Screening, prevention, and treatment for hyperinfection syndrome and disseminated infections caused by *Strongyloides stercoralis*

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Purpose of review
This review discusses the latest approaches to the diagnosis and treatment of patients with strongyloidiasis, with an emphasis on infection in the immunocompromised host and the risk for disseminated strongyloidiasis.

Recent findings
The differences in acute, chronic, accelerated autoinfection, and disseminated disease in *Strongyloides stercoralis* infection are explored with particular emphasis on early diagnosis, treatment, and prevention. The goals of treatment are investigated for the different infection states. Predisposing risks for dissemination are delineated, and the roles played for newer diagnostics in the identification of at-risk individuals are detailed.

Summary
The use of newer diagnostic tests and broader screening of immunocompromised patients from *Strongyloides*-endemic areas is of paramount importance, particularly if prevention of life-threatening dissemination is the goal.

Keywords
anthelmintic therapy, immunocompromised, infection, screening, *Strongyloides*

INTRODUCTION

Strongyloides stercoralis is an intestinal nematode acquired primarily in the tropics or subtropics, estimated to infect approximately 100 million people worldwide [1]. It commonly causes chronic, asymptomatic infection, but a change in immune status can lead to an increase in parasite burden, hyperinfection syndrome, dissemination, and death if unrecognized. Corticosteroid use is commonly associated with hyperinfection syndrome. Diagnosis of *Strongyloides* infection has traditionally been based on serial stool examinations for larvae, though more recently serologic approaches have gained primacy. Even newer techniques (e.g. molecular-based diagnostics, high throughput immunoassays) have become available and put into clinical use in some research centers. One to two days of ivermectin is the treatment of choice for chronic, asymptomatic infection. For hyperinfection syndrome and disseminated infections, ivermectin is the drug of choice (with albendazole as a second-line therapy), though duration of therapy (and route of administration) must be individualized with the endpoint being complete eradication of the parasite. There is no test of cure currently available, although IgG antibody levels have been shown to decline within 6 months of successful treatment, and DNA-based diagnostics have recently been shown to hold promise as a proof-of-cure technique.

BIOLOGY OF *STRONGYLOIDES STERCORALIS*

The life cycle of *S. stercoralis* has been well described. Like other gastrointestinal helminth parasites, most patients are infected by exposure to contaminated

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KEY POINTS

- Hyperinfection syndrome and dissemination of *Strongyloides* infection are associated with a high mortality rate.
- More sensitive and specific diagnostics for *Strongyloides* infections have been developed that are either molecular (e.g. real-time PCR) or based on *Strongyloides*-specific immunoassays.
- Screening for and preemptive treatment of *Strongyloides* infection should be considered for 'at-risk' populations.

soil when residing in endemic areas [2▪]. For *Strongyloides* infections, the endemic areas include most tropical and subtropical weather zones on all continents except Antarctica [1]. Infection is initiated by infectious larvae penetrating the skin, often on the soles of the feet [3]. Recently, these larvae have been found contaminating local vegetation or soil exposed to human excrement [4▪]. Once the larvae penetrate the skin, they travel through the bloodstream entering the alveolar space of the lungs; this lung migration can cause a pneumonitis, but most commonly is clinically asymptomatic. Larvae are then expectorated, traveling through the trachea and then swallowed. The larvae mature into adult worms, mate and release eggs in the gastrointestinal tract. Most eggs hatch into rhabditiform larvae and are excreted; some transform into infectious (filariform) larvae and penetrate the perirectal mucosa or skin, thereby reentering the circulatory system and starting the cycle again [5]. Because of this autoinfection cycle, a person can remain infected with *Strongyloides* for decades [6▪].

ACUTE STRONGYLOIDIASIS

The clinical manifestations of acute strongyloidiasis can be associated with the path of larval migration 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 such as diarrhea, constipation, abdominal pain, or anorexia.

CHRONIC STRONGYLOIDIASIS

Chronic strongyloidiasis most frequently causes asymptomatic infection in immunocompetent individuals. As up to 75% of persons may have peripheral eosinophilia or elevated total IgE levels greater than 250 IU/ml [7], *Strongyloides* should be considered in the differential diagnosis of high grade and persistent eosinophilia in travelers to or immigrants from endemic areas [8▪].

Symptomatic individuals may have diarrhea, constipation, or intermittent vomiting. Dermatologic manifestations such as recurrent urticaria can occur, as can *larva currens*, pruritic linear streaks located along the lower trunk, thighs, and buttocks as a result of migrating larvae.

Unusual manifestations of chronic strongyloidiasis include reactive arthritis [9], nephrotic syndrome [10], chronic malabsorption [11], duodenal obstruction [12], focal hepatic lesions [13], and recurrent asthma [14].

HYPERINFECTION SYNDROME

Hyperinfection describes the syndrome of accelerated autoinfection, generally the result of an alteration in 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 the detection of increased numbers of larvae in stool and sputum is the hallmark of hyperinfection. Hyperinfection syndrome has been described as late as 64 years after an individual has left an endemic area [15].

Recurrent paralytic ileus associated with protein losing enteropathy and diarrhea giving rise to hypoalbuminemia and peripheral edema has been seen [16]. Common pulmonary manifestations include wheezing, hoarseness, palpitations, atrial fibrillation, dyspnea, or, rarely, massive hemoptysis. Radiographs most frequently demonstrate focal or bilateral interstitial infiltrates.

DISSEMINATED INFECTION

Disseminated infection occurs when larvae migrate away from the lung and gastrointestinal tract into other organ systems [17]. Penetration of large numbers of larvae through the intestinal wall can be associated with microbial sepsis as larvae carry organisms with them into the bloodstream [18]. Organisms that have been reported to cause sepsis in such patients include group D *streptococci*, *Candida* [19]; *Streptococcus bovis* [20], *Escherichia coli*, *Klebsiella pneumoniae*, *Proteus mirabilis*, *Pseudomonas*, *Enterococcus faecalis*, coagulase-negative staphylococci, and *Streptococcus pneumoniae*. The risk of sepsis is increased especially if the patient is already immunosuppressed.

If untreated, the mortality rate of disseminated disease approaches 100% [21].

Cutaneous periumbilical purpura has been described in patients with disseminated disease because of migration of larvae through vessel walls in the dermis [22▪].

CORTICOSTEROIDS AND OTHER AGENTS

Corticosteroids have a particularly strong and specific association with the development of hyperinfection syndrome and dissemination. Other immunosuppressive therapies and underlying conditions may also predispose to dissemination. However, the concomitant administration of steroids in most of these other conditions makes it difficult to assign a direct causal association. Hyperinfection syndrome has been described regardless of dose, duration, or route of administration of corticosteroids. Even short courses (6–17 days) of steroids in immunocompetent patients without underlying immunosuppressive conditions have even been associated with hyperinfection syndrome and death [23]. Conditions associated with hyperinfection syndrome are as follows:

(1) Drugs/biologics (glucocorticoids are commonly given with other immunosuppressive therapies and attributing the risk of any of these drugs and therapies alone to risk of dissemination is uncertain):
   (a) corticosteroids;
   (b) vinca alkaloids;
   (c) azathioprine;
   (d) cyclophosphamide;
   (e) chlorambucil;
   (f) 6-mercaptopurine;
   (g) methotrexate;
   (h) bleomycin;
   (i) adriamycin;
   (j) doxorubicin;
   (k) daunorubicin;
   (l) ifosfamide;
   (m) melphalan;
   (n) carmustine;
   (o) VP16;
   (p) mitoxantrone;
   (q) etanercept;
   (r) inflixumab;
   (s) rituximab;
   (t) antithymocyte globulin;
   (u) anti-CD3 (OKT3);
   (v) mycophenolate mofetil;
   (w) total body irradiation;
(2) Diseases:
   (a) Human T-cell lymphotropic virus type 1 (HTLV-1);
   (b) hypogammaglobulinemia (associated with nephrotic syndrome, multiple myeloma);
   (c) hematologic malignancies;
   (d) solid-organ transplantation;
   (e) hematopoietic stem cell transplantation;
   (f) HIV and immune reconstitution inflammatory syndrome (IRIS).

HUMAN T-CELL LYMPHOTROPIC VIRUS TYPE 1 INFECTION

HTLV-1 represents a significant risk factor for the development of hyperinfection syndrome or disseminated strongyloidiasis [24]. A growing body of evidence points to the synergistic relationship between HTLV-1 and *Strongyloides*. Higher rates of *Strongyloides* infection have been found in HTLV-1 patients [24]. *Strongyloides* infection has been shown to influence the natural history of HTLV-1 infection [25▪▪] and has been considered a co-factor in the development of HTLV-1 associated diseases [26].

HIV

Strongyloidiasis was once considered an AIDS defining illness [27], yet there is no evidence that a low CD4 count will increase the risk of dissemination or decrease the chance of clearing an infection [28▪]. Severe infection with *Strongyloides* has not been observed frequently with HIV-infected patients [29]. Hyperinfection syndrome is associated with the use of corticosteroids in HIV [30▪] and in IRIS [31]. Whether IRIS occurs after the initiation of antiretroviral therapy in *Strongyloides*-infected patients remains unclear.

STRONGYLOIDES INFECTION IN THE TRANSPLANTED PATIENT

Solid-organ transplants [25▪▪,26,27], hematopoietic stem cell transplants (HSCT), and their preconditioning regimens and subsequent immunosuppression have been linked to dissemination of *Strongyloides*. Among the different types of transplants, HSCT has the highest incidence of fatal dissemination with a higher mortality than in other types of transplants [32]. Transplanted patients have unique regimens that increase their risk of dissemination. Immunosuppression is used for preconditioning (see above) and then to prevent rejection; lifelong immunosuppression is needed.

A unique complication of transplants is the development of graft-versus-host disease (GVHD). Especially in HSCT, in which current techniques are increasingly using nonmyeloablative allogeneic stem cell transplantation that does not completely deplete the immune cells of the recipient and is better tolerated, the risk of GVHD is greater than

for other approaches [33]. Because the main therapy for acute GVHD is corticosteroids, it is at the time that steroids are given in the setting of chronic strongyloidiasis that the risk for dissemination is high [34,35].

Because of geographical proximity to the United States, immigrants from Central and South America that are being transplanted are a sizeable 'at-risk' population for dissemination of *Strongyloides* [36]. Organ donors have also been shown to transmit *Strongyloides* infection, with cases of solid-organ transplant-associated *Strongyloides* infections having been reported [37].

OTHER

Several case reports have supported an association between *Strongyloides* infection and hypogammaglobulinemia, associated with multiple myeloma and nephrotic syndrome [38–40].

CURRENT DIAGNOSTIC TESTING

Current standard of care is the classic stool microscopy exam for parasitic ova and larvae with a reported 75.9% sensitivity for the first assay [41]. The sensitivity rises to 92% when done in triplicate. It is labor intensive and dependent on operator skill. Modern techniques include real-time polymerase chain reaction (RT-PCR), ELISA, and luciferase immunoprecipitation systems (LIPS) assays that have improved sensitivities enormously.

ELISA serologic assays measures IgG responses to *Strongyloides* crude somatic antigen extracts in serum. It takes 4–6 weeks to mount an immune response and can lead to a false-negative result in acute infections [42▪]. The test can also remain positive after treatment for extended periods of time [43]. In addition, there is serological cross-reactivity with some patients with active filarial infections [44]. The use of a *Strongyloides*-specific antigen (NIE) has improved the specificity of these ELISA-based immunoassays [42▪].

Molecular diagnostics such as RT-PCR assays have been investigated for a stool-based assay [45▪]. It is a highly specific tool with improved sensitivity compared to microscopy [45▪,46]. RT-PCR, like microscopy, only identifies active *Strongyloides* infection as positivity has been shown to be lost following definitive treatment (Mejia *et al.*, unpublished data). RT-PCR is not available at all diagnostic centers and, at the moment, is only applicable in research settings.

LIPS assays are newer immunologic techniques that rely on rapid immunoprecipitation and detection in a high-throughput format [47]. By using two *Strongyloides*-specific recombinant antigens, this test has been shown to be superior to other types of immunoassays [42▪,47]. Another benefit of LIPS over standard immunoassays is the evidence of reversion to seronegative following treatment [47], a property that can be useful in monitoring populations following mass drug administration (MDA) and to assess posttreatment efficacies of drugs.

Diagnosis of hyperinfection syndrome and disseminated *Strongyloides* infection is not difficult because of the large numbers of larvae often seen in the stool or other bodily fluids including CSF, pleural fluid, and bronchoalveolar lavage (BAL) fluid.

TREATMENT OF STRONGYLOIDIASIS

Oral ivermectin at 200 μg/kg for 2 days remains the treatment of choice for uncomplicated *Strongyloides* infections [48▪▪]. Albendazole at 400 mg twice a day for 3–7 days has been shown to be slightly less effective than ivermectin for the treatment of uncomplicated *Strongyloides* [48▪▪] and should be considered an alternative therapy. Thiabendazole (25 mg/kg/day) for 3 days can also be used, but because of gastrointestinal side-effects, its use has been supplanted by ivermectin. Treatment of *Strongyloides* infection is as follows:

(1) Strongyloidiasis (uncomplicated):
   (a) ivermectin, 200 μg/kg, orally daily for 2 days.
(2) Alternatives:
   (a) albendazole, 400 mg, orally twice a day for 3–7 days; or
   (b) thiabendazole, 25 mg/kg orally twice a day for 3 days.
(3) Hyperinfection and disseminated strongyloidiasis:
   (a) (i) if possible, reduction of immunosuppressive therapy;
   (ii) ivermectin, 200 μg/kg/day, orally, until negative stool exam persists for 2 weeks;
   (b) for malabsorption, or patients unable to tolerate orally or deteriorating clinical status:
   (i) subcutaneous: parenteral ivermectin, 200 μg/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 (not FDA approved, case reports, no clear evidence-based trials);
   (ii) rectal: ivermectin, 200 μg/kg, daily, until negative stool exam persists for 2 weeks (not FDA approved, case reports, no clear evidence-based trials).

Hyperinfection syndrome should be considered a potential medical emergency. Thus, treatment should be started immediately if this is being considered. Although no controlled trials have been performed in hyperinfection syndrome, daily ivermectin has been the *de facto* treatment with the length of treatment being for a minimum of 2 weeks (and often until there has been evidence of two full weeks of negative stool examination). Reduction of immunosuppressive therapy should also be an important part of treatment, but obviously needs to be weighed against the long-term outcomes of the underlying disease. With a mortality of 85–100% in disseminated *Strongyloides* infection, a brief reduction or termination of immunosuppressants may be vital to allow for clearance of the parasites. There have been case reports of the improved efficacy of combination treatment with ivermectin and albendazole [49], but no randomized trials have been done; however, it has often been considered a reasoned approach.

Other methods of ivermectin administration may have to be used, particularly when patients are unable to take oral medication (even through a nasogastric tube) because of severe systemic illness of paralytic ileus. These include per rectal and parenteral formulations [50]. The parenteral formulation is a veterinary formulation of ivermectin and should be reserved for extreme situations with no other options for clearing *Strongyloides* infection [51].

Contraindications for treatment with ivermectin include patients with high-grade microfilaremia of *Loa loa* from endemic areas of West Africa and because of the encephalopathy seen in these individuals following ivermectin treatment [52]. In patients with high levels of *Loa loa* microfilaremia, albendazole is a good alternative for the treatment of strongyloidiasis.

PREVENTION OF DISSEMINATION AND HYPERINFECTION SYNDROME

Dissemination is a dangerous medical condition with extremely high mortality. It affects specific patients with acquired immunodeficiencies such as HTLV-1 or iatrogenically by immunosuppressive agents. Although multiple agents have been implicated in increasing the risk of hyperinfection syndrome, corticosteroids administration carries the greatest risk; interestingly, disseminated *Strongyloides* infection has occurred within a week of corticosteroid initiation [23].

Screening patients for asymptomatic *Strongyloides* infection is crucial to prevent hyperinfection syndrome. Among the available tests (stool examination, molecular diagnostics, and serologies), serologic tests are both the most reliable and the most sensitive especially in populations from *Strongyloides*-endemic areas. Anyone at high risk for dissemination who has a potential *Strongyloides*-exposure history should be screened, most notably those with diseases associated with hyperinfection syndrome and those requiring immunosuppressive therapy for whatever reason.

Finally, given the cost of laboratory investigations for *S. stercoralis* identification and the delay between ordering serology and getting the results (often 2 weeks or more), some would advocate empiric treatment with ivermectin in 'at-risk' patients. Whether this approach will be adopted remains an open, but important, question for policy makers.

CONCLUSION

Although *Strongyloides* often causes chronic and clinically asymptomatic infection, parasite number can increase substantially in those who are immunocompromised, leading to hyperinfection, dissemination, and death if unrecognized. Prevention of this serious set of sequelae of *Strongyloides* infection involves treating all chronically infected, asymptomatic individuals. Patients from *Strongyloides* endemic areas taking corticosteroids must be considered high risk for hyperinfection syndrome and newer diagnostic tests and broader screening of immunocompromised patients from *Strongyloides*-endemic areas is of paramount importance, particularly if prevention of life-threatening dissemination is the goal.

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Conflicts of interest

There are no conflicts of interest.

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Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 476).

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