

Hypereosinophilic Syndrome

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Abstract Hypereosinophilic syndrome consists of a group of disorders characterized by abnormal accumulation of eosinophils in the blood or peripheral tissues, independent of known secondary causes of eosinophilia such as parasitic infection. Clinical manifestations of the condition are highly variable, ranging from asymptomatic eosinophilia to severe tissue damage and end-organ failure. This entity has been recognized for decades, with early studies identifying distinct groups of patients with differing symptoms, exam findings, laboratory abnormalities, and prognosis. In the past, these patients were treated with non-targeted immunosuppressive agents, often with limited efficacy. More recently, advances in the knowledge of eosinophil biology and molecular diagnostics have allowed for more specific delineation of the many disease subgroups that characterize hypereosinophilic syndrome. Identification of these groups has led to a personalized management approach to the condition, with improved diagnostic techniques as well as stratification of patients into more effective treatment groups. This review will discuss the evolution of the definition of hypereosinophilic syndrome, outline current disease classifications, provide a guide for evaluation and monitoring, and discuss current and future therapeutic modalities.

Keywords Eosinophilia · Hypereosinophilic syndrome · HES · L-HES · M-HES · Chronic eosinophilic leukemia · CEL · FIP1L1-PDGFRα

Abbreviations

HES	Hypereosinophilic syndrome
L-HES	Lymphocytic variant hypereosinophilic syndrome
M-HES	Myeloproliferative hypereosinophilic syndrome
CEL	Chronic eosinophilic leukemia
EGPA	Eosinophilic granulomatosis with polyangiitis
FIP1L1	Fip1-like 1
F/P	Fip1-like 1 platelet-derived growth factor receptor alpha
PDGFRα	Platelet-derived growth factor receptor alpha

Introduction

Definition/Background

Eosinophilia is defined as an elevation in the absolute eosinophil count (AEC), with severity divided into mild (AEC from 500 to 1500/mm³), moderate (AEC 1500–5000/mm³), and severe (AEC >5000/mm³) classifications [1]. In early descriptions of eosinophilia, there were often clear associations with causes including parasitic infections, malignancy, and autoimmune conditions. As more cases were reported and formally studied, a distinct patient population emerged. This group exhibited marked peripheral eosinophilia and end-organ eosinophilic infiltration with associated damage despite a lack of known etiology. The term “hypereosinophilic syndrome” (HES) was coined to describe this condition.

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In 1975, Chusid et al. established formal diagnostic criteria for HES to compare their own cohort of hypereosinophilic patients to all known patients described in the English-speaking literature. There were three initial requirements outlined for diagnosis of HES in this study. First, patients were required to have persistent eosinophilia $>1500/\text{mm}^3$ for greater than 6 months (or death before 6 months associated with signs and symptoms of hypereosinophilic disease). In addition, the diagnosis required a lack of evidence of secondary causes of eosinophilia. Finally, presumptive signs and symptoms of end-organ damage secondary to eosinophilia, including involvement of the skin, heart, lungs, gastrointestinal tract, or nervous system were needed [2]. These diagnostic criteria not only allowed for better characterization of patients but also provided a starting point for other studies to further define this unique patient population. Even in early studies of HES, it became clear that while patients often met the diagnostic criteria as outlined by Chusid, there were distinct subgroups with respect to presenting features, laboratory characteristics, complications, response to therapy, and natural history of disease.

This definition of HES was used for several decades. With advances in diagnostic and treatment modalities, the subgroups of HES patients became more clearly distinguished. Those with unique clinical and laboratory characteristics and variant responses to therapy were able to be better described in terms of molecular phenotypes. In 2006, a working group modified the definition of HES to include other previously distinct disease entities associated with eosinophilia, including eosinophilic granulomatosis with polyangiitis (EGPA, formerly known as Churg-Strauss syndrome), chronic eosinophilic pneumonia, and eosinophilic gastrointestinal disorders (EGIDs) [3].

In 2010, revisions to the previous HES diagnostic criteria were recommended based on further observations of patient subtypes. Given that some HES patients may develop severe clinical sequelae prior to the 6-month diagnostic period outlined in the Chusid's original definition, it was recommended that this time limit be eliminated. Rather, it was suggested to use an elevation of the AEC $>1500/\text{mm}^3$ on at least two occasions [4]. Further, as there were patients that developed significant tissue eosinophil infiltration and end-organ damage with peripheral AEC $<1500/\text{mm}^3$, it was recommended that an absolute AEC value not be a requirement for diagnosis. Patients with substantial tissue eosinophilia and marked peripheral eosinophilia could qualify for diagnosis. It was also recommended that the definition of HES includes the various molecular causes that had been elucidated since earlier descriptions. Finally, elimination of the requirement for end-organ damage was recommended, as it became clear that a subgroup of patients with elevated AEC did not develop end-organ dysfunction. These patients did not necessarily require treatment, but it was suggested that they may benefit from more regular monitoring [4].

Article/Discussion

Diagnosis/Classifications

Causes of Eosinophilia: Medications

Upon evaluation of eosinophilia, a careful history of medication use should be taken, with particular attention to groups of medications known to cause elevated AEC including anticonvulsants, antibiotics, and herbal supplements. However, it should be noted that any medication can cause eosinophilia. Eosinophilia may occur as the only manifestation of an adverse reaction to a medication and may be asymptomatic. Recent initiation of a medication is not a requirement for eosinophilia, as medications that have been used for years may be implicated. Furthermore, depending on the degree of eosinophilia, presence of end-organ dysfunction, and necessity of the medication in question, it may not be necessary to stop the offending agent [5]. Complications related to eosinophilia may be organ-specific. For instance, eosinophilic pulmonary infiltrates may be observed with multiple medications including nitrofurantoin and non-steroidal anti-inflammatory drugs [6]. Eosinophilic complications of acute interstitial nephritis (AIN) can be seen secondary to treatment with semi-synthetic penicillins, phenytoin, and cimetidine among others [7]. Hypersensitivity vasculitis may be characteristically seen during treatment with allopurinol [5].

Eosinophilia may also be part of a more generalized systemic drug reaction, such as drug rash, eosinophilia, and systemic symptoms (DRESS) syndrome, also known as drug-induced hypersensitivity syndrome (DIHS). DIHS often presents with fevers, hematologic abnormalities (including eosinophilia), and lymphadenopathy within 4–12 weeks of starting a causative medication. Inflammation of end organs, including pneumonitis, carditis, and hepatitis may be present. Symptoms may persist for weeks after cessation of the offending medication. Mortality in DIHS may be as high as 10–20 % [8]. Although not comprehensive, some medications that commonly cause eosinophilia and DIHS are outlined in Table 1.

Causes of Eosinophilia: Infections

Parasitic infections are also a common cause of elevated AEC, with tissue invasive helminthic infection being the most frequent worldwide cause of eosinophilia. Evaluation for any history of travel and potential parasite exposure is critical in hypereosinophilic patients. While a full discussion of parasitic infections is beyond the scope of this article, stool studies for ova and parasites on three separate occasions, as well as serologic assessment for specific helminths, may be appropriate. Evaluation for *Strongyloides stercoralis*, a helminthic parasite localized in tropical and subtropical climates as well as the southeastern USA, warrants specific mention. This parasite

Table 1 Selected medications with eosinophilic complications

Medications causing organ-specific eosinophilic dysfunction	Medications causing DIHS
Pulmonary	Anticonvulsants
Pulmonary infiltrates	• Carbamazepine
• Sulfasalazine	• Phenytoin
• Nitrofurantoin	• Phenobarbital
• Non-steroidal anti-inflammatories	• Lamotrigine
Renal	• Zonisamide
Acute interstitial nephritis	Antimicrobials
• Semi-synthetic penicillins	• Metronidazole
• Cephalosporins	• Piperacillin-tazobactam
• Sulfonamides	• Ceftriaxone
• Phenytoin	• Nitrofurantoin
• Cimetidine	• Minocycline
• Non-steroidal anti-inflammatories	Antiretrovirals
• Allopurinol	• Abacavir
Gastrointestinal	• Nevirapine
Enterocolitis	Sulfonamides/sulfones
• Non-steroidal anti-inflammatories	• Trimethoprim-sulfamethoxazole
Hepatitis	• Dapsone
• Tetracyclines	• Sulfasalazine
• Penicillins	Non-steroidal anti-inflammatories
Vasculitis	• Diclofenac
• Allopurinol	• Ibuprofen
Asymptomatic eosinophilia	• Naproxen
• Penicillins	Other
• Cephalosporins	• Allopurinol
• Quinine	• Amitriptyline
• Fluoroquinolones	• Fluoxetine

DIHS drug-induced hypersensitivity syndrome

can penetrate the skin after contact with feces-contaminated soil or water. Patients infected with *Strongyloides* can remain clinically silent for decades [9]. Eosinophilic elevation in *Strongyloidiasis* is variable, with some affected patients demonstrating no eosinophilia [10]. Stool evaluation for ova and parasites is relatively non-specific for *Strongyloides*; serologic testing is the recommended diagnostic modality [11]. Perhaps most importantly, treatment with corticosteroids can lead to fatal disseminated infection in affected patients, making early diagnosis paramount prior to initiation of therapy if possible [11]. Other parasites such as *Isospora belli* and *Sarcocystis hominis* are less frequent causes of eosinophilia [12, 13].

Other types of infection have a variable influence on eosinophil counts. Viral infections, such as HIV or human T cell leukemia virus (HTLV), are known causes of eosinophilia [14]. Elevations in eosinophil count can also be observed in the setting of fungal infections. *Coccidiomycosis* is known to cause eosinophilia, with more significant elevations noted in disseminated disease [15]. *Aspergillus* can cause eosinophilia as well, often in the setting of allergic bronchopulmonary aspergillosis (ABPA). If an infection leads to adrenal insufficiency, loss of

endogenous glucocorticoids can result in eosinophilia [16]. Bacterial infections typically suppress eosinophil counts; eosinophilia in this setting should prompt an evaluation for another cause, such as antibiotics or antipyretics [17].

Causes of Eosinophilia: Other

There are many other conditions which are known to cause secondary eosinophilia, and these should be considered in the differential diagnosis based on the clinical presentation. Of note, the degree of hypereosinophilia may be helpful in determining the causative etiology. For instance, while atopy is known to be associated with eosinophilia, it is uncommon for an AEC >1500/mm³ to be caused by atopic conditions alone. Conversely, persistently elevated AECs, particularly in the presence of asthma, should raise suspicion for pulmonary diseases such as EGPA or ABPA. While not a comprehensive list, some of the common causes of eosinophilia are outlined in Table 2. After a focused history and physical examination, a recommended approach to diagnostic evaluation is provided in Fig. 1.

If a cause of eosinophilia is not apparent, consideration of HES is appropriate. HES has been divided into multiple subgroups based upon clinical, laboratory, and molecular features. Major categories of HES include myeloproliferative HES (M-HES) and lymphocytic HES (L-HES), with some other well-defined clinical entities. A classification scheme for HES has been outlined for reference in Fig. 2.

Hypereosinophilic Syndrome

Myeloproliferative HES Some HES patients have been found to have eosinophilia in the presence of defined myeloid malignancies; others lack a defined malignancy but have laboratory or bone marrow abnormalities commonly seen in association with myeloproliferative disease, including hepatosplenomegaly, anemia, thrombocytopenia, and eosinophil-related tissue damage and fibrosis. These patients are categorized as having M-HES [4].

The initial clinical description of M-HES identified a population of patients, often young males, presenting with the constellation of findings outlined above. They proved difficult to treat and had aggressive disease and an overall poor prognosis. With advances in immunologic diagnostic techniques, discoveries regarding the mechanism and treatment of M-HES were made. It was noted that there were patients that had a dramatic clinical improvement after addition of imatinib, a tyrosine kinase inhibitor, to their therapeutic regimen [18]. This led to a search for the molecular defect responsible for this distinct clinical phenotype and robust therapeutic response. The majority of these patients were found to have a gene fusion of Fip1-like 1 (*FIP1L1*) and platelet-derived growth factor receptor alpha (*PDGFRα*) (*F/P*) [19]. The *F/P* fusion is caused by the deletion of an 800 kb region containing

Table 2 Selected causes of eosinophilia

Infections	Parasitic (helminths, ectoparasites, <i>Isospora</i> , <i>Sarcocystis</i>)
	Viral (HIV, HTLV)
	Fungal (coccidiomycosis)
	Bacterial (tuberculosis)
Medications	Antibiotics (penicillins, cephalosporins, quinolones, sulfonamides)
	NSAIDs
	Antiepileptics (phenytoin, valproate)
	Antidepressants (fluoxetine, amitriptyline)
	Anti-hypertensives (ACE inhibitors, beta blockers)
Hematologic/neoplastic disorders	Systemic mastocytosis
	Solid tumors (adenocarcinoma, squamous cell carcinoma)
	Hematologic malignancy (CML, CEL, Hodgkin's lymphoma)
Immune dysregulation	Autoimmune lymphoproliferative syndrome (ALPS)
	Hyper-IgE syndrome
	Eosinophilic granulomatosis and polyangiitis (EGPA)
	Sarcoidosis
	Inflammatory bowel disease
	Immunoglobulin G4-related disease (IgG4-RD)
Allergic disorders	Allergic rhinitis
	Asthma
	Atopic dermatitis
	Allergic bronchopulmonary aspergillosis (ABPA)
Other	Adrenal insufficiency
	Cholesterol embolization
	Irradiation
	Eosinophilic gastrointestinal disorders (EGID)
	Rare hypereosinophilic syndromes (idiopathic HES, L-HES, M-HES)

ACE angiotensin-converting enzyme, *CML* chronic myelogenous leukemia, *HIV* human immunodeficiency virus, *CEL* chronic eosinophilic leukemia, *HTLV* human T-lymphotrophic virus, *L-HES* lymphocytic hypereosinophilic syndrome, *M-HES* myeloproliferative hypereosinophilic syndrome, *NSAIDs* non-steroidal anti-inflammatory drugs

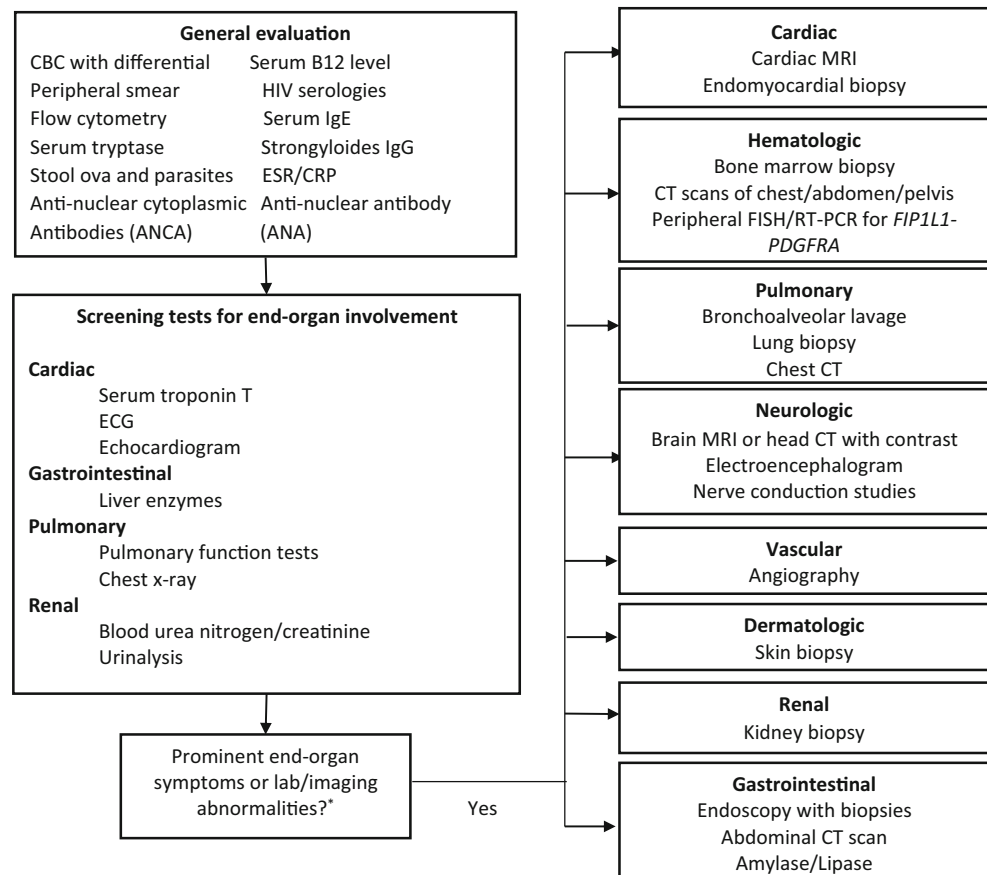
the *CHIC2* gene on chromosome 4q12, and presence of the abnormality can be detected by FISH or RT-PCR of peripheral blood or bone marrow [17, 19]. The deletion leads to a gain of function, constitutively active tyrosine kinase. As a result, there is persistent transformation of hematopoietic stem cells and expansion of the eosinophil population [19]. In a retrospective review of patients from 11 centers in the USA and

Europe, it was found that of 161 HES patients tested for the F/P mutation, 18 (11 %) were positive; all of these patients were male [20]. The F/P-positive population of myeloproliferative HES exhibits one of the most well-characterized molecular defects leading to hypereosinophilia. Not only can this gene fusion be utilized for diagnostic purposes, it is also useful for therapeutic stratification as well. It has been noted that some patients with myeloproliferative features respond at least partially to imatinib despite a lack of F/P mutations, potentially implicating other, as yet uncharacterized, tyrosine kinases in disease pathogenesis [21].

As previously discussed, some M-HES patients present with characteristic laboratory and clinical features but have negative PDGFRA screening for the F/P fusion gene or other described fusion partners. Other well-characterized variants of M-HES are defined by abnormalities of *PDGFRB* and *FGFR1* [22]. These mutations can lead to clonal eosinophilia with potential progression to aggressive myeloid malignancies which may be refractory to treatment [23]. If there is evidence of M-HES with negative F/P screening, it is recommended that assessment for these other translocations be performed as well [23]. If the aforementioned evaluation is negative, patients must meet four or more of the following criteria to qualify for the diagnosis of M-HES: dysplastic eosinophils on peripheral smear, serum vitamin B₁₂ level >1000 pg/ml, serum tryptase >12 ng/ml, anemia and/or thrombocytopenia, hepatosplenomegaly, bone marrow cellularity >80 %, myelofibrosis, or spindle-shaped mast cells in the bone marrow [3].

Chronic eosinophilic leukemia (CEL) is another condition in which myeloproliferation and significant eosinophilia co-exist. By definition, CEL patients display >2 % blasts in the peripheral blood or >5 % in the bone marrow, but both compartments must contain <20 % blasts. Hypereosinophilia may also present with other defined neoplastic processes such as systemic mastocytosis, acute and chronic myelogenous leukemia, or chronic myelomonocytic leukemia [1]. For this reason, it is necessary to rule out malignancy in any patient presenting with significant eosinophilia.

Lymphocytic HES In L-HES, eosinophilia is generated by increased production of eosinophil hematopoietins, particularly interleukin-5 (IL-5), by populations of activated T lymphocytes. These abnormal populations of T lymphocytes exhibit atypical patterns of surface markers and can be characterized from peripheral blood with flow cytometry and/or T cell receptor rearrangement studies. The most commonly found T cell subset in this condition is CD3⁺CD4⁺, but other abnormal phenotypes may include CD3⁺CD4⁺CD8⁺ and CD3⁺CD4⁺CD7⁺ [24]. Identification of T cell receptor clonality by rearrangement analysis is strongly supportive of L-HES but is not sufficient to make the diagnosis alone [17, 25]. Other factors indicative of L-HES include elevations in serum IgE level and thymus and activation-regulated

Fig. 1 Recommended lab/procedural evaluation of eosinophilia

*Additional studies may be indicated based on clinical background

chemokine (TARC, CCL-17). Unlike the predominantly male M-HES population, L-HES cases are evenly divided between males and females. L-HES patients may also exhibit a high prevalence of dermatologic manifestations and may also have obstructive lung disease and gastrointestinal symptoms among other complications. Tissue fibrosis and myelofibrosis are uncommon in this condition [17]. Although the disease course is generally more protracted, there must be specific concern for progression to lymphoma, particularly in the CD3⁺CD4⁺ population [24].

Within the L-HES subgroup, there are patients that do not have identifiable clonal T cell populations but may have aberrant T cell immunophenotyping and evidence of T cell activation [17, 25]. It is estimated that 10–15 % of HES patients may fall within the L-HES phenotype, but this is likely an underestimate due to the inability to detect certain aberrant immunophenotypes [17].

Other HES Variants Aside from M-HES and L-HES, there are other well-established categories of HES. Familial HES is a rare condition in which marked eosinophilia of unclear

etiology presents in successive generations. Often, the eosinophilia is asymptomatic, but some affected family members develop clinical manifestations similar to F/P-positive HES with cardiac fibrosis and neurologic abnormalities [26]. While the exact mechanisms underlying familial HES are unknown, studies have localized the responsible gene to the region of 5q31-33, the cytokine gene cluster. Genes crucial to eosinophil development and function including IL-3, IL-5, and GM-CSF are also located in this region [27].

Overlap disorders are conditions that exhibit organ-restricted eosinophilia, which may be associated with peripheral eosinophilia [28]. Eosinophilic gastrointestinal disorders are often categorized as part of this group. Patients with EGID may present with nausea, vomiting, diarrhea, abdominal pain, dysmotility, and failure to thrive depending upon the degree and location of eosinophilic infiltration. Eosinophilic esophagitis is linked to food allergy and cytokines associated with atopic disease such as IL-5 and IL-13; these associations are less clear for other forms of EGID [29]. Other examples of overlap disorders include eosinophilic pneumonia and eosinophilia-myalgia syndrome. It is important to distinguish

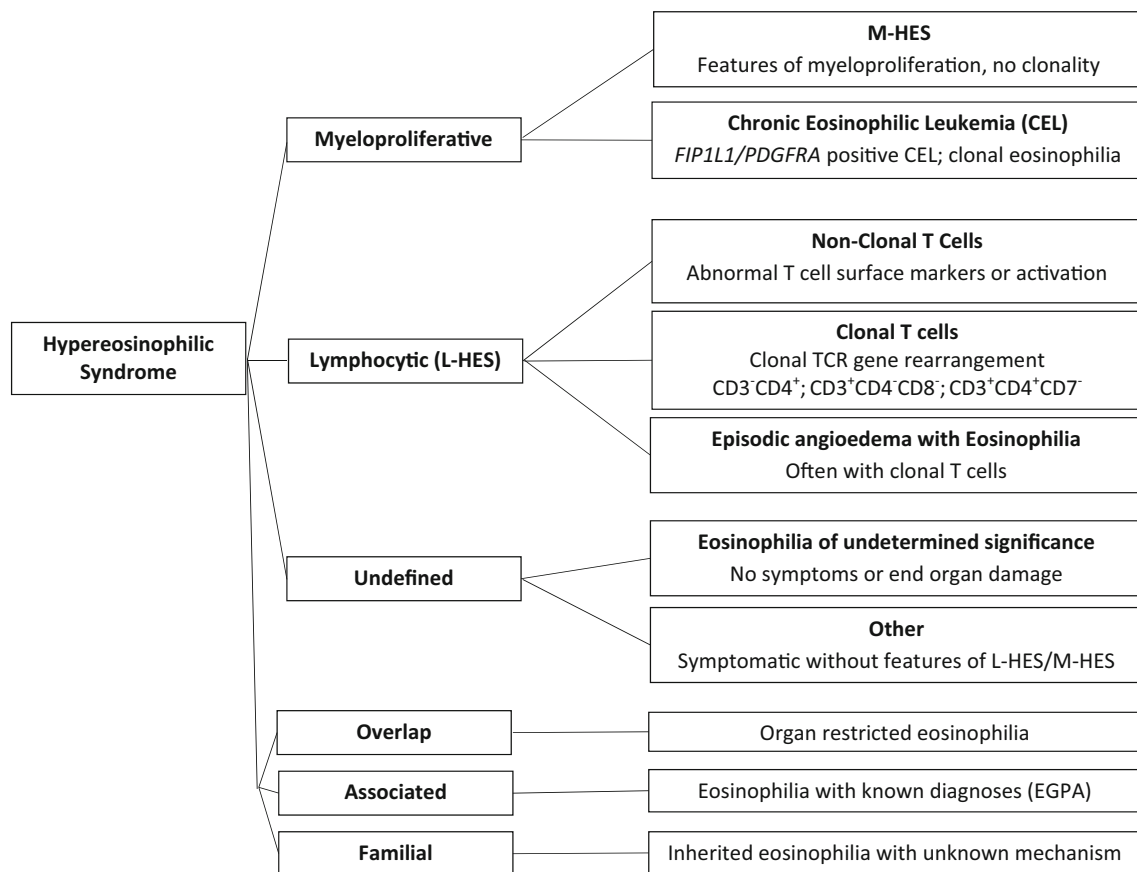


Fig. 2 Classifications of hypereosinophilic syndrome. Adapted from Simon et al. [4] and Cogan and Roufousse [25]

patients with overlap disorders, as treatments may vary significantly from other forms of HES [3].

The category of “associated” HES is comprised of significant peripheral eosinophilia in the setting of conditions known to cause eosinophilia. These include EGPA, systemic mastocytosis, inflammatory bowel disease, sarcoidosis, and HIV among others. Again, it is important to consider these disorders in the differential diagnosis and evaluation of eosinophilia, as management may be tailored to the underlying disease state. There is also an entity known as Gleich’s syndrome or episodic angioedema with eosinophilia (EAE) which is characterized by episodic occurrences of significant eosinophilia, often with associated angioedema, which may occur in a cyclical fashion [30, 31]. A recent study noted cyclical variations in neutrophil and lymphocyte counts in EAE patients. Of the four patients described, all had aberrant populations of CD3⁺CD4⁺ T cells as well. The cytokine profile in EAE indicates that eosinophilia may be lymphocyte-driven [31].

Some patients, considered to have benign eosinophilia, may present with persistent AEC $\geq 1500/\text{mm}^3$ but never develop signs of end-organ dysfunction. These patients may be termed hypereosinophilia of undetermined significance (HEus) [32]. These patients still require careful follow-up to

monitor for development of disease. Conversely, with complex HES, patients may have evidence of end-organ dysfunction but cannot be easily classified in any of the existing categories.

Complications Since early descriptions of HES, it has been recognized that hypereosinophilia is associated with dysfunction in a variety of organ systems. As further information has been elucidated regarding HES subtypes, the association between clinical phenotypes and distinct complications has emerged as well. The most common systems involved in HES include hematologic, cutaneous, cardiovascular, pulmonary, and neurologic, among others [12].

While eosinophilia is a presenting feature of HES, there are other commonly associated hematologic abnormalities. Some of these features, such as anemia and immature eosinophils in the peripheral blood and bone marrow, were described in Chusid’s initial description of HES [2]. These hematologic variations were further explored further by Flaum et al., in an analysis of 32 patients with hypereosinophilic syndrome treated at the National Institutes of Health over approximately 10 years. This study noted that eosinophils may appear morphologically normal in HES patients or may exhibit distinct structural abnormalities. Common atypical findings included

increased cell size, irregular cytoplasmic granulation, and cytoplasmic vacuolization. Nuclear abnormalities were found to be variable, including hyposegmentation and hypersegmentation. In terms of non-eosinophil granulocytes, abnormalities of both nuclear and cytoplasmic maturation both in the bone marrow and periphery were described. Anemia was found in more than 75 % of these patients and was often associated with dacryocytosis or circulating nucleated erythrocytes. Thrombocytopenia was found to be more common than thrombocytosis and was thought to be a result of decreased marrow megakaryocytosis. Myelofibrosis was described in several patients, many of whom demonstrated a more severe clinical phenotype [13]. Hepatosplenomegaly can also be a prominent clinical finding in HES, as previously discussed.

The skin is one of the most frequently involved organ systems in HES, with over 50 % of patients developing cutaneous manifestations; skin abnormalities are commonly the presenting feature of HES. There is a particularly high prevalence of skin involvement in CD3⁺CD4⁺ L-HES patients, with as many as 94 % of these patients developing skin abnormalities [12, 33]. Mucosal ulceration, which can be a particularly painful and difficult to treat manifestation, is a distinguishing feature of M-HES. These ulcers involve mucosal surfaces and may be misdiagnosed as Bechet's syndrome; however, lesions in these patients tend to be larger than ulcers associated with Bechet's, and patients may not exhibit some of the other characteristic features of that process, such as uveitis and synovitis. The ulcers may be refractory to general HES treatments, although they have shown improvement after treatment with imatinib [33]. Cardiac involvement in HES may lead to skin findings including splinter hemorrhages and nail bed infarcts. L-HES is more frequently associated with generalized pruritus, eczema, erythroderma, and urticaria. Other dermatologic findings in HES include episodic angioedema, urticaria, and pruritic erythematous eruptions. Patients may also develop erythema annulare centrifugum, necrotizing vasculitis, and livedo reticularis [33].

Cardiovascular complications of HES may be present in 40–60 % of patients and can be a significant cause of morbidity and mortality [25, 34]. Cardiac disease associated with HES is often subdivided into acute necrotic, thrombotic, and late fibrotic stages. The acute necrotic stage may occur within 1–2 months of demonstrable eosinophilia; it is characterized by eosinophilic infiltration of the myocardium with cellular necrosis secondary to eosinophil degranulation. Often within a year of the necrotic stage, patients may develop mural thrombi which may involve the ventricular walls, outflow tract, and subvalvular regions. There is likely a role of endothelial disruption and associated hypercoagulability in this process. Following thrombus formation, at an average of 2 years after onset of eosinophilia, patients may proceed to cardiac fibrosis. This may involve scarring of the

endocardium and chordae tendinae, leading to dilated cardiomyopathy and progressive valvular dysfunction. Often, this will lead to incompetence of the atrioventricular valves with regurgitant flow. Depending upon their degree of cardiac involvement and stage of progression, patients may present with symptoms ranging from chest pain and dyspnea to significant embolic events and arrhythmia [34].

Neurologic involvement in HES patients is highly variable. As previously discussed, cardiac involvement can lead to the development of thrombi. Embolization can result in transient ischemia attacks or embolic strokes with associated sequelae. It has also been suggested that there may be a role for thrombus formation locally within cerebral vessels, although this has been more difficult to establish [12]. Patients with HES and history of thrombus formation have been shown to have recurrences of clot despite adequate medical anticoagulation [35]. Primary central nervous system (CNS) dysfunction is another distinct neurologic complication associated with eosinophilia. This can manifest as encephalopathy, with resultant behavioral changes, memory loss, and confusion. Exam findings may include predominant upper motor neuron signs such as increased muscle tone and deep tendon reflexes [36]. Seizures, intracranial hemorrhage, and dementia have been reported but are less common [12]. Peripheral neuropathies also occur in the setting of HES. These are variable in presentation and may consist of isolated sensory or motor deficits or a mixture of both. This may lead to numbness, painful paresthesias, weakness, or muscle atrophy secondary to denervation [36].

Pulmonary involvement occurs in approximately 40 % of HES patients and may present with shortness of breath, cough, or imaging abnormalities [37]. There are some well-recognized respiratory manifestations associated with particular HES subsets, such as asthma in patients with EGPA. Lung complications can occur secondary to acute or chronic pulmonary embolic disease or associated cardiac dysfunction. Further, cardiac involvement can result in pleural effusions [37]. Approximately 15–30 % of patients may develop infiltrative pulmonary disease. The infiltrates may be focal or diffuse, with no predisposition to particular zones of the lung. Bronchoalveolar lavage may demonstrate large percentages of eosinophils; it may be difficult to distinguish HES from other eosinophilic pneumonias on this basis. Fibrotic lung disease can also occur, particularly in patients with evidence of fibrotic lung diseases in other organ systems [12].

HES may present with rheumatologic manifestations. Certain features of eosinophil physiology may account for these types of complications. Eosinophil cationic protein (ECP), one of the characteristic proteins secreted by eosinophils, has been shown to induce collagen contraction and release of fibrogenic cytokines such as TGF- β and IL-1 β [38]. Thrombosis is another complication that can be seen in eosinophilic vasculitis. This may be induced by multiple mechanisms,

including activation of the coagulation cascade by tissue factor released during eosinophil degranulation or inhibition of anticoagulant proteins by major basic protein (MBP), another distinct protein secreted by eosinophils [38]. Neuropathies can be associated with eosinophilic vasculitis as well. This may be a result of eosinophilic perivascular infiltration, which has been demonstrated in a nerve biopsy of a patient with eosinophilic vasculitis [38]. Patients with rheumatologic complications of HES may present with arthralgias, non-erosive polyarthritis, joint effusions with synovial fluid eosinophilia, and Raynaud's phenomenon [12].

The gastrointestinal system can be adversely affected by HES. Symptoms may result from eosinophilic cytotoxicity to epithelium, induction of inflammatory cytokines, and disruption of the enteric nervous system by eosinophil-derived mediators [39]. Presenting symptoms of GI involvement include failure to thrive, abdominal pain, vomiting, diarrhea, and dysphagia. There can be an overlap in clinical characteristics with EGID. Significant peripheral eosinophilia, as well as involvement of other end-organ systems, may be seen more frequently in HES than EGID [39].

The myriad of potential complications in HES, partially outlined in Table 3, underscores the potential for diagnostic difficulty, as well as the importance of increased vigilance in monitoring with respect to these patients. Various complications may also require independent management in addition to treatment of the underlying HES.

Management Appropriate choice of therapy in HES requires several considerations, including degree of eosinophilia or associated end-organ dysfunction, need to reduce eosinophilia quickly, underlying pathophysiology of eosinophilia, and possible adverse effects of therapy. Here, we review some of the more commonly used HES therapies.

Corticosteroids Corticosteroids have been some of the most widely utilized and most effective therapeutic agents in the treatment of HES. In a multicenter study including 188 HES patients, it was found that 81 % had been initially treated with steroids. The median dose of prednisone or equivalent steroid was 40 mg daily. Nearly 75 % were on maintenance steroids for some period of time, with an average dose of 10 mg prednisone daily. Duration of therapy ranged from 2 months to 20 years. Eighty-five percent of patients on steroid monotherapy had a partial or complete remission within 1 month of therapy [20]. The response to corticosteroid therapy is generally rapid, with reports of eosinophilia resolving within hours [40].

HES phenotype may help predict responsiveness to therapy with steroids. Previous reports suggest that patients with elevated serum IgE levels may have a more favorable response to corticosteroids [41]; however, no statistically difference in steroid responsiveness was

found in patients with elevated IgE levels in subsequent evaluations [20]. In contrast, patients with elevations in TARC have been found to have significantly better responses to steroid therapy [20, 42]. Patients with L-HES have been shown to have generally favorable responses to steroid therapy, although the dose required to elicit a response may vary. Steroids can decrease levels of aberrant CD3⁺CD4⁺T cells in L-HES, which may provide some of the associated reduction in eosinophilia [25]. Patients with M-HES variants are generally thought to be less responsive to steroid therapy [20]. The recommended starting dose of prednisone is 0.5–1 mg/kg daily, although if eosinophilia and symptoms are not severe, a lower dose may be attempted first and titrated as appropriate [25]. Given the number of complications associated with chronic corticosteroid therapy, it may be desirable to maintain therapy with a steroid-sparing agent when possible.

Hydroxyurea Hydroxyurea is a commonly used second-line agent for HES. It is readily available and relatively inexpensive, making it a reasonable therapeutic option. Recommended dosing is around 0.5–2 g daily; however, this may be dose-limited at the higher end of this spectrum due to side effects including hematologic and GI toxicity. It acts centrally to impair eosinophil development rather than directly on peripheral eosinophils; this leads to a slower onset of action than that of corticosteroids, making it a less desirable option if there is a requirement to rapidly lower eosinophilia [25]. Some studies have indicated that this is an effective combination agent; in one prospective trial, 15 patients with F/P-negative HES and no history of treatment were started on a course of 2 g hydroxyurea and 1 mg/kg prednisone daily. This resulted in a complete remission in 60 % of patients and a partial remission in the other 40 % [43]. Ogbogu's group found that 69 % of the 36 patients treated with hydroxyurea and corticosteroid therapy in their study achieved at least partial remission. In 18 patients being treated with hydroxyurea monotherapy at an average dose of 1 g daily, 33 % had a complete response, with 39 % exhibiting a partial response. Ultimately, hydroxyurea was stopped in the majority of patients due to lack of efficacy or adverse effects [20]. Generally, hydroxyurea should not be used alone as initial monotherapy and may be most effective when used in conjunction with corticosteroids or interferon- α [25].

Interferon- α Interferon- α (IFN- α) affects multiple cell lines, giving it potential efficacy in a variety of HES subtypes. The drug targets eosinophils but has also been shown to inhibit proliferation of CD4⁺ T cells and IL-5 production by CD3⁺CD4⁺ T cells in vitro [25]. Clinically, this agent initially showed benefit in patients that were not responsive to therapy with hydroxyurea and corticosteroids [44]. In the large

Table 3 Selected end-organ manifestations of hypereosinophilic syndrome

Hematologic	Anemia
	Thrombocytopenia
	Myelofibrosis
	Hepatosplenomegaly
Cardiac	Necrotizing myocarditis
	Mural thrombus formation
	Fibrosis (i.e., endocardium, chordae tendinae)
Pulmonary	Embolitic disease
	Asthma
	Infiltrative eosinophilic disease
	Pleural effusions
Dermatologic	Mucosal ulceration
	Nail bed infarcts
	Splinter hemorrhages
	Eczema
	Erythroderma
	Urticaria/angioedema
Neurologic	Cerebral vessel thrombosis
	Encephalopathy
	Peripheral neuropathy
	Seizures
Rheumatologic	Vasculitis
	Non-erosive polyarthritis
	Joint effusions
	Raynaud's phenomenon
Gastrointestinal	Dysmotility
	Malabsorption
	Fibrosis/stricture

multicenter study, 46/188 patients had been treated with IFN- α at a median dose of 14 million units weekly. Twelve had received the agent as monotherapy, with two achieving complete remission and four with partial remission. When used as combination therapy, 18/24 patients on corticosteroids and IFN- α achieved complete or partial remission. IFN- α was ultimately discontinued in approximately 90 % of patients, primarily due to intolerance and lack of efficacy [20]. Side effects are an important consideration when starting IFN- α , as commonly patients will develop myelosuppression, transaminitis, autoantibody formation, fatigue, myalgias, depression, and suicidal ideation. Flu-like symptoms may lessen over time when IFN- α is started at a low dose and slowly titrated up to an effective level, but the risk of other side effects remains [25]. IFN- α remains a viable therapeutic option, particularly for F/P-negative variants of HES. However, lack of approval for this indication may make this an expensive treatment, and the significant issues with medication intolerance must be considered.

Tyrosine Kinase Inhibitors The role of tyrosine kinase inhibitors in the elucidation of some of the molecular mechanisms of M-HES has been described earlier. This association led to the increased utilization of these agents in the treatment of HES, often with substantial efficacy.

The role of the F/P fusion and resultant tyrosine kinase activity in the development of M-HES has been clearly established. Several factors have prompted the recommendation of early screening for F/P fusion in an appropriate patient population. These include widely available F/P testing, as well as the availability of imatinib as an effective treatment in F/P-positive patients who previously had a poor prognosis. In terms of response to therapy, in the multicenter study of 188 HES patients, 18 patients, all of whom were male, tested positive for the F/P fusion. Seventeen F/P-positive patients were treated with imatinib at a median dose of 400 mg daily; 15/17 (88 %) had complete remission. Only two patients had no response. Of note, 10/43 (23 %) of the F/P-negative patients treated with imatinib exhibited some type of therapeutic response to this agent [20]. This illustrates not only the highly effective nature of imatinib in patients with the F/P fusion but also the potential for therapeutic efficacy in F/P-negative patients, raising the question of yet to be identified tyrosine kinase mutations.

Of note, it has been shown that while complete molecular remission can frequently be achieved with imatinib, upon cessation of therapy, evidence of the F/P fusion gene often reappears; this indicates a population of F/P-positive stem cells that persists throughout treatment [25]. There is concern that patients with cessation in treatment or treatment with sub-optimal doses of imatinib may develop resistant clones, so indefinite treatment is recommended [25, 45]. In the initial study describing the mechanism of response of HES patients to imatinib, a T674I mutation in the PDGFR α kinase domain was described, conferring resistance to the treatment [19]. While some studies have indicated that doses as low as 100 mg weekly may be able to maintain molecular remission, doses below 100 mg daily are not recommended due to concerns for resistant clonal emergence [25, 45].

While imatinib is generally well-tolerated, there have been reports of the acute development of congestive heart failure after initiation of the medication, presumably due to release of cytotoxic eosinophil mediators within the myocardium; this complication has been shown to be increased in patients with known elevations of serum troponin, and it is recommended that if imatinib treatment is initiated in this patient population, they should be started on at least 1 mg/kg prednisone concurrently in attempts to obviate this complication [25].

Imatinib is recommended as a clear first-line therapy in patients with F/P-positive HES. Given the potential for benefit and relatively modest side effect profile, it may be a reasonable option to treat with an empiric trial of imatinib, particularly in patients who exhibit indicators of myeloproliferative

disease. However, many F/P-negative patients will have no response or a partial response to treatment, even at doses higher than those used for treatment of F/P-positive patients [25].

Two other tyrosine kinase inhibitors, nilotinib and sorafenib, have been shown in vitro and in murine models to be effective against the native F/P fusion as well as the T674I mutation leading to imatinib resistance. However, clinical studies of their use in mutant F/P-positive CEL patients have shown a relative lack of efficacy. Dasitinib has shown efficacy in vitro on native F/P, with efficacy similar to imatinib [25]. Ponatinib, another tyrosine kinase inhibitor, has been shown to inhibit proliferation of primary FIP1L1-PDGFR α -positive eosinophils in a dose-dependent manner. Ponatinib is also a potent inducer of apoptosis in neoplastic eosinophils [46]. Further clinical studies are required to determine whether these results can be translated to clinical efficacy in HES patients. In short, while other tyrosine kinase inhibitors have shown experimental promise, imatinib is the most well-studied and effective option presently.

Immunomodulatory Agents Mepolizumab is a humanized monoclonal antibody against IL-5 that has been investigated for treatment of multiple conditions involving eosinophilic pathology including asthma, eosinophilic esophagitis, and EGPA [47]. Given the role of IL-5 in the pathogenesis of some HES variants, a double-blind placebo controlled study was conducted to evaluate the role of mepolizumab as a steroid-sparing therapy in patients with F/P-negative HES [48]. Patients underwent a run-in period, during which they achieved clinical stability on steroid monotherapy consisting of 20–60 mg prednisone daily. They were then randomized to receive monthly infusions of 750 mg mepolizumab or placebo over a 36-week study period. Forty-six patients were randomized to receive mepolizumab, of which 36 completed the study; 15 of the 42 patients assigned to the placebo reached completion of the study, with lack of efficacy cited as the primary reason for withdrawal in the majority of patients. Patients were monitored during a clinical taper, with a primary endpoint of disease control on ≤ 10 prednisone daily for at least 8 weeks. Thirty-six patients (84 %) receiving mepolizumab were able to reach reduced prednisone therapy to the goal dose, while only 18 (43 %) of the placebo group was able to do so, a statistically significant difference. This difference was even more pronounced in patients requiring greater than 30 mg prednisone daily at baseline for disease control. Treatment failure was ultimately observed in 21 % of patients receiving mepolizumab, versus 69 % in the placebo group. Patients in the treatment group also exhibited significant reductions in blood eosinophil counts, as well as levels of eosinophil-derived neurotoxin, an eosinophil granule protein implicated in tissue and vascular damage. No major adverse events thought to be related to the administration of study drug

were reported. The overall safety of mepolizumab was further established by a study with continued follow-up of 78 of these patients with ongoing administration of the drug [49]. Mepolizumab administration was continued at 750 mg with an average dosing interval of 9–12 weeks; the mean exposure duration was 251 weeks. When adverse events were adjusted for medication exposure, the rate was similar to that of the placebo group of the initial study. There were four subjects which may have had serious adverse events related to therapy, including expansion of previously documented clonal T cell populations. Overall, these studies helped to demonstrate the relative safety and efficacy of long-term mepolizumab use as steroid-sparing therapy in F/P-negative HES. Mepolizumab is not currently approved for the treatment of HES; however, it may be available to patients with life-threatening disease who have failed at least three other therapies via an ongoing, phase III compassionate use trial [25, 50].

Similarly, reslizumab is a humanized anti-IL-5 monoclonal antibody that has been studied in other eosinophilic disorders, with limited published data in HES. In one small, open-label study of HES and eosinophilic gastroenteritis, reslizumab was shown to suppress eosinophilia for at least 12 weeks in two of four subjects with treatment-refractory HES [47]. Further study is required to determine the potential role for reslizumab in the treatment of HES.

Alemtuzumab is a monoclonal antibody against CD52, a surface glycoprotein present on T cells, B cells, monocytes, macrophages, NK cells, and eosinophils. It has been approved for treatment in B cell chronic lymphocytic leukemia, but it was also noted that it improved eosinophilia when used as part of a bone marrow transplant protocol. Later, a case study was reported of 11 HES patients treated with intravenous or subcutaneous alemtuzumab. Two of the patients qualified for the diagnosis of CEL. Ten of 11 achieved complete hematologic remission within approximately 2 weeks and maintained remission for a median of 3 months, with a range of 1.5–17 months. Adverse events were reported, with three patients having transfusion reactions and two with CMV reactivation requiring treatment. Given its non-specific cellular targeting, cytopenias are another known side effect of alemtuzumab, and additional study is required to determine whether the benefits may outweigh the risk of use of this medication [47]. It is currently recommended that treatment with alemtuzumab be reserved for patients with severe disease that is refractory to standard therapies [25].

Cytotoxic Therapies Several cytotoxic agents have been attempted as maintenance therapy for HES, including cyclophosphamide, cyclosporine, methotrexate, busulfan, and chlorambucil. Reports of efficacy are limited, and these agents have significant side effect profiles [25]. In a large multicenter retrospective study, cyclosporine was the most commonly administered cytotoxic agent, but 82 % of patients treated had to

be stopped due to medication intolerance [20]. Vincristine has been reported to cause disease regression in acute settings, particularly in pediatric patients [25]. These agents are generally not recommended as first-line therapy.

Allogeneic Stem Cell Transplantation For patients that have not been responsive to standard therapeutic regimens, stem cell transplant may be an option. Particular subgroups that may be appropriate for transplantation include F/P-positive patients that are unresponsive to imatinib or patients initially presenting with L-HES that progress to lymphoma. There are high rates of treatment-related morbidity and mortality associated with this process, so this must be considered when deciding which patients may benefit most from this therapy [25].

Future/Novel Therapies It is clear that advances in the understanding of disease pathophysiology in HES have opened up new avenues for treatment. As knowledge continues to develop, other therapies must be considered. There are ongoing studies based on some of these novel therapies and other molecular components that may be reasonable therapeutic targets to pursue in the future.

Benralizumab is a humanized monoclonal antibody against the IL-5 receptor component IL-5R α . Binding of benralizumab has multiple effects, including inhibiting IL-5-mediated activation of the IL-5 receptor, enhancing antibody-mediated cell-mediated cytotoxicity of eosinophils, and inducing potent eosinophilic proapoptotic activity [25, 47]. It is thought that targeting IL-5R α may produce more effective eosinophil reduction than therapy directed at IL-5 itself, as other eosinophilopoietic factors may circumvent the requirement for IL-5 in some cases [25]. A phase I trial of asthmatics, eosinophilia was reduced in a dose-dependent fashion with administration of benralizumab, with eosinopenia lasting longer than 12 weeks in the highest dose groups [47]. This therapy shows potential in the treatment of HES, and clinical trials are currently underway (clinicaltrials.gov, NCT02130882). There are specific molecules important to eosinophil survival that may prove to be potential therapeutic targets as well. It has been shown that anti-Siglec-8 can directly induce apoptosis of human eosinophils, making this one possible route of therapy [51]. Additionally, interference with inhibitory eosinophilic signaling molecules, such as CD172a, may impact eosinophil tissue recruitment and survival. Disruption of eosinophil migration may be an effective therapeutic strategy as well. CCR3 is an eosinophil-selective chemokine critical to recruitment of eosinophils to certain tissues. Neutralizing antibodies to CCR3 and its ligand, CCL11, are currently being investigated in human subjects. Natalizumab is a monoclonal antibody against VLA-4, an integrin crucial to eosinophil recruitment to the lung. While commercially available under special conditions for the treatment of multiple sclerosis (MS), no studies

of HES patients have been conducted due to the risk of progressive multifocal leukoencephalopathy demonstrated in treated MS patients. Prostaglandin D₂ and its receptor CRTH2 have also been proposed as potential therapeutic targets due to their role in eosinophil mobilization, activation, and chemoattraction [47]. As more information is elucidated regarding eosinophil biology, activation, and migration, vigorous study will be required to determine how these processes may be safely and effectively targeted for therapeutic effect in HES.

Conclusions

Decades of elucidation of the pathophysiology, diagnosis, and treatment of HES have revealed how prescient the initial descriptions of HES were. HES indeed represents a spectrum of disease, with phenotypic classifications that continue to evolve. Advances in research and technology have allowed for characterization of some forms of HES on a molecular level, and this understanding has translated to improved diagnostics and more personalized approaches to treatment. As clinical trials continue and new targets of therapy are identified for investigation, knowledge of HES will advance, ultimately resulting in improvements in patient care and quality of life.

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