Published in final edited form as:

Semin Hematol. 2012 April ; 49(2): 160–170. doi:10.1053/j.seminhematol.2012.01.002.

Therapeutic Approaches to Patients with Hypereosinophilic Syndromes

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Introduction

Recent advances in diagnostic approaches and therapeutic options have prompted re-evaluation of the definition and classification of hypereosinophilic disorders^{1–3} (see Valent in this issue). Although there is general agreement that hypereosinophilic syndromes (HESs) represent a heterogeneous group of uncommon disorders characterized by persistent blood eosinophilia $>1,500/\text{mm}^3$, there is considerable debate regarding the specific disorders that must be excluded to make a diagnosis of a HES, and the definition of and requirement for organ pathology at the time of diagnosis.

For treatment purposes, the identification and exclusion of patients with eosinophilia secondary to common disorders, such as parasitic helminth infection, allergy, drug or chemical hypersensitivity, and cancer, are paramount (see Mejia and Nutman in this issue), since such disorders require specific interventions directed at the underlying cause rather than at the eosinophilia itself. Exclusion of such patients can be difficult, however, since patients with very different underlying diseases can present with identical clinical manifestations. For example, marked peripheral eosinophilia complicated by endomyocardial fibrosis has been reported in FIP1L1/PDGFR α -positive myeloid neoplasms^{4–6}, pre-B cell ALL⁷, and infection with the filarial parasite *Loa loa*⁸. Conversely, whereas patients with eosinophilic conditions of known etiology, such as FIP1L1/PDGFR α -positive myeloproliferative neoplasms (MPN) and CD3-CD4⁺ T cell driven HES, for which the clinical manifestations are predominantly (or entirely) related to the eosinophilia, merit inclusion in a treatment-based classification of HESs, the therapeutic approaches may be quite different depending on the specific molecular mechanisms involved.

A second obstacle to the development of a rational approach to treatment of HESs is the fact that, with the exception of one large multicenter retrospective study⁹, the available data on treatment responses to conventional therapy are restricted to single case reports and small case series. This lack of data precludes rigorous comparisons of standard therapies to novel

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CONFLICT OF INTEREST: The authors declare no conflicts of interest.

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targeted therapies except in cases where the difference in outcome is dramatic, as in imatinib therapy of FIP1L1-PDGFR α -positive MPN¹⁰, or when treatment-refractory patients are selected for study, as in the multicenter trial of mepolizumab as a steroid-sparing agent in FIP1L1-PDGFR α -negative HES¹¹. Nevertheless, some general conclusions can be drawn.

In the following article, we propose a general approach to the treatment of HESs based on the current state of knowledge in the field. As newer targeted agents become available and our understanding of the molecular mechanisms driving eosinophilia in patients with HESs increases, the specifics of the proposed algorithm will require modification, although the basic principles should remain unchanged.

Initial management of aggressive disease (Figure 1)

Unless a specific etiology is identified, peripheral eosinophilia $>1,500/\text{mm}^3$ with rapidly progressive or life-threatening clinical manifestations should be treated as quickly as possible with high-dose intravenous corticosteroids (at least 1 mg/kg prednisone equivalent). Since steroids can interfere with the interpretation of tissue biopsies and other diagnostic tests, every effort should be made to perform a minimal diagnostic evaluation prior to the initiation of steroids (see Table 1). Priority should be given to tests for which a positive result will alter the therapeutic approach and for which false-negative results may occur in the presence of corticosteroid therapy, including tissue biopsies and CT assessment of lymphadenopathy and splenomegaly. Patients with potential prior exposure to *Strongyloides* should receive concomitant empiric therapy with ivermectin (200 mcg/kg/day for two days) to prevent potentially fatal hyperinfection syndrome¹².

If there is no response after 2–3 days of high-dose corticosteroid therapy, addition of a second agent is indicated. Unfortunately, a standardized approach to the selection of the most appropriate second agent is impossible, since a number of factors must be considered, including the acuity of the clinical manifestations, the pharmacologic and side effect profile of the therapeutic agent, and the most likely diagnosis. For example, a patient presenting with eosinophilia and recurrent thromboembolic events might be treated with cyclophosphamide for presumed Churg-Strauss vasculitis if they had a history of asthma and an elevated serum IgE level or with imatinib for presumed FIP1L1/PDGFR α -positive myeloproliferative neoplasm if they had splenomegaly and an elevated serum B12 level. In neither case would interferon- α be appropriate because of the slow onset of action (up to 2 weeks) and potential to cause or aggravate ischemic disorders.

Once the patient is stabilized, every effort should be made to complete the diagnostic evaluation with the dual goal of definitively excluding alternative diagnoses (see Mejia and Nutman in this issue) and categorizing the patient into the most appropriate HES variant.

Treatment-based approach to HESs

With the recent proliferation of therapeutic agents targeting specific immunologic and signaling pathways, it has become increasingly important to identify subgroups of patients likely to benefit from specific treatment approaches. Although several classification schemes for HESs exist^{1–3}; see Valent in this issue), the etiology and pathogenesis remains undefined in the majority of patients, and none of the current schemes perfectly corresponds to logical treatment-based algorithms.

The first therapeutic question that needs to be addressed is whether treatment is indicated at all. From a practical standpoint, there are patients with unexplained eosinophilia $>1,500/\text{mm}^3$ who may not require therapy. The first group consists of FIP1L1/PDGFR α -negative patients who are completely asymptomatic without evidence of organ involvement or

laboratory abnormalities other than eosinophilia. These patients with hypereosinophilia of unknown significance (or benign eosinophilia) may or may not progress to a HES and require close follow-up^{1,3}. Patients with familial eosinophilia are a special subset of this group in whom there is a genetic basis for the eosinophilia, and clinical manifestations related to the eosinophilia develop in only a subset of affected family members¹³.

Once the decision has been made to initiate treatment, systemic corticosteroids are the first line treatment for most patients⁹ with a few notable exceptions, including patients with myeloproliferative features and those with organ-restricted or cyclic disease. The choice of second-line therapies may also differ between patients with specific clinical features. Since steroid therapy may alter the results of diagnostic testing, classification of patients into appropriate subgroups should precede the initiation of steroid therapy, if possible. The most important of these treatment-guided subgroups and their impact on therapeutic choices are discussed in the following section. The therapeutic agents themselves are reviewed elsewhere in this issue (see Butterfield and Weiler).

HESs with myeloproliferative features

A subset of patients with HESs presents with clinical and laboratory features suggestive of myeloproliferative disease (see Noel in this issue), including splenomegaly, anemia, thrombocytopenia, dysplastic eosinophils, and elevated serum B12 and tryptase levels⁵. The bone marrow is hypercellular with marked eosinophilia, increased vascularity, reticulin fibrosis and other evidence of myeloproliferation and/or myelodysplasia. Although some of these patients have cytogenetic abnormalities or a detectable mutation, such as FIP1L1/PDGFRA or JAK2 V617F, currently available techniques are insufficient to categorize the remaining patients according to current WHO guidelines^{2,3}.

Among the identifiable causes of HESs, the FIP1L1/PDGFRA fusion gene is clearly the most common, affecting between 10 and 14% of patients presenting with a HES^{9,14}, as defined by unexplained eosinophilia $>1,500/\text{mm}^3$ and evidence of eosinophil-mediated organ dysfunction. These patients typically do not respond to corticosteroid therapy and, in the absence of treatment, have an aggressive course with a poor prognosis⁵. Fortunately, the FIP1L1/PDGFRA mutation is exquisitely sensitive to imatinib therapy^{10,14-16}. Rapid institution of therapy is extremely important to prevent irreversible complications, including endomyocardial fibrosis and sequelae of thromboembolic events¹⁷. Since rare cases of acute myocardial necrosis have been reported in patients with pre-existing cardiac involvement following initiation of imatinib therapy^{4,6,7}, a baseline echocardiogram and serum troponin level are recommended prior to treatment⁶. Administration of high-dose corticosteroids during the first two weeks of imatinib therapy to 'at-risk' patients with elevated serum troponin levels and/or echocardiographic findings consistent with eosinophilic cardiac involvement has been advocated to prevent this complication¹⁸, although at least one case of myocardial necrosis has occurred on high dose steroid-therapy⁷.

Despite controversy as to the most appropriate starting dose, it is clear that nearly all patients with the FIP1L1/PDGFRA mutation can ultimately be managed with low-dose imatinib (100 mg daily to as low as 100 mg weekly)^{14,19,20}. The response to therapy is very rapid with the majority of patients experiencing clinical and hematologic responses within the first week of therapy and resolution of bone marrow abnormalities within the first month^{14,16,19}. Consequently, a lack of hematologic response at 2-4 weeks is concerning for primary resistance, a rare, but reported event^{21,22}.

Once a stable dosing regimen is achieved, drug efficacy and toxicity should be monitored with monthly eosinophil counts and regular clinical assessments, including

echocardiography (to assess ejection fraction and progression or development of endomyocardial fibrosis) and liver function tests. Molecular testing may take up to 12–18 months to become negative, but once negative, provides an excellent monitoring tool, since molecular relapse appears to precede clinical relapse by weeks to months^{15,23}. Quantitative PCR to assess FIP1L1/PDGFR α mRNA levels may prove to be more useful in predicting relapse, but is not currently commercially available²⁰.

Imatinib does not appear to be curative in FIP1L1/PDGFR α -positive disease^{15,23}, but secondary resistance is uncommon even in the setting of low-dose imatinib therapy, possibly due to the limited repertoire of possible PDGFR α kinase domain mutations²⁴. When resistance does occur or patients develop side effects necessitating a change in therapy, a different tyrosine kinase inhibitor may be effective. In this regard, *in vitro* studies have demonstrated efficacy of a number of tyrosine kinase inhibitors, including nilotinib, sorafenib, and PKC412, against imatinib-resistant FIP1L1/PDGFR α -positive cell lines. Clinical data in imatinib-resistant disease are limited to two cases of successful treatment with nilotinib²⁵ and a single case of sorafenib treatment in which outgrowth of a novel resistant clone occurred after an initial response to therapy²⁶. Responses to dasatinib and nilotinib have also been reported in 1 patient each with imatinib-sensitive FIP1L1/PDGFR α -positive disease in the setting of imatinib intolerance^{27,28}. Bone marrow transplantation has been used successfully in FIP1L1/PDGFR α -positive disease^{29,30}, but should be reserved for symptomatic patients unresponsive to tyrosine kinase inhibitors.

A clinical picture consistent with a HES can also be seen in the setting of other PDGFR α fusion partners, with PDGFR α point mutations and less frequently with PDGFR β fusion genes (see Noel in this issue). These patients also demonstrate rapid and complete responses to imatinib and should be treated and followed in the same way as patients with FIP1L1/PDGFR α -associated disease. In contrast, patients with marked eosinophilia and molecular abnormalities involving other genes, such as JAK2 and FGFR1, or with cytogenetic abnormalities are less likely to respond to imatinib, but may respond, at least partially, to interferon- α , hydroxyurea or other agents^{31,32}. In such patients, typing for potential bone marrow transplantation should be initiated early.

Imatinib response rates in patients with FIP1L1/PDGFR α -negative HESs have ranged from 14–60%^{9,10,14–16,19}. Whether the presence of myeloproliferative features is a predictor of response in such patients is, however, unknown. Consequently, steroids remain first-line therapy in this subgroup of patients. In patients who fail or are intolerant to steroids, a one month trial of standard-dose imatinib (400 mg daily) is recommended, based on published case reports indicating that such patients require higher doses and respond less quickly than patients with mutations involving the PDGFR α ³³. Persistent eosinophilia $>1,500/\text{mm}^3$ after one month should be considered a treatment failure and treatment with alternative agents should be initiated. Repeat bone marrow examination is suggested after one month of imatinib therapy in all subjects to confirm remission, but is particularly important in patients with a suboptimal response to imatinib to ensure that an underlying malignancy was not missed⁷.

HESs with single organ involvement

Organ-restricted eosinophilic disorders, including eosinophilic gastrointestinal disease, eosinophilic pneumonia and eosinophilic dermatitis, can be accompanied by peripheral eosinophilia $>1,500/\text{mm}^3$. In some cases, these disorders, particularly those without severe or life-threatening manifestations, can be treated effectively with topical steroids alone. Persistent or severe symptoms and/or evidence of progression to multisystem involvement require systemic therapy and should be approached in the same manner as other HESs.

HES with features of Churg-Strauss Syndrome

Definitive pathologic diagnosis of Churg-Strauss Syndrome (CSS) requires the demonstration of eosinophilic vasculitis in a tissue other than the skin. Although the presence of ≥ 4 of the clinical criteria proposed by the American College of Rheumatology is suggestive of a diagnosis of CSS³⁴, these criteria were developed for the identification of subjects with vasculitis for research studies of CSS and should not be used as diagnostic criteria for individual patients. Furthermore, their utility in the absence of proven vasculitis remains unclear. Thus, the presence of asthma and sinus disease with polyps, common disorders in the general population, when accompanied by eosinophilia $>1,500/\text{mm}^3$ presents a diagnostic dilemma. Many of these patients have a history of pneumonia, for which they received steroids with or without antibiotic therapy. Even when patients present with ongoing clinical manifestations (i.e., pulmonary infiltrates, symptoms of peripheral neuropathy, myocarditis), they are often already on low- or moderate-dose corticosteroid therapy and biopsies may be indeterminate.

Clearly, the safest approach is to treat patients with presumed or possible CSS as if they had biopsy-proven disease. However, the benefits of a prolonged course of high-dose steroids with or without cyclophosphamide, the recommended therapy for active CSS³⁵, must be weighed against the potential toxicities of these agents. The most appropriate maintenance therapy for patients who require more than 10 mg prednisone daily for suppression of eosinophilia and symptoms is also controversial. Methotrexate, a commonly used maintenance therapy in CSS, is rarely used in HESs⁹. Conversely, hydroxyurea, a second-line agent in HESs, is not considered a treatment of choice in CSS³⁵. Interferon-alpha appears to be effective in both conditions, but is associated with potential toxicities^{9,36}. Mepolizumab has been shown to be safe and effective as a steroid-sparing agent in both HESs and CSS^{11,37}, but is not FDA-approved for any indication and is currently only available for compassionate use in patients with life-threatening, treatment refractory HESs.

HES with evidence of an aberrant or clonal T cell population

As many as 10–15% of patients with HESs have an aberrant or clonal population of T cells producing cytokines, such as IL-5 and IL-3, that induce eosinophilia^(9,38, see Roufosse et al. in this issue). Although corticosteroid therapy is often effective in these patients with lymphocytic variant HES (L-HES) and is considered first-line therapy, moderate to high doses (30–60 mg prednisone) may be required to suppress eosinophilia and symptoms. Interferon-alpha is the most commonly used steroid-sparing agent in this subgroup of patients. Concomitant therapy with low-dose corticosteroids has been recommended due to theoretical concerns of clone outgrowth based on in vitro data showing prolonged survival of T cell clones in the presence of interferon-alpha³⁹. Other commercially available agents effective in the treatment of T cell disorders, including alemtuzumab and cyclosporine, have been used in L-HES with limited success^{9,40}. Mepolizumab appears to be safe and effective in patients with L-HES⁴¹, but is currently unavailable except for compassionate use. Imatinib is ineffective in L-HES, except perhaps in patients with a T cell clone in the setting of concomitant FIP1L1/PDGFRA-positive disease⁴².

Progression to lymphoma does occur in L-HES, albeit in a small percentage of patients. Consequently, absolute lymphocyte counts should be followed monthly and the proportion of aberrant cells assessed periodically and when lymphocyte numbers increase³⁸. Cytogenetic abnormalities, particularly 6q-chromosomal deletions⁴³, may herald the development of lymphoma.

HES with episodic angioedema

Angioedema is a relatively common manifestation of HES ⁴⁴, especially in the setting of L-HES. In rare cases, the angioedema occurs monthly in a cyclic pattern that is preceded by a dramatic increase in serum IL-5 and eosinophilia ⁴⁵. Aberrant T cell populations (CD3-CD4+) have been described in these patients, suggesting that episodic angioedema and eosinophilia (Gleich's syndrome) is a subtype or clinical manifestation of L-HES ⁴⁶. Patients with Gleich's syndrome have a number of features that distinguish them from other patients with HES, including increased serum IgM levels ⁴⁵. Although intermittent short courses of corticosteroids provide symptomatic relief and eosinophil reduction during episodes, the utility of continuous steroid therapy to prevent episodes is unproven. Since progression to eosinophil-mediated organ dysfunction appears to be extremely uncommon and the episodes of angioedema and eosinophilia are self-limited, many patients choose to be treated only when they are symptomatic or to forego treatment entirely.

Treatment Algorithm for HES

A simplified approach to treatment of HESs is outlined in Figure 2. This treatment-based algorithm assumes that secondary causes of eosinophilia, such as helminth infection and solid organ neoplasms, requiring therapy directed at an offending agent or underlying disorder have been excluded, that the minimum evaluation outlined in Table 1 has been completed, and that the patient is clinically stable.

Based on the clinical findings and results of preliminary testing, patients with presumed HES should be classified according to the scheme proposed in Table 2. For patients with a documented FIP1L1/PDGFRA mutation, imatinib therapy (100–400 mg daily) is the treatment of choice, regardless of clinical symptomatology. High-dose steroids should be administered concurrently if there is an elevated serum troponin or clinical or echocardiographic evidence of cardiac involvement. A lack of hematologic response within 1–2 weeks should raise concern for primary resistance and prompt an increase in the imatinib dose to 400 mg daily, as well as initiation of HLA typing for bone marrow transplantation should medical therapy be unsuccessful. If the eosinophil count does not respond to an increased dose of imatinib, a trial of a different tyrosine kinase inhibitor with *in vitro* activity against T6741, the most common resistance mutation, is indicated.

Since results of cytogenetic and molecular testing may not be available for several days to weeks, a trial of imatinib may be appropriate initial therapy in some patients with myeloproliferative HES and unknown molecular status, particularly when characteristic features of FIP1L1/PDGFRA-positive MPN are present (Table 2). For patients with FIP1L1/PDGFRA-negative myeloproliferative HES, however, high dose corticosteroid therapy (1 mg/kg prednisone equivalent) remains first-line therapy. If the eosinophil count does not drop dramatically within 2–3 days, imatinib (400 mg daily) should be added. If this fails, alternatives include newer tyrosine kinase inhibitors, interferon-alpha and, in the setting of aggressive disease, bone marrow transplantation.

The second group of patients that require urgent assessment and treatment are those with a clinical history and/or findings consistent with eosinophilic vasculitis (CSS). Although high-dose corticosteroids alone are the initial treatment of choice for patients without poor-prognostic factors ⁴⁷, the early addition of cyclophosphamide has been shown to decrease morbidity and mortality in patients with more severe and/or steroid-refractory disease ⁴⁸. Once eosinophilia and clinical manifestations are controlled, high-dose steroids should be continued for at least one month before beginning a slow taper. The most effective dosing and duration of cyclophosphamide therapy is unknown.

Whether or not to initiate systemic corticosteroid therapy in an asymptomatic patient with eosinophilia $>1,500/\text{mm}^3$ is a complex decision that depends on the length of time the eosinophilia has been present, the level of eosinophilia and the comfort level of the treating physician. In general, longstanding (months to years) moderate ($<5,000/\text{mm}^3$) levels of eosinophilia in the absence of any signs or symptoms can be monitored closely without treatment. Although a small subset of patients with single organ involvement and mild symptoms may benefit from topical therapy alone, most symptomatic patients with eosinophilia $>1,500/\text{mm}^3$ should be treated with systemic corticosteroids.

With the exception of patients with known or presumed imatinib-responsive M-HES, corticosteroid therapy remains the initial treatment of choice for most symptomatic patients with HES. The optimal initial dose unknown; however, a reasonable approach is to begin therapy at a prednisone equivalent of 1 mg/kg for moderate to severe disease and 0.5 mg/kg for mild disease. If the eosinophil count and symptoms resolve, the dose can be tapered slowly in an attempt to establish the minimum dose necessary for disease control. If there is no response or the dose cannot be tapered over time to a maintenance dose of ≤ 10 mg daily, alternative agents should be considered. Hydroxyurea and interferon-alpha are the most commonly used second-line agents and appear to have similar efficacy in HESs⁹. Imatinib is a reasonable alternative, especially in patients with features of myeloproliferative disease. Which agent to use in a given patient should be based on the side effect profile and cost of the drug and patient preference, except in the case of L-HES, where interferon-alpha is preferred (see Roufosse in this issue). In patients who fail to respond and/or are intolerant of conventional therapies, alternative therapies (including investigational agents) should be considered.

Adjunctive therapies

Although the primary goal treatment of HESs is to decrease the numbers of eosinophils in the peripheral blood and tissues, additional therapies are sometimes required to prevent secondary complications of HESs and/or their therapy.

Anticoagulation

Thromboembolic events are a major cause of morbidity and mortality in patients with HESs, particularly in the setting of eosinophilic cardiac involvement, where they may occur in up to 25% of patients^{49,50}. Not only are several different eosinophil-derived mediators and cytokines capable of activating and damaging endothelial cells and platelets^{51,52}, but eosinophils have been shown to express and release tissue factor⁵³ and plasminogen activator inhibitor-2⁵⁴, both of which promote thrombogenesis. Unfortunately, numerous case reports and series have documented recurrent emboli despite adequate anticoagulation with warfarin^{50,55} or heparin⁵⁶. Clearly, these events can best be reduced or prevented by reducing eosinophil counts to normal levels in the blood and tissues. When this is not possible, however, anticoagulation should be reserved for high-risk patients (i.e., with evidence of intracardiac thrombosis or recurrent thromboembolic events) or when anticoagulation is indicated for other reasons.

There are no data to support the preferential use of heparin, low molecular weight heparin, warfarin or newer agents in patients with HES, but data from studies of secondary prevention after acute coronary syndrome would suggest that anti-platelet therapy is likely to be less effective than other modalities⁵⁷. The recommended duration of anticoagulation is also unclear, but discontinuation of therapy can be considered if eosinophilia is reliably controlled, as in imatinib treatment of FIP1L1/PDGFRA-positive disease, and there is no evidence of residual thrombus. Finally, although eosinophilia may be the primary cause of hypercoagulability in a patient with HES and a thromboembolic event, other potentially

contributing factors, including immobility, acquired or genetic causes, hormone therapy or other offending drug use, should be considered and appropriate interventions initiated.

Prevention of steroid toxicity

Since HESs are chronic diseases and patients are often treated with corticosteroids for many months or years, close observation for signs of steroid toxicity, including diabetes, hypertension, osteoporosis, cataracts, glaucoma, myopathy and depression, is essential. American College of Rheumatology (ACR) Task Force guidelines should be followed to prevent osteoporosis⁵⁸. These include: 1) calcium intake of 1200 mg/day and vitamin D intake of 800 international units/day through diet and/or supplements for all patients taking corticosteroids, 2) serial bone mineral density scanning and 3) bisphosphonate treatment in all high-risk patients, as well as post-menopausal women and men ≥ 50 years of age beginning corticosteroid therapy with an anticipated duration of ≥ 3 months. Although official guidelines are lacking, prophylaxis to prevent *Pneumocystis jiroveci* infection is generally recommended for patients receiving ≥ 20 mg of prednisone equivalent daily for >1 month.

Anti-depressants

As is the case in a wide variety of chronic illnesses, depression is extremely common in patients with a HES. Although the causes are likely multifactorial in this setting, depression can be provoked or exacerbated by corticosteroid and/or interferon-alpha therapy. Consequently, vigilance for subtle signs of depression is an important part of the management of patients with HESs. In addition, empiric antidepressant therapy should be considered prior to initiation of interferon-alpha therapy.

Conclusions

Given the heterogeneity of HESs, which range from asymptomatic eosinophilia of unknown significance to eosinophilic leukemia, a unified approach to patient management is difficult. Consequently, a systematic approach, taking into account the severity and nature of the clinical manifestations, the mechanism of action and side effect profiles of available therapies, and the underlying etiology of the eosinophilia (if known), is essential. The flexibility of this approach will become increasingly important as newer targeted therapies and diagnostic tests become available.

Acknowledgments

SUPPORT: This work was supported by the Intramural Program of the NIAID/NIH (ADK) and the Swiss National Science Foundation (HUS).

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Figure 1.
Initial approach to the patient with eosinophilia $>1,500/\text{mm}^3$

A

B

C

Figure 2.
Treatment-based algorithm for HESs

Table 1

Optimal minimum evaluation prior to initiation of therapy in patients with presumed HES

Routine laboratory testing	Specialized laboratory testing	Procedures
CBC with differential	FIP1L1/PDGFR α analysis by PCR or FISH	Bone marrow biopsy and aspirate with cytogenetics
Routine chemistries, including tests of liver and renal function	T and B cell receptor rearrangement studies	Chest/abdomen/pelvis CT with contrast
Serum immunoglobulin levels, including IgE	Lymphocyte phenotyping by flow cytometry *	Transthoracic echocardiogram
Serum B12 level	Serum tryptase level	Pulmonary function tests, including lung volumes
Serum troponin level		Biopsy of affected tissues (if feasible)
Serum ANCA with corresponding autoantibodies ** (if vasculitis suspected)		Other testing as indicated by signs and symptoms

* Antibodies specific for the following additional markers should be included if routine phenotyping is normal and L-HES is suspected: CD2, Cd5, CD6, CD7, CD25, CD27, CD45RO, TCR α/β , TCR γ/δ , HLA-DR and CD95

** c-ANCA-PR3/p-ANCA-MPO

Table 2

Treatment-based classification of HESs

Subgroup	Criteria for Definitive Diagnosis	Criteria for Probable Diagnosis
M-HES	<ul style="list-style-type: none"> Demonstrated molecular or cytogenetic abnormality associated with HES, including PDGFRA fusion genes Exclusion of D816V KIT-positive systemic mastocytosis, CMML-eo and other hematologic malignancies in which eosinophils are not the primary lineage affected 	<p>≥ 4 of the following features¹⁶:</p> <ul style="list-style-type: none"> elevated serum B12 level elevated serum tryptase level splenomegaly anemia or thrombocytopenia increased circulating myeloid precursors dysplastic eosinophils myelofibrosis increased scattered spindle-shaped mast cells in bone marrow (without paratrabecular aggregates)
L-HES	<ul style="list-style-type: none"> Cytokine-producing clonal T cells Exclusion of leukemia/lymphoma 	<ul style="list-style-type: none"> Cytokine-producing non-clonal T cells T cells with an abnormal immunophenotype
Organ-restricted HES	<ul style="list-style-type: none"> Since progression to other organ systems in the future cannot be excluded, definitive diagnosis is impossible 	<ul style="list-style-type: none"> Biopsy demonstrating marked tissue eosinophilia confined to a single organ system No evidence of defined trigger (i.e., drug hypersensitivity, helminth infection)
HES with eosinophilic vasculitis (CSS)	<ul style="list-style-type: none"> Biopsy demonstrating eosinophilic vasculitis 	<p>≥ 4 of the following criteria³⁴:</p> <ul style="list-style-type: none"> Asthma Peripheral blood eosinophilia >10% Mono- or polyneuropathy Non-fixed pulmonary infiltrates Paranasal sinus abnormality Extravascular eosinophils in tissue biopsy
Cyclic angioedema and eosinophilia (Gleich's syndrome)	<ul style="list-style-type: none"> Demonstration of 24–30 day cycling of eosinophils and symptoms in the absence of therapy 	<ul style="list-style-type: none"> Periodic eosinophilia and angioedema Increased serum IL-5 Presence of CD3-CD4+ T cells Increased serum IgM
Hypereosinophilia of unknown significance	<ul style="list-style-type: none"> None 	<ul style="list-style-type: none"> Asymptomatic peripheral blood eosinophilia >1,500/mm³ with no evidence of tissue infiltration or organ dysfunction
Familial eosinophilia	<ul style="list-style-type: none"> Demonstration of autosomal dominant inheritance or genetic linkage 	<ul style="list-style-type: none"> Peripheral blood eosinophilia >1,500/mm³ with or without symptoms in genetically-related family members from several generations