# Hypereosinophilic Syndrome: Current Approach to Diagnosis and Treatment*

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## Key Words

chronic eosinophilic leukemia, eosinophil-associated gastrointestinal disorders, Churg-Strauss vasculitis, episodic angioedema and eosinophilia, chronic eosinophilic pneumonia, familial eosinophilia

## Abstract

Hypereosinophilic syndrome is a heterogeneous group of rare disorders characterized by marked blood or tissue eosinophilia resulting in a wide variety of clinical manifestations. Although the existence of clinical subtypes (or variants) of HES has been appreciated for some time, the recent characterization of some of these variants at the molecular and immunologic levels has demonstrated dramatic differences in disease pathogenesis, response to treatment, and prognosis depending on the etiology of the eosinophilia. This, together with the availability of novel targeted therapies, including tyrosine kinase inhibitors and monoclonal antibodies, has fundamentally altered the approach to the diagnosis and treatment of HES.

## INTRODUCTION

Hypereosinophilic syndrome (HES) is a diverse group of rare disorders characterized by marked peripheral blood and tissue eosinophilia that results in a wide variety of clinical manifestations, ranging from fatigue and other nonspecific complaints to potentially fatal endomyocardial fibrosis and neurologic involvement (1). A number of HES subtypes, or variants, with distinct etiologies have recently been identified (2–4). Clinical characterization of patients with these HES variants suggests that the underlying etiology of the eosinophilia may influence the degree of eosinophil activation and, consequently, play an important role in determining the severity and distribution of organ damage in HES (5, 6). The ability to distinguish between these HES variants combined with the availability of new treatment modalities, including tyrosine kinase inhibitors and monoclonal antibodies, that target specific molecules involved in disease pathogenesis, have revolutionized the diagnosis and treatment of HES.

**HES:** hypereosinophilic syndrome

**M-HES:** myeloproliferative-variant hypereosinophilic syndrome

**L-HES:** lymphocytic-variant hypereosinophilic syndrome

**CSS:** Churg-Strauss syndrome (vasculitis)

**EAE:** episodic angioedema and eosinophilia

**EGID:** eosinophil-associated gastrointestinal disorder

## DEFINITION OF HYPEREOSINOPHILIC SYNDROME

HES was first defined by Chusid et al. in 1975 by the following criteria (7): (*a*) sustained blood eosinophilia $\geq$1500 mm$^{-3}$ lasting for >6 months, (*b*) no identifiable cause, including parasitic infections and allergic disorders, and (*c*) signs and symptoms of organ involvement. Although this definition has proven very useful in identifying patients with rare eosinophil-associated disorders, it has four limitations.

First, although it has been appreciated that HES is comprised of many distinct disorders that differ with respect to clinical presentation, prognosis and response to therapy, recent advances in diagnostic techniques have led to the identification of underlying etiologies in some HES variants, including myeloproliferative-variant HES (M-HES)/chronic eosinophilic leukemia (2, 6), lymphocytic-variant HES (L-HES) (4, 8) and familial eosinophilia (3).

Second, a number of defined clinical syndromes, including Churg-Strauss syndrome (CSS) and episodic angioedema and eosinophilia (EAE), have traditionally been excluded from this definition even though they can be difficult to distinguish clinically from classic HES and are typically associated with marked peripheral eosinophilia. Furthermore, some patients with EAE have or develop phenotypically aberrant populations of lymphocytes (9) suggesting that EAE may be a form of L-HES.

Third, organ-restricted eosinophilic disorders, such as eosinophil-associated gastrointestinal disorder (EGID) and chronic eosinophilic pneumonia, are associated with peripheral eosinophilia in some but not all patients, despite a likely role for eosinophils in disease pathogenesis.

Finally, the absence of clinical manifestations in a patient with eosinophilia $\geq$1500 mm$^{-3}$ may reflect early disease rather than a benign laboratory abnormality.

The above-described issues led, in 2006, to the publication of a workshop summary report in which the definition of HES was expanded to include all disorders in which (*a*) eosinophils are markedly elevated in the peripheral blood ($\geq$1500 mm$^{-3}$) and (*b*) a secondary cause, such as parasitic infection, drug hypersensitivity reaction, or nonhematologic malignancy, cannot be identified (10) (see **Figure 1**). This new definition includes the HES variants whose mechanism is known, as well as disorders, such as EGID and chronic eosinophilic pneumonia, in which tissue eosinophilia is not consistently associated with blood eosinophilia $\geq$1500 mm$^{-3}$. It also includes eosinophil-associated diseases that were previously considered separate from HES, such as CSS and eosinophilia-myalgia syndrome, or may progress to HES, including EAE (Gleich's syndrome) and benign eosinophilia (eosinophilia $\geq$1500 mm$^{-3}$ in the absence of symptoms).

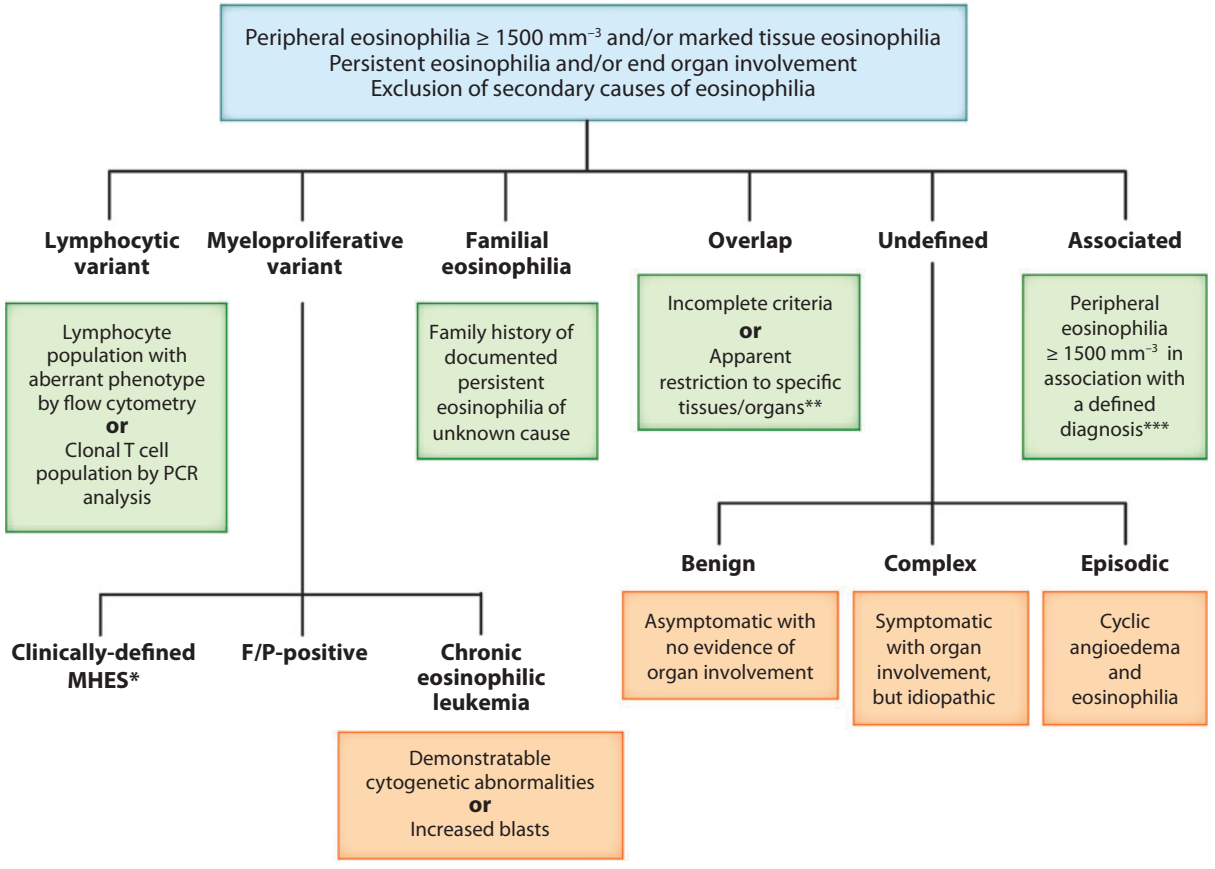


**Figure 1**

Classification of hypereosinophilic syndrome (HES) variants. *M-HES is clinically defined as peripheral eosinophilia ≥1500 $mm^{-3}$ and at least four of the following features: dysplastic eosinophils on peripheral smear, serum B12 level >1000 pg $ml^{-1}$, serum tryptase level >12 ng $ml^{-1}$, anemia and/or thrombocytopenia, hepatosplenomegaly, bone marrow cellularity >80%, spindle-shaped mast cells, myelofibrosis. **Examples of organ-restricted eosinophilic disorders that are inconsistently associated with peripheral blood eosinophilia include eosinophil-associated gastrointestinal disorders (EGID), chronic eosinophilic pneumonia, and eosinophilic fasciitis, among others. When accompanied by peripheral eosinophilia, these disorders meet Chusid's criteria for HES. ***Primary disorders that may be associated with peripheral blood eosinophilia ≥1500 $mm^{-3}$ include a wide range of disorders associated with immunodysregulation, such as inflammatory bowel disease, sarcoid, and autoimmune lymphoproliferative syndrome.

## Differential Diagnosis of HES

The clinical manifestations of secondary eosinophilia may be indistinguishable from those of HES, as in the case of endomyocardial fibrosis due to the hypereosinophilia of filarial infection (11) or pulmonary infiltrates and eosinophilia in the setting of a drug hypersensitivity reaction (12). Consequently, a diagnosis of HES requires exclusion of the many secondary causes of marked blood and tissue eosinophilia, including parasitic helminth infection, drug hypersensitivity reactions, and neoplasms (other than eosinophilic leukemia) (see **Table 1**). This is particularly important because the treatment of many of these disorders is dramatically different from that of HES. Although it is beyond the scope of this review to provide an exhaustive approach to the differential diagnosis of HES, three concepts are worth noting.

**Table 1 Selected causes of secondary eosinophilia**

| Category | Examples | Comment |
|---|---|---|
| Allergic disorders | asthma | mild to moderate eosinophilia |
| | atopic dermatitis | |
| | allergic rhinitis | |
| Drug hypersensitivity | diverse (see text) | ranges from asymptomatic to systemic and life-threatening |
| Infection | | |
| parasitic | helminth | with the exception of those listed, protozoa do not cause eosinophilia |
| | ectoparasite (scabies, myiasis) | |
| | protozoa (isosopora, sarcocystis) | |
| bacterial | resolving scarlet fever | bacterial infection generally causes eosinopenia |
| | chronic tuberculosis | |
| fungal | coccidiomycosis | |
| | allergic bronchopulmonary aspergillosis | |
| viral | HIV | associated with advanced infection, drug hypersensitivity, and/or hypoadrenalism |
| Neoplasm | myelogenous leukemia | in some hematologic neoplasms, eosinophils may be part of the neoplastic clone |
| | lymphocytic leukemia | |
| | lymphoma | |
| | adenocarcinoma of the bowel, lung, ovary or other solid organs | |
| Diseases associated with immunodysregulation | connective tissue disorders | |
| | sarcoid | |
| | ulcerative colitis | |
| | autoimmune lymphoproliferative syndrome | |
| Other | hypoadrenalism | |
| | radiation exposure | |
| | cholesterol embolization | |
| | systemic mastocytosis | |



First, drug hypersensitivity reactions are among the most common causes of marked peripheral eosinophilia, especially in the United States and Europe, and they can occur in response to many common prescription and nonprescription drugs, as well as dietary supplements and herbal preparations. Drug hypersensitivity reactions can be asymptomatic or accompanied by clinical manifestations, including but not limited to eosinophilic dermatitis, pulmonary infiltrates, interstitial nephritis, and hepatitis. The pattern of clinical involvement may suggest a particular agent, as in the case of interstitial nephritis and semisynthetic penicillins (13) or eosinophilia-myalgia syndrome and tryptophan (14); however, in most cases of drug hypersensitivity, the cause is not immediately apparent. Furthermore, the length of time of drug exposure before eosinophilia develops can be days to years. Multisystem involvement also occurs, as in the DRESS syndrome (drug rash with eosinophilia and systemic symptoms) (15), further complicating the distinction between drug hypersensitivity and HES. In view

of these considerations, the first step in any evaluation of marked persistent eosinophilia should be a careful drug history and discontinuation of all possible offending agents. For severe drug reactions, including DRESS syndrome, adjunct treatment with steroids may be helpful (16). It should be noted that, in some cases, eosinophilia requires months to resolve.

Second, although parasitic infections are often cited as the most common cause of eosinophilia worldwide, persistent marked eosinophilia tends to be restricted to helminth infections with a tissue invasion stage and ectoparasite infestations, including scabies (17) and myiasis (18). Whereas routine stool examinations are sufficient to diagnose many intestinal helminths, their sensitivity is poor in the detection of strongyloidiasis and schistosomiasis, two common infections that may be asymptomatic, persistent (up to several decades) and associated with potentially life-threatening complications (hyperinfection syndrome and central nervous system involvement, respectively). Tissue parasites, including filariae, *Trichinella*, and agents of visceral larva migrans, will also be missed. Thus, a detailed travel and exposure history is essential in the evaluation of marked eosinophilia. Serologic assessments and other specific diagnostic tests should be performed as suggested by the exposure history with one exception: serologic testing for strongyloidiasis should be performed and/or empiric treatment given for any patient with marked eosinophilia in whom steroid treatment is being contemplated to prevent the development of hyperinfection syndrome. Despite the lack of controlled trials, an empiric course of a broad-spectrum anthelmintic, such as albendazole or ivermectin, should also be considered before embarking on an extensive evaluation for presumed HES in patients with a history of exposure to helminth infection in whom a diagnosis remains elusive.

Finally, it is becoming increasingly clear that marked eosinophilia can occur in association with a wide variety of conditions associated with lymphocyte dysregulation or proliferation, including sarcoid (19), inflammatory bowel disease (20), advanced HIV infection (21), lymphoid neoplasms (22), and autoimmune lymphoproliferative syndrome (ALPS) (23). Eosinophilia appears to be a marker of advanced disease and poor prognosis in these disorders (21, 23, 24), despite the fact that direct sequelae of the eosinophilia are uncommon.

## Diagnostic Evaluation of Marked Eosinophilia

Given the broad spectrum of disorders associated with eosinophilia, the most appropriate evaluation of an individual patient with persistent, unexplained eosinophilia $\geq 1500\ mm^{-3}$ depends on a number of factors, including the duration and degree of the eosinophilia, the severity and nature of the end-organ manifestations, and the exposure history. Nevertheless, a minimum standard for all patients should include a complete history and physical examination, complete blood count and differential, routine chemistries, serum IgE and B12 levels, HIV serology, electrocardiogram, echocardiogram, pulmonary function tests, chest and abdominal computed tomography, and bone marrow aspirate and biopsy. Additional procedures and diagnostic biopsies should be guided by the clinical manifestations.

# HYPEREOSINOPHILIC SYNDROME VARIANTS

End-organ complications and prognosis are notoriously heterogeneous in patients with HES. This has led to the concept of HES subtypes or variants that can be distinguished on the basis of clinical and laboratory characteristics (10) (see **Figure 1**). The molecular and/or immunologic mechanisms of disease have begun to be identified for some of these HES variants, including M-HES (2, 25), L-HES (4, 8), EAE (26), eosinophilic esophagitis (27), and familial eosinophilia (3). Although these variants account for a minority of patients with HES in

most series (28, 29), their recognition is critical for optimal patient management because the clinical manifestations, responses to treatment, and prognosis vary considerably depending on the etiology of the eosinophilia.

**FIP1L1/PDGFRA (F/P):** Fip-1-like 1/platelet derived growth factor receptor alpha

## Myeloproliferative-Variant HES

The most convincing example of the correlation between a clinical HES variant and a specific molecular etiology is, without doubt, M-HES. Although it had been appreciated for some time that some patients with HES had features of a myeloproliferative disorder, it was the observation that the tyrosine kinase inhibitor imatinib had a dramatic effect in these patients that led to the identification of FIP1L1/PDGFRA (F/P), an imatinib-sensitive fusion tyrosine kinase caused by an interstitial deletion in chromosome 4 (2). This mutation can be detected by fluorescence in situ hybridization (FISH) and/or reverse transcriptase–polymerase chain reaction (RT-PCR) of peripheral blood or bone marrow. The F/P fusion was subsequently found to be present in the majority of patients with M-HES, a clinically defined HES variant characterized by an extreme male predominance, pathologic evidence of eosinophil-related tissue damage and tissue fibrosis, elevated serum tryptase levels, and myeloproliferative features, including splenomegaly, anemia, thrombocytopenia, bone marrow hypercellularity with reticulin fibrosis, and increased numbers of atypical mast cells (6). Prior to the availability of imatinib, mortality in this subgroup of patients was 30% within three years following diagnosis.

Although several additional fusion kinases have been identified in isolated patients (30), it is important to note that a molecular etiology cannot be identified in all patients with clinically defined M-HES. Some of these patients do respond to imatinib, however, providing strong evidence for the participation of other fusion partners and/or tyrosine kinases in disease pathogenesis (31).

There has been considerable controversy regarding the most appropriate designation (HES, chronic eosinophilic leukemia, or systemic mastocytosis) for F/P-positive disease. Each of these terms is used in the published literature to describe patients with this disorder (32). The most recent classification of myeloid disorders by the World Health Organization attempts to solve this problem by creating a separate category for myeloid neoplasms associated with eosinophilia and abnormalities of PDGFRA (33). Although recent data suggest that the most common form of systemic mastocytosis (associated with the imatinib-resistant D816KIT mutation) can be differentiated from F/P-positive disease using a simple clinical scoring system (34), M-HES without a known mutation may be clinically indistinguishable from F/P-positive disease. This has important implications with respect to therapeutic decisions (see below).

## Lymphocytic-Variant HES

Since the initial description of a patient with the clinical features of HES and the presence of a phenotypically aberrant lymphocyte clone (35), it has become increasingly apparent that L-HES is a distinct clinical variant of HES. The mechanism of eosinophilia in this variant is thought to be the production of eosinophilopoietic cytokines, particularly interleukin 5 (IL-5), by clonal populations of phenotypically abnormal, activated T lymphocytes. Definitive diagnosis relies on the demonstration of such a clone, most often CD3-CD4$^+$, in the peripheral blood by flow cytometry (36) (see **Table 2**). Demonstration of T cell clonality by T cell receptor rearrangement analysis is not essential but strongly supports this diagnosis. Serum elevations of IgE (36) and activation-regulated chemokine (TARC) (37) are common in patients with L-HES and may be helpful in making a presumptive diagnosis when flow cytometry is unavailable. Serum IL-5 levels, on the other hand, are not helpful as they may be normal or elevated in patients with L-HES and do not predict therapeutic responses (38).

In contrast to patients with M-HES, who typically have aggressive steroid-refractory

**Table 2 Diagnosis of selected HES variants[a]**

| |
|---|
| **Myeloproliferative variant** |
| Definitive |
| F/P or another PDGFRA fusion by RT-PCR, FISH, or other methods |
| eosinophil clonality by HUMARA analysis, karyotype, or other modality |
| Presumptive |
| ≥4 of the following: |
| increased serum tryptase level |
| increased serum B12 level |
| splenomegaly |
| anemia, thrombocytopenia |
| increased circulating myeloid precursors |
| dysplastic eosinophils |
| myelofibrosis |
| increased spindle-shaped mast cells in the bone marrow |
| clinical and hematologic response to imatinib or other tyrosine kinase inhibitors |
| **Lymphoproliferative variant** |
| Definitive |
| phenotypically aberrant T cell population[b] |
| clonal T cell rearrangement pattern by PCR |
| increased T cell production of eosinophilopoietic cytokines |
| Supportive |
| increased serum TARC |
| increased serum IgE |
| predominantly cutaneous manifestations |
| history of atopy |
| steroid-responsive |

[a]Abbreviations: FIP1L1/PDGFRA (F/P), Fip-1-like 1/platelet derived growth factor receptor alpha; RT-PCR, reverse transcriptase–polymerase chain reaction; FISH, fluorescence in situ hybridization; HUMARA, human androgen receptor gene analysis; TARC, T cell activation-regulated chemokine.

[b]Antibodies specific for the following additional markers should be included if routine phenotyping is normal and the lymphoproliferative variant is suspected: CD2, CD5, CD6, CD7, CD8, CD25, CD27, CD45RO, TCRα/β, TCRγ/δ, HLA-DR and CD95.



disease, L-HES generally has a more protracted course. L-HES occurs with equal frequency in men and women and is characterized by a high prevalence of dermatologic manifestations. Gastrointestinal symptoms and obstructive lung disease are also common, whereas tissue fibrosis, including endomyocardial fibrosis and myelofibrosis, are rarely seen. Although most patients respond to steroid therapy, the disease manifestations, as well as the side effects of treatment, are often debilitating. Furthermore, progression to lymphoma appears to occur with increased frequency in patients with L-HES, especially those with CD3-CD4$^+$ lymphocyte populations, and should be considered in the setting of increasing numbers of aberrant T cells or the development of lymphadenopathy (36). The presence of cytogenetic abnormalities appears to herald the development of lymphoma (39).

Although current estimates of the prevalence of L-HES are in the range of 10%–15% of patients meeting Chusid's criteria for HES (29, 40), this is likely an underestimate because current methods used to detect aberrant lymphocyte populations are insensitive. This hypothesis is perhaps best supported by the findings in episodic angioedema and eosinophilia (EAE),

a rare condition in which cyclic eosinophilia is accompanied by self-limited episodes of angioedema (26). Whereas EAE has been considered an undefined HES (see **Figure 1**), the finding that cyclic increases in serum IL-5 precede the eosinophilia in most cases of EAE, as well as the fact that some patients with this syndrome develop detectable T cell clones (9), suggests that this unusual clinical syndrome should, in fact, be classified as an L-HES. In patients whose primary complaint is swelling and/or weight gain, it is useful to measure eosinophil counts every three days for several weeks off therapy in order to identify this syndrome, since the periodicity can be missed in the setting of intermittent steroid treatment or if eosinophil counts are only obtained when symptoms are present.

### Familial Eosinophilia

Familial clustering has been described in a number of eosinophilic syndromes, including CSS (41) and eosinophilic esophagitis (42), but it appears to be uncommon in undefined HES, with only a few reports in the literature to date. In one such family, the gene responsible for the eosinophilia has been mapped to chromosome 5q31–33 (3). Despite marked eosinophilia (2000–6000/$mm^3$) from birth, a minority of family members appear to develop clinical manifestations consistent with the relative lack of evidence of eosinophil activation in these patients compared to patients with nonfamilial HES (5). When clinical disease does occur, it resembles F/P-associated HES with endomyocardial fibrosis and neurologic complications (43). Whether the sudden disease progression in a small number of these patients after a lifetime of asymptomatic eosinophilia represents a second mutation remains unknown at this time.

### Other HES Variants

For mutation-positive M-HES and L-HES, a definitive diagnosis can be made if specialized testing is available (see **Table 2**). However, for the majority of HES variants, diagnosis is less straightforward (though equally important). For example, a patient presenting with unexplained pulmonary infiltrates and peripheral eosinophilia could have any of several disorders, including chronic eosinophilic pneumonia, drug hypersensitivity, idiopathic HES, or CSS. Although most of these disorders can be managed with low-dose steroids to control symptoms, CSS is a multi-organ disease that requires immediate administration of high-dose corticosteroids (and in some cases cytotoxic agents) to prevent the potentially life-threatening complications of systemic vasculitis.

At present, there is no set of clinical and laboratory criteria that can reliably distinguish between undefined HES and most overlap syndromes. Even the gold standard for the diagnosis of CSS, the demonstration of eosinophilic vasculitis, is inadequate, since corticosteroids must often be initiated for clinical reasons prior to the procurement of biopsy specimens. The issue of diagnosis is even more complex when considering primary disorders associated with eosinophilia, in which eosinophilia is commonly, but not always, a marker of the underlying immunodysregulation and has no direct pathologic consequence (23). Finally, although some patients with eosinophilia $\geq$1500 $mm^{-3}$ remain asymptomatic for many years, it is unclear whether these patients represent one end of the spectrum of HES or a normal variant. Clearly, better diagnostic modalities are needed, both to prevent unnecessary and potentially toxic treatment of patients with high peripheral blood eosinophil counts but a low risk of developing life-threatening or disabling complications and, conversely, to recognize and aggressively treat patients at increased risk of disease progression.

## CURRENT APPROACHES TO THERAPY

Until recently, therapeutic interventions for all types of HES were similar. Corticosteroids were the first-line agent, followed by a variety of cytotoxic and immunomodulatory therapies,

including hydroxyurea and interferon-alpha. Although steroids remain the most commonly used therapy for most patients with HES, the development of novel targeted agents, including tyrosine kinase inhibitors and monoclonal antibodies, coupled with the recognition that HES variants behave differently with respect to treatment responses and prognosis, has dramatically altered the approach to treatment of HES.

## Corticosteroid Therapy

Steroids remain the first-line treatment for most patients with HES, with the exception of proven M-HES (see **Table 2**) (44). Steroids should also be used in addition to imatinib in patients with evidence of myocarditis, as suggested by electro- or echocardiographic assessment or the presence of an elevated serum troponin level, to prevent myocardial necrosis (45). Although the most appropriate initial steroid dose and the duration of steroid therapy have not been studied, it seems prudent to start with a moderate to high dose (≥40 mg prednisone equivalent) and to taper very slowly while following the eosinophil count closely. Using this approach, most, but not all, patients will respond initially to steroid therapy, and some will be able to be maintained on low doses for long periods. Over time, however, the toxicities of steroid therapy become limiting and alternative therapies must be used.

## Cytotoxic Agents

A number of cytotoxic therapies have been used for the management of steroid-refractory HES. Of these, hydroxyurea has been the most extensively studied and, at doses of up to 2 g $day^{-1}$, is associated with few side effects (46). Hydroxyurea is rarely useful as a single agent for the treatment of HES owing to dose-limiting cytopenias and other side effects (44). Furthermore, hydroxyurea cannot be used to acutely lower the eosinophil count because a therapeutic effect is generally not achieved for up to two weeks. Hydroxyurea in low doses (500–1000 mg daily) has been shown to enhance the efficacy of other agents, including prednisone (46), interferon-alpha (47), and imatinib (48), and is, therefore, of some utility in the treatment of HES.

## Immunomodulatory Agents

Immunomodulatory agents with effects on Th2 cytokine production and T cell proliferation, including interferon-alpha, cyclosporine, and intravenous immunoglobulin, have been shown to have a therapeutic effect in HES (44). Of these, interferon-alpha has been the most successful, achieving stable responses with relatively low doses (1–2 mU $day^{-1}$) over prolonged periods of time. Rarely, patients have remained in remission for extended periods following cessation of interferon therapy, suggesting that interferon may be curative in a small subset of individuals.

Even at low doses, systemic toxicity is common with interferon therapy and can be dose-limiting. The successful use of pegylated interferon to reduce the frequency of injections has been reported in HES, although the side-effect profile is comparable to that of the standard formulation (44). Combination therapy with steroids has been recommended in L-HES to prevent expansion of the clonal population and progression to lymphoma as a result of interferon inhibition of apoptosis of clonal $CD3^-CD4^+$ T cells (49).

## Tyrosine Kinase Inhibitors

Imatinib mesylate, a tyrosine kinase inhibitor, is the first agent to be approved by the U.S. Food and Drug Administration (FDA) for the treatment of HES and is considered the treatment of choice for F/P-positive HES and chronic eosinophilic leukemia. Response rates in this subgroup of patients are rapid and dramatic, with clinical, hematologic, and molecular remission rates approaching 100% within one month of treatment initiation (50) and few documented cases of drug resistance (2, 51). Unfortunately, imatinib is not curative in this disorder

(52). It is important to note that cardiac involvement is irreversible unless treatment is begun before fibrosis leads to permanent anatomic alterations (50, 53). Although side effects of imatinib therapy are generally mild and rarely lead to discontinuation of therapy, cardiac decompensation has been reported in patients with pre-existent cardiac involvement. This observation has prompted the recommendation for screening of all patients with a serum troponin prior to therapy initiation (45).

Clinical remission and normalization of eosinophil counts have been reported in patients treated with imatinib at doses as low as 100 mg weekly (54); however, some patients continue to have molecular evidence of the mutation at low doses. Furthermore, in view of the data from studies in chronic myelogenous leukemia, which suggest that clinical relapse is more common in patients with detectable residual disease, it seems prudent to begin imatinib treatment at 400 mg to achieve molecular remission and to then decrease the dose slowly, watching closely for evidence of molecular relapse.

The utility of imatinib therapy in patients without a PDGFRA-fusion kinase remains to be determined, although some patients, especially those who meet the clinical criteria for M-HES, have demonstrated a response (2, 28). In general, responses have been slower and have required higher imatinib doses than those in patients with F/P-associated disease. The development of resistance may also be more frequent (55). Imatinib does not appear to be useful in treating patients with L-HES or CSS and should not be used as first-line therapy in these patients (36).

Although imatinib is the only tyrosine kinase inhibitor FDA-approved for the treatment of HES and for which there are clinical data in patients with HES, several other commercially available agents, including nilotinib (56) and sorafenib (57), have demonstrated efficacy against FIP1L1/PDGFRA in vitro and in animal models. These are likely to be useful in patients with F/P-positive HES who fail a trial of imatinib.

## Monoclonal Antibody Therapy

Although humanized monoclonal anti-IL5 antibodies were first developed for the treatment of asthma, studies to date have failed to show improvement in clinical endpoints despite reduction of blood and sputum eosinophilia (58–60). Whether this therapeutic failure is due to incomplete depletion of eosinophils in lung tissue (61), inappropriate selection of study subjects, or the lack of a role for eosinophils in asthma remains uncertain.

In contrast, monoclonal anti-IL-5 antibody therapy for HES has a number of unique advantages related to the specificity of IL-5 for the eosinophil lineage and the central role of eosinophils in HES. Preliminary studies using two different anti-IL-5 antibodies, reslizumab (Schering-Plough, now being developed by Ception Technology) and mepolizumab (GlaxoSmithKline), demonstrated a dramatic and prolonged lowering of the peripheral eosinophil count in response to a single dose of antibody in a majority of HES patients regardless of the underlying etiology or baseline IL-5 level (62, 63). The therapy was extremely well tolerated, although a rebound in symptoms and eosinophilia associated with an increase in serum IL-5 levels was noted in one study as antibody levels decreased (64). More recently, mepolizumab was demonstrated to be safe and effective as a steroid-sparing agent in a multicenter, placebo-controlled trial of steroid-responsive, F/P-negative HES (38). Clinical, as well as histologic, improvement has also been reported in four patients with eosinophilic esophagitis who received three monthly doses of mepolizumab (65). Additional monoclonal antibodies targeting the eosinophil lineage, including a monoclonal antibody to the IL-5 receptor (MEDI-563, MedImmune), are currently in development and may prove promising. Unfortunately, none of these agents are currently available except in the context of clinical studies.

Of note, alemtuzumab, a monoclonal antibody to CD52 approved for use in T and B cell leukemias, has been used in isolated cases of

HES with some success (66), although its utility in the treatment of HES is limited by its side effects.

## Bone Marrow Transplantation

Bone marrow transplantation (BMT), including nonmyeloablative peripheral stem cell transplantation, has been used successfully in the treatment of HES. Although BMT is, at the present time, the only curative therapy for this disorder, the morbidity and mortality of the procedure preclude its use in most patients with HES. Hence, BMT should be reserved for patients with M-HES resistant to tyrosine kinase inhibitor therapy and patients with other forms of HES in whom end-organ damage is severe and progressive despite aggressive therapy.

### SUMMARY POINTS

1. HES is a heterogeneous group of rare disorders with differing etiologies.
2. The clinical manifestations of HES may be indistinguishable from those of secondary eosinophilia.
3. HES variant is an important predictor of disease pathogenesis, response to treatment, and prognosis.
4. Steroids remain the mainstay of treatment for most patients with HES.
5. Treatment with tyrosine kinase inhibitors is indicated for patients with proven M-HES.
6. Novel monoclonal antibody therapies, especially those targeting eosinophils, show promise for the treatment of HES.

### FUTURE ISSUES

1. Clinical criteria to distinguish HES variants.
2. Delineation of the molecular mechanisms for additional HES variants.
3. Identification of reliable noninvasive markers of disease activity and response to therapy.
4. Development of novel therapies targeting eosinophilopoiesis and eosinophil tissue infiltration.

## DISCLOSURE STATEMENT

The author is not aware of any biases that might be perceived as affecting the objectivity of this review.

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**Errata**

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