Diagnosis of *Strongyloides stercoralis* Infection

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*Strongyloides stercoralis* infects 30 million people in 70 countries. Infection usually results in asymptomatic chronic disease of the gut, which can remain undetected for decades. However, in patients receiving long-term corticosteroid therapy, hyperinfection can occur, resulting in high mortality rates (up to 87%). Strongyloidiasis is difficult to diagnose because the parasite load is low and the larval output is irregular. Results of a single stool examination by use of conventional techniques fail to detect larvae in up to 70% of cases. Several immunodiagnostic assays have been found ineffective in detecting disseminated infections and show extensive cross-reactivity with hookworms, filariae, and schistosomes. Although it is important to detect latent *S. stercoralis* infections before administering chemotherapy or before the onset of immunosuppression in patients at risk, a specific and sensitive diagnostic test is lacking. This review describes the clinical manifestations of strongyloidiasis, as well as various diagnostic tests and treatment strategies.

Strongyloidiasis is caused by 2 species of the intestinal nematode *Strongyloides*. The most common and globally distributed human pathogen of clinical importance is *Strongyloides stercoralis*. The other species, *Strongyloides fuelleborni*, is found sporadically in Africa and Papua New Guinea [1–3]. Strongyloidiasis affects anywhere from 30 to 100 million people worldwide [3, 4] and is endemic in Southeast Asia, Latin America, sub-Saharan Africa, and parts of the southeastern United States (tables 1 and 2) [2, 3, 8]. The unique ability of this nematode to replicate in the human host permits cycles of autoinfection, leading to chronic disease that can last for several decades [1–3].

*S. stercoralis* was first reported in 1876 in the stools of French soldiers on duty in Vietnam who had severe diarrhea, and the disease the organism produces was known for many years as Cochinchina diarrhea [1]. The elucidation of the complete life cycle (figure 1) occurred 50 years after the discovery of the worm. *S. stercoralis* has a complex life cycle in which parthenogenetic females (i.e., capable of reproducing without males) embedded in the intestinal mucosa lay embryonated eggs that hatch internally [1, 33]. The resultant first-stage larvae (L1; rhabditiform larvae) are passed out in the feces and may develop directly into second (L2)–stage and third (L3; filariform larvae)–stage larvae may develop through 4 free-living larval stages to become free-living adult males and females. The free-living adults reproduce sexually to produce L1, which also develop to L2. The L1 of either cycle can penetrate the skin of the human host, pass through the circulation to the lungs, enter the airways, be swallowed, and finally reach the intestine, where they mature into adult egg-laying females (figure 1).

In autoinfection, larvae that have developed to the infective third stage within the gastrointestinal tract penetrate the intestinal mucosa and then migrate to the definitive site in the small intestine or to parenteral sites (e.g., lungs) [1, 34]. Some have argued that the pulmonary route is just one of the several possible pathways for the larvae to reach the duodenum [35]. In any event, this ability to establish a cycle of repeated endogenous reinfection within the host invariably results in chronic infection that can last for several decades; the current record appears to be 65 years [2].

Chronic infections with *S. stercoralis* can be clinically inapparent or can lead to cutaneous, gastrointestinal, or pulmonary symptoms [1, 2, 8, 36–38]. Skin involvement is characterized by a migratory, serpiginous, urticarial rash, termed larva currens [1, 2]. The larvae in many cases invade the skin in the perianal region and are extremely motile. The buttocks, groin, and trunk are more commonly affected by larva currens than the extremities and the head [2]. Gastrointestinal symptoms of strongyloidiasis include diarrhea, abdominal discomfort, nausea, and anorexia [1, 2, 8]. Abdominal bloating is the most common complaint.
Table 1. Surveys of the prevalence of *Strongyloides stercoralis* in the United States.

<table>
<thead>
<tr>
<th>Location</th>
<th>No. of specimens examined</th>
<th>Specimens positive for <em>S. stercoralis,</em> %</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Harlan County, KY</td>
<td>125</td>
<td>4.0</td>
<td>[5]</td>
</tr>
<tr>
<td>Williamson, TN</td>
<td>221</td>
<td>1.0</td>
<td>[6]</td>
</tr>
<tr>
<td>Clay County, KY</td>
<td>561</td>
<td>3.0</td>
<td>[7]</td>
</tr>
<tr>
<td>Lexington, KY</td>
<td>3271</td>
<td>2.5</td>
<td>[7]</td>
</tr>
<tr>
<td>Johnson City, TN</td>
<td>575</td>
<td>4.0</td>
<td>[8]</td>
</tr>
<tr>
<td>Charleston, WV</td>
<td>4566</td>
<td>0.4</td>
<td>[9]</td>
</tr>
<tr>
<td>Baltimore, MD</td>
<td>51</td>
<td>3.9</td>
<td>[10]</td>
</tr>
<tr>
<td>Delaware, MD</td>
<td>339</td>
<td>0.6</td>
<td>[11]</td>
</tr>
<tr>
<td>New Orleans, LA</td>
<td>8458</td>
<td>0.4</td>
<td>[12]</td>
</tr>
<tr>
<td>Chicago, IL</td>
<td>358</td>
<td>1.7</td>
<td>[13]</td>
</tr>
<tr>
<td>New York, NY</td>
<td>10,072</td>
<td>1.0</td>
<td>[14]</td>
</tr>
<tr>
<td>Seattle, WA*</td>
<td>201</td>
<td>2.5</td>
<td>[15]</td>
</tr>
</tbody>
</table>

* Among refugees from Asia.

When malabsorption is present, the radiographic findings are similar to those of tropical sprue, including increased diameter of the small intestinal lumen, generalized hypotonia, and edema [39]. The symptoms of pulmonary strongyloidiasis (hyperinfection) include cough and shortness of breath [1, 2, 8, 37–41]. Diagnosis is difficult because many patients have baseline pulmonary complaints [40, 41].

In hyperinfection and dissemination, complete disruption of the mucosal patterns, ulcerations, and paralytic ileus have been observed. In the presence of dissemination, pulmonary involvement may be heralded by bilateral edema and patchy, often rapidly changing infiltrates [1, 2, 8, 37–41]. Bacterial and fungal infections often occur in cases of hyperinfection because of the leakage of gut flora from a bowel damaged by moving larvae [1, 2]. The enteric bacteria are carried by invasive L₃ larvae on their outer surfaces [1, 2]. This can result in septicemia, pneumonia, meningitis, and disseminated bacterial or fungal infection in many parts of the body, including the lungs [1, 2, 8, 36–38]. Massive secondary bacterial infections are frequently the immediate cause of death in patients with the hyperinfection syndrome.

The term “hyperinfection” is often used to denote autoinfection, a phenomenon in which the number of worms increases tremendously and the worms are detectable in extraintestinal regions, especially the lungs. The term “disseminated” is usually restricted to infections in which worms are found in ectopic sites (e.g., the brain). However, as Grove [1] points out, a simpler approach would be to recognize that there is a spectrum of severity of infection and that is hard to precisely quantify; it is simpler to categorize disease as “ uncomplicated strongyloidiasis” or as “severe, complicated strongyloidiasis.”

The potential for severe disease is high in certain people at high risk for acquiring strongyloidiasis [1, 2, 8, 36, 39]. The high-risk group includes the following: patients with altered cellular immunity, especially those receiving long-term steroid therapy; patients with lymphoma; kidney allograft recipients; travelers to areas of endemicity; and prisoners and other institutionalized people [1, 2, 8, 36, 39–43]. Most patients who develop hyperinfection syndrome are receiving corticosteroids, often for chronic obstructive pulmonary disease [8, 44, 45]. Hence, pulmonary strongyloidiasis may mimic an exacerbation of underlying chronic obstructive pulmonary disease [8, 40, 41]. Furthermore, in the past few years, a very limited number of patients with AIDS and extraintestinal strongyloidiasis have been reported [1, 2, 36–38]. Some conditions associated with HIV infection are known to predispose to hyperinfection syndrome, including inanition and the use of steroids. In fact, the list of immunosuppressive diseases associated with hyperinfection is unified by having corticosteroid treatment as a common denominator. However, it is now apparent that strongyloidiasis is not an important opportunistic infection associated with AIDS; the infection should still be searched for and promptly treated in HIV-infected patients who have a history of residence in and/or travel to areas of endemicity. On the other hand, strongyloidiasis appears to be a relevant opportunistic infection in patients infected with human T-lymphotropic virus 1 [1, 2, 36–38].

The diagnosis of strongyloidiasis should be suspected if there are clinical signs and symptoms, eosinophilia, or suggestive serologic findings [1–3, 8, 36]. Definitive diagnosis of strongyloidiasis is usually made on the basis of detection of larvae in the United States.

Table 2. Recent data on *Strongyloides stercoralis* prevalence in some developing nations.

<table>
<thead>
<tr>
<th>Location</th>
<th>No. of specimens examined</th>
<th>Specimens positive for <em>S. stercoralis,</em> %</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abidjan</td>
<td>1001</td>
<td>1.4</td>
<td>[16]</td>
</tr>
<tr>
<td>Argentina</td>
<td>36</td>
<td>83.3</td>
<td>[17]</td>
</tr>
<tr>
<td>Argentina</td>
<td>207</td>
<td>2.0</td>
<td>[18]</td>
</tr>
<tr>
<td>Brazil</td>
<td>200</td>
<td>2.5</td>
<td>[19]</td>
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<tr>
<td>Brazil</td>
<td>900</td>
<td>13.0</td>
<td>[20]</td>
</tr>
<tr>
<td>Ethiopia</td>
<td>1239</td>
<td>13.0</td>
<td>[21]</td>
</tr>
<tr>
<td>Guinea</td>
<td>800</td>
<td>6.4</td>
<td>[22]</td>
</tr>
<tr>
<td>Honduras</td>
<td>266</td>
<td>2.6</td>
<td>[23]</td>
</tr>
<tr>
<td>Israel</td>
<td>106</td>
<td>0.9</td>
<td>[24]</td>
</tr>
<tr>
<td>Kenya</td>
<td>230</td>
<td>4.0</td>
<td>[25]</td>
</tr>
<tr>
<td>Laos</td>
<td>669</td>
<td>19.0</td>
<td>[26]</td>
</tr>
<tr>
<td>Mexico</td>
<td>100</td>
<td>2.0</td>
<td>[27]</td>
</tr>
<tr>
<td>Nigeria</td>
<td>2008</td>
<td>25.1</td>
<td>[28]</td>
</tr>
<tr>
<td>Romania</td>
<td>231</td>
<td>6.9</td>
<td>[29]</td>
</tr>
<tr>
<td>Sierra Leone</td>
<td>1164</td>
<td>3.8</td>
<td>[30]</td>
</tr>
<tr>
<td>Sudan</td>
<td>275</td>
<td>3.3</td>
<td>[31]</td>
</tr>
<tr>
<td>Thailand</td>
<td>491</td>
<td>11.2</td>
<td>[32]</td>
</tr>
</tbody>
</table>
in the stool (figure 2A). However, in a majority of uncomplicated cases of strongyloidiasis, the intestinal worm load is often very low and the output of larvae is minimal [2]. Eosinophilia is usually the only indication to the presence of *S. stercoralis* infection, but it is mild (5%–15%) and nonspecific [1–3, 8, 36]. In more than two-thirds of cases, there are ≤25 larvae per gram of stool [2]. It has been shown that a single stool examination fails to detect larvae in up to 70% of cases. Repeated examinations of stool specimens improve the chances of finding parasites; in some studies, diagnostic sensitivity increases to 50% with 3 stool examinations and can approach 100% if 7 serial stool samples are examined [46, 47].

A number of techniques have been used to discern larvae in stool samples, including direct smear of feces in saline–Lugol iodine stain, Baermann concentration, formalin-ethyl acetate concentration, Harada-Mori filter paper culture, and nutrient agar plate cultures (figure 2) [48–50]. Concentrating the stool with formalin-ethyl acetate increases the yield, but dead individual larvae are more difficult to discern at low magnification. The Baermann method and the Harada-Mori filter paper capitalize on the ability of *S. stercoralis* to enter a free-living cycle of development. These methods are much more sensitive than single stool-smears, but they are rarely standard procedures in clinical parasitology laboratories [51]. In the Harada-Mori technique, filter paper containing fresh fecal material is placed in a test tube with water that continuously soaks the filter paper by capillary action. Incubation at 30°C provides conditions suitable for the development of larvae, which can migrate to either side of the filter paper [48–50]. In the Baermann procedure, stool is placed on mesh screen and a coarse fabric in a funnel that is filled with warm water and connected to a clamped tubing. After an hour of incubation, larvae crawl out of the fecal suspension and migrate into the warm water, from where they can be collected by centrifugation [48–50].

In the agar culture method, the stool sample is placed on a nutrient agar plate and incubated for at least 2 days [50, 52]. As the larvae crawl over the agar, they carry bacteria with them, creating visible tracks (figure 2C) [53]. Motile *S. stercoralis* larvae can also be seen with the aid of a dissecting microscope [54]. A comparative study that used >1300 stool samples and

**Figure 1.** Life cycle of *Strongyloides stercoralis*
4 different methods of stool examination (direct fecal smear, formalin-ethyl acetate concentration, Harada-Mori filter paper culture, and agar plate culture) found the agar plate culture method to be 96% sensitive [55]. In another study, the agar plate culture method was found to be 4.4 times more efficient than the direct smear procedure [23]. Although the agar plate method is laborious and time-consuming (requiring ~2–3 days), it is more sensitive than other procedures (e.g., wet mount analysis) for detection of larvae in feces [56]. As Grove [1] points out, “the balance of opinion probably favors the agar plate culture method but this is perhaps more expensive and complex” (p. 281).

Although some studies have reported that the examination of duodenal aspirate is very sensitive, this invasive method is recommended only for children, when it is necessary to rapidly demonstrate the presence of parasites, as in the case of an immunocompromised child who is suspected of having overwhelming infection [2, 39]. Microscopic examination of a single specimen of duodenal fluid was found to be more sensitive than wet mount analysis of stools samples for the detection of larvae [57]. This method identified 76% of patients; the parasite was found exclusively in duodenal fluid (and not in feces) in 67% of patients. The string test—a gelatin capsule containing a string that is swallowed by the patient and retrieved after a few hours—enjoyed a brief period of popularity, but currently it is used infrequently [58]. Also, in some cases, histological examination of duodenal or jejunal biopsy specimens may reveal *S. stercoralis* embedded in the mucosa [36, 39].

Detection of *S. stercoralis* larvae is usually easier in cases of hyperinfection, because large numbers of worms are involved in disseminated infections [2, 36, 39]. The larvae can be identified in wet preparations of sputum, bronchoalveolar lavage fluid, bronchial washings and brushings, lung biopsies, or examination of pleural fluid by means of Gram, Papanicolaou, or acid-fast (auramine O and Kinyoun) staining procedures [2, 37–41, 51, 59]. Findings of chest radiographs are usually variable; pulmonary infiltrates, when present, may be alveolar or interstitial, diffuse or focal, unilateral or bilateral [60]. Lung consolidation, occasional caviation, and even abscess formation have also been reported [37–39]. The varying appearance of chest radiographs is due to different types of bacterial superinfection, particularly by gram-negative bacilli.

Because it is imperative to examine multiple stool samples to make a correct diagnosis, it is important to note that failure to detect larvae in a stool examination does not necessarily indicate the unequivocal absence of the infection [1, 2]. Hence, there is a great need for a highly specific and efficient serodiagnostic test for *S. stercoralis* that has the potential to be used even in multiple helminth infections. Several immunodiagnostic assays have been tested over the years, with limited success, including skin testing with larval extracts, indirect immunoflu-
to persist long-term in the host and the tendency to produce autoinfective L3 larvae, which are relatively resistant to chemical disease—that is, any truly effective anthelmintic must kill every infective L1 larvae, which are relatively resistant to chemical agents [1, 2]. Additionally, the poor sensitivity of diagnostic stool examination makes it even harder to determine the efficacy of treatment, because a true cure cannot be pronounced on the basis of negative findings of a follow-up stool examination alone. Thiaobendazole (Mintezol; Merck & Company) has been the drug of choice for the treatment of strongyloidiasis, despite the associated gastrointestinal side effects and a high relapse rate [1, 56]. However, recent studies have shown that ivermectin (Stromectol; Merck & Company) is the best drug for the treatment of uncomplicated S. stercoralis infection [81].
It is well tolerated and has a higher cure rate than thiabendazole. Other drugs, such as mebendazole (Vermox; McNeil Consumer Healthcare) and albendazole, have had variable therapeutic efficacy [2]. Ivermectin has been found to be the most effective drug in treating disseminated strongyloidiasis [82] in patients with chronic intestinal disease, including children [83] and adults [84]. Recently, ivermectin has also been registered as the drug of choice in the World Health Organization’s list of essential drugs for the treatment of *S. stercoralis* [85].

In summary, stool examination is currently the primary technique for the detection of *S. stercoralis* infection. If the diagnosis is strongly suspected and special techniques are not available, several specimens collected on different days should be examined. Generally, there are no distinctive clinical symptoms that suggest infection, although guaiac-positive stools and eosinophilia are common among infected patients. Almost all deaths due to helminths in the United States result from *S. stercoralis* hyperinfection [86, 87]. Mortality rates due to hyperinfection can be as high as 87% [88]. Because most of the fatal infections caused by *S. stercoralis* can be prevented by early detection and treatment of asymptomatic chronic infections, a comprehensive screening program that includes examination of eosinophilia should be applied to detect latent *S. stercoralis* infection before the start of chemotherapy, before immunosuppression, and before initiating steroid therapy for patients in endemic areas who are at risk.

**Acknowledgment**

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**References**


