Severe strongyloidiasis: a systematic review of case reports

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Abstract

Background

Strongyloidiasis is usually a chronic, asymptomatic or pauci-symptomatic infection, but in case of immunosuppression it can turn into a fatal disease. It is therefore mandatory to recognize and treat the infection before it becomes life-threatening. Some narrative reviews have reported the most frequent characteristics of hyperinfection syndrome (HS) and disseminated strongyloidiasis (DS), but to our knowledge no systematic review has been published.

Methods

We conducted a structured search using PubMed, in order to collect case reports and short case series on HS/DS published from 1991 to 2011. We restricted search to papers in English, Spanish, Italian and French. Case reports were classified as HS/DS according to given definitions.

Results

Records screened were 821, and 311 were excluded through titles and abstract evaluation. Of 510 full-text articles assessed for eligibility, 213 were included in qualitative synthesis. As some of them were short case series, eventually the number of cases analyzed was 244.

Steroids were the main risk factors for development of HS and DS (67% cases): they were mostly administered for underlying conditions (e.g. lymphomas, rheumatic diseases). However, steroids were sometimes empirically prescribed to treat signs and symptoms probably caused by unsuspected/unrecognized strongyloidiasis, misinterpreted for instance as “idiopathic eosinophilia”. Diagnosis was always obtained by microscopic examination of biological samples, while serology was performed in a few cases (6.5%). Only in 3 out of 29 cases of solid organ/bone
marrow transplantation there is mention of pre-transplant serological screening. Diagnosis was made post-mortem in 12% cases. Therapeutic regimens used were exceedingly different in drugs selection and combination, administration route and duration. No significant difference in fatality rate was observed between patients with DS (68.5%) and HS (60%).

**Conclusions**

The absence of any proper screening for strongyloidiasis before the prescription of steroids highlights the physicians’ lack of awareness of *Strongyloides* infection. Unfortunately, a high index of suspicion is crucial to avoid delayed diagnosis and treatment. On the other hand, current classification in HS and DS seems not to be useful in clinical practice and should probably be revised. The variety of therapeutic schemes used, often including drugs proven ineffective in randomized clinical trials, clearly shows the gaps in knowledge of the management of these patients.

**Keywords**

Strongyloidiasis, *Strongyloides*, hyperinfection, disseminated strongyloidiasis, review

**Background**

Strongyloidiasis is a neglected condition caused by *Strongyloides stercoralis* (*S. stercoralis*), a soil – transmitted helminth mainly diffused in tropical and subtropical regions, but also present in small areas of low endemicity in temperate climates[1]. Most infected individuals are asymptomatic or may present aspecific and intermittent symptoms, affecting mostly intestine (from mild abdominal pain, intermittent or persistent diarrhea to more severe conditions that can mimic inflammatory bowel disease), lungs (cough, wheezing and asthma, chronic bronchitis) and the skin
(pruritus, rash). Systemic symptoms like weight loss and cachexia may also occur[2]. Immune suppressed subjects tend to develop severe infection, hyperinfection syndrome (HS) and disseminated strongyloidiasis (DS), that is potentially fatal [3]. Therefore, it is mandatory to diagnose and treat the chronic infection, before it can turn into a life-threatening disease. Unfortunately, the index of suspicion of health care providers seems to be low, especially in non-endemic countries[4]. Moreover, there are still gaps in knowledge regarding many aspects of the infection, such as diagnosis and treatment response[2].

Our aim was to systematically review case reports of severe strongyloidiasis, in order to outline the main features of hyperinfection and disseminated strongyloidiasis and the difficulties in their management.

**Methods**

We made a systematic review of case reports/short case series published in PubMed from January 1991 to April 2011. We considered papers available in the following languages: English, Spanish, Italian, French.

The electronic search strategy was as follows: `disease (strongyl*, anguillulose) AND severity of cases (disseminat*, hyperinfect*, severe, death, fatal, mortality) OR disease (strongyl*, anguillulose) AND associated conditions (tumor*, cancer, haematolog*, lymphom*, leukem*, leukaem*, neoplas*, malignan*, HTLV*, HIV, AIDS, hypogammaglobulinemia, rheumat*, “biological agents”, diabet*, transplant*, COPD, steroid*, glucocorticoid*, Immunosuppression [MeSH], Immunocompromised Host [MeSH])` and limiting the search to humans. Search was done on March 20th 2011.
Definitions used for case - inclusion[5]: - Dissemination: larvae found in any organ, other than the respiratory and the gastrointestinal tracts. - Hyperinfection: infection confined to lungs and gastrointestinal tract, but signs/symptoms of severe diseases in relation to elevated number of larvae; in particular, necessity of intensive care, presence of sepsis/meningitis by enteric bacteria, death (without any other clear underlying cause).

Results

Data synthesis

Our search strategy permitted to identify 821 papers, of which 311 were excluded by title and abstract evaluation. Full-text papers were then assessed for eligibility according to the given criteria. Among the 213 papers included, some were short case series, eventually the number of cases analyzed was 244 (see PRISMA – “Preferred Reporting Items for systematic Reviews and Meta-Analyses” - flow chart - figure 1).

Countries

Most of the cases were diagnosed in countries with no or low endemicity, such as the USA (75 cases) [6-67], Belgium (two cases) [68, 69], France (14 cases) [70-81], Germany (two cases) [82, 83], Greece (three cases) [84-86], Italy (six cases) [87-92], the Netherlands (four cases) [93-96], Spain (ten cases) [97-106], Switzerland (one case) [107], UK (eight cases) [108-115] and Canada (seven cases) [116-122]. In 70 cases the patients were immigrants (Fig. 2.): they mostly moved from Central-South America and the Caribbean[6, 9, 11-13, 17, 22, 25, 26, 31, 32, 34, 36-39, 45, 48, 50, 51, 54, 58, 59, 61, 64, 71, 80, 82, 91, 94, 95, 102, 107, 116, 117, 120, 122, 123] to the
USA, Canada or Europe; 16 African patients migrated to Europe, the USA or Israel[13, 20, 23, 46, 57, 69, 74, 76, 78, 90, 103, 106, 108, 124, 125], 13 patients from South Eastern Asia[13, 42, 44, 75, 79, 80, 110, 113, 115, 118, 119, 126] to Europe, Canada, the USA, Australia. A few patients presumably acquired the infection during military service in an endemic country [8, 18, 27, 81, 111].

Risk factors

According to the case definitions, 171 cases were classified as hyperinfection and 73 cases as dissemination.

One hundred and sixty four (67%) patients were taking corticosteroids, mostly because of chronic clinical conditions, such as: COPD (chronic obstructive pulmonary disease)/asthma, organ transplant, leukaemia/lymphoma (table 1).

Five patients were receiving steroids for eosinophilia and/or aspecific symptoms caused by *S. stercoralis* itself. A patient even underwent bone marrow transplant because of an unexplained eosinophilia misdiagnosed as “idiopathic hypereosinophilic syndrome”[40]; after receiving steroids and immunosuppressive therapy he developed hyperinfection (but only limited autopsy was performed, so we cannot rule out dissemination) and died.

Dissemination occurred in 10 patients who underwent organ transplant; all but 2 died. Other transplant patients died from hyperinfection, but autopsy was not done, then we cannot rule out dissemination. On the other hand, autopsy confirmed hyperinfection in other 3 transplant patients, two of whom had also coinfection with CMV[66, 127].

Other transplant patients survived, in particular 4 of them who received the veterinary formulation of ivermectin via rectal enema[30] or subcutaneously[13, 49, 53].

HTLV1 infection is a well known risk factor (sometimes in association with related haematological malignancies), of which we found 24 reports. Ten of the 24 patients
(41.6%) died. A very peculiar case is described by Porto et al[128]: in a HTLV1 – positive patient under evaluation for infertility, S. stercoralis larvae were found in the urine analysis and all parasite stages (including adult female) in the sperm. The patient was successfully treated with a single dose of cambendazole, followed by a single dose of ivermectin. One patient had HTLV1-HIV coinfection[74]; he developed an E. coli meningitis but successfully responded to ivermectin, two doses given some days (not specified how many) apart.

We found 38 reports on HIV-positive patients, 26 (68%) of whom died (Figure 3). Seven HIV patients were also receiving steroids for suspected Pneumocystis jiroveci pneumonia[129, 130], immune reconstitution inflammatory syndrome[64], misdiagnosis of asthma[17], Wegener granulomatosis[131], toxoplasmosis encephalitis[131], cerebral TB with vasculitis[76]; six out of seven died.

Four case reports/case series describe uncommon risk factors such as alcoholism[132, 133] and malnutrition[134, 135]. In none of those cases the patients were receiving corticosteroids or other immunosuppressive treatment. A patient with history of alcohol abuse had undergone gastrectomy, that might partially explain the enhancement of the infection, leading to the patient’s death[132]. The other heavy drinker had an episode of acute pancreatitis that, according to the authors, may have precipitated infection of ascitic fluid with S. stercoralis[133].

Although he did not have any apparent risk factors (neither chronic conditions nor immunosuppressant therapies), a patient developed hyperinfection and died two days after having started therapy with thiabendazole[100]. Unfortunately autopsy was denied.
**Diagnosis**

Eosinophilia was present in 55/244 cases (22.5%) overall, and only in 12/73 cases (16.4%) of dissemination. In all cases *S. stercoralis* was found at microscopy examination of biological samples. Serology was performed only in 16/244 patients (6.5%) (table 2). In a couple of organ transplant recipients, an ELISA test was negative pre-transplant, but resulted positive in the deceased donors (test performed retrospectively)[19, 96]. In other two cases serology (ELISA) was negative: a HIV-infected person, who had larvae in stool and sputum[136] and a patient with dermatomyositis, under chronic treatment with prednisone and methotrexate, who died from disseminated strongyloidiasis (larvae found at autopsy in skin, lungs, small and large bowel, gall bladder, vessels of meninges and cervical spinal cord)[59]. Diagnosis was obtained post mortem in 29 cases (12%). Autopsy was performed in 51 cases.

**Therapy**

Therapies given are very different in relation to the drugs used and the length of treatment. Forty-two patients did not receive any treatment because the diagnosis was made too late, in fact they all died.

In table 3 we summarize the drugs used. In the “other drugs” group we found mebendazole[7, 83, 89, 137-141], cambendazole[128, 131], levamisole[142, 143], pyrantel pamoate[34, 67], diethylcarbamazine [144].

Albendazole was used as single drug even in recent case reports; since 2008 we found patients treated with only albendazole in reports from Pakistan[145], Romania[133], Taiwan[146], Israel[124], Kuwait[147], Argentina[148], Malaysia[149], Greece[85], Thailand[150].
In most cases the administration route was oral, followed by nasogastric tube administration. Some patients received ivermectin subcutaneously (veterinary formulation), a few cases were treated with retention enema (table 4).

Turner et al[122] describe a patient with disseminated infection who started therapy with albendazole and ivermectin by nasogastric tube, that was shifted to subcutaneous ivermectin after 3 days because of acute deterioration of clinical conditions, requiring mechanical ventilation, intubation and vasopressor support. Despite a gradual improvement of all the parameters, he remained in an unexplained comatose state, with hypersalivation, until he died of aspiration pneumonia. The authors speculate that high levels of plasma ivermectin, due to a condition of hypoalbuminemia, might have caused CNS toxicity, that is a rare but described side effect.

A patient who developed disseminated strongyloidiasis after an empiric steroid treatment for pruritic rash, was treated with albendazole[126]. Only one dose could be given, as the patient died. After his death, a review of his clinical records showed that he had been previously diagnosed with strongyloidiasis and treated with a 3-day course of albendazole; although serology persisted positive and eosinophilia was still present 6 and 12 months after treatment, the patient did not receive any further therapy. Another patient who died from *Strongyloides* hyperinfection had never been treated before for the parasitosis, despite previous positive serology.[60]

**Outcome**

The recorded deaths were 153/244 (62.7%). No significant difference in fatality rate was observed between patients with dissemination (50/73= 68.5%) and with hyperinfection (102/171 = 60%).
All the patients who did not receive a specific treatment died. In figure 4 is reported the number of deaths among patients who received treatment with albendazole (25/34 = 73.5%), ivermectin (18/38 = 47%) and thiabendazole (28/55 = 51%); patients receiving combination therapies were excluded from analysis.

**Discussion**

Considering that a considerable number of case reports are described in non endemic countries, we assume that fatal cases must be quite frequent in endemic countries, although they’re not frequently published in the literature.

The main risk factors identified in this review have been reported previously, in particular steroids are frequently the trigger for developing severe strongyloidiasis. Unfortunately it was not possible to extract from the case reports the cumulative dosage and the duration of the corticosteroids treatment. Although the association with steroids should be well known, there are still papers reporting cases of patients under steroids who were not previously screened for strongyloidiasis. Moreover, we found papers reporting severe strongyloidiasis in patients who were previously diagnosed with the infection but had not received a proper treatment. Once more, the lack of familiarity with strongyloidiasis by health care providers is the weak link in the chain; this is also highlighted by the fact that in 12% of cases the diagnosis was made post mortem. Eosinophil count is often normal in severe strongyloidiasis, hence this test has limited excluding power.

Serology is not frequently performed, in fact in case of hyperinfection and dissemination the diagnosis is easily made by direct examination of the biological samples. Serology would be most useful in chronic infections, before hyperinfection
and/or dissemination occur, while in patients who are already immune suppressed its sensitivity is probably lower.

Limits in our results are due to lack of information in the case descriptions. Moreover, cases in which autopsy was not performed sometimes couldn’t allow a proper classification. Actually, in 65 patients we classified as having hyperinfection, autopsy was not done, hence it is not possible to rule out dissemination. Moreover, we found the same fatality rate for patients with hyperinfection and with dissemination, but a misclassification might have played a role. In fact, we think that from a clinical, practical point of view the distinction between hyperinfection and dissemination is not essential, because they’re both severe conditions requiring immediate assessment and cure.

In general, the best drug to treat strongyloidiasis is ivermectin which is effective and well tolerated. There are still some concerns about the treatment schedule of chronic infection, and this is even more debated in case of hyperinfection/dissemination. In fact there are no specific guidelines and the case reports we collected outline a Babylon of different therapeutic schemes. Subcutaneous ivermectin (veterinary formulation) has been used on empiric basis, when intestinal absorption is decreased or the patient cannot swallow tablets. On the other hand, albendazole is still used even as a single drug, although it has been proved to be poorly effective. In some cases, this might be due to the scarce availability of ivermectin in many countries.

**Conclusions**

The first step to be done to guarantee an adequate management of infected patients is to avoid a delayed diagnosis. Unfortunately unfamiliarity with strongyloidiasis by health care providers still seems to be the main cause of the delay. Therefore diffusion
of information should be warranted, and collaboration among different specialists (oncologists, rheumatologists…) is desirable in order to provide common and adequate protocols for screening and treatment of at – risk patients.

In the meantime, research is necessary to fill the gaps in knowledge that still remain, particularly in the diagnosis and treatment fields. However, ivermectin is currently the gold standard for treatment of strongyloidiasis, so it is no more ethical to use other drugs. Moreover, ivermectin is in the WHO model lists of essential medicines[151], so it should be registered and easily available, in particular in endemic countries.

**Competing interests**

The authors declare that they have no competing interests

**Authors' contributions**

DB searched PubMed, analyzed the data and wrote the manuscript. ARM analyzed the data and critically reviewed the manuscript. AA created the search strategy and analyzed the data. JM, FG and JVDE gave intellectual content and critically reviewed the manuscript. ZB conceptualized the review and critically reviewed the manuscript.

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**Figures**

**Figure 1** - PRISMA flow chart: data collection and selection of studies

**Figure 2** - Distribution of immigrant patients per provenience (continent).

**Figure 3.** Deaths in the HIV patients subgroup

**Figure 4.** Numbers of deaths among patients treated with a single antiparasitic drug
### Tables

**Table 1 - Patients under steroid treatment: reasons for prescription**

<table>
<thead>
<tr>
<th>Condition</th>
<th>N (%)</th>
<th>References</th>
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</thead>
<tbody>
<tr>
<td>COPD/asthma/lung fibrosis</td>
<td>30 (18.3)</td>
<td>[7, 8, 11, 16-18, 27, 58, 60, 70, 73, 75, 80, 89, 97, 104, 123-125, 137, 146, 152-158]</td>
</tr>
<tr>
<td>Leukemia/lymphoma</td>
<td>13 (7.9)</td>
<td>[6, 15, 57, 78, 113, 117, 138, 139, 148, 159-161]</td>
</tr>
<tr>
<td>SLE</td>
<td>9 (5.5)</td>
<td>[23, 25, 45, 102, 162-165]</td>
</tr>
<tr>
<td>Rheumatoid arthritis</td>
<td>4 (2.4)</td>
<td>[42, 62, 142, 166]</td>
</tr>
<tr>
<td>IBD</td>
<td>6 (3.6)</td>
<td>[18, 98, 99, 115, 167, 168]</td>
</tr>
<tr>
<td>Sarcoidosis</td>
<td>2 (1.2)</td>
<td>[24, 84]</td>
</tr>
<tr>
<td>Cancer</td>
<td>8 (4.8)</td>
<td>[13, 52, 56, 111, 118, 169-171]</td>
</tr>
<tr>
<td>Organ/bone marrow transplant</td>
<td>25 (15.2)</td>
<td>[7, 10, 13, 19, 29, 30, 33, 35, 40, 46, 47, 49, 51, 53, 93, 96, 101, 127, 147, 148, 172-174]</td>
</tr>
<tr>
<td>Glomerulonephritis/CRI</td>
<td>6 (3.6)</td>
<td>[81, 82, 105, 175-177]</td>
</tr>
<tr>
<td>“Idiopathic” eosinophilia</td>
<td>3 (1.8)</td>
<td>[178]</td>
</tr>
<tr>
<td>Multiple myeloma/myelodisplasia</td>
<td>6 (3.6)</td>
<td>[31, 145, 152, 179-181]</td>
</tr>
<tr>
<td>Aspecific symptoms</td>
<td>2 (1.2)</td>
<td>[44, 126]</td>
</tr>
<tr>
<td>Other clinical conditions</td>
<td>46 (28)</td>
<td>[13, 18, 25, 43, 48, 59, 61, 76, 77, 79, 85-87, 92, 106, 110, 116, 119, 131, 134, 139, 149, 150, 182-191]</td>
</tr>
<tr>
<td>HIV-related opportunistic infections/IRIS</td>
<td>4 (2.4)</td>
<td>[64, 129-131]</td>
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</table>
Table 2 - Patients tested with serology: chronic conditions and corticosteroids therapy

<table>
<thead>
<tr>
<th>Year</th>
<th>Chronic condition</th>
<th>Corticosteroids</th>
<th>Serology</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1991</td>
<td>polychondritis</td>
<td>Yes</td>
<td>positive</td>
<td>[48]</td>
</tr>
<tr>
<td>1994</td>
<td>COPD</td>
<td>Yes</td>
<td>positive</td>
<td>[16]</td>
</tr>
<tr>
<td>1996</td>
<td>HIV</td>
<td>No</td>
<td>negative</td>
<td>[136]</td>
</tr>
<tr>
<td>2001</td>
<td>none</td>
<td>Yes</td>
<td>positive</td>
<td>[126]</td>
</tr>
<tr>
<td></td>
<td>bronchogenic carcinoma</td>
<td>Yes</td>
<td>positive</td>
<td>[111]</td>
</tr>
<tr>
<td>2004</td>
<td>bronchogenic carcinoma</td>
<td>Yes</td>
<td>positive</td>
<td>[155]</td>
</tr>
<tr>
<td>2005</td>
<td>multiple myeloma</td>
<td>Yes</td>
<td>positive</td>
<td>[31]</td>
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<tr>
<td>2005</td>
<td>multiple myeloma</td>
<td>Yes</td>
<td>positive</td>
<td>[179]</td>
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<tr>
<td>2005</td>
<td>nephrotic syndrome</td>
<td>No</td>
<td>positive</td>
<td>[179]</td>
</tr>
<tr>
<td>2007</td>
<td>nephrotic syndrome</td>
<td>Yes</td>
<td>positive</td>
<td>[91]</td>
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<tr>
<td>2008</td>
<td>none</td>
<td>Yes</td>
<td>positive</td>
<td>[95]</td>
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<tr>
<td>2008</td>
<td>asthma</td>
<td>Yes</td>
<td>positive</td>
<td>[60]</td>
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<tr>
<td>2009</td>
<td>heart transplant</td>
<td>Yes</td>
<td>negative</td>
<td>[96]</td>
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<tr>
<td>2009</td>
<td>lung transplant</td>
<td>Yes</td>
<td>positive</td>
<td>[51]</td>
</tr>
<tr>
<td>2010</td>
<td>dermatomyositis</td>
<td>Yes</td>
<td>negative</td>
<td>[59]</td>
</tr>
<tr>
<td>2011</td>
<td>renal transplant</td>
<td>Yes</td>
<td>negative</td>
<td>[19]</td>
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### Table 3 - Treatments

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<th>Drug</th>
<th>Albendazole</th>
<th>Ivermectin</th>
<th>Thiabendazole</th>
<th>Other drugs</th>
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<tbody>
<tr>
<td><strong>Used as single treatment</strong></td>
<td>34</td>
<td>38</td>
<td>55</td>
<td>6</td>
</tr>
<tr>
<td><strong>In combination</strong></td>
<td>14</td>
<td>41</td>
<td>5</td>
<td>8</td>
</tr>
<tr>
<td><strong>Total of patients treated</strong></td>
<td>48</td>
<td>79</td>
<td>60</td>
<td>14</td>
</tr>
</tbody>
</table>

### Table 4 - Administration routes other than oral

<table>
<thead>
<tr>
<th>Administration route</th>
<th>NSG/enteral</th>
<th>Subcutaneous</th>
<th>Rectal/enema</th>
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</thead>
<tbody>
<tr>
<td><strong>N. of treatments</strong></td>
<td>29</td>
<td>19</td>
<td>9</td>
</tr>
<tr>
<td>Ref</td>
<td>[13, 29-31, 36, 46, 47, 49, 51, 52, 63, 40, 49, 50, 53, 30, 32, 47, 64, 82, 90, 98, 101, 64, 66, 76, 78, 53, 64, 147]</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>118, 122, 130, 147, 82, 109, 110, 169, 171, 173, 192</td>
<td>118, 122, 171, 182</td>
<td></td>
</tr>
</tbody>
</table>
Figure 1.

- **Identification**: Records identified through database searching, n = 821
- **Screening**: Records screened, n = 821
- **Eligibility**: Full-text articles assessed for eligibility, n = 510
  - Full-text articles excluded: n = 208 case reports on strongyloidiasis but not on dissemination/hyperinfection
  - n = 89 articles were not case reports (e.g. reviews)
- **Included**: Papers included in qualitative synthesis, n = 213
- **Included**: Cases analyzed, n = 244
Figure 2
Figure 3

<table>
<thead>
<tr>
<th></th>
<th>Total HIV+</th>
<th>Pts with O.I.</th>
<th>Pts under steroids</th>
<th>Pts with TB coinfection</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dead</td>
<td>26</td>
<td>3</td>
<td>6</td>
<td>3</td>
</tr>
<tr>
<td>Survived</td>
<td>12</td>
<td>0</td>
<td>1</td>
<td>0</td>
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Figure 4