J Clin Haematol. 2026;7(1):57–64.

Journal of Clinical Haematology Commentary

Commentary on 'Idiopathic Hyper-Eosinophilic Syndrome–A Case Based Update'

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Received date: December 24, 2025, **Accepted date:** July 10, 2026

Citation: Vinodhini M. Commentary on 'Idiopathic Hyper-Eosinophilic Syndrome–A Case Based Update'. J Clin Haematol. 2026;7(1):57–64.

Abstract

Idiopathic hypereosinophilic syndrome encompasses a less common haematologic entity which is diagnosed after exclusion of clonal, reactive, familial, and secondary causes of eosinophilia. Its diverse clinical presentation involving any organ or system is well known and may be life threatening if untreated. Cardiac and neurologic manifestation require multidisciplinary management. Although corticosteroid represents the first line treatment of choice, disease progression and treatment failure limit long term survival. Novel prognostic and surrogate markers of disease severity are currently under investigation. Incorporation of biologic agents targeting cytokine release showed promising results in eosinophilic asthma, atopic dermatitis and nasal polyposis. These agents along with tyrosine kinase inhibitors have changed treatment paradigm and added potential benefit by minimizing toxicity.

Keywords: Bendralizumab, Cardiac failure, Eosinophilic infiltration, Absolute eosinophil count

Introduction

Hypereosinophilic syndrome (HES) is an uncommon haematologic condition affecting any age group with varied clinical and etiological spectrum. It may occur due to primary or clonal somatic mutation driven neoplasm and secondary, reactive, allergic or less identified causes. Idiopathic HES is neither reactive nor clonal disorder as it arises from widespread eosinophil-driven cytokine release manifesting as multisystem disease with cardiopulmonary compromise. Therapeutic options in HES range from treatment of underlying cause, cessation of offending agent in secondary forms to chemotherapy, targeted drugs and allogenic stem cell transplant in clonal refractory cases.

Classification

Eosinophilia is defined as absolute eosinophil count (AEC) exceeding 0.5×10^9/L on two or more occasions at least one month apart. Majority of eosinophilia in clinical practice are secondary/reactive causes due to IL-5 overproduction and include T- helper (Th)2 cytokine profile. Clonal eosinophilia due to genetic aberration is rare in clinical practice. Clinical presentation ranges from fatigue, skin lesion, gastrointestinal (GI) or pulmonary damage, stroke, peripheral neuropathy, cardiac failure, thrombo-embolic complication and sudden death.

Hyper Eosinophilia (HE)

Includes absolute eosinophil count ≥ 1.5×10^9/L on two sessions at least four weeks apart except for those with rapid organ dysfunction due to eosinophil granule and lipid mediators where time limit of four weeks is excluded. Tissue HE is defined as the presence or absence of peripheral blood HE when eosinophils constitute 20% or more in bone marrow, extensive eosinophil deposit exceeding normal limit or immunostaining for eosinophil peroxidase or eosinophil basic protein is positive [1]. Depending upon AEC, further subdivisions include mild, moderate and severe as per International Co-Operative Group classification on Eosinophil disorders (ICOG-Eo) [2]. Persistent eosinophilia is diagnosed when eosinophilia is present for more than two occasions at least two weeks apart. Mild HE includes AEC between 0.5 to1.5×10^9/L, moderate if AEC between 1.5 to 5 $x10^9$/L and severe if more than 5×10^9/L [1,3]. Hypereosinophilic syndrome

(HES) includes AEC>1.5×10^9/L with end organ damage regardless of underlying etiology.

In this commentary based on an index case of idiopathic HES with cardiac failure, we discuss a brief overview of HES subtypes, their diagnosis and management with a special focus on idiopathic HES in index case and novel treatment strategies.

Overview of HES and Clinical Subtypes

HES includes diverse etiology and essentially any organ/system may be susceptible to eosinophilia. Various classifications have been proposed for HES. In 2022, International consensus classification of eosinophilic disorders and World Health Organization (WHO) proposed a semi-molecular classification of HES into myeloid/lymphoid neoplasm with eosinophilia and tyrosine kinase gene fusion (MLN-Eo-TK) and chronic eosinophilic leukemia [4]. Lymphocytic HES occurs due to aberrant or clonal T cell driven cytokine and represents a grey zone between neoplastic and reactive category. Idiopathic HES is a diagnosis of exclusion. Updated recommendation by Valent in 2021 classified eosinophil disorders into HES familial, HES neoplastic, HES reactive and HES of undetermined significance [1]. In view of such complex heterogeneity, the classification proposed by international eosinophil society [5] based on distinct clinical subtypes is followed in this commentary.

a) Myeloproliferative HES occurs due to clinically distinct driver mutations leading to myeloid neoplasm and eosinophilia. It is noted in 11% cases [6]. They are associated with chromosomal abnormalities leading to translocation, fusion genes and tyrosine kinase gene rearrangements with consequent oncogenic potential. **Table 1** demonstrates various HES subtypes and disease mechanisms.

b) Lymphocytic HES are at risk of development of occult T cell malignancy or lymphoma. Though the detection of clonal T cells producing type 2 cytokines is gold standard for diagnosis, identification of aberrant T cell surface markers by immunophenotyping establishes diagnosis in majority. Consequently, it is crucial to distinguish lymphocytic HES from surface markers expressed in other T cell lymphoid malignancies. Occasionally lymphocytic HES may progress to frank lymphoid malignancy after being stable.

c) Overlap HES is the second common following idiopathic HES. They may be organ restricted or clinically defined multi-system syndromes such as eosinophilic granulomatosis with polyangitis (EGPA) or eosinophilic gastrointestinal diseases.

d) Familial HES include family history of eosinophilia, harbor other somatic abnormalities and seen in more than one family member [7].

Table 1. Mechanism of HES subtypes.

Subtype	Disease Mechanism	Diagnosis
Myeloproliferative	Due to primary driver mutation and gene rearrangement involving tyrosine kinase receptor	*ETV6-PDGFRbeta*, *FIP1L1-PDGFRalpha* following deletion in chromosome 4q12 and *FGFR1* fusion genes from t(5;12), t(8;9)/*PCM1::JAK2;* t(9;12)/*ETV6::ABL1*, t(12;13)/*ETV6::FLT3, ETV6::LYN*; *FGFR1OP::RET ETV6::NTRK3*; *ETV6::FGFR2*; *RANBP2::ALK*; *BCR::RET*; chromosome 4q12 and t(8;13) [10].
Lymphocytic	Occurs due to aberrant, clonal T cell activation driven by IL-5, IL4, and IL-13	Classically CD4+/CD3 negative T cells, less frequently both CD4/CD3 negative T cells, TCR alpha/beta T cells and CD3+/CD4+/CD7 negative T cells [11]
Associated	Secondary to offending agent/other disorder	To identify underlying hypersensitivity reaction, parasitic infestation, drug, autoimmune disorder, metabolic causes or neoplasm
Familial	Present in multiple family member	Few distinct syndromes include Wiskott Aldrich Syndrome, Omenn syndrome, Gleich syndrome, and Hyper IgE syndrome
Overlap	Distinct involvement of single organ/manifest as syndrome	Atopic asthma, eosinophilic dermatitis, fasciitis, pneumonia, and gastro-intestinal disorders [12]
Idiopathic	Diagnosed after excluding all known subtypes	Varied clinical presentation due to cardiac, neurologic, gastrointestinal, or dermatologic manifestations
Hyper eosinophilia of unknown significance	Persistent eosinophilia without any organ damage or driver mutation	After exclusion of other subtypes and lack of organ/system involvement

e) **Associated HES** occurs due to underlying hypersensitivity reaction, parasitic infestation, drugs, immunodeficiency disorder or neoplasm [8].

f) **Idiopathic HES (iHES)** is the most common subtype which is diagnosed when AEC>1.5×10^9/L, organ dysfunction not attributable to other causes, absence of any detectable clonal myeloid or lymphoid population on immunophenotyping and lack of molecular or somatic genetic mutation. Recent literature addresses multiple somatic mutations and gene variants such as *PRTFDC*, *TYRO3*, *TDG*, *TYW1B*, and *ZNF880* associated with idiopathic HES using exome sequencing [9].

g) **Hyper eosinophilia of unknown significance** represents a subtype of asymptomatic, persistent eosinophilia without any organ damage despite absence of treatment.

h) **Chronic Eosinophilic Leukemia (CEL)** is considered when HE is associated with clonal genetic marker and abnormal bone marrow morphology such as erythroid or megakaryocytic dysplasia. Diagnosis is established by the exclusion of other neoplasms such as MLN-Eo-TK, Systemic Mastocytosis (SM), Chronic Myelomonocytic Leukemia (CMML), Philadelphia negative Myeloproliferative Neoplasm (MPN), Myelodysplastic Syndrome (MDS) and Acute Myeloid Leukemia (AML).

Index case

A nine-year-old male child presented with progressive, generalized hyperpigmented, pruritic, papulo-nodular skin lesions associated with left ventricular dysfunction without intramural thrombus and ejection fraction of 45%. His median peripheral blood AEC was 3.49×10^9/L over more than six months. There was neither a significant family history nor an association with atopy or immunodeficiency disorder.

Manifestation of Idiopathic HES

Eosinophilia related clinical manifestations are non-specific, heterogenous, multisystemic and multifaceted. Cutaneous involvement may range from maculo-papular rash, urticaria, intense pruritis, ulceration, angioedema, nodular and pustular lesions. Pulmonary manifestation includes rhinosinusitis, eosinophilic pneumonia, and eosinophilic pleural effusion resulting in cough, dyspnea, fatigue, and fever [13]. Cytokine mediated tissue damage in gastrointestinal system manifests as colitis, gastritis, esophagitis and weight loss. Haematological involvement include anemia, thrombocytopenia due to marrow infiltration, organomegaly, lymphadenopathy and splenomegaly. Cardiovascular complications are life threatening and range from endomyocardial fibrosis due to eosinophil deposition, valvular dysfunction, intracardiac thrombus, and cardiac failure. Other complications masquerade immune mediated/ vasculitic disorder and include stroke, encephalopathy, peripheral neuropathy, arthritis, myalgia, renal vasculitis, optic neuritis, thrombosis and aneurysm.

Evaluation of Idiopathic HES

A careful clinical history to exclude secondary, familial causes, associated T cell malignancies, Hodgkins lymphoma, medication, immunodeficiency, travel, allergy and family history are mandatory for comprehensive evaluation. Laboratory profile include complete blood count, biochemistry, liver and renal function test, serum immunoglobulin (Ig) IgE, IgG, IgA, IgM, serum vitamin B12, plasma Epstein Barr virus (EBV) deoxy ribonucleic acid (DNA), autoimmune work up, complement level, serum protein electrophoresis, stool for ova, cyst, culture, bone marrow examination for karyotyping, real time polymerase chain reaction (RT-PCR), next-generation sequencing, Fluorescence In situ Hybridization (FISH), immunophenotyping for Cluster of Differentiation (CD)7, CD25, human leucocyte antigen (HLA)-DR, T-cell receptor (TCR) γ/δ, CD45RO, CD2, TCR α/β, CD95, CD4, CD3, CD5, CD27, CD8, conventional karytotyping as well as genetic mutation analysis for clonality and serum tryptase.

Positron Emission Tomography-Computed Tomography (PET-CT), lymph node excision biopsy, immunohistochemistry, imaging of chest, abdomen and pelvis, pulmonary function test including diffusion capacity of lung for carbon monoxide (DLCO), chest X-ray, High resolution CT, bronchoalveolar lavage fluid analysis, echocardiography, serum troponin T, N-terminal pro brain natriuretic peptide (NT-proBNP) and cardiac magnetic resonance imaging (MRI) are indicated to identify systemic involvement and organ specific complication [14]. Serum thymus and activation regulated chemokine (TARC), lung biopsy, immunohistochemical staining for eosinophil peroxidase, immunoglobulin E (IgE), T-cell cytokine profile such as Granulocyte Monocyte-Colony Stimulating Factor (GM-CSF), Interleukin (IL)-2, Interferon (IFN)-α, IL-4, IL-5, IL-13, IL-3 are performed in selected cases [15]. Analysis of single cell intracellular cytokine level by flow cytometry, cytokine measurement in culture supernatant of aberrant T-cells, T-cell receptor gene rearrangement are complex, expensive with limited availability in few centers. Histopathological examination of skin lesions demonstrates dense perivascular inflammatory infiltrate comprising eosinophils, lymphocytes with no cellular atypia in dermis extending up to subcutis.

Case (Continued)

He was diagnosed as idiopathic HES with eosinophilic cardiomyopathy after exclusion of clonal myeloid/lymphoid neoplasm or allergic and immunological causes by bone marrow morphology, immunophenotyping, genetic, molecular, sequencing and imaging studies. NT Pro BNP, Troponin I and Troponin T were elevated.

Overview of Management of HES

Although the primary goal of treatment is to reduce eosinophil mediated inflammation, cytokine release and end organ damage, it is prudent to initiate treatment after identification of HES subtype and detection of driver mutation rather than solely upon absolute eosinophil count. However, in clinical practice, majority of physicians commence treatment when AEC is above 1.5×10^9/L due to attributable symptoms.

Systemic corticosteroids still continue to be the first line of treatment except in cases due to myeloid HES arising from clonal mutation. In proven clinical cases due to *ETV6-PDGFRbeta, FIP1L1-PDGFRalpha*, tyrosine kinase inhibitors such as imatinib, pemigatinib, ruxolitinb, nilotinib has demonstrated efficacy [16,17]. In cases of overlap HES such as gastrointestinal disease treatment is topical steroid. In associated HES secondary to parasitic infestation, drugs or neoplasm, treatment is removal of offending agent. **Table 2** depicts various treatment options in HES subtypes.

Management of Idiopathic HES

Rapid worsening organ dysfunction resulting in eosinophilic cardiomyopathy, cardiac failure or ischemic stroke are noted in many HES subtypes as well as in iHES. It mandates multidisciplinary organ specific, individualized approach. Treatment algorithm comprising corticosteroids, immunosuppressive agents and targeted biologics are incorporated sequentially as per risk profile, response and adverse effect in idiopathic HES.

First line

Prednisolone at the dose of 1 mg/kg/day is the first recommended agent of choice to inhibit eosinophil proliferation, cytokine release, inflammatory damage and T-cell activation in idiopathic HES.

Second line

Although second line options such as hydroxyurea, IFN-α, imatinib, methotrexate, azathioprine, mycophenolate,

Table 2. Treatment options in HES subtypes.

Sl. No	Subtype of HES	First line	Second line	Remarks
1	Myeloid	Imatinib, ruxolitinib depending upon tyrosine kinase receptor mutation	Cytotoxic agents or immunomodulators if no response to first line agents; In relapsed/ refractory *FGFR1*-rearranged neoplasm, pemigatinib has shown efficacy [18]	Corticosteroid is the treatment of choice during initial management of HES. In resistant cases, either hydroxyurea or combination chemotherapy are preferred
2	Lymphocytic	Corticosteroid is the first line as most cases are cytokine driven resulting from clonal T lymphoid population	Immunomodulators in steroid refractory cases	Third lines such as cytotoxic or biologics such as mepolizumab or benralizumab are preferred in refractory cases
3	Associated	Removal of causal agent	Anti histamines, diethyl carbamazine, albendazole, and corticosteroid	Mepolizumab dose of 750 mg subcutaneous monthly for 3–6 doses
4	Familial	Corticosteroid	Hydroxyurea	Intermittent flares and gastrointestinal symptoms are common [19]
5	Overlap	Topical agents for eosinophilic esophagitis, bendralizumab or mepolizumab	Methotreaxate, dupilumab, omalizumab, depemokimab	Bendralizumab 30 mg subcutaneous every 4 weeks is approved in severe eosinophilic asthma and EGPA
6	Idiopathic	Corticosteroid, Imatinib, Hydroxyurea	Immunomodulators, cytotoxic agents, biotherapeutics such as mepolizumab, bendralizumab and reslizumab	Allogenic stem cell transplant in aggressive cases.
7	Hyper eosinophilia of undetermined significance	No treatment if patient is asymptomatic	Wait and watch	Complications such as thromboembolism or organ involvement such as myocarditis or neurologic manifestations require treatment

cyclosporine A and biologics are preferred as steroid sparing agent in iHES, their efficacy is limited due to sparse data. They are chosen with caution in the background of cytopenia due to marrow infiltration as organ damage resulting in cardiac failure, myocarditis, thromboembolism, renal and hepatic impairment may further deteriorate clinical status. Administration of conventional chemotherapy such as etoposide, vincristine, cyclophosphamide may be warranted in aggressive, less amenable and extensive disease.

Third line

It includes cyclosporine, cladribine, cytarabine, dexpramipexole demonstrated efficacy in neurologic dysfunction and ischemic stroke but carried a high rate of treatment failure and discontinuation.

Case (Continued)

In view of eosinophilic cardiomyopathy, he was initially started on pulse steroid along with heparin prophylaxis. Sequential therapy with hydroxyurea, imatinib, cytotoxic chemotherapy comprising etoposide, vincristine and prednisolone (EOP) did not demonstrate any clinical benefit. AEC and cardiac failure were refractory to conventional supportive care measures.

Biologics in Idiopathic HES

As iHES still remain within an unidentified genomic and molecular zone, efficacy of single line treatment is uncertain. Cardiac, renal, lymphoreticular, hematopoietic and rheumatologic manifestation rarely respond to IL-5/IL-5R targeting biologic agents. **Table 3** illustrates various biotherapeutics currently under trial in iHES. Lack of response to one anti IL-5 agent does not preclude the success with other agent in view of variable response to biologics targeting the IL-5 axis [20]. Allogenic hematopoietic stem cell transplants offer the only chance of cure for refractory and persistent HES.

Table 3. Biologics which are under trial in idiopathic HES.

Characteristics	Mepolizumab	Benralizumab	Reslizumab	Dupilumab	Depemokimab
Target	Humanized anti-IL-5 IgG1 kappa monoclonal antibody	Afucosylated humanized IgG1-κ anti-IL-5 receptor alpha monoclonal antibody	Humanized anti-IL5 IgG4 monoclonal antibody	IL-4 receptor alpha antagonist	Humanized anti IL-5 IgG1 monoclonal antibody
Mechanism of action	Interferes with binding to IL-5 receptor alpha and neutralizes free IL-5	Binds to IL-5 receptor alpha and interferes with binding of IL-5	Interferes with binding to IL-5 receptor alpha and neutralizes free IL-5	Blocks T helper 2 cytokines Il-4 and IL-13 and results in downregulation of JAK-STAT signaling pathway	Blocks IL-5 from binding to IL-5 receptor alpha expressed on eosinophils, mast cells, basophils
Time to response	24 hours	24 hours	24 hours	3–7 days	4–10 days
Elimination half life	16–26 days with subcutaneous dose	15 days	24 days	21 days	20 weeks (due to triple amino acid substitution called YTE modification, increasing its binding affinity to neonatal Fc receptor)
Age	Above 18 years	Above 6 years	Above 18 years	Above 6 years	Above 12 years
Dosing	300 mg subcutaneously (SC) every 4 weeks in IHES (10 mg/kg in children)	30 mg SC every 4 weeks for 3 doses, thereafter every 8 weeks	3 mg/kg every 4 weeks intravenous	600 mg loading dose followed by 300 mg every 2 weeks subcutaneous	100 mg subcutaneous every 6 months
Food and drug administration (FDA) approval	Idiopathic hyper eosinophilic syndrome in age> 12 years, severe eosinophilic asthma, EGPA, chronic rhinosinusitis with nasal polyposis	Severe eosinophilic asthma	Severe eosinophilic asthma	Eosinophilic esophagitis, atopic dermatitis, prurigo nodularis, eosinophilic asthma	Severe eosinophilic asthma

Characteristics	Mepolizumab	Benralizumab	Reslizumab	Dupilumab	Depemokimab
Adverse events	Headache, injection site reaction, backpain, fatigue	Headache, pyrexia, nasopharyngitis, hypersensitivity, injection-site reactions	Myalgia, swollen tongue, asthma exacerbation	Transient eosinophilia, erythema, edema and conjunctivitis	Nasopharyngitis and upper respiratory infection
Clinical Trial	SPHERE trial- phase 3 trial in age 6–17 years with HES [29]	NATRON- A phase 2+3 study in HES	Currently none in HES	Add-on therapy for HES with partial response biologic agents	DESTINY- phase 2 trial
Study design	Open label phase 3	Double blind phase 3	Currently none in HES	Open label Phase 2	Double bind phase 3
Comparator	None	Placebo	Currently none in HES	None	Placebo
Primary Outcome	Number of flares experienced in a year	Time to first worsening or flares of HES	Currently none in HES	Clinical improvement at 24 weeks and reduction in symptoms	Flare frequency

Mepolizumab

It is the first FDA approved humanized monoclonal antibody targeted against IL-5 for the treatment of *PDGFRA* negative HES. It has also shown efficacy for the treatment of overlap, lymphocytic and idiopathic cases [21]. Several placebo-controlled multicenter studies and clinical trials have demonstrated superior response, tolerability and steroid-sparing activity of mepolizumab [8,20]. Sustained reduction in AEC along with serum IL-5 level in *PDGFRA* negative HES and lymphocytic HES following mepolizumab at the dose of 750 mg IV every month was well documented [22].

Benralizumab

It has proven efficacy in iHES due to Antibody Dependent Cell-mediated Cytotoxicity (ADCC) against eosinophils, its precursors, mast cells and basophils, resulting in complete eosinophil depletion [23]. Lack of interference from high serum IL-5 level highlights its efficacy where eosinophil may be IL-5 independent in few HES disorders. Although AEC level correlated with response to anti IL-5/IL-5 receptor biologic agents in eosinophilic asthma, neither historic peak AEC/baseline AEC nor IL-5 levels predicted response to mepolizumab in phase 3 trial of steroid responsive *PDGFRA* negative HES as well as to benralizumab in phase 2 trial in steroid refractory *PDGFRA* negative HES [24].

Other agents such as **dupilumab,** which blocks IL-4/IL-13 signaling and inhibits eotaxin mediated migration of eosinophil and end organ damage, has been studied as add-on therapy [25]. In cases with persistent dermatologic, sino-pulmonary and gastrointestinal symptoms already on other anti-IL-5/IL-5R biologic agent, dupilumab showed sustained clinical remission. Another ultra long-term acting biologic agent, **depemokimab** with high IL-5 binding affinity has demonstrated efficacy even with 6-monthly dosing intervals [26].

Alemtuzumab was evaluated in refractory HES and showed more than 80% response rates [27]. **Omalizumab** showed efficacy in placebo-controlled studies of moderate to severe asthma. In few cases of eosinophilic esophagitis and allergen driven eosinophilic disease, superior benefit of omalizumab was reported compared to iHES [28].

Case (Continued)

Benralizumab was added along with EOP regime for two cycles after explaining grave prognosis and lack of consent for allogenic transplant. Though transient clinical improvement and AEC decline were noted, cardiac failure and skin lesion were progressive. As a desperate measure, peg interferon alfa 2a was supplemented along with ongoing chemotherapy at weekly interval for two weeks. Despite aggressive and persistent salvage measures, clinical condition deteriorated and patient succumbed to refractory eosinophilia and cardiogenic shock.

Treatment failure following first- and second-line choices pose major therapeutic challenges owing to rapid disease progression in involved organ. The choice of treatment, selection of one agent over the other, both first- and second-line resistance, organ specific toxicity profile, patient/physician preferences, multi-factorial parameters influencing response rates, lack of long-term safety data of biologics underscore the need for multi-centric data in this subset.

Case (Continued)

Initial decline in AEC following steroid and immuno-chemotherapy was successful in this case but cardiac damage due to eosinophil infiltration and tissue damaging cytokines were irreversible which led to treatment failure. Despite absence of regulatory approval and safety data for bendralizumab in cardiac failure, there was transient AEC reduction and symptomatic improvement.

This unique case illustrates the young age of disease onset, variable presentation, aggressive clinical course, short time duration between diagnosis and development of complication, frequent skin and cardiac flare-up, diagnostic and management challenges due to lack of approved biologics in pediatric iHES. Uncertain prognostic role of serum biomarkers for disease monitoring, paucity of surrogate markers except AEC, lack of treatment guidelines following failure of first line therapy, preferable choice of second line therapy considering age and disease profile are major limitations. Minimal data on long term safety of biologics, combination or sequential therapy of novel agents in refractory cases and multidisciplinary role on allogenic stem cell and cardiac transplantation in these cases need further exploration.

Conclusion

Bridging the knowledge gap between clinical heterogeneity, molecular profile and prognostic factors enable further sub-classification into high or low risk disease groups, focus on patient/disease-centric management, incorporate biologics earlier to attenuate organ damage and achieve therapeutic cure in aggressive cases. Future promising strategies include identification of novel circulating biomarkers and analyzing the clinical role of existing markers such as IL-5, IgE and TARC particularly in persistent and treatment refractory HES. Targeted biologics-based consensus guideline and treatment recommendation in the era of generative artificial intelligence and precision medicine to minimize treatment failure, organ damage and prolong survival are unmet future needs in this rare subset.

Acknowledgement

To all the patients who grant us permission to learn, treat and teach.

Author Contribution

MV contributed to the concept, preparation, and drafting of the manuscript.

Conflict of Interest

The author declares that there are no conflicts of interest.

Funding

No funding was received for the preparation of this article.

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