Strongyloidiasis in Transplant Patients

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Strongyloides stercoralis is an intestinal nematode that can persist in the human host for decades after the initial infection and can progress to fulminant hyperinfection syndrome in immunocompromised hosts. We describe a patient who died of Strongyloides hyperinfection syndrome 2 months after orthotopic heart transplantation and discuss approaches to prevention, diagnosis, and treatment. Current practice guidelines recommend screening for and treatment of Strongyloides infection before transplantation, but physicians in the United States often miss opportunities to identify patients with chronic strongyloidiasis. Screening tests have limitations, and clinical suspicion remains an important component of the evaluation before transplantation. After immunocompromised patients develop hyperinfection syndrome, diagnosis is often delayed and mortality is high, so emphasis must be placed on screening and treatment before transplantation. We review current strategies for prevention, diagnosis, and treatment of chronic intestinal strongyloidiasis in patients who will undergo transplantation and discuss the clinical features and management of Strongyloides hyperinfection syndrome in transplant recipients.

CASE REPORT

A 63-year-old man was hospitalized for 5 months for severe heart failure, until he underwent heart transplantation. He had immigrated to the United States from Addis Ababa, Ethiopia, in 1979 at age 34 years and subsequently had never traveled to an area where strongyloidiasis was known to be endemic. Findings of a gastrointestinal evaluation (including colonoscopy) for constipation and anemia several years before transplantation were negative.

The case reported here illustrates important features of infection with Strongyloides stercoralis and highlights several key aspects of hyperinfection syndrome: the specific vulnerability of transplant recipients to hyperinfection with this parasite, often decades after their initial exposure; high mortality among immunosuppressed patients; and diagnostic difficulties. In this article, we review the clinical aspects of Strongyloides infection in transplant recipients and provide specific recommendations regarding prevention, diagnosis, and treatment of Strongyloides hyperinfection syndrome.

He received antithymocyte globulin and methylprednisolone (500 mg intravenously and then 125 mg intravenously twice a day for 5 days, followed by gradual dose reduction), followed by maintenance immunosuppression with tacrolimus, mycophenolate mofetil, and 25 mg of prednisone daily. Two months after transplantation, the patient presented to the outpatient clinic with increasing shortness of breath, vague abdominal pain, and nausea. He was afebrile, and his vital signs were notable for tachypnea, with a respiratory rate of 28 breaths/min and labored breathing; his O2 saturation was 92% while breathing room air, and his blood pressure was 108/58. Findings of a physical examination were remarkable for mild abdominal tenderness. The complete blood count showed a normal white blood cell count and lymphopenia but no eosinophilia. Plain radiographs of his chest (Figure 1A) showed bilateral interstitial infiltrates. A computed tomography scan of the chest (Figure 1B) showed multiple small intralobular opacities diffusely.

On hospital day 2, the patient required intubation and mechanical ventilation because of progressive dyspnea and hypotension. On day 3, bronchoscopy showed diffuse alveolar hemorrhage, but results of all bronchoalveolar studies, including direct examinations and cultures for bacteria, fungi, and mycobacteria; respiratory virus polymerase chain reaction (PCR); and blood and urine cultures were negative. Acute respiratory distress syndrome or bacterial pneumonia was suspected, and treatment with broad-spectrum antibiotics was begun. Progressive septic physiology requiring vasopressor therapy developed, and stress-dose steroid treatment (meth-
Figure 1. Chest radiograph (A) and computed tomography scan (B) at the time of diagnosis of Strongyloides hyperinfection syndrome. C, Microscopic image of the sputum wet mount examination. D, Sputum culture chocolate agar plate demonstrating serpentine bacterial trails.

Oral ivermectin tablets (200 μg/kg daily) were crushed and delivered via a nasogastric tube, although the patient had an ileus and this route was considered suboptimal. Efforts to acquire parenteral ivermectin (ie, veterinary formulation) were unsuccessful. The patient died on hospital day 6, only 36 h after the diagnosis of Strongyloides hyperinfection syndrome was made.

EPIDEMIOLOGY

S. stercoralis is a nematode with a complex life cycle (Figure 2) that is present worldwide in tropical and subtropical regions. Unlike other helminthic parasites, Strongyloides can complete its entire life cycle within the human host through an autoinfection cycle, living and reproducing in the small bowel mucosa. This may result in decades-long infection; thus, infection must be considered even in persons with remote exposure to the parasite [1, 2].

Transplant recipients are at risk for developing Strongyloides hyperinfection syndrome, from chronic intestinal Strongyloides infection, acquisition of primary Strongyloides infection in areas of endemcity, or allograft transmission. Progression of chronic intestinal infection that is present before transplantation appears to be the most common mechanism.
Chronic strongyloidiasis is asymptomatic in one-half of affected patients and is associated with minimal or intermittent gastrointestinal symptoms in others [12]. A serpiginous “larva currens” skin rash, usually in the pelvic area, is highly suggestive of Strongyloides infection, although it is seen in only a proportion of patients. Laboratory findings are nonspecific but can include intermittent eosinophilia.

Hyperinfection syndrome develops when immunosuppression reduces the usual immune surveillance, triggering an augmentation of the normal life cycle of the parasite and causing massive increases in the reproductive cycle of larvae. Larvae proliferate dramatically in the duodenum, migrate through the bowel wall, and then travel through the venous system to the lungs and back to the small bowel [13]. This can produce worsening pulmonary function, starting with wheezing, and in some patients, can progress to an acute respiratory distress syndrome–like picture, with respiratory failure and death. Many patients concurrently have a spectrum of gastrointestinal symptoms, including abdominal pain, dyspepsia, diarrhea, or constipation, or severe manifestations including ileus, obstruction, and gastrointestinal bleeding [12].

A frequent complication of hyperinfection syndrome is bacteremia due to gram-negative enteric organisms, caused by larvae migrating from the bowel through the venous system [14]. The presence of gram-negative sepsis is itself life threatening and can obscure the underlying diagnosis. Disseminated Strongyloides infection occurs when larvae travel through the venous system to other locations in the body, leading to translocation of intestinal bacteria. Meningitis, cholecystitis, liver abscess, pancreatitis, and other syndromes have been described [14].

Defects in cell-mediated immunity and corticosteroid use [15, 16] are considered to be the major risk factors for development of Strongyloides hyperinfection in immunocompromised hosts [17]. There is evidence that cyclosporine has direct antiparasitic activity in mice [12], and it may provide protection against Strongyloides hyperinfection syndrome [18]. There has been only 1 reported case of hyperinfection occurring in patients who receive cyclosporine [19]. In contrast, tacrolimus provides no similar protection [20].

The true incidence of Strongyloides hyperinfection syndrome among transplant recipients is unknown, but it appears to be uncommon. Since one of the earliest cases of kidney transplant–related Strongyloides hyperinfection was described in 1971 [21], multiple cases have been reported involving solid-organ transplant recipients (Tables 1 and 2). Cohort studies involving transplant recipients in areas of endemicity, including Brazil, South Africa, and Kuwait, have noted only occasional cases of strongyloidiasis. It is not known whether Strongyloides hyper-

\[ \text{Figure 2. Life cycle of Strongyloides stercoralis. Used with permission from the Centers for Disease Control and Prevention, Division of Parasitic Diseases.} \]
Table 1. Reported Cases of Strongyloidiasis in Renal Transplant Recipients

<table>
<thead>
<tr>
<th>Reference</th>
<th>No. of cases</th>
<th>Onset of disease posttransplantation</th>
<th>Geographic exposure to <em>Strongyloides</em></th>
<th>Symptoms before transplantation</th>
<th>Eosinophilia before transplantation</th>
<th>Screened for <em>Strongyloides</em></th>
<th>Clinical syndrome</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>DeVault et al, 1990 [22]</td>
<td>34</td>
<td>&lt;1 month in 3 cases, 1-6 months in 28 cases, &gt;6 months in 3 cases</td>
<td>Southeast US (33 cases)</td>
<td>8 cases</td>
<td>8 cases</td>
<td>NR</td>
<td>SHS in 22 cases, DS in 7 cases, GIS in 5 cases</td>
<td>18 (49%) Died</td>
</tr>
<tr>
<td>Palau and Pankey, 1997 [19]</td>
<td>1</td>
<td>52 days</td>
<td>Louisiana</td>
<td>No</td>
<td>No</td>
<td>Yes^a</td>
<td>SHS</td>
<td>Survived</td>
</tr>
<tr>
<td>Somani et al, 2002 [23]</td>
<td>1</td>
<td>6 months</td>
<td>India</td>
<td>No</td>
<td>No</td>
<td>NR</td>
<td>SHS</td>
<td>Died</td>
</tr>
<tr>
<td>Tarr et al, 2003 [24]</td>
<td>1</td>
<td>12 weeks</td>
<td>North Carolina</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>SHS</td>
<td>Survived</td>
</tr>
<tr>
<td>Prasad et al, 2006 [25]</td>
<td>1</td>
<td>18 days</td>
<td>India</td>
<td>No</td>
<td>No</td>
<td>Yes^a</td>
<td>GIS</td>
<td>Survived</td>
</tr>
<tr>
<td>Varar et al, 2007 [26]</td>
<td>11</td>
<td>NR</td>
<td>Brazil</td>
<td>NR</td>
<td>NR</td>
<td>No</td>
<td>SHS in 3 cases, GIS in 8 cases</td>
<td>1 (9%) Died</td>
</tr>
<tr>
<td>Said et al, 2007 [27]</td>
<td>3</td>
<td>&lt;90 days</td>
<td>South Asian donors</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>SHS</td>
<td>3 (100%) Died</td>
</tr>
<tr>
<td>Morrell et al, 2008 [28]</td>
<td>1</td>
<td>12 weeks</td>
<td>Southeast US</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>SHS</td>
<td>Died</td>
</tr>
<tr>
<td>Huston et al, 2009 [29]</td>
<td>1</td>
<td>3 months</td>
<td>South Korea; donor from Puerto Rico</td>
<td>NR</td>
<td>NR</td>
<td>No</td>
<td>SHS</td>
<td>Survived</td>
</tr>
</tbody>
</table>

**NOTE.** There were a total of 54 cases reported. Of the 54 case patients, 8 (15%) had symptoms before transplantation, 8 (15%) had eosinophilia, 2 (4%) were screened, 33 (61%) had SHS, 7 (13%) had DS, 14 (26%) had GIS, and 24 (44%) died. DS, disseminated strongyloidiasis; GIS, gastrointestinal strongyloidiasis; NR, not reported; SHS, *Strongyloides* hyperinfection syndrome.

^a Ova and parasite examination of stool.
<table>
<thead>
<tr>
<th>Reference</th>
<th>Organ allograft</th>
<th>No. of cases</th>
<th>Onset of disease posttransplantation</th>
<th>Geographic exposure to Strongyloides</th>
<th>Symptoms before transplantation</th>
<th>Eosinophilia before transplantation</th>
<th>Screened before transplantation</th>
<th>Clinical syndrome</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Case in present report</td>
<td>Heart</td>
<td>1</td>
<td>Day 70</td>
<td>Ethiopia</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>SHS</td>
<td>Died</td>
</tr>
<tr>
<td>El-Masry and O’Donnell, 2005 [30]</td>
<td>Heart</td>
<td>1</td>
<td>Day 41</td>
<td>Kentucky</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes&lt;sup&gt;a&lt;/sup&gt;</td>
<td>SHS</td>
<td>Died</td>
</tr>
<tr>
<td>Schaeffer et al, 2003 [31]</td>
<td>Heart</td>
<td>1</td>
<td>Day 70</td>
<td>Visited Kentucky</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>SHS, DS</td>
<td>Died</td>
</tr>
<tr>
<td>Mizuno et al, 2009 [32]</td>
<td>Heart and kidney</td>
<td>1</td>
<td>Day 36 (autopsy)</td>
<td>Florida</td>
<td>No</td>
<td>Yes, prominent</td>
<td>No</td>
<td>SHS</td>
<td>Died</td>
</tr>
<tr>
<td>Vilela et al, 2008 [33]</td>
<td>Liver</td>
<td>1</td>
<td>9 months</td>
<td>Brazil</td>
<td>No</td>
<td>Yes, mild</td>
<td>NR</td>
<td>SHS</td>
<td>Died</td>
</tr>
<tr>
<td>Lichtenberger et al, 2008 [34]</td>
<td>Liver</td>
<td>1</td>
<td>4 months</td>
<td>North Carolina</td>
<td>NR</td>
<td>NR</td>
<td>No</td>
<td>SHS</td>
<td>Survived</td>
</tr>
<tr>
<td>Patel et al, 2008 [35]</td>
<td>Intestine</td>
<td>1</td>
<td>9 months</td>
<td>None&lt;sup&gt;b&lt;/sup&gt;</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>SHS</td>
<td>Died</td>
</tr>
<tr>
<td>Ben-Youssef et al, 2005 [36]</td>
<td>Pancreas</td>
<td>1</td>
<td>Day 49</td>
<td>None&lt;sup&gt;b&lt;/sup&gt;</td>
<td>No</td>
<td>No</td>
<td>NR</td>
<td>GIS</td>
<td>Survived</td>
</tr>
<tr>
<td>Balagopal et al, 2009 [37]</td>
<td>Lung</td>
<td>1</td>
<td>Day 16</td>
<td>Peru</td>
<td>Yes</td>
<td>Yes, prominent</td>
<td>No</td>
<td>SHS</td>
<td>Died</td>
</tr>
</tbody>
</table>

**NOTE.** There were a total of 9 cases reported. The range for onset of disease was 36–270 days. Of the 9 case patients, 7 (78%) had exposure to *Strongyloides*, 3 (33%) had symptoms before transplantation, 6 (67%) had eosinophilia, 1 (11%) was screened, 8 (89%) had SHS, and 7 (78%) died. DS, disseminated strongyloidiasis; GIS, gastrointestinal strongyloidiasis; NR, not reported; SHS, *Strongyloides* hyperinfection syndrome.

<sup>a</sup> Ova and parasite examination of stool.
<sup>b</sup> Suspected allograft transmission.
infection syndrome remains uncommon because of more-aggressive pretransplantation screening in areas of endemcity, preferential use of cyclosporine, a higher prevalence of routine “deworming” in countries where *Strongyloides* species are endemc, or other unknown factors that influence progression to hyperinfection syndrome.

A review of *Strongyloides* hyperinfection syndrome in renal transplant recipients reported that disease typically occurred during the first 3 months after transplantation and that it most likely resulted from progression of chronic intestinal infection, presumably acquired before transplantation in an area of endemcity [22] (Table 1). The crude mortality rate was 49% overall, with a higher mortality from extraintestinal strongyloidiasis. Few patients had been screened and/or treated for strongyloidiasis before transplantation.

Cases of *Strongyloides* hyperinfection have been reported in recipients of liver transplants [33, 34], heart transplants [30, 31], lung transplants [37] and combined heart and kidney transplants [32]; all recipients in these cases had potential exposure before transplantation in an area where *Strongyloides* species are endemic. Cases have also been reported in recipients of pancreas transplants [36] and intestinal transplants [35]; as described below, these cases likely resulted from allograft transmission (Table 2).

In hematopoietic stem cell transplant recipients, 7 cases of hyperinfection after transplant, 6 of which were fatal [38], have been reported (Table 3). Compared with solid-organ transplant recipients, the onset of *Strongyloides* hyperinfection in hematopoietic stem cell transplant recipients appears to be earlier, with some cases occurring in the immediate posttransplantation period, possibly because of more-intensive immunosuppression regimen [38]. Autologous transplantation has been thought to confer a lower risk than does allogeneic transplantation, but fatal hyperinfection has also been reported after autologous hematopoietic stem cell transplantation [40, 41]. There are several reported cases of posttransplantation *Strongyloides* hyperinfection syndrome in which the clinical circumstances and laboratory results strongly suggest transmission of *Strongyloides* larvae via the allograft (Table 4).

**SCREENING FOR CHRONIC STRONGYLOIDIASIS**

Identification and treatment of chronic intestinal strongyloidiasis is the most important step to decrease the likelihood of progression to the devastating and often fatal *Strongyloides* hyperinfection syndrome after transplantation. A careful history of residence in or travel to areas of endemcity, including in the distant past, should be assessed before transplantation. A recent survey of physicians found that only 9% of US-trained physicians could recognize a case presentation of a person in need of screening for strongyloidiasis (compared with 56% of foreign-trained physicians) [46].

Current guidelines from the Infectious Diseases Society of America, the American Society of Transplantation, the Centers for Disease Control and Prevention, and the American Society of Blood and Marrow Transplantation recommend *Strongyloides* immunoglobulin G (IgG) enzyme-linked immunosorbent assay (ELISA) antibody testing for patients from an area of endemcity or for patients with gastrointestinal symptoms or eosinophilia before solid-organ transplantation or hematopoietic stem cell (including autologous) transplantation [47, 48]. Stool screening is recommended when serological testing is unavailable or when serological findings are negative in a patient with significant symptoms, eosinophilia, or a history of exposure. There currently are no data regarding the cost-effectiveness of screening for strongyloidiasis before transplantation, nor are there data on whether an approach of empirical therapy (rather than a “test and treat” strategy) would be more appropriate.

Eosinophilia, a common marker for helminth infections, may be present only intermittently in patients with chronic strongyloidiasis, and if noted, should prompt a careful pretransplantation evaluation. Among nonrenal solid-organ transplant recipients (Table 2), 6 (67%) of 9 patients had eosinophilia before transplantation. However, given its low sensitivity and specificity and the known effect of corticosteroids of decreasing the blood eosinophil count, the absence of eosinophilia cannot reliably exclude chronic *Strongyloides* infection.

Examination of ova and parasites in stool has relatively poor sensitivity because larvae are excreted in small quantities and intermittently; a single specimen has a sensitivity of only 15%–30% [49]. Sensitivity increases to nearly 100% if 7 consecutive daily stool specimens are examined in an expert laboratory [8], but this may be impractical. Stool culture techniques can improve detection of larvae in stool but are not routinely performed in most laboratories [50].

Currently, serological testing for *Strongyloides* is widely available in reference laboratories. ELISA IgG antibody tests have an estimated sensitivity of ~90% for patients with documented *Strongyloides* larvae in stool specimens who are from regions where *Strongyloides* is not endemic [51]. Some patients, however, including the case patient described here, may be among the 5%–10% with false-negative or indeterminate results of serological testing. Thus, clinical suspicion remains important, and a negative result of antibody testing must be interpreted cautiously and in combination with a patient’s risk factors, results of other laboratory tests, and symptoms. False-positive test results can occur because of the presence of other parasitic infections. A positive result of antibody testing may also occur in a patient who has been treated in the past but who does not
Table 3. Reported Cases of *Strongyloides* Hyperinfection in Hematopoietic Stem Cell Transplant (HSCT) Recipients

<table>
<thead>
<tr>
<th>Reference</th>
<th>Type of HSCT</th>
<th>No. of patients</th>
<th>Onset of disease, hospital day</th>
<th>Geographic exposure to <em>Strongyloides</em></th>
<th>Symptoms before transplantation</th>
<th>Eosinophilia before transplantation</th>
<th>Screened before transplantation</th>
<th>Clinical syndrome</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Steiner et al, 2002 [39]</td>
<td>Allogeneic</td>
<td>1</td>
<td>16</td>
<td>Europe</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Hematuria</td>
<td>Died of CMV on day 167</td>
</tr>
<tr>
<td>Orient et al, 2003 [40]</td>
<td>Autologous</td>
<td>1</td>
<td>480</td>
<td>India</td>
<td>No</td>
<td>No</td>
<td>NR</td>
<td>SHS</td>
<td>Died</td>
</tr>
<tr>
<td>Safdar et al, 2004 [41]*</td>
<td>Allogeneic and autologous</td>
<td>2</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>No</td>
<td>SHS</td>
<td>Died</td>
</tr>
<tr>
<td>Gupta et al, 2006 [42]*</td>
<td>Autologous</td>
<td>1</td>
<td>24</td>
<td>Puerto Rico</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>SHS</td>
<td>Died</td>
</tr>
<tr>
<td>Qazilbash et al, 2006 [43]</td>
<td>Allogeneic</td>
<td>1</td>
<td>21</td>
<td>Louisiana</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes*</td>
<td>SHS</td>
<td>Died</td>
</tr>
<tr>
<td>Dulley et al, 2008 [44]</td>
<td>Allogeneic</td>
<td>1</td>
<td>54</td>
<td>Brazil</td>
<td>NR</td>
<td>NR</td>
<td>Yes*</td>
<td>SHS</td>
<td>Survived</td>
</tr>
<tr>
<td>Wirk and Wingard, 2008 [38]</td>
<td>Allogeneic</td>
<td>1</td>
<td>2</td>
<td>Florida</td>
<td>Yes (IBS)</td>
<td>Yes</td>
<td>Yes*</td>
<td>SHS, DS</td>
<td>Died</td>
</tr>
</tbody>
</table>

**NOTE.** There were a total of 7 cases reported, of which 2 (29%) were autologous HSCT. The range for onset of disease was 2–480 days. Of the 7 case patients, 6 (86%) had exposure to *Strongyloides*, 2 (29%) had symptoms before transplantation, 3 (43%) had eosinophilia, 3 (43%) were screened, 6 (86%) had SHS, and 6 (86%) died. CMV, cytomegalovirus; DS, disseminated strongyloidiasis; IBS, irritable bowel syndrome; NR, not reported; SHS, *Strongyloides* hyperinfection syndrome.

* Duplicate case reported by Safdar et al and Gupta et al.
* Multiple stool samples were negative for ova and parasites.
* Three stool samples were negative for ova and parasites.
* One stool sample was negative for ova and parasites.
Table 4. Reported Cases of Possible Allograft Transmission of *Strongyloides stercoralis*

<table>
<thead>
<tr>
<th>Reference, transplant recipient</th>
<th>Organ allograft</th>
<th>Time to onset of disease posttransplantation</th>
<th>Syndrome(s)</th>
<th>Donor risk of <em>Strongyloides</em></th>
<th>Notes</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hoy et al, 1981 [45]</td>
<td>52-year-old female</td>
<td>Kidney</td>
<td>33 days</td>
<td>SHS</td>
<td>Not reported</td>
<td>Both kidney recipients from this donor developed strongyloidiasis</td>
</tr>
<tr>
<td></td>
<td>10-year-old female</td>
<td>Kidney</td>
<td>64 days</td>
<td>Cough, hematuria, fever</td>
<td>Not reported</td>
<td>Both kidney recipients from this donor developed strongyloidiasis</td>
</tr>
<tr>
<td>Said et al, 2007 [27]</td>
<td>52-year-old male</td>
<td>Kidney</td>
<td>48 days</td>
<td>SHS</td>
<td>South Asian donor</td>
<td>The other kidney from the donor went to a recipient receiving cyclosporine, who did not get disease</td>
</tr>
<tr>
<td></td>
<td>43-year-old female</td>
<td>Kidney</td>
<td>90 days</td>
<td>SHS</td>
<td>South Asian donor</td>
<td>Both kidney recipients from this donor developed SHS</td>
</tr>
<tr>
<td></td>
<td>43-year-old female</td>
<td>Kidney</td>
<td>92 days</td>
<td>SHS</td>
<td>South Asian donor</td>
<td>Both kidney recipients from this donor developed SHS</td>
</tr>
<tr>
<td>Ben-Youssef et al, 2005 [36]</td>
<td>41-year-old male</td>
<td>Pancreas</td>
<td>49 days</td>
<td>Hematuria, epigastric pain</td>
<td>Donor was confirmed to be IgG positive for <em>Strongyloides</em></td>
<td>Survived</td>
</tr>
<tr>
<td>Patel et al, 2008 [35]</td>
<td>62-year-old female</td>
<td>Intestine</td>
<td>9 months</td>
<td>SHS, DS</td>
<td>Donor from Honduras</td>
<td>Recipient had no risk factors</td>
</tr>
<tr>
<td>Huston et al, 2009 [29]</td>
<td>61-year-old female</td>
<td>Kidney</td>
<td>3 months</td>
<td>SHS</td>
<td>Donor from Puerto Rico</td>
<td>Recipient was born in South Korea</td>
</tr>
</tbody>
</table>

**NOTE.** There were a total of 8 reported cases. The range for onset of disease was 33–270 days. Of all 8 case patients, 6 had donors from areas of endemicity, and 5 (63%) died. DS, disseminated strongyloidiasis; IgG, immunoglobulin G; SHS, *Strongyloides* hyperinfection syndrome.
have active infection (Table 5). Newer diagnostics under development may offer advantages over current tests; these include the luciferase immunoprecipitation system assay [52] and PCR of stool [53] but are not yet widely clinically available.

**DIAGNOSIS OF HYPERINFECTION SYNDROME**

*Strongyloides* hyperinfection syndrome is uncommon, and clinical diagnosis is often delayed; in one series, it was delayed for a mean of 5 days after hospital presentation [22]. Once hyperinfection is considered, the large burden of larvae makes diagnosis relatively easy; filariform larvae can be seen in wet-mount preparations from sputum or bronchoalveolar lavage fluid samples and brushings, although, as our case demonstrates, larvae may be missed unless there is a high level of suspicion. Larvae are more easily found in stool specimens and have been noted in a variety of sites of dissemination, including cerebrospinal fluid, liver biopsy specimens, pleural fluid, and urine.

Biopsy of the duodenum demonstrating rhabditiform larvae is a frequent method of diagnosis for transplant recipients, who may undergo upper gastrointestinal endoscopy for suspicion of cytomegalovirus disease or other opportunistic infection. Larvae can also be demonstrated in skin biopsy specimens collected from the site of a larva currens rash, but this finding is only variably present in patients with *Strongyloides* hyperinfection syndrome and was not found in the case described here [28].

**TREATMENT OF CHRONIC INTESTINAL STRONGYLOIDIASIS AND HYPERINFECTION SYNDROME**

Treatment of chronic intestinal strongyloidiasis should be given before immunosuppression therapy, if possible. Reports of treatment failures or relapses after antiparasitic therapy, including treatment with albendazole, thiabendazole, and ivermectin [54, 55], appear to be more frequent among immunosuppressed patients. Patients infected with human T cell lymphotropic virus 1 (HTLV-1) are especially susceptible to strongyloidiasis and may be more likely to experience failure of standard therapy [56]; guidelines recommend routine screening for HTLV-1 before organ transplantation [47]. Current clinical guidelines recommend empirical treatment for strongyloidiasis before hematopoietic stem cell transplantation and solid-organ transplantation for patients with exposure to areas of endemcity, even if results of diagnostic testing are negative [57]. Because cases of hyperinfection syndrome have occurred in patients with a minimal exposure history and because treatment is generally well tolerated, clinicians should be inclusive when deciding whom to treat.

In clinical trials, ivermectin is more effective than thiabendazole or albendazole for the treatment of chronic strongyloidiasis, is better tolerated [58, 59], and is now considered first-line therapy [15]. The recommended dose of ivermectin for treatment of chronic intestinal strongyloidiasis is 200 μg/kg (orally), given once daily for 2 days [60]. Some recommend a repeat dose after 2 weeks (the duration of 1 autoinfection cycle), to ensure eradication [61] (Table 6). Ivermectin is US Food and Drug Administration (FDA) approved for only the oral form.

Immunosuppressed patients with chronic intestinal strongyloidiasis may require longer courses of therapy, with some recommendations for 2 weeks of daily therapy to extend over the full life cycle of the parasite, followed by posttreatment monitoring to document clearance of infection. Some have suggested that continuous suppressive therapy may be required for immunosuppressed patients, especially when albendazole or thiabendazole is used [22, 62]. Antibody titers can be followed, to document response to treatment [63], although these may be less useful for immunosuppressed patients, and significant changes in titers may not be seen for several months. Patients with certain coexisting parasitic infections (eg, loiasis,
<table>
<thead>
<tr>
<th>Drug</th>
<th>Treatment regimen</th>
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<tbody>
<tr>
<td>First choice: ivermectin</td>
<td>200 µg/kg orally once a day for 2 days; consider a repeat dose after 2 weeks</td>
<td>Verify cure. Immunocompromised hosts may require longer duration and/or suppressive therapy.</td>
<td>200 µg/kg orally once a day, until larvae are not detected at any site; repeat 1 dose at 2 weeks after clearance of larvae</td>
<td>Consider intravenous ivermectin in severe cases or rectal or subcutaneous ivermectin (not FDA approved). Consider combination therapy with albendazole.</td>
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<tr>
<td>Second choice</td>
<td></td>
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<tr>
<td>Albendazole (not FDA approved)</td>
<td>400 mg orally twice a day for 3 days</td>
<td>Verify cure or consider a repeat dose after 2 weeks. Immunocompromised hosts may require longer duration and/or suppressive therapy</td>
<td>400 mg orally twice a day, until larvae are not detected at any site</td>
<td>Consider combination therapy with ivermectin</td>
</tr>
<tr>
<td>Thiabendazole</td>
<td>25 mg/kg orally twice a day for 3 days</td>
<td>Verify cure or consider a repeat dose after 2 weeks. Immunocompromised hosts may require longer duration and/or suppressive therapy</td>
<td>25 mg/kg orally twice a day, until larvae are not detected at any site</td>
<td>Consider combination therapy with ivermectin</td>
</tr>
</tbody>
</table>

**NOTE.** FDA, US Food and Drug Administration.
cysticercosis, or onchocerciasis) may experience inflammatory reactions during antiparasitic therapy, so appropriate evaluation and monitoring is important [64].

Although screening for Strongyloides with serological and/or parasitological evaluation before transplantation or immunosuppressive therapy is recommended for patients with risk factors, presumptive treatment of high-risk patients is also reasonable, given the diagnostic difficulties and limitations discussed above. For patients with parasitologically confirmed strongyloidiasis, some guidelines recommend postponing transplantation until a treatment course of ivermectin can be completed and microscopic cure can be confirmed, with >3 stool samples testing negative [48]. Because treatment regimens are <100% effective, a definite diagnosis of strongyloidiasis provides valuable information before transplantation and should prompt appropriate monitoring, rapid evaluation, and empirical therapy if compatible symptoms develop in the posttransplantation period.

In patients with hyperinfection syndrome, ivermectin is considered the first-line agent, and longer courses of treatment are indicated. If patients are unable to tolerate oral medication or if intestinal absorption is impaired because of critical illness, there are documented cases of successful treatment using veterinary intravenous formulations of ivermectin [65, 66]. Although this therapy is not FDA approved, it has been obtained with an emergency-use investigational drug application [29]. There are also case reports of response in patients treated with ivermectin enema [24] and with subcutaneous injection of ivermectin [67]. Treatment is continued daily until microscopic clearance of larvae from all infected sites is documented. In reported cases, this has sometimes taken several weeks. Patients should be evaluated and treated for concomitant bacterial infections.

When hyperinfection syndrome is diagnosed in transplant recipients, a therapeutic response can be difficult to achieve, and high mortality rates are common. Hematopoietic stem cell transplant recipients have particularly poor outcomes; the only series to date noted 85% mortality [38]. Renal transplant recipients had up to 50% mortality in 2 large case series [22, 68]. Prognosis appears to be improved for patients with elevated eosinophil counts and for patients whose corticosteroid treatment is rapidly tapered [12].

CONCLUSIONS

Despite well-described risk factors for this devastating complication, cases of Strongyloides hyperinfection syndrome continue to occur in transplant recipients. A high index of suspicion is necessary to identify and treat patients with chronic intestinal strongyloidiasis before immunosuppression is begun. Multiple deaths from hyperinfection syndrome have occurred in the United States among transplant recipients from areas of endemicity; their risk for strongyloidiasis was not recognized until their presentation with hyperinfection syndrome.

Current guidelines recommend serological screening (or stool examination in selected cases) to detect chronic intestinal strongyloidiasis in at-risk patients before transplantation. Because the currently available laboratory tests are not sufficiently sensitive to exclude the diagnosis and because treatment regimens are generally well tolerated, empirical therapy for high-risk patients from areas of endemicity should be considered, even if results of the diagnostic evaluation are negative.

Although the majority of cases of hyperinfection are presumed to develop from chronic intestinal strongyloidiasis, allograft transmission may also occur. Currently, screening of donors for chronic Strongyloides infection is not routinely done but should be considered on a case-by-case basis for donors with known risk factors or during investigation of strongyloidiasis in transplant recipients without other known risk factors.

Diagnosis of Strongyloides hyperinfection syndrome in transplant recipients requires a high level of suspicion, and the mortality rate of the syndrome is >50%. Treatment of Strongyloides hyperinfection syndrome should include daily doses of ivermectin until parasitological clearance from infected sites is documented, diagnosis and treatment of concomitant infections, and cautious reduction in immunosuppression therapy as tolerated.

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References


