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Short Report: Management of Chronic Strongyloidiasis in Immigrants and Refugees: Is Serologic Testing Useful?

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Abstract. We assessed the usefulness of serologic testing in monitoring strongyloidiasis in immigrants after treatment with two doses of ivermectin. An observational study was conducted in a group of Cambodian immigrants residing in Melbourne who were treated for strongyloidiasis and followed-up in a general practice setting. Two doses of ivermectin (200 μg/kg) were administered orally. Periodic serologic enzyme-linked immunosorbent assay testing was undertaken for up to 30 months after treatment. Antibody titers for *Strongyloides* sp. decreased in 95% (38 of 40) of the patients, 47.5% (19 of 40) had a decrease in optical density to less than 0.5, and 65% (26 of 40) reached levels consistent with a cure during the follow-up period. Serologic testing for *Strongyloides* sp. is a useful tool for monitoring a decrease in antibody levels after effective treatment. This testing should be carried out 6–12 months after treatment to ensure a sustained downward trend suggestive of cure.

INTRODUCTION

Strongyloidiasis is a relatively common disease among immigrants from certain regions, including South East Asian countries and parts of Africa.[1–4] This disease is thought to be a life-long infection if left untreated, and a life-threatening hyperinfection can develop in certain circumstances.[5,6] Many cases remain undetected because most of those infected are asymptomatic or have only mild gastrointestinal or skin symptoms. Treatment is not always effective and some persons may continue to harbor the causative parasite *Strongyloides stercoralis* after drug therapy.[2] It is therefore important to test those at risk of infection, treat them if they are parasite positive, and monitor the response to treatment.

Ivermectin is currently considered to be the treatment of choice for strongyloidiasis in most patients,[7] and a number of studies have demonstrated superiority when compared with albendazole[8–11] and thiabendazole,[12,13] in terms of safety, efficacy, and side effect profile. Reported cure rates with ivermectin range from 94% to 100% after two doses administered 1–14 days apart.[11,13–17] However, the most effective dosing regimen has not been determined.[18,19]

A number of tests are currently used to detect infection with *S. stercoralis*, including stool testing and serologic analysis.[20] Both of these tests have limitations. In those with chronic strongyloidiasis, larval output in stools is often low and microscopic examination of a single stool sample is negative in up to 70% of cases.[20] The diagnostic sensitivity can be increased by the use of repeated samples.[21] The most sensitive morphologic method is the agar plate technique.[22] However, it is expensive, requires fresh feces, and takes several days to obtain a result.

The *Strongyloides* sp. enzyme-linked immunosorbent assay detects IgG antibodies and has been used for screening and diagnosis, as well as post-treatment monitoring,[10,23–27] alone or in combination with stool testing. One of the difficulties in assessing this method is that there is no gold standard for diagnosis. In most cases, the diagnostic accuracy of serologic testing has been measured in persons with known positive stool samples, with reported sensitivity and specificity levels of 93% and 95%, respectively.[19] In studies where the test has been used for post-treatment monitoring, results have been variable but in general demonstrate a slow decrease in antibody titer (measured as optical density [OD]) after presumed effective treatment; follow-up periods range from six months to two years.[10,23–26]

In this study, we report on treatment and follow-up of a sample of Cambodian immigrants in Melbourne who were diagnosed with strongyloidiasis by serologic analysis and in some cases by positive microscopic results for stool samples.[28] The main purpose of this study was to explore the usefulness of serologic testing for post-treatment monitoring in patients who had received ivermectin treatment.

MATERIALS AND METHODS

In July–August 2002, a convenience sample of 234 Cambodian-born adults participated in a health assessment study conducted in two general practice clinics in Melbourne, Australia. Eighty-two (36%) of 230 participants were found to have strongyloidiasis (defined as a positive *Strongyloides* sp. enzyme-linked immunosorbent assay result and/or *Strongyloides* sp. larvae detected by stool microscopy)[28] and were advised by telephone and letter to return to their nominated general practitioner for treatment and follow-up. The patient follow-up protocol (which included treatment guidelines, suggested timing for post-treatment monitoring, and tests to be performed) was circulated to general practice clinics, and meetings were held to clarify the proposed patient management. The general practitioners then contacted patients to return for treatment. Ethics approval was obtained for the follow-up component of the study from the Royal Melbourne Hospital Human Research Ethics Committee.

Treatment and follow-up. General practitioners were advised to treat patients with strongyloidiasis with two doses of ivermectin (200 μg/kg) two weeks apart, and to follow-up patients with serologic analysis for *Strongyloides* sp. for up to 24 months.[18]

Sample collection and testing. Blood samples were collected for *S. stercoralis* antibody testing and an eosinophil count.

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Eosinophil counts were performed on fresh samples (normal range ≤ 400 eosinophils/μL). For antibody testing, blood was separated, and the serum was stored at −20°C to enable testing in batches at the Victorian Infectious Diseases Reference Laboratory (VIDRL) in North Melbourne. An in-house ELISA based on the method of Genta and Lillibridge[29] was used, with *S. ratti* antigen obtained from the State Health Laboratory (Perth, Western Australia, Australia) or the Institute of Clinical Pathology and Medical Research (Sydney, New South Wales, Australia). This test was originally demonstrated to have a sensitivity of 93% and a specificity of 95%.[30] The VIDRL defined an OD > 0.5 as positive for *S. stercoralis* infection, based on a reference range determined from a comparison of the distribution of OD values in uninfected controls with sera of those with microscopically confirmed infection. To eliminate run-to-run variation in the ELISA, all sera collected from a patient were tested in parallel in the same run, and results used for analysis were from a single run, with no transformation or averaging. To verify the consistency of the assay, multiple assay runs were performed over the course of the study period comparing negative, low-positive, and positive control sera. Performance over a range of serum antibody concentrations was examined by using serial dilutions of a positive control.

Data collection and analysis. Data on drug administration and laboratory results were retrieved from medical records at the general practice clinics, and from VIDRL databases. Data were entered into an Excel® (Microsoft, Redmond, WA) spreadsheet and analyzed by using Stata® version 8.2 (StataCorp, College Station, TX).

For the purpose of analysis, results from the most recent serologic test performed were used. A cure was defined as a decrease in OD to ≤ 0.5, or when the ratio of post-treatment to pre-treatment OD decreased to < 0.6, as described by Kobayashi and others.[25]

RESULTS

Of the 82 participants with strongyloidiasis in the original study, all were born in Cambodia and had resided in Australia for 2–28 years (median = 14 years). They ranged in age from 16 to 78 years (median = 46 years), and 48 (59%) were male. The pre-treatment *Strongyloides* sp. serologic results ranged from an OD of 0.53 to 2.79 (mean = 1.22, median = 1.14). Eosinophilia (> 400 eosinophils/μL) was present in 36 (44%) of 82 patients. Only 10 of the 82 patients initially screened had *Strongyloides* sp. isolated in feces. Thus, this test was not repeated at follow-up visits.

Evaluable information on treatment and follow-up serologic testing was available for 40 patients (Figure 1) who received two doses of ivermectin. The median time between doses was 9.9 months (range = 5.1–14.8 months). There was no significant difference between mean serologic results or eosinophilia at baseline between the 40 patients who were evaluated and those who were not evaluated (P = 0.113 and 0.621, respectively).

Because follow-up testing was performed opportunistically, participants had a variable number of post-treatment serologic tests: 17 (42.5%) had 1 test, 16 (40%) had 2 tests, and 7 (17.5%) had 3 tests. Only 1 patient had serologic testing 3–6 months after treatment, 26 (65%) had serologic testing 6–12 months after treatment, and 13 (32.5%) had serologic testing more than 1 year after treatment. The spread of OD

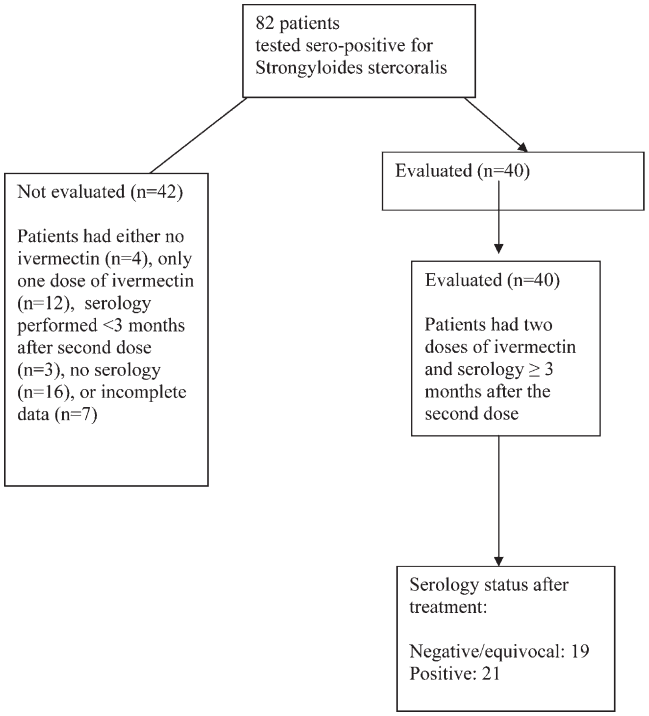

FIGURE 1. Evaluation of patients treated for strongyloidiasis with two doses of ivermectin and outcomes.

values before and after treatment is shown in Figure 2. The mean difference between baseline and post-treatment OD values was 0.73 (95% confidence interval = 0.51–0.94).

Post-treatment serologic testing showed that 21 patients were positive (OD > 0.5), 19 patients (47.5%) had an OD decrease to ≤ 0.5, and 22 (55%) had a post-treatment to pre-treatment OD ratio < 0.6. A total of 26 patients (65%) had either an OD decrease to ≤ 0.5 or a post-treatment to pre-treatment OD ratio < 0.6, which was a response consistent with a cure. Figure 3 shows the change in OD in persons from baseline serologic testing to post-treatment serologic testing. The median OD decrease was 0.55. A decrease in OD

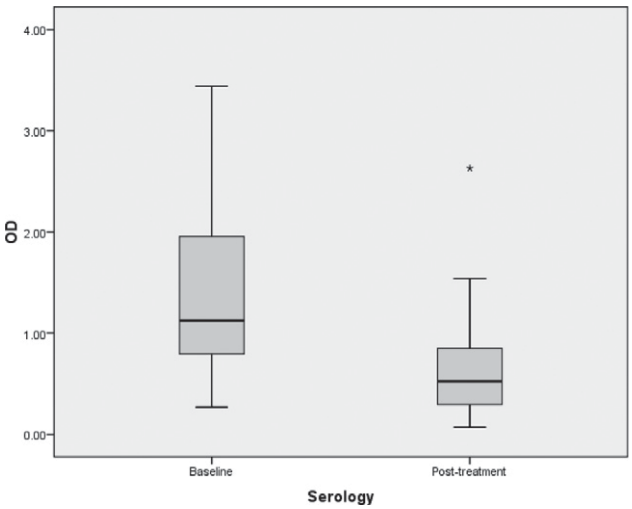

FIGURE 2. Change in mean serologic (enzyme-linked immunosorbent assay) results at baseline and after two doses of treatment with ivermectin.

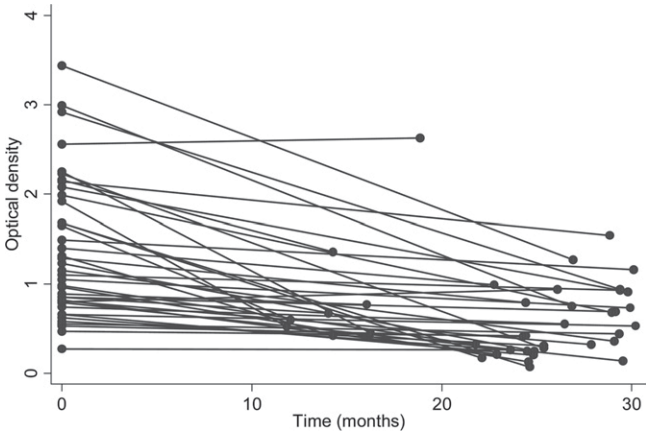

FIGURE 3. Decline in enzyme-linked immunosorbent assay optical density over time from baseline to final post-treatment serologic testing in 40 patients who had received two doses of ivermectin.

between baseline and the most recent post-treatment sample tested was evident in 38 (95%) of 40 patients. The remaining two (5%) patients showed an increase in the final OD, which raised the possibility of persistent infection. There was no correlation between age and change in serologic levels (R^2 = 0.08, Spearmans $\rho = 0.054$, age range = 20–78 years), and no difference in cure rate between those with a baseline OD > 1 compared with those with an OD ≤ 1.

Thirty of 40 patients had eosinophil counts determined before and after treatment (mean count before treatment = 400 eosinophils/μL, mean count after treatment = 190 eosinophils/μL; $P < 0.05$). Of 20 patients with eosinophil data and who were cured, 11 had eosinophilia at baseline, and 8 resolved after treatment. Of the 10 patients in the sample who failed to achieve a cure in the follow-up period, none had eosinophilia at baseline and none had eosinophilia after treatment. There was also no correlation between age and baseline eosinophil levels ($P = 0.075$).

Forty-two patients failed to meet inclusion criteria for this analysis (Figure 1). Of the 12 patients receiving only one dose of ivermectin, 4 had evaluable serologic results. Of these patients, 2 (50%) had a decrease in the post-treatment to pre-treatment OD ratio to < 0.6. Of the three patients who had serologic results checked less than three months after treatment with two doses of ivermectin, all patients had a ratio < 0.6.

DISCUSSION

In this study, treatment of strongyloidiasis with ivermectin resulted in a decrease in *Strongyloides* sp. antibody levels in almost all patients during the follow-up period. In 47.5% (19 of 40) of the patients, the OD reading had decreased below the threshold of 0.5. If an OD reading of ≤ 0.5 and/or a post-treatment to pre-treatment OD ratio < 0.6 is used to assess outcome as suggested by Kobayashi and others,[25] 65% of the study group could be considered cured during the follow-up period. These findings show that serologic testing is a useful tool in monitoring response to treatment with ivermectin in immigrant patients with chronic strongyloidiasis. The results suggest that patients with strongyloidiasis will need prolonged follow-up if negative serologic results are used to define a cure. However, recent literature suggests that two doses of ivermectin given 1–14 days apart has a cure rate of 94–100%.[11,13–17] Thus, follow-up beyond 12 months may not be cost-effective.

The main limitation of the study was that patients often missed scheduled appointments. Therefore, the timing of treatment and follow-up was variable. General practitioners gave treatment and performed serologic testing opportunistically whenever patients attended their clinics for other reasons. In spite of these variations, the downward trend in antibody levels in almost all patients suggests that serologic testing can be used to monitor response to effective treatment of strongyloidiasis with ivermectin in a general practice clinic setting. Patients with filariasis or hydatid disease may have had a serologic response to ivermectin because these conditions may have cross-reacting antibodies.[31] However, we believe that this is unlikely in this patient group because they had been in Australia for a median of 14 years and were well.

The results of our study extend and corroborate the work on the use of serologic testing for diagnosis and post-treatment monitoring by other groups.[10,23–26] Most studies suggest that long-term follow up after treatment with ivermectin using serologic testing is feasible and desirable to try to ensure that eradication of the parasite has occurred. For example, in a study in Japan, Kobayashi and others found that 18 months after thiabendazole treatment, only 32% of patients showing parasitologic cure remained positive (OD > 0.5) by serologic testing.[25] These investigators suggested that a follow-up period > 12–18 months may be required. Similarly, in a study of immigrants in Canada, Loutfy et al. found that the proportion of patients cured (post-treatment to pre-treatment OD ratio < 0.6) increased over time, with 92% of patients being cured at follow-up 9–18 months after treatment.[23] Page and Dempsey showed that 9 of 10 Aboriginal patients in Australia treated with a single dose of ivermectin were negative (OD ≤ 0.4) on follow-up serologic testing at some time between 6 and 21 months after treatment.[10] In a previous study in Laotian immigrants, 50% of the patients treated with albendazole had an increase in *Strongyloides* antibody levels during follow-up. We concluded that this was most likely explained by a high treatment failure rate.[31] Thus, our strategy in the current study was to treat with two doses of ivermectin so that post treatment serologic results could be evaluated in patients that had had effective treatment. Our results concur with those of others,[23,25,32] which suggest follow-up serologic testing after 3 and 12 months would give a reasonable indication of cure if a sustained downward trend in antibody levels had occurred. In this study, patients experienced difficulty in keeping follow-up appointments because of family and work commitments. Thus, a single test performed at 6–12 months post-ivermectin treatment may be a practical solution in some patients.

In conclusion, our results show that 65% of patients treated with two doses of ivermectin had a response to treatment indicating a probable cure, suggesting that *Strongyloides* sp. serology is a useful tool for monitoring decreases in antibody levels after treatment.

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