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Review Article

Pathology Section

Hypereosinophilic Syndrome: A Narrative Review of Pathogenesis, Clinical Spectrum and Evolving Therapeutic Strategies

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ABSTRACT

Hypereosinophilic Syndrome (HES) represents a heterogeneous group of disorders, which are characterised by the persistent eosinophilia and progressive, multisystemic damage of organs. This narrative review article synthesises current-evidence on aetiopathogenesis, clinical features, diagnosis, along with various novel therapeutic options for HES management. Pathogenesis of HES usually involves two mechanisms: First one is sustained eosinophil overproduction driven by clonal, lymphocytic, or reactive pathways. Another mechanism is eosinophil-mediated tissue injury which is resulted through cytotoxic granule proteins, cytokines and pro-inflammatory cascades. Advances in molecular diagnostic methods such as detection of Factor Interacting with PAPOLA and CPSF1-Platelet-Derived Growth Factor Receptor Alpha (PDGFRA), Platelet-Derived Growth Factor Receptor Beta (PDGFRB) and Fibroblast Growth Factor Receptor 1 (FGFR1) and Janus Kinase 2 (JAK2) rearrangements also refined classification of HES into myeloid, lymphocytic, idiopathic and secondary variants, thus it further helps enabling more targeted management. Histopathological findings usually demonstrate dense eosinophilic infiltrates having tissue necrosis and fibrosis, while microbiological studies also proved to be helpful in excluding parasitic as well as infectious triggers. Management of HES got evolved from broad immunosuppression along with corticosteroids to the mutation-directed therapy, biologics targeting Interleukin-5 (IL-5)/ Interleukin-5 Receptor (IL-5R), as well as experimental agents like Siglec-8 inhibitors, JAK-pathway modulators. Despite having such therapeutic progress, challenges remain in early diagnosis, predicting disease trajectory, as well as preventing irreversible organ dysfunction. Future directions should focus further on single-cell multi-omics, development of non invasive biomarkers, as well as Artificial Intelligence (AI)-based risk prediction models for HES. The present review thus highlights the need for an integrated multidisciplinary care and continued research for optimisation of outcomes for patients with HES. The present narrative review article aimed to highlight about current understanding of pathogenesis, clinical features, diagnosis as well as evolving targeted management strategies for HES along with emphasis on precision medicine, future research directions.

Keywords: Eosinophilia, Immunopathology, Molecular diagnostics, Targeted therapy, Tissue infiltration

INTRODUCTION

A heterogeneous group of disorders, which is characterised by persistent and significant eosinophilia, typically an Absolute Eosinophil Count (AEC) >1.5×10^9/L and organ or tissue damage, which is usually attributed to an infiltration or activation of eosinophils, without presence of any other related-identifiable cause, such as parasitic infection, allergic disease or malignancy, is called as HES [1]. The clinical manifestation of HES is highly variable in nature, as few patients of HES can also remain asymptomatic, while others might develop life-threatening, end-organ involvement, like cardiac, neurologic, pulmonary, gastrointestinal complications [1,2]. During the past few decades, advancement in molecular diagnostics as well as an improved understanding of eosinophil biology further enabled adequate sub-classification of HES and a more personalised therapeutic approach [3]. Discoveries of specific molecular aberrations (such as the FIP1L1–PDGFRA fusion gene) along with the role of aberrant T-cell clones producing Interleukin-5 (IL-5) have led to more targeted treatment approaches, thus it improves both outcomes and prognosis in patients [4].

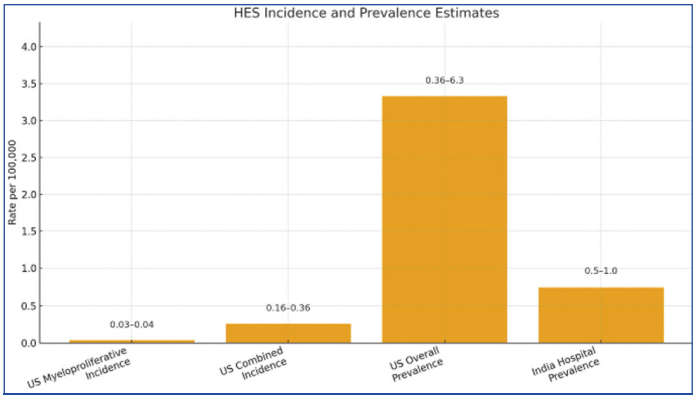
The modern understanding of HES was developed gradually over the past several decades [5]. Although such related cases of unexplained eosinophilia were already described in the early 20th century, by Hardy WR and Anderson RE formally introduced the term “hypereosinophilic syndromes” in 1968 for describing a constellation of conditions marked by persistent eosinophilia with systemic involvement [5]. In 1975, Chusid MJ et al., proposed the first standardised diagnostic criteria, thereby defined idiopathic HES as eosinophilia count ≥1.5×10^9/L which persists for six months with organ dysfunction and no other identifiable causation associated with it [6]. HES is rare and its true population incidence as well as prevalence remain imprecisely defined because most data depicted comes from registry analyses, single-centre cohorts and case series rather than population-based studies [7]. In large registry analyses study from the United States, myeloproliferative forms of HES are reported with crude incidence rates approximately 0.03-0.04 per 100,000 person-years, but broader estimates that combine different HES subtypes show higher age-adjusted incidence which ranges from 0.16-0.36 per 100,000 approximately with prevalence estimating between 0.36 and 6.3 per 100,000 people [7].

Considering the Indian context, there are no well-defined population-based epidemiologic studies; available information comes from tertiary-centre series, hospital cohorts and case reports [7,8]. An Indian hospital series that evaluated and studied patients with hypereosinophilia described prevalence, which is approximately 0.5-1.0 cases per 100,000 of hospital population [8]. More recent case series and cohort studies from India continue to highlight that parasitic and reactive causes are relatively common for marked eosinophilia, thus underscore differences in the relative secondary against primary (i.e., idiopathic) HES as compared to western cohort study populations [8,9]. Comparison of HES incidence and prevalence estimates is depicted in [Table/Fig-1] [8,9].

DISCUSSION

Aetiologic and Molecular Classification of Hypereosinophilic Syndromes (HES)

The HES is now classified mainly based on the aetiology as well as molecular driver into three major groups namely: 1) primary (clonal/



[Table/Fig-1]: Comparison of HES incidence and prevalence estimates shown using midpoint bars [8,9].

myeloid) eosinophilia, in which a hematologic neoplasm drives eosinophil expansion; 2) secondary (reactive) eosinophilia, because identifiable causes are parasitic infection, allergic or autoimmune disease, drug reactions, or solid-tumour/lymphoid malignancies; and 3) idiopathic HES, when there is sustained hypereosinophilia with involvement of organ that also persists after thorough evaluation and no cause or clonality is found [10]. This classification (primary/clonal; secondary/reactive; idiopathic) is emphasised in expert consensus and major reviews as it helps directly to guide in targeted testing along with adequate therapy [10].

The sub-classification which is applicable in clinical practice and by the World Health Organisation (WHO)/consensus groups refines the "primary" and "other" categories into clinically and molecularly meaningful entities [11]. Key named subtypes are myeloid/lymphoid neoplasms with eosinophilia along with defined rearrangements (PDGFRA, PDGFRB, FGFR1 and provisional PCM1-JAK2), these are really very important because they are targetable and are formally recognised by WHO [11]. Chronic Eosinophilic Leukaemia, Not Otherwise Specified (CEL-NOS) is further described under clonal disease without any presence of defining fusion [11]. The lymphocytic (L-HES) variant (clonal/oligoclonal T-cell populations producing IL-5) is thereby identified separately as its pathogenesis and treatment are different from myeloid forms [11]. Few other sub-classifications includes organ-restricted eosinophilic disorders, episodic Gleich syndrome, also Hypereosinophilia of undetermined significance (HEus) which are described specifically for asymptomatic as well as non-organ-damaging eosinophilia [11]. Classification and Sub-classification of HES is described in [Table/Fig-2].

Clinical Involvement and Symptomatology in Hypereosinophilic Syndrome (HES)

Clinical manifestations of HES are mainly depended on which organs are getting infiltrated through eosinophils [12]. Persistently marked blood eosinophilia which is usually ≥1.5×10^9/L, also drives tissue damage through release of cytotoxic granule proteins {e.g., Major Basic Protein (MBP), Eosinophil Cationic Protein (ECP)}, reactive oxygen species, along with profibrotic mediators (such as TGF-β), which results into fibrosis and organ dysfunction [12]. Patients can further present with symptoms such as fever, weight loss, night sweats, fatigue, anorexia, arthralgias, or myalgias [3,13]. Gastrointestinal system is also commonly involved, which manifest with pain abdomen, diarrhoea, nausea or vomiting, sometimes associated with eosinophilic gastritis or enterocolitis [13]. Cardiovascular complications are very important which include endomyocardial fibrosis, valvular dysfunction and thromboembolic events due to vascular injury, thrombotic or embolic phenomena are present in a large fraction of patients with HES [2,14].

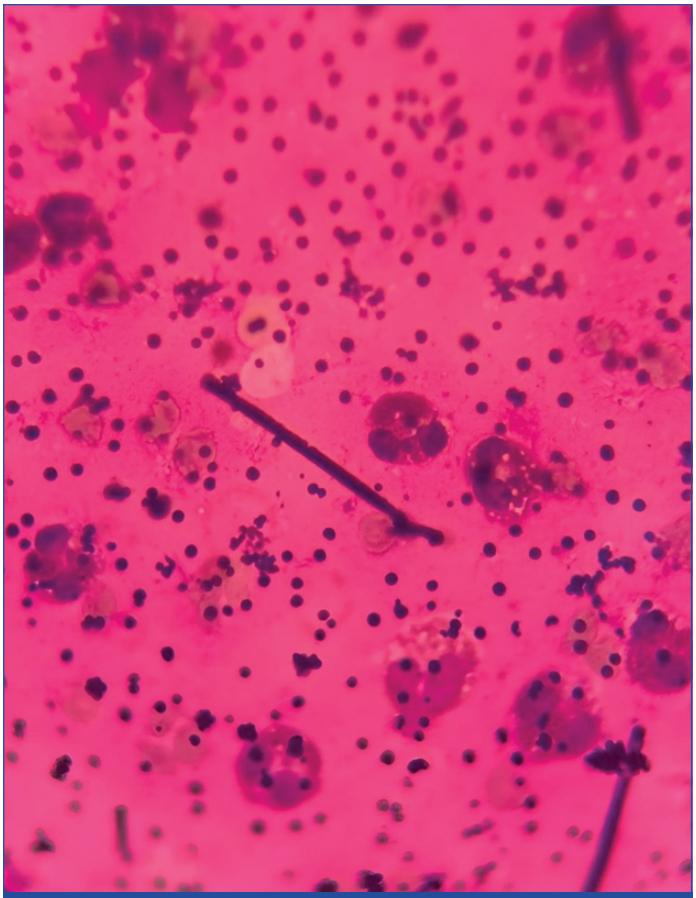
In addition to involvement of internal organs, respiratory systems are frequently affected [15,16]. Pleural fluid cytology may demonstrate eosinophil-rich effusion in patients with HES as shown in [Table/Fig-3] [15,16].

Cutaneous manifestations are observed in a substantial proportion of HES cases; patients have urticarial or eczematous lesions, angioedema, pruritic papules or nodules, which are sometimes resistant to therapy [16]. Histopathology in most of the cases shows spongiosis with heavy eosinophilic infiltrates as depicted in [Table/Fig-4] [16].

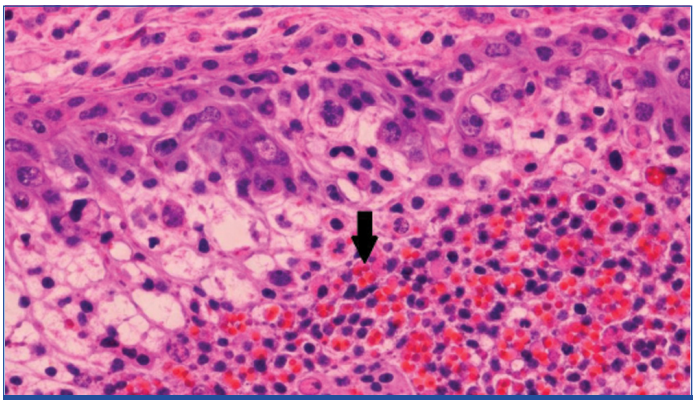
Respiratory symptoms are cough, wheezing and dyspnoea [15]. Chronic cough related to HES can also be linked to airway eosinophilic

Main category	Definition	Key sub-types/sub-classification	Important features	Management approach	Referenceses
1. Primary (Clonal / Myeloid) Eosinophilia	Eosinophil expansion driven by an underlying haematologic neoplasm or myeloid clone.	Myeloid/Lymphoid Neoplasms with Eosinophilia and Defined Rearrangements: • PDGFRA fusion • PDGFRB fusion • FGFR1 rearrangements • PCM1–JAK2 (provisional WHO entity) Chronic Eosinophilic Leukaemia – NOS (CEL-NOS)	• WHO-recognised targetable tyrosine kinase fusions. • FGFR1 and PCM1-JAK2 associated with aggressive biology. • CEL-NOS=clonal eosinophilia without defining fusions.	• Tyrosine kinase inhibitors (e.g., imatinib for PDGFRA/B) • Cytoreductive therapy or HSCT in aggressive/refractory disease	[10,11].
2. Secondary (Reactive) eosinophilia	Eosinophilia due to an identifiable external cause.	• Parasitic infections • Allergic disorders • Autoimmune diseases • Drug reactions • Solid tumours / lymphoid malignancies	• IL-5 driven. • Treatment requires identifying and correcting underlying cause.	• Treat underlying cause • Corticosteroids or immunosuppression if clinically indicated	[10].
3. Idiopathic HES	Sustained hypereosinophilia with organ involvement and no identifiable cause or clonality even after complete evaluation.	• Idiopathic HES (classic) • HEus - asymptomatic, no organ damage	• Diagnosis of exclusion. • HEus is an observational category without organ injury.	• Corticosteroids (first-line) • Anti–IL-5/IL-5R therapy for steroid-refractory disease • Observation alone for HEus	[10,11].
4. Lymphocytic variant(L-HES)	Caused by clonal/oligoclonal T-cell populations secreting excess IL-5.	• L-HES as a distinct clinicopathologic entity	• Different pathogenesis from myeloid HES. • Often steroid-responsive. • Requires immunophenotyping and T-cell clonality studies.	• Corticosteroids (first-line) • Immunomodulatory agents or anti–IL-5 therapy in refractory cases	[11].
5. Other clinically relevant entities	Disorders with eosinophilia that do not fit classical HES categories.	• Organ-restricted eosinophilic disorders • Episodic angioedema with eosinophilia (Gleich syndrome)	• Episodic or localised patterns. • Important for clinical management and prognosis.	• Organ-directed therapy • Short-course systemic or topical corticosteroids • Anti–IL-5/IL-5R therapy for recurrent or steroid-dependent disease • Long-term monitoring for disease evolution	[11].

[Table/Fig-2]: Classification and Sub-classification of Hypereosinophilic Syndrome (HES); [10,11].



[Table/Fig-3]: Pleural fluid cytology showing eosinophil-rich effusion in a patient with HES (H&E stain, x100).

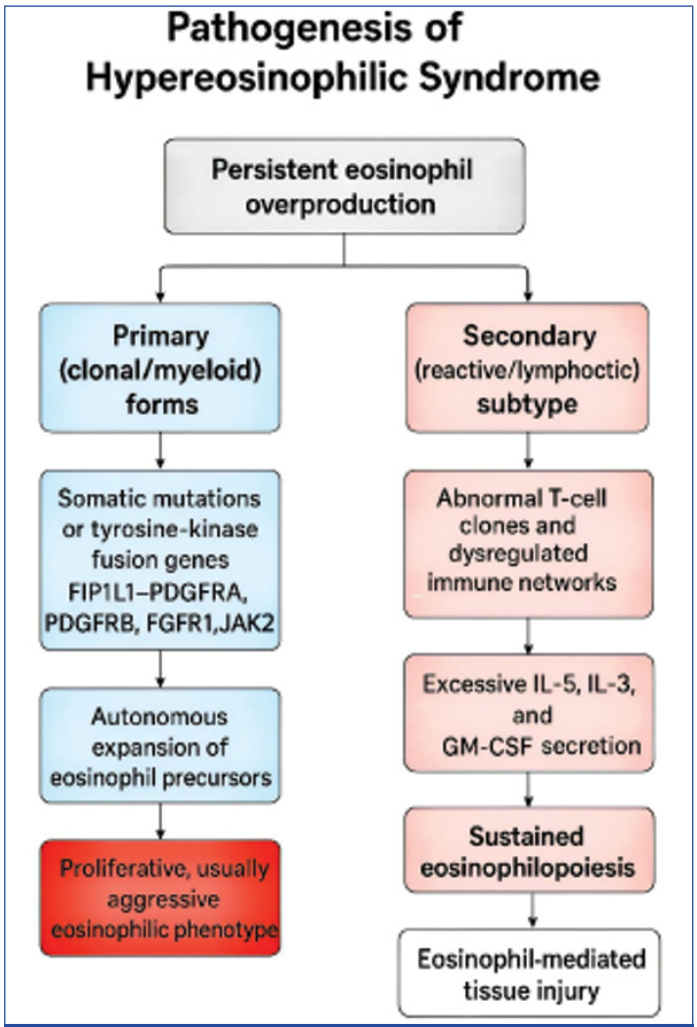


[Table/Fig-4]: Histopathology of HES showing spongiosis with dense eosinophilic infiltrates as pointed with arrow (H&E stain, x100);

inflammation as well as bronchial hyperreactivity even in the absence of classical allergic triggers [15]. Neurological involvement in HES cases usually presents with peripheral neuropathy, this is the prominent feature which distinguishes it from other similar eosinophilic conditions such as eosinophilic granulomatosis with polyangiitis [17]. Renal involvement in HES is very uncommon but also clinically important, which typically presents as eosinophil-mediated tubulointerstitial nephritis, proteinuria, as well as progressive renal impairment due to infiltration of eosinophils, related vascular injury [18].

Aetiopathogenesis and Pathophysiology of Hypereosinophilic Syndrome (HES)

Development of HES is mainly related to two biological processes that are, persistent eosinophil overproduction and eosinophil-mediated tissue injury [19]. In primary (clonal/myeloid) forms, somatic mutations or tyrosine-kinase fusion genes particularly FIP1L1–PDGFRA, PDGFRB, FGFR1, JAK2 and other recently identified driver lesions which results into autonomous expansion of eosinophil precursors [20]. These aberrant molecular signals thus bypass normal IL-5-dependent regulation as well as generates a proliferative, usually aggressive eosinophilic phenotype [20]. In the secondary (reactive/lymphocytic) subtype of HES, abnormal T-cell clones and dysregulated immune networks that cause secretion of excessive IL-5, IL-3 and Granulocyte-Macrophage Colony-stimulating Factor (GM-CSF), finally leading to production of sustained eosinophilopoiesis despite not having intrinsic myeloid defects [19,21]. Recently, it is also highlighted that many "idiopathic" cases can harbour subtle clonal haematopoiesis as well as cytokine abnormalities, which suggest an overlapping pathogenic-mechanisms, rather than strictly distinct associated phenomena [19,22]. Pathogenesis of HES have been depicted through [Table/Fig-5].



[Table/Fig-5]: Pathogenesis of HES [19.22].

The pathophysiology behind organ damage mainly includes activation, trafficking and degranulation of eosinophils within the tissues [23]. Activated eosinophils thereby release cytotoxic granule proteins, which are inclusive of MBP, ECP, eosinophil peroxidase, as well as eosinophil-derived neurotoxinthat cause direct epithelial and endothelial injury, microvascular thrombosis and parenchymal necrosis [19,23]. Eosinophil-derived cytokines, chemokines, lipid mediators, also reactive oxygen species further result into amplification of local inflammation and stimulate fibroblast activation, leading to progressive fibrosis in organs such as the heart, lungs and gastrointestinal tract [24]. Additionally, Eosinophil Extracellular Traps (EETs), can contribute thrombosis, sustained inflammation, thus driving towards the multisystemic involvement pathology [19,24].

Comprehensive Diagnostic Approach to Hypereosinophilic Syndrome (HES)

The diagnosis of HES is based mainly on demonstrating persistent and marked eosinophilia along with evidence of organ damage which is eosinophil-mediated, after excluding other secondary

causes for it [2,6,25]. Contemporary and new guidelines have replaced the older requirement of ≥6 months of eosinophilia with a more clinically practical threshold of AEC ≥1.5×10^9/L which is found on at least two occasions [26]. Evaluation of such suspected HES cases, begins with a detailed clinical history and examination which is focused mainly on allergic diseases, parasitic exposure, autoimmune disorders, as well as drug reactions, as these represent common secondary causes of eosinophilia [26]. Baseline laboratory examination further includes complete blood counts, serum tryptase, vitamin B12, Immunoglobulin E (IgE), liver and renal function tests and stool ova-parasite examination [27,28]. Chest radiography, echocardiography, along with abdominal ultrasonography are routinely recommended for screening early cardiac, pulmonary and hepatosplenic involvement [28].

Skin biopsies often show a perivascular and interstitial dermal infiltrate which are rich in eosinophils along with dermal oedema, characteristic "flame figures" from eosinophil degranulation is present in some cases [2,16]. Occasionally cutaneous microthrombi and vasculitic changes are also described in various cases of HES [16]. Gastrointestinal histopathological specimens also demonstrate dense mucosal as well as submucosal eosinophilic infiltrates along with ulceration or erosive injury [13]. Cardiac involvement if present in cases of HES (which are eosinophilic myocarditis / Loeffler endocarditis) shows endomyocardial eosinophilic infiltration with myocyte necrosis in the acute phase of necrosis, which is followed by thrombus formation, followed by endomyocardial fibrosis in chronic phases. Thus, endomyocardial biopsy is known diagnostic gold standard when there is suspected cardiac disease [2,14,29]. Bone-marrow findings, usually vary from reactive eosinophilia to hypercellular marrow along with marked eosinophilia, as well as in myeloid/clonal cases there may be additional presence of dysplasia or increased blasts [30].

Serology is used to diagnose helminthic infections in cases of clinical suspicion, but targeted blood tests including blood cultures, respiratory viral PCR, is performed in suspected other systemic infection [10,12]. In addition to exclusion of infection, modern diagnostic algorithms are inclusive of molecular testing of blood and bone marrow for the recognition of clonal markers (FIP1L1-PDGFRA and other PDGFRA/B, FGFR1 or JAK2 rearrangements) as well as peripheral-blood or marrow cytogenetics/Next-Generation Sequencing (NGS) panels for identifying myeloid neoplasms; these molecular results thus help in directly changing management approaches (e.g., imatinib-responsive PDGFRA-fusion cases) [25,31]. Flow cytometry examination results of HES patients may have aberrant clonal T-cell populations (e.g., CD3–CD4+ phenotype), which drive expansion of eosinophil through overproduction of IL-5 [32]. Finally, routine histopathology is often required, in which adjunctive special stains and microbiologic correlation (culture/PCR/serology) is done because tissue eosinophilia itself is not specific for HES and may reflect parasitic, drug, allergic or other causes [16].

Once secondary and clonal causes for hyper-eosinophilia are excluded, patients fulfilling criteria for eosinophilia with organ damage are diagnosed with Idiopathic HES [33]. Additional assessments in such Idiopathic HES cases include, cardiac MRI specifically done for assessing myocardial involvement, pulmonary function tests, nerve conduction studies, as well as tissue biopsies which are used to document end-organ injury essential for confirming clinically significant phase of disease [2,33,34]. Comprehensive diagnostic approach to HES is described in [Table/Fig-6] [2,6,10,12-16,25-34].

Diagnostic domain	Key findings/tests	Purpose/ interpretation	References
Diagnostic criteria	• Persistent eosinophilia with AEC ≥1.5×10^9/L on ≥2 occasions	Confirms marked eosinophilia using updated guidelines (no longer requires ≥6 months)	[2,6,25,26]
Initial clinical evaluation	• Detailed history: allergy, parasitic exposure, autoimmune disease, drug reactions • Physical examination	Identifies common secondary causes of eosinophilia	[26]
Basic laboratory work-up	• CBC • Serum tryptase • Vitamin B12 • IgE levels • LFTs and RFTs • Stool ova/parasite examination	Screens for secondary causes (allergic, infectious, metabolic, haematologic)	[27,28]
Baseline imaging	• Chest X-ray • echocardiography • abdominal ultrasonography	Detects cardiopulmonary or hepatosplenic involvement	[28]
Skin histopathology	• Perivascular and interstitial dermal eosinophilic infiltrates • Dermal oedema • "Flame figures" • Occasional microthrombi/vasculitis	Identifies cutaneous involvement; helps differentiate from other dermatoses	[2,16]
Gastrointestinal histopathology	• Dense mucosal and submucosal eosinophilic infiltrates • Ulceration or erosive injury	Indicates GI involvement and helps exclude other causes	[13]
Cardiac histopathology	• Endomyocardial eosinophilic infiltration • Myocyte necrosis (acute phase) • Thrombus formation • Endomyocardial fibrosis (chronic phase)	Endomyocardial biopsy=gold standard for suspected eosinophilic myocarditis / Loeffler endocarditis	[2,14,29]
Bone marrow assessment	• Hypercellular marrow with marked eosinophilia • Reactive vs. clonal patterns • Dysplasia or increased blasts (myeloid cases)	Differentiates reactive vs. clonal/ myeloid HES	[30]
Microbiology/ infection work-up	• Serology for helminths • Blood cultures • Respiratory viral PCR	Rules out parasitic and infectious causes of eosinophilia	[10,12]
Molecular testing	• FIP1L1-PDGFRA, PDGFRA/B, FGFR1, JAK2 rearrangements • Cytogenetics and NGS panels	Identifies clonal HES; directs targeted therapy (e.g., imatinib)	[25,31]
Flow cytometry	• Aberrant clonal T-cell populations (e.g., CD3–CD4+)	Detects lymphocytic variant HES producing IL-5–mediated eosinophilia	[32]
Histopathology+ microbiology correlation	• Tissue biopsy with special stains • Culture/PCR/serology correlation	Distinguishes HES from parasitic, drug-induced and allergic eosinophilia	[16]
Diagnosis of idiopathic HES	• Exclusion of secondary and clonal causes • Eosinophilia+organ damage	Defines Idiopathic HES diagnosis	[33]
Additional tests in idiopathic HES	• Cardiac MRI • Pulmonary function tests • Nerve conduction studies • Tissue biopsies for organ involvement	Further evaluates extent of organ damage	[2,33,34]

[Table/Fig-6]: Comprehensive Diagnostic Approach to HES.
AEC: Absolute eosinophil count; CBC: Complete blood count; LFT: Liver function test; RFT: Renal function test; PCR: Polymerase chain reaction; MRI: Magnetic resonance imaging; GI: Gastrointestinal tract [2,6,10,12-16,25-34].

Management of Hypereosinophilic Syndromes (HES)

Treatment approaches for primary (Myeloid) HES: Management of primary or myeloid HES cases depends mainly on the early molecular diagnosis because its treatment is strongly determined

by the underlying driver mutation [35]. Patients having FIP1L1–PDGFRA, PDGFRB, FGFR1, JAK2, or other myeloid gene rearrangements respond dramatically to imatinib, which is considered first-line therapy even at low doses (e.g., 100 mg/day) [35,36]. Nearby-complete hematologic and molecular remission is possible with the help of imatinib and rapid symptom reversal in PDGFRA-positive disease [36]. For patients having FGFR1 or other non PDGFRA gene mutations, multikinase inhibitors as well as targeted agents are usually required [35]. Corticosteroids are used in initial phase of organ damage (e.g., cardiac involvement) which requires rapid eosinophil reduction before any molecular results of patient are available [37]. Patients with myeloid HES without any targetable mutations require cytoreductive therapy which includes, hydroxyurea, interferon-α [11,37].

Treatment approaches for Lymphocytic-variant HES (L-HES): Lymphocytic-variant HES, is mostly steroid-responsive but it also often requires long-term steroid-sparing therapy because of frequent relapse. Systemic corticosteroids are known first-line therapy for symptomatic disease which is inclusive of prednisone ~0.5-1 mg/kg/day with taperingdoses [38]. For chronic disease control, interferon-α and hydroxyurea remained assecond-line agents, especially in cases of steroid-dependent patients [38]. Robust benefit is demonstrated from anti–IL-5 biologics (mepolizumab) as well as anti–IL-5Rα agents (benralizumab) to reduce eosinophilia, prevent disease flares and further achieve steroid tapering [38,39]. These biologics have shown particular utility in L-HES because they are involved in directly counteracting IL-5–driven proliferation of eosinophils from the abnormal clones of T-cell [38]. Rare refractory cases can further require additional immunomodulators such as cyclosporine, methotrexate or participation in clinical trials evaluating monoclonal antibodies targeting upstream cytokines [11,40].

Treatment approaches for reactive (Secondary) HES: Reactive HES thereby requires therapy which is directed primarily at the underlying cause. When parasitic infections (e.g., Strongyloides) are identified; in such cases, treatment involves ivermectin/albendazole that is essential before initiating immunosuppression [10,41]. Drug-induced eosinophilia calls for immediate withdrawal of the offending agent [42]. An involved agent also requires the use of corticosteroids in cases of severe organ-involvement [42]. Secondary HES is associated with autoimmune diseases, allergic disorders, connective-tissue disease, as well as malignancies [41]. These are adequately managed with treatment of the primary pathology, such as immunosuppressants for autoimmune conditions, chemotherapy for haematologic malignancies [41]. Mepolizumab is also considered for managing persistent eosinophilia, even in cases where underlying causative condition is addressed, but it is not a known first-line option for management of Reactive HES subtype [39].

Management of idiopathic HES: Idiopathic HES is treated initially with usage of corticosteroids, followed by tapering dose, once it is controlled [43]. The main steroid sparing drug available is Mepolozumab along with benralizumab for refractory cases of Idiopathic HES [39,43]. If biologics are not feasible then in such cases, hydroxyurea or interferon-α may be used [43]. Regular molecular re-evaluation is advised as its helps in detecting evolving clonal subtype of HES [43]. Management of the HES is depicted in [Table/Fig-7] [10,11,35-43].

Emerging Targeted and Immune-modulating Therapies for HES

Emerging treatment option for HES is focused on strategies which selectively help removal or silencing of pathogenic eosinophils. One of the most actively investigated approaches is Siglec-8–directed therapy which includes lirentelimab (AK002) that binds Siglec-8 on eosinophils and mast cells thus promotes depletion/inhibition [44]. Siglec-8-directed therapy is useful in cases where tissue-resident eosinophils and mast cell interactions driven eosinophilic pathology is present, also IL-5 pathway blockadeis inadequate [44]. JAK inhibitors namely; ruxolitinib, tofacitinibhave produced meaningful responses in small series of lymphocytic-variant and clonal eosinophilic disorders, particularly when a JAK-activating lesion or a T-cell–driven cytokine signature is present [45,46]. Case reports and series also describe responses of chronic eosinophilic leukaemia with JAK1/2 alterations to JAK inhibition [45,46]. Similarly, novel small-molecule and kinase inhibitors are also being under evaluation for non PDGFRA myeloid drivers, which thereby reflect a trend of precision-medicine for matching targeted agents for the evolving molecular diagnosis [41]. C-C Chemokine Receptor type 3 (CCR3) and EGF-like module-containing mucin-like hormone receptor-like 1 (EMR1)antagonists/antibodies also aim to block trafficking of eosinophil, cause selective eosinophilic depletion [47]. These can be helpful as complementary options for refractory tissue disease for HES [47]. Similarly, broader immune modulators which cause alteration of type-2 signalling (for example, IL-4/IL-13 blockade with dupilumab) also have shown utility in few selected case reports although it carries a risk of paradoxical eosinophilic complications [48].

Prognostic Factors and Survival Outcomes in Hypereosinophilic Syndrome (HES)

The HES is a heterogeneous disorder having historically very poor outcomes which is largely driven by end-organ damage usually cardiac involvement which remains a major cause of mortality

HES subtype	First-line therapy	Second-line/Additional therapy	Special notes	References
Primary (Myeloid) HES	• Imatinib (low dose 100 mg/day) for FIP1L1–PDGFRA, PDGFRB, FGFR1, JAK2 and other rearrangements. • Corticosteroids for urgent organ damage before molecular results.	• Multikinase inhibitors or targeted therapies for FGFR1 or non PDGFRA mutations. • Hydroxyurea, interferon-α for non targetable mutation cases.	• Imatinib induces near-complete hematologic and molecular remission. • Rapid response in PDGFRA-positive disease.	[11,35-37].
Lymphocytic-Variant HES (L-HES)	• Systemic corticosteroids (Prednisone 0.5–1 mg/kg/day with taper).	• Interferon-α, hydroxyurea for steroid-dependent disease. • Mepolizumab, benralizumab to control eosinophilia and reduce relapses. • Cyclosporine, methotrexate, or trial monoclonal antibodies for refractory cases.	• Often steroid-responsive but relapse-prone. • Biologics effective due to IL-5–driven eosinophil proliferation by abnormal T-cell clones.	[11,38-40].
Reactive (Secondary) HES	• Treat underlying cause (infection, drug reaction, autoimmune disease, malignancy).	• Ivermectin/albendazole for parasitic infections before immunosuppression. • Corticosteroids for severe organ involvement. • Chemotherapy for malignancy-associated eosinophilia. • Mepolizumab for persistent eosinophilia only after primary cause controlled.	• Immediate withdrawal of causative drug in drug-induced cases. • Therapy guided entirely by underlying pathology.	[10,39,41,42].
Idiopathic HES	• Corticosteroids first-line with tapering.	• Mepolizumab (main steroid-sparing agent). • Benralizumab for refractory disease. • Hydroxyurea, interferon-α if biologics unavailable.	• Requires ongoing molecular re-evaluation to detect emerging clonal subtype.	[39,43].

[Table/Fig-7]: Management of the HES [10,11,35-43].

[49,50]. Early retrospective studies reported overall survival rates of approximately 80% at 5 years as well as declining substantially by 10-15 years having adverse prognostic factors inclusive of myeloproliferative phenotype, male sex, high peak eosinophil counts, corticosteroid-refractory eosinophilia as well as cardiac disease such as endomyocardial fibrosis [51]. Contemporary cohort analyses reinforce that cardiac dysfunction is predominant cause of death in patients having HES along with other fatal outcomes attributable to infection, thromboembolic events, or unrelated malignancy [49]. More recent multicentre data specifically in idiopathic cases of HES show improved long-term survival, with 5-year overall survival exceeding 88%, as well as identify age >50 years, anaemia, thrombotic tendency, renal failure, dyspnoea as factors associated with poorer outcomes [50]. Therapy like corticosteroids, steroid-sparing agents (hydroxyurea or interferon-alpha), biologics like anti-IL-5 (mepolizumab), have improved disease control-survival when compared to historical cohorts [51,52]. Overall, prompt diagnosis, early intervention, vigilant monitoring for organ involvement usually cardiac and usage of targeted therapies are main aspects of favourable long-term prognosis in HES [50,52].

Future Directions and Research Priorities for HES

Future work must integrate single-cell multi-omics for identifying pathogenic eosinophil sub-populations as well as must investigate further in microbiome-driven modulation of eosinophil activity [53,54]. Research must develop an adequate non invasive imaging biomarkers for monitoring tissue infiltration also create AI-based predictive models for complications and treatment response for HES [19]. Finally, global prospective registries can be helpful in establishing long-term outcomes and real-world treatment effectiveness [55].

CONCLUSION(S)

The HES represents a very complex spectrum of disorders which is unified by persistent eosinophilia and risk of multisystem organ injury. Advancements in molecular diagnostic methods, immuno-phenotyping, along with imaging reshaped the ways for accurately classifying HES into its clonal, reactive, lymphocytic and idiopathic forms. Thus, helpful for drafting more precise as well as personalised treatment strategies. Timely diagnosis, exclusion of various secondary causes, also earlier molecular testing thereby remains centre for management of HES cases. Emerging biologics along with targeted therapies continue to improve outcomes of patients with HES, but its long-term monitoring is essential due to risk of relapse as well as heterogeneous nature of the disease.

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