Title
How I Treat Hypereosinophilic Syndromes

Short Title
Hypereosinophilic Syndromes

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Abstract

Hypereosinophilic syndromes (HES) are a heterogeneous group of uncommon disorders characterized by marked peripheral eosinophilia and end organ manifestations attributable to the eosinophilia or unexplained in the clinical setting. Whereas corticosteroids remain the mainstay of treatment for most patients, recent diagnostic advances and the development of novel targeted therapies, including tyrosine kinase inhibitors and humanized monoclonal antibodies, have increased the complexity of therapeutic decisions in HES. This review presents a treatment-based approach to the diagnosis and classification of patients with peripheral blood eosinophilia ≥1,500/mm³ and discusses the role of currently available therapeutic agents in the treatment of these patients.

Introduction

The idiopathic hypereosinophilic syndrome (HES) was first defined by Chusid in 1975 as 1) persistent eosinophilia of ≥1500 eosinophils/mm³ for longer than 6 months, or death before 6 months associated with signs and symptoms of hypereosinophilic disease, 2) a lack of evidence for parasites, allergic or other known causes of eosinophilia and 3) presumptive signs and symptoms of organ involvement. Although it was recognized at the time that this definition included a spectrum of disorders that varied considerably in their clinical manifestations, responses to treatment and prognosis, few diagnostic tests were available to reliably distinguish among potential HES variants. Consequently, therapeutic decisions were limited. Corticosteroids were first line therapy for most patients meeting criteria for HES. Alternative therapies for patients failing corticosteroid
therapy included cytotoxic agents, such as hydroxyurea and vincristine, and immunomodulatory agents, of which interferon-α showed the most promise.

Despite aggressive therapy, some patients with HES developed severe, often fatal, complications, including endomyocardial fibrosis and neurologic involvement. Many of these patients were men with markedly elevated leukocyte counts, anemia, thrombocytopenia, splenomegaly and other features of myeloproliferative disease. The discovery of the fusion tyrosine kinase FIP1L1/PDGFRA (F/P), the most common mutation associated with this “myeloproliferative variant” HES (M-HES), both confirmed that a subset of HES patients has a form of chronic eosinophilic leukemia (CEL) and provided an explanation for the response of these patients to the tyrosine kinase inhibitor, imatinib. This has dramatically altered the approach to treatment in HES. Similarly, the identification of a second distinct subset of HES patients with lymphocytic variant HES (L-HES) in whom eosinophilia is due to the secretion of eosinophilopoietic cytokines by phenotypically aberrant populations of T cells (as defined by flow cytometry) has had important implications with respect to treatment choice and monitoring for this subgroup of HES patients.

As additional HES variants are identified and the number of targeted therapies continues to expand, it will becoming increasingly important to identify the HES variants most likely to respond to specific therapies and to define the long-term efficacy and toxicities of these agents. This review presents an approach to the diagnosis and treatment of
patients presenting with eosinophilia $\geq 1500/\text{mm}^3$ that is based on the current state of knowledge with respect to the etiologies of HES and available therapies.

**Confirmation of the diagnosis of HES**

Since the differential diagnosis of eosinophilia $\geq 1500/\text{mm}^3$ is quite broad, the most important step in treating HES is excluding disorders associated with secondary eosinophilia that require specific therapies not directed primarily at the eosinophilia. These include parasitic infections, drug hypersensitivity reactions and neoplasms (Table 1). Although the optimal evaluation will differ for individual patients and is beyond the scope of this review, a number of general principles warrant mention.

First, the clinical manifestations of HES can be indistinguishable from those due to marked eosinophilia of other causes. Endomyocardial fibrosis, for example, has been reported in association with eosinophilia in a wide variety of disorders, including *Loa loa* infection $^{10}$ and adenocarcinoma of the lung $^{11}$. Second, drug hypersensitivity reactions should always be considered early in the evaluation of unexplained eosinophilia. Although some agents are associated with specific clinical syndromes, such as semisynthetic penicillins and interstitial nephritis, the clinical manifestations of drug-induced eosinophilia are often indistinguishable from those of HES. Furthermore, the list of agents that have been associated with eosinophilia is extensive and includes prescription and non-prescription drugs as well as dietary supplements and herbal remedies. Consequently, all non-essential agents should be discontinued before a diagnosis of HES is made. Third, evaluation for a parasitic cause of eosinophilia should
be dictated by the exposure history, clinical signs and symptoms. The exception is strongyloidiasis, which is often asymptomatic and is endemic worldwide. Because of the possibility that patients treated with steroids can develop hyperinfection syndrome, a potentially fatal form of strongyloidiasis, *Strongyloides* infection should be excluded by serologic testing in all patients with eosinophilia and a plausible history of exposure. Finally, eosinophilia can precede other clinical manifestations of an occult neoplasm, sometimes by many years. Thus, patients suspected of having HES should be evaluated with radiologic studies, bone marrow examination and other testing for neoplasia as appropriate depending on the patient’s age, gender and other risk factors.

Since the identification of the F/P chromosomal mutation in patients with M-HES and the demonstration of clonal T cells in patients with L-HES, there has been controversy over the classification of hypereosinophilic syndromes and whether these clinical entities, reclassified in the 2008 WHO guidelines as myeloid neoplasms and peripheral T cell lymphoma not otherwise specified, respectively, should be considered part of the continuum of HES. Although strictly speaking, the new WHO classification is correct, I believe that there is value in grouping patients by clinical presentation with respect to treatment decisions. This is a similar approach to that of Chusid and his contemporaries, who viewed HES as “a continuum of hypereosinophilic disease with eosinophilic leukemia existing at one pole.”
Differentiation of HES subtypes

At a 2005 international consensus workshop on the treatment of HES, a classification scheme was proposed with the goal of subdividing patients meeting the definition of HES into clinical groups (or variants) to facilitate the approach to treatment. Six clinical groups were described: 1) myeloproliferative variant HES (including F/P-negative HES with myeloproliferative features, F/P-positive HES/CEL, and CEL with cytogenetic abnormalities and/or increased blasts); 2) lymphocytic variant HES (HES with a demonstrable clonal or phenotypically aberrant lymphocyte population); 3) familial eosinophilia (including an autosomal dominant form of marked eosinophilia that has been mapped to chromosome 5q31-33); 5) undefined HES (idiopathic HES with or without symptoms, including episodic variants); 6) overlap HES (eosinophilic disease restricted to a single organ system accompanied by peripheral eosinophilia ≥1500/mm³) and associated HES (eosinophilia ≥1500/mm³ in the setting of another diagnosis, such as sarcoidosis or inflammatory bowel disease, in which eosinophilia has been described as a feature in a subset of affected patients). Although the proposed scheme is far from perfect and is likely to evolve as additional diagnostic tools become available, it provides a framework upon which to base treatment decisions.

General approach to treatment

The first question to address with respect to treatment of HES is whether the patient requires urgent intervention. Patients presenting with potentially life-threatening complications, including cardiac or neurologic involvement, and marked eosinophilia should be treated empirically with high dose corticosteroids (e.g. intravenous
methyprednisolone at a dose of 1 mg/kg/day) to prevent progression of end organ
damage. Although every effort should be made to obtain necessary diagnostic studies,
including bloodwork, imaging studies and biopsies of affected tissues prior to initiating
corticosteroid therapy, treatment should not be delayed in the face of worsening signs and
symptoms. Empiric double dose ivermectin (200 mcg/kg x 2 days) should be given to
patients with potential exposure to *Strongyloides*.

In patients with aggressive disease unresponsive to several days of high dose
corticosteroids, addition of a second agent should be guided by the clinical presentation.
Imatinib therapy should be considered early in a male patient presenting with new onset
myocarditis and marked eosinophilia; whereas a female patient with a history of asthma
and nasal polyps presenting with myocarditis and dramatic eosinophilia would be more
likely to have Churg-Strauss vasculitis and to benefit from sustained corticosteroid
therapy. Vincristine, used to rapidly lower eosinophil counts in patients with HES,
should be reserved for patients with rapidly progressive, life-threatening disease
unresponsive to high dose steroids and imatinib therapy.

Once the patient is clinically stable, the evaluation should proceed with the goal of
confirming the diagnosis of HES and classifying the patient into one of the described
HES variants (Figure 2). Treatment of M-HES, L-HES and idiopathic HES will be
discussed below. Distinguishing between these disorders and the associated or overlap
syndromes can be extremely difficult and is beyond the scope of this review. At the
present time, there are no data to suggest that familial eosinophilia requires treatment
unless signs and symptoms of organ involvement become apparent \textsuperscript{15}, in which case the approach would be similar to that for treatment of undefined HES.

Regardless of the etiology of the eosinophilia, patients should be monitored at least at six-month intervals for progression of organ involvement. In addition to the evaluation of known affected organ systems, occult cardiac and/or pulmonary involvement should be assessed with serum troponin levels, EKG, echocardiography and pulmonary function testing.

**Treatment of HES variants**

Myeloproliferative HES/CEL. The availability of the tyrosine kinase inhibitor, imatinib mesylate, has led to a dramatic decrease in the morbidity and mortality of F/P-positive HES/CEL. Response rates approach 100\% in most series, and primary drug resistance is rare \textsuperscript{16}. Consequently, imatinib has become the first-line treatment of choice for this condition, irrespective of the severity of clinical manifestations. Although the utility of imatinib therapy in patients who do not have a detectable PDGFRA fusion gene remains controversial \textsuperscript{17}, a trial of imatinib should be considered in patients presenting with aggressive disease unresponsive to corticosteroids and/or features of myeloproliferative disease. Of note, D816KIT-positive systemic mastocytosis overlaps in clinical presentation with F/P-positive HES/CEL but is resistant to imatinib \textsuperscript{18,19}. The two disorders can most reliably be distinguished by molecular testing, although a clinical scoring index has been developed that can be useful if such testing is not available \textsuperscript{20}. 

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The F/P fusion is 50-fold more sensitive to imatinib than bcr/abl, and molecular remission can be maintained in most patients with F/P-positive disease with low doses of imatinib (as little as 100 mg/week in some series). Nevertheless, data from chronic myelogenous leukemia (CML) suggest that initiation of therapy with higher doses (e.g. 400 mg/day) leads to longer remission. Thus, it seems prudent to initiate therapy with imatinib 400 mg/day and to taper the dose only after a complete and stable clinical, hematologic and molecular remission has been achieved.

Rapid institution of therapy is important to prevent irreversible damage, including endomyocardial fibrosis and sequelae of thromboembolic events. The side effect profile of imatinib in HES/CEL appears to be similar to that described for CML with the exception of acute necrotizing myocarditis, a rare complication described in patients with HES and pre-existent cardiac involvement. Consequently, it is recommended that patients with known cardiac manifestations or an elevated serum troponin receive high dose corticosteroids during the first two weeks of imatinib therapy.

In patients with PDGFRA-associated disease, the response to imatinib therapy is extremely rapid with resolution of eosinophilia and improvement in clinical symptoms occurring within the first week of therapy and normalization of bone marrow studies within the first month. Molecular remission occurs in most, if not all, patients, but may take considerably longer (12-18 months in some cases). Although the kinetics of response tends to be slower in patients without the F/P mutation and higher doses of imatinib may be necessary, persistent eosinophilia >1500/mm³ after 1 month
treatment should be considered a treatment failure. Repeat bone marrow examination should be performed in all patients within the first several months of imatinib therapy to confirm remission. This is particularly true for F/P mutation-negative patients experiencing a suboptimal or partial response to therapy, as unmasking of pre-B cell acute lymphoblastic leukemia by imatinib has been reported in at least one patient presenting with characteristic clinical manifestations of HES 28.

Once a stable dosing regimen is achieved, efficacy should be monitored with monthly eosinophil counts and regular assessment of organ involvement (see above). Since molecular relapse typically occurs prior to the recurrence of eosinophilia and clinical manifestations 29, F/P-positive patients should be tested for the presence of the fusion gene every 3-6 months. A positive test should raise concern for drug resistance and prompt an increase in imatinib dose.

Imatinib therapy controls, but does not cure, HES/CEL 29, and isolated instances of drug resistance have been reported 3,26. Other tyrosine kinase inhibitors effective in the treatment of CML, including nilotinib 30 and sorafenib, 31 have been demonstrated to have activity against F/P in vitro and are likely to be useful clinically in the event of imatinib-resistance. Bone marrow transplantation remains the only curative option and has been used successfully in F/P-positive HES/CEL 32, but should be reserved for patients with aggressive disease unresponsive to tyrosine kinase inhibition.
Lymphocytic variant HES (L-HES). Corticosteroids are the first line therapy for symptomatic L-HES, and most patients respond rapidly to moderate to high dose therapy (30-60 mg prednisone equivalent daily). Once the eosinophil count has normalized and symptoms have improved, slow tapering to ≤10 mg prednisone equivalent daily should be attempted. In patients who experience significant corticosteroid side effects or who fail to respond adequately to therapy, a second agent should be added. Among commercially available steroid-sparing agents, interferon-α has effects on both eosinophils and T cells and has been used most extensively. Because of theoretical considerations that interferon-α monotherapy could lead to outgrowth of the abnormal lymphocyte populations in some patients, it has been suggested that interferon-α be administered only in combination with glucocorticoids in patients with proven L-HES.

Alternative agents for which there is some evidence of efficacy in L-HES include mepolizumab and alemtuzumab. In contrast, data to date suggest that imatinib is not effective in L-HES, although it should be noted that rare cases of T cell clones accompanying F/P-positive HES/CEL have been reported.

Because of the increased risk of development of T cell lymphoma in patients with L-HES, lymphocyte counts should be followed every three months and the proportion of aberrant T cells assessed by peripheral blood flow cytometry every six months. Follow-up bone marrow examination with cytogenetics should be performed at regular intervals (every 1-2 years) as cytogenetic abnormalities, particularly 6q- chromosomal deletions, may be an early marker of progression to lymphoma.
Undefined HES.

Despite comprehensive evaluation, more than 50% of patients with HES cannot be classified into either of the two previously discussed categories. Such patients can, however, be divided into three groups on the basis of clinical manifestations: benign (without evidence of end organ involvement, including subclinical cardiac involvement as assessed by serum troponin levels), complex (with evidence of multisystem involvement) and episodic (with clinical signs and symptoms that remit and recur spontaneously).

Although patients with prolonged asymptomatic eosinophilia $\geq 1500/\text{mm}^3$ (benign eosinophilia) certainly exist, it may be difficult at the time of presentation to distinguish these patients from patients with early HES who will go on to develop clinical manifestations. A variety of clinical markers of disease progression have been proposed, including serum levels of eosinophil granule proteins; however, none has been validated to date. Thus, since the agents used to treat HES are not without toxicity and can be very costly, it seems prudent to follow clinically asymptomatic patients with idiopathic HES closely without treatment for the development of signs and symptoms.

The mainstay of treatment for symptomatic idiopathic HES, whether constant or episodic, remains glucocorticoids. Whereas the majority of patients will respond, at least initially, to high dose corticosteroids (e.g. prednisone 1 mg/kg daily), the most appropriate starting and maintenance doses are unknown and should be guided by the clinical manifestations
in the individual patient. For example, a patient with aggressive disease or in whom Churg-Strauss vasculitis is suspected should be treated with high dose corticosteroids for a minimum of 2-4 weeks before a slow taper to the lowest dose at which symptoms and eosinophilia remain suppressed. Conversely, a patient with dermatologic manifestations and no other organ involvement could be started on low dose therapy (10-20 mg prednisone) with dose adjustment depending on the clinical response. In patients with gastrointestinal symptoms who do not respond to oral corticosteroids, a short course of intravenous therapy should be considered to ensure absorption with conversion to oral steroids once a clinical response is achieved.

As in L-HES, a slow taper to ≤10 mg prednisone equivalent should be attempted. Patients requiring higher corticosteroid doses, or in whom significant toxicity develops, should receive a second agent. Daily hydroxyurea (1-2 g orally) and interferon-α (1-3 mU subcutaneously), the most widely used agents, are each effective in approximately 30% of patients, although toxicity is common. Low dose hydroxyurea (500 mg daily) appears to potentiate the effects of interferon-α without increasing its toxicity and is a reasonable alternative. As discussed above, a trial of imatinib should be considered for steroid-refractory patients, as rare responses in F/P-negative patients have been reported. A number of additional agents, including chlorambucil, vincristine, etoposide, cladribine, cytarabine, methotrexate, cyclosporine and cyclophosphamide, have been used to treat small numbers of steroid-unresponsive patients with varying success, but cannot be routinely recommended.
Among the agents in clinical development, mepolizumab (GlaxoSmithKline), a humanized monoclonal anti-IL-5 antibody, has been the best studied. After promising results in pilot studies, a double-blind, placebo-controlled trial in 85 F/P-mutation negative patients demonstrated that monthly mepolizumab was safe and effective as a steroid-sparing agent in HES. Mepolizumab is currently available only for compassionate use in patients with life-threatening HES refractory to standard therapies (www.clinicaltrials.gov).

Conclusions

HES are a heterogeneous group of uncommon disorders, ranging from benign idiopathic eosinophilia to eosinophilic leukemia. Consequently, therapeutic choices should be guided not only by the severity of the clinical manifestations and the side effect profile of the agents, but by the underlying etiology of the eosinophilia. As the number of new and expensive targeted therapies continues to grow, a logical etiology-based approach to treatment will become increasingly important.

Acknowledgments

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References


Table 1. Causes of marked eosinophilia other than HES

<table>
<thead>
<tr>
<th>Category</th>
<th>Examples (non-inclusive)</th>
</tr>
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<tbody>
<tr>
<td>Allergic disorders*</td>
<td>Asthma, atopic dermatitis</td>
</tr>
<tr>
<td>Drug hypersensitivity</td>
<td>Varied</td>
</tr>
<tr>
<td>Infection</td>
<td></td>
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<tr>
<td>Helminth</td>
<td>Varied, including strongyloidiasis, hookworm infection, filariasis</td>
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<tr>
<td>Ectoparasite</td>
<td>Scabies, myiasis</td>
</tr>
<tr>
<td>Protozoan</td>
<td>Isosporiasis, <em>Sarcocystis</em> myositis</td>
</tr>
<tr>
<td>Bacterial</td>
<td>Chronic tuberculosis, resolving scarlet fever</td>
</tr>
<tr>
<td>Fungal</td>
<td>Varied, including coccidiomycosis, allergic bronchopulmonary aspergillosis</td>
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<tr>
<td>Viral</td>
<td>HIV</td>
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<tr>
<td>Neoplasm</td>
<td>Leukemia</td>
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<td></td>
<td>Lymphoma</td>
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<td></td>
<td>Solid organ adenocarcinoma</td>
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<tr>
<td>Autoimmune and idiopathic disorders**</td>
<td>Connective tissue disorders</td>
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<tr>
<td></td>
<td>Sarcoidosis</td>
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<tr>
<td></td>
<td>Inflammatory bowel disease</td>
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<tr>
<td></td>
<td>Autoimmune lymphoproliferative disorder</td>
</tr>
<tr>
<td>Other</td>
<td>Hypoadrenalism</td>
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<tr>
<td></td>
<td>Radiation exposure</td>
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<tr>
<td></td>
<td>Cholesterol embolization</td>
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IL-2 therapy

*Allergic disorders, including asthma and atopic dermatitis, are common in patients with L-HES and idiopathic HES. Consequently, the distinction between allergic disease with marked eosinophilia and HES with concomitant allergic disease may be impossible.

**Marked peripheral blood eosinophilia can occur in the setting of a wide variety of autoimmune and idiopathic disorders, particularly those characterized by abnormal lymphocyte proliferation or activation. Signs and symptoms of HES are infrequent and can be difficult to distinguish from manifestations of the underlying disorder.
Figure 1. Initial approach to the patient with possible HES

Peripheral eosinophilia $\geq 1,500/mm^3$

Severe or potentially life-threatening clinical manifestations
OR
Eosinophil count >100,000/mm$^3$

Yes

Limited diagnostic evaluation to include:
- Routine blood studies
- Serum troponin
- Serum tryptase and B12 levels
- FIP1L1/PDGFRA analysis
- Lymphocyte clonality studies
- Bone marrow biopsy with cytogenetics
- Chest/abdomen/pelvis CT
- Echocardiogram
- Biopsy of affected tissues (if feasible)

No

Proceed with evaluation for possible HES

Empiric treatment with high dose steroids (+ ivermectin, if potential exposure to *Stronglyloides*)

Response?

Yes

Proceed with evaluation

No

Add second agent
Figure 2. Evaluation of the patient with possible HES.

Peripheral eosinophilia ≥1,500/mm³

Secondary cause requiring specific treatment not directed at eosinophilia*

Yes

Treat as appropriate

Resolution?

Yes

STOP

No

Continue evaluation for presumed HES to include:
- Routine blood studies
- Serum troponin
- Serum tryptase and B12 levels
- FIP1L1/PDGFRA analysis
- Lymphocyte clonality studies
- Bone marrow biopsy with cytogenetics
- Chest/abdomen/pelvis CT
- Echocardiogram
- Pulmonary function tests
- Biopsy of affected tissues (if feasible)
- Other testing as indicated by signs and symptoms

No

Continue evaluation for presumed HES

* These include, but are not limited to, drug hypersensitivity, infection, hypoadrenalism, and solid organ neoplasm.
Figure 3. Treatment-based approach to the patient with presumed HES.

<table>
<thead>
<tr>
<th>HES variant</th>
<th>First-line therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>M-HES/CEL</td>
<td>Imatinib mesylate 400 mg po daily (+ steroids if evidence of cardiac involvement)</td>
</tr>
<tr>
<td>L-HES</td>
<td>Corticosteroids</td>
</tr>
<tr>
<td>Familial HES</td>
<td>Asymptomatic: no therapy Symptomatic: see IHES</td>
</tr>
<tr>
<td>Overlap HES</td>
<td>Dictated by organ involved – often topical corticosteroids</td>
</tr>
<tr>
<td>Associated HES</td>
<td>Treat underlying disorder</td>
</tr>
<tr>
<td>Episodic?</td>
<td>Corticosteroids</td>
</tr>
<tr>
<td>Idiopathic HES</td>
<td>Corticosteroids</td>
</tr>
<tr>
<td>Benign HES</td>
<td>No therapy</td>
</tr>
</tbody>
</table>

* ≥4 of the following: dysplastic eosinophils, serum B12 >1000 pg/ml, serum tryptase > 12 ng/ml, anemia and/or thrombocytopenia, splenomegaly, bone marrow cellularity >80%, myelofibrosis, spindle-shaped mast cells >25%
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