eggs and rhabditiform larvae, leading to increased number of filariform larvae and dissemination [13]. If the immune response is manipulated to Th1, for example, providing IL-12 (Th-1 immune response modulating cytokine), eosinophils levels are decreased and protective immunity can be lost [14].

Furthermore, the innate immune response (early response mainly by macrophages, dendritic cells, neutrophils) and the

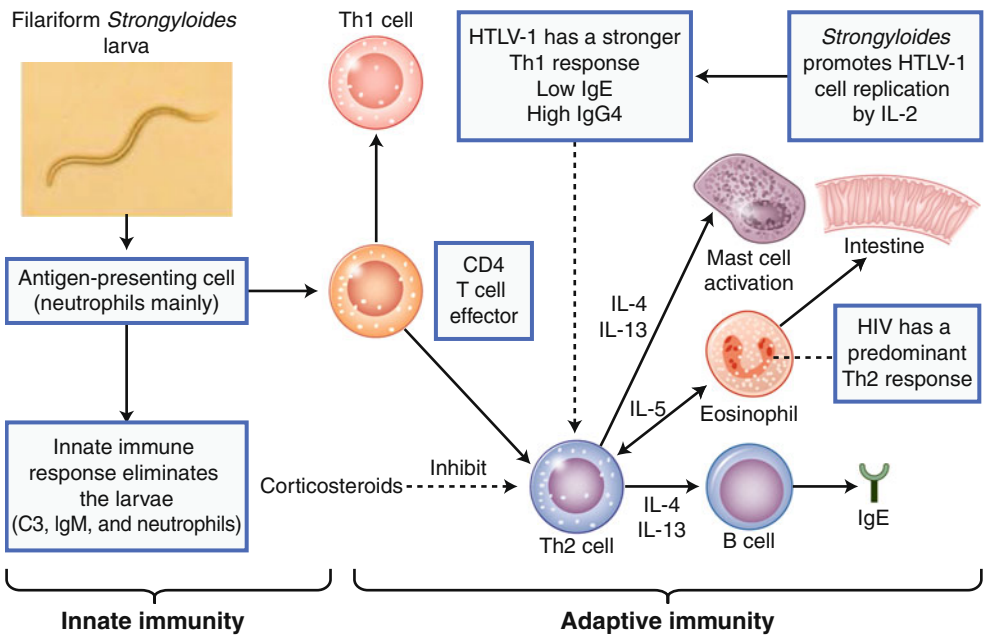

Fig. 1 Immune response of *Strongyloides* infection. *HTLV* human T-cell lymphotrophic virus; *IL* interleukin; *Th* helper T cell.

adaptive protective immune response (B and T lymphocytes) are activated during the initial *Strongyloides* infection [15]. Killing of the infective *S. stercoralis* larvae by immunized mice is dependent on the interaction among C3 (common factor of the complement system), IgM, and neutrophils. A probable immune induction of specific antibodies and granulocytes may be implicated on parasite clearance. A mouse model infected with live filariform larvae (L3) elicited high levels both on tissues and peripheral blood of IgG1, IgM, IgA, and eosinophils [16]. Likewise, IgM, C3, and eosinophils were found either attached to the outer surface of L3 larva or nearby [17]. IgM and IgG antibodies are both protective against larval *S. stercoralis*, but they recognize different antigens and use different killing mechanisms which, in turn, together synergize efficiently to kill the worm [18]. Filariform larvae, the infective larvae present during HS, can modify their body and evade the host immune response [19]. B-cell immune response is also important during the infection. When T-cell and B-cell–mediated responses are suppressed in mice, *S. stercoralis* attack was attributable mainly to deficiencies in B-cell–mediated immunity [20].

Immunity in *Strongyloides* infection is possible. A protective immunity induced by a previous infection or antigen-immunization depends on the stage of the infection and operates through different effector mechanisms [21]. Mice have been provided with immunity by transferring human IgG [22]. Moreover, L2 strains could have more potent stimulus of humoral response than L3 in mice [23]. Interestingly, in some nematodes, the Th1 response is elucidated with low intensity of infection, whereas Th2 is induced with high doses of worms [24]. Herein, Th2-type response increases quantitatively in response to higher doses of *Strongyloides ratti* infections [25]. However, no differences are observed when a maximum dose of worms is administered or a cumulative worm exposure time is tested [26]. Finally, a definite designation of Th1 or Th2 can be obscured, depending on when the analysis is performed during the course or time of the infection [27].

In humans, production of IgG, IgA, and IgE immunoglobulins is marked during the initial invasive phase (primoinfection). Specific IgG2 and IgG4 serum levels are more elevated in immunocompetent than immunocompromised subjects, but only IgG4 is present in the chronic infected cases [28]. In chronic cases with autoinfection, the humoral immune response has a main role in the control of the infection: IgA modulates larva excretion rate, IgE regulates autoinfection, and IgG4 may block IgE-mediated immune responses [29]. Also, IgG4 serum titers are significantly higher in patients with refractory infection after being treated with albendazole [30]. In general, eosinophilia is a common response (Th2 response) [31], but its absence is commonly seen in immunocompromised patients, a sign of poor prognosis [32]. Finally, immune response in humans against *Strongyloides* infection is difficult to study because of time, age, and intensity of infection; previous or current co-parasite infections; previous *Strongyloides* infections; and immunodeficiencies related to viruses, malignancies, and iatrogenic or congenital conditions.

Clinical Syndromes in *Strongyloides* Infection

The clinical presentation of strongyloidiasis can range from an indolent to a life-threatening condition. These are grouped in five major clinical syndromes: 1) acute infection (with Loeffler's syndrome or transient eosinophilic pulmonary infiltrates); 2) chronic intestinal infection; 3) oligo-asymptomatic autoinfection; 4) symptomatic autoinfection; and 5) hyperinfection syndrome (HS) with dissemination [2, 33, 34].

It is extremely uncommon to see the acute infection in clinical practice; reports are mainly in volunteers [35]. Chronic intestinal infection (latent) occurs mainly in endemic countries and occasionally is seen in travelers, immigrants, and refugees [36, 37••]. Asymptomatic autoinfection occurs in immunocompetent persons in endemic areas; this is the stage responsible for persistent infection (lasting for decades). Symptomatic autoinfection with epigastric pain and diarrhea occurs in people living in endemic areas and those with malnutrition, alcoholism, diabetes, or any immunodeficiency [37••]. Dissemination and/or HS occurs in iatrogenic immunocompromised subjects (e.g., pulses of corticosteroids or anti-tumor necrosis factor (TNF) therapy or other immunosuppressants), those coinfected with human T-lymphotropic virus type 1 (HTLV-1), diabetic patients, patients with hypochlorhydria, those with hematologic malignancies (especially lymphoma), kidney transplant recipients, patients with impaired gut motility, patients with tuberculosis or protein-caloric malnutrition secondary to chronic *Strongyloides* diarrhea [2], and even in malnourished infants [38]. HS with dissemination carries the highest mortality rate (15–87%) [39]. It is characterized by severe diarrhea, abdominal pain, fever, and hypotension with meningitis and bacteremia caused by enteric flora organisms [34]. When the local infection is severe, the inflammatory process around the duodenum may cause obstruction. Obstruction during the severe form of the infection can have significant implications for treatment options because most of the available drugs for *Strongyloides* infection are administrated orally (approved by the Food and Drug Administration [FDA]). Parenteral administration is an option, but no drugs are approved by the FDA for this route. Eight cases of duodenum obstruction caused by *Strongyloides* infection with underlying lymphoma, HTLV-

1 coinfection, and malnutrition have been reported in the medical literature from 1970 to 2010, with a mortality rate of 33% [40•].

Lack of Eosinophilia in a Patient with *Strongyloides* Infection: An Ominous Sign

As described above, eosinophils, mediated by IL-5, are part of the Th2 immune response to *Strongyloides* infection [41]. IL-5 is produced mostly by helper T lymphocytes, mast cells, eosinophils, and natural killer cells [42, 43]. IL-5 may play a protective role in the migration of the *Strongyloides* larvae after a second infection, measured by a reduction of eosinophilia and burden of worms in infected mice treated with anti–IL-5 [44]. The association between eosinophilia and IL-5 overproduction makes the latter an appealing target for potential therapeutic interventions. Eosinophils are involved on larva killing during innate immunity, and they induced production of protective antibodies (mainly IgM) within adaptive immune response [45]. In humans, eosinophilia is higher in healthy than in immunocompromised people. In addition, among four groups of infected subjects with *Strongyloides* (those with HIV, those with chronic illness, users of immunosuppressant drugs, and relatively healthy subjects), the HIV group had less significant eosinophilia (P=0.004) than other groups. On the other hand, healthy subjects mounted a strong peripheral eosinophilia [46]. In a recent series of 33 reported cases of strongyloidiasis, two of five patients (40%) with HS presented with eosinophilia; from the total cases reported, only 64% (N=21) had eosinophilia (>500 eosinophils/mm^3) [37••]. The lack of eosinophilia in the sickest patients with either HS or dissemination is likely caused by a weak or deficient Th2 response. Therefore, lack of peripheral eosinophilia is an ominous sign that may contribute to decreased suspicion of a parasitic infection.

Strongyloides and HTLV-1 Coinfection

HTLV-1 and *Strongyloides* infection is a potentially lethal combination [33]. The risk of developing strongyloidiasis is twofold among those coinfected with HTLV-1 compared to healthy people [47]. A predominant Th-1 cell response is strong in HTLV-1 infection, with high production of IFN-γ and TNF-α by Th1 cells [48] and a weaker Th2 response. Therefore, the decrease in IL-4, IL-13, IL-5, and IgE reduces mast cell degranulation [49, 50], and impairs eosinophil recruitment and parasite-killing activity [51]. More rhabditiform larvae remain alive, which transform into L3 filariform larvae, with the potential of developing HS and dissemination [52]. Some cytokines (e.g., IgG4 and IFN-γ) are increased in HTLV-1 patients than in controls [53, 54]. IFN-γ suppresses IL-4 and therefore IgE production; this mechanism may explain treatment failure in this population [54]. Interestingly, *Strongyloides* infection can influence the natural history of HTLV-1 infection by promoting polyclonal proliferation of HTLV-1–infected cells through activation of the IL-2/IL-2R system and can be a cofactor for developing HTLV-1–associated diseases [53]. Also, after treating *Strongyloides* with ivermectin in a patient with HTLV-1–associated adult T-cell leukemia-lymphoma, HTLV-1 RNA viral load reduced dramatically, suggesting that *Strongyloides* was a potent stimulus for virus expression [55]. On the other hand, a patient with *Strongyloides* who failed therapy with ivermectin, thiabendazole, or albendazole should be considered HTLV-1 coinfected until proven otherwise [47, 52, 56]. For the above reasons, it is reasonable to investigate HTLV-1 infection in patients with *Strongyloides*, especially those who fail therapy [57].

Strongyloides Infection in HIV Patients

There is a notable absence of disseminated strongyloidiasis in advancing HIV disease [58], so that the Centers for Disease Control and Prevention (CDC) excluded HS as a criterion of AIDS (CDC, 1987). An explanation may be an increased Th2 response and a decreased Th1 cytokine profile seen commonly in AIDS [59]. This increased Th2 response may protect against severe forms of strongyloidiasis, but can predispose to accelerate replication of HIV-1 [60, 61]. Also, lower CD4 levels are associated with indirect development of *Strongyloides* and less likelihood for dissemination [62]. If Th2 response is overexpressed in HIV patients, the eosinophil counts should be higher. However, lack of eosinophilia in HIV-infected patients with strongyloidiasis has been described [46]. This paradoxical immune response is not fully understood, but either HIV decreases the eosinophils, or another immunological mechanism inhibits the eosinophils in peripheral blood or in precursor cells. Th2 response may help to control the latent *Strongyloides* infection to develop HS, but does not protect against cryptosporidial infection, which needs Th1 response to be eliminated [63]. In AIDS, the polarized Th2 response is more closely associated to coccidian rather than helminthic infections [64].

HS has been seen in AIDS patients because of the use of corticosteroids for immune reconstitution inflammatory syndrome (IRIS) or during IRIS [65, 66]. Only 14 HIV cases with disseminated strongyloidiasis have been reported in the English-language literature until 1994 [67]. Filariform larvae were reported in the ascitic fluid of a patient with HIV who had ascites and peripheral edema [68].

Perhaps the associated profound immunosuppression in AIDS may eventually increase the risk for HS or dissemination in some cases; however, this risk is not as high as in other immunocompromised conditions.

Overall, the prevalence of *Strongyloides* infection is higher in HIV-positive patients compared with the general population. Studies done in endemic areas showed significant differences. In South America, *Strongyloides* infection was present in 4% of HIV patients, whereas the prevalence was 1% in the general population [69]. In Africa, 12.6% (N=214) were infected with *Strongyloides* in the HIV population, whereas 0.6% (N=164) of non–HIV-infected patients were infected [70]. In Central America, *Strongyloides* infection was present in 7.7% of HIV patients and in 0% of the HIV-negative patients [71]. In conclusion, strong evidence exists that *Strongyloides* infection is more prevalent in HIV patients. Screening tests for *Strongyloides* should be mandatory for HIV patients coming from endemic areas.

Strongyloides Infection in the Transplanted Patient

A major US cancer center found 25 cases with *Strongyloides* infection between 1971 and 2003 (1.0 per 10,000 in new cancer cases); only two patients with hematopoietic stem cell transplantation (HSCT) were reported, and both died with HS [72]. Among the transplant population, the HSCT recipients are the most commonly reported in the literature with fatal *Strongyloides* hyperinfection. In addition, five of six cases died after HSCT (83% mortality) because of strongyloidiasis complications [73•]. This alarming mortality favors for screening tests for strongyloidiasis in this particular HSCT population. The epidemiologic factor and clinical picture (unexplained eosinophilia, serpiginous skin lesions, pulmonary or gastrointestinal symptoms) may justify starting empiric therapy (ivermectin) in selected cases despite negative stool tests. Even asymptomatic patients who have been in endemic areas should undergo testing for *S. stercoralis* before HSCT. Baseline serology and follow-up titers are recommended because these immunocompromised patients may require repetitive courses of the antiparasitic (e.g., monthly during intense immunosuppression).

Among immigrants, Hispanics have been the most frequently reported with strongyloidiasis. This finding raises a particular concern because a high number of transplanted patients are Hispanics (the third most common ethnicity according to http://optn.transplant.hrsa.gov/latestData/rptData.asp). In 2008, a total of 27,281 organs were transplanted in the United States [74], of which 3,765 recipients and 1,119 donors were Hispanic. In a European study during 2004 and 2007, half the patients with strongyloidiasis (N=33) were from South America [37••].

Donors also can transmit the infection. A cadaveric kidney donor transmitted *Strongyloides* to the recipient [75]. Another case of intestinal transplant from a middle-aged woman from Central America (donor) was suspected as the source of HS in the recipient, who died [76•]. Two recipients of renal allografts from a single donor developed disseminated strongyloidiasis [77]. A pancreas allograft recipient with no exposure to an endemic area developed strongyloidiasis [78]. Therefore, screening tests should be performed in the recipient and donor (serology), based on epidemiological risk factors and country of origin.

Finally, a recent study of screening tests for strongyloidiasis in the Hispanic transplant list found that 6% (N=83) of them had serology positive for *Strongyloides* [79•]. If about 4,800 Hispanic persons are both donors and recipients for transplantation per year in the United States, it is possible that about 290 of them carry *Strongyloides* infection. Effective therapy might prevent significant complications and perhaps reduce mortality. Of note, among the authoctonus US transplant cases with strongyloidiasis, most of them acquired the infection in Kentucky or Tennessee [80, 81••, 82]. In conclusion, screening programs in the transplant population may also involve other people from the Southeast in North America, not only immigrants.

Strongyloides Infection in Rheumatological Conditions

In the rheumatologic field, corticosteroids are commonly associated with HS. Other immunomodulating drugs have been associated with increased risk for HS; however, a direct relationship is difficult to establish because most of these patients are also on corticosteroids upon presentation [83]. A review for HS prophylaxis in immunocompromised rheumatic patients concluded that no evidence was found in literature (from 1966 to 2008) to suggest an anthelminthic regimen as prophylaxis. However, the study concluded that ivermectin is the most safe and effective drug for treatment of *Strongyloides* infection (based on 13 clinical trials), with a dose every 6 months (expert opinion) in permanent residents from endemic areas [80].

Human Cases of Strongyloidiasis with HS or Dissemination Reported in the United States between 2006 and 2010

Human cases in the United States were collected in the period between 2006 and 2010 from the available literature (Table 1). The objective was to report new developments in the severe *Strongyloides* cases seen in the United States. Medline, as the data base, was used to collect the cases. Keywords such as "*Strongyloides*" and "Strongyloidiasis"

combined with "US or USA" or "North America" were used. A total of 16 cases of HS or dissemination were reported during this time. The age range was 19–74 years old (median 51.5 years old). Mortality was 69% (N=16) (Table 1).

Applicability of Current Diagnostic Tests in Developed Countries

It should be mandatory to implement, perform, and spread the use of highly sensitive stool and serological tests for *Strongyloides* in developed countries. Diagnosis of *S. stercoralis* is difficult because stool examination with conventional techniques (e.g., direct smear) fails to detect the helminth larvae [84]. Serology does not differentiate between remote, recent, current, or resolved infection. Moreover, a negative serological result does not rule out *Strongyloides* infection. For instance, a case of disseminated infection with presence of *S. stercoralis* larvae in sputum revealed a low titer (0.13), which was negative by laboratory reference values (< 1.49 considered negative) [85]. Serology has been reported to have a negative predictive value of 95%; however, this finding was in a nonimmunocompromised population [86]. A false-negative serology result may be associated with the immunosuppression related to the hematological malignancy or chemotherapy. Although a stool parasitological test may be time-consuming, and may fail to detect the larvae because of intermittent excretion or the need for technical training, it is the simplest, most inexpensive, and reproducible test to perform in any health center. Table 2 provides a summary of the sensitivity of each parasitological test. Overall, the agar plate is the most sensitive, simplest, and effective method to detect the larvae. A minimum of three fresh stool samples (not conserved in formalin) from separate days should be analyzed. [81•, 87]. Special attention must be given to the morphological features of the larvae because hookworm larvae may also be present if the patient is coinfected; however, coinfection is extremely rare in the United States. The Baermann technique can also be easily implemented in a microbiology laboratory with a minimum technical training [88]. It is important to detect latent *S. stercoralis* infections before administering chemotherapy or before the onset of immunosuppression in patients at risk, but specific and sensitive diagnostic routine tests are not readily available in the United States [89].

Treatment of Chronic Strongyloidiasis Except for HS or Disseminated Disease

The treatment of choice for chronic strongyloidiasis is ivermectin, 200 μg/kg/day, for 2 days for chronic active or latent stages. An alternative is thiabendazole, 25 mg/kg/day administered twice a day (after meals to decrease side effects) for 3 days. According to a study that included 32 children with chronic strongyloidiasis, the efficacy of thiabendazole was 91% with follow-up at 90 days after therapy with agar plate stool cultures and the Baermann technique [31]. Adverse effects were headache, dizziness, and epigastralgia in 6.2% of individuals. It was concluded that the studied scheme showed a high effectiveness rate and was well tolerated [31]. A previous study evaluating thiabendazole and ivermectin for chronic strongyloidiasis showed a cure rate of 78% (N=31) for thiabendazole, 77% (N=17) with ivermectin on a single day, and 100% (N=35) with ivermectin on 2 consecutive days. Thiabendazole was in general well tolerated, with only participants (16%) experiencing side effects (asthenia, epigastralgia, and disorientation) [90]. In both studies, when the eosinophilia continued after treatment, a high percentage of not-cure rate was observed; therefore, a persistent eosinophilia is suspicion for treatment failure.

Albendazole has a low efficacy for *Strongyloides* infection (< 50%), and despite its broad availability in the world, it is not recommended to treat *Strongyloides*. Three days of albendazole, 400 mg daily, had a cure rate of only 38% (N=24) for chronic strongyloidiasis, whereas the cure rate for ivermectin, 150–200 μg/kg, in a single dose, was 83% (N=29) (P<0.01) [91]. Another study using the same doses showed a cure rate of 45% for albendazole and 83% for ivermectin (N=301) [92]. Currently, because of concerns about the efficacy of albendazole in strongyloidiasis, it is strongly recommended to have this drug as a third alternative, after ivermectin and thiabendazole (in that order).

Management of HS and Dissemination Syndromes Caused by *Strongyloides*

The available clinical trials have assessed drug treatment of *S. stercoralis* infection in patients with chronic strongyloidiasis. Clinical trials are lacking in the hyperinfection and dissemination syndromes because of the small number of cases seen in clinical practice, delayed diagnosis, existing complications, and high mortality from brain infarcts or other irreversible complications. However, a recommended regimen for immunocompromised patients with hyperinfection or disseminated strongyloidiasis can be ivermectin, 200 μg/kg, by mouth daily for 2 days, repeated in 2 and 4 weeks [93, 94]. Thiabendazole, 2 g daily for 3 days, and then 1 g daily for a cycle of 30 days or more (as many times as necessary, according to treatment response) has a cure rate≥80% for HS, but has significant side effects (Alvarez H, personal communication). The 2-week interval is

Table 1 Clinical presentation in patients with hyperinfection syndrome or dissemination caused by *Strongyloides* infection in the United States between 2006 and 2010

Patient	Demographics (Country of origin)	Clinical presentation	Risk factors	Treatment	Diagnosis (Outcome)[a]	Study
1.	64 y, M	Pancreatitis, respiratory failure	Prednisone	IVM	Stools	Jones et al. [107]
	Puerto Rico	*E. coli* and *S. viridans* bacteremia	Asthma		(Survived)	
2.	58 y, F	E. coli bacteremia,	COPD	N/A	Skin autopsy	Russo et al. [108]
	Unknown	VRE meningiti	Systemic steroids		(Died)	
3.	19 y, M	Ileus, Pneumoniae	Malnutrition	IVM[b]	BAL	Satou et al. [99]
	Mexico		AIDS		(Survived)	
4.	74 y, M	Pulmonary nodules	NHL		BAL	Ali et al. [109]
	Jamaica	Respiratory failure	Prednisolone		(Died)	
5.	52 y, M	Diffuse alveolar hemorrhage	Post HSCT	IVM	BAL	Datry et al. [91]
	Puerto Rico			ABZ	(Died)	
6.	38 y, F	Sepsis with *E. coli*,	SLE	ABZ	Duodenum	Marti et al. [92]
	Dom. Republic	*Klebsiella*, and *E. faecalis*	Prednisone	IVM	(survived)	
7.	63 y, M Philippines	*E. coli* bacteriemia	RA	IVM	BAL	Simpson et al. [83]
		Respiratory failure	TNF-α inhibitor	TBZ	(Survived)	
8.	68 y, M[b]	Periumbilical *Strongyloides*	Transplanted	ABZ	BAL	Weiser et al. [75]
	USA	Thumbprint purpura		IVM	(Died)	
9.	51 y, F	Respiratory failure, SBO	Dexamethasone	IVM	BAL	Aregawi et al. [110]
	USA			ABZ	(Survived)	
10.	44 y, F	*Klebsiella*, VRE bacteremia	Post HSCT	IVM	BAL	Wirk & Wingard [73•]
	Fl, USA	Respiratory failure			(Died)	
11.	62 y, F	Sepsis, lung infiltrates	Intestinal	IVM	BAL	Patel et al. [76•]
	Italy	VRE, *Klebsiella* bacteremia	Transplant	TBZ	(Died)	
12.	42 y, F	Intraabdominal sepsis	Malnutrition	IVM	Duodenum	Cruz et al. [40•]
	Brazil	Duodenal obstruction		ABZ	(Died)	
13.	31 y, M	Ileus, respiratory failure	Prednisone for	IVM	BAL	Grein et al. [65]
	Hispanic		IRIS	ABZ	(Died)	
14.	42 y, M[c]	Leukocytosis, eosinophilia	Diabetes	ABZ	Stools	Dalia & Colvin [111]
	Colombia				(Survived)	
15.	59 y, F	Hemorrhagic meningitis, SAH	CLL	IVM	Sputum	Marchi Blatt [85]
	KY, USA	Encephalitis, pulmonary infiltrates Alemtuzumab			(Died)	
16.	33 y, M	VRE meningitis, enteritis	HTLV-1	IVM	Stools	Riedel et al. [112]
	Sierra Leone				(Died)	
17.	63 y, M	Respiratory failure, hypotension	Post heart	IVM	Sputum	Roxby et al. [113••]
	Ethiopia	Abdominal pain	transplant		(Died)	

[a]Mortality: 11 deaths/total number of cases with hyperinfection syndrome (N=16)=69%.

[b]Renal cadaveric transplant from Honduran woman positive for *S. stercoralis* serology.

[c]This is not a case of hyperinfection syndrome.

ABZ albendazole; *AIDS* acquired immunodeficiency syndrome; *BAL* bronchoalveolar lavage; *CLL* chronic lymphocytic leukemia; *COPD* chronic obstructive pulmonary disease; *F* female; *HSCT* hematopoietic stem cell transplantation; *HTLV-1* human T-lymphotropic virus type 1; *IRIS* immune reconstitution inflammatory syndrome; *IVM* ivermectin; *M* male; *N/A* not applicable because diagnosis was at autopsy; *NHL* non-Hodgkin lymphoma; *RA* rheumatoid arthritis; *SAH* subarachnoid hemorrhage; *SBO* small bowel obstruction; *SLE* systemic lupus erythematosus; *TBZ* thiabendazole; *VRE* vancomycin-resistant enterococcus.

Table 2 Sensitivity of various tests for *Strongyloides stercoralis* infection

Test	Sensitivity
Agar plate	85–97%, 58–85%
Dancescu culture	82–93%
Harada-Mori culture	70–100%
Modified Baermann in cup	50–100%
Direct smear	5–44%, 24%–50%
Duodenal aspirate	76%
ELISA-IgG (serum)	80–100%, 88%
EIA (CDC)	95%
PCR (stools)	95%

CDC Centers for Disease Control and Prevention; *EIA* enzyme immunoassay; *ELISA* enzyme-linked immunosorbent assay; *PCR* polymerase chain reaction.

(*Data from* Santiago and Leitão [81•] and Gyorkos et al. [87].)

because the drug therapeutic action is extended for about 14 days.

Interestingly, some patients develop HS a few days after starting the antiparasitic therapy [65, 95, 96•], as well as dissemination [95], but the underlying mechanism is poorly understood. Possible explanations include albendazole-resistant *S. stercoralis*, delayed response to therapy, or induction of an inflammatory response that resulted in tissue damage and dissemination. A patient who received ivermectin, 15 mg daily, and thiabendazole, 3 g daily, had relief of symptoms within 3 days; however, 10 days later, the patient had respiratory failure, *Klebsiella pneumoniae* bacteremia, and proven larvae of *Strongyloides* in bronchoalveolar lavage [95]. After receiving subcutaneous ivermectin, another patient experienced definite clinical improvement associated with increased serum ivermectin levels. Despite this, the patient's respiratory distress returned and she ultimately died of respiratory failure caused by persistent *Strongyloides* infection [65]. In this last case, ivermectin levels were measured in serum; however, it is possible that the complications of the disease may be irreversible despite immense therapeutic efforts. This phenomenon of worsening disease after antiparasitic treatment (in this case, ivermectin along with thiabendazole) also may be caused by insufficient parasitic therapy, poor absorption, lack of follow-up, low efficacy of therapy, continuation of immunosuppressant, drug interactions making the antiparasitic therapy less effective, malabsorption, noncompliance, among other explanations.

Another factor to consider is hypoalbuminemia, because use of the parenteral form of ivermectin may affect pharmacokinetics and distribution. Ivermectin is highly bound to serum albumin, and lower levels of albumin can increase clearance of unbound drug, and in addition may contribute to tissue edema, which can slow absorption and increase the volume of distribution [97]. Increased clearance or volume of distribution may interfere with achievement of effective levels in many systems, including the central nervous system (CNS) [85]. If clinical status does not improve while using the oral regimen, it is recommended to measure the levels of ivermectin, or to start the parenteral form. Serum ivermectin levels ranging from 11.4 to 49.6 ng/dL have been correlated to microscopic evidence of *Strongyloides* eradication, and less than 1% penetrates to the CNS [85]. Once the larvae reach the CNS, either the drug levels in the brain are insufficient to kill the larvae or the damage is irreversible. It has been hypothesized that *Strongyloides* larvae may cause cerebral infarcts when disseminated to the CNS by capillary obstruction (seen on MRI as diffuse infarcts), possibly consistent with widespread capillary-level lesions [81•]. Promptly initiating parenteral ivermectin may prevent further dissemination of the larvae to other organs, including the CNS.

In general, ivermectin is preferable for HS or dissemination because it is superior to albendazole, given its cidal action on both the larval and adult forms of *S. stercoralis* [98, 99]. Administration of ivermectin as a rectal enema may help; 7 days of ivermectin retention enema showed a clinical improvement in 72 h [100]. Parenteral administration of ivermectin has been used as compassionate care in patients with ileus and worsening clinical status. Of note, parenteral anthelminthic drugs are not licensed for human use, and institutional review board approval is required for compassionate use; the veterinary formulation of ivermectin can be used subcutaneously in selected cases (e.g., ileus, poor oral absorption, intubated patient on vasopressors, or by clinical judgment). Reduction of immunosuppression, including minimizing corticosteroid use, is also recommended, as well as the empiric use of broad-spectrum antibiotics for enteric pathogens, including vancomycin-resistant enterococcus. In addition, a case of *Strongyloides* HS that was unresponsive to oral ivermectin and oral albendazole was controlled by subcutaneous administration of a veterinary preparation of ivermectin [101, 102]. However, deaths have been reported despite the use of parenteral ivermectin in disseminated strongyloidiasis [95]. Further clinical studies with this parenteral therapy option for ivermectin should be assessed in selected cases infected with *Strongyloides*. However, a standard dose, dosing interval, and length of therapy remain to be determined. The few published case reports have used ivermectin, 200 μg/kg, subcutaneously every 48 h, until oral therapy can be administered, and then continued for 2 and 4 weeks [103•].

Patients should have follow-up stool examinations to show clearance of the larvae, resolution of eosinophilia (if previously present), and declining serology titers;

however, false-negative results have been reported in severely immunocompromised patients. Finally, to prevent potential further dissemination of the filariform larvae to the nursing staff, extreme care is recommended when stools, nasogastric, or respiratory secretions are handled for analysis; furthermore, the microbiology staff should be notified of the suspicion or follow-up of *Strongyloides* larvae in the sample. Whether the patient with HS or disseminated disease needs to be in contact isolation remains controversial. A study showed that 41 nursing staff subjects who had close contact with two patients with dissemination of *Strongyloides* larvae did not have any evidence of *Strongyloides* infection by means of coprological or serological evidence (except for one borderline serological case) [104].

Conclusions

Mortality in the 16 collected cases with HS reported in the US literature from 2006 to 2010 remains high (69%). The majority of cases with *Strongyloides* infection are immigrants from Central and South America. Particularly at risk for severe infections are those who underwent immunosuppression without being screened or treated. The transplant population is a vulnerable population, and a significant number of immigrants from endemic countries serve both as recipients and donors. *Strongyloides* infection is more prevalent in HIV patients, and the potential of HS is imminent if IRIS is present after starting antiretrovirals, or if systemic corticosteroids are used for IRIS in patients from endemic areas. Screening tests for this population should be mandatory. Agar culture is the most sensitive parasitological stool method to detect larvae. Absence of eosinophilia does not rule out strongyloidiasis, and should not be used as screening. Routine administration of anthelminthic therapy is advised for potentially infected patients [105, 106]. Because this infection requires follow-up, it is ideal to make the diagnosis before treatment, and frequent doses (biweekly or monthly) may be recommended. Reduction of immunosuppressant doses may help during the HS, because antiparasitic therapy seems insufficient. The best approach to therapy in patients with disseminated disease is still an open question.

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- • Of importance
- •• Of major importance

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