

Evaluation and Differential Diagnosis of Persistent Marked Eosinophilia



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KEYWORDS

- Eosinophilia • Hypereosinophilic syndrome • *FIP1L1-PDGFR*A
- Lymphocytic hypereosinophilic syndrome (L-HES)
- Myeloproliferative hypereosinophilic syndrome (M-HES)

KEY POINTS

- The causes of peripheral blood eosinophilia are varied, ranging from benign eosinophilia to malignancy; a careful history and physical examination along with directed clinical evaluation may help determine the cause.
- Although drug allergy is the most common cause of hypereosinophilia in the United States, parasitic diseases are the most common cause worldwide.
- Hypereosinophilic syndrome is a diagnosis of exclusion; however, it should be considered in patients with peripheral eosinophilia of unknown cause, because delay in diagnosis may result in end-organ damage.
- In recent years, advances in molecular diagnostics have improved the ability of physicians to identify and treat hypereosinophilic syndrome.

EOSINOPHIL BIOLOGY

In order to better appreciate the implications of eosinophilia and eosinophilic tissue infiltration, it is helpful to have an understanding of eosinophil development, structure, and function. Eosinophils are terminally differentiated granulocytes derived in the bone marrow from CD34+ hematopoietic stem cells.¹ Cytokines integral to the transition from progenitor cells to eosinophils include interleukin (IL)-3, IL-5, and granulocyte-macrophage colony-stimulating factor (GM-CSF); IL-5 also participates in regulation of other aspects of eosinophil function, including release of mature cells from the

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bone marrow and migration into tissue.² Progression toward the eosinophil lineage is directed by several key transcription factors, including GATA-binding protein 1 (GATA-1), PU.1, interferon consensus-binding protein, and CCAAT-enhancer binding proteins.³ The half-life of eosinophils in the peripheral blood is approximately 18 hours, and under normal circumstances they represent only 1% to 5% peripheral blood leukocytes. However, their survival is significantly prolonged after recruitment into tissue, where they represent a more substantial proportion of the cellular population.^{3,4}

Eosinophils have a characteristic morphology, with bilobed nuclei and numerous cytoplasmic granules that bind to the dye eosin, leading to a distinct pink coloration of the cytoplasm on microscopy.^{5,6} Their specific granules contain hydrolytic enzymes and cationic granule proteins including major basic protein (MBP), eosinophil peroxidase, eosinophil-derived neurotoxin (EDN), and eosinophil cationic protein.⁶ These proteins are responsible for many fundamental activities of eosinophils. Specific granules also contain cytokines, chemokines, and growth factors, such as CC chemokine ligand 5 (CCL5)/regulated on activation, normal T cell expressed and secreted (RANTES), CCL11/eotaxin, GM-CSF, IL-2, IL-4, IL-5, IL-6, IL-13, transforming growth factor alpha, and tumor necrosis factor alpha.⁶ As these mediators are preformed and do not require *de novo* synthesis, activated eosinophils can respond rapidly to changes in the environment, promoting efficient cellular recruitment and coordinated immune responses.

Understanding the normal mechanisms of eosinophil development and proliferation is essential for identifying the derangements in these pathways that lead to eosinophilia. Similarly, knowledge of eosinophil function provides a framework for comprehension of the abnormalities that can occur in the setting of increased eosinophil number or activity.

EOSINOPHILIA

Eosinophilia is defined as an increase in the peripheral absolute eosinophil count (AEC). There are defined categories including mild (AEC from 500–1500/mm³), moderate (AEC 1500–5000/mm³), and severe (AEC >5000/mm³).⁷ The clinical impact of eosinophilia is variable. The severity of symptoms does not always correlate with the degree of eosinophilia; some patients with substantial peripheral eosinophil increases remain asymptomatic, whereas others with mild eosinophilia have severe complications.⁸ The fact that blood eosinophil counts may not be representative of eosinophilic tissue infiltration may be partially responsible for this. Eosinophil counts in tissue are generally higher than those present in peripheral blood, and the release of preformed mediators in associated tissue often leads to the clinical manifestations and complications of eosinophilia.⁹ The discrepancy between degree of eosinophilia and manifestation of clinical symptoms may also be explained by differences in the degree of eosinophil activation. Studies of members of an asymptomatic family with hypereosinophilia (2000–5000 eosinophils/mm³) showed that they had relative lack of eosinophil activation (decreased serum levels of EDN and MBP, and decreased surface expression of CD25) compared with those with nonfamilial hypereosinophilic syndrome (HES).¹⁰

The causes of eosinophilia are varied, and are further explored later in this article. It is essential to systematically approach patients who present with unexplained eosinophilia, because the treatments may vary by cause and the urgency of management may be guided by the presence or absence of end-organ manifestations. A detailed discussion of end-organ manifestations associated with eosinophilia is provided by Akuthota and Weller elsewhere in this issue.

CAUSES OF HYPEREOSINOPHILIA

Drug Hypersensitivity

Medications are a frequent cause of eosinophilia, and are likely the most common cause in areas with a low prevalence of parasitic infection.¹¹ Although prescription medications can cause increased eosinophil counts, any medication, including over-the-counter drugs, herbal therapies, and dietary supplements, can be implicated and should be considered as part of the diagnostic evaluation. As such, a detailed medication history should be obtained in any patient presenting with eosinophilia.

Drug-induced eosinophilia may be asymptomatic and found incidentally, as is commonly the case with cephalosporins, quinine, and quinolones.¹² Eosinophilia does not necessarily require cessation of a causative medication; the prescribing physician must take into account the necessity of the medication, available alternatives, and presence of end-organ complications related to eosinophilia. In some situations, the medication may be continued under close monitoring.⁹

In other cases, eosinophilia related to medication use may lead to organ-specific complications. For instance, eosinophilic pulmonary infiltrates have been well described during treatment with multiple medications, including sulfasalazine, nitrofurantoin, and nonsteroidal anti-inflammatory drugs (NSAIDs).¹³ Acute interstitial nephritis (AIN) is another condition associated with organ-specific eosinophilic complications. This condition has been noted secondary to semisynthetic penicillins, cephalosporins, NSAIDs, sulfonamides, phenytoin, cimetidine, and allopurinol, among others.¹⁴ Although renal interstitial eosinophilic infiltration is a characteristic of AIN, eosinophiluria is considered to lack diagnostic sensitivity, with one study of 51 patients with suspected AIN showing a positive predictive value of less than 40%.^{14,15} Treatment of these conditions involves cessation of the causative medication, but patients may also require additional supportive care specific to the organ system involved.

Eosinophilia with multiorgan system involvement secondary to medication use has also been described. Eosinophilia-myalgia syndrome (EMS) is a disorder in which increased eosinophil counts are associated with severe myalgias, neuropathy, dermatologic induration, and varied multisystem complaints. EMS has been most commonly reported secondary to impurities of ingested L-tryptophan linked specifically in the United States to a company producing contaminated L-tryptophan supplements.¹⁶ A similar deadly epidemic, known as toxic oil syndrome, occurred with the ingestion of contaminated rapeseed oil in Spain.¹⁷ L-tryptophan-induced EMS is now rarely seen, and toxic oil syndrome has not recurred.¹⁸

Drug rash with eosinophilia and systemic symptoms syndrome, also known as drug-induced hypersensitivity syndrome (DIHS), warrants specific mention because mortality may be as high as 10% to 20% in affected patients.¹⁹ DIHS generally develops around 4 to 12 weeks after initiation of a causative medication, and may persist for weeks beyond cessation of the drug. Patients frequently present with fevers, lymphadenopathy, and hematologic abnormalities, including AEC greater than 1500/mm³. End-organ involvement may include hepatitis, interstitial nephritis, pneumonitis, and carditis.¹⁹ Medications are not the only known cause, and DIHS can result from reactivation of latent viruses such as human herpesvirus (HHV)-6, HHV-7, Epstein-Barr virus, and cytomegalovirus.^{20,21}

Some medications commonly associated with eosinophilia and DIHS are shown in **Box 1**; this list is not comprehensive. Any prescription medication, supplement, or over-the-counter medication can lead to eosinophilia.

Box 1 Medications commonly associated with eosinophilia and DIHS	
Antibiotics • Penicillins • Cephalosporins • Fluoroquinolones • Tetracyclines • Doxycycline • Linezolid • Nitrofurantoin • Metronidazole	Antiinflammatories • Piroxicam • Naproxen • Diclofenac • Ibuprofen
Antiepileptics • Phenytoin • Carbamazepine • Phenobarbital • Lamotrigine • Valproate	Sulfonamides/sulfones • Dapsone • Sulfasalazine • Trimethoprim-sulfamethoxazole
Antidepressants • Desipramine • Amitriptyline • Fluoxetine	Antihypertensives • Hydrochlorothiazide • β-Blockers • Angiotensin-converting enzyme inhibitors
	Other • Abacavir • Nevirapine • Allopurinol • Ranitidine • Cyclosporine

Allergic Disorders

Eosinophilia can be observed in the setting of conditions such as atopic dermatitis, allergic rhinitis, and asthma, although generally the AEC is less than 1500/mm³ in the setting of these conditions. Severe atopic dermatitis and marked eosinophilia may prompt evaluation for rare causes of immune deficiency and immune dysregulation such as hyper-immunoglobulin (Ig) E syndrome and Omenn syndrome (reviewed by Williams and colleagues elsewhere in this issue).

Allergic bronchopulmonary aspergillosis (ABPA) and allergic bronchopulmonary mycoses (ABPM) are hypersensitivity reactions to fungi resulting in increased total IgE levels, presence of IgE and IgG to *Aspergillus fumigatus* (or other fungi), bronchiectasis, and pulmonary infiltrates in the setting of asthma.²² Pronounced eosinophilia in the setting of asthma also raises concern for eosinophilic granulomatosis with polyangiitis (EGPA), formerly known as Churg-Strauss syndrome, which is further explored later in this article.

Infection

Tissue invasive parasitic helminth infection is the most common cause of eosinophilia worldwide.²³ *Strongyloides stercoralis*, a helminthic parasite found in tropical and sub-tropical climates, including the southeastern United States, can cause variable degrees of eosinophilia. *Strongyloides* infection may be prolonged, having been documented to persist for decades, and may be asymptomatic.²⁴ Importantly,

some individuals with strongyloidiasis do not have associated eosinophilia.²⁵ Treatment with corticosteroids in the setting of strongyloidiasis can lead to a disseminated and fatal infection, so screening for this condition is indicated before treatment if possible.²⁶ Less commonly, eosinophilia can be found in the setting of infection with other parasites, such as *Iso spor a belli* and *Sarcocystis hominis*.^{27,28} Ectoparasites, such as scabies, are also known to cause eosinophilia.²⁹

Bacterial infection generally leads to low peripheral eosinophil counts.³⁰ Eosinophilia in the setting of a significant bacterial infection warrants evaluation for another cause, such as an antibiotic being used to treat the infection. Alternatively, viral infections such as human T-cell leukemia virus (HTLV) and human immunodeficiency virus (HIV) can be associated with eosinophilia. HTLV has been associated with eosinophilia in the setting of dermatologic disorders including induration and ulceration of the skin with a CD8 predominant cellular infiltration; it has been theorized that eosinophilia in this setting may be related directly to skin damage versus induction of a cytokine profile promoting eosinophilia.³¹ Patients coinfect ed with HTLV-1 and *Strongyloides* have a modified immune response to the parasite, consisting of increased levels of interferon gamma and decreased production of IL-4, IL-5, IL-13, and IgE; the efficacy of strongyloidiasis treatment is decreased in these individuals.³² Eosinophilia can be associated with HIV infection; factors that may contribute to eosinophilia in this population include immune dysregulation, increased medication use, and HIV-associated eosinophilic folliculitis.^{33,34} Fungal infections can also be a cause of eosinophilia. Primary coccidioidomycosis can be associated with eosinophilia, with more significant increases associated with disseminated disease.³⁵ Eosinophilia associated with *Aspergillus* is primarily seen in ABPA, as outlined earlier. A more extensive review of infectious causes of eosinophilia is provided by O'Connell and Nutman elsewhere in this issue.

Overall, there are several factors that may suppress eosinophilia in the setting of infection, such as hyperthermia, acute illness, and treatment with corticosteroids. When these situations are remedied, eosinophilia may become apparent. Adrenal insufficiency may also result in eosinophilia, particularly in acutely ill patients, because of the loss of endogenous glucocorticoids.³⁶

Neoplasm

Eosinophilia may be found in association with various types of malignancy. Solid tumors may be associated with peripheral eosinophilia and may lead to infiltration of eosinophils into the area immediately involved with the mass.³⁷ Local eosinophilic infiltration may be more common in carcinoma of the lung, squamous cell carcinoma of the vagina, penis, skin, and nasopharynx, and transitional cell carcinoma of the bladder. Peripheral eosinophilia has been reported in the setting of carcinoma of the kidney, adrenal glands, thyroid, liver, gallbladder, pancreas, and breast; peritoneal mesothelioma; and liposarcoma.³⁷ Mechanisms contributing to the eosinophilia in this setting may include eosinophilotactic responses to tumor necrosis, increased eosinophil production in the bone marrow caused by tumor cell dissemination, and increased tumor production of eosinophilopoietins such as IL-3, IL-5, and GM-CSF.³⁸

Eosinophilia may also result from hematologic malignancies of both myeloid and lymphoid origins. Examples include chronic myelogenous leukemia (CML), Hodgkin and non-Hodgkin lymphoma, and peripheral T-cell lymphomas, such as Sézary syndrome, adult T-cell leukemia/lymphoma, and angioimmunoblastic T-cell lymphoma.³⁹

Other

EGPA, formerly known as Churg-Strauss syndrome, is a condition of necrotizing vasculitis and extravascular granulomatous disease that can be associated with asthma and prominent eosinophilia. Patients may show sinusitis or other paranasal abnormalities, migratory lung infiltrates, peripheral neuropathy, and eosinophilic end-organ complications involving the heart, gastrointestinal (GI) tract, and lungs.⁴⁰ Antineutrophil cytoplasmic antibodies (ANCA), typically antimyeloperoxidase, can be associated with EGPA, although these are found in only approximately 40% of patients.⁴¹ The presence of ANCA may have implications regarding disease phenotype. Although there is overlap between clinical presentations, ANCA-positive EGPA tends to be associated with features such as necrotizing glomerulonephritis, pulmonary hemorrhage, and mononeuritis multiplex. ANCA-negative EGPA often shows more significant eosinophilic tissue infiltration, including eosinophilic gastritis/enteritis and complications associated with toxic products of eosinophils.⁴¹

Eosinophilia can be found in association with rheumatologic diseases, including IgG4-related disease, eosinophilic myositis, diffuse fasciitis with eosinophilia, and various systemic autoimmune disorders such as systemic lupus erythematosus, Sjögren syndrome, rheumatoid arthritis, and Behcet's disease. Rheumatologic conditions associated with eosinophilia are further explored elsewhere in this issue by Tamaki and colleagues. Systemic mastocytosis (SM) may also be associated with eosinophilia, with up to 28% of patients showing eosinophilia greater than 650 eosinophils/mm³.⁴² Eosinophilia in SM has been reported in patients with the D816V mutation in the *KIT* gene, and shows overlapping features with myeloproliferative variant HES such as splenomegaly and increased serum tryptase and vitamin B₁₂ levels.⁴² However, despite these similarities, the dysfunction caused in SM is thought to be secondary to the mastocytosis rather than clonal eosinophilia.⁴³

As previously mentioned, eosinophilia accompanied by unusual or recurrent infections should prompt evaluation for certain immune deficiencies (see O'Connell and Nutman elsewhere in this issue). Examples of primary immune deficiencies associated with eosinophilia include autoimmune lymphoproliferative syndrome (ALPS), Omenn syndrome, and hyper-IgE syndromes (related to mutations in signal transducer and activator of transcription 3 [*STAT3*] or dedicator of cytokinesis 8 [*DOCK8*]). Characteristic features, such as an expanded CD4⁺ CD8⁻, T cell receptor (TCR) $\alpha\beta$ ⁺, CD3⁺ T-cell population (also known as double-negative T cells), lymphadenopathy, and hepatosplenomegaly, should prompt further evaluation for ALPS. In contrast, high levels of serum IgE and severe eczema are suggestive of hyper-IgE syndrome.

There are several distinct syndromes associated with eosinophilia, including Kimura disease, Gleich's syndrome, and nodules, eosinophilia, rheumatism, dermatitis, and swelling (NERDS) syndrome. Kimura disease is a rare inflammatory condition that presents primarily, but not exclusively, in Asian men. It is associated with subcutaneous nodularity and lymphoid infiltrates involving the salivary glands. There is often lymphadenopathy of the head and neck, although the axillae and groin may be involved as well. Eosinophilic microabscesses may be seen histologically, and serum abnormalities include increased IgE levels and eosinophilia. This condition has been associated with nephrotic syndrome, bronchial asthma, ulcerative colitis, and aortitis. The cause remains unknown; treatment consists of surgical resection of nodules or involved lymph nodes, with some reports indicating a benefit of corticosteroids.⁴⁴

Gleich's syndrome, also known as episodic angioedema with eosinophilia (EAE), consists of cyclic episodes of eosinophilia with associated symptoms including fevers, weight gain, and angioedema. Khoury and colleagues⁴⁵ recently studied 4 patients

with this rare condition. In addition to variable eosinophilia, these patients showed multilineage cell cycling, with episodic changes in neutrophil and lymphocyte counts with a periodicity of 25 to 35 days. All patients studied had aberrant populations of CD3⁺CD4⁺ T cells, with 3 of 4 showing clonal populations of T cells. Intracellular cytokine profiles in these patients suggest that eosinophilia and eosinophil activation may be lymphocyte driven. Other characteristic features of EAE include increased IgM levels and variable hypocomplementemia; EAE is generally steroid responsive and has a good prognosis.⁴⁶

The initial patients described presenting with NERDS showed pronounced eosinophilia, articular nodules on extensor tendons, dermatitis, and intermittent swelling of the hands and feet. Rheumatologic complaints included myalgias and stiffness in the hands, knees, and elbows. One patient showed a positive rheumatoid factor with a high titer as well as borderline hypocomplementemia. She responded well to long-term prednisone therapy, whereas the second patient did not require steroid therapy; the condition is considered largely benign.⁴⁷

Marked peripheral eosinophilia may also be seen in association with organ-restricted eosinophilic disorders, such as eosinophilic gastrointestinal disorder (EGID), chronic eosinophilic pneumonia, and Wells syndrome. EGIDs, including eosinophilic esophagitis, eosinophilic gastritis, eosinophilic gastroenteritis, eosinophilic enteritis, and eosinophilic colitis, are characterized by tissue eosinophilia that primarily affects the gastrointestinal tract. Presenting symptoms vary depending on the affected organ and may include dysphagia, reflux, nausea/vomiting, abdominal pain, diarrhea, and failure to thrive.⁴⁸ The diagnosis is made through endoscopy and biopsies showing abnormal eosinophilic infiltration; for example, although eosinophils are not typically found in Peyer's patches or the intraepithelial region, they can be present in these locations in the setting of EGID.⁴⁹ Many patients with EGID are atopic; the associated gastrointestinal diseases show features of both IgE-mediated and non-IgE-mediated hypersensitivity.⁵⁰ Peripheral eosinophilia may be present at levels of greater than 1500/mm³ in patients with EGID. However, limited studies have shown that these patients may be at lower risk of cardiac or bone marrow involvement; despite this, surveillance for end-organ complications is recommended in this setting.⁵¹

Although not a comprehensive list, selected causes of eosinophilia are outlined in Fig. 1.

Hypereosinophilic Syndrome

The criteria for HES were established by Chusid and colleagues⁵² in the mid-1970s to better characterize a cohort of patients with increased AECs without a clear secondary cause. At the time, the diagnostic criteria included AEC greater than 1500/mm³ for more than 6 months, evidence of end-organ complications of eosinophilia, and lack of a known secondary cause. It was apparent even then that there were phenotypic differences within this patient population, with significant variability in clinical course and response to therapy.

The definition of HES has undergone revisions as understanding of disease processes and efficacy of treatment have advanced. In 2006 the term HES was expanded to include other systemic conditions known to cause eosinophilia, including EGID, EGPA, and chronic eosinophilic pneumonia.² A working group further refined the definition in 2010, with new considerations for disease variability and defined molecular subtypes. With recognition that significant complications could occur with low levels of peripheral eosinophilia, the absolute cutoff of 1500 eosinophils/mm³ was eliminated

Infections	•Parasitic (helminths, ectoparasites, <i>Isospora</i>, <i>Sarcocystis</i>) •Viral (HIV, HTLV) •Fungal (coccidiomycosis) •Bacterial (tuberculosis)
Medications	•Antibiotics (penicillins, cephalosporins, quinolones, sulfonamides) •NSAIDs •Antiepileptics (phenytoin, valproate) •Antidepressants (fluoxetine, amitriptyline) •Antihypertensives (ACE inhibitors, β-blockers)
Hematologic/Neoplastic Disorders	•Systemic mastocytosis •Solid tumors (adenocarcinoma, squamous cell carcinoma) •Hematologic malignancy (CML, CEL, Hodgkin lymphoma)
Immune Dysregulation	•ALPS •Hyper-IgE syndrome •EGPA •Sarcoidosis •Inflammatory bowel disease •Immunoglobulin G4 related disease (IgG4-RD)
Allergic Disorders	•Allergic rhinitis •Asthma •Atopic dermatitis •ABPA
Other	•Adrenal insufficiency •Cholesterol embolization •Irradiation •EGID •Rare hypereosinophilic syndromes (idiopathic HES, L-HES, M-HES)

Fig. 1. Selected causes of eosinophilia. ACE, angiotensin-converting enzyme; CEL, chronic eosinophilic leukemia; L-HES, lymphocytic HES; M-HES, myeloproliferative HES.

if eosinophilic complications were present. Further, because some forms of HES can be rapidly progressive, the requirement of persistently elevated AEC over a 6-month time frame was removed in favor of increases of greater than 1500 eosinophils/mm³ on 2 occasions. End-organ damage was also discarded as a diagnostic parameter, because patients with significant eosinophilia may never show complications secondary to tissue damage. In addition, exclusion of secondary causes remains a diagnostic necessity, although it was recommended that secondary causes be amended to include molecularly defined disease subtypes that had been established since the initial description of HES.⁵³

By following the evolution of the definition of HES, it becomes clear that understanding of the condition has advanced significantly since it was initially recognized. This improved knowledge base has been established through monitoring the natural history of cohorts of patients, technological advancements allowing molecular characterization of disease subtypes, and observing responses to therapy. Established clinical variants of HES include myeloproliferative HES (M-HES) and lymphocytic HES (L-HES), as well as other defined categories. The HES subtypes are outlined in **Fig. 2.**

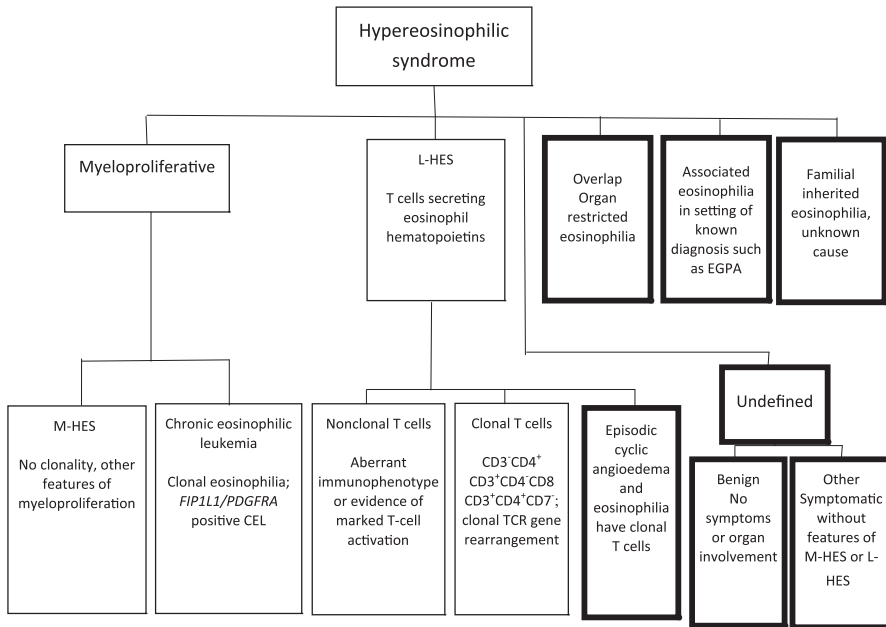


Fig. 2. Variants of HES. The heavy outline connotes conditions that may be associated with T cell-driven eosinophilia. (Adapted from Simon H-U, Rothenburg ME, Bochner BS, et al. Refining the definition of hypereosinophilic syndrome. *J Allergy Clin Immunol* 2010;126:45–9; and Cogan E, Roufosse F. Clinical management of the hypereosinophilic syndromes. *Expert Rev Hematol* 2012;5(3):275–90.)

Lymphocytic Hypereosinophilic Syndrome

In L-HES, aberrant populations of activated T cells generate eosinophilopoietins, resulting in marked peripheral eosinophilia. These T cells show abnormal patterns of cell surface markers, with the most common being CD3⁺CD4⁺; other atypical patterns that have been characterized include CD3⁺CD4[−]CD8[−] and CD3⁺CD4⁺CD7[−]. The presence of these irregular cells allows these lymphocyte populations to be identified via T-cell receptor rearrangement studies and flow cytometric analysis.⁵⁴ Other abnormal laboratory parameters include increased levels of thymus and activation-regulated chemokine (TARC)/CCL17 and increases in serum IgE.^{55,56} Although IL-5 has been implicated in the generation of eosinophilia in L-HES, increased IL-5 levels neither correlate with the presence of L-HES nor predict therapeutic response.⁵⁷

Myeloproliferative Hypereosinophilic Syndrome

Patients with M-HES show eosinophilia in the setting of features consistent with myeloproliferative disorders, including anemia, thrombocytopenia, hepatosplenomegaly, and eosinophilic tissue damage and/or fibrosis.⁵³ Initial descriptions of M-HES included young male patients with aggressive disease that proved refractory to standard treatments. It was later discovered that these patients showed marked clinical improvement with imatinib, a tyrosine kinase inhibitor.⁵⁸ Many of these patients were found to have a deletion of an 800-kb region on chromosome 4q12 containing the *CHIC2* gene; this led to an abnormal fusion of Fip1-like 1 (*FIP1L1*) and platelet-derived growth factor receptor alpha (*PDGFRA*), or

FIP1L1-PDGFR (F/P). The fusion product resulted in production of a constitutively active tyrosine kinase, modifying hematopoietic stem cells and leading to eosinophilia.^{7,58} This mutation can be useful in identifying patients with M-HES, as well as determining potential response to therapy. Some patients without the F/P mutation have responded favorably to imatinib, potentially implicating other tyrosine kinases in disease processes.⁵⁹

There have been other variants of M-HES associated with abnormalities in platelet-derived growth factor receptor beta (*PDGFRB*) and fibroblast growth factor receptor 1 (*FGFR1*).⁹ Patients with *PDGFRB* rearrangements may develop various myeloid neoplasms, including chronic eosinophilic leukemia, chronic myelomonocytic leukemia (often with eosinophilia), and atypical chronic myeloid leukemia (usually with eosinophilia). Like malignancies associated with *PDGFR* rearrangement, neoplasms related to *PDGFRB* abnormalities are often clinically responsive to imatinib.⁶⁰ Myeloid malignancies associated with *FGFR1* rearrangements may subsequently undergo myeloid or lymphoblastic transformation, or both. Although *FGFR1* encodes a tyrosine kinase, patients are more refractory to treatment and early allogeneic hematopoietic stem cell transplantation may be warranted.⁶⁰

If there is suspicion for M-HES, screening for F/P is recommended. M-HES may be present without any of these mutations if patients meet at least 4 of the following criteria: serum vitamin B₁₂ level greater than 1000 pg/mL, serum tryptase level greater than 12 ng/mL, anemia and/or thrombocytopenia, hepatosplenomegaly, bone marrow cellularity greater than 80%, myelofibrosis, dysplastic eosinophils on peripheral smear, or spindle-shaped mast cells in the bone marrow.⁹

Myeloproliferative features may also coexist with eosinophilia in the setting of chronic eosinophilic leukemia (CEL), which is discussed in detail elsewhere in this issue.

Other Categories of Hypereosinophilic Syndrome

There are other clinically defined subgroups of HES, including associated, overlap, familial, and undefined; many conditions comprising these subgroups are discussed earlier. Associated HES is characterized by an AEC greater than 1500/mm³ and is associated with another known condition.⁵³ These conditions include EGPA, SM, and sarcoidosis. Overlap HES consists of organ-specific eosinophilic disorders associated with peripheral eosinophilia, with examples including EGID and eosinophilic pneumonia. Familial HES is a rare autosomal dominant condition in which marked eosinophilia presents in successive generations. The eosinophilia may be asymptomatic, but some affected individuals develop complications, including cardiac fibrosis and neurologic abnormalities.⁶¹ Although the exact cause is unknown, the responsible gene has been localized to 5q31-q33, in the region of the cytokine gene cluster. This area also contains genes encoding IL-3, IL-5, and GM-CSF, all of which are important to eosinophil development and function.⁶²

Undefined HES consists of benign eosinophilia, episodic eosinophilia, and other eosinophilia that does not fit distinctly into another category. Episodic HES presents with intermittent eosinophilia and angioedema, and was discussed earlier in the article as Gleich's syndrome. Benign eosinophilia, also known as hypereosinophilia of unknown significance (HE_{US}), is prolonged eosinophilia that does not result in significant clinical manifestations. A recent retrospective study by Chen and colleagues⁶³ found that of 210 patients referred for unexplained eosinophilia, 8 of the 36 subjects who were *FIP1L1-PDGFR* negative with unexplained eosinophilia greater than 1500/mm³ on no therapy at the time of referral remained asymptomatic without clinical or laboratory evidence of end-organ dysfunction for at least 5 years. The eosinophilia

had been identified on routine blood work in all 8 subjects. Levels of IL-5, GM-CSF, IL-9, and IL-17A were similar in subjects with HE_{US} and symptomatic HES.

Approach to the Evaluation of Patients with Persistent, Marked Eosinophilia

In any patient with eosinophilia, the first step is to determine the urgency of evaluation. Patients with exceptionally high peripheral eosinophil counts or end-organ damage that may be attributable to eosinophilic infiltration may require inpatient admission with supportive care and expedited work-up. If these factors are not present, evaluation may occur in the outpatient setting in a stepwise fashion.

Given the myriad of secondary causes, obtaining a thorough history is vital. Because eosinophilic tissue infiltration can affect nearly any organ, a review of systems with particular attention to hematologic, neurologic, dermatologic, cardiovascular, and pulmonary systems should be obtained.⁶⁴ Organ-specific symptoms may be present, such as abdominal pain and nausea in the setting of EGID. Inquiries regarding constitutional or B symptoms should also be made to assess for any signs of malignancy or lymphoproliferation. Any family or personal history of chronic medical conditions known to be associated with eosinophilia including autoimmune disease, atopy, and malignancy, should be addressed. It is important to take a detailed travel history, with a focus on any tropical or developing areas that may be endemic for causative parasites or infectious agents. It is necessary to review medication lists with specific attention to supplements, over-the-counter medications, and any recent medications that may have had a transient course, such as antibiotic or nonsteroidal anti-inflammatory drug (NSAID) use. Note that the causative medication need not be initiated recently, because even those that have been used consistently for years have been implicated in causing eosinophilia. An occupational history may reveal potential environmental exposures leading to eosinophilia as well.

The physical examination is also important in narrowing the differential diagnosis in the setting of eosinophilia. Examination of the skin can help to assess for evidence of external causes of eosinophilia, such as scabies. There may also be evidence of cutaneous malignancies, such as Sézary syndrome. Some eosinophilic phenotypes have more characteristic skin findings; for instance, patients with L-HES often have generalized pruritus, urticaria, and erythroderma.⁶⁵ Lymphadenopathy may be an indicator of a specific disease entity, such as Kimura syndrome or lymphoma. The presence of hepatosplenomegaly may indicate the presence of a malignancy. Eosinophilic infiltration of the heart can lead to valvular dysfunction with resultant murmurs, arrhythmias, and evidence of heart failure.⁶⁶ Pulmonary involvement in eosinophilic disease can result in variable findings, including weight loss, lung infiltrates, and fibrosis.⁶⁷ Eosinophilic end-organ damage may be evident in other ways as well, such as jaundice in the setting of liver damage, or edema with renal disease.

If no clear cause of eosinophilia is ascertained by history or physical examination, laboratory assessment can be a helpful tool to assess for the cause. Laboratory evaluation should be considered in any patient with AEC greater than 1500/mm³ on 2 or more occasions, patients with AEC 500 to 1500/mm³ with potential exposure to infectious agents, or AEC greater than 500/mm³ in the setting of end-organ dysfunction.⁶⁸ A recommended diagnostic approach is provided in [Fig. 3](#). Depending on the urgency of evaluation, clinical suspicion, and the results of the initial laboratory work-up, a more focused set of tests may be indicated. If HES is confirmed, monitoring for evidence of end-organ complications is of the utmost importance. The type and frequency of these evaluations depends on previous end-organ complications, degree of eosinophilia, and existing comorbidities.

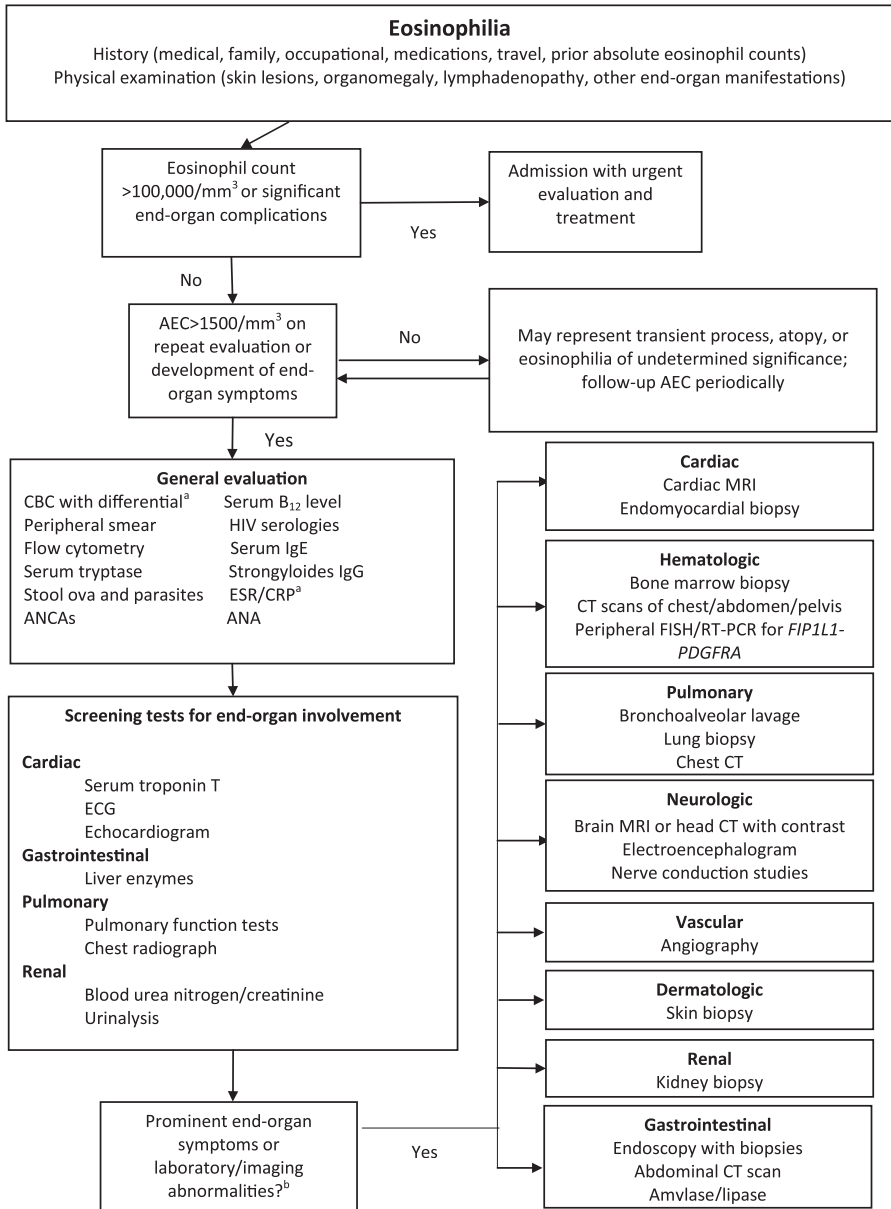


Fig. 3. Algorithm for evaluation of hypereosinophilia. ^a Studies that may be affected by concurrent steroid use. ^b Other studies for end-organ involvement may be warranted based on clinical presentation. ANA, antinuclear antibody; CBC, complete blood count; CRP, C-reactive protein; CT, computed tomography; ECG, electrocardiogram; ESR, erythrocyte sedimentation rate; FISH, fluorescent in situ hybridization; RT-PCR, reverse transcription polymerase chain reaction.

SUMMARY

Identifying the cause of persistent eosinophilia is vital; implications of an increased AEC may range from a benign finding to an aggressive malignancy. Clinical history, physical examination, and laboratory studies can all aid in distinguishing reactive causes of eosinophilia, such as medications and parasites, from primary causes, such as HES. Treatment is highly variable depending on the underlying basis of disease. Although advances in molecular diagnostics and therapies have ushered in changes in the diagnosis and treatment of eosinophilia, the importance of determining the underlying cause remains the same.

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