Hypereosinophilic Syndrome (HES) Roadmap:

A Guided Workflow for Improved Diagnosis and Treatment in HES

National Jewish Health®
Breathing Science is Life.®

START HERE

A DIAGNOSIS AND CLASSIFICATION [1, 2, 3]

1 Absolute eosinophil count ≥ 1500/μl AND/OR Tissue eosinophilia?

- no → Consider other causes (Table 1); Monitor for progression
- yes

2 Initial workup

History
- Onset, magnitude, temporal associations of eosinophilia
- Comorbid conditions
- Exposures, travel
- Medications
- Infection
- Family history of eosinophilia
- Symptoms: Organ specific, fever, constitutional

Physical exam
- Sinus disease
- Mucosal ulcers
- Adventitious lung sounds
- Heart murmurs, rubs
- Lymphadenopathy
- Liver/spleen enlargement
- Abdominal tenderness
- Joint/muscle abnormality
- Skin rash, edema
- Neuropathy, weakness

Lab Tests
- CBC with diff
- Peripheral smear
- Serum tryptase
- Serum B12
- Stool ova & parasites
- Liver/kidney tests
- Amylase/lipase
- Troponin
- ANA
- ANCA
- HIV serology
- Serum immunoglobulins
- *Strongyloides* IgG
- ESR/CRP
- LDH
- Urinalysis

Studies
- ECG
- Echocardiogram
- PFTs
- Pulse oximetry
- CXR

3 Additional workup to evaluate for evidence of end-organ damage or dysfunction

Cardiac
- Cardiac MRI
- Endomyocardial biopsy

Pulmonary
- Chest CT (high resolution)
- Bronchoalveolar lavage
- Lung biopsy

Hematologic
- Bone marrow biopsy with cytogenetics
- Peripheral FISH/RT-PCR for FIP1L1-PDGFRA
- Lymphocyte phenotyping (flow cytometry)
- T- and B-cell rearrangement studies
- PET scan
- Lymph node biopsy

GI
- Abdomen & pelvis CT
- Endoscopy with biopsy

Dermatologic
- Skin biopsy

Renal
- 24 hour urine test
- Kidney biopsy

Vascular
- Angiography

Neurologic
- Brain MRI or CT with contrast
- EEG
- Nerve conduction studies/EMG
- Nerve biopsy

4 Evidence of end-organ damage or dysfunction?

- yes → **5** Secondary causes of hypereosinophilia excluded?
  - yes → **B** DETERMINE HES CLINICAL VARIANT
  - no → Hypereosinophilia
    - Consider other causes (Table 1)
      - Consider HE_{US}
      - Consider subspecialty referral
      - Monitor for progression
    - yes → **B** DETERMINE HES CLINICAL VARIANT
- no → **C** HYPEREOSINOPHILIA: INITIAL TREATMENT APPROACH [2]

1 Absolute eosinophil count ≥ 1500/μl

2 Symptoms?

- no → Clinical manifestation of myeloid neoplasm?
  - no → HE_{US}: Consider close monitoring off therapy; obtain family history
  - yes → Proceed as if symptomatic
- yes

3 Life-threatening?

- no → **Comprehensive evaluation:** see algorithm for HES Diagnosis and Classification; Initiate therapy based on clinical variant
- yes → Begin diagnostic workup but do not delay treatment; prioritize tests that are affected by glucocorticoid therapy

4 Suspected or proven *PDGFR*-associated neoplasm?

- yes → HES → Imatinib +/- glucocorticoid (high-dose* if cardiac involvement)
- no → Features of EGPA?
  - no → HES → High-dose glucocorticoid*
  - yes → High-dose glucocorticoid* + cyclophosphamide

*If potential exposure to *Strongyloides* at any time, treat empirically with concomitant ivermectin for 2 days.

Table 1 — Secondary causes of eosinophilia and hypereosinophilia [1, 4]

Category with examples (not inclusive)

Allergic disorders
- Asthma, atopic dermatitis, allergic rhinitis

Drug hypersensitivity

Infection
- Helminthic/Ectoparasite
- Protozoan
- Fungal
- Bacterial
- Viral, including HIV infection

Neoplasms
- Leukemia
- Lymphoma
- Adenocarcinoma

Immunologic disorders
- Immunodeficiency: hyper-IgE syndrome, Omenn's syndrome, DOCK8 deficiency
- Autoimmune diseases: sarcoidosis, inflammatory bowel disease, IgG4 disease, other connective tissue disorders

Miscellaneous
- Radiation exposure
- Cholesterol emboli
- Hypoadrenalism
- IL-2 therapy

Table 2 — [1, 2, 4, 5]

HES CLINICAL VARIANT	ETIOLOGIES/CHARACTERISTICS
Myeloproliferative variant	Clinically-defined MHES, FIP1L1/PDGFRA positive, or chronic eosinophilic leukemia
Lymphocytic variant	Lymphocyte population with aberrant phenotype by flow cytometry OR clonal T cell population by PCR analysis; lymphocytes secrete IL-5 or other cytokines that drive eosinophilia
Familial eosinophilia	Family history of documented persistent eosinophilia. Autosomal dominant. Mutations associated with IL-5 overexpression
Overlap	Incomplete criteria OR apparent restriction to specific tissues/organs (eg, eosinophil-associated GI disorders (EGID), chronic eosinophilic pneumonia, eosinophilic fasciitis); EGPA
Idiopathic	Benign (asymptomatic with no evidence of organ involvement), complex (symptomatic with organ involvement but idiopathic), or episodic (cyclic angioedema and eosinophilia)
Associated	Peripheral eosinophilia ≥ 1500/μl associated with a defined diagnosis (eg, inflammatory bowel disease, sarcoidosis, autoimmune lymphoproliferative syndrome, other secondary causes (Table 1))

Table 3 — [1, 2, 4, 5]

HES CLINICAL VARIANT	TREATMENT
Myeloproliferative variant	Imatinib, a tyrosine kinase inhibitor, is first line for known or suspected PDGFR-associated myeloid neoplasms Add glucocorticoid if cardiac involvement or insufficient control with imatinib
Lymphocytic variant	Short-term glucocorticoid is first line Hydroxyurea is preferred second line Imatinib, interferon-α, pegylated interferon, methotrexate, cyclosporine are other second line
Familial eosinophilia	Monitor clinically if no symptoms or tissue organ damage Glucocorticoid if symptomatic and/or evidence of organ involvement Immunomodulators such as hydroxyurea, interferon-α, or anti-IL5 therapy
Overlap	Glucocorticoid and/or immunomodulators if symptomatic and/or evidence of tissue damage Swallowed glucocorticoid and/or diet modification for EGID Short-term glucocorticoid is first line for EGPA Mepolizumab, cyclophosphamide, methotrexate are second line for EGPA
Idiopathic	Monitor clinically if no symptoms or tissue organ damage Glucocorticoid if symptomatic and/or evidence of tissue damage Immunomodulators such as hydroxyurea, interferon-α, or anti-IL5 therapy
Associated	Identify and treat underlying cause of hypereosinophilia

Abbreviations

EGPA, eosinophilic granulomatosis with polyangiitis (formerly Churg-Strauss syndrome)

HES, hypereosinophilic syndrome

HE_{US}, hypereosinophilia of unknown significance

MHES, myeloid hypereosinophilic syndrome

PDGFR, platelet-derived growth factor receptor gene

References

1) Khoury P, Bochner BS. Consultation for elevated blood eosinophils: clinical presentations, high value diagnostic tests, and treatment options. *J Allergy Clin Immunol Pract*. 2018;6(5):1446-1453. | 2) Klion A. Hypereosinophilic syndrome: approach to treatment in the era of precision medicine. *Hematology Am Soc Hematol Educ Program*. 2018;2018(1):326-331. | 3) Schuster B, Zink A, Eyerich K. Medical algorithm: diagnosis and treatment of hypereosinophilic syndrome. *Allergy*. 2020;00:1-4. | 4) Klion AD. Eosinophilia: a pragmatic approach to diagnosis and treatment. *Hematology Am Soc Hematol Educ Program*. 2015;2015:92-97. | 5) Klion AD, Ackerman SJ, Bochner BS. Contributions of eosinophils to human health and disease. *Annu Rev Pathol*. 2020;15:179-209.

This reference aid was developed as part of an educational activity supported by an educational grant from GlaxoSmithKline.