REVIEW ARTICLE

Eosinophilia in Returning Travelers and Migrants

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SUMMARY

Introduction: Eosinophilia in travelers returning from tropical countries is often caused by helminths. The high eosinophil counts arise particularly from tissue migration of invasive larvae.

Methods: Review of literature selected by means of a Medline search using the MeSH terms "eosinophilia" and "helminth."

Results: The patient's geographic and alimentary history may suggest infection with particular parasitic worms. A targeted diagnostic approach is suggested. The physician should concentrate on the principal signs and be guided by the geographic and alimentary history. Elaborate diagnostic measures are seldom indicated.

Discussion: Although eosinophilia alone has low positive predictive value for a worm infection, it points clearly to helminthosis if the patient has recently returned from the tropics and the eosinophilia is new.

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Eosinophilia has a wide variety of causes, including allergic illnesses, skin diseases, malignant conditions or even medication use (1). Nonparasitic causes should therefore also be considered when attempting to establish the cause of eosinophilia (1). New-onset eosinophilia following a visit to the tropics, however, is most likely due to a worm infection (helminthosis). Up to 5% of asymptomatic travelers returning from the tropics have eosinophilia requiring diagnostic clarification and between 14% and 48% of these travelers with eosinophilia are suffering from a parasitosis requiring treatment (2–6). Screening of immigrants with eosinophilia has shown that helminths are present in up to 77% of cases depending on the country of origin (7, 8). On the other hand, the sensitivity and specificity of eosinophilia for diagnosing helminthosis are low and the positive predictive value was only about 10% in some studies (4).

In medical practice, an increased percentage of eosinophilic granulocytes in the differential blood count is often erroneously referred to as "eosinophilia." In fact, the decisive factor is the number of eosinophilic granulocytes per µL blood. Healthy persons have on average fewer than 450 eosinophils per µL blood. Depending on the time of day, this value can vary by as much as 40% depending on the cortisol level (9). The patient's age, physical training condition as well as environmental factors (especially allergen exposure) also influence the eosinophil count in peripheral blood. The degree of eosinophilia can be categorized as follows:

- Mild eosinophilia: up to 1500/µL
- Moderate to severe eosinophilia >1500/µL (according to [10], modified).

Another helpful laboratory parameter is total IgE. An increase in the IgE concentration occurs in various worm diseases. Mutual pathophysiological relationships, but only a low correlation exist between IgE and eosinophilia (11).

No guidelines are yet available for diagnostic evaluation of eosinophilia in the primary care setting. Physicians frequently contact institutes of tropical medicine for advice. In the following, the authors recommend structured screening programs guided by the geographic history and cardinal symptoms. These programs are based on epidemiological data on imported diseases (12–20), especially surveillance data from the GeoSentinel Network (21–23). An economical procedure and the lowest possible stress for the patient were also

Figure 1:
Subconjunctival
localization
of Loa loa

among the goals in developing these programs. The authors propose screening programs for "generalists" and not for specialists assumed to possess detailed knowledge of the routes of transmission and clinical presentations, even of very rare tropical infectious diseases. In doubtful cases a physician specializing in tropical medicine has to be consulted who possesses specialized knowledge of the prevalences and clinical manifestations of rare tropical diseases.

The most important helminthoses—including clinical signs, diagnosis, and treatment—are summarized in the *e-table*.

Systematic search for evidence

The diagnosis and treatment of tropical diseases should be evidence based. Unfortunately, no sufficiently controlled studies are available on many topics of tropical medicine. Many of the studies that are available were performed in developing countries and their results cannot be extrapolated to Germany. Moreover, many parasitic diseases are rarely imported into industrialized countries, with the result that there are no adequate case numbers. It is therefore difficult to state methods with which to interpret and assess the level of evidence. The Cochrane Collaboration studies are also of limited assistance because for the reasons outlined above they cover only

small partial areas of tropical medicine and most of the topics addressed focus on developing countries. It is therefore not surprising that there are hardly any international guidelines. Germany also lacks guidelines for the diagnostic evaluation of eosinophilia in travelers returning from the tropics and migrants. This article is a reflection of expert opinion and was produced on the basis of an informal consensus. The authors performed a review of literature selected by means of a Medline search using the MeSH terms "eosinophilia" and "helminth" for the period 1983 to 2008.

Diagnostic strategies

Since helminth infections can result in serious health impairment and eosinophilia can also point to the presence of various malignant diseases, rapid and efficient diagnostic clarification is essential. Whereas in most cases the treatment of worm diseases is easy, cost effective and safe, an unstructured investigation of eosinophilia is often time consuming, cost intensive and burdensome for the patient. If test results are negative but there is a continued suspicion of helminthosis, an expert in tropical medicine should be consulted.

History

The geographic history is especially important. Some helminths have worldwide prevalence, while others are found only in circumscribed geographic areas. Loa loa *(figure 1)*, for example, is found only in Central and West Africa. Ascaris, on the other hand, has a worldwide distribution. Travelers returning from schistosomiasis-endemic regions, for example, must be questioned specifically about contact with natural fresh waters. An alimentary history can also provide useful information regarding the type of worm infection. Liver flukes, for example, are usually transmitted by the consumption of aquatic plants such as watercress, lung flukes by fresh water crabs and the herring worm by raw sea fish *(table 1)*.

Laboratory diagnostics

Besides quantifying eosinophilia in the differential blood count, primary importance attaches to direct identification of pathogens and immune diagnostics.

TABLE 1

Helminths transmitted by foods (e20–e22)

Food	Pathogen
Fish, if raw or insufficiently heated	Anisakis and Pseudoterranova, Clonorchis sinensis, Opisthorchis, Diphyllobothrium latum
Pork	Taenia solium
Beef	Taenia saginata
Watercress, water spinach etc.	Fasciola
Shellfish and crustaceans	Paragonimus
Fish, frogs, snakes, pets fed with fish	Gnathostoma
Pork, wild boar, bear, horse, walrus etc.	Trichinella

TABLE 2

Diagnosis of asymptomatic eosinophilia

Eosinophilia per μL blood	Recommended screening program	Special features
≤1500	3 × stool test for worm eggs, if negative: Strongyloides and schistosome antibodies in serum (if patient from schistosomiasis-endemic region; see box 1)	If results negative: re-test after 3 months
>1500	3 x stool test for worm eggs, 1 × Baermann stool test for Strongyloides stercoralis larvae; Strongyloides, schistosome (if patient from schistosomiasis-endemic region; see box 1), Fasciola (if patient not from schistosomiasis-endemic region) and cysticercal anti-bodies in serum; ECG, chest X-ray, abdominal sonography	If patient from sub-Saharan Africa: additionally Filaria antibodies in serum; if results negative: refer to specialist in tropical medicine

Most desirable is the direct detection of adult worms, larvae in the blood or worm eggs in feces because this is an unequivocal result and requires no interpretation, as for instance in immune diagnostic procedures. For infections with adult worms or with worm larvae which are localized in the tissue, however, direct detection is often not possible. It is then necessary to resort to antibody diagnosis. It should be noted that cross reactions are common within the three groups of tapeworms (cestodes), roundworms (nematodes), and flukes (trematodes). In migrants and travelers who frequently sojourn in tropical regions, the possibility of a serological scar should be considered. Molecular biological techniques, especially the polymerase chain reaction (PCR), will in future simplify the diagnosis of tropical diseases and improve specificity. For example, a PCR for the detection of schistosomiasis is currently being developed.

Asymptomatic eosinophilia

New-onset asymptomatic eosinophilia following a journey to the tropics should first prompt the physician to rule out the presence of parasitic diseases even if the patient has an allergic predisposition. *Table 2* presents a structured screening program for this purpose. First it is recommended to analyze the stool three times for worm eggs on three consecutive days. If the stool analyses are negative, tests should be performed for Strongyloides stercoralis. This worm has a worldwide distribution in warm countries (e1). The larvae usually hatch while still in the intestine, which is why the eggs are not detectable in the normal stool tests *(figure 2)*. It is important to exclude Strongyloidiasis because internal and external autoinfection can lead to chronic, persisting disease. It is also possible for a potentially life-threatening hyper-infection syndrome to develop in immunosuppressed persons. A search should also be made for antibodies against schistosomes if the patient has spent time in a schistosomiasis-endemic region *(box 1)* and the stool samples have tested negative.

Severe eosinophilia (>1500/μL blood) often cannot be sufficiently explained by the detection of worm eggs in the stool. Additional antibody tests for a cestode

Figure 2:
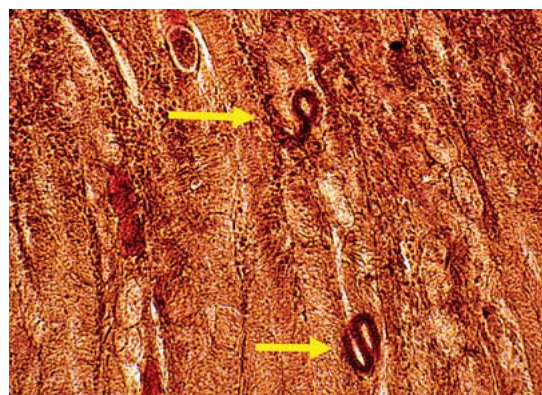Larvae of Strongyloides stercoralis in the small intestine

BOX 1

Overview of schistosomiasis-endemic regions*

Schistosomiasis is endemic in the following regions of the world:

Africa, Eastern Brazil, Venezuela, Yemen, Saudi Arabia, Oman, Iraq, Syria, Iran, China, Laos, Cambodia, Phillipines, Sulawesi

* more rarely also in other countries (e2, e23)

Figure 3:
Computed tomography. Lesions of the liver in infection with liver flukes (Fasciola hepatica)

TABLE 3

Diagnosis of eosinophilia with fever

Origin (see *box 1*)	Recommended screening program	Special features
From schistosomiasis-endemic region	3 × stool test for worm eggs Schistosome antibodies in serum ECG, chest X-ray, abdominal sonography If negative: tests as for eosinophilia and fever not from schistosomiasis-endemic region (see below)	For acute schistosomiasis (Katayama syndrome) poss. no eggs yet in stool or urine, poss. repeat diagnostic tests after 4 weeks If results negative: refer to specialist in tropical medicine
Not from schistosomiasis-endemic region	3 × stool test for worm eggs, 1 × Baermann stool test for Strongyloides stercoralis larvae Strongyloides, Trichinella, Toxocara and Fasciola antibodies in serum ECG, chest X-ray, abdominal sonography	If results negative: refer to specialist in tropical medicine

(tapeworm), a trematode (fluke), and a nematode (roundworm) should thus always be performed. Because of the cross reactions within these groups, a positive antibody test should then be the starting point for further investigations appropriate to the geographic and alimentary history. Chest radiography in two planes is useful in excluding eosinophilic pulmonary infiltrates that can develop during the larval migration of various helminths (frequently: Ascaris, hookworm, or Strongyloides). Upper abdominal imaging (sonography or CT; *figure 3*) can reveal hepatic lesions that substantiate the suspicion of an infection with liver flukes. Electrocardiography should also rule out nonspecific endomyocardial damage that can develop due to eosinophil degranulation products. If no evidence of the origin of the eosinophilia is found, clarification by a specialist is required.

Fever

The geographic history is particularly important in patients with eosinophilia and fever *(box 1 and table 3)*.

The commonest cause of fever in travelers returning from schistosomiasis-endemic regions and who present with eosinophilia is Katayama syndrome (e2, e3). About 14 to 90 days after initial contact with schistosomes, this acute form of schistosomiasis produces clinical symptoms comprising nocturnal fever, cough, myalgia, headache and abdominal pain developing as a reaction to the maturing worms. In this infectious phase, therefore, usually no eggs are yet excreted in the urine (bladder schistosomiasis) or stools (intestinal schistosomiasis). Antibody diagnosis may initially also give negative results. In such cases the patient should be re-examined after about four weeks and in severe courses a shorter interval is recommended. If eggs are then found, the schistosome species can be identified from the egg morphology, allowing targeted treatment.

In patients who have not visited a schistosomiasis-endemic region, an infection with Fasciola spp. (liver fluke) may be a possible cause of eosinophilia with subfebrile temperatures (e4). These patients are found to have intrahepatic space occupying lesions in imaging

TABLE 4

Diagnosis of eosinophilia with cutaneous swellings

Type of cutaneous swelling	Recommended screening program	Special features
Periorbital edema	Blood filtration for Trichina larvae Trichinella antibodies in serum	If results negative: refer to specialist in tropical medicine
Urticaria	3 × stool test for worm eggs 1 × Baermann stool test for Strongyloides stercoralis larvae Strongyloides antibodies in serum Schistosome antibodies in serum (if patient from schistosomiasis-endemic region see *box 1*)	For patients from sub-Saharan Africa additionally: Filaria antibodies in serum If results negative: refer to specialist in tropical medicine
Subcutaneous swellings, poss. migrating	3 x stool test for worm eggs 1 x Baermann stool test for Strongyloides stercoralis larvae Strongyloides, Gnasthosoma, Filaria and Paragonimus antibodies in serum	For patients from Central Africa: 3 × blood test for microfilaria in blood (perform test at about 12 noon) If results negative: refer to specialist in tropical medicine

TABLE 5

Diagnosis of eosinophilia with abdominal pain

Recommended screening program	Special features
3 × stool test for worm eggs, 1 × Baermann stool test for Strongyloides stercoralis larvae Strongyloides, Fasciola, Toxocara antibodies in serum Anisakis antibodies in serum (with corresponding alimentary history; see *table 1*) ECG, chest X-ray, abdominal sonography	If results negative: refer to specialist in tropical medicine

studies and also test positive for antibodies. The patient's further management should then be entrusted to a specialist.

Cutaneous swellings

Periorbital edema in patients with a relevant history—for example following consumption of insufficiently cooked pork or wild boar meat—*(table 1)* is typical of trichinosis (e5). Blood filtration for trichina larvae should then be performed; a suitable serological screening test is also available *(table 4)*.

If urticaria is present, however, a Katayama syndrome should be considered the prime candidate. Alternating subcutaneous swellings occur in gnathostomiasis (e6) and also in loiasis (Calabar swelling). Patients originally from Central and West Africa can therefore immediately be tested for Loa loa (e7). The latest data from the Geo-Sentinel Surveillance Network show that filaria - such as Loa loa - can also be transmitted during short trips to endemic regions (22).

Abdominal pain

Abdominal pain associated with eosinophilia suggests the presence of acute disease *(table 5)*. Persons infected with liver flukes (such as Fasciola) experience permanent or intermittent pain. Abdominal pain and elevated laboratory values for transaminases may be a sign of toxocariasis (e8). Anisakiasis (caused mainly by the herring worm Anisakis spp. and the codworm Pseudoterranova spp.) may be associated with acute disease symptoms such as acute abdomen or chronic gastroenteritis with recurrent abdominal pain (e9). These diseases, however, are reported less from the tropics than from Holland, Japan, and the American coastal regions. These worms are transmitted by the consumption of raw or insufficiently heated fish *(table 1)*. A sonographic examination should always be performed if there is eosinophilia and abdominal pain, for example in order to identify any liver lesions. Rare causes such as Ascaris lumbricoides that has migrated into the bile duct can also be detected by ultrasonography.

Elevated transaminase concentrations

Toxocariasis can lead to increased transaminase concentrations *(box 2)*. Infections with Toxocara canis are common worldwide but only rarely become symptomatic.

Diarrhea

Diarrhea frequently occurs after a period spent in the tropics, but helminths are only rarely the cause of acute traveler's diarrhea (e10). If the diarrhea is associated with eosinophilia, the usual screening procedure must be extended. Besides the obligatory screening for Strongyloidiasis, the early stage of trichinosis should also be considered *(box 3)*.

Pulmonary infiltrates

Worm larvae that pass through the lung cause transient pulmonary infiltrates (e11, e12). If this suspicion is present, a stool test should be arranged for about 4 to 6 weeks after the presumed date of infection *(table 6)*. Echinococcosis may manifest in the form of pulmonary, possibly septated cysts on chest radiograph or thoracic CT, and the diagnosis can be substantiated by an antibody test (e13). Imported infections with lung flukes

BOX 2

Diagnosis of eosinophilia with elevated transaminase concentrations

- 3 × stool test for worm eggs
- Baermann stool test for Strongyloides stercoralis larvae
- Strongyloides, Fasciola and Toxocara antibodies in serum

BOX 3

Diagnosis of eosinophilia and diarrhea

- 3 × stool test for worm eggs
- 1 × Baermann stool test for Strongyloides stercoralis larvae
- Strongyloides antibodies in serum
- Trichinella antibodies in serum (with corresponding history; see *table 1*)

TABLE 6

Diagnosis of eosinophilia with pulmonary infiltrates

Recommended screening program	Special features
3 x stool test for worm eggs (if result negative: repeat stool test after 4 weeks) 1 x Baermann stool test for Strongyloides stercoralis larvae (if result negative: repeat stool test after 4 weeks) Strongyloides, Toxocara, and Paragonimus antibodies in serum	Cystic structure in imaging: Echinococcus antibodies in serum; if positive, refer to specialized center Patient from Indian subcontinent: suspicion of tropical pulmonary eosinophilia: refer to specialist in tropical medicine

(Paragonimus) have only been described in migrants in a small number of individual cases. The worm cyst with pericystic infiltration appears in the radiograph as an extensive opacity and on CT as an annular structure. The diagnosis is confirmed by the detection of eggs in sputum and stools and by specific antibodies in the serum (e14). Immigrants from South and South East Asia with asthmatic complaints, pulmonary infiltrates, and pronounced eosinophilia in very rare cases have "tropical pulmonary eosinophilia," a special variant of lymphatic filariasis. These patients should be referred to a specialist (e15).

Key messages

- When eosinophilia is present after periods in the tropics, worm diseases should always be considered.

- In infection with intestinal worms, comparatively low eosinophilia is generally found.

- In patients with high eosinophilia, tissue worms should be strongly suspected.

- In migrants with eosinophilia from the tropics and subtropics, strongyloidiasis should always be ruled out.

- For fever and pronounced eosinophilia after a period in a schistosomiasis endemic region, the possibility of Katayama syndrome should always be considered.

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I

E-TABLE

Clinical presentation, diagnosis, and treatment of major worm diseases (e16–e19)

Pathogen	Clinical symptoms	Eosinophil count*1	Diagnosis	Treatment
Adult nematodes (roundworms) in the intestine				
Ascaris lumbricoides (maw worm)	Larval migration causes pulmonary symptoms, rarely ileus, liver abscesses, obstructive jaundice	Greatly increased during larval migration, later slightly increased or normal	Detection of eggs in stool	Mebendazole 2 x 100 mg/d for 3 days
Ancylostoma, Necator (hookworm)	Larval migration causes pulmonary symptoms, abdominal complaints, poss. (iron deficiency) anemia	Greatly increased during larval migration, later slightly increased or normal	Detection of eggs in stool	Mebendazole 2 x 100 mg/d for 3 days
Strongyloides stercoralis (dwarf threadworm)	Larval migration causes pulmonary symptoms, abdominal complaints, severe courses in immunodeficiency	Initially greatly increased, later moderately to slightly increased, in immunodeficiency poss. normal (!)	Detection of larvae in stool (e.g. Baermann test) or duodenal secretion	Albendazole 2 x 400 mg/d or ivermectin*2 1 x 200 µg/kg for 1 to 2 days, repeated after 2 weeks
Trichuris trichiura (whipworm)	Rarely rectal prolapse	Slightly increased to normal	Detection of eggs in stool	Mebendazole 2 x 100 mg/d for 3 days
Enterobius vermicularis (pinworm)	Perianal pruritus, rarely vaginitis, appendicitis	Slightly increased to normal	Detection of eggs in perianal swab sample	Mebendazole 1 x 100 mg/d, repeated after 2 and 4 weeks
Trichostrongylus spp.	Diarrhea, abdominal pain	Slightly increased to normal	Detection of eggs in stool	Mebendazole 2 x 100 mg/d for 3 days
Adult nematodes (roundworms) in tissue				
Onchocera volvulus	Dermatitis, subcutaneous nodules, ocular involvement	Usually increased	Detection of adult worms in skin nodules (poss. by ultrasonography) or of microfilaria in the skin (skin snip)	Ivermectin*2 150 µg/kg, poss. additionally doxycycline*2 100 mg/d for 6 weeks
Loa loa	Cutaneous swellings, subconjunctival worm migration	Often greatly increased	Detection of microfilaria in blood	Diethylcarbamazine*2 Caution with high microfilaria counts
Wuchereria bancrofti, Brugia malayi	Lymph vessel obstruction or even elephantiasis, lymphadenitis, lymphangitis	In early stages	Detection of microfilaria in blood	Diethylcarbamazine*2
Nematode larvae				
Anisakis spp.	Abdominal pain	Slightly to moderately increased	Clinical and serological	Endoscopically, poss. surgically
Toxocara spp. (visceral larva migrans)	Generalized symptoms, poss. focal neurological signs, ocular symptoms	Moderately to greatly increased	Clinical and serological	Albendazole 2 x 400 mg/d over 2 to 4 weeks
Gnathostoma spp.	Subcutaneous or visceral larva migrans syndrome	Moderately to greatly increased	Clinical and serological	Albendazole 2 x 400 mg/d over 3 weeks poss. also surgical removal
Trichinella spp. (trichinosis)	Abdominal complaints, myalgia, periorbital edema, poss. focal neurological signs	Moderately to greatly increased	Clinical, blood test for larvae, serological	Mebendazole 2 x 200 mg/d for 2 weeks or albendazole 400 mg/d over 2 weeks, poss. additionally corticosteroids
Cestodes (tapeworms) in the intestine				
Taenia saginata (beef tapeworm)	Abdominal complaints	Normal to slightly increased	Detection of proglottids in stool	Niclosamide 1 x 2 g or praziquantel 1 x 10 mg/kg
Taenia solium (pork tapeworm)	Abdominal complaints	Normal to slightly increased	Detection of proglottids in stool	Niclosamide 1 x 2 g or praziquantel 1 x 10 mg/kg
Diphyllobothrium latum (fish tapeworm)	Poss. megaloblastic anemia with glossitis	Normal to slightly increased	Detection of eggs in stool	Niclosamide 1 x 2 g or praziquantel 1 x 25 mg/kg
Hymenolepsis nana (dwarf tapeworm)	Abdominal complaints, diarrhea	Normal to slightly increased	Detection of eggs in stool	Praziquantel 1 x 25 mg/kg
Tapeworm larvae in tissue				
Taenia solium (cysticercosis)	Focal neurological signs, subcutaneous nodules	Normal to slightly increased	Imaging, immunodiagnostics	Albendazole 15 mg/kg/d for 30 days
Echinococcus granulosus and E. multilocularis	Intrahepatic cysts	Normal to slightly increased	Imaging, immunodiagnostics	Albendazole 15 mg/kg/d for 30 days, often several cycles necessary
Trematodes (leeches, flukes)				
Schistosoma haematobium	Initially poss. fever ("Katayama fever"), dysuria, hematuria, hydronephrosis	In Katayama fever greatly increased, later slightly increased	Detection of eggs in urine or in rectal biopsies	Praziquantel 40 mg/kg/d for 3 days
Schistosoma mansoni, S. japonicum, S. intercalatum	Initially poss. fever ("Katayama fever"), abdominal complaints, bloody stool, poss. hepatic fibrosis	In Katayama fever greatly increased, later slightly increased	Detection of eggs in stool or in colon biopsies	Praziquantel 40–60 mg/kg/d for 3 days
Fasciolepsis buski (large intestinal fluke)	Nonspecific symptoms	Normal to slightly increased	Detection of eggs in stool	Praziquantel 1 x 15 mg/kg
Fasciola spp. (large liver fluke)	Hepatomegaly (often painful), liver abscesses, biliary tract symptoms	In early infection greatly increased, later slightly increased	Detection of eggs in stool and duodenal secretion, adult worm in ultrasonography	Triclabendazole*2 1 x 10 mg/kg for severe infections up to 20 mg/kg
Clonorchis and Opisthorchis spp. (Chinese and cat liver fluke)	Biliary tract symptoms, pyrogenic cholangitis, cholangiocarcinoma	In early infection greatly increased, later slightly increased	Detection of eggs in stool and duodenal secretion	Praziquantel 3 x 25 mg/kg/d for 2 days
Paragonimus spp. (lung fluke)	Chronic cough, chest pain, hemoptyses or brownish tinged sputum	In early infection greatly increased, later normal	Detection of eggs in stool and sputum, x-ray	Praziquantel 3 x 25 mg/kg/d for 2 days

*1 Degree of eosinophilia classified according to Brigden (10; modified): mild eosinophilia ≦1500/µL, moderate to severe eosinophilia >1500/µL
*2 Off-label use, only after consulting a specialist in tropical medicine