

## Cutaneous Larva Migrans in Travelers: A Prospective Study, with Assessment of Therapy with Ivermectin

Olivier Bouchaud,<sup>1</sup> Sandrine Houzé,<sup>2</sup>  
Ricarda Schiemann,<sup>1</sup> Rémy Durand,<sup>2</sup>  
Pascal Ralaimazava,<sup>1</sup> Catherine Ruggeri,<sup>1</sup>  
and Jean-Pierre Coulaud<sup>1</sup>

Departments of <sup>1</sup>Infectious and Tropical Diseases and <sup>2</sup>Parasitology,  
Bichat Claude Bernard Hospital, Paris, France

The purpose of this prospective study was to update epidemiological data on cutaneous larva migrans (CLM) and to assess the therapeutic efficacy of ivermectin. We performed the study between June 1994 and December 1998 at our travel clinic. Ivermectin (a single dose of 200 g/kg) was offered to all the patients with CLM, and its efficacy and tolerability were assessed by a questionnaire. Sixty-four patients were enrolled. All were European and had stayed in tropical areas. After the patients had returned from their destinations, 55% had lesions occur within a mean of 16 days (range, 1–120 days; >1 month in 7 patients). The initial diagnosis was wrong in 55% of patients. The mean number of lesions was 3 (range, 1–15), and the main sites were the feet (48%) and buttocks (23%). The cure rate after a single dose of ivermectin was 77%. In 14 patients, 1 or 2 supplementary doses were necessary, and the overall cure rate was 97%. The median time required for pruritus and lesions to disappear was 3 and 7 days, respectively. No systemic adverse effects were reported. Physicians' knowledge of CLM, which can have a long incubation period, is poor. Single-dose ivermectin therapy appears to be effective and well tolerated, even if several treatments are sometimes necessary.

Cutaneous larva migrans (CLM) is a skin disease caused by penetration of the skin by canine or feline *Ancylostoma* larvae. The main species is *Ancylostoma braziliense*, but *Ancylostoma caninum*, *Uncinaria stenocephala*, and other canine or feline species can also be responsible [1–3].

*A. braziliense* is a cosmopolitan parasite that seems to infect most dogs in tropical regions of developing countries [2, 4]. CLM is mainly described in hot climates, including southeast Asia, Africa, Latin America, the Caribbean, and even the southeastern United States [5]. Rare cases have been reported in temperate areas [6, 7], especially in summer [8]. Most cases diagnosed in industrialized countries involve travelers returning from tropical areas.

Dogs and cats that have been infested with CLM eliminate the eggs in their feces. The eggs remain latent on the ground until, depending on external temperature and humidity, they transform into larvae that become infectious after 2 molts, acquiring the ability to penetrate the skin of a new host. Humans are incidental hosts in which the larvae cannot complete their natural cycle [1, 5]. The larvae therefore remain blocked in the dermis, where they can move around, probably through the secretion of a hyaluronidase [9]. After an incubation period of

uncertain duration [5], a lesion appears in the form of a highly pruriginous, linear, serpiginous eruption (figure 1).

The diagnosis is simple and does not require laboratory tests [1, 3, 5]. The lesion is due to a local allergic reaction. The larva is situated 1–2 cm ahead of the track [3], which explains why local invasive treatments of the visible track (such as surgery or cryotherapy) are often ineffective; they can also have untoward cosmetic consequences and therefore are not recommended [3, 5]. Only the skin in contact with the ground is usually affected, but pulmonary involvement has been described [10]. Hypereosinophilia can be observed [11]. In the absence of treatment, the larva dies and is resorbed after several weeks or months [12].

Since demonstration of the efficacy of albendazole [13, 14], conventional treatments with topical thiabendazole [3, 15, 16] and oral thiabendazole [12, 16] have been gradually abandoned because of the difficulty of their use or their adverse effects. More recently, a single dose of ivermectin, 200 g/kg, yielded impressive preliminary results [16–20].

Although CLM accounted for 25% of consultations for tropical skin diseases in a French travel clinic [16], the disease remains rare, and general practitioners' and dermatologists' knowledge of CLM is poor. This has led to an underestimation of the number of cases involving travelers, in addition to poor diagnosis and inappropriate treatment [5].

The first aim of this study was to reassess epidemiological data on this disease, because the available data were old and were derived from retrospective studies. The second aim was to evaluate the efficacy and tolerability of ivermectin, because

---

Received 21 January 2000; electronically published 7 September 2000.

Reprints or correspondence: Dr. Olivier Bouchaud, Hôpital Bichat Claude Bernard, 46 rue Henri Huchard 75018 Paris, France (olivier.bouchaud@bch.ap-hop-paris.fr).

**Clinical Infectious Diseases** 2000;31:493–98

© 2000 by the Infectious Diseases Society of America. All rights reserved.  
1058-4838/2000/3102-0017\$03.00



Figure 1. Typical aspect of cutaneous larva migrans

previous publications discuss a relatively small number of patients.

### Patients and Methods

The study was done prospectively in our outpatient travel clinic in Paris, between June 1994 and December 1998. Diagnosis of CLM, which was made by 3 physicians with extensive experience in tropical medicine, was made on the basis of clinical signs alone. All patients with CLM who gave their informed consent to participate in the study were enrolled, with the exception of those patients who were pregnant, who were breast-feeding, or who had a history of allergy to ivermectin.

Data were collected during an interview and a standardized physical examination and included age, sex, the country where infection occurred and the duration of stay, the date of onset of lesions, the number of medical consultations before presentation at our travel clinic, and the number and location of the lesions. Because it was not possible to determine the precise day of infection, the incubation period was estimated in 2 ways. For patients whose lesions had occurred before their return from travel, the time between their arrival in an area of endemicity and the onset of the lesions was used to define the maximum incubation period. This approach overestimates the incubation period, because it assumes that infection takes place immediately on arrival, but it is useful in the case of brief stays (short incubation periods). For patients whose lesions occurred after their return, the time between their return and the onset of the lesions was used to define the minimum incubation period. This approach underestimates the incubation period, because it assumes that infection took place on the last day of the stay.

The first-line treatment chosen for use in this study was administration of a single dose of ivermectin (Merck Sharp and Dohme,

Paris), 200 g/kg (in the form of 2 tablets for adults), taken between meals in the presence of the investigator. Given the few available data on use of ivermectin for this indication, treatment was given in an open, noncomparative manner. Efficacy and tolerability were assessed on the basis of answers to a standardized patient questionnaire recording the number of days before the pruritus and lesions disappeared and any adverse effects that occurred. Disappearance of the lesions was defined as the disappearance of local inflammatory signs.

The questionnaire was returned to the investigator by mail, between the 15th and 30th day after treatment. If the questionnaire was not returned, information was gathered by telephone. Patients were seen again only in cases of failure or relapse. These patients were offered a second (or third) identical treatment with ivermectin.

### Results

Sixty-four patients were enrolled, including 2 infants (aged 17 and 20 months). The mean patient age was 33 years (range, 1.5–73 years), and there were 37 men and 27 women. All the patients were Europeans returning from tropical areas. Travel destinations and the number of patients who traveled to each destination were as follows (figure 2): the Caribbean, 25 (39%); Asia, 16 (25%); Latin America, 12 (19%); and Africa 11 (17%). The mean duration of stay was 28 days (range, 6–90 days; median, 21 days). CLM was diagnosed in 19 patients (30%) in the first semester (January through June) and in 45 patients (70%) in the second semester (July through December).

The mean time between arrival in the country of endemicity and the onset of symptoms was 28 days (range, 5–135 days; median, 21 days). In 29 patients (45%), CLM occurred during the stay, within a mean of 15 days (range, 5–60 days) after arrival. In 4 patients, this period was only ~1 week (8, 7, 7, and 5 days). In 35 patients (55%), the lesions occurred after the patient's return, within a mean of 16 days (range, 1–120 days). In 7 patients, the lesions occurred >1 month after return (at 75 and 120 days in 2 patients).

The mean interval between onset of lesions and consultation at our travel clinic was 26 days (range, 1–90 days; median, 15 days). Thirty-five patients (55%) had already consulted a general practitioner or dermatologist (mean no. of consultations, 2; range, 1–6 consultations) before the correct diagnosis was made at our travel clinic. In most cases, inappropriate treatments, including local administration of steroids and cryotherapy (with liquid nitrogen or solid carbon dioxide), were given. Nine patients consulted after failure of either oral treatment with thiabendazole (4 patients) or flubendazole (1) or local treatment with thiabendazole (2) or flubendazole (2). These data are summarized in table 1.

All the patients complained of pruritus. The number of lesions and their main locations are indicated in table 1. The hands were involved in 2 patients, the face in 1 patient, and the external genitalia in 4 patients (3 males and 1 female). The lesions were superinfected in 5 patients.

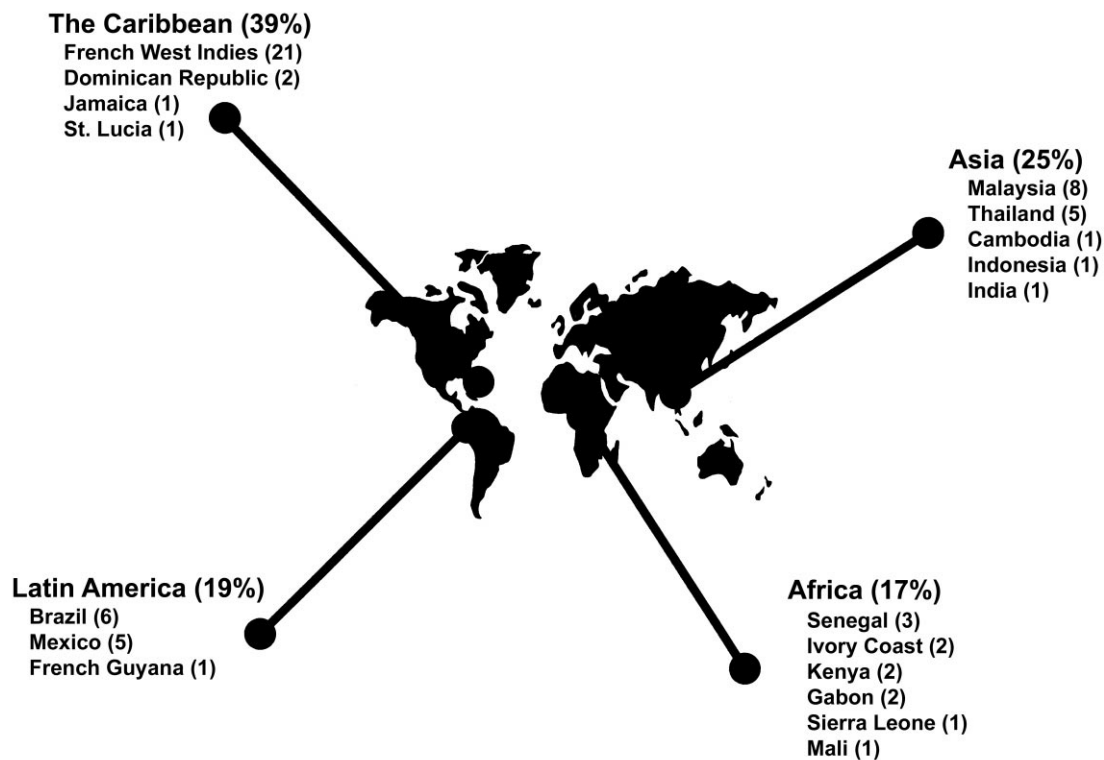


Figure 2. Countries visited by 64 patients with cutaneous larva migrans

All but 2 of the patients subsequently received ivermectin. Two patients refused this treatment and were treated successfully (1 with local albendazole and 1 with oral thiabendazole). Ivermectin, 200  $\mu\text{g}/\text{kg}$ , was given to the 2 infants; good efficacy and tolerability were noted, although 1 infant received a second dose on day 8 because of a lack of any improvement.

All but 2 of the patients who received ivermectin were cured (table 2). However, 8 patients (each of whom relapsed once) required a second treatment, and 4 (each of whom relapsed twice) required a third treatment with the same regimen. In these 12 patients, the mean time to relapse was 21 days (range, 5–30 days). For 2 other patients, a second dose (at 8 and 21 days after the first dose) was necessary because of a lack of improvement. Thus, of the 60 patients cured by ivermectin, a single dose was inadequate for 14 (23%).

One of the 2 patients not cured by ivermectin was treated successfully with albendazole (400 mg/d for 3 days) after 3 unsuccessful doses of ivermectin. The second patient showed no improvement on day 8 after ivermectin treatment and was then lost to follow-up.

The mean intervals between ivermectin intake and the disappearance of pruritus and the disappearance of lesions are indicated in table 2. No systemic adverse effects were observed. Only 1 local adverse effect was reported: 1 patient had an in-

flammatory reaction develop around the lesions on the third day after administration of the ivermectin dose. This was complicated 4 days later by bullous detachment necessitating a few days of hospitalization for local treatment.

## Discussion

The incubation period of CLM is uncertain [5] but is classically described as brief, usually lasting hours to days [3, 5, 7, 12, 16]. Experimental studies have shown that pruritus can begin after a few hours and that larval migration can begin after 4 days [5, 21]. In the present study, 4 patients had short maximal incubation periods ( $\leq 8$  days).

Jelinek et al. [3] reported the onset of symptoms >15 days after return from countries of endemicity in 25% of patients, suggesting a minimum incubation period of 2 weeks. Furthermore, in the same study, 2 patients had symptoms develop 7 months after their return, but native infection was judged to be very unlikely [3]. In our study, 11 patients (17%) had symptoms develop >15 days after their return; 7 of these had symptoms develop >1 month later. One patient had CLM develop 4 months after his return, and again native infection was very unlikely.

Pruritus, which is sometimes severe and prevents sleep [5], is

**Table 1.** Main characteristics of 64 patients with cutaneous larva migrans (CLM).

Characteristic	Value
Interval between arrival in the country with endemic CLM and onset of CLM, mean d (range)/median d	28 (5–135)/21
Onset of CLM during stay, no. (%)	29 (45)
Interval between arrival and onset, mean d (range)	15 (5–60)
Onset of CLM after return, no. (%)	35 (55)
Interval between return and onset, mean d (range)	16 (1–120)
Interval between onset of CLM and diagnosis, mean d (range)/median d	26 (1–90)/15
Previously given wrong medical advice, no. (%)	35 (55)
Consultations, mean no. (range)	2 (1–6)
Lesions, mean no. (range)	3 (1–15)
Only 1 lesion, no. (%)	16 (25)
Main sites of CLM, no. (%) <sup>a</sup>	
Feet	31 (48)
Buttocks	15 (23)
Thighs	10 (16)
Abdomen	6 (9)
Chest	5 (8)
Other(s)	15 (23)

Note. Data represent no. (%) of patients, unless otherwise indicated.

<sup>a</sup> Percentages total >100% because some cases involved >1 site.

characteristic of CLM. It was noted in 100% of patients in the present study and in 98% of patients in the study of Davies et al. [5]. The foot is the most frequent site of CLM, followed by the buttocks and thighs. The face is rarely affected. There was 1 case of facial involvement in our study, and apparently only 1 other case is described in the literature [22].

Superinfection of CLM is the main complication and can markedly hinder diagnosis. It appears to be rare, however, because Davies et al. observed no such cases [5] and we saw only 5 (8%) in our series.

Before the consultation at which the correct diagnosis was made, symptoms had lasted for a mean of 26 days (>1 month in 20 patients and 3 months in 4 patients). This long period before diagnosis was emphasized by Jelinek et al. [3], who reported that it was >1 month in 30% of patients and was 9 months in 1 patient. In a case reported by Richey et al. [23], 22 months elapsed before diagnosis. Late diagnosis may be explained in part by general practitioners' and dermatologists' poor knowledge of CLM. A diagnostic error and/or inappropriate treatment was found by Davies et al. [5] in 58% of patients, by Jelinek et al. [3] in 22% of patients, and by us in 55% of patients. One of our patients had 6 other consultations before attending our travel clinic.

All the patients in our study were Europeans traveling to tropical areas. Our travel clinic receives many African immigrants who have visited their countries of origin, but none had CLM diagnosed during the study period. The same was true in a German study involving 98 patients [3]. Similarly, there were only 2 immigrants among the 60 patients in the Canadian study by Davies et al. [5]. A behavioral explanation seems probable; immigrants usually do not visit beaches during their vacation.

Comparison of the different countries in which infection oc-

curred, in this and in other studies, would have little meaning, because destinations tend to depend on the habits of tourists in each country. However, like Jelinek et al. [3], we were surprised by the lack of patients returning from the Mediterranean basin (Greece, Turkey, etc.), which is a frequent holiday destination for Europeans. One possible explanation is of a parasitological nature. *A. braziliense*, which is by far the most frequently involved species, is mainly encountered in tropical areas, whereas *A. caninum* and *U. stenocephala* are mainly found in the northern hemisphere and are less frequently incriminated [2].

The Caribbean was the principal region involved (in 75% of cases) in both our study and the Canadian series [5]. Davies et al. [5] reported two cases contracted in Florida. The seasonal variations observed in our study appeared to coincide simply with holiday periods. Table 3 summarizes comparative epidemiological data from our study and the 2 main studies described in the literature [3, 5].

The therapeutic efficacy of ivermectin in CLM has rarely been tested. In an open study, 10 patients who received ivermectin (12 mg in a single dose) were cured, whereas among 11 patients receiving albendazole (400 mg in a single dose) in the comparative group, 1 showed no clinical response and 5 relapsed [18]. In 2 noncomparative studies involving 9 patients from Cameroon who were receiving a single dose of ivermectin, 150 µg/kg [19], and 12 French patients who were treated with a single dose of ivermectin, 200 µg/kg [20], all the subjects were cured. In another prospective noncomparative study, 57 of 58 patients were considered to be cured with use of ivermectin [16].

In our study, the overall cure rate was 97% (2 failures), but, in 14 cases (23%), a second or third treatment was necessary because of relapse or lack of response to the first dose. The calculated cure rate after a single dose of ivermectin was 77%. The median interval required for the pruritus and lesions to disappear was 3 and 7 days, respectively, whereas the median time to response (defined as complete disappearance of all signs and symptoms) in the only published study giving this information was 1 day [18]. The value of repeated treatment after initial failure was recently emphasized [24].

**Table 2.** Efficacy of ivermectin in 62 patients with cutaneous larva migrans.

Variable	Value
No. of patients	
Included in the study	64
Treated with ivermectin	62
Cured	60 <sup>a</sup>
With 1 course	46 <sup>b</sup>
With 2 or 3 courses	14 <sup>c</sup>
Interval, mean d (range)/median d, between ivermectin therapy and disappearance of	
Pruritus	3 (1–20)/3
Lesions	9 (1–30)/7

<sup>a</sup> Global cure rate, 97%.

<sup>b</sup> Cure rate with 1 course, 77%.

<sup>c</sup> Includes 12 patients with relapses.

**Table 3.** Comparative epidemiological data from our series and previous studies.

Variable	Description or value, by study site		
	Canada	Germany	France
Date [reference]	1993 [5]	1994 [3]	2000 [PS]
Type of study (no. of subjects)	Retrospective (60)	Retrospective (98)	Prospective (64)
Population	Canadian (97%), immigrant (3%)	German (100%)	French (100%)
Duration of symptoms, mean weeks	NA	5.6	4
Interval between return and diagnosis, mean weeks	NA	5	4
Cases incorrectly diagnosed initially, %	58	22	55
Onset of lesions, % of patients			
After return	NA	75	55
>15 d after return	NA	25	17
Pruritus, % of patients	98	NA	100
Lesions, mean no. (range)	1.7 (1–6)	NA	3 (1–15)
Site of lesion, % of patients			
Feet	87	62	48
Buttocks	5	13	23
Thighs	5	9	16

NOTE. NA, not available; PS, present study.

The tolerability of ivermectin was good, because no systemic reactions were noted in our study or in the other studies using ivermectin in this indication [16–20, 24]. A local bullous reaction occurred in 1 patient in our study, and a similar reaction was noted by Caumes et al. [18] in 2 patients (1 treated with ivermectin and 1 treated with albendazole).

Finally, we used ivermectin successfully and safely in 2 infants aged <2 years. To our knowledge, this is the first time that the use of ivermectin for this indication in young children has been reported.

Tropical beaches carry a risk for travelers of contracting CLM. This study emphasizes the fact that the incubation period can be very long (several weeks or months). The frequency of cases of CLM that continue to progress for several weeks or months after travelers return from areas of endemicity is explained in part by the fact that nonspecialists in tropical medicine lack knowledge of this parasitic skin disease. However, the diagnosis is simple, and treatment with ivermectin is simple, effective, and well tolerated, even if its efficacy in our study was lower and less rapid than in previous series.

#### Acknowledgment

We are grateful to David Young for his help in preparing the manuscript.

#### References

- Elliot DL, Tolle SW, Goldberg L, Miller JB. Pet-associated illness. *N Engl J Med* **1985**;313:985–95.
- Marcial-Rojas RA. Cutaneous larva migrans of hookworm origin. In: Marcial-Rojas RA, ed. Protozoal and helminthic diseases. New York: Robert E Krieger Publishing, **1975**:747–52.
- Jelinek T, Maiwald H, Nothdurft HD, Löscher T. Cutaneous larva migrans in travelers: synopsis of histories, symptoms and treatment of 98 patients. *Clin Infect Dis* **1994**;19:1062–6.
- Malgor R, Oku Y, Gallardo R, Yarzabal I. High prevalence of *Ancylostoma* spp infection in dogs, associated with endemic focus of human cutaneous larva migrans in Tacuarembó, Uruguay. *Parasite* **1996**;3:131–4.
- Davies HD, Sakuls P, Keystone PS. Creeping eruption: a review of clinical presentation and management of 60 cases presenting to a tropical disease unit. *Arch Dermatol* **1993**;129:588–91.
- Zimmermann R, Combemale P, Piens MA, Dupin M, Le Coz C. Cutaneous larva migrans autochthonous in France: a propos of a case. *Ann Dermatol Venereol* **1995**;122:711–4.
- Herbener D, Borak J. Cutaneous larva migrans in northern climates. *Am J Emerg Med* **1988**;6:462–4.
- Klose C, Mravak S, Geb M, Bienzle U, Meyer CG. Autochthonous cutaneous larva migrans in Germany. *Trop Med Int Health* **1996**;1:503–4.
- Hotez PJ, Narasimhan S, Haggerty J, et al. Hyaluronidase from infective *Ancylostoma* hookworm larvae and its possible function as a virulence factor in tissue invasion and in cutaneous larva migrans. *Infect Immun* **1992**;60:1018–23.
- Butland RJ, Coulson IH. Pulmonary eosinophilia associated with cutaneous larva migrans. *Thorax* **1985**;40:76–7.
- Leicht SS, Youngberg GA. Cutaneous larva migrans. *Am Fam Physician* **1987**;35:163–8.
- Katz R, Ziegler J, Blank H. The natural course of creeping eruption and treatment with thiabendazole. *Arch Dermatol* **1965**;91:420–4.
- Sanguigni S, Marangi M, Teggi A, De Rosa F. Albendazole in the therapy of cutaneous larva migrans. *Trans R Soc Trop Med Hyg* **1990**;84:831.
- Rizzitelli G, Scarabelli G, Veraldi S. Albendazole: a new therapeutic regimen in cutaneous larva migrans. *Int J Dermatol* **1997**;36:700–3.
- Harland PS, Meakins RH, Harland RH. Treatment of cutaneous larva migrans with local thiabendazole. *BMJ* **1977**;2:772.
- Caumes E, Carrière J, Guernonprez G, Bricaire F, Danis M, Gentilini M. Dermatoses associated with travel to tropical countries: a prospective study of the diagnosis and management of 269 patients presenting to a tropical disease unit. *Clin Infect Dis* **1995**;20:542–8.
- Ottesen EA, Campbell WC. Ivermectin in human medicine. *J Antimicrob Chemother* **1994**;34:195–203.
- Caumes E, Carrière J, Detry A, Gaxotte P, Danis M, Gentilini M. A randomized trial of ivermectin versus albendazole for the treatment of cutaneous larva migrans. *Am J Trop Med Hyg* **1993**;49:641–4.
- Louis FJ, De Quincenet G, Louis JP. Intérêt de l'ivermectine en prise unique dans le traitement du syndrome de larva migrans cutanée. *Press Med* **1992**;21:1483.
- Caumes E, Detry A, Paris L, Danis M, Gentilini M, Gaxotte P. Efficacy of ivermectin in the therapy of cutaneous larva migrans. *Arch Dermatol* **1992**;128:994–5.

21. Canizares O. Larva migrans. In: Canizares O, Harman R, eds, Clinical tropical dermatology. Boston: Blackwell Scientific, 1975;210-1.
22. André J, Bernard M, Ledoux M, Achten G. Larva migrans of the oral mucosa. *Dermatologica* 1988;176:296-8.
23. Richey TK, Gentry RH, Fitzpatrick JE, Morgan AM. Persistent cutaneous larva migrans due to *Ancylostoma* species. *South Med J* 1996;89:609-11.
24. Van Den Enden E, Stevens A, Gompel AV. Treatment of cutaneous larva migrans. *N Engl J Med* 1998;339:1246-7.