IN BRIEF

Eosinophilia

Chloe E. Opper, MD,*† Kristina L. Simeonsson, MD, MSPH,* Karin Hillenbrand, MD, MPH*

*Brody School of Medicine at East Carolina University, Greenville, NC
†ECU Health Medical Center, Greenville, NC

INTRODUCTION

Eosinophils are differentiated white blood cells containing cytoplasmic granules that stain pink with eosin. Differentiation and survival are promoted by cytokines, especially interleukin-5; therefore, an increase in eosinophils reflects inflammation. Eosinophil granules contain proteins that are cytotoxic to parasites and have a role in maintaining the body's inflammatory response, but they can also cause organ damage when released in tissues. Recognition of eosinophilia is important for identifying cause and mitigating ongoing tissue damage.

Eosinophils dwell primarily in tissues throughout the body and compose only a small percentage of peripheral blood leukocytes. The absolute eosinophil count (AEC) is normally less than 450/μL ($<0.45\times10^9$/L). Eosinophilia is most often defined as an AEC greater than 500/μL ($>0.5\times10^9$/L) and can be divided into 3 categories: mild (500–1,500/μL [$0.5–1.5\times10^9$/L]), moderate (1,500–5,000/μL [$1.5–5.0\times10^9$/L]), and severe (>5,000/μL [$>5.0\times10^9$/L]). Hypereosinophilia refers to a moderate or severe elevation in AEC persistent for at least 1 month.

A modest elevation of eosinophils in the peripheral circulation may signal a higher burden in body tissues, and clinical manifestations and complications correspond to tissue burden rather than degree of eosinophilia. Any organ system can be susceptible to damage from sustained eosinophilia, but dermatologic, pulmonary, and gastrointestinal manifestations are most common. Myocardial damage and neurologic involvement occur less frequently.

Reliable data regarding the epidemiology of eosinophilia in children are limited, and available studies reflect referral bias. Data suggest that eosinophilia during childhood is most often secondary to another disease (reactive) rather than a primary abnormality of leukocytes. Population studies assessing blood counts in children have suggested that eosinophilia is often unrecognized by clinicians. Fortunately, most cases are self-limited, but underrecognition can be highly problematic if sustained eosinophilia results in damage to organ tissues.

CAUSES

The differential diagnosis of eosinophilia is broad and includes benign conditions as well as disorders with potentially severe organ dysfunction and life-threatening sequelae. The degree of eosinophilia does not typically correlate with etiology or with severity of disease. Although classification schemas vary, most cases of eosinophilia during childhood are secondary to another disease state.

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Allergic conditions, including asthma, allergic rhinitis, eczema, and urticaria, are the most common causes of mild to moderate eosinophilia for children in the United States. Eosinophils proliferate during asthma exacerbation and cause chronic airway damage with decreased pulmonary function. Drug-induced eosinophilia in children occurs most commonly with antibiotics, nonsteroidal anti-inflammatory drugs, and antiepileptics, but it can be triggered by any drug, herb, or supplement. Drug reaction with eosinophilia and systemic symptoms (DRESS) is a potentially life-threatening reaction presenting with fever, malaise, lymphadenopathy, exfoliating rash, hypereosinophilia, and multiple organ involvement presenting 2 to 8 weeks after exposure.

Although the eosinophil count is commonly suppressed in bacterial and viral infections, eosinophilia is typically present from the onset in parasitic infections. Tissue-invasive parasites such as hookworm, *Trichinella*, and *Toxocara* are more likely to cause eosinophilia than those that remain in the intestine, such as *Giardia* or *Entamoeba*. Scabies can also induce eosinophilia. Young children are especially vulnerable to parasites because of their unhygienic practices: children with pica risk ingestion of *Toxocara* found in animal feces, and those playing barefoot in sandy soil may develop cutaneous larva migrans. Some parasites, including *Strongyloides* and *Toxocara,* are endemic worldwide and should be considered regardless of travel history. Other parasites that are more common outside the United States, such as *Schistosoma* and *Filaria,* are a risk for international adoptees, immigrants, refugees, and travelers. Additional risk factors for parasitic infection include ingestion of wild game, undercooked meats, or raw produce.

Loeffler syndrome with cough, low-grade fever, and pulmonary infiltrates is a transient eosinophilic pneumonitis that can develop in response to parasitic infection. Allergic bronchopulmonary aspergillosis is a reaction secondary to *Aspergillus* infection and should be suspected in children with severe asthma or cystic fibrosis who have persistent pulmonary symptoms and eosinophilia. Diagnosis is critical to prevent permanent bronchiectasis and pulmonary fibrosis. Not all eosinophilic pneumonias are caused by infection; clinicians should ask about use of inhalational drugs of abuse such as cocaine and vaping with tetrahydrocannabinol.

Eosinophilic esophagitis and other immune-mediated gastrointestinal disorders, including chronic hepatitis and inflammatory bowel disease, may present with eosinophilia. Symptoms of eosinophilic esophagitis are triggered by food antigens, with progressive eosinophilic inflammation of the esophagus leading to fibrosis and strictures. Young children may present with nonspecific symptoms, including feeding difficulties, vomiting, abdominal pain, or failure to thrive, whereas adolescents and adults present with more classic symptoms of dysphagia and food impaction.

Rare causes of eosinophilia in children include connective tissue disorders, malignancies, and immunodeficiencies. Eosinophilic granulomatosis with polyangiitis presents with chronic sinusitis, refractory asthma, and moderate to severe eosinophilia. Systemic lupus erythematosus and disorders with inflammatory arthritis can cause eosinophilia and should be considered when symptoms suggest rheumatologic disease. Eosinophilia occurs in association with lymphoid and myeloid malignancies as well as with solid tumors and can be seen after stem cell transplant. Primary immunodeficiency syndromes should be suspected in a young infant with eosinophilia and recurrent or unusual infection or early, severe eczema.

EVALUATION

Mild eosinophilia occurs frequently in children, is often an incidental finding, and is usually transient and clinically unimportant. Persistent hypereosinophilia is less common and should be evaluated to identify conditions that can be treated and uncover and mitigate ongoing tissue damage. Because the degree of eosinophilia may not reflect the extent of tissue involvement, even mild eosinophilia should be noted and monitored. All children with eosinophilia should undergo a thorough history and physical examination, looking for the etiology and evidence of tissue involvement. History should assess risk factors for parasitic infection and include a detailed drug history. History and examination should also identify symptoms of organ dysfunction. Previous eosinophil counts should be reviewed if available. Further evaluation and frequency of monitoring is guided by the AEC as well as findings from history and examination.

Red flags prompting urgent evaluation or referral include acute onset of fever, adenopathy, organomegaly, or evidence of organ dysfunction. In the absence of these red flags, mild and moderate eosinophilia can generally be managed with periodic monitoring (Fig 1). When eosinophilia is persistent or severe, additional laboratory studies should include a peripheral blood smear, tests of liver and renal function, urinalysis, and studies for parasites; serum immunoglobulin E, electrocardiography, and chest radiography may also be useful.

Therapy is directed at treating the underlying condition when identified. Because parasites are a common cause of

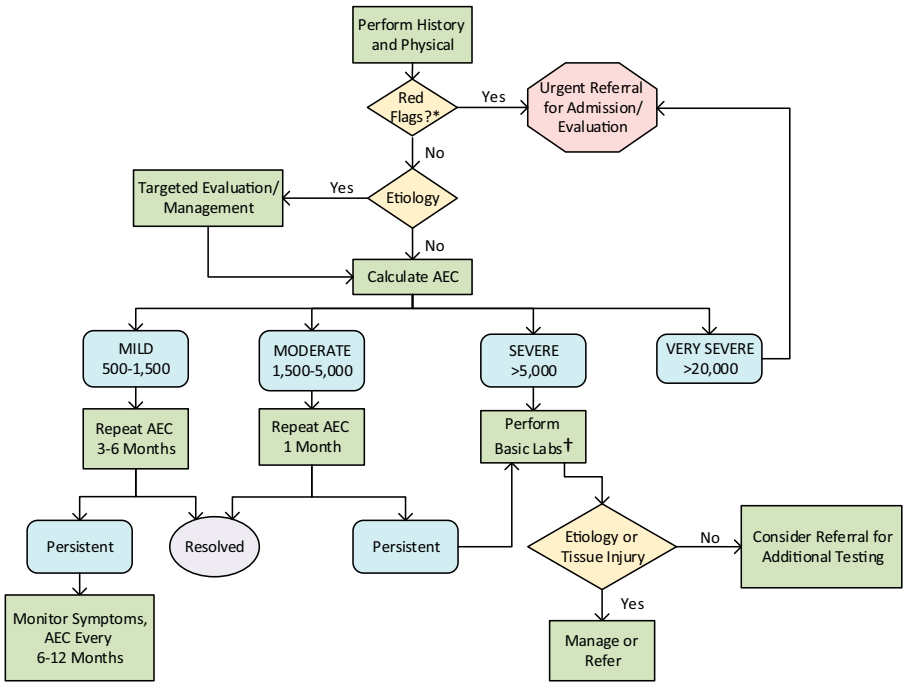

Figure 1. Approach to the evaluation of eosinophilia. *Red flags prompting urgent referral and/or admission include acute onset of fever, adenopathy, or organomegaly and evidence of pulmonary, neurologic, or cardiac dysfunction. †Basic laboratory testing: complete blood cell count with differential cell count and peripheral smear, tests of liver and renal function, urinalysis, stool/serology for parasites. Consider serum immunoglobulin E, electrocardiography, chest radiography. AEC=absolute eosinophil count.

eosinophilia in children, some sources recommend stool/serology studies for evidence of parasites in all children when another etiology is not found and empirical treatment even if negative. Hospitalization is warranted for children with an extremely elevated AEC (≥20,000/μL [$\geq 20 \times 10^9$/L]) and those with findings suggestive of cardiac, neurologic, or pulmonary dysfunction. Systemic corticosteroids may be needed to treat acute organ dysfunction. Prognosis depends on the etiology as well as the degree of organ involvement.

COMMENT: In reflecting on the content of this In Brief, I realized that during my 3 decades of clinical practice, I usually attributed elevation of the eosinophilia count to allergic and atopic diagnoses. The comment that eosinophilia may be underrecognized by clinicians really resonated with me, and this In Brief helps to remind all of us as pediatricians of when to consider additional etiologies and to focus on this abnormal laboratory finding.

I had a personal experience of the importance of eosinophilia when I was hospitalized with fever, multiorgan involvement, and rash. After 8 days of being a "medical mystery," one of the infectious diseases physicians recommended a repeated complete blood cell count with a differential cell count, which revealed an elevation of eosinophils. Further questioning revealed that I had been started on a new medication 16 days before the onset of fever, and I then met the criteria for the rare DRESS syndrome. Many of my colleagues with whom I shared my experience thanked me for telling them about my diagnosis because DRESS syndrome was a question on their board certification examinations and they had not ever seen this in clinical practice! Yet the take-home message to me, as a patient and a clinician-educator, is the importance of asking the timing of medication initiation in the context of fever, rash, and multiorgan involvement and then checking for eosinophilia. I am grateful that the diagnosis was made as quickly as it was and reminded me again of the importance of eosinophilia.

–Janet Serwint, MD
Associate Editor, In Brief