Strongyloidiasis: Epidemiology, Clinical Manifestations and New Methods for Diagnosis and Treatment

*Atsushi Saito, MD, PhD**

First Department of Internal Medicine, Faculty of Medicine, University of the Ryukyus, Okinawa, Japan

INTRODUCTION

Strongyloidiasis is a parasitic disease caused by the intestinal nematodes of the genus Strongyloides. Of the 52 known species, however, only *Strongyloides stercoralis* frequently causes human disease. The parasite, which infects humans by the percutaneous route, is represented by small round worms 1–2 mm in size that are found mainly in the duodenum and upper part of the small bowel.

Strongyloidiasis has two distinct clinical manifestations: intestinal strongyloidiasis, in which the parasite causes gastrointestinal symptoms, and disseminated strongyloidiasis in the immunocompromised host[1] with extraintestinal strongyloidiasis. The disease is usually rare in temperate regions. Recently, however, it has attracted attention as the cause of diarrhea in the so-called gay bowel syndrome. It is also a potential complication of AIDS.[2]

In Japan, strongyloidiasis remains relatively common in the country's only subtropical region, Okinawa, even though the incidence of intestinal parasites decreased sharply after the war.[3] In clinical practice, meningitis or septicemia due to gram-negative bacilli may appear as a complication of disseminated strongyloidiasis in patients who are both Strongyloides-infected and immunocompromised.[4-6]

The picture is further complicated because Kyushu, and especially Okinawa, exhibits the country's highest prevalence of antibodies to type 1 human T-lymphotropic virus (HTLV-1), the virus that causes adult T-cell leukemia (ATL). Strongyloides infection is high in patients positive for antibodies to HTLV-1 becoming more frequent as their immune status declines and as they progress from carrier status to onset of ATL.[7,8]

The present paper reviews the epidemiology and clinical manifestations of strongyloidiasis, and describes the author's new methods for its diagnosis and treatment.

EPIDEMIOLOGY

Strongyloides stercolaris is widely distributed in tropical and subtropical regions. About 1945, it was estimated that approximately 35 million people around the world were infected. These data are old, however. Furthermore, the lack of an established, standard diagnostic method leaves it unclear how many people in the world are actually infected with this parasite. According to comparatively recent reports, the carrier rates in various regions include 26% in the Congo,[9] 48% in central Africa[9] and 0.4 to 4% in the southeastern part of the United States.[10] The carrier rate among Thai elementary school children was reported to be 21.9% using ordinary agar plate cultures which was newly developed by our group.[11]

In Japan, there are carriers outside Okinawa and the Amami islands in the southwestern part of Kagoshima prefecture, but almost all recent reports come from those tropical and subtropical areas. The carrier rate in Okinawa was reported as 1 to 2% using conventional test methods, but testing by the ordinary agar plate culture method we have proposed[12] revealed a mean positive rate of 6.2% among the general population in communities in the mid-southern part of Okinawa. When this method was improved, the rate rose to 11.2%, with 98.5% of the carriers being 40 years of age or older.[13] Furthermore, the carrier rate among the general population in Okinoerabu region of the Amami islands in Kagoshima prefecture was 4% according to the ordinary agar plate culture method; none of the carriers was in the age range 20–49.[14]

Strongyloidiasis is a particular problem for patients with impaired cellular immunity: Igra-Siegman et al.[15] reported that 86% of 103 hyperinfected patients had had their immunity reduced either by an underlying disease or by therapeutic administration of immunosuppressants. Furthermore, the mortality rate was 77% in immunocompromised hosts, but only 43% in hosts without compromised immune systems.

Strongyloides infection is strongly associated with both ATL and AIDS. Japan has the highest ATL prevalence in the world, with the incidence especially high in Okinawa and Kyushu. In our study on inpatients[16] (Tables 1, 2), antibody to HTLV-1 was significantly more

common in Strongyloides-positive patients than in those negative for the parasite (44.4% vs. 19.0%). The relationship held in reverse as well: patients positive for antibody to HTLV-1 showed significantly higher rates of Strongyloides infection than those without antibody (18.2% vs. 6.1%). It seems reasonable to suppose that reduced immunity due to the HTLV-1 infection resulted in a high susceptibility to Strongyloides infection, accounting for the correlation between the two conditions.

Patients with severe disease or with hyperinfection have lower levels of immunoglobulins and eosinophils than do those with mild disease and without hyperinfection.[17,18]

When we studied 12 treatment-resistant patients and 58 patients in whom antiparasitic treatment was successful,[19] the former showed a much higher prevalence of antibody to HTLV-1 (66.7% vs. 20.7%). Antiparasitic treatment was effective in 92% of antibody-negative patients, while 40% of antibody-positive patients were resistant to treatment. The treatment-resistant patients also showed low eosinophil and IgE levels (Table 3). This led to the speculation that HTLV-1 infection affected patients eosinophil status in some way.[20]

Among 13,042 American AIDS patients, 73% were reported to be homosexual or bisexual, and at least 3.9% (370) of these to be highly susceptible to Strongyloides infection.[21] Only four actual cases were identified, however. This has been interpreted as reflecting any or all of underdiagnosis, underreporting, or the reduction in

Table 1. Relationship between presence of antibody to HTLV-1 and rate of infection with Strongyloides stercoralis.

Antibody to HTLV-1	Strongyloidiasis	Infection rate
Positive (88 cases)	Positive (16 cases)	18.2%
Negative (327 cases)	Positive (20 cases)	6.1%

Table 2. Relationship between infection with Strongyloides stercoralis and presence of antibody to HTLV-1.

Strongyloidiasis	Antibody to HTLV-1	% positive
Positive (36 cases)	Positive (16 cases)	44.4
Negative (379 cases)	Positive (72 cases)	19.1

AIDS patients' cellular immunity having less influence on infection by multicellular organisms such as Strongyloides[21,22] than on infection by single-cell organisms such as Toxoplasma.

CLINICAL MANIFESTATIONS

Intestinal strongyloidiasis

The main clinical manifestations of intestinal strongyloidiasis are nutritional deficiencies and gastrointestinal symptoms. It has long been known that parasitic Strongyloides in the intestinal tract are among the causes of diarrhea in the so-called gay bowel syndrome; they are also one of the causes of symptoms such

Table 3. Comparison of laboratory data between patients positive and negative for antibodies to HTLV-1.

Outcome	Eradicated		Resistant	
Anti-HTLV-1	Positive (n = 12)	Negative (n = 46)	Positive (n = 8)	Negative (n = 4)
Eosinophils (/mm3)				
Before treatment	253.5 ± 162.8*	582.0 ± 436.9[a]	237.3 ± 121.4	324.0 ± 96.3
During treatment	143.9 ± 126.1*	278.7 ± 266.9	225.5 ± 366.6	305.0 ± 109.1
After treatment	172.6 ± 144.8	220.6 ± 221.4	115.6 ± 94.4*	311.3 ± 115.1
Gammaglobulin (g/dl)				
Before treatment	1.18 ± 0.25*	1.03 ± 0.20	1.32 ± 0.40	1.01 ± 0.20
During treatment	1.18 ± 0.22*	1.02 ± 0.19	1.12 ± 0.36	0.96 ± 0.18
After treatment	1.14 ± 0.19*	1.01 ± 0.17	1.06 ± 0.23	1.06 ± 0.22
IgG (mg/dl)				
Before treatment	1633.3 ± 325.5*	1481.0 ± 203.9	1837.9 ± 450.5	1513.3 ± 222.0
During treatment	1639.6 ± 342.0	1496.2 ± 234.4	1646.7 ± 314.1	1460.0 ± 251.0
After treatment	1542.6 ± 280.4	1478.5 ± 233.3	1388.7 ± 582.0	1461.5 ± 393.3
IgE (IU/ml)				
Before treatment	488.3 ± 1086.3*	1233.8 ± 2289.3	255.0 ± 545.8	151.0 ± 221.1
During treatment	170.4 ± 174.1*	1388.1 ± 2297.3	353.2 ± 710.8	254.5 ± 244.0
After treatment	526.0 ± 1047.0	1044.4 ± 2435.0	554.3 ± 809.2	172.5 ± 209.1
OKT/OKT8				
Before treatment	2.84 ± 20.6	1.92 ± 0.85	2.97 ± 2.35	1.97 ± 0.91
After treatment	3.36 ± 1.83*	1.76 ± 0.59	—	—

[a] Mean ± SD
* $P < 0.05$ vs. anti-HTLV-1 negative patients by two sample Wilcoxen test.
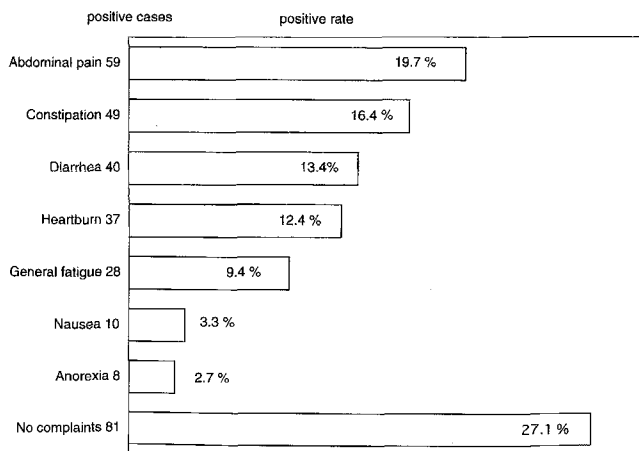
**Fig. 1:** Subjective complaints of 299 patients with strongyloidiasis.

as diarrhea, bloody stool and a feeling of distention in the abdomen seen in male homosexuals with or without full-blown AIDS.[2,22]

Strongyloides carriers lead a normal life, and many are completely healthy. Some, however, present with subjective symptoms, which are typically gastrointestinal. Although they are not specific to strongyloidiasis, these symptoms include abdominal pain, constipation, diarrhea, soft feces, general malaise and weight loss (Fig. 1).

In mild cases, intestinal changes cannot be detected by routine imaging procedures. In moderate to severe cases, however, abdominal plain x-ray, upper GI radiography or endoscopy may reveal relatively characteristic findings: abnormal gas, intestinal enlargement, hypertrophy and disappearance of the small intestine's furrowed wall, bleeding, erosion and ulceration.[23-26] Figure 2 shows findings on endoscopic examination of the duodenal mucosa and from a biopsy specimen obtained in the same area.

Disseminated strongyloidiasis

In hosts whose cellular immunity is compromised, Strongyloides infection presents as a systemic disease
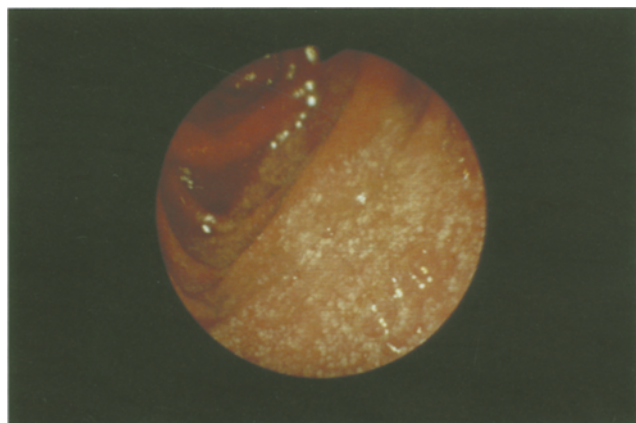
known as disseminated strongyloidiasis; this infection is often fatal.[1,4-6]

Disseminated strongyloidiasis is characterized by autoinfection, with the larvae invading the body via the intestines. Since the larvae bring with them bacteria (mainly gram-negative bacilli) from the intestines, sepsis, bacterial pneumonia and purulent meningitis may be seen. If purulent meningitis caused by gram-negative bacilli or enterococci occurs in adults, preexisting Strongyloides infection should be suspected. In Japan, it is also reasonable to suspect that these patients may have ATL or carry its causative virus, HTLV-1. The important clinical manifestations of disseminated strongyloidiasis are shown in Table 4.

Another important clinical feature of disseminated strongyloidiasis is the pulmonary lesions associated with this disease. Figure 3 shows the three main mechanisms that may produce these lesions.[27-29] The most dangerous complication is intra-alveolar hemorrhage, which may result either from direct mechanical destruction of the pulmonary capillaries or as a result of allergic reactions. Mechanical destruction may be produced either by rhabditiform larvae, produced by adults as heterotropic parasites in the lungs, by filariform larvae produced in the intestines, or by both. Allergic reactions typically occur as a result of increased amounts of antigen (parasites) in the lungs of hosts sensitized by a previous latent infection. Another pulmonary lesion is bacterial pneumonia caused by piggyback transport of bacteria from the intestines.

Figure 4 shows a rhabditiform larva in the sputum (left) and larva in an intra-alveolar hemorrhage (right).

NEW DIAGNOSTIC METHOD

As a parasitic disease, strongyloidiasis results in eosinophilia and elevated IgE levels in the peripheral blood. Since this feature is not disease-specific, however, parasites must be detected in the feces. Measure-
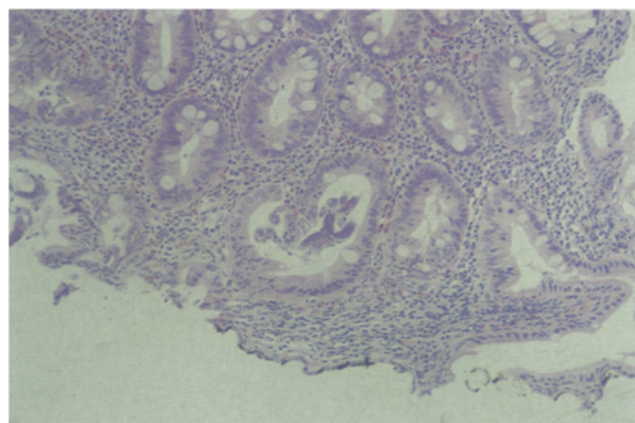

Fig. 2: Endoscopic and histological findings of strongyloidiasis. Endoscopy (left) shows a huge number of small white powder-like protrusions due to edema of the duodenal villi. In a biopsy specimen (right: HE staining), the villous structure of the mucosa has become flat and partial desquamation of the mucosal epithelium is seen. Edema and infiltration of inflammatory cells mixed with eosinophils are present in the lamina propria of the mucosa. A parasite is seen in the crypt.
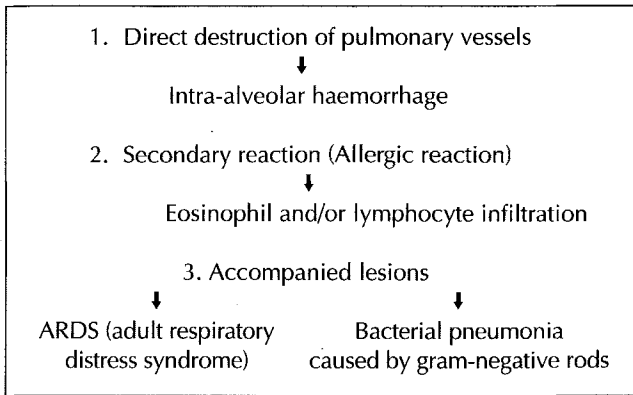
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│  1. Direct destruction of pulmonary vessels      │
│                        ↓                          │
│          Intra-alveolar haemorrhage               │
│                                                   │
│  2. Secondary reaction (Allergic reaction)        │
│                        ↓                          │
│        Eosinophil and/or lymphocyte infiltration  │
│                                                   │
│            3. Accompanied lesions                 │
│              ↓                    ↓               │
│    ARDS (adult respiratory     Bacterial pneumonia│
│      distress syndrome)     caused by gram-negative rods │
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Fig. 3: *Mechanism of pulmonary manifestations of strongyloidiasis.*

Table 4. *Clinical manifestations of disseminated strongyloidiasis.*

Host	Immunocompromised HTLV-1 infection; administration of corticosteroid; marignant diseases, etc.
Parasite	Over-infestation; Hyperinfection, "Piggy back" transport of enteric bacteria
Parasite outside intestine	Filariform or rhabditiform in sputum; Filariform in urine
Clinical features	Bacterial pneumonia; pulmonary heamorrhage; ARDS; bacterial meningitis; sepsis; DIC
Chest x-ray findings	Bilateral diffuse alveolar infiltrates; interstitial infiltrates; bronchopneumonia; pulmonary abscess
Mortality rate	50–70%

ment of serum antibody titers is epidemiologically useful in identifying those who have been infected at some time in their lives, but is of no diagnostic value in determining current infection.[30–32]

The conventional methods used for detection of Strongyloides include the MGL method and the in vitro filter paper culture method, either individually or in combination. The ordinary agar plate culture method our group developed is a simple and very useful method, as evidenced by the studies in which it has been used.[3,7,12,16,33,34] The results of a comparison between conventional methods and the ordinary agar place culture method are summarized in Table 5. The new method, procedures for which are outlined below, has a sensitivity four to ten times higher than that of conventional methods.

Samples

Samples of feces must be as fresh as possible; the detection rate falls rapidly when samples are refrigerated. In addition to feces, duodenal juice, bile or sputum can be used.

Medium

To prevent infection of testing personnel, we have developed special SA plates for Strongyloides testing.[3,4,12,34] These plates are commercially available in Japan.

Culture method

Ordinary agar plates (15–20 ml) are prepared in the inner dish of sterilized double Petri dishes (outer dish, 10 cm in diameter and 12 cm high; inner dish, 8 cm in diameter and 8 cm high). Twenty-five percent glycerin in water is then placed in the outer dish (sterilization not required). Two to three grams of sample are placed in the center of the dish, and the dishes are incubated at 28°C for 1–2 days.

Evaluation

The surface of the medium is observed from the first day of culture under a low-power microscope. If the characteristic trails are seen (and especially if free-moving larvae are found when the trail is followed), the sample is considered positive (Fig. 5). Many trails are commonly observed, and bacteria present in the sample are typically seen growing along the trails (Fig. 6). Diagnosis can also be made by observing the characteristic trails made by adults and larvae (Fig. 7) or by observing adults, larvae and eggs simultaneously in the cultures (Fig. 8).

If an actual parasite can be located, detailed identification is possible by collecting it for observation under a high-power microscope.

Table 5. *Comparison of ordinary agar plate culture method and conventional methods.*

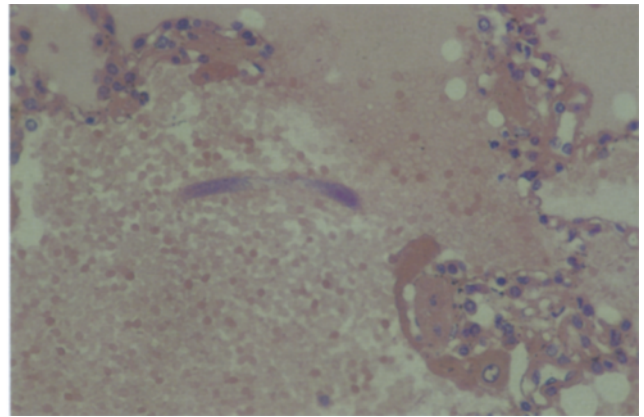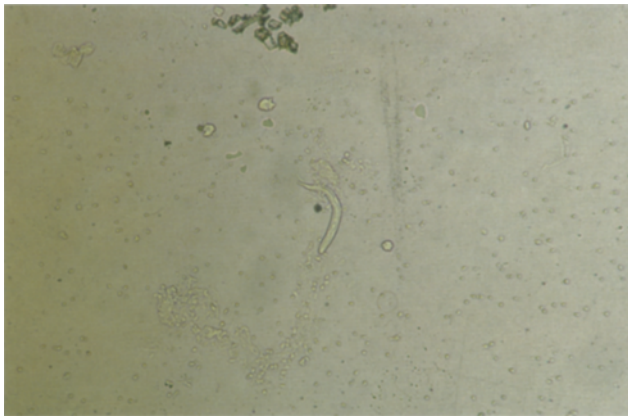| Test method	No. of samples	No. of positive cases	Positive rate
Study 1 (High infection region)			
MGL method	1150	49	4.3%
Filter paper culture method	1150	34	3.0%
Ordinary agar plate method	1150	207	18.0%
Study 2 (Health screening)			
Direct smear method	1017	0	0.0%
Filter paper culture method	1017	3	0.3%
Ordinary agar plate method	1017	46	4.5%

Fig. 4: Rhabditiform larva of Strongyloides (left: unstained specimen) in the sputum and a parasite in the intra-alveolar hemorrhage of a patient given a steroid (right: HE staining).
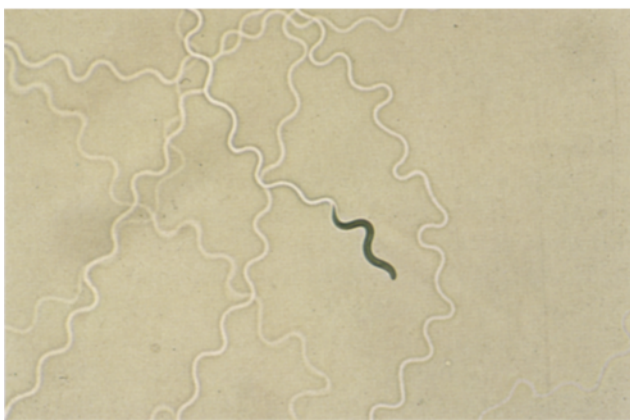

Fig. 5: Free moving larva can be seen under the microscope before the formation of bacterial colonies. If the characteristic trail is followed, an actively moving larva is seen.
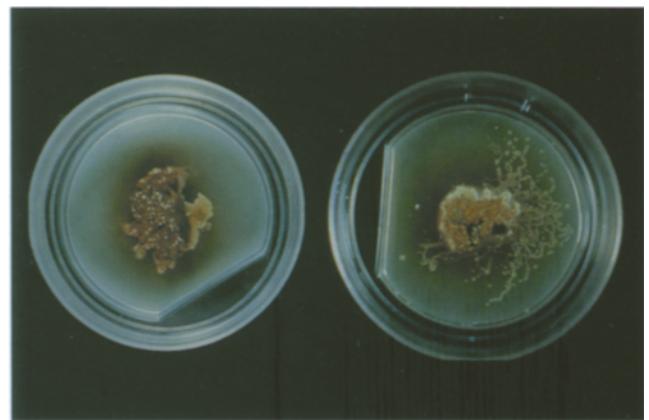
Fig. 6: Second day of culture. Bacterial colonies with characteristic shapes are formed along the trails produced by the larvae. Left, negative; right, positive.
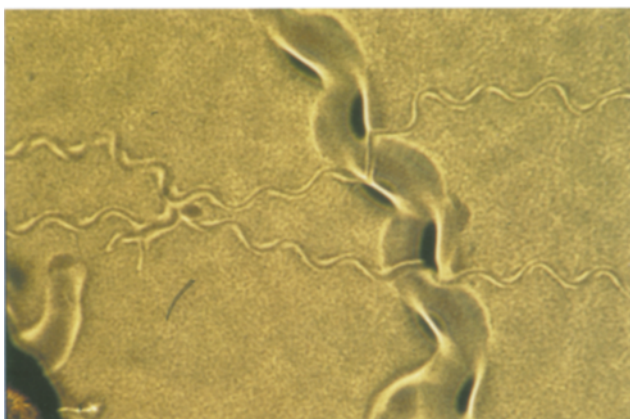

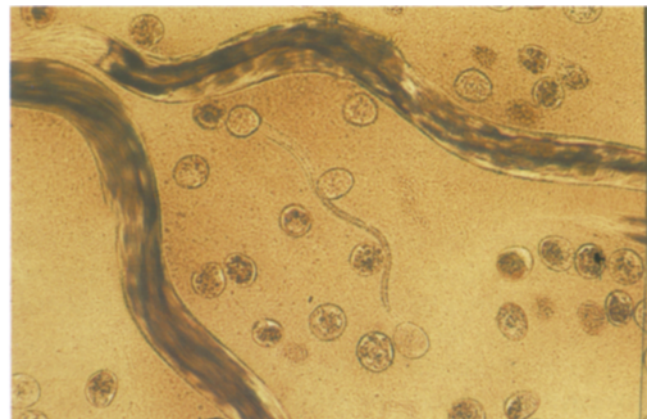**Fig. 7:** Trails of larvae and adults. Each has a characteristic shapes.

Fig. 8: After two days of culture. Adults, larvae and eggs are seen on the culture.

TREATMENT

Results of treatment with thiabendazole, mebendazole, albendazole and ivermectin

Table 6 summarizes the results our group has obtained in treating strongyloidiasis patients with one of four drugs; thiabendazole, mebendazole, albendazole or ivermectin or with a combination of thiabendazole and mebendazole. Although few drugs are fully effective, the strongest anthelmintic effect was found with thiabendazole. It is administered at a dose of 25–50 mg/kg bid for two or three consecutive days. Relapses are fre-

Table 6. Administration methods, anthelmintic effects and adverse reactions of various therapeutic agents.

	Regimen	Period after start of treatment / Rate of eradication		Adverse reactions	Liver dysfunction
Thiabendazole (162 cases)	1,500 mg t.i.d. 3 days, 3–4 courses every 2 weeks	7 days / 6 months / 24 months /	100% 100% 100%	General malaise (24.4 %) Nausea (22.5 %) Dizziness (23.8 %) Overall (67.5 %)	33.8 %
Thiabendazole + Mebendazole (26 cases)	1,500 mg t.i.d., 5 days, 200 mg b.i.d., 9 days, two of the above courses	7 days / 2 years /	100% 100%	Nausea (7.7 %)	52.2 %
Mebendazole (33 cases)	200 mg b.i.d., 28 days	7 days / 2 years /	83.3% 93.8%	Headache (9.1 %) Constipation (9.1 %)	71.4 %
Mebendazole (47 cases)	200 mg b.i.d., 5 days, another 5 days after 2-day interval, two of these courses	18–20 months /	78.6%	No subjective symptoms	51.1 %
Mebendazole (13cases)	Final 5 days omitted from the above	18 –20 months /	60.0%	No subjective symptoms	30.3 %
Mebendazole (16 cases)	200 mg, b.i.d., 4 days, another 4 days after 3-day interval	23 days / 8months / 16 months /	93.8% 69.2% 71.4%	No subjective symptoms	25.0 %
Albendazole (27 cases)	400 mg, b.i.d., 3 days, another 3 days after 11 day interval	10 days /	66.2%	Headache (25 %)	43.8 %
Ivermectin (125 cases)	1 tablet (6 mg) once, another one tablet after 2 weeks	14 days / 6 months / 1 year / 2 years /	91.6% 96.5% 98.1% 97.4%	Diziness (2.4 %) Nausea (1.6 %) Overall (7.2 %)	10.4 %

quent after a single course, however; two to three courses of treatment are required to completely eliminate the parasite. This drug has severe adverse reactions, with nausea, vomiting, dizziness, anorexia or liver dysfunction occurring in 60% or more of the patients treated.[35–36] We used this drug at a dose of 1500 mg/person (about 30 mg/kg).

Pyrvinium pamoate (Poquil), administered at a dose of 5.0 mg/kg for five consecutive days, has almost no adverse reactions. However, since this agent is not absorbed, it is ineffective against heterotopic parasites and migrating larvae. In Japan, the decrease in the frequency of parasitic diseases led to marketing of this drug being discontinued several years ago.

Mebendazole has very few adverse reactions and produces no subjective symptoms in treated patients, but has a lower anthelmintic rate than thiabendazole. It is therefore generally considered at best the second-choice drug. Our group has performed various studies varying the dosage, administration period or concomitant drugs of mebendazole.[37–41] Satisfactory long-term anthelmintic effects (positive change rate after 6 months: 76.2%) were obtained at a dosage of 200 mg b.i.d. for 28 days. Elevated S-GOT and S-GPT levels were seen in over 60% of the treated patients, however. We are currently studying the effect of shortening the administration period or

of administering the drug at intervals (for example, three courses of 200 mg for three days and then no dosing for four days).

Albendazole did not exhibit a satisfactory anthelmintic rate. Mild headache occurred in 25% of patients and the incidence of liver dysfunction (43.8%) was high.

Ivermectin has few adverse reactions and excellent anthelmintic effects. It appears to be the best agent clinically, and is therefore described more fully in the next section.

Usefulness of ivermectin

Ivermectin (IVM), a white to yellowish white crystalline powder, is a lipid compound insoluble in water. It acts against nematodes by promoting the release of an inhibitory neurotransmitter (GABA) from the presynaptic nerve ending, thus inhibiting transmission of nerve signals from the ventral cord connector neurons to the motor neurons. Edwards[42] reported that the peak blood level was 52 ± 11 ng/ml, reached in 3.0 ± 0.5 hours when a dose of 200 µg/kg was administered. The drug's sustained serum level suggests that it should be effective against larvae in the tissues.

IVM is easy to administer. It comes in small round white tablets 9 mm in diameter and 2 mm thick, each contain-

ing 6 mg of drug. According to the literature, the dosage is 150 μg/kg[43] or 140–200 μg/kg,[9] administered only once. We administered two courses of one tablet each, with a two-week interval between doses. This regimen was established in consideration of the time from autoinfection until appearance of parasites in the intestines — the drug may not be effective against larvae and eggs in the tissues — and two weeks is the established period between percutaneous infection and appearance of the parasite in the feces.

The following results were all obtained at the dosage described above, although the literature suggests it may be inadequate in patients weighing over 40 kg.

As shown in the bottom part of Table 6, the anthelmintic rate at this dose was 91.6% after two weeks and 90.0% after 3 months. Seven of the nine patients in whom the parasites were not eliminated underwent retreatment with IVM, and all became negative. Therefore, the total anthelmintic rate one year after the initial treatment was 98.1%. Only 39 patients came to the hospital for testing after two years, but the anthelmintic rate was maintained at 97.4%. One patient, who was negative in tests two weeks and 9, 15 and 18 months after initial treatment, first became positive after two years. This patient became negative once more when retreated with IVM.

These results show that even when the parasites are not eliminated by treatment with one tablet of IVM followed by one more tablet after two weeks, further retreatment often leads to success. Our results did not confirm previous reports of differences in dose per unit body weight between patients showing an anthelmintic response and those who do not. We found no significant difference in IVM dose per unit body weight between the 108 patients who were consistently negative following initial treatment and the 10 patients who were positive even once during frequent post-treatment testing. However, we did find significant differences with regard to the presence of anti-HTLV-1 antibody, the number of eosinophils in the peripheral blood and IgE levels; these results are consistent with previously reported findings.[44]

Table 7 shows the incidence of subjective and objective adverse effects and of abnormal laboratory findings after administration of the first and second tablets. The incidence of adverse effects, primarily minor gastrointestinal symptoms, was lower after the second administration, two weeks following the first tablet. Exanthema was seen as a hypersensitivity reaction in one patient, but no treatment was necessary.

In evaluating laboratory findings, S-GOT and S-GPT values were considered abnormal when the value was elevated by at least 20% over the prior value, if the prior value was within the normal range, or when it was elevated by at least two times the prior value if that was already abnormal. The tests were performed 13 days after the administration of each tablet. The frequency of liver dysfunction, including elevated S-GOT and S-

Table 7. Incidence of side effects in the treatment with ivermectin.

	After first administration % (No. of Pts.)	After second administration % (No. of Pts.)
Dizziness	2.4 (3)	—
Nausea	1.6 (2)	—
Diarrhea	1.6 (2)	—
Blurred vision	0.8 (1)	—
Borborygmus	0.8 (1)	—
Malaise	0.8 (1)	—
Anorexia	0.8 (1)	—
General malaise	0.8 (1)	—
Itching	—	—
Exanthema	—	0.8 (1)
Myalgia	0.8 (1)	—
Others	3.2 (4)	—
Total	7.2 (9)	3.2 (5)

GPT values, is shown in Fig. 2. As with subjective and objective adverse effects, the frequency was lower after the second administration. The severity of liver dysfunction was mild in almost all patients, and no elevations above 200 IU/L were noted.

Adverse reactions of IVM when used to treat conditions other than strongyloidiasis have been reported by Ette et al.,[45] Pacoue et al.,[46] DeSole et al.,[47] Rothova et al.[48] and Lariviere et al.[49] In these studies, almost all patients showed a lower frequency of adverse reactions after the second dose than after the first. This may reflect the elimination of many *Onchocerca volvulus* in the first administration of IVM, as well as patients' decreased nervousness concerning adverse reactions following the second administration resulting in fewer complaints. Our study supported these observations, and indicated that IVM is currently the most useful agent against *Strongyloides stercoralis*.

CONCLUSION

Strongyloidosis is a parasitic disease of the intestines, seen mainly in tropical areas. It is quite likely that, because its manifestations are milder than those of other tropical diseases, it may be overlooked in regions where parasitic diseases such as hookworms and roundworms are endemic. With future improvements in hygiene and the resulting decreases in parasitic diseases, increasing attention will be focused on strongyloidiasis in tropical regions — a phenomenon currently being observed in Okinawa.

Studies on the diagnosis and treatment of apparently healthy Strongyloides carriers have only just started. These studies can be expected to play a major role in improving the near-future health and welfare of people in tropical regions of the world. Parasitic diseases in Japan have a strong local character; a long-term eradication program, with due consideration to HTLV-1 infection, must be instituted.

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