Treatment of Patients with Refractory Giardiasis

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Giardia lamblia is one of the most common parasitic infections. Although standard treatments are usually curative, some immunocompromised patients, including patients with acquired immunodeficiency syndrome as well as healthy patients, have giardiasis that is refractory to recommended regimens. We report our experience with 6 patients with giardiasis, for whom therapy with a combination of quinacrine and metronidazole resulted in cures for 5 of the 6 patients.

Giardia lamblia is the most common gastrointestinal parasite in the United States and in most developed countries [1, 2]. It is the cause of both epidemic and endemic diarrhea and upset of the gastrointestinal system. There are a number of drugs whose efficacies are well studied and that have been accepted for the treatment of patients with this infection. The published rates of cure vary for different regimens, but they are frequently reported to be >90% [1, 3–7]. Nevertheless, some individuals experience treatment failure, despite having received successive courses of treatment that have been documented to result in a cure for most patients.

There are 6 potential causes of treatment failures: reinfection, inadequate drug levels, immunosuppression, resistance to the drug, sequestration in the gallbladder or pancreatic ducts, and unknown reasons. In the normal clinical situation, the presence of immunosuppression, reinfection, or sequestration [8, 9] can usually be determined. Certain immunosuppressed patients, such as those with common variable hypogammaglobulinemia [10–12] and those with lymphoproliferative diseases that involve the gastrointestinal tract [13–15], seem abnormally susceptible to giardiasis, and their infections are frequently difficult to cure. Although patients with HIV infection and AIDS can usually be successfully treated [16], some of these patients develop life-threatening giardiasis and do not respond to usual therapies [17]. Reinfection is common in regions where infection is highly endemic and where environmental contamination is high [18]. In developed countries, where the prevalence of infection is low and exposure is infrequent, reinfection is not frequently a cause of treatment failure. Patients who experience abnormal pharmacokinetics or who are infected with organisms that are resistant to treatment are rarely documented. Exactly what pharmacological factors are important in the successful treatment of patients with giardiasis has not been determined.

Patients who do not respond to treatment usually receive multiple courses of standard drugs; frequently, the duration of treatment is increased, the dose is increased, or both. In the United States, these drugs most frequently are metronidazole and furazolidone. Quinacrine is no longer routinely available, but it can be obtained from a pharmacy that formulates its own stock (e.g., Panorama Pharmacy). Tinidazole is commonly used in regions other than the United States. For infections that are refractory to these agents, other treat-
ment options include drugs with known in vitro activity but with no or limited information on in vivo efficacy.

We have advised, consulted, and cared for an increasing number of patients infected with *Giardia* that are unresponsive to the usual suggested medical treatments, and we report our experience. The findings of the patients who comprise the case report are summarized in table 1.

**CASE REPORTS**

**Patient 1.** A 47-year-old woman was referred to the National Institutes of Health (NIH) for giardiasis that was unresponsive to standard treatments. In January 1995, the patient complained of belching, nausea, bloating, abdominal distention and discomfort, and occasional loose stools. The results of an extensive evaluation were initially negative, but repeated esophagogastroduodenoscopy performed in July 1995 revealed *Giardia* trophozoites in duodenal biopsy specimens. The patient received metronidazole, 250 mg given t.i.d. for 2 weeks, which resulted in transient improvement of symptoms, followed by treatment for 6 weeks. After the patient received such treatment, *Giardia* trophozoites were still present in duodenal biopsy specimens. In July 1996, she was treated with oral metronidazole, 750 mg given b.i.d. for 4 weeks, followed by 500 mg given b.i.d. for 2 weeks, which resulted in a decrease in the frequency of belching; however, other symptoms persisted, and duodenal samples that were obtained during therapy again demonstrated *Giardia* trophozoites. After the patient discontinued therapy, her original symptoms returned. She was referred to the NIH for further evaluation and treatment.

The patient and her husband denied having known risk factors for giardiasis, and her history did not suggest the presence of immunodeficiency. The findings of HIV serological testing, tests for quantitative serum levels of immunoglobulin, IgG subclasses, and serum levels of protein, and immunoelctrophoresis were unremarkable. Subsequently, the patient underwent 2 sequential treatment regimens that consisted of tinidazole, 2 g given once followed by 500 mg given q.d. for 14 days, followed by a combination of tinidazole, 500 mg given q.d., and doxycycline, 100 mg given b.i.d., for 21 days. Before the commencement of each treatment regimen, stool samples tested positive for *Giardia* by means of EIA and stool examinations, but they became negative during therapy, only to revert to positive after the treatments. Transient improvement of symptoms was noted during treatment. A 21-day course of combination therapy with oral quinacrine, 100 mg given t.i.d., and oral metronidazole, 250 mg given t.i.d., resulted in the following drug-related side effects: mild headache, dizziness, and subtle yellow discoloration of the skin. Stool samples obtained immediately before the commencement of treatment again demonstrated the presence of *Giardia*, according to EIA, but they became negative for *Giardia* both during treatment and for 3 months after completion of therapy, according to both microscopic examination and EIA. Successive esophagogastroduodenoscopy and examination of duodenal biopsy specimens found no evidence of *Giardia* or of histopathologic abnormalities. Although there was moderate improvement in symptoms, some epigastric discomfort remained but responded to empirical treatment with omeprazole. The patient has remained healthy for the past 2 years.

**Patient 2.** A 46-year-old woman had common variable hypogammaglobulinemia diagnosed in 1987 after she experienced repeated bouts of sinusitis. In August 1990, the patient was evaluated at the NIH for nausea and intermittent loose stools that began 2 months prior to evaluation, after she went on a canoe trip. Stool samples that were assessed for ova and parasites tested positive for *Giardia* cysts, and she received metronidazole, 250 mg given b.i.d. for 2 weeks. At the time of this admission to the hospital, she also had lactose intolerance, sinusitis, and pernicious anemia diagnosed. Stool samples assessed for ova and parasites subsequently tested positive twice for *Giardia* cysts, and in February 1991, she received a 2-week course of metronidazole, 500

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**Table 1. Histories of patients with refractory giardiasis.**

<table>
<thead>
<tr>
<th>Patient</th>
<th>Underlying disease</th>
<th>Duration of giardiasis</th>
<th>Unsuccessful treatment</th>
<th>Successful treatment</th>
<th>Duration of follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>None</td>
<td>1.5 years</td>
<td>Mtz, T, T/Dox</td>
<td>Q/Mtz</td>
<td>2 years</td>
</tr>
<tr>
<td>2</td>
<td>Common variable hypogammaglobulinemia</td>
<td>6 months</td>
<td>Mtz</td>
<td>Q/Mtz</td>
<td>10 months</td>
</tr>
<tr>
<td>3</td>
<td>AIDS</td>
<td>4 years&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Mtz, T, Pm, A, Dox</td>
<td>Pm/f, T/Q, B/Pm</td>
<td>20 months</td>
</tr>
<tr>
<td>4</td>
<td>AIDS</td>
<td>15 months</td>
<td>Mtz, F, Pm, A</td>
<td>Q/Mtz</td>
<td>2 months</td>
</tr>
<tr>
<td>5</td>
<td>Complex immunodeficiency</td>
<td>1.5 years</td>
<td>Mtz</td>
<td>Q/Mtz</td>
<td>2 months</td>
</tr>
<tr>
<td>6</td>
<td>None&lt;sup&gt;b&lt;/sup&gt;</td>
<td>8 months</td>
<td>Mtz, F</td>
<td>Q/Mtz</td>
<td>2 months</td>
</tr>
</tbody>
</table>

**NOTE.**

A, albendazole; B, bacitracin; Dox, doxycycline; F, furazolidone; mo. month; Mtz, metronidazole; Pm, paromomycin; Q, quinacrine; T, tinidazole.

<sup>a</sup> Infection recurred during the 4-year period.

<sup>b</sup> Subsequently received a diagnosis of and died of cancer.
mg given b.i.d., and quinacrine, 100 mg given t.i.d. Two months after the patient completed therapy, she complained of watery diarrhea, which she had experienced for 3 days. Stool samples tested negative for *Giardia* 2 times, but *Campylobacter coli* was detected. She was treated with erythromycin; afterward, her stool samples still tested positive for *C. coli*, so she began therapy with amoxicillin-clavulanate.

**Patient 3.** A 41-year-old white man with AIDS developed intestinal giardiasis in 1995 after a trip to Mexico and southern California, at which time his CD4 cell count was 4 cells/µL. He was treated with metronidazole for 2 weeks, but stool samples still tested positive for *Giardia* cysts. Subsequent treatment regimens that involved tinidazole, paromomycin, and albendazole were also unsuccessful. He was later successfully treated with paromomycin and furazolidone; therapy with paromomycin, which was used as a single agent, was continued for a total of 6 months. Giardiasis developed again in March 1998, ~1 year after paromomycin therapy was discontinued. The patient received metronidazole, 500 mg given t.i.d. for 2 weeks, which resulted in some improvement in symptoms; however, the results of EIAs of stool samples remained positive for *Giardia*. After a 2-week course of tinidazole, 2 g given q.d., and quinacrine, 100 mg given t.i.d., his symptoms resolved and the results of EIA of his stool samples became negative for *Giardia*.

In June 1998, the patient developed intestinal microsporidiosis due to *Encephalitozoon intestinalis* and was administered albendazole, 400 mg given b.i.d. for 3 weeks. *Giardia* appeared in his stool samples during this period, accompanied by bloating and worsening diarrhea. Quinacrine, 100 mg given b.i.d., was added to the patient’s treatment regimen. Because there was no relief after a week of treatment, and because microsporidia disappeared from his stool, albendazole was discontinued and the anti-*Giardia* regimen was changed to quinacrine, 100 mg given b.i.d., doxycycline, 100 mg given b.i.d., and atorvastatin, 10 mg given q.d. After another week without relief, he began receiving a 3-week course of quinacrine, 100 mg given t.i.d., and tinidazole, 2 g given q.d. His symptoms improved, and the results of stool examinations became negative for *Giardia*.

A week after the patient completed this course of therapy (in late October 1998), his transaminase levels were found to be elevated. Alanine aminotransferase levels reached a peak of 871 U/L, which necessitated discontinuation of antiretroviral therapy. When giardiasis recurred in February 1999, quinacrine-tinidazole was given in the previously successful dosages; the patient experienced relief of symptoms, and the results of stool examinations became negative after treatment. At follow-up, transaminase levels were again found to be elevated: the alanine aminotransferase levels reached a peak of 1413 U/L, and antiretroviral therapy was again discontinued. Giardiasis recurred in April 1999. A 99mTc-N-substituted-2-6-dimethylphenylcarbamoyl ethylinodiacetic acid (i.e., HIDA) scan did not reveal any abnormalities. Because of concerns about hepatotoxicity from quinacrine-tinidazole, the patient received albendazole, 400 mg given q.d., and was advised to eat tofu and to avoid dairy products. Tofu was suggested because it contains the isoflavone for-monomentin, a compound with in vitro and in vivo activity against *Giardia* [19]. His symptoms improved and became tolerable, but he continued to have 3–4 loose stools per day, and stool specimens continued to test positive for *Giardia*.

In July 1999, the patient was admitted for an opportunistic fungal infection of the sinuses. During this period of hospitalization, he developed progressive weight loss due to multiple factors, and a more satisfactory treatment of his giardiasis became a priority. A regimen of orally administered bacitracin capsules, 120,000 U given every 12 h, and paromomycin, 500 mg given b.i.d., was chosen because these are luminal agents with anti-*Giardia* activity, and they would likely not interfere with the medications that he was taking. His diarrhea resolved within a few days, and the results of microscopic examination and of EIA of his stool samples became negative for *Giardia*. This regimen was continued for 3 months. He reported no side effects, having 1–2 soft stools per day. Approximately 11 months after discontinuation of the paromomycin and bacitracin, he continues to be relatively asymptomatic, and the results of microscopic evaluation and EIA of his stool samples have remained repeatedly negative for *Giardia*. His CD4 cell count, which was 15 cells/µL at the time that bacitracin and paromomycin were discontinued, has increased to >100 cells/µL, perhaps because of increased absorption of his highly active antiretroviral therapy (HAART) regimen.

**Patient 4.** A 39-year-old man, who had HIV infection diagnosed in 1988, had AIDS and a CD4 cell count of 24 cells/µL. He had a history of resolved giardiasis in April 1995. He had giardiasis diagnosed in February 1996 after a camping trip, and he was treated with multiple courses of metronidazole because of recurrent symptoms and repeatedly positive results of EIAs and examinations of stool samples. In May 1996, the patient’s stool samples were still testing positive, and he received a suboptimal dose of oral furazolidone, 100 mg given q.d. for 10 days. Results of EIAs of stool samples were again positive in August 1996, and he received a correct dose of furazolidone, 100 mg given q.i.d. for 10 days, with some improvement of symptoms. In November 1996, he had increased diarrhea, and giardiasis was again diagnosed on the basis of positive results of EIA and microscopy. Treatment with oral metronidazole, 250 mg given t.i.d. for 10 days, resulted in stool samples that tested negative by microscopy but positive by EIA; a 20-day course of metronidazole resulted in slight improvement of symptoms, but stool samples again tested positive for *Giardia* in January 1997. He received oral albendazole, 400 mg given q.d. for 14 days, and had a questionable symptomatic response, but 1 month later, the results of EIAs of stool samples remained...
positive; he was then given oral paromomycin, 500 mg given t.i.d. for 10 days. Again, symptoms improved, but giardiasis recurred after treatment was stopped. In May 1997, he received a 21-day course of oral metronidazole, 750 mg given t.i.d., and oral quinacrine, 100 mg given t.i.d.. During this time, he had Pneumocystis carinii pneumonia, disseminated Mycobacterium avium infection, and ileus.

By July 1997, diarrhea had resolved and the patient was gaining weight after a 8.8-kg (19.5-lb) weight loss. Results of EIAs of stool samples were negative in May 1997 and July 1997. Despite having received various regimens of HAART, the patient’s CD4 cell count was 7 cells/µL, and the plasma level of HIV RNA, was repeatedly 50,000–100,000 copies/mL during this time, which suggests that immune reconstitution was not responsible for curing his giardiasis. Although reinfection cannot entirely be eliminated as a cause, several possible sources of infection were investigated and ruled out.

Patient 5. A 30-year-old man was referred to the NIH for evaluation of an immunodeficiency syndrome associated with hypogammaglobulinemia, CD4 cell lymphopenia, cytomegalovirus (CMV) colitis, and giardiasis. The patient was healthy until 1.5 years prior to the time of admission to the hospital, when he developed an upper respiratory illness followed by diarrhea (8–10 watery stools per day) and weight loss of 16.8 kg (37.4 lb). Two to 3 months prior to admission to the hospital, he had undergone evaluation elsewhere that revealed hypogammaglobulinemia, a depressed CD4 cell count, CMV colitis, and giardiasis. Laboratory studies revealed a CD4 count of 208 cells/µL, hypogammaglobulinemia with an IgG level of 170 mg/dL, an IgM level of 19 mg/dL, and a nondetectable IgA level. Further studies, including assessment of lymph node, bone marrow, and intestinal biopsy specimens, did not reveal the causes of his immunosuppression. The results of HIV serological tests were repeatedly negative, and cultures of stool samples failed to reveal other pathogens. He was initially treated with metronidazole, 250 mg given q.i.d., for an extended but unclear duration; this treatment failed to eradicate the parasite, although it did result in some improvement in his gastrointestinal symptoms.

After further evaluations, the patient began receiving treatment with ganciclovir, 5 mg immunoglobulin, and another course of metronidazole, 250 mg given q.i.d. His condition improved while he followed this regimen, with considerable weight gain of metronidazole, 250 mg given q.i.d. His condition improved with ganciclovir, iv immunoglobulin, and another course of therapy was begun, and the dosages of metronidazole and quinacrine were increased to 500 mg given t.i.d. and 100 mg given t.i.d., respectively. This treatment regimen was continued for 5 weeks, and on at least 2 occasions after the discontinuation of therapy, the results of EIAs for Giardia antigen and of stool assessments for ova and parasites were negative. Cultures of stool samples again yielded C. jejuni, but the organism was eradicated with a course of ciprofloxacin.

Patient 6. A 48-year-old man was healthy until August 1996, when he developed fever, epigastric pain, bloating, diarrhea, and dehydration ~6 weeks after a camping trip. Giardia was the only pathogen identified, and he was treated with a bolus of iv metronidazole followed by a 5-day course of orally administered metronidazole. Although his symptoms improved, he still complained of having 3–4 diarrheal stools per day, epigastric discomfort, and tenderness. Giardia trophozoites and cysts were detected during an examination of stool samples. He was again treated with oral metronidazole, 250 mg given t.i.d. for 10 days, and although there was some initial improvement in symptoms, the symptoms returned after the cessation of treatment, and Giardia was again detected in an examination of stool samples. By March 1997, the patient had lost 13.4 kg (29.7 pounds) and had continuing epigastric pain and diarrhea. Another 10-day course of metronidazole led to no improvement of symptoms. Upper endoscopy revealed chronic duodenitis, many Giardia trophozoites, and mild gastric fibrosis. Colonoscopy revealed proctitis. His symptoms continued after he received a 10-day course of furazolidone, 100 mg given t.i.d., and examinations of stool samples continued to show Giardia trophozoites. Quantitative levels of immunoglobulins were normal and the results of HIV serological tests were negative. Stool samples tested negative for bacterial pathogens and other gastrointestinal parasites. There was no activity or source that was suggestive of repeated exposure to Giardia. In May 1997, the patient commenced a 21-day course of therapy with metronidazole, 750 mg given t.i.d., and quinacrine, 100 mg given t.i.d. On the last day of combined therapy, the patient experienced a seizure that was possibly related to this treatment. The patient’s abdominal symptoms resolved, and the results of 6 stool examinations for ova and parasites and of 1 EIA for Giardia, all of which were performed during a 2-month period, were negative.

DISCUSSION

These 6 patients represent a diverse group of immunocompetent and immunocompromised patients whose infections were not cured after they received standard courses of therapy for giardiasis. Patient 5 displayed features of both humoral and cellular deficiency, and patient 2 had common variable hypogammaglobulinemia diagnosed. Patients 1 and 6 had no defined immunodeficiency.
Patients with AIDS represented the third type of immunocompromised patient with refractory giardiasis in our series. *Giardia* infections are relatively common in homosexual populations, but severe infections that are resistant to treatment have rarely been mentioned [16]. However, 2 recent reports suggest that giardiasis in patients with AIDS may be more severe and frequent than was previously thought [20, 21]. Although HIV-infected patients who are infected with *Giardia* can normally be treated successfully, there appears to be a subgroup of patients with low CD4 counts who develop severe and sometimes life-threatening disease and who are difficult to treat and cure [17]. We have recently been consulted regarding the care of an additional 5 patients with AIDS whose infections were unresponsive to usual therapies. Exactly how these patients differ from most patients with AIDS is unclear. Although B cell dysfunction has traditionally been thought to increase both susceptibility to infection with *Giardia* and the rate of treatment failure [22], more recent evidence indicates that T cells may be important. T cells were required to control infections with *Giardia lamblia* in an adult mouse model [23], and evidence suggests that T cell dysfunction occurs in patients with common variable hypogammaglobulinemia [15, 24–26].

All 6 of the patients we have discussed were treated with metronidazole or tinidazole in combination with quinacrine, and this regimen resulted in cure for 5 of the 6 patients; in the sixth patient (patient 3), the infection was temporarily eradicated. The use of this combination of drugs for management of giardiasis was previously documented in 2 case reports, each of which described a patient who had giardiasis that was refractory to multiple courses of metronidazole or quinacrine and who was cured by use of both drugs in combination [27, 28]. In vitro studies performed in the initial study did not show in vitro resistance to either of the drugs but did show additive effects when both drugs were combined [28]. The present report supports the effectiveness of this combination for management of giardiasis that is refractory to standard treatments. Quinacrine alone was not tried, so its usefulness in refractory cases is unclear. Previous experience with use of this drug as a single agent was associated with significant rates of treatment failure [29]. We suggest that the metronidazole-quinacrine combination is the most likely to result in the eradication of *Giardia* in refractory cases.

Our impression, which is based on use of this combination since our previous report was published [28], is that the combination was as safe as the single agents used alone. However, a number of possible troublesome side effects were possibly related to this therapy in the present series, including significant liver function abnormalities in one patient and seizure in another. We are aware of 2 episodes of transient psychoses, a known complication of quinacrine [30], in others who received the combined regimen. There are a number of possible reasons for complications, including interaction with various drugs and the formulation of quinacrine, which may have changed. Liver function abnormalities and seizures are described in association with quinacrine therapy [31, 32], but they are rarely associated with nitroimidazoles (metronidazole or tinidazole) therapy. Peripheral neuropathy is limiting in longer-term treatment with nitroimidazoles; encephalopathy, convulsions, and liver failure are unusual but reported complications of nitroimidazole therapy [33–35]. Our experience with dosing and duration of treatment is limited, and the lowest effective dose and duration have not been defined.

Other potentially useful drugs were used in this series. Albendazole has known in vitro [36, 37] and in vivo [38–40] efficacy in the treatment of patients with giardiasis. However, although at times symptoms were suppressed and the results of microscopic examination of stool samples reverted to negative, effects were transient, and no patients were cured by this drug. Other drugs with known in vitro efficacy (including doxycycline [41]; 3-hydroxyl-3-methylglutaryl-coenzyme A reductase inhibitors [42], such as atorvastatin; and formononemint, an isolavone found in such legumes as soybeans, that has significant in vitro and modest in vivo activity) were tried without obvious effectiveness [19, 43]. According to patient 3, eating fresh tofu appeared to alleviate his symptoms modestly. At the present time, there are no studies to indicate whether frequently used drugs, such as HMG CoA reductase inhibitors or foods that contain compounds with anti-*Giardia* activity (e.g., tofu), alter the course or the intensity of infection. Table 2 lists a number of drugs that are possibly useful for the management of refractory giardiasis.

The use of bacitracin and paromomycin, the regimen used to cure patient 3, is based on the clinical and experimental studies of Andrews et al. [45], who used bacitracin or Zn bacitracin (with or without neomycin) and achieved rates of cure of 87%–94%. We used paromomycin, an aminoglycoside that is more frequently employed in the treatment of patients with giardiasis, as a substitute for neomycin [44]. The regimen that we used may be particularly useful for patients with infections that are refractory to treatment and for pregnant patients, for whom nonabsorbed drugs are preferred. The usefulness of bacitracin alone was not evaluated.

The in vitro drug susceptibilities of *Giardia* that were isolated from patients who are refractory to treatment have been evaluated in only a few instances [28, 53, 54]. The methods for testing drug susceptibilities are not standardized. The isolated trophozoites of one patient, whose infection was unresponsive to metronidazole or quinacrine but was cured after administration of combined therapy, showed additive effects in vitro. The putative resistant isolate had drug susceptibilities that were similar to those of other isolates [28]. In the second instance, one isolate was almost 10 times less sensitive to metronidazole.
of EIA assays for laboratory tests. We rely on the high sensitivity and specificity of EIA assays for Giardia, which detect soluble Giardia cyst wall proteins [59]. The results of this assay normally revert to negative when patients are treated effectively. In all patients who had been treated with quinacrine, the Giardia antigen was no longer detected in stool samples by day 5 of treatment [60]; the duration of antigen persistence in the stool when other drugs are used has not been defined, but it should be similar. A persistently positive Giardia antigen test result that occurs during a course of treatment suggests ineffective treatment. As was observed in some of our patients, other gastrointestinal diseases may mimic giardiasis, and infections with Giardia are common enough to be present when other processes are causing symptoms. When giardiasis is responsible for symptoms and effective therapy is initiated, improvement in symptoms, cessation of cyst excretion, negative results of stool antigen assays by EIA are commonly found.

Acknowledgment

We thank Ms. Sheryl Rathke for editorial assistance.

References

9. Formononetin In vivo (mouse) [19].
10. Fenbendazole In vivo (dog, calves) [50, 51].
11. Doxycycline In vitro [41].
12. Monensin sodium In vitro [52].
13. Atorvastatin In vitro [42].

Table 2. Selected partial list of possible alternative drugs for the treatment of patients with refractory giardiasis.

<table>
<thead>
<tr>
<th>Drug</th>
<th>In vivo efficacy (host) or in vitro susceptibility</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paromomycin</td>
<td>In vivo (human)</td>
<td>[44]</td>
</tr>
<tr>
<td>Albendazole</td>
<td>In vivo (human)</td>
<td>[38, 39]</td>
</tr>
<tr>
<td>Bacitracin</td>
<td>In vivo (human)</td>
<td>[45]</td>
</tr>
<tr>
<td>Neomycin</td>
<td>In vivo (human)</td>
<td>[45]</td>
</tr>
<tr>
<td>DL-propanolol</td>
<td>In vivo (human)?, D-propanolol in vitro</td>
<td>[46, 47]</td>
</tr>
<tr>
<td>Niridazole</td>
<td>In vivo (mouse)</td>
<td>[48]</td>
</tr>
<tr>
<td>Nitrofurantoin</td>
<td>In vivo (mouse)</td>
<td>[48]</td>
</tr>
<tr>
<td>Disulfram</td>
<td>In vivo (mouse)</td>
<td>[49]</td>
</tr>
<tr>
<td>Formononetin</td>
<td>In vivo (mouse)</td>
<td>[19]</td>
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<tr>
<td>Fenbendazole</td>
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<td>Doxycycline</td>
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<td>Monensin sodium</td>
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</tr>
<tr>
<td>Atorvastatin</td>
<td>In vitro</td>
<td>[42]</td>
</tr>
</tbody>
</table>

NOTE. Many S′ nitroimidazoles and some benzimidazoles have in vivo efficacy in the treatment of Giardia infections. Most of the aforementioned drugs, as well as those that are frequently used at the present time, are excluded from the listing. There are no standard assays for measuring in vitro susceptibility or in vivo efficacy in animals. The in vitro susceptibility of drugs with accepted in vivo efficacy in humans is not shown.

than was the most sensitive isolate, and the authors briefly mention, without supporting documentation, that this patient experienced failure to respond to treatment [53]. In the last instance [55], isolates from 2 patients who were unresponsive to metronidazole were susceptible to metronidazole in vitro. There is strong evidence that induced resistance to the nitroimidazoles in vitro is due to the inability of the parasite′s oxidoreductase to convert these compounds to their toxic metabolite [55–58]. To determine whether this holds true in vivo would require sequence analysis of the enzyme in clinical isolates recovered from patients with infections that are refractory to nitroimidazoles. Another report claims that the organisms that had infected children and that were clinically resistant to treatment with furazolidone had decreased susceptibility to the drug in vitro [54].

It is important to assess the efficacy of treatments by use of laboratory tests. We rely on the high sensitivity and specificity of EIA assays for Giardia, which detect soluble Giardia cyst wall proteins [59]. The results of this assay normally revert to negative when patients are treated effectively. In all patients who had been treated with quinacrine, the Giardia antigen was no longer detected in stool samples by day 5 of treatment [60]; the duration of antigen persistence in the stool when other drugs are used has not been defined, but it should be similar. A persistently positive Giardia antigen test result that occurs during a course of treatment suggests ineffective treatment. As