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Hypereosinophilic Syndrome: Differential Diagnosis, Management, and Long-Term Care

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ABSTRACT

Background: *Hypereosinophilic syndrome (HES) comprises disorders in which blood and/or tissue hypereosinophilia causes organ damage. The underlying mechanism and severity of organ involvement determine treatment and prognosis. Hypereosinophilia without attributable organ damage is distinct from HES.*

Objective: *To review differential diagnoses, current treatment options, prognostic evidence, complication prevention, patient education, and coordination of long-term care in HES.*

Methods: *This narrative review integrates selected consensus guidance, clinical trials, observational studies, and regulatory product information available through November 10, 2026. It distinguishes evidence of efficacy from authorized indications and does not constitute a systematic review or formal risk-of-bias assessment.*

Results: *The etiological workup considers infection, drug hypersensitivity, inflammatory disease, immune dysregulation, and neoplasia while assessing organ injury in parallel. Important overlapping disorders include eosinophilic granulomatosis with polyangiitis, episodic angioedema with eosinophilia, eosinophilia-myalgia syndrome, and IgG4-related disease. Urgent glucocorticoid treatment is often required for threatened organs, with concurrent assessment and management of Strongyloides risk. Imatinib is central to PDGFRA- and PDGFRB-rearranged neoplasms. Mepolizumab and benralizumab reduce flares in selected patients; their authorized populations differ by jurisdiction. Hydroxyurea, interferon alfa, other targeted therapies, and transplantation retain roles in selected disease subtypes. Prognosis depends on the underlying disorder and the reversibility of existing injury. Monitoring must address clinical activity, molecular disease where relevant, and treatment toxicity rather than eosinophil counts alone.*

Conclusion: *Effective care requires etiological treatment, prompt protection of threatened organs, reduction of cumulative treatment toxicity, and sustained follow-up. Clear patient education and an accountable multidisciplinary care plan support continuity; comparative evidence on the independent effects of coordinated-care models in HES remains limited.*

Keywords
Hypereosinophilic syndrome, Differential diagnosis, Treatment, Prognosis, Organ damage, Biologic therapy, Tyrosine kinase inhibitors, Complications, Patient education, Multidisciplinary care.

Abbreviations
HES: Hypereosinophilic syndrome, HE: Hypereosinophilia, AEC: Absolute Eosinophil Count, EU: European Union, US: United States, L-HES: Lymphocytic HES, I-HES: Idiopathic HES, M-HES: Myeloid HES, EGPA: Eosinophilic granulomatosis with polyangiitis, DRESS: Drug reaction with eosinophilia and systemic symptoms, MLN-TK: Myeloid/lymphoid neoplasms with tyrosine kinase gene fusions, CEL: Chronic eosinophilic leukemia, IgG4-RD: Immunoglobulin G4-related disease, Gleich syndrome: Episodic angioedema with eosinophilia, EMS: Eosinophilia-myalgia syndrome, HE-US: HE of unknown significance, CBCs: Complete blood counts, L-HES: Lymphocytic HES, IL: Interleukin, ANCA: Antineutrophil cytoplasmic antibodies, MPO: Myeloperoxidase, ACR/EULAR criteria: American College of Rheumatology/ EULAR – European Alliance of Associations for Rheumatology, CDC: Centers for Disease Control and Prevention, TCR: T-cell receptor, IFN-α: Interferon alfa, IL-5Rα: IL-5 receptor alpha, ADCC: Antibody-dependent cellular cytotoxicity, JAK: Janus kinase, CCR4: C-C chemokine receptor 4, BNP: B-type natriuretic peptide, NT-proBNP: N-terminal pro-B-type Natriuretic Peptide, ECG: Electrocardiography.

Introduction
Hypereosinophilic syndrome (HES) is a clinical syndrome defined by blood and/or tissue hypereosinophilia (HE) with eosinophil-attributable organ injury. Blood HE generally requires an absolute eosinophil count (AEC) $\geq 1.5 \times 10^9$/L on two examinations at least two weeks apart. Tissue-restricted HES may occur below that blood threshold. HE without eosinophil-related organ dysfunction is not HES, and an elevated AEC alone does not establish the cause of a patient's symptoms [1,2].

Eosinophil-mediated injury can involve the heart, lungs, skin, gastrointestinal tract, nervous system, and blood vessels. Cardiac injury and thrombosis deserve early attention because clinically silent disease may progress to irreversible fibrosis or embolic complications. Clinical severity does not consistently track the blood eosinophil count [3,4].

The clinical syndrome must be distinguished from its underlying cause. Reactive, neoplastic, familial, lymphocytic, and idiopathic disease have different treatment implications. An aberrant T-cell population can drive reactive eosinophilia, whereas a defining kinase fusion establishes a specific hematological neoplasm. Tissue distribution describes a phenotype rather than a separate cause [1,5].

Treatment aims to control eosinophil-related disease, treat the underlying disorder, protect organ function, and limit cumulative toxicity. Glucocorticoids remain central to initial control in many non-neoplastic forms, while kinase inhibitors and biologics have transformed selected disease settings. Availability of a targeted agent does not establish its suitability for every HES subtype or for an acute organ-threatening flare [6,7].

This review focuses on differential diagnosis and management. It integrates established guidance with newer trial evidence and current European Union (EU) and United States (US) product information; regulatory status is summarized as of November 10, 2026 [8-12].

Differential Diagnosis
The differential diagnosis asks two questions: what drives the eosinophilia, and are eosinophils responsible for organ injury? These investigations proceed together. A patient may have a recognized reactive disease and still meet the clinical definition of

Major disease groups
Table 1: Major groups in the differential diagnosis.

Disease group	Representative conditions	Discriminating assessment
Allergic and airway disease	Atopy, asthma, allergic bronchopulmonary aspergillosis	Marked persistent HE requires assessment for an additional cause
Infection	Strongyloides, Toxocara, Schistosoma and other helminths	Exposure-directed serology and repeated or specialized stool tests
Drug hypersensitivity	Isolated drug eosinophilia or DRESS	Complete drug and supplement timeline; systemic injury assessment
Systemic inflammation	EGPA and other inflammatory diseases	Vasculitic and organ-specific findings; negative ANCA does not exclude EGPA
Neoplasia	MLN-TK, CEL, systemic mastocytosis, other myeloid neoplasms, lymphoma, solid tumors	Marrow, fusion or mutation testing, flow cytometry and tissue sampling as indicated
Immune or other systemic disease	Inborn errors of immunity, IgG4-RD, adrenal insufficiency	Clinical pattern, immunological assessment and targeted testing
Defined eosinophilic syndromes	Gleich syndrome and EMS	Cyclical angioedema or exposure-associated myalgia and fasciitis
Unexplained HE without injury	HE-US	Exclude relevant causes and monitor for evolving organ injury

Note: DRESS, drug reaction with eosinophilia and systemic symptoms; MLN-TK, myeloid/lymphoid neoplasms with tyrosine kinase gene fusions; CEL, chronic eosinophilic leukemia. Based on consensus guidance [1,6,14].

HES when eosinophils contribute to organ damage. Conversely, eosinophilia accompanying another disease does not establish that causal link [1,6].

Etiological assessment distinguishes reactive or cytokine-driven HE, neoplastic HE, inherited disease, and otherwise unexplained HE. Lymphocytic HES (L-HES) is a reactive eosinophilic disorder driven by an aberrant T-cell population; idiopathic HES requires organ injury and an appropriately negative etiological evaluation [1,13].

Tissue-restricted disease is a distributional phenotype. Assessment uses the relevant organ-specific clinicopathological criteria, alongside investigation of reactive and clonal causes [1].

The differential diagnosis should be based not only on the AEC, but also on the clinical presentation, medical history, drug exposure, laboratory parameters, imaging findings and, when necessary, histopathological and molecular genetic investigations. Prior medication exposure, remote travel, pretreatment blood counts, and evidence suggesting an inherited immune disorder can materially change the workup [6,14].

An established diagnosis such as EGPA or a defined eosinophilic gastrointestinal disorder should be retained. The broad HES framework may describe eosinophil-attributable injury in some patients, but it does not replace disease-specific diagnostic or management criteria [1,15].

HE of unknown significance

HE of unknown significance (HE-US) denotes persistent unexplained HE without eosinophil-attributable organ damage and without an identified reactive, neoplastic, or familial explanation. It is a provisional category requiring longitudinal reassessment. HE-US and idiopathic HES are distinguished by the presence of organ injury, not by the magnitude of the AEC [1].

Some patients with HE-US remain stable for years; others develop organ injury or an identifiable underlying disorder. Surveillance should include serial complete blood counts (CBCs) with differential, review of new symptoms, and targeted organ assessment. Repeat molecular, marrow, or tissue testing is appropriate when the clinical picture changes. A rising AEC should prompt reassessment rather than automatic conversion of the diagnosis to HES [1,2].

Related eosinophilic and fibroinflammatory disorders

Several recognizable disorders overlap clinically with HES. Their characteristic patterns guide investigation, but no single symptom or nonspecific biomarker is sufficient to distinguish them. The following conditions are particularly relevant [6,14].

Episodic angioedema with eosinophilia

Episodic angioedema with eosinophilia, or Gleich syndrome, features recurrent angioedema with marked blood eosinophilia, often accompanied by urticaria, fever, fluid-related weight gain, and increased polyclonal IgM. Episodes classically recur every three to four weeks, although patterns vary. The syndrome was first described in 1984 [16,17].

Cyclical symptoms and eosinophil counts support recognition. Immunoglobulin measurements and longitudinal blood counts can document the pattern. An aberrant T-cell population may be present, and selected cases overlap with L-HES [13,17].

Interleukin-5 (IL-5) and related cytokine activity contribute to eosinophil expansion. A demonstrable T-cell clone is neither universal nor independently sufficient to establish the syndrome [17].

Gleich syndrome often lacks the severe internal-organ injury characteristic of some HES variants, but organ involvement should still be assessed. Management depends on symptoms and mechanism; the presence of an eosinophil-driving T-cell population may influence the choice of a steroid-sparing agent [8,17].

Table 2: Distinguishing HE of unknown significance from HES.

Feature	HE-US	HES
Blood HE	Present	Usually present; tissue-restricted HES may occur below blood threshold
Eosinophil-attributable organ injury	Absent	Required
Underlying explanation	None identified after appropriate assessment	May be reactive, neoplastic, familial, lymphocytic or idiopathic
Management principle	Surveillance and etiological reassessment	Protect organs and treat according to cause and severity

Note: HE-US and HES are not interchangeable diagnoses [1].

Eosinophilic granulomatosis with polyangiitis

Eosinophilic granulomatosis with polyangiitis (EGPA) is an inflammatory disease characterized by asthma, eosinophilic inflammation, and small- or medium-vessel vasculitis. Adult-onset asthma, chronic rhinosinusitis with nasal polyps, pulmonary infiltrates, neuropathy, purpura, and cardiac, gastrointestinal, or renal disease raise suspicion. Clinical expression is heterogeneous, and proof of every classical pathological feature is not required in every patient [15].

Antineutrophil cytoplasmic antibodies (ANCA), most often directed against myeloperoxidase (MPO), occur in approximately 30–40% of patients. Negative ANCA does not exclude EGPA. ANCA-positive disease more often includes glomerulonephritis and vasculitic neuropathy, whereas cardiac involvement is more prominent in many ANCA-negative cohorts. These are overlapping tendencies, not mutually exclusive categories [15].

Evidence of vasculitis, glomerulonephritis, mononeuritis multiplex, or a compatible tissue biopsy helps distinguish EGPA from other eosinophilic conditions. Asthma and nasal polyps alone are insufficient. Tissue findings may include eosinophilic

inflammation, necrotizing vasculitis, or granulomas, but sampling and prior glucocorticoids can reduce diagnostic yield [15].

The 2022 ACR/EULAR criteria are classification criteria for patients with established small- or medium-vessel vasculitis after exclusion of mimics. They should not be applied as a stand-alone diagnostic score to unselected patients with eosinophilia [18].

EGPA and the broad HES syndrome concept may overlap when eosinophils contribute to injury. Nevertheless, EGPA-specific assessment remains necessary because vasculitic activity and organ threat influence treatment beyond the eosinophil count [1,15].

Eosinophilia-myalgia syndrome

Eosinophilia-myalgia syndrome (EMS) is an exposure-associated systemic disorder recognized during the 1989 outbreak linked to L-tryptophan-containing supplements. Severe myalgia, blood eosinophilia, edema, skin induration, fascial inflammation, neuropathy, and pulmonary involvement are characteristic. Chronic disability can persist after the eosinophilia resolves [19,20].

Manufacturing contaminants and host susceptibility have been implicated. The contaminant 1,1′-ethylidenebis(tryptophan), termed Peak E, was investigated, but a single universally established causal mechanism has not been demonstrated [21].

The historical CDC surveillance definition included debilitating generalized myalgia, AEC $\geq 1.0 \times 10^9$/L, and exclusion of an alternative explanation. These epidemic surveillance criteria are not a universal contemporary diagnostic rule: a clinical diagnosis may be considered when the full historical case definition is not met. A compatible supplement history is informative but should be assessed alongside the clinical course and exclusion of mimics [22].

Biopsy can show fasciitis, perimyositis, perivascular inflammation, and later fibrosis. The prominence of muscle and fascial disease helps distinguish EMS from other causes of HE, including eosinophilic fasciitis and systemic HES [20].

IgG4-related disease

Immunoglobulin G4-related disease (IgG4-RD) is a systemic immune-mediated fibroinflammatory disorder. It can involve the pancreas, bile ducts, salivary or lacrimal glands, kidneys, lungs, retroperitoneum, and lymph nodes. Associated eosinophilia and polyclonal hypergammaglobulinemia can create a clinical overlap with HES [23].

Serum IgG4 can be elevated, but an isolated increase does not establish IgG4-RD; some well-characterized cases have normal levels. Elevated IgE and blood eosinophilia are also nonspecific. Imaging, organ pattern, tissue morphology, and exclusion of malignancy or other mimics are essential [23,24].

Characteristic tissue findings include dense lymphoplasmacytic inflammation, storiform fibrosis, and obliterative phlebitis, with increased IgG4-positive plasma cells. The full triad is not equally apparent in every organ or small biopsy. A raised IgG4-positive/IgG-positive plasma-cell ratio, commonly above 40%, is supportive only in the appropriate morphological context; absolute cell thresholds vary by organ and specimen [24,25].

In IgG4-RD, eosinophilia may accompany a fibroinflammatory process without being the dominant cause of organ injury. In HES, the causal contribution of eosinophils is central. Increased serum IgG4 or tissue IgG4-positive cells alone cannot resolve this distinction. Lymph node specimens are particularly vulnerable to nonspecific interpretation and may require expert review or sampling of a more informative involved organ [23,25].

Table 3: Distinguishing patterns in related disorders.

Condition	Pattern that raises suspicion	Main interpretive caution
Gleich syndrome	Cyclical angioedema, urticaria, weight gain and eosinophilia; IgM may rise	Assess for organ injury and an aberrant T-cell population
EGPA	Asthma, nasal polyps, eosinophilia and systemic vasculitic or organ manifestations	ANCA may be negative; classification criteria do not replace diagnosis
EMS	Severe myalgia, fascia or muscle involvement and compatible supplement exposure	Historical surveillance criteria are not a universal diagnostic threshold
IgG4-RD	Characteristic organ distribution and fibroinflammatory tissue disease	Serum IgG4 or IgG4-positive cells alone are insufficient

Note: IgM, immunoglobulin M; EGPA, eosinophilic granulomatosis with polyangiitis; EMS, eosinophilia-myalgia syndrome [15,17,22,25].

Diagnostic pitfalls

HE-US is not HES; tissue-restricted HES is not a fifth etiological category. Negative ANCA does not exclude EGPA, and elevated IgG4 does not establish IgG4-RD. Clonality on T-cell receptor (TCR) gene rearrangement testing alone does not establish L-HES or lymphoma. Likewise, an age-related somatic mutation alone does not prove neoplastic eosinophilia. These distinctions require integrated clinical and pathological interpretation [1,5,13,15,23].

Treatment and management

The therapeutic approach to HES should be individualized according to the underlying etiology, disease subtype, clinical manifestations, severity of organ involvement, and risk of irreversible tissue damage. The primary objectives of treatment are to control eosinophil proliferation and activation, reduce peripheral blood eosinophil counts, alleviate clinical manifestations, prevent further eosinophil-mediated tissue injury, and preserve organ function. An additional goal, particularly in patients requiring prolonged therapy, is to minimize treatment-related toxicity and achieve sustained disease control with the lowest possible corticosteroid exposure [6,7].

Treatment selection depends primarily on the identification of the underlying cause of eosinophilia. Patients with secondary (reactive) eosinophilia should receive treatment directed at the

underlying condition, including discontinuation of the causative medication, appropriate antiparasitic therapy, or treatment of an associated inflammatory, autoimmune, infectious, or neoplastic disorder. In patients with unexplained hypereosinophilia, a comprehensive diagnostic evaluation is necessary to exclude clonal hematological disorders, particularly myeloid neoplasms associated with the FIP1L1::PDGFRA fusion gene and other tyrosine kinase rearrangements [5,6].

Treatment is usually driven by attributable symptoms, organ dysfunction, and the underlying disorder. Stable HE-US may be observed without eosinophil-lowering medication, with follow-up often every three to six months according to clinical stability. This principle does not apply to a molecularly defined neoplasm for which treatment is indicated even before eosinophil-mediated damage is apparent [2,6].

Conversely, patients with symptomatic HES or evidence of progressive organ involvement require prompt therapeutic intervention. Life-threatening manifestations, including eosinophilic myocarditis, rapidly progressive pulmonary disease, neurological involvement, intracardiac thrombosis, and severe vascular complications, warrant immediate treatment, irrespective of the peripheral eosinophil count [4].

Severe and organ-threatening disease

No AEC threshold independently defines severe HES. Urgent treatment is indicated for suspected eosinophilic myocarditis, acute respiratory compromise, major neurological disease, thrombosis, or other progressive organ injury. Blood eosinophil depletion alone is not an adequate measure of successful resuscitation or organ recovery [4,6].

Systemic glucocorticoids are commonly used for acute eosinophil-mediated organ injury while the cause is investigated. Typical adult regimens include prednisone or prednisolone 0.5–1 mg/kg/day; severe visceral disease is generally treated toward the higher end. In selected emergencies, intravenous methylprednisolone 5–15 mg/kg/day, up to 1 g/day for one to three days, may precede oral treatment. These are specialist, severity-dependent regimens supported mainly by clinical guidance rather than dose-comparison trials [6,7].

Assess Strongyloides risk before systemic glucocorticoids whenever feasible, including remote residence or travel in endemic areas. In threatened-organ disease, urgent management and risk-directed antiparasitic measures proceed together. Ivermectin 200 µg/kg orally daily for one to two days is a regimen for uncomplicated infection; it is not the regimen for hyperinfection or disseminated disease. Severe strongyloidiasis requires specialist treatment, usually daily ivermectin until stool and/or sputum remain negative for two weeks, with reduction of immunosuppression where possible. Suspected Loa loa coinfection requires particular caution before ivermectin [26,27].

Clinical and hematological responses to glucocorticoids are often rapid, with a substantial reduction in peripheral blood eosinophil counts frequently observed within 24–48 hours. However, the response should be assessed using a combination of clinical improvement, serial eosinophil counts, and objective evaluation of affected organs rather than relying exclusively on a predefined percentage reduction in the eosinophil count [6].

If glucocorticoids fail or clonal disease is suspected, early hematology input and mechanism-directed escalation are needed. Hydroxyurea may be used for cytoreduction in selected cases. Leukapheresis is exceptional and does not control the underlying production or tissue disease; an isolated high AEC is not an indication for the procedure [5,6].

Established intracardiac thrombus or arterial or venous thrombosis warrants assessment for anticoagulation alongside control of eosinophilic disease. Agent selection and duration depend on thrombus location, bleeding risk, residual cardiac disease, and other risk factors. There is no basis for automatic long-term anticoagulation solely because eosinophilia is present [4,28].

Systemic glucocorticoids

Systemic glucocorticoids are generally considered first-line therapy for idiopathic HES and lymphocytic HES (L-HES), as well as for several reactive forms associated with eosinophilic inflammation. Prednisone or prednisolone is commonly initiated at a dose of 0.5–1 mg/kg/day, depending on the severity of clinical manifestations and the extent of organ involvement. In patients with less severe disease, lower doses may be sufficient [6,7].

In the historical multicenter cohort of 188 patients, corticosteroid monotherapy produced a complete or partial response in 120 of 141 treated patients, or 85%, at one month. This is a treated-subgroup result from a retrospective referral cohort, not an expected response rate for every molecular subtype [29].

After control is achieved, taper according to symptoms, organ recovery, blood counts, and relapse history. The historical cohort reported a median maintenance prednisone dose of 10 mg/day, which describes past practice rather than a current treatment target. Persistent dependence or repeated courses should prompt a steroid-sparing strategy [8,29].

The prolonged administration of systemic corticosteroids is associated with significant adverse effects, including osteoporosis, hyperglycemia, arterial hypertension, weight gain, increased susceptibility to infections, adrenal suppression, cataracts, and cardiovascular complications. Therefore, in patients with corticosteroid dependence, inadequate disease control, or treatment-related toxicity, steroid-sparing therapeutic strategies should be considered [6].

Topical, inhaled, or locally acting corticosteroids may control selected limited skin, airway, or gastrointestinal manifestations and reduce systemic exposure. They are insufficient for threatened cardiac, neurological, vascular, or other major systemic disease [7].

Imatinib and other kinase-directed treatments

Imatinib is first-line treatment for susceptible PDGFRA- or PDGFRB-rearranged myeloid/lymphoid neoplasms. FIP1L1::PDGFRA activates a kinase signaling pathway that is particularly sensitive to imatinib; treatment should not await glucocorticoid failure. A confirmed fusion defines the underlying neoplasm, whether or not the patient also has HES-related injury [5,30].

Imatinib inhibits ABL, KIT, PDGFRA, and PDGFRB kinase activity. Responses depend on the specific molecular lesion; the presence of a myeloid phenotype alone does not guarantee sensitivity [5,30].

Patients with FIP1L1::PDGFRA-positive disease typically demonstrate a rapid and profound hematological response, often within several days of treatment initiation. Molecular remission may follow over subsequent weeks or months. Importantly, treatment should be initiated as soon as the molecular abnormality is identified, without waiting for failure of glucocorticoid therapy [31].

An initial imatinib dose of 100 mg orally daily is commonly effective in FIP1L1::PDGFRA-positive disease. PDGFRB-rearranged disease is often started at 400 mg daily. Dose selection and any escalation require consideration of the fusion, response, toxicity, interacting medicines, and organ function; these regimens should not be generalized to all fusion-negative CEL or HES [6,30].

In patients with cardiac involvement, particularly elevated troponin levels or evidence of eosinophilic myocarditis, concomitant systemic glucocorticoid therapy should be considered when initiating imatinib. This precaution is intended to reduce the risk of acute cardiac deterioration associated with rapid eosinophil destruction and the release of inflammatory mediators [4,6].

Imatinib is generally well tolerated, although adverse effects may include fluid retention, peripheral edema, nausea, muscle cramps, fatigue, rash, cytopenias, and hepatotoxicity. Regular monitoring of blood counts, liver function, renal function, and clinical response is recommended [5].

Pemigatinib targets FGFR1-rearranged myeloid/lymphoid neoplasms. Its US indication covers adults with relapsed or refractory disease; the labeled regimen is 13.5 mg orally daily continuously. This differs from the intermittent cholangiocarcinoma schedule. The EU authorization does not include this hematological indication; a 2025 extension application was refused. Clinical evidence, marketing authorization, and access therefore require separate interpretation [32-34].

Hydroxyurea

Hydroxyurea (hydroxycarbamide) is a cytoreductive agent that inhibits ribonucleotide reductase, thereby interfering with DNA synthesis and suppressing the proliferation of rapidly dividing hematopoietic cells, including eosinophil precursors [35].

Hydroxyurea is an off-label cytoreductive option for selected patients with persistent symptomatic disease, glucocorticoid dependence, or an immediate need for additional cytoreduction. It is not a substitute for a highly effective fusion-directed treatment when one is indicated [6,35].

A starting dose of 500–1,000 mg orally daily is commonly used in stable adults, with titration according to counts, response, and tolerability. Some patients require 1–2 g/day; emergency dosing and renal impairment require specialist adjustment [6,35].
Evidence of efficacy derives predominantly from observational experience. The retrospective 188-patient cohort supports activity in some patients but does not establish superiority of a particular hydroxyurea combination over modern biologic treatment [29].

The principal adverse effects include myelosuppression, anemia, neutropenia, thrombocytopenia, gastrointestinal disturbances, mucocutaneous toxicity, and, with prolonged exposure, skin and nail changes. Regular monitoring of complete blood counts and renal and hepatic function is required. Counseling must also address reproductive toxicity and pregnancy prevention where relevant [6].

Interferon alfa

Interferon alfa (IFN-α) has antiproliferative and immunomodulatory effects on eosinophils and T-cell-driven cytokine activity. It remains an off-label steroid-sparing option, particularly in selected L-HES cases, but tolerability often limits sustained treatment [6,35].

Interferon-α has demonstrated clinical efficacy in patients with FIP1L1: PDGFRA-negative HES, particularly in those with L-HES, corticosteroid dependence, or inadequate response to conventional treatment. It may be administered as monotherapy or in combination with glucocorticoids, depending on disease severity and treatment response [6].

Pegylated interferon alfa-2a permits less frequent dosing. Specialist practice may begin at 45 µg subcutaneously once weekly and increase gradually according to response and tolerability. This is an individualized off-label regimen, not an HES-specific licensed dose [6].

Despite its therapeutic benefits, IFN-α has a relatively broad adverse-effect profile. Common complications include influenza-like symptoms, fatigue, myalgia, anorexia, weight loss, transaminase elevation, and myelosuppression. More serious adverse effects include depression, other psychiatric manifestations, and suicidal ideation. Thyroid dysfunction and autoimmune complications may also occur. Consequently, careful monitoring of blood counts, liver function, thyroid function, and psychological status is necessary during treatment [6].

Selection should account for psychiatric history, liver or thyroid disease, autoimmune illness, fertility or pregnancy plans, and the

availability of alternatives. In L-HES, an eosinophil-lowering response should not be assumed to eradicate the aberrant T-cell population [6,13].

Biologic therapies directed at eosinophils

The development of biological agents targeting eosinophil-associated cytokines has substantially expanded the therapeutic options for patients with HES, particularly those with FIP1L1::PDGFRA-negative disease, recurrent exacerbations, corticosteroid dependence, or inadequate response to conventional immunosuppressive treatment [36,37].

IL-5 and its receptor are important therapeutic targets. Mepolizumab neutralizes IL-5, whereas benralizumab binds IL-5 receptor alpha (IL-5Rα) and promotes eosinophil depletion. Different targets do not establish comparative clinical superiority [38,39].

Mepolizumab

Mepolizumab is a humanized monoclonal antibody directed against IL-5. By binding circulating IL-5, it prevents interaction with the IL-5 receptor on eosinophils and their progenitors, thereby reducing eosinophil maturation, activation, and survival [38].

Mepolizumab is a steroid-sparing option for selected patients with recurrent or persistent HES without an identified non-hematological secondary cause. L-HES patients may respond, but cytokine blockade does not reliably suppress the associated abnormal T-cell population [13,36].

The 2008 randomized trial used mepolizumab 750 mg intravenously every four weeks, a historical study regimen. Prednisone was reduced to ≤10 mg/day for at least eight consecutive weeks without increased disease activity in 84% of mepolizumab recipients versus 43% of placebo recipients. These findings support a steroid-sparing effect but should not be confused with current subcutaneous dosing [38].

The subsequent 32-week phase III trial randomized 108 patients to mepolizumab 300 mg subcutaneously every four weeks or placebo alongside background therapy. The composite of at least one flare or study withdrawal occurred in 15/54 (28%) versus 30/54 (56%), respectively (P = 0.002), a 50% relative reduction. This composite endpoint is distinct from time to first flare. The trial was not designed to demonstrate a survival benefit [36].

The HES dose is 300 mg subcutaneously every four weeks, generally as three 100 mg injections. EU authorization covers inadequately controlled HES in adults without an identifiable non-haematological secondary cause. The US indication covers patients aged ≥12 years with HES for at least six months and without such a secondary cause. The US label's duration requirement is a treatment-indication criterion, not a reason to postpone recognition or emergency treatment of HES [9,11].

Product information describes hypersensitivity and injection-site reactions and recommends attention to helminth infection risk. Glucocorticoids should be tapered gradually rather than stopped abruptly when mepolizumab is introduced [9,11].

Benralizumab

Benralizumab is a humanized, afucosylated monoclonal antibody directed against the alpha subunit of the IL-5 receptor (IL-5Rα), expressed on eosinophils and basophils. Unlike mepolizumab, which neutralizes circulating IL-5, benralizumab directly targets IL-5Rα and induces eosinophil depletion through antibody-dependent cellular cytotoxicity (ADCC), mediated primarily by natural killer cells [39].

The 2019 phase II study of 20 patients with PDGFRA-negative HES found an AEC reduction of at least 50% at week 12 in 9/10 benralizumab-treated patients versus 3/10 placebo recipients. This small trial established a signal of activity that was subsequently evaluated using clinical flare outcomes [39].

In the 2026 NATRON trial, 134 patients underwent randomization and 133 received treatment and entered the reported analysis. Benralizumab 30 mg subcutaneously every four weeks or placebo was added to background therapy for 24 weeks. Time to first HES flare favored benralizumab (hazard ratio 0.35; 95% confidence interval 0.18–0.69; P = 0.0024). Adverse events occurred in 64.2% versus 66.7%, respectively. The study supports flare reduction, not a demonstrated long-term survival advantage [37].

Benralizumab now has an HES indication in both the EU and US. EU authorization covers add-on treatment of inadequately controlled HES in patients aged ≥12 years weighing ≥35 kg without an identifiable non-haematological secondary cause. The US indication covers patients aged ≥12 years without an identifiable non-hematological secondary cause. Both use 30 mg subcutaneously every four weeks for HES; the every-eight-week

Table 4: Authorized biologic regimens for HES.

Medicine and region	Authorized HES population	HES regimen
Mepolizumab EU	Adults with inadequately controlled HES without an identifiable non-haematological secondary cause	300 mg subcutaneously every 4 weeks
Mepolizumab US	Age ≥12 years; HES for ≥6 months; no identifiable non-hematological secondary cause	300 mg subcutaneously every 4 weeks
Benralizumab EU	Age ≥12 years and weight ≥35 kg; inadequately controlled HES without an identifiable non-haematological secondary cause	30 mg subcutaneously every 4 weeks
Benralizumab US	Age ≥12 years; no identifiable non-hematological secondary cause	30 mg subcutaneously every 4 weeks

Note: EU indications are add-on indications. Summarized from product information available on November 10, 2026; local reimbursement is a separate issue [9-12].

asthma maintenance schedule does not apply [10,12].

Emerging and selected refractory disease treatments

Depemokimab, a long-acting anti-IL-5 antibody, is being evaluated in adults with HES in the randomized phase III DESTINY study (NCT05334368). A trial registry entry is evidence of investigation, not of established efficacy or an HES marketing authorization [40].

In highly selected refractory L-HES, small reports describe Janus kinase (JAK) inhibition or targeting C-C chemokine receptor 4 (CCR4) on abnormal T cells. These approaches remain specialist, off-label strategies with limited evidence and should not be placed on the same evidential footing as randomized HES biologic trials. Enrollment in an appropriate trial is preferable when available [41,42].

There is no controlled evidence establishing either biologic as an emergency replacement for glucocorticoids in severe HES. The EU benralizumab information specifically notes that life-threatening HES was not studied; new life-threatening manifestations require urgent reassessment [8,10].

Treatment according to underlying disease

Neoplastic HES. Name the underlying hematological entity and select treatment according to its molecular driver and disease phase. Imatinib is central to susceptible PDGFRA- or PDGFRB-rearranged disease. FGFR1-, JAK2-, FLT3-, and other fusion-associated neoplasms require individualized kinase-directed and/or hematological treatment; advanced disease may warrant allogeneic transplantation. A generic HES label must not delay treatment of the neoplasm [30].

L-HES. Glucocorticoids usually provide initial symptom control. Mepolizumab, benralizumab, or pegylated IFN-α can be considered when disease persists or steroid toxicity becomes problematic, with selection influenced by whether manifestations appear primarily eosinophil- or T-cell-driven. Longitudinal T-cell and lymphoma assessment remains necessary even when eosinophils normalize [8,13].

Idiopathic HES. Initial therapy is generally glucocorticoid-based for symptomatic disease, followed by a steroid-sparing treatment when the clinical course warrants it. Biologics are supported for selected inadequately controlled or recurrent disease; they have not been established as replacements for urgent first-line treatment of a major organ-threatening flare [8,9,10].

Secondary (reactive) HES. Treatment should primarily target the underlying cause. This may involve antiparasitic treatment, discontinuation of an offending drug, immunosuppressive therapy for autoimmune or inflammatory disease, or appropriate treatment of an associated malignancy. Eosinophil-directed treatment may be necessary when severe or persistent organ damage occurs despite treatment of the underlying condition [6].

Monitoring and long-term management

Long-term monitoring is an essential component of HES management because disease activity may fluctuate and organ involvement may progress despite an apparent reduction in peripheral blood eosinophilia [7].

Treatment response should be evaluated using a combination of clinical, hematological, biochemical, and imaging parameters. The monitoring strategy should be individualized according to the affected organs, underlying HES subtype, and treatment regimen [6].

- Serial CBC with differential and absolute eosinophil count.
- Assessment of clinical manifestations, including constitutional symptoms, skin lesions, respiratory symptoms, gastrointestinal disturbances, and neurological abnormalities.
- Cardiac assessment using troponin, B-type natriuretic peptide (BNP) or NT-proBNP, electrocardiography (ECG), echocardiography, and cardiac magnetic resonance when indicated.
- Monitoring of liver and renal function.
- Assessment of treatment-related adverse effects, particularly corticosteroid-associated metabolic and skeletal complications and cytopenias associated with cytoreductive treatment.
- Molecular monitoring in patients with defined clonal abnormalities, particularly those receiving tyrosine kinase inhibitors.
- Repeat imaging and tissue investigations when there is evidence of persistent or progressive organ involvement.

Assess more frequently after a treatment change or acute organ injury, then extend intervals when the clinical course is stable. No single follow-up schedule suits all HES variants. Rising eosinophils, new symptoms, altered blood-cell lineages, or new organ abnormalities should trigger reassessment of both disease activity and the original etiological diagnosis [2,6].

In patients receiving imatinib for FIP1L1::PDGFRA-positive disease, molecular monitoring is particularly important because hematological remission does not necessarily indicate complete molecular remission. Long-term treatment is generally required, and discontinuation should only be considered in carefully selected patients under specialist hematological supervision [30,31].

Similarly, patients with L-HES require prolonged follow-up because of the possibility of persistent aberrant T-cell populations and the potential development of lymphoproliferative complications [43].

Prognosis

Prognosis is determined by the underlying disorder, disease phase, treatment response, and reversibility of organ injury. Stable HE-US can have a prolonged course without treatment, but this should not be described as the asymptomatic end of HES. In established HES, persistent cardiac, neurological, or thrombotic injury can drive morbidity even after eosinophilia is controlled [1,4,5].

Although reliable prognostic biomarkers applicable to all

HES variants have not yet been established, several clinical, hematological, and molecular characteristics have been associated with an increased risk of disease progression and adverse outcomes. In particular, cardiac involvement, central nervous system manifestations, and thromboembolic complications are among the most important determinants of morbidity and mortality. The degree of peripheral blood eosinophilia alone is not a reliable predictor of prognosis, since substantial tissue damage may occur even in patients without extremely elevated absolute eosinophil counts [4,5].

Prognosis according to subtype

Idiopathic HES (I-HES). The prognosis of idiopathic HES is variable and depends largely on the extent of organ involvement at diagnosis, disease activity, and response to treatment. Patients without significant cardiac, neurological, or thromboembolic complications may achieve prolonged disease control with glucocorticoids or eosinophil-targeted biological therapies. Nevertheless, recurrent disease exacerbations, corticosteroid dependence, and progressive organ damage may occur in a subset of patients. Early recognition of cardiac involvement and timely initiation of appropriate treatment are particularly important for improving long-term outcomes [7].

Myeloid HES (M-HES). The prognosis of myeloid HES depends strongly on the underlying molecular abnormality. Historically, clonal eosinophilic disorders were associated with considerable morbidity and mortality, particularly when complicated by progressive myeloproliferation, bone marrow fibrosis, and cardiac involvement. However, the introduction of tyrosine kinase inhibitors, particularly imatinib, has dramatically improved the prognosis of patients with FIP1L1::PDGFRA-positive disease [5,30].

In the French cohort of 151 patients with FIP1L1::PDGFRA-positive myeloid neoplasia, 148 received imatinib. The main results report overall survival of 99%, 98%, and 89% at one, five, and ten years in this treated subgroup. These are subtype-specific observational estimates; they do not represent survival for all HES or prove a treatment effect against a randomized control [31].

CEL and kinase-rearranged neoplasms other than PDGFRA- or PDGFRB-associated disease have heterogeneous outcomes, with risks related to marrow abnormalities, blast phase, lineage involvement, and resistance. FGFR1-associated disease can respond substantially to pemigatinib, but evidence comes from a single-arm trial and advanced disease may still require transplantation. Historical statements that all myeloid HES has a uniformly poor prognosis are no longer appropriate [5,30,32].

Lymphocytic HES (L-HES). The clinical course of L-HES is frequently chronic and relapsing, with many patients requiring long-term treatment to maintain disease control. Although corticosteroids and steroid-sparing therapies can provide effective clinical and hematological responses, persistent aberrant T-cell populations may remain detectable despite normalization of peripheral blood eosinophil counts [13].

A systematic review assembled 148 published L-HES cases and estimated ten-year overall survival at 81.6% (95% confidence interval 68.1–89.8%); T-cell lymphoma was reported in 19 patients. Case-based aggregation, variable follow-up, selection, and publication bias limit interpretation. The observed fraction is not a prospective transformation rate, and exploratory associations should not be used as a validated individual risk model [43].

Consequently, long-term hematological follow-up is recommended, particularly in patients with persistent lymphadenopathy, progressive lymphocytosis, constitutional symptoms, or evolving abnormalities in T-cell immunophenotyping [43].

Secondary (reactive) HES. The prognosis of secondary HES is primarily determined by the underlying disease and the extent of eosinophil-mediated tissue damage. In patients with drug-induced or parasitic eosinophilia, withdrawal of the causative agent or appropriate antiparasitic treatment may result in complete resolution. In contrast, secondary eosinophilia associated with malignancies or systemic inflammatory disorders may have a less favorable outcome depending on the underlying condition [6].

Organ injury and prognostic interpretation

Cardiac involvement is one of the most important determinants of adverse outcomes in HES. Eosinophil-mediated cardiac injury may progress through three overlapping pathological stages: inflammatory (necrotic), thrombotic, and fibrotic. These changes may lead to eosinophilic myocarditis, intracardiac thrombus formation, endomyocardial fibrosis, restrictive cardiomyopathy, and ultimately congestive heart failure [3,28].

Importantly, cardiac dysfunction may develop insidiously and does not necessarily correlate with the degree of peripheral blood eosinophilia. Delayed diagnosis may result in irreversible myocardial fibrosis and persistent cardiac dysfunction despite successful suppression of eosinophilia. Therefore, early cardiac assessment, including echocardiography, cardiac biomarkers, and cardiac magnetic resonance imaging when indicated, is essential for improving prognosis [4].

Neurological involvement, particularly cerebrovascular events and thromboembolic complications, is another important adverse prognostic factor. Arterial and venous thrombosis may result in significant morbidity, including stroke, pulmonary embolism, and other ischemic complications. Early recognition and appropriate management of thrombotic manifestations are therefore important components of long-term disease control [4,44].

Other manifestations associated with significant morbidity include pulmonary fibrosis, chronic respiratory impairment, gastrointestinal involvement, renal dysfunction, and progressive neurological deficits. The reversibility of these complications depends on the duration and severity of tissue injury and the timing of therapeutic intervention [7].

Prognostic factors and evidence limitations

No universal validated prognostic score applies across all HES variants. Important considerations include cardiac and neurological injury, prior thrombosis, a high-risk hematological diagnosis, cytopenias, abnormal marrow morphology, persistent disease despite appropriate treatment, and evolving lymphoproliferation. Associations are subtype-dependent and should not be converted into a single numerical risk estimate [4,5,43].

Regular clinical and laboratory follow-up is essential, even in patients who achieve remission. Monitoring should include complete blood counts with differential, assessment of organ-specific manifestations, and appropriate biochemical and imaging investigations. Particular attention should be paid to cardiac function and the development of new thromboembolic or neurological complications [6].

Impact of therapeutic advances

Molecular diagnosis identifies patients who can benefit markedly from kinase inhibition, while randomized biologic trials demonstrate reduced flares in selected HES populations. These advances should be distinguished from evidence of cure, reversal of established fibrosis, or improved overall survival, which is more limited for non-neoplastic HES [31,36,37].

Mepolizumab and benralizumab trials differ in populations, follow-up, and endpoints. Their results cannot be ranked as a head-to-head efficacy comparison. Selection should consider the patient's phenotype, prior treatment, authorized indication, access, and preferences [36,37].

Established heart failure, valvular disease, or endomyocardial fibrosis may require conventional cardiac treatment, thrombus management, and, in selected advanced cases, surgical or transplant assessment. Successful suppression of eosinophils does not reliably reverse fixed structural damage [4,28].

Allogeneic hematopoietic stem cell transplantation remains a potentially curative treatment option for selected patients with aggressive, refractory, or advanced clonal hematological disorders. However, its use is limited by treatment-related morbidity and mortality, and it should be considered in specialized centers following careful assessment of individual risk and expected benefit [30].

Research priorities

Longer follow-up is needed to establish sustained remission, tissue recovery, prevention of irreversible injury, and survival under newer therapies. Predictive biomarkers and prospective estimates of lymphoma risk in L-HES remain important gaps. Patient-reported function and cumulative glucocorticoid toxicity should accompany blood-count endpoints [36,37,43].

Complications and their prevention

Complications of HES result from eosinophil-mediated tissue inflammation, cytotoxicity, thrombosis, and subsequent fibrosis. Their clinical presentation and severity depend on the organs involved, the underlying HES subtype, and the duration and intensity of eosinophilic activity. Although virtually any organ system may be affected, the heart, lungs, skin, gastrointestinal tract, nervous system, and vascular system are among the most frequently involved. Importantly, the degree of organ damage does not always correlate with the peripheral blood eosinophil count, and clinically significant cardiac or thromboembolic complications may develop in patients with relatively modest eosinophilia [4,7].

Cardiac complications include eosinophilic myocarditis, intracardiac thrombi, embolization, endomyocardial fibrosis, restrictive physiology, valve dysfunction, and arrhythmias. Early assessment combines ECG, biomarkers, and echocardiography, with cardiac magnetic resonance or biopsy in selected cases. New symptoms or biomarker abnormalities warrant reassessment even when the AEC is controlled. Prevention depends on prompt disease control and management of established cardiac pathology [4].

Thromboembolic complications may occur as a consequence of eosinophil-induced endothelial damage, activation of coagulation pathways, and intracardiac thrombus formation. These events include cerebral and systemic arterial embolism, ischemic stroke, deep venous thrombosis, and, less commonly, other arterial or venous thrombotic events. Cardiac mural thrombi may be a particularly important source of systemic emboli, contributing to neurological deficits and peripheral ischemia. Anticoagulation addresses an established thrombotic indication and does not replace control of eosinophilic disease [4,28].

Neurological complications encompass both central and peripheral nervous system involvement. Central manifestations include ischemic stroke, encephalopathy, altered mental status, and other neurological deficits, which may result from thromboembolism, small-vessel injury, or direct eosinophil-mediated tissue damage. Peripheral nervous system involvement may present as sensorimotor or autonomic neuropathy, mononeuritis multiplex, and, occasionally, severe or persistent neurological disability [44].

Pulmonary complications include eosinophilic pulmonary infiltrates, interstitial abnormalities, bronchial involvement, pleural effusions, and respiratory impairment. Clinical manifestations range from cough, wheezing, and dyspnea to hypoxemia and, in severe cases, respiratory failure. Chronic or recurrent pulmonary inflammation may result in persistent functional impairment [7].

Gastrointestinal and hepatobiliary complications may include eosinophilic gastritis, enteritis, or colitis, presenting with abdominal pain, nausea, vomiting, diarrhea, malabsorption, gastrointestinal bleeding, and weight loss. Severe tissue involvement may lead to ulceration, protein-losing enteropathy, or other consequences of extensive gastrointestinal inflammation. Hepatic involvement, although less common, may manifest as hepatomegaly or abnormal liver biochemical tests [7].

Cutaneous complications are frequent and may include urticaria,

angioedema, eczema-like or papular eruptions, erythematous plaques, pruritus, and, less commonly, ulcerative or vasculitic lesions. Although often not life-threatening, persistent skin involvement may substantially impair quality of life [7].

Hematological progression depends on the underlying disease. Selected myeloid neoplasms can progress to acute leukemia, while L-HES may precede a peripheral T-cell lymphoma. New cytopenias, increasing blasts, progressive organomegaly or lymphadenopathy, constitutional symptoms, or a changing aberrant T-cell population require investigation. Malignant transformation is not an inevitable feature of all HES [5,43].

Prevention also requires attention to treatment toxicity: glucocorticoid-related infection, adrenal suppression and bone loss; cytoreductive myelosuppression; and agent-specific hepatic, ocular, metabolic, or immune complications. The monitoring plan should specify who reviews abnormal results and how treatment changes will be communicated [6,33].

Patient education and shared decisions

Patient education is an important component of the long-term management of HE and HES. Patients should be informed that eosinophil-mediated tissue injury may affect multiple organ systems and can develop insidiously, even in the absence of prominent symptoms or markedly elevated peripheral blood eosinophil counts. Therefore, new, persistent, recurrent, or unexplained symptoms should prompt timely medical evaluation [7].

Patients should receive clear instructions to seek emergency assessment for chest pain, new severe breathlessness, syncope, a focal neurological deficit, or suspected thromboembolism. Persistent cough, fever, new skin disease, abdominal symptoms, weight loss, or deteriorating exercise tolerance warrant timely review. The plan should distinguish an emergency from a routine update and give an appropriate contact route [4,7].

A regularly updated history should cover the following [6]:

- Medication exposure: all prescription and nonprescription medications, including recently initiated, discontinued, or intermittently used drugs, as well as over-the-counter preparations, herbal products, vitamins, and dietary supplements. Drug-induced eosinophilia and severe hypersensitivity reactions, including DRESS, may develop after a delay following drug exposure.
- Travel and environmental exposures: previous residence and travel, including remote stays in helminth-endemic regions; soil, water, food, animal, and occupational exposures. Strongyloides can persist for decades, making remote exposure clinically relevant before immunosuppression [26,27].
- Personal and family medical history: previous eosinophil counts, allergic or atopic disorders, asthma, chronic rhinosinusitis, autoimmune or inflammatory diseases, parasitic infections, hematologic disorders, malignancies, and relevant family history.
- Previous investigations and treatment: prior blood counts, laboratory and imaging results, tissue biopsies, hematologic or molecular testing, previous treatments for eosinophilia, and treatment responses or adverse effects.

Patients should understand the importance of adhering to the recommended monitoring schedule, even when symptoms have resolved. Follow-up should be individualized according to the underlying HES subtype, disease activity, treatment, and evidence of organ involvement. It may include serial complete blood counts with differential, assessment of renal and hepatic function, cardiac biomarkers, electrocardiography, echocardiography, pulmonary function testing, and other organ-specific investigations as clinically indicated. Patients should not assume that normalization of the peripheral eosinophil count necessarily indicates complete resolution of tissue injury or established organ damage [6,7].

Treatment education should cover the purpose of each medicine, likely adverse effects, missed doses, and laboratory monitoring. Glucocorticoids must not be stopped abruptly; tapering and any adrenal-risk precautions require a written plan. Discuss infection symptoms, vaccination and prevention appropriate to the actual regimen, bone health, metabolic monitoring, and reproductive precautions when relevant. For self-injected biologics, provide technique and storage training and explain hypersensitivity symptoms [6,9,10].

Patients should maintain an updated medication list, relevant prior eosinophil counts and test results, and contact details for the coordinating clinician. Shared decisions should include symptom burden, treatment burden, fertility or pregnancy plans when relevant, affordability and access, and the uncertainty around long-term outcomes [7].

Coordinating the healthcare team

HES care often spans hematology, allergy and clinical immunology, internal medicine, and relevant organ specialties. A designated coordinating clinician and a shared problem list help integrate the syndrome diagnosis, underlying cause, organ damage, and treatment plan. This is a recommended organizational approach; comparative evidence on its independent effects in HES remains limited [7].

A core team should generally include a hematologist, allergist/immunologist, and internist, with additional specialists involved according to the patient's clinical presentation and disease subtype. Cardiologists should be consulted when cardiac involvement is suspected or confirmed, particularly in patients with myocarditis, endomyocardial fibrosis, intracardiac thrombosis, arrhythmias, or heart failure. Pulmonologists may be required for eosinophilic pulmonary infiltrates, asthma, or respiratory impairment; gastroenterologists for gastrointestinal involvement; neurologists for central or peripheral nervous system manifestations; dermatologists for persistent or diagnostically challenging cutaneous lesions; and rheumatologists when vasculitis or systemic autoimmune disease is suspected. Clinical pathologists,

Table 5: Responsibilities in coordinated follow-up.

Responsibility	Typical lead	Information shared with the team
Overall plan and escalation	Designated coordinating clinician	Working diagnosis, treatment goals and contact route
Neoplastic or lymphocytic disease	Hematologist with immunology input	Fusion or clone status, molecular surveillance and progression concerns
Organ function	Relevant organ specialist	Baseline injury, recovery, residual damage and red flags
Medicines and self-management	Prescriber, pharmacist and nurse	Interactions, monitoring, adherence and injection or tapering plan
Continuity and prevention	Primary care with specialist support	Vaccination, metabolic and bone health, appointments and new symptoms

Note: The exact allocation depends on local services and disease subtype. This is a practical care framework, not a tested outcome prediction model [6,7].

hematopathologists, and molecular geneticists also play important roles in the interpretation of tissue biopsies, bone marrow findings, immunophenotyping, cytogenetic studies, and molecular testing [6,7].

Early recognition and appropriate referral are essential to reduce diagnostic delays and prevent irreversible organ damage. Because patients may initially present to different medical specialties with nonspecific symptoms, healthcare professionals across primary and secondary care should be familiar with clinical features that raise suspicion of HE or HES. Once persistent or otherwise unexplained eosinophilia is identified, a structured diagnostic evaluation should be initiated, with referral to a center experienced in eosinophilic disorders when the diagnosis is uncertain, clonal disease is suspected, or significant organ involvement is present [14].

Communication and shared decision-making among team members are critical when determining the underlying HES subtype and selecting treatment. Therapeutic strategies differ substantially between myeloid or molecularly defined HES, lymphocytic-variant HES, idiopathic HES, and reactive eosinophilic disorders. For example, patients with FIP1L1::PDGFRA-associated disease may benefit from targeted tyrosine kinase inhibition, whereas patients with other forms of HES may require glucocorticoids, eosinophil-targeted biologic therapy, immunomodulatory treatment, or treatment directed at an underlying condition. In patients with severe or life-threatening organ involvement, urgent treatment decisions should be coordinated without delaying necessary intervention while awaiting completion of the entire diagnostic work-up [5,6].

The care plan should assign responsibility for blood and molecular monitoring, organ surveillance, medication interactions, adverse-event review, and decisions about tapering or escalation. Pharmacists and nurses can support reconciliation, adherence, injection training, and recognition of toxicity. Primary care should receive the current diagnosis, emergency advice, and follow-up schedule [6,7].

Multidisciplinary discussions are particularly useful when eosinophil-attributable injury is uncertain, a kinase or T-cell abnormality is difficult to interpret, disease is treatment-refractory, or transplantation is being considered. Shared records and referral pathways can reduce duplicated investigations and inconsistent advice [6,7].

Care should be evaluated using clinical stability, organ function, flare frequency, cumulative glucocorticoid exposure, treatment toxicity, patient-reported function, and continuity of follow-up. Improvements in these measures should not be assumed to prove a survival benefit from care coordination alone [7].

Conclusion

HES management requires evidence of eosinophil-attributable disease, an etiological diagnosis whenever possible, and timely treatment of threatened organs. Fusion-directed therapy is decisive for susceptible neoplasms, while glucocorticoids and steroid-sparing agents control selected non-neoplastic disease. Contemporary biologic trials support fewer flares, but leave important questions about sustained tissue recovery and long-term survival [1,5,36,37].

Long-term care must address residual organ injury, treatment toxicity, recurrent disease, and possible hematological evolution. Shared decisions and clearly assigned follow-up responsibilities make this heterogeneous disorder more manageable and help patients report meaningful changes promptly [6,7].

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