Published in final edited form as:
Curr Infect Dis Rep. 2008 May ; 10(2): 105–110.

Strongyloides stercoralis Infection in the Immunocompromised Host

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Abstract

Strongyloides stercoralis is an intestinal nematode acquired in the tropics or subtropics. Most often, it causes chronic, asymptomatic infection, but a change in immune status can increase parasite numbers, leading to hyperinfection syndrome, dissemination, and death if unrecognized. Corticosteroid use is most commonly associated with hyperinfection syndrome. Diagnosis of *Strongyloides* infection is based on serology and serial stool examinations for larvae. The treatment of choice for chronic, asymptomatic infection is oral ivermectin. Alternative pharmacologic agents include albendazole and thiabendazole. For hyperinfection syndrome, ivermectin remains the drug of choice, though therapy duration must be individualized with the end point being complete parasite eradication. Recurrent strongyloidiasis should prompt an evaluation for human T-cell lymphotropic virus type 1 coinfection. No test of cure is currently available, although immunoglobulin G antibody levels have been shown to decline within 6 months of successful treatment.

Introduction

Strongyloides stercoralis is an intestinal nematode that infects 3 million to 100 million people worldwide [1]. Although this parasite most commonly causes asymptomatic infection, an alteration in host immune status (eg, corticosteroids) can lead to fatal, fulminant infection. With widespread use of immunosuppressive agents and increased migration from *Strongyloides*-endemic areas (eg, the tropics and subtropics), numerous opportunities exist for clinicians to encounter hyperinfection syndrome in industrialized countries. Because exposures may be remote and patients unsuspecting, increased awareness among clinicians is critical to identifying and treating this parasite.

Epidemiology

Although endemic to the tropics and subtropics, foci of infection occur in temperate regions such as Japan, Italy, Australia, and the United States [1]. Within the United States, prevalence rates up to 4% have been noted in Kentucky and rural Appalachia [2]. Immigrants and refugees comprise a significant population at risk for strongyloidiasis. In one survey, 46% of Sudanese refugees in the United States had evidence of *Strongyloides* infection by serology [3•]. Although *Strongyloides* is most commonly acquired transcutaneously (as discussed in the later section on Life Cycle), several reports raise speculation about alternate routes of transmission [4]. A Japanese study observed a higher

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Disclosures
The authors have reported no conflicts of interest relevant to this article.

prevalence of *Strongyloides* infection in patients with *Blastocystis hominis*, a protozoan acquired by the fecal oral route [4]. Person-to-person transmission can occur with close contact (eg, kissing), according to one case report [5]. However, standard contact precautions appear to be sufficient to prevent nosocomial transmission [6]. Transmission of *Strongyloides* infection after transplantation of kidneys, pancreatic allograft, or intestines has been suggested in instances when donors but not recipients had a history of travel to a *Strongyloides*-endemic area [7–9].

Life Cycle

Human infection is acquired transcutaneously by contact with infectious filariform larvae in contaminated soil. In the classic pulmonary route, filariform larvae enter the circulation, migrate to the lungs, ascend the tracheobronchial tree, and reach the small intestine after being swallowed. In the small intestine, the larvae molt twice to become adult females that lay eggs in the intestinal mucosa. The eggs hatch into noninfectious rhabditiform larvae that are shed in the stool to become either filariform larvae (direct development) or free-living adult males and females that produce larvae (indirect development). Autoinfection occurs when filariform larvae penetrate the intestinal mucosa or perianal skin to re-enter the circulation and migrate to the lungs.

In the immunocompetent host, cellular immune effector mechanisms and intrinsic parasite biology are believed to regulate the population density of adult worms in the intestine [1]. With an altered host immune status (eg, exposure to corticosteroids), even one adult female can multiply rapidly by parthenogenesis, leading to accelerated autoinfection and/or dissemination. The parasite's ability to persist and multiply indefinitely in a host distinguishes *S. stercoralis* from other helminths.

Clinical Manifestations

Acute strongyloidiasis

The clinical manifestations of acute strongyloidiasis can be associated with the path of larval migration from the skin to the small intestine. Infected individuals may experience irritation at the site of skin penetration by larvae, followed by tracheal irritation or dry cough, and ultimately gastrointestinal symptoms (eg, diarrhea, constipation, abdominal pain, anorexia) [10].

Chronic strongyloidiasis

Chronic strongyloidiasis most frequently causes asymptomatic infection in the immunocompetent individual. Up to 75% of people may have peripheral eosinophilia or elevated immunoglobulin E levels; therefore, *Strongyloides* should be considered in the differential diagnosis of high-grade and/or persistent eosinophilia in travelers or expatriates from endemic areas [11•].

Symptomatic individuals may complain of diarrhea, constipation, intermittent vomiting, or borborygmus [10]. Chronic urticaria [12] or larva currens (ie, pruritic linear streaks located along the lower trunk, thighs, and buttocks) may be presenting signs or symptoms of infection. Unusual manifestations of chronic strongyloidiasis include arthritis [13], nephrotic syndrome [14], chronic malabsorption [15], duodenal obstruction [16,17], focal hepatic lesions [18], and recurrent asthma [19].

Hyperinfection syndrome/disseminated strongyloidiasis

Hyperinfection syndrome refers to accelerated autoinfection, generally the result of an altered immune status. The distinction between autoinfection and hyperinfection is not

strictly defined, but hyperinfection syndrome implies the presence of signs and symptoms attributable to increased larval migration. Development or exacerbation of gastrointestinal and pulmonary symptoms is seen, and increased numbers of larvae in stool and/or sputum is the hallmark of hyperinfection. Disseminated infection occurs when larvae migrate beyond the organs of the autoinfective cycle (lung and gastrointestinal tract), although this may occur at low levels during chronic strongyloidiasis [2]. Untreated, the mortality rate of hyperinfection syndrome and/or disseminated disease approaches 100% [1].

Hyperinfection syndrome has occurred as late as 65 years after an individual has left a *Strongyloides*-endemic area [12,20]. Eosinophil counts may be normal or even suppressed [10]. Gastrointestinal symptoms commonly occur and may include crampy abdominal pain or bloating, watery diarrhea, constipation, anorexia, weight loss, difficulty swallowing, sore throat, nausea, or vomiting [10]. Diffuse abdominal tenderness and hypoactive bowel sounds may be due to ileus and small bowel obstruction [10]. Protein losing enteropathy can give rise to hypoalbuminemia with peripheral edema and ascites [21]. Mesenteric lymphadenopathy has been reported to cause intestinal pseudo-obstruction in HIV-infected patients with hyperinfection syndrome [22]. Mucosal ulceration can occur in the small intestine as a result of direct invasion of larvae and may be associated with occult blood, hematochezia, or life-threatening gastrointestinal bleeding [23].

Penetration of many larvae through the intestinal wall can be associated with gram-negative sepsis, as larvae carry enteric microorganisms with them into the bloodstream. Recurrent gram-negative sepsis in an individual with history of residence in or travel to an endemic area should prompt consideration of strongyloidiasis. Organisms reported to cause sepsis in such patients include Group D streptococci, *Streptococcus bovis* meningitis and bacteremia, *Escherichia coli*, *Klebsiella pneumoniae*, *Proteus mirabilis*, Pseudomonas, *Enterococcus faecalis*, coagulasenegative staphylococci, and *Streptococcus pneumonia* [10]. Of note, systemic candidiasis has been observed in patients on immunosuppressive regimens [10]. A small, retrospective study suggested that enteric infections—though most commonly associated with disseminated disease—may even occur in chronically infected individuals [2].

Either aseptic or gram-negative meningitis can be associated with disseminated strongyloidiasis [10]. Larvae have been recovered from cerebrospinal fluid, meningeal vessels, dura, epidural, subdural, and subarachnoid spaces [10].

When present, pulmonary manifestations include cough, wheezing, hoarseness, palpitations, atrial fibrillation, pleuritic chest pain, or dyspnea [10]. Petechial hemorrhage, hyperemia of the bronchial mucosa, or, rarely, massive hemoptysis have been reported [10]. Chest radiographs most frequently demonstrate focal or bilateral interstitial infiltrates [10].

Cutaneous periumbilical purpura has been described in patients with disseminated disease due to migration of larvae through vessel walls in the dermis [24]. The syndrome of inappropriate secretion of antidiuretic hormone has also been associated with disseminated infection [25].

Immunocompromised conditions

Corticosteroids—For reasons that are not entirely clear, corticosteroids have a particularly strong and specific association with the development of hyperinfection syndrome. Hyperinfection syndrome has been described regardless of dose or route of steroid administration. Even short courses of steroids in immunocompetent patients have led to hyperinfection syndrome and death [26]. Of note, several episodes of disseminated strongyloidiasis have been described with the use of traditional Chinese medications, which

contain synthetic steroidal compounds [25]. Other therapies or conditions may predispose to dissemination, although the concomitant administration of steroids in most cases makes it difficult to assign a direct causal association (Table 1).

Human T-cell lymphotropic virus type 1 infection—A growing body of evidence points to the synergistic relationship between human T-cell lymphotropic virus type 1 (HTLV-1) and *Strongyloides*. Higher rates of *Strongyloides* infection have been found in HTLV-1/ *Strongyloides*–coinfected patients. Relapsing *Strongyloides* infection despite treatment should prompt consideration of HTLV-1 infection [27]. HTLV-1 enhances susceptibility to *Strongyloides* infection as a result of diminished immunoglobulin E levels and a bias toward a T helper 1 rather than T helper 2 immune response [28]. In turn, *Strongyloides* may facilitate HTLV-1 virus replication, as suggested by a measurable decline in HTLV-1 messenger RNA levels in one patient after treatment with ivermectin [29]. *Strongyloides* has been proposed to accelerate the progression of HTLV-1 to adult T-cell leukemia in coinfected patients [30].

HIV—Hyperinfection syndrome has not been observed frequently with HIV-infected patients despite vast numbers of coinfected individuals. A recent study postulates that lower $CD4^+$ counts may favor indirect rather than direct development of *Strongyloides* larvae based on the proportion of free-living adult and infective larvae in stools of coinfected patients [31]. Whether immune reconstitution syndrome occurs after the antiretroviral therapy initiation in *Strongyloides*-infected patients remains unclear, although case reports have raised this issue [32].

Other conditions

Case reports have supported an association between *Strongyloides* infection and primary hypogammaglobulinemia [33]. In such cases, refractoriness to anthelmintic therapy has been noted [10]. Hematologic malignancies such as lymphoma have been associated with hyperinfection syndrome in the absence of corticosteroid use [10]. Relatively few cases of infection following bone marrow transplantation have been reported (Table 1) [10].

Diagnosis

In chronically infected, asymptomatic individuals, strongyloidiasis diagnosis can be challenging. Definitive diagnosis relies on detection of larvae in the stool. However, intermittent and scanty excretion of larvae limits the utility of stool studies. Diagnostic sensitivity can improve to 100% when seven stool samples are studied [34]. Various investigators have attempted to improve the diagnostic yield of stool exams using techniques such as direct smear of feces in saline/Lugol's iodine stain, Baermann concentration, Harada-Mori filter paper culture, quantitative formalin ethyl acetate concentration technique, and nutrient agar plate cultures [34]. Of these, the agar plate culture has been found to be the most sensitive, even in immunocompromised patients. Using this method, larvae could be detected in approximately 50% of stool samples from individuals with antibody responses to *Strongyloides* antigen [35]. Duodenal aspiration is more sensitive than stool examination, but it is an invasive procedure, which makes it a less favorable option. Duodenal biopsy can demonstrate parasites nested in the gastric crypts or duodenal glands, as well as eosinophil infiltration of the lamina propria [36].

Enzyme linked immunosorbent assay (ELISA) has been increasingly used in conjunction with stool studies to increase diagnostic sensitivity. The high negative predictive value of the ELISA can be particularly useful in excluding strongyloidiasis as part of the differential diagnosis. Despite its usefulness, serodiagnosis has several limitations, including cross-reactivity in patients with active filarial infections, lower sensitivity in patients with

hematologic malignancies or HTLV-1 infection, and inability to distinguish between current and past infection [34]. In addition, the current ELISA relies on the labor-intensive preparation of larval antigen from stool samples of heavily infected humans or experimentally infected animals. Various techniques have been developed in an effort to improve on the drawbacks of serologic-based assays. Recombinant antigens (eg, the NIE antigen) have been proposed as a convenient alternative to the crude antigen currently used [37]. Recently, a dipstick assay was found to be easily and quickly performed and correlated well with ELISA results [38]. A gelatin particle agglutination test has been proposed as an alternative to ELISA for mass screening in endemic areas because of its low cost and convenience [39]. An immediate hypersensitivity skin test has been used in a research setting quite effectively, although it may have limited utility in HTLV-1–infected patients [40].

In hyperinfection syndrome, parasitologic diagnosis is simplified by the presence of many larvae in stool and sputum. Larvae have been incidentally found in blood smears, ascitic fluid, and bronchoalveolar lavage specimens [10].

Treatment

To prevent the development of hyperinfection syndrome, chronically infected, asymptomatic individuals must be treated. Because even one remaining adult female can multiply and cause disseminated disease, the goal of treatment is complete eradication of the parasite. The current treatment of choice for chronic strongyloidiasis is single-dose ivermectin (Table 2), although some studies have suggested that two doses of ivermectin, 200 μg/kg, given on consecutive days may have greater efficacy [41]. Ivermectin has better tolerability compared with thiabendazole [42]. In a randomized trial, up to 95% of patients on thiabendazole experienced side effects, compared with 18% of ivermectin-treated patients [43]. Side effects of thiabendazole include general fatigue, dizziness, headache, nausea, anorexia, abdominal pain, liver dysfunction, and neuropsychiatric symptoms [43]. Ivermectin has superior efficacy when compared with albendazole, the cure rates of which range from 45% to 77% [42,44]. Decreased cure rates have been observed in patients with HTLV-1 coinfection regardless of treatment regimen [28]. The US Centers for Disease Control and Prevention has recommended presumptive predeparture treatment of refugees at risk for *Strongyloides* [3•]. In such cases, ivermectin should not be given to individuals from Western and Central Africa in whom coinfection with *Loa loa* has not been excluded. High levels of *L. loa* microfilaremia can precipitate life-threatening encephalopathy in patients treated with ivermectin. The presumptive use of albendazole must be weighed against the risk of exacerbating inflammatory reactions in patients with neurocysticercosis or those from parasite-endemic areas with a seizure history of unknown etiology.

For disseminated strongyloidiasis, oral ivermectin should be given daily until stool examinations are negative for at least 2 weeks (the duration of the autoinfective cycle) or longer if patients remain immunosuppressed. Off-label rectal administration of ivermectin or thiabendazole, though useful in some critically ill patients [45], can be problematic in patients with severe diarrhea. Patients with paralytic ileus can have difficulty absorbing oral ivermectin due to tissue edema, larger volume of distribution, and increased clearance of unbound drug. Lower serum ivermectin levels than those in normal subjects after oral administration have been demonstrated in patients with paralytic ileus [46••]. However, parenteral formulations of ivermectin are not approved currently for use in humans; they have only been administered under compassionate use Investigational New Drug exemptions. Experience with subcutaneous ivermectin is based on a few case reports of improved serum drug levels with this route. However, faster drug clearance and lower

steady state concentrations were also observed, presumably due to severe hypoalbuminemia, because ivermectin is highly protein bound [46••].

Despite treatment, fatal progression to acute respiratory distress syndrome can occur even with successful eradication of larvae [20]. Several questions remain unanswered with respect to the treatment of critically ill patients with hyperinfection syndrome. For instance, the ideal dose duration and route of therapy for hyperinfection syndrome has not been studied systematically. Whether to continue or decrease corticosteroid dose in critically ill patients also remains unclear.

Although no test of cure currently exists, serology response by ELISA after treatment can be a useful tool in monitoring treatment response, because antibody levels have been shown to decrease significantly within 6 months after anthelmintic therapy [47]. Serial stool examinations remain the gold standard to assess cure (Table 2).

Prevention

For persons living in endemic areas, foot protection should be emphasized to prevent cutaneous transmission of the disease. No protective vaccine currently exists. However, a recent animal study demonstrated that DNA immunization with Na+K+ATPase induced protective immunity to challenge with *Strongyloides* larvae in mice [48].

Mass treatment programs have been proposed as a solution to the challenges of identifying chronically infected *Strongyloides* patients at risk for hyperinfection syndrome. A small unblinded, uncontrolled study in a Brazilian community demonstrated a 94% reduction in prevalence following treatment with ivermectin that was sustained for 9 months [49].

Conclusions

Although *S. stercoralis* often causes chronic and clinically asymptomatic infection, parasite number can increase substantially in the immunocompromised host, leading to hyperinfection, dissemination, and death if unrecognized. To prevent this, all chronically infected, asymptomatic persons should be treated. Patients from *Strongyloides*-endemic areas taking corticosteroids must be considered high risk for hyperinfection syndrome, even years after leaving the endemic area. The current method for diagnosis includes serology and serial stool studies for larvae, though limitations of serology include poor specificity and inability to distinguish past from current infection. Nevertheless, the entire diagnostic armamentarium should be brought to bear on a patient with presumptive strongyloidiasis with an eye toward treatment to prevent the often serious sequelae associated with hyperinfection syndrome.

Acknowledgments

This work was supported by the Division of Intramural Research, National Institutes of Allergy and Infectious Diseases.

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Table 1

Therapies and diseases associated with hyperinfection syndrome

Therapies*	
Corticosteroids	Doxorubicin
Vinca alkaloids	Daunorubicin
Azathioprine	Ifosfamide
Cyclophosphamide	Melphalan
Antithymocyte globulin	Carmustine
Anti-CD3	VP16
Chlorambucil	Mitoxantrone
6-mercaptopurine	Total body irradiation
Methotrexate	Etanercept
Bleomycin	
Diseases	
HTLV-1	Malnutrition
Hypogammaglobulinemia	Hematologic malignancies (eg, lymphoma)

*Glucocorticoids were administered concurrently with many of the drugs listed in this table, and attributing hyperinfection syndrome to any of these drugs alone is difficult.

HTLV-1— human T-cell lymphotropic virus type 1.

Table 2

Treating *Strongyloides* infection

Chronic strongyloidiasis (adults)
Ivermectin, 200 μg/kg, by mouth daily for 1–2 days* (patient weight > 15 kg)
Relative contraindications:
Patients with *Loa loa* microfilaremia
Children < 1 year of age or persons weighing less than 15 kg
Pregnant or lactating women
Alternatives:
Albendazole, 400 mg, by mouth twice a day for 2–7 days*
Thiabendazole, 25 mg/kg by mouth twice a day for 3 days
Hyperinfection syndrome
Ivermectin, 200 μg/kg/day, by mouth, until negative stool exams persist for 2 weeks
For patients unable to tolerate therapy by mouth, consider subcutaneous and per rectum formulations

*Optimal duration of therapy unknown.