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Strongyloides stercoralis

1. INTRODUCTION

Strongyloides stercoralis, the causative agent of strongyloidiasis, is an intestinal nematod classified in the genus Strongyloides. The latter are plasmids widely distributed as intestinal parasites in mammals. *S. stercoralis* (known also as *S. intestinalis*, *Anguillula intestinalis*, *A. stercoralis*) is a roundworm occuring mainly in tropical and subtropical countries *(1)*. In the U. S., strongyloidiasis is endemic in certain southern regions (eastern Kentucky, Tennessee, Lousiana, and southern Appalachia) *(2–4)*, although cases have been reported in all major geographic areas of the country *(2,3,5–18)*, with fatal outcomes being reported in malnourished children from socioeconomically deprived circumstances *(13,19,20)*.

S. stercoralis is uniquely capable of perpetuating itself both in the soil and within the human host *(21,22)*. Strongyloidiasis may be characterized with overwhelming proliferation of worms in the gastrointestinal tract and by maturation of noninfective rhabtidiform larvae into the infective filariform larvae before the latter are excreted into the stool. In addition, the worms can cause damage directly by invading tissues or by carrying with them intestinal microorganisms that cause secondary infections *(5,6,23–31)*.

S. stercoralis, which inhabits the gastrointestinal tract of a substantial proportion of the human population, can cause a chronic and essentially asymptomatic infection showing little if any symptoms in the immunocompetent host *(18,32–37)*. However, in the presence of abnormalities in the immune responses *(38,39)* (mainly cellular *[5,6,40,41]* but also humoral immunity), hyperinfection may develop *(8,23,27,42–47)*.

Clinically, strongyloidiasis is often asymptomatic but may be manifested by abdominal pain, distention, or ileus, and by secondary infections due to enteric (bacterial or fungal) microorganisms.

2. STRONGYLOIDIASIS AS OPPORTUNISTIC INFECTION IN IMMUNOCOMPROMISED HOSTS

Because the parasite is uniquely able to carry out its entire life cycle inside the human body, in immunocompromised patients strongyloidiasis can lead to a hyperinfection syndrome with high morbiduty and mortality due to the accelerated endogenous autoinfection *(1,6,45–47)*.

Patients on corticosteroid therapy *(5,6,48–54)* renal-transplant recipients *(55–60)* or renal deficiency *(23,27,61–63)*, patients with systemic lupus erythematosus (SLE) *(38)*, diabetes *(64–66)*, asthma *(25,29,50)*, chronic dermatosis *(10,23,27,61)*, chronic infections (lepromatous leprosy *[23,38]*, tuberculoid leprosy *[38]*, and tuberculosis *[23,27,67]*) as well as those with neoplastic conditions (lymphoma, leukemia, and solid tumors) *(6–9,23,24,28,38,61,68–74)*, protein-calorie malnutrition *(10,19,23,32,75,76)* (shown to compromise cell-mediated immunity *[23,77]*), chronic alcoholism *(11,78,79)*, and achlorhydria *(12,80,81)*, are all at higher risk and may develop systemic

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strongyloidiasis. Parana et al. *(82)* described two cases of severe strongyloidiasis coincident with ribavirin plus interferon therapy for treating hepatitis C virus infection pointing to a possible role of ribavirin in modifying the immune response to *S. stercoralis*.

Patients infected with HIV *(83–85)* and the human T-lymphotropic virus type 1 (HTLV-1) *(86–90)* may be also at high risk for strongyloidiasis. High prevalence of HTLV-1-directed antibodies has been found in carriers of *S. stercoralis (91,92)*. Occurrence of strongyloidiosis always progresses to hyperinfestation or dissemination with severe clinical carriers of HTLV-1 *(93)*. This phenomenon may be linked to selective immunosuppression by the retrovirus (as evidenced by the very low total serum levels of IgE) creating a favorable environment for nematode proliferation *(94)*. Furthermore, it has been also suggested that the *Strongyloides* infection may, in turn, contribute to the leukemogenesis by HTLV-1 in cases of adult T-cell leukemia lymphoma *(87,95)*.

Disseminated strongyloidiasis and the hyperinfection syndrome are among the opportunistic infections that would be considered indicative for underlying cell-mediated immunodeficiency such as in patients with AIDS *(83,96,97)*. Sexually active homosexual men are at increased risk for *S. stercoralis* infection, which can be acquired as a sexually transmitted disease.

The underrepresentation of the hyperinfection among the opportunistic infections linked to AIDS may be explained, at least partially, with the specific immunodeficiency state of AIDS, which may be more conducive to reactivation of infection with unicellular protozoa (e.g., *Toxoplasma gondii*) rather than to proliferation of infections involving complex, multicellular worms *(96)*. Other factors, such as underdiagnosis and underreporting may also account for the small number of strongyloidiasis cases in AIDS patients.

According to Gompels et al. *(83)*, there was compelling evidence to suggest that the development of hypeinfection occurred only in a subset of doubly infected patients because of the greater severity of HIV-induced immunodeficiency and the presence of an additional defect of the host defense, such as granulocytopenia. That is, that cell-mediated immunodeficiency due to HIV alone will not predispose to *Strongyloides* hyperinfection, but will also require a reduced numbers or function of granulocytes.

In cases reported in the literature *(84,98–104)*, the disease has been localized mainly in the intestines. Peripheral blood eosinophilia is common. Spillover infection to the colon did occur *(105)*.

Because *S. stercoralis* can pass through the lungs it can induce also chronic obstructive pulmonary disease *(106)* and extensive intra-alveolar hemorrhage *(107,108)*. Pulmonary signs and symptoms include cough, shortness of breath, wheezing, and hepoptysis, adult respiratory distress syndrome (ARDS), and pulmonary infiltrates *(108)*.

Severe disseminated strongyloidiasis can often be fatal *(52,64,66,71,106,109)*. Kiyuna et al. *(110)* have reported a case of periarteritis nodosa associated with disseminated strongyloidiasis. In addition to gastrointestinal and pulmonary disease, cutaneous manifestations (urticaria, maculopapular exanthema, localized or generalized pruritus, and prurigo) may also arise from the migration of the larvae in the skin *(47)*. Strongyloidiasis presenting as generalized prurigo nodularis and lichen simplex chronicus was described by Jacob and Patten *(111)*.

Cases associated with nephrotic syndrome brought on by infection of *S. stercoralis* have also been reported *(112,113)*. The remission of the nephrotic syndrome after treatment of the infection suggested the possibility of *Strongyloides*-associated glomerulonephtitis *(113)*. Cases of reactive arthritis induced by *S. stercoralis* are exceedingly rare *(114)*.

The eosinophil count is typically elevated in immunocompetent patients *(115,120)*, but is usually absent in immunosuppressed patients with the hyperinfection syndrome *(52,115–117)*. As reported by Aziz et al. *(32)* as many as 94% of patients with strongyloidiasis showed peripheral blood eosinophilia as a symptom of the disease. Savage et al. *(121)* reported an unusual case of an immunosuppressed patient with strongyloidiasis who was minimally symptomatic but with a dramatic increase in his eosinophil count. Although the mechanism of this phenomenon was unclear some synergistic association between the eosinophilopoietic effects of helminth infection *(117,122)* and chemotherapy *(123)* seemed plausible. In several other reports *(115,124–126)*, cases of immunosuppressed patients

with mild strongyloidiasis and higher eosinophilic counts, have also been described. Because there is no eosinophilia in AIDS patients, it may be the lack of eosinophils that is the most relevant factor to predisposition *(83)*.

Although individuals with asymptomatic infection do not have raised IgE titers, it is often a feature in immunocompromised patients, such as AIDS *(83)*. It has been suggested that greater survival may be associated with higher IgE levels *(1)*.

3. CORTICOSTEROID THERAPY AS A PREDISPOSING FACTOR FOR STRONGYLOIDIASIS

One of the major stages of the development cycle of *S. stercoralis* within the human body is the transformation of rhabdiform larvae into invasive filariform larvae in the gut *(5)*. On average, it takes between 24–48 h for this process to complete. There is evidence that the conversion of rhabdiform larve into the filariform could be altered by corticosteroid administration *(22)*. It has been established by several groups *(127–129)*, that during corticosteroid administration in animals infected with *Nippostrongylus brasiliensis* or *S. ratti*, there have been an absolute rise in worm numbers and a fractional increase in invasive filariform larve relative to rhabdiform larvae in the intestinal tracts. However, the mechanism of this augmentation of metamorphosis is poorly understood. Moreover, the corticosteroids may also reduce the local inflammation which, in turn, may further impair the containment of the parasites allowing increased number of invasive filiform larvae to penetrate the gut wall and complete the endogenous autoinfection cycle. Finally, the immunosuppression activity of corticosteroids (or any other immunosuppressive drug, such as azathioprine and cyclophosphamide) will also help enhance the predisposition of the host to hyperinfection *(5,50,51,53)*.

4. TREATMENT OF STRONGYLOIDIASIS

Even though the morbidity and mortality rates are relatively high, especially in immunocompromised hosts with hyperinfection syndrome, those patients who receive prompt and adequate treatment have a reasonably favorable prognosis to survive.

Thiabendazole, a 2-(4-thiazolyl)benzimidazole anthelmintic agent, has been the drug of choice in the treatment of strongyloidiosis especially in cases of refractory infections *(10)*. Thiabendazole, however, is not available for parenteral administration. Thiabendazole has been especially effective in immunocompetent patients *(130,131)*. For uncomplicated gastrointestinal infections, the usual recommended dose has been 25 mg/kg b.i.d. for 2 or more d *(5,6,11,38,62,83,96)*. However, in immunocompromised patients, the therapy may take longer than that *(132)*, as well as the necessity of higher doses *(5,6,109,133,134)*. According to Levi et al. *(109)*, in cases of prolonged therapy, daily administration of 3 g of thiabendazole may be adequate. Adam et al. *(24)* have used courses of 15–40 g of thiabendazole for over 10–15 d in order to achieve favorable response.

Because of its adverse side effects (dizziness, hypotension, neurotoxicity, leukopenia *[135]*, elevated hepatic enzymes *[135,136]*, and often severe cholestatic hepatitis *[137,138]*) in some patients, at least the prophylatic use of thiabendazole is controversial and did not receive wide acceptance *(139)*. Levi et al. *(109)* suggested cambendazole as an useful alternative for disseminated strongyloidiasis in cases of intolerance (high incidence of liver dysfunction) to thiabendazole. Persistent infection despite of adequate antiparasitic therapy with thiabendazole has been associated with the development of lung abscesses *(14)* harboring the parasite. The lesions are refractory to oral medication and may result in death. To this end, surgical resection or drainage may be helpful *(5)*.

Scowden et al. *(5)* treated a number of immunocompromised patients with strongyloidiasis using combination of thiabendazole (15–25 mg/kg, b.i.d., orally or via a nasogastric tube) and metronidazole.

In spite of thiabendazole therapy, in two cases *(140,141)* of ARDS associated with *S. stercoralis,* the outcome was fatal. In one of the reported cases *(141)*, ARDS had developed after successful therapy of the parasitic disease and coincided with the rapid taper of the immunosuppressive corti-

costeroid therapy. In two previous reports by the same group *(142,143)*, treatment of pulmonary strongyloidiasis has been successful despite continued therapy with high-dose systemic corticosteroids. One recommended treatment regimen for patients with ARDS involved thiabendazole (25 mg/kg, b.i.d.) given for 7 d rather than the 3-d treatment with the same dose applied to patients without ARDS *(108)*.

Savage et al. *(121)* treated strongyloidiasis in an immunosuppressed patient with albendazole (also a benzimidazole derivative) at daily doses of 400 mg given in four 3-d cycles. Other reports *(144–146)* have corroborated the efficacy of this dose regimen. In another treatment regimen, albendazole was administered at 400 mg given twice daily for 6 d, followed by a maintenance dose of 400 mg once daily *(73)*. Hanck and Holzer *(48)* also reported the use of oral albendazole to treat an immunosuppressed patient on corticosteroid therapy, and severe diarrhea and dehydration because of strongyloidiasis. Significant improvement has been reported in a case of fulminating strongyloidiasis complicating kala-azar after treatment with albendazole *(147)*.

Recent reports have indicated that ivermectin, a macrolide antibiotic primarily known for its activity against onchocerciasis, was also efficacious in the treatment of strongyloidiasis in immunocompetent patients with cure rates averaging 94% *(92,148)*. Ivermectin has been used in HIV-infected patients with *S. stercoralis*-associated hyperinfection *(84,85)*. Two regimens have been applied: a single 200-µg/kg daily oral dose *(84,149)*, or the same dose given on a multiple schedule (on d 1, 2, 15, and 16) *(84)*. All seven patients who received multiple doses showed sustained clinical and parasitological cure, whereas one of two patients who were given the single dose relapsed promptly and fatally. Ashraf et al. *(150)* also reported a case of strongyloidiasis in a patient with hypogammaglobulinemia in which ivermectin failed to clear the nematode larvae from stool, despite repeated courses of treatment throughout 14 mo. Nevertheless, because of its different pharmacokinetic profile and lesser toxicity, ivermectin may become an attractive alternative to thiabendazole.

Other drugs that have been used in the treatment of strongyloidiasis were pyrvinium pamoate and mebendazole. Giannoulis et al. *(151)* used in a patient with disseminated strongyloidiasis mebendazole (200 mg b.i.d., over a 3-d period) with dramatic clinical improvement; the dose regimen was repeated in 2 and 5 wk to completely eliminate the nematode from feces. As the case with thiabendazole, mebendazole has also been associated with high incidence of liver dysfunction *(152)*. In addition, relapse of pulmonary strongyloidiasis after medication with mebendazole (100 mg b.i.d.) was ceased, has been reported *(106)*. To this end, it is important to note that because of the high relapse rate of pulmonary strongyloidiasis (15%), serial follow-up of stool and sputum should be carried out.

Whereas in some studies pyrvinium pamoate and mebendazole were found to be effective against hookworms (*Necator Americana*, *Ancylostoma duodenale*, *A. caninum*, *A. brasiliensis*), their efficacy against strongyloidiasis was questionable *(119,152)*.

4.1. Comparative Studies

Toma et al. *(153)* have undertaken a study to compare the efficacy of ivermectin (6 mg in a single dose), albendazole (400 mg daily for 3 d), and pyrvinium pamoate (5 mg/kg daily for 3 d) in 211 patients with strongyloidiasis. For each treatment, the same regimen was repeated once 2 wk later, and the efficacy was assessed at wk 2, 6 mo, and 12 mo after the second course of treatment. The coprological cure rates were 97.0% (65 out of 67 patients), 77.4% (65 out of 84), and 23.3% (14 out of 60 patients) for ivermectin, albendazole and pyrvinium pamoate, respectively. In general, the cure rates were lower in males and patients with concurrent HTLV-1 infection.

A comparative randomized trial of a single dose ivermectin (200 µg/kg) vs albendazole (400 mg daily for 3 d) for treatment of 301 children with strongyloidiasis showed ivermectin to be superior with cure rates of 83% and 45%, respectively *(154)*. No severe side effects were observed and mild side effects were of transient nature for both treatments.

An open randomized study for comparing the efficacy of albendazole (400 mg, b.i.d. for 5 d; group A) and thiabendazole (1.0 g, b.i.d. for 5 d; group B) in chronic strongyloidiasis was conducted

in 1990–1992 *(155)*. The cure rates for group A (23 patients) and group B (12 patients) were 95% and 100%, respectively.

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