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Eosinophilia in Infectious Diseases

Elise M. O'Connell, MD and **Thomas B. Nutman, MD**

Helminth Immunology Section, Laboratory of Parasitic Diseases, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, MD 20892-0425

Abstract

In determining the etiology of eosinophilia, it is necessary to consider the type of patient, including previous travel and exposure history, comorbidities, and symptoms. In this review, we discuss the approach to the patient with eosinophilia from an infectious diseases perspective based on symptom complexes.

Keywords

Eosinophilia; infection; fever; travel; immigrant; refugee

I. Introduction

Eosinophilia can be caused by both infectious and non-infectious processes, many of which may be clinically indistinguishable. Narrowing the differential diagnosis can be achieved by considering the type of patient, accompanying symptoms, duration of eosinophilia, and, to a certain extent, the degree of eosinophilia. In general, refugees/immigrants originally from resource-limited countries, along with travelers/expatriates to these same areas, have a high likelihood of eosinophilia being caused by parasitic helminth infections. Patients from high-income countries without a significant travel history are much more likely to have allergic, autoimmune, malignancy-related or other underlying causes for their eosinophilia.

Thus, in this review, we will be discussing the infectious causes of eosinophilia in travelers, non-travelers, and immigrants separately, and will examine the causes in the context of symptom location and/or organ system involvement. Since most *infectious* causes of peripheral blood eosinophilia are parasitic, this review has an emphasis on eosinophilia in the traveler and immigrant/refugee, who are most likely to acquire these infections. For simplicity we define eosinophilia as an absolute eosinophil count of >500/μL and classify <1000/μL as being mild and those >1500/μL as being marked.

Corresponding Author: Elise M. O'Connell, MD, Clinical Fellow, Laboratory of Parasitic Diseases, National Institute of Allergy and Infectious Diseases, Bethesda, MD, oconnellem@mail.nih.gov.

Dr. Nutman is Head, Helminth Immunology Section and Head, Clinical Parasitology Section, Laboratory of Parasitic Diseases, National Institute of Allergy and Infectious Diseases, Bethesda, MD

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II. Initial Approach

Eosinophilia is often identified as part of a complete blood count (CBC) done either routinely or as part of an evaluation for a particular symptom complex. It is helpful to know whether the eosinophilia has developed acutely or is chronic (see Table 1), although this is not always possible. In the setting of an acute febrile illness with eosinophilia, however, historical eosinophil counts become less important. If eosinophilia (particularly >1,000/μL) is found in the context of fever, the same process driving the eosinophilia is most likely causing the acute illness. Studies have demonstrated suppression of peripheral eosinophil counts in patients during acute bacterial and viral infections [1, 2]. Therefore, eosinophilia in the context of an acute illness points toward a non-infectious (e.g. autoimmune), parasitic (e.g. acute schistosomiasis), or fungal (e.g. coccidiomycosis) etiology as the cause of the illness [1].

In helminth infections, eosinophilia is usually most pronounced early in infection, coinciding with the larval migration through tissues, which then slowly decreases over time. Protozoa, in general, do not cause eosinophilia with the exception of *Cystisospora belli* and *Sarcocystis* spp. While HIV alone is unlikely to be a significant cause of eosinophilia, HIV status should be assessed in all patients presenting with eosinophilia, as it increases suspicion for eosinophilia-associated diseases not seen in immunocompetent patients (e.g. eosinophilic folliculitis, *Cystisospora belli*) [3-5].

A thorough review of symptoms and physical exam should be performed on every patient with eosinophilia of unknown etiology. A detailed travel history including residence abroad should be assessed to classify the type of patient and guide the evaluation, as some helminth infections can persist for decades after leaving endemic areas (e.g. the filariae, schistosomes, Echinococcus, *S. stercoralis*). Medications (including over the counter and dietary supplements) must be reviewed, as they are a common cause of otherwise asymptomatic eosinophilia. Notably, a stool ova and parasite exam can be helpful in diagnosing some hepatobiliary/intestinal parasites (Table 2), but is a relatively insensitive test. Symptoms often do not correspond with when eggs will be found in the stool, and many parasites that cause eosinophilia are not found in the stool.

III. Eosinophilia in the Short Term Traveler

The locations of (see Table 1) and exposures during (including consumption of raw/undercooked meat or seafood and water contact) travel and symptoms should guide the clinical evaluation with respect to infectious diseases. While many of the following infections can be subclinical in some patients, we will discuss them with their most typical presenting characteristics. Notably, however, **ascariasis** most commonly presents without any symptoms. Rarely, Loeffler's syndrome (cough, low-grade fevers, transient lung infiltrates, and mild to marked eosinophilia) occurs 3-9 days following infection with Ascaris [6, 7].

III. A. Infectious causes of eosinophilia and fevers in the traveler

Fevers associated with peripheral eosinophilia in a traveler are most commonly associated with acute schistosomiasis, infections with other flukes, or with a drug reaction. We discuss, in turn, those infections in which fever and eosinophilia are associated with particular symptom complexes.

III.A.1. Eosinophilia with fevers and abdominal and/or pulmonary symptoms in the traveler

1. **Acute schistosomiasis ("Katayama fever")** is one of the most common causes of travel-acquired eosinophilia [8]. While symptom onset varies slightly depending on the schistosome species, symptoms often begin 3-4 weeks (range 2-9) following infection [9] that occurs through contact with cercarial-containing fresh water. The most common presenting complaints are a combination of malaise, myalgia, diarrhea, cough, abdominal pain, fevers, and/or headache [8-13] A minority of patients develop urticaria with the onset of symptoms. Despite its eponym, up to 30% of patients never have fever [8]. Hepatomegaly and mild liver enzyme elevations may be seen. Eosinophilia is present in nearly all patients commonly ranging between 3,000-7,000/μl [8, 10]. Symptoms improve over several weeks to months [11], even in the absence of treatment. Eggs are only detectable in the urine/stool at ∼6 weeks following exposure, while schistosome-specific IgM is detectable at 4-5 weeks and IgG at 5-8 weeks following exposure [9]. With treatment, eosinophil counts often normalize within 4-12 months [8, 10].

2. **Fascioliasis** is acquired by ingesting contaminated freshwater vegetables or water (see Table 1). Patients typically present with fevers, leukocytosis, high-grade eosinophilia, and right upper quadrant pain [14-16]. Elevated serum transaminases with normal bilirubin levels are commonly seen. Computational tomography (CT) during this time shows non-contrast enhancing, low-attenuated liver lesions [17], and liver biopsy often shows eosinophilic granulomas [14]. Over 2-4 months without treatment, symptoms and eosinophilia may slowly improve as the larvae migrate to the biliary tree, at which time intermittent elevations in bilirubin and liver transaminases may be seen as a reflection of biliary obstruction [18]. At this stage, eggs may be seen on stool examination.

3. **Opisthorchiasis** is endemic to Southeast Asia and the states of the former Soviet Union, though in recent years outbreaks in visitors to Italy have been reported [19, 20]. Two to three weeks after ingestion of raw fish, symptoms of fever, abdominal pain, headache, diarrhea, nausea and vomiting can be seen, occasionally accompanied by jaundice. Laboratory abnormalities may lag slightly behind the clinical course and consist of cholestatic liver enzyme abnormalities with peripheral eosinophilia. The severity of cholestasis correlates with degree of eosinophilia, which is typically very marked and commonly exceeds 10,000/μL. CT can reveal hypodense lesions in the liver. Eggs are not detected in the stool until at least 5 weeks following infection. Symptoms respond quickly to treatment and eosinophilia normalizes within 3 months [19-22].

4. **Clonorchiasis** is endemic to East and Southeast Asia. Unlike opisthorchiasis acute infections with *Clonorchis* spp. are typically clinically asymptomatic or with subtle, nonspecific complaints [23]. However, particularly in travelers, an acute syndrome with right upper quadrant pain, nausea, and occasional fever or cough may develop [23, 24]. Eosinophilia is typically greater than 1,500/μl, and eggs appear in the stool 3-4 weeks following infection [24].

5. **Gnathostomiasis** is endemic in most Asian countries and is increasing in prevalence in Latin America. Larvae are ingested from raw fish, shellfish, eel, frog, or chicken. Within 24-48 hours following ingestion of contaminated food, patients may develop severe abdominal pain with nausea, vomiting, and diarrhea along with generalized malaise, urticaria, headache, and fever. Often there is a marked eosinophilia during this time [25-28]. Following this acute stage, migratory swellings typically develop (see below). Occasionally, visceral involvement may occur in the setting of migration of larvae through the lungs (effusions, cough, hemoptysis), the abdomen (mass, abdominal pain, hematuria), the eyes (anterior uveitis), and even the CNS (see Table 3) [25].

6. **Paragonimiasis** is most commonly caused by *P. westermani* in Southeast Asia (other species are found elsewhere). Infection is usually acquired through ingestion of uncooked crab or crayfish. Fever is a frequent (but not universal) finding, along with dyspnea, chest pain, cough, and hemoptysis that begin several months after exposure [29-31]. Eosinophilia is typically marked [32], and peaks 1-2 months following the onset of illness (correlates with pleural involvement). The eosinophilia slowly decreases as the parenchymal disease evolves [33].

7. **Capillariasis** due to *Capillaria hepatica* is an extremely unusual illness (<100 reported cases) that can be acquired through ingestion of contaminated soil [34, 35]. Patients present with fevers (83%), hepatomegaly (87%), and eosinophilia (87%)[36]. Liver transaminases are commonly elevated, and very rarely, elevations of bilirubin and jaundice are seen [36]. The severity of infection appears proportional to the number of mature eggs ingested [37, 38]. Imaging reveals space-occupying lesions [34, 38, 39], and liver biopsies can show adult worms, eggs, and/or inflammatory cells with eosinophils and granulomata [36].

III.A.2 Eosinophilia with fevers and myositis in the traveler

1. **Trichinellosis** is caused by consumption of undercooked domestic pork, wild boar, bear, deer and walrus [40-43]. The average incubation period is 1-4 weeks depending on larval load and the *Trichinella* species [40, 41, 44, 45]. Approximately 90% of patients present with an absolute eosinophil count >1,000/μl. Nearly all patients have fever and myalgia as presenting complaints (occasionally preceded by diarrhea), and edema (including periorbital or facial) is seen in the majority of patients. CPK is elevated in 60-85%, and liver transaminases may be elevated 5-10 times above normal levels. The acute illness typically improves in 2-5 weeks, but myalgia can take months to resolve. Eosinophilia can take 6 months or longer to normalize [40, 41, 44-47].

2. **Muscular sarcocystosis** has occurred in travelers in several recent outbreaks after visiting rural peninsular Malaysia [48], Pangkor Island [49], and Tiomen Island [50]. In these outbreaks, 2-8 weeks following exposure patients developed fever and myalgia, sometimes preceded by a short diarrheal illness. Other prominent symptoms were fatigue and headache. Less commonly seen were weakness, rash or muscle swelling (including facial swelling). Commonly the muscles of mastication, back muscles, and calf muscles were involved. Eosinophilia and CPK elevations are very frequently seen (although not universally), and may not develop until after initial clinical presentation. Symptoms usually last for approximately 2 months (although relapse is possible). Cardiac involvement has been reported [51, 52].

III.A.3. Eosinophilia with fevers and CNS symptoms in the traveler—See section VI “Eosinophilic meningitis”

III.B. Infectious causes of eosinophilia and gastrointestinal symptoms (without fever) in the traveler

Travel-associated diarrhea is overwhelmingly associated with bacterial causes [53]. However, in travelers returning from the low and middle-income countries, helminth infections are the most common etiology of abdominal complaints when accompanied by eosinophilia [54, 55].

1. **Hookworm infections** are endemic worldwide and typically cause abdominal pain, increased flatus, nausea, vomiting, and diarrhea approximately 30-45 days following infection, coinciding with a significant rise in peripheral blood eosinophils [56]. Loeffler's syndrome (transient pulmonary infiltrates due to larval migration through the lungs) with low-grade fevers may occur prior to the development of abdominal symptoms (approximately 8-21 days after infection) in some cases, but most people are asymptomatic in the pre-patent period [56]. Marked eosinophilia frequently develops (1500-4,000/μL) and often diminishes to a small degree at the time of patency. Eggs appear in the stool 1-2 months following exposure. Following treatment, eosinophil counts typically normalize within 2-3 months [56].

2. **Strongyloidiasis** is rarely acquired in the short-term traveler [57], likely due to the need for bare skin to have prolonged contact with soil for transmission to occur, as well as the reduced relative frequency of travel to Africa and Asia, where it is most frequently acquired. It causes mild eosinophilia (in 88% of infected patients) [58] that can be associated with diarrhea, abdominal discomfort, or no symptoms at all [59].

3. ***Cystoisopora belli*** **(formerly** ***Isospora belli*****)** is a protozoan found worldwide, especially in tropical and subtropical areas. In the otherwise healthy host, it causes a self-limited diarrheal illness with transient fever and weight loss that can last 2-6 weeks, but can take longer to resolve in rare cases [60-63]. In the setting of immunosuppression, diarrhea with malabsorption, dehydration, and weight loss is common. Symptoms may persist for months, and may be the presenting manifestation of underlying malignancy, HIV, or primary immunodeficiency

[64-67]. In approximately 50% of patients a mild eosinophilia is seen over the course of illness [68, 69].

4. **Echinostomiasis** (*Echinostoma* spp.) is caused by intestinal flukes endemic in East Asia and is acquired through ingesting uncooked fresh or brackish water fish, shellfish, and amphibians [70]. Within a few weeks, a diarrheal illness with abdominal pain can be seen with accompanying eosinophilia that peaks 4 weeks following infection [71].

III.C. Infectious causes of eosinophilia and allergic or dermatologic/soft tissue symptoms in the traveler

1. **Anisakiasis** is most common in Japan and Europe (mostly Spain). It causes a spectrum of illness that ranges from severe acute abdominal pain secondary to edema of the stomach or small intestine to a purely allergic reaction (i.e. urticaria, angioedema, or anaphylaxis) without abdominal symptoms. Some patients present with an overlapping symptom complex that includes abdominal pain and urticaria or angioedema (rarely anaphylaxis) [72]. The key to the diagnosis is eliciting the history of recent raw fish ingestion. In the case of acute upper gastrointestinal symptoms, raw fish is often ingested within hours of symptom development whereas those with more lower GI tract symptoms may present several days following raw fish consumption. Typical CT imaging in the cases with abdominal symptoms reveals thickened, edematous walls of the stomach or proximal small intestine [73]. Eosinophilia typically does not develop until several days following the onset of clinical symptoms [74].

2. **Ascariasis** is endemic worldwide and is acquired through fecal-oral contamination. With heavy inoculum, *A. lumbricoides* infection can cause generalized urticaria shortly after infection [7], although typically the infection is subclinical.

3. **Cutaneous larva migrans** is a common travel related infection acquired on beaches in tropical areas. Days to weeks following skin contact with contaminated sand, linear, serpiginous, highly pruritic cutaneous lesions develop due to dog/cat hookworm (*Ancylostoma canium, A. braziliense*) larvae penetrating intact skin. Pruritus and lesions last several weeks to months if not treated. Mild peripheral blood eosinophilia is seen in <10% of patients [75-77].

4. **Onchocerciasis** is transmitted by the bite of the black fly in much of Africa. In travelers, symptoms often start within months following exposure, but there may be a significant time interval between exposure and symptom development [78-80]. The most common manifestations are pruritus, rash (commonly a papular dermatitis), and fixed extremity swelling [79-82]. In 80% of travelers, marked eosinophilia is seen (1,000-2,000/μL) [55, 80, 81], but microfilariae are difficult to find in skin snips from travelers due to the relatively low burden of infection that results from a short exposure [80, 83].

5. **Lymphatic filariasis** is rarely found in returned travelers, although it has been reported [78, 84]. Symptoms usually develop 1-2 months following infection [85]. Extremity edema (proximal>distal) or scrotal swelling which may be associated

with a painful lymph node and mild to marked eosinophilia are the most notable findings [84].

6. **Loiasis**, caused by *Loa loa* in travelers to Central/West Africa, is frequently very symptomatic in those acquiring the infection through travel [86]. However, microfilariae are not often detected in the blood in these patients [87, 88]. The minimum latency period appears to be 4-6 months [88], but it may take years [89] following infection for symptoms to develop. In the visitor and expatriate, Calabar swellings (migratory angioedema) on the limbs and/or face are the most common symptoms. The swellings are non-painful and non-pruritic, but can occasionally appear erythematous, and typically resolve in 1-3 days [90]. Other symptoms commonly seen are pruritus and urticaria [88]. Eosinophilia is essentially universal in non-endemic patients, typically marked (average is 3,000-4,000/μL) [86, 87, 89] and may mediate some of the pathologic findings in this infection.

7. **Gnathostomiasis,** acquired most commonly from uncooked fish in Southeast Asia or Latin America causes subcutaneous nodules or swellings, which migrate to various areas of the body and can last for years. It may begin shortly after an acute febrile gastrointestinal illness, but this stage may be subclinical or occur weeks to months prior to onset of cutaneous symptoms [25]. The swellings frequently last 1-2 weeks at a time and are associated with pruritus, erythema, pain [25, 91], or without other symptoms [92]. In one series of patients with chronic migratory swellings, only 50% had eosinophilia (900-2,000/μl) and eosinophilia normalized following treatment [92].

8. **Paragonimiasis** can cause non-tender, migratory subcutaneous nodules which rarely appear at the time of pulmonary involvement [31, 32] but more commonly precede lung symptoms, or can occur without other symptoms altogether [32] [93]. Lesions are typically on the abdominal wall [94], and have rarely been reported in travelers [93].

Eosinophilia in the Traveler Conclusions—Despite extensive evaluation, up to 60% of travelers with eosinophilia never have an underlying cause defined for their eosinophilia identified [55, 58]. In the cases where patients remain asymptomatic and testing is negative, it is reasonable to simply monitor the eosinophil count periodically, as most eosinophilia in these cases will self-resolve. Another approach is to treat empirically for soil transmitted helminths and flukes with a one-day treatment of albendazole, ivermectin, and praziquantel, and monitor for eosinophil resolution.

IV. Eosinophilia in Indigenous Population (Immigrant/Refugees) and Long-Term Residents

All of the short term travel-associated infections can be seen in these patients, particularly in immigrants who return abroad to visit friends and relatives, as they are more likely to acquire new helminth infections on short trips compared to tourists [95]. Patients with chronic, longstanding exposure to parasitic infections typically have more subtle or different symptoms, and eosinophilia, when present, is less impressive. Therefore, for some infections

already mentioned, we again discuss them here, highlighting the differences in symptom complexes in the immigrant/refugee [10, 86, 87, 96, 97].

IV.A. Infectious causes of eosinophilia and gastrointestinal symptoms in the immigrant

1. **Echinococcosis** due to *E. granulosus* (hydatid cysts), while not commonly associated with eosinophilia [98, 99] can cause intermittent eosinophilia [100-104] likely due to spontaneous cyst leakage or occult intrabiliary rupture [105]. However, immediately following a clinically significant cyst rupture (often iatrogenic), eosinophil counts are transiently suppressed (<500) while neutrophils significantly increase [106-108]. Eosinophils then progressively rise to moderately high levels over the next several days to weeks [108-110]. Abdominal pain with an elevated bilirubin is seen if the cyst ruptures into the biliary tree. Cysts can also grow large and cause symptoms related to mass effect. Less commonly, cysts develop in the lungs causing respiratory symptoms or pain [99]. *E. multilocularis* is associated with eosinophilia less frequently that *with E. granulosis*, but rarely, mild eosinophil elevations may be seen [111-114].

2. **Ascariasis**, particularly in children, can cause abdominal complaints in patients from endemic areas due to heavy worm burdens, which can cause intestinal obstruction [115], appendicitis [116], or cholangitis [117]. In chronic infection, eosinophilia is not common and when present is mild [118-120].

3. **Trichuriasis** can, in situations where there are extremely large worm burdens, cause a dysentery syndrome that is associated with a mild to marked eosinophilia, severe iron deficiency anemia, and rectal prolapse (the latter 2 more commonly seen in children) [121-123].

4. **Strongyloidiasis** can persist for many decades following infection because of its autoinfective cycle. Although chronic strongyloidiasis is typically asymptomatic, clinical findings, including chronic abdominal discomfort, excessive flatus and/or diarrhea, are present in up to 16% of patients [124, 125]. Refugees with proven *S. stercoralis* infection have eosinophilia approximately 25% of the time [96].

5. **Opisthorchis** and **Clonorchis** are biliary flukes that, while distributed differently geographically, in chronic form are largely indistinguishable clinically. Chronic infections are typically asymptomatic or accompanied by nonspecific abdominal symptoms (pain, flatulence, dyspepsia). Alterations in liver enzymes or bilirubin are not seen unless complications develop (i.e. cholangitis, cholelithiasis, cholangiocarcinoma). Most patients have a mild eosinophilia (<1,000/μl). Ultrasound findings of increased periductal echogenicity (indicating periductal fibrosis) are specific for these flukes. It is important to make the diagnosis given the significantly elevated well-established risk of cholangiocarcinoma caused by chronic infection [126-130].

6. ***Hymenolepis nana*** is a common intestinal tapeworm found in tropical and subtropical countries [131-134]. It can be transmitted person to person and has an autoinfective cycle [134]. While typically asymptomatic, it can cause diarrhea and

abdominal pain, and has highest rates in children [133]. Eosinophilia may be absent [135, 136] or be as marked (up to 2,000/μL) [137].

7. Chronic ***S. mansoni*** **infection** may result in what has been termed **"hepatosplenic schistosomiasis,"** which is caused by schistosome eggs occluding the portal venules, causing periportal fibrosis and pre-sinusoidal portal hypertension. With lifelong exposure, hepatomegaly and/or splenomegaly peaks in the 2nd-3rd decade of life along with symptoms of bloody stools and colicky abdominal pain [138, 139]. Varices can develop but cirrhosis is not seen [165]. Mild eosinophilia (<1000/μL) is seen in approximately 50% of patients [139].

IV.B. Infectious causes of eosinophilia and pulmonary symptoms in the immigrant

1. **Paragonimiasis** is acquired in East Asia, the Americas, and Central/West Africa through ingesting uncooked crabs, crayfish, or wild boar flesh. Patients from endemic areas frequently present with a subacute to chronic cough, often mildly productive with blood-streaked sputum [140-143]. Up to 17% of patients with lung infections have no symptoms [33]. The most common imaging findings are effusions (20-60%) or pleural thickening seen adjacent to a pulmonary nodule. Consolidation or cavitary lesions can also be seen [141, 144, 145] and may be mistaken for tuberculosis. Moderate to marked eosinophilia helps distinguish paragonimiasis from tuberculosis, although up to 25% of patients can have a normal peripheral eosinophil count [32, 33, 146, 147].

2. **Echinococcal cyst** of the lung causes a rise in eosinophils several days following rupture. Patients are symptomatic with chest pain and/or cough. X-ray frequently misdiagnoses ruptured lung cysts as pneumonia [108] or pneumothorax [148].

3. **Tropical pulmonary eosinophilia** is an immunologically mediated hypersensitivity to *W. bancrofti* or *B. malayi* seen rarely in patients from regions where lymphatic filariasis is endemic. Patients present with an asthma-like illness, with nocturnal cough, wheezing, dyspnea, but have a much higher eosinophilia (nearly always >3,000/μL, often 10,000-20,000/μL). Radiographs often demonstrate an interstitial infiltrate. Symptoms and eosinophilia have a dramatic improvement with treatment for lymphatic filariasis [149, 150].

4. **Chronic schistosomiasis** can result in eggs traveling anywhere in the body where they are encased in an eosinophil-rich granuloma. Therefore, rarely in chronic schistosomiasis pulmonary angiopathy and cor pulmonale have been described due to migration of eggs to the lungs [151].

IV.C. Infectious causes of eosinophilia and genitourinary symptoms in the immigrant

Chronic schistosomiasis caused by *S. haematobium* is a common infection in Africa and should be suspected in a patient from there with symptoms of hematuria, chronic suprapubic pain, or obstructive uropathy [11, 151]. Hematuria and dysuria can develop within months of infection (due to bladder ulcerations}, occur intermittently, and hydronephrosis may develop within the first 3 years of infection [11, 152]. In women, eggs can also deposit around the cervix, vagina, and ovaries [151], and has been associated with infertility and

increased susceptibility to HIV [153, 154]. While eosinophils may be elevated early in chronic infection, it typically decreases over subsequent years.

IV.D. Infectious causes of allergic and/or dermatologic symptoms in the immigrant

1. **Echinococcal cyst** can cause anaphylaxis following rupture into the peritoneal or pleural cavity [99].
2. **Strongyloidiasis** can cause chronic urticaria or "larva currens," presumably as a reaction to migrating filariform larvae. These cause extremely pruritic serpiginous lesions found typically on the buttocks, thighs, or lower torso [125]. *Larva currens* is extremely uncommon in an acute infection, and is more often seen years after the infection was initiated [124, 155]. If the patient becomes immunosuppressed with steroid use or HTLV-1, dissemination can occur, and dissemination to the skin causes purpuric lesions [156]. Eosinophilia is rarely seen (approximately 16% of cases) [187] in the setting of dissemination.
3. **Sparganosis** is most often acquired in East Asia from ingesting uncooked amphibian or reptile meat or drinking unpurified stream water [157]. In its most common form, sparganosis causes a firm subcutaneous mass, however this is not associated with eosinophilia [157-161]. Leukocytosis and marked eosinophilia is seen, however, with the proliferative form (*Sparganum proliferum*) that is accompanied by systemic illness and disseminated serpiginous cutaneous lesions that are extremely pruritic [162-164]. This form has also been reported to manifest years after the typical subcutaneous nodules have resolved [163]. Eosinophilia can also be seen with CNS manifestations (see Table 3).
4. **Onchocerciasis** usually presents with chronic pruritic papular dermatitis (mimicking atopic dermatitis). Depigmentation, scaling, lichenification, and diffuse papules may be seen on the lower extremities in chronic infection [165-167], and there may be enlarged inguinal lymph nodes as well [168]. Approximately 80% will have mild eosinophilia [167]. However, there is an immunologically hyper-reactive form termed localized onchocercal dermatitis (or "sowda") that is associated with hyperpigmentation, reactive edema and few (if any) microfilariae in the skin. Eosinophilia is typically marked in these patients [169-171], but the diagnosis is difficult to make definitively and often relies on serology or a typical post-treatment response.
5. **Loiaisis** in immigrants from endemic areas is often clinically asymptomatic, although it can present as an eyeworm or with Calabar swellings. Only ∼50% have mild eosinophilia (<1,000/μl) although usually microfilaremia can be detected on mid-day blood exam [86, 87, 172].
6. **Lymphatic filariaisis** is a chronic filarial infection that may present acutely with retrograde adenolymphangitis or subacutely with lymphedema of the extremities or scrotum [173-175]. Approximately 20% of patients chronically infected will have eosinophilia [176].

Eosinophilia in the Immigrant/Refugee Conclusion—The immigrant/refugee coming from parasitic endemic areas with unexplained eosinophilia, even without symptoms, should have an infectious workup targeting previous exposures.

V. Infectious Causes of Eosinophilia in the Patient Irrespective of Travel/ Exposure History

Important considerations in approaching eosinophilia in these patients are preexisting diagnoses and medications (even if started years ago). Mild eosinophilia can commonly be caused by atopic dermatitis and asthma. However, in patients with eosinophilia over 1500/μL, an alternative diagnosis should be sought. Asymptomatic eosinophilia in a patient without a history of travel outside of the US and Europe is unlikely to have an infectious cause, with one exception being strongyloidiasis in areas of the US and Europe where it is still endemic (see below).

V.A. Infectious causes of eosinophilia and pulmonary symptoms

1. **Allergic bronchopulmonary aspergillosis** (ABPA) results in increased airway hyper-responsiveness secondary to allergic hypersensitivity to *Aspergillus* spp. colonizing the airways. Patients with chronic lung disease and bronchiectasis, particularly patients with cystic fibrosis, are more likely to develop ABPA. Blood eosinophilia (>500/μL) is a criteria to make the diagnosis, but the eosinophils in the peripheral blood are commonly >3,000/μL particularly during exacerbations [177].

2. **Coccicioidomycosis** has been increasing in the Southwest US in recent years [178]. In localized pulmonary infection, mild eosinophilia may be seen in 30-50% of cases [179, 180]. In disseminated (particularly liver and skin) disease, marked eosinophilia can be seen [180-182].

3. **Tuberculosis** in North America and Europe today is typically seen in the context of HIV or immigration, and so patients may have multiple reasons for developing eosinophilia. In a series prior to 1943, approximately 10% of TB patients had a very mild eosinophilia (6-10%), but it was never seen in the setting of high fevers [183] (i.e. TB is not in the differential diagnosis of fever and eosinophilia).

4. **Paragonimiasis** acquired in the United States is caused by infection with *P. kellicotti*. In recent years nearly all cases have been acquired in Missouri [184] as a result of eating raw infected crayfish. The average incubation period was ∼4 weeks (range 2-12 weeks). All patients had cough, pleural effusion, and eosinophilia (mean 1,600 [range 800-3,600/μL]), and most had fever and weight loss [184]. Imaging revealed a nodule (“worm nodule”) connected to the pleura by a linear track in 50% of patients, and rarely patients had pneumothoraces [185]. Unlike *P. westermani* acquired outside of the United States, paragonimiasis acquired in the US was not found to have cavitary lesions or bronchiectasis [185].

5. ***Dirofilaria immitis*,** the dog heartworm, is a zoonosis that can be transmitted from dogs to humans through mosquitos. It causes an asymptomatic pulmonary nodule

in 50% of people. Those with symptoms experience cough, chest pains, and fevers. Only ∼10% of patients have eosinophilia [186].

6. **Myiasis** is the term given to the development of fly larvae in human tissues. Most commonly this occurs in subcutaneous sites due to *Dermatobium* spp. (botfly in South/Central America) and *Cordylobia anthrophaga* (tumbu fly in Africa); however, these do not cause eosinophilia. Invasive fly larvae that have the ability to penetrate beyond subcutaneous tissues, however, can cause marked eosinophilia so dramatic it can mimic hypereosinophilic syndrome. While *Hypoderma bovis* and *H. lineatum* are the most common cause of invasive myiasis, it is altogether an extremely rare entity. *Hypoderma* spp. are found in the Northern Hemisphere (including the US and Canada), primarily where cattle are raised. After eggs are inadvertently laid on human skin, hatched larvae burrow and migrate through subcutaneous tissues for weeks, occasionally to deeper tissues (pleura, pericardium, brain)[187-192].

V.B. Infectious causes of eosinophilia and abdominal symptoms

1. **Basidiobolomycosis** is an emerging fungal infection that causes mass or inflammatory lesions in the gastrointestinal tract, most commonly the colon. Sporadic cases have occurred worldwide, but 40% have been in the southwestern part of the United States. Patients present with abdominal pain and GI symptoms concordant with the location of their lesion(s). Eosinophilia has been seen in all published cases, typically between 1,000-2,000/μL [193, 194].

2. **Visceral larva migrans (VLM)** is caused by ingesting dirt contaminated with dog/cat feces containing *Toxocara canis* or *T. cati*. This is primarily seen in children with pica (average age 1-4 years). Symptoms are proportional to ingested inoculum, and fevers, abdominal pain with hepatomegaly (due to eosinophilic abscesses), and asthmalike difficulty breathing is frequently seen. Eosinophilia is very pronounced, with counts as high as 15,000-100,000/μL, and the eosinophilia can take years to fully resolve. In older children (7-10 years old) and rarely adults, ocular involvement with eosinophilia can be seen without other systemic symptoms. Ingesting a very low inoculum can cause an asymptomatic eosinophilia that can persist for over a year [195-198]. Extremely rarely, cardiac [199, 200] or neurologic complications (see Table 3) may result.

3. **Strongyloidiasis** is endemic worldwide and remains one of the few helminth parasites capable of being acquired in the US. It is found in areas of low socioeconomic status in the Appalachian regions of Kentucky [201], Tennessee, North Carolina, and Virginia [202], and possibly other areas in the southern US which have not been surveyed recently. Patients can have nonspecific abdominal bloating, but frequently have no symptoms whatsoever. Eosinophilia (typically mild) is seen in less than half of patients [202].

V.C. Infectious causes of eosinophilia and dermatologic symptoms

1. **Eosinophilic folliculitis** is seen in the setting of HIV/AIDS, but has been reported following bone marrow transplant and hematologic malignancy. Pruritus typically develops on the trunk. In the setting of HIV, eosinophilic folliculitis causes mild eosinophilia [203].
2. **Crusted scabies** results from a significant infestation of the mite and the failure of the host to mount an adequate immune response. Thus it is seen in patients with HIV/AIDS or other underlying diseases associated immunosuppression. In approximately 50% of patients, marked eosinophilia can develop along with overt skin abnormalities [204].

Eosinophilia in the Non-Traveler Conclusion—The asymptomatic non-traveler with an eosinophil count <1,500/μL can be safely monitored periodically to ensure eosinophils are not rising over time. However, patients with symptoms or with marked eosinophilia should undergo further evaluation to determine an etiology, which will commonly be allergic (e.g. eosinophilic enteritis), autoimmune (e.g. sarcoidosis), myeloproliferative (e.g. mastocytosis), or malignant (e.g. Hodgkin's lymphoma) in nature.

VI Eosinophilic Meningitis

Eosinophilic meningitis, which may or may not be associated with peripheral eosinophilia, has a limited number of possible infectious etiologies. The most common infectious causes, presenting features, and cerebral spinal fluid (CSF) features are presented in Table 3. It is important to note that occasionally CSF will not be eosinophil-rich very early in the course. Therefore, if there is suspicion of one of the causes from Table 3 as the etiology for meningitis, repeat lumbar puncture several days into illness may be necessary to identify CNS eosinophilia.

VII Final Remarks

In summary, the type of patient, their exposure history, and symptom complex (or lack thereof) should guide the evaluation of unexplained eosinophilia. Rarely, in the case of immune dysfunction/immunodeficiency, eosinophilia may be present in the context of an infection that by itself does not normally cause eosinophilia. Therefore, in complicated cases, it is often necessary for the infectious disease specialist to work alongside colleagues with differing expertise in determining the etiologies for both infectious and non-infectious eosinophilia.

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Key Points

- Eosinophilia >1,000/μL in the setting of acute illness essentially excludes bacteriaor viruses as an etiology for the acute illness.
- Strongyloidiasis is found worldwide, including in areas of the US. Anyone witheosinophilia who comes from an endemic area should have a serologic testperformed if available.
- Acute schistosomiasis should be suspected in any traveler returning from Africawith eosinophilia and fever
- Immigrants or refugees can have very subtle or no symptoms from parasiticinfections and often have very mild eosinophilia
- Some helminth infections can persist for many years following acquisition.

Table 1

Infectious causes of eosinophilia and likelihood of seeing listed etiologies in practice in North America or Europe as well as geographic locations of acquisition, duration of eosinophilia, and main anatomic site affected

Eosinophilia Cause (Infectious etiology)	Main Geographic Location(s)	Duration of Eosinophilia[1]		Main Anatomic Site(s) of Infection
		Acute	Chronic	
Common causes of acute eosinophilia seen in clinical practice in North America and Europe[1,2]				
Coccidioides spp.[3]	Southwest US	X		Lungs, skin, CNS, liver
Echinococcus granulosus (days following rupture)	Europe, South America, Australia	X		Liver, lung
Fasciola spp.	South America, Europe, Asia, Egypt	X		Liver
Schistosoma haematobium	Throughout Africa, specifically the Nile, large rivers and lakes as well as smaller bodies of freshwater	X	X	Genitourinary tract
Schistosoma mansoni	Africa, South America, Carribean	X	X	Liver, GI
Trichinella spp.	Worldwide	X	X	Muscle, GI
Causes of acute eosinophilia RARELY seen in clinical practice in North America and Europe				
Anisakis spp.[4]	Japan, Europe	X		GI
Ascaris lumbricoides	Latin America, Sub-Saharan Africa, Asia, Western Pacific	X		GI
Angiostrongylus cantonensis	Southeast Asia, Pacific Basin, Africa, Caribbean, Central America	X		CNS
Cystoisospora belli (Formerly *Isospora belli*)	Tropical regions	X	X	
Dirofilaria immitis	Worldwide	X		Lung
Gnathostoma spp.	Southeast Asia, Latin America	X	X	Subcutaneous tissue, CNS
Hookworm (*A. duodenale* and *N. americanus*)	Latin America, Sub-Saharan Africa, Asia, Western Pacific	X	X	GI
Paragonimus kellicotti	Mississippi River drainage basin, US [192], most from Missouri	X	X	Lungs, subcutaneous tissue, CNS
Sarcocystis spp.	Southeast Asia, especially Malaysia	X		Muscle, GI Subcutaneous, skin
Schistosoma intercalatum	Central and West Africa	X	X	Liver, GI
Schistosoma japonicum	Indonesia, China, Southeast Asia	X	X	Liver, GI
Schistosoma mekongi	Cambodia, Laos	X	X	Liver, GI
Toxocara spp. (Visceral larval migrans)	Worldwide	X	X	Liver, eye, lung
Causes of acute eosinophilia EXTREMELY RARELY seen in clinical practice in North America and Europe				
Basidiobolus ranarum	Worldwide, especially South US	X		GI
B aylisascaris procyonis	North America	X		CNS, eye, liver, lung
Capillaria hepatica	Worldwide	X		Liver

Eosinophilia Cause (Infectious etiology)	Main Geographic Location(s)	Duration of Eosinophilia[1]		Main Anatomic Site(s) of Infection
		Acute	Chronic	
Dicrocoeliasis *(Dicrocoelium dendriticum)*	Europe, Middle East, northern Asia, North America, northern Africa	X		Hepatobiliary, GI
Echinostoma spp.	Asia	X		GI
Myiasis (esp. *Hypoderma* spp.)	Northern Hemisphere	X		Subcutaneous, skin, rarely deeper tissues
Sparganosis (*Spirometra* spp., *Sparganum proliferum*)	Asia, rare sporadic reports worldwide	X		Subcutaneous, skin, eye, CNS
Tropical pulmonary eosinophilia	South Asia	X	X	Lungs
Trichostrongyloides spp.	Worldwide	X	X	GI
Causes of chronic eosinophilia COMMONLY seen in clinical practice in North America and Europe				
Strongyl oides stercoralis[5]	Worldwide	X	X	GI, skin
Clonorchis spp.	East Asia	X	X	Hepatobiliary
Opisthorchis spp.	Southeast Asia, former Soviet Union	X	X	Hepatobiliary
Paragonimus spp. (non-kellicotti)	Southeast Asia, Central/West Africa, Latin America	X	X	Hepatobiliary
Causes of chronic eosinophilia RARELY seen in clinical practice in North America and Europe				
Loa loa	Central/West Africa	X	X	Subcutaneous tissue, eye
Lymphatic filariasis (*W.bancrofti, B. malayi*)	Sub-Saharan Africa, Southeast Asia (Including India), Western Pacific	X	X	Lymphatics, blood
Mansonella ozzardi	Latin America, the Carribean	X	X	Blood
Mansonella perstans	Sub-Saharan Africa, South America	X	X	Blood
Mansonella streptocerca	Africa	X	X	Skin
Onchocerca volvulus	Sub-Saharan Africa	X	X	Skin, subcutaneous tissue

[1] While many diseases listed here can present as either chronic or acute eosinophilia (as indicated by this column), disease etiologies have been grouped by their most common presentations.

[2] Some listed processes are more likely to cause eosinophilia than others. This table is organized by what the clinician in North America or Europe is most likely to see in terms of causes of eosinophilia in their clinical practice (which takes into account generally how often the organism causes eosinophilia and how common people are infected and seek medical attention).

[3] Most often seen in Western US, very rare in Europe

[4] When seen in Europe is mostly the Netherlands, Spain, and Italy, extremely rare in the US.

[5] Strongyloidiasis is by far the most common infectious cause of chronic eosinophilia

Table 2
Parasitic causes of eosinophilia and diagnostic tests of choice

Parasite	Diagnostic test
Angiostrongylus	Larvae in CSF, PCR of CSF (CDC).
Anisakis spp	<12 hrs from raw fish/squid ingestion: EGD for visualization of larvae >12hrs from ingestion: Anti-Anisakis IgG and IgA [86]
Ascaris lumbricoides	Eggs in stool, serology
B aylisascaris procyonis	Larva or larval tracks seen on ocular exam. Serology (EIA, reference lab)
Basidiobolus ranarum	Fungal elements on histopathologic exam, fungal culture of surgical specimen.
Brachylaima spp.	Eggs in stool
Capillaria hepatica	Eggs/worms on liver biopsy Serology—high titer (Low titer indicates spurious infection from ingesting infected liver)
Coccidioides spp.	Fungal elements on histopathologic exam, fungal culture of surgical specimen, serology (complement fixation).
Clonorchis spp.	Eggs in stool, Serology (not available in US)
Cystoisospora belli (formerly *Isospera belli*)	Oocysts in stool
Dicrocoelium dendritium	Ova in stool (after abstaining from ingestion of liver)
Dirofilaria immitis	Worm in surgical specimen, appearance on radiograph.
Echinococcus granulosus	Combination of imaging (appearance on ultrasound or CT) and serology (50-75% sensitive)[126]
Fasciola spp.	Serology Eggs in stool (late in disease)
Gnathostoma spp.	Larvae in biopsy, serology (reference lab)
Hookworm (*A. duodenale* and *N. americanus*)	Eggs in stool
Loa loa	MF in mid-day blood (concentrate with filtration) Serology (Nonspecific filarial antibody, reference lab). Presence of eyeworm
Lymphatic filariasis (*W. bancrofti, B. malayi*)	MF in nighttime blood (concentrate with filtration) Serology (Nonspecific filarial antibody, reference lab) Circulating filarial antigen card test (not available in US)
Mansonella perstans, M. ozzardi	MF in blood (concentrate with filtration)
Mansonella streptocerca	Skin snips
Onchocerca volvulus	Skin snips, Serology (Nonspecific filarial antibody, reference lab)
Opisthorchis spp.	Eggs in stool
Paragonimus spp.	Serology (ELISA or Immunoblot)[48, 193]. Eggs in sputum (sensitivity 60%, 2 samples) [194] Eggs in stool (insensitive) [166].
Sarcocystis spp.	Muscle biopsy
Schistosoma haematobium	Eggs in urine, Serology
Schistosoma intercalatum	Eggs in stool, Serology
Schistosoma japonicum	Eggs in stool, Serology
Schistosoma mansoni	Eggs in stool/rectal biopsy, Serology
Schistosoma mekongi	Eggs in stool

Parasite	**Diagnostic test**
Strongyloides stercoralis	Serology (SSIR and NIE IgG LIPS sensitivity 100%, spec 100%) [195], Larvae in stool (insensitive except in hyperinfection)
Sparganosis (*Spirometra* spp., *Sparganum proliferum*)	Sparganum in infected tissue. For CNS disease, positive CSF ELISA, typical CT findings, and history of eating frogs or snakes from endemic area strongly supports diagnosis [205]
Toxocara canis (Visceral larva migrans)	Serology. Larvae in liver biopsy (rarely seen).
Trichinella spp.	Serology, muscle biopsy
Trichostrongyloides spp.	Eggs in stool

Table 3

Infectious causes and symptoms of eosinophilic meningitis

Organism	Risk	Symptoms	MRI Abnormalities			Eosinophilia	
			White Matter Increased Signal on T2/FLAIR	Hydroce phalus	Mass Lesion(s)	Frequency of Peripheral eosinophilia	CSF Degree of Eosinophilia
Angiostrongylus cantonensis [206-208]	Consumption of raw snails, frogs, shellfish, fish, or contaminated vegetables or water.	HA, NV	X			77-90%	+++
Baylisascaris procyonis [209-211]	Ingestion of eggs in raccoon feces (toddlers/young children)	Fever, ataxia, development al regression, SZ	X	X		5-45%	+++
Coccidioides spp. [180, 182, 212-214]	Residing in endemic area. Males of Hispanic, African, and Asian ethnicity. Immunocompromised (HIV, steroid use).	HA, AMS, fever		X	X	19-75%	+/-
Gnathostoma spp. [25, 206, 215]	Ingestion of uncooked fish, amphibians, reptiles, poultry, pork from endemic area (see Table 1)	Sudden pain followed by limb paralysis, urinary retention, AMS	X			~50%	++
Paragonimus spp. [216]	Consuming uncooked freshwater crabs or crayfish	HA, NV, paralysis, SZ			X	~88%	+/-
Schistosoma spp. [217-221]	Freshwater contact in an endemic area (see Table 1)	HA, AMS, SZ, limb weakness			X	>50%	+/-
Spirometra spp., *Sparganum proliferum* [205, 222]	Ingestion of snakes, frogs, or untreated freshwater	Sz, hemiparesis, HA	X	X	X	~25%	ND*
Taenia solium (Neurocysticercosis) Sotelo, 1985; Earnest, 1987; Shandera, 1994; Castillo-Iglesias, 2005; Monteiro, 1993}	Ingestion of stool from a human infected with pig tapeworm.	SZ, HA, NV, AMS		X	X		+
Toxocara canis or *T. cati* [223, 224]	Ingestion of eggs in dog/cat feces	AMS, SZ, paralysis.			X	>50%	++

HA Headache, AMS altered mental status, SZ seizure, NV nausea/vomiting

+ <50 eosinophils/μL

++ 50-500 eosinophils/μL

+++>500 eosinophils/μL

* No Data