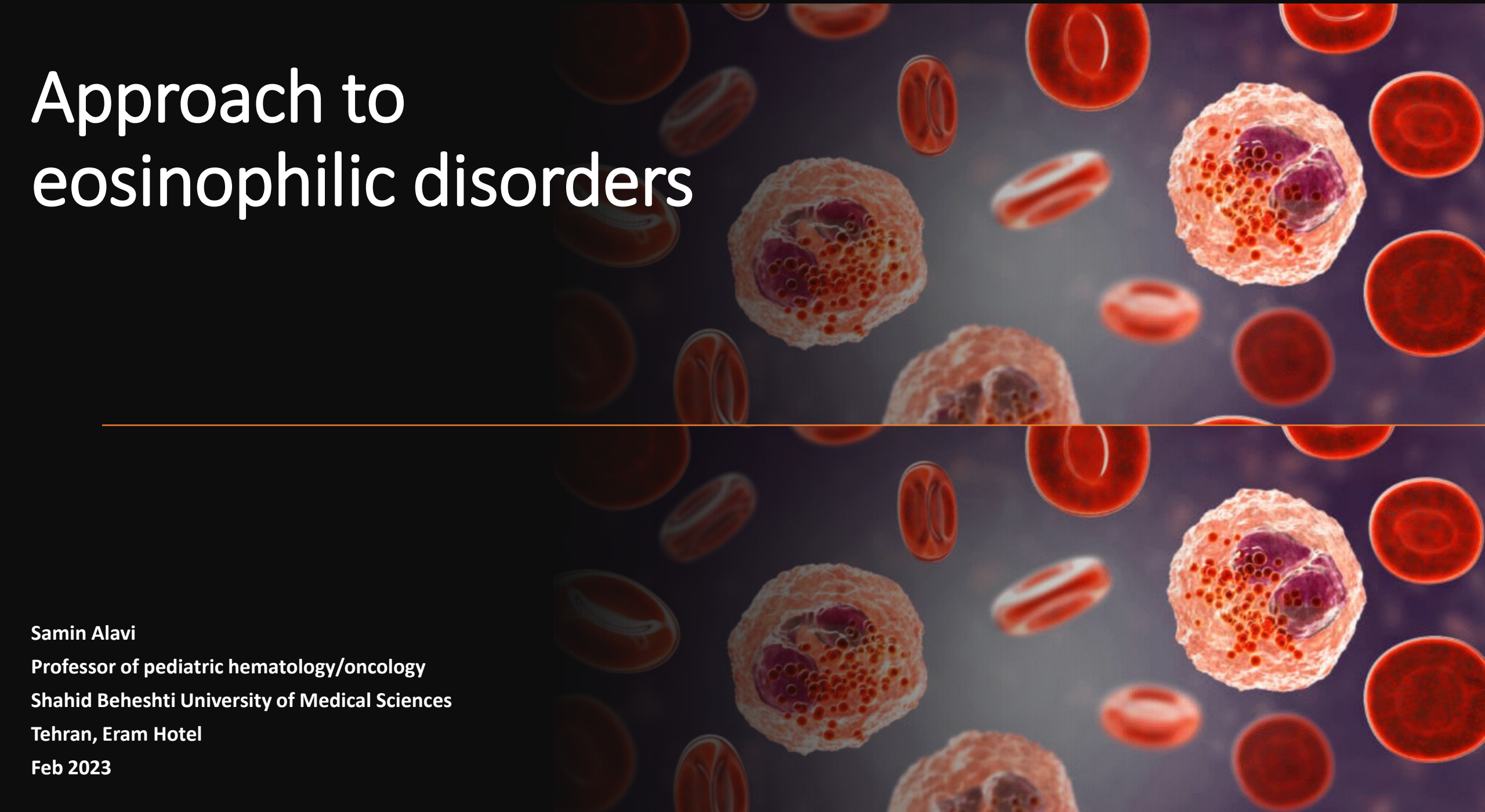
Approach to eosinophilic disorders



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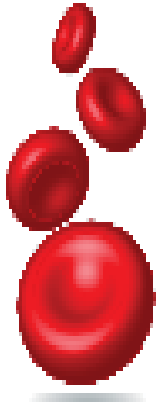

ANNUAL CLINICAL UPDATES IN HEMATOLOGICAL MALIGNANCIES

World Health Organization-defined eosinophilic disorders: 2017 update on diagnosis, risk stratification, and management

WHO-2017 update on eosinophilic disorders:
Definition of eosinophilia

- Upper limit of normal eosinophils in the peripheral blood is 3%-5% of WBCs with absolute eosinophil count (AEC) of 350-500/mm^3

- The severity of eosinophilia:
  mild (500-1500/ mm^3)
  moderate (AEC 1500–5000/ mm^3)
  severe (AEC >5000/ mm^3).

- Mild blood eosinophilia is common, occurring in 3% to 10% of individuals.

- **“Blood hypereosinophilia”** is defined as an AEC >1500/mm^3
- **“Tissue HE” is defined as:**

(1) Eosinophils > 20% of nucleated cells in a BM aspirate.
(2) Tissue infiltration by eosinophils is markedly increased.
(3) Extensive deposition of eosinophil-derived proteins in tissue as demonstrated by immunostaining.

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Table 1. *Criteria and definitions*

Hypereosinophilia (HE)
Absolute eosinophil count > 1.5 x 10^9/l on at least two occasions with an interval of ≥ 1 month **and/or** histologically proven eosinophilia in tissue defined as: 1. Bone marrow aspiration with ≥ 20% eosinophils and/or 2. Histologically proven tissue infiltration and/or 3. Deposition of eosinophil-granule proteins
Hypereosinophilic syndrome (HES)
Hypereosinophilic syndrome is defined as: 1. Existence of hypereosinophilia as defined above and 2. Eosinophil-mediated organ dysfunction and/or damage and 3. No other identifiable etiology for eosinophilia

Note: Adapted from Valent P, Klion AD, Horny HP, et al. Contemporary consensus proposal on criteria and classification of eosinophilic disorders and related syndromes. J. Allergy Clin Immunol. 2012;130:607-12.

Diagnosis of hypereosinophilia
Step 1: Exclude secondary (reactive) causes of eosinophilia "polyclonal Eosinophilia"

- Allergy/atopy, hypersensitivity, drug reaction, collagen-vascular disease (Churg-Strauss, Wegener's, SLE), pulmonary eosinophilic diseases, ABPA, allergic gastroenteritis (with associated peripheral eosinophilia), and metabolic conditions such as adrenal insufficiency

- Rare conditions associated with eosinophilia: Familial eosinophilia, immunodeficiency states such as: hyper IgE Syndrome, Omenn Syndrome, Dock8 deficiency, episodic angioedema and eosinophilia (Gleich's syndrome)

- Non-myeloid malignancies may be associated with secondary eosinophilia which results from the production of cytokines such as IL-3, IL-5, and GM-CSF such as: T-cell lymphomas, hodgkin lymphoma, and ALL

Table 1. Differential diagnosis of hypereosinophilia

Category	Examples (not inclusive)
Allergic disorders*	Asthma, atopic dermatitis
Drug hypersensitivity	Varied†
Infection	
Helminthic	Varied, including strongyloidiasis, trichinellosis, filariasis, schistosomiasis, hookworm
Ectoparasite	Scabies, myiasis
Protozoan	Isosporiasis, sarcocystis myositis
Fungal	Coccidiomycosis, allergic bronchopulmonary aspergillosis, histoplasmosis
Viral	HIV
Neoplasms	Leukemia, lymphoma, adenocarcinoma
Immunologic disorders‡	
Immunodeficiency	DOCK8 deficiency, Hyper-IgE syndrome, Omenn's syndrome
Autoimmune and idiopathic	Sarcoidosis, inflammatory bowel disease, IgG4 disease, and other connective tissue disorders
Miscellaneous	Radiation exposure, cholesterol emboli, hypoadrenalism, IL-2 therapy
Rare eosinophilic disorders	Idiopathic hypereosinophilic syndrome, eosinophilic granulomatosis with polyangiitis (formerly Churg-Strauss syndrome), eosinophilic gastrointestinal disorders

Revised 2016 (WHO) classification of myeloid neoplasms

TABLE 1 Revised 2016 World Health Organization (WHO) classification of myeloid neoplasms

1. Acute myeloid leukemia and related neoplasms

2. Myeloproliferative neoplasms (MPN)
   - Chronic myeloid leukemia, *BCR-ABL1* positive
   - Chronic neutrophilic leukemia
   - Polycythemia vera
   - Primary myelofibrosis (PMF)
     - i PMF, prefibrotic/early stage
     - ii PMF, overt fibrotic stage
   - Essential thrombocythemia
   - Chronic eosinophilic leukemia, not otherwise specified
   - Myeloproliferative neoplasms, unclassifiable

3. Myelodysplastic syndromes (MDS)
   - MDS with single lineage dysplasia
   - MDS with ring sideroblasts (MDS-RS)
     - MDS-RS with single lineage dysplasia
     - MDS-RS with multilineage dysplasia
   - MDS with multilineage dysplasia
   - MDS with excess blasts
   - MDS with isolated del(5q)
   - MDS, unclassifiable
     - i Provisional entity: Refractory cytopenia of childhood
   - Myeloid neoplasms with germ line predisposition

4. MDS/MPN
   - Chronic myelomonocytic leukemia
   - Atypical chronic myeloid leukemia, *BCR-ABL1* negative
   - Juvenile myelomonocytic leukemia
   - MDS/MPN with ring sideroblasts and thrombocytosis (MDS/MPN-RS-T)
   - MDS/MPN, unclassifiable

5. Mastocytosis

6. Myeloid/lymphoid neoplasms associated with eosinophilia and rearrangement of *PDGFRA*, *PDGFRB*, or *FGFR1*, or with *PCM1-JAK2*
   - Myeloid/lymphoid neoplasms with *PDGFRA* rearrangement
   - Myeloid neoplasms with *PDGFRB* rearrangement
   - Myeloid/lymphoid neoplasms with *FGFR1* abnormalities
   - Provisional entity: Myeloid/lymphoid neoplasms with *PCM1-JAK2*

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Special Report

International Consensus Classification of Myeloid Neoplasms and Acute Leukemias: integrating morphologic, clinical, and genomic data

Blood, 15 SEPTEMBER 2022 | VOLUME 140, NUMBER 11

International Consensus Classification of Myeloid Neoplasms and Acute Leukemias

Table 1. Major ICC categories of myeloid neoplasms and acute leukemias

MPNs
- Chronic myeloid leukemia
- Polycythemia vera
- Essential thrombocythemia
- Primary myelofibrosis
  - Early/prefibrotic primary myelofibrosis
  - Overt primary myelofibrosis
- Chronic neutrophilic leukemia
- Chronic eosinophilic leukemia, not otherwise specified
- MPN, unclassifiable

Myeloid/lymphoid neoplasms with eosinophilia and tyrosine kinase gene fusions
- Myeloid/lymphoid neoplasm with *PDGFRA* rearrangement
- Myeloid/lymphoid neoplasm with *PDGFRB* rearrangement
- Myeloid/lymphoid neoplasm with *FGFR1* rearrangement
- Myeloid/lymphoid neoplasm with *JAK2* rearrangement
- Myeloid/lymphoid neoplasm with *FLT3* rearrangement
- Myeloid/lymphoid neoplasm with *ETV6::ABL1*

Mastocytosis

Myelodysplastic/myeloproliferative neoplasms
- Chronic myelomonocytic leukemia
- Clonal cytopenia with monocytosis of undetermined significance
- Clonal monocytosis of undetermined significance
- Atypical chronic myeloid leukemia
- Myelodysplastic/myeloproliferative neoplasm with thrombocytosis and *SF3B1* mutation
- Myelodysplastic/myeloproliferative neoplasm with ring sideroblasts and thrombocytosis, not otherwise specified
- Myelodysplastic/myeloproliferative neoplasm, not otherwise specified

Premalignant clonal cytopenias and myelodysplastic syndromes
- Clonal cytopenia of undetermined significance
- Myelodysplastic syndrome with mutated *SF3B1*
- Myelodysplastic syndrome with del(5q)
- Myelodysplastic syndrome with mutated *TP53*
- Myelodysplastic syndrome, not otherwise specified (MDS, NOS)
  - MDS, NOS without dysplasia
  - MDS, NOS with single lineage dysplasia
  - MDS, NOS with multilineage dysplasia
- Myelodysplastic syndrome with excess blasts
- Myelodysplastic syndrome/acute myeloid leukemia (MDS/AML)
  - MDS/AML with mutated *TP53*
  - MDS/AML with myelodysplasia-related gene mutations
  - MDS/AML with myelodysplasia-related cytogenetic abnormalities
  - MDS/AML, not otherwise specified

Pediatric and/or germline mutation-associated disorders
- Juvenile myelomonocytic leukemia
- Juvenile myelomonocytic leukemia-like neoplasms
- Noonan syndrome-associated myeloproliferative disorder
- Refractory cytopenia of childhood
- Hematologic neoplasms with germline predisposition

Acute myeloid leukemias (Tables 25 and 26)

Myeloid proliferations associated with Down syndrome

Blastic plasmacytoid dendritic cell neoplasm

Acute leukemia of ambiguous lineage
- Acute undifferentiated leukemia
- Mixed phenotype acute leukemia (MPAL) with t(9;22)(q34.1;q11.2); *BCR::ABL1*
- MPAL, with t(v;11q23.3); *KMT2A* rearranged
- MPAL, B/myeloid, NOS
- MPAL, T/myeloid, NOS

B-lymphoblastic leukemia/lymphoma (Tables 27 and 28; supplemental Table 6)

T-lymphoblastic leukemia/lymphoma (Table 27; supplemental Table 6)

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Myeloid/lymphoid neoplasms associated with eosinophilia

Myeloid/lymphoid neoplasms with eosinophilia and tyrosine kinase gene fusions

Primary or clonal Eosinophilia

Molecular genetic abnormalities in myeloid/lymphoid neoplasms associated with eosinophilia

Table 10. Molecular genetic abnormalities in myeloid/lymphoid neoplasms associated with eosinophilia

Disease	Presentation	Genetics	Treatment
PDGFRA	Eosinophilia ↑Serum tryptase ↑Marrow mast cells	Cryptic deletion at 4q12 *FIP1L1-PDGFRA*, at least 66 other partners	Respond to TKI
PDGFRB	Eosinophilia Monocytosis mimicking CMML	t(5;12)(q32;p13.2) *ETV6-PDGFRB*, at least 25 other partners	Respond to TKI
FGFR1	Eosinophilia Often presents with T-ALL or AML	Translocations of 8p11.2 *FGFR1*-various partners	Poor prognosis; do not respond to TKI
PCM1-JAK2	Eosinophilia Rarely presents with T-LBL or B-ALL Bone marrow shows left-shifted erythroid predominance and lymphoid aggregates	t(8;9)(p22;p24.1) *PCM1-JAK2*	May respond to JAK2 inhibitors

The 2016 revision to the World Health Organization classification of myeloid neoplasms and acute leukemia

Step 2: primary (clonal) eosinophilia-1

Myeloid/lymphoid neoplasm associated with FIP1L1/PDGFRA

- **Prominent eosinophilia**
- Presence of a FIP1L1/PDGFRA fusion gene (in-frame deletion of 4q12) or a variant fusion gene with rearrangement of PDGFRA
- The FIP1L1-PDGFRA fusion has also been found in cases of AML and T-cell LL associated with eosinophilia.
- In cases where FIP1L1/PDGFRA screening is not available, evaluation of serum tryptase can be a useful marker for FIP1L1-PDGFRA positive disease

FIP1L1/PDGFRA positive myeloid neoplasms/eosinophilia

- 10% of cases of eosinophilia
- Majority are male
- Not detected by standard cytogenetic…….FISH or PCR should be done
- Myeloproliferative features +: anemia, thrombocytopenia, splenomegaly, marrow fibrosis, increased mast cells
- Remarkable sensitivity to Imatinib (100 mg/day)

primary (clonal) eosinophilia-2

Myeloid/lymphoid neoplasms associated with ETV6/PDGFRB

- Demonstration of PDGFRB/ETV6 fusion gene due to t(5;12)(q31/q33) or variant fusion gene with rearrangement of PDGFRB
- **Prominent eosinophilia** , sometimes with neutrophilia or monocytosis

primary (clonal) eosinophilia-3

Myeloid/lymphoid neoplasms associated with FGFR1 rearrangement

8p11 MPN

- A rare, aggressive group of hematologic malignancies that share *FGFR1* gene rearrangement at the 8p11 locus. Presence of t(8;13) or variant translocations leading to FGFR1 rearrangement (at least 14 translocations)

- **Prominent eosinophilia**

- AML or precursor T or B lymphoblastic leukemia/lymphoma or MPAL (3 pheno)

primary (clonal) eosinophilia-4

Myeloid/lymphoid neoplasms with PCM1-JAK2 fusion

- Presence of t(8;9)or a variant translocation leading to JAK2 rearrangements: t(9;12) or t(9;922)(JAK2/BCR)
- **Prominent eosinophilia**
- Lymphadenopathy/hepatosplenomegaly, and myelofibrosis

Table 10. Genetic abnormalities, clinical presentations, and targeted therapy of myeloid/lymphoid neoplasms with eosinophilia and tyrosine kinase gene fusions

TK gene	Most common fusion	Partner genes/ variants	Typical clinical and BM manifestations	Targeted therapy
PDGFRA	Cryptic deletion at 4q12/ *FIP1L1::PDGFRA*	*CDK5RAP2; STRN; KIF5B; TNKS2; ETV6, BCR*	Common: CEL-like BM with frequent extramedullary involvement Others: B-ALL/LL, AML or mast cell proliferations	Excellent response to TKI
PDGFRB	t(5;12)(q32;p13.2)/ *ETV6::PDGFRB*	.30 partners, cryptic	Common: CEL-like or monocytosis with eosinophilia Others: ALL/LL, AML or mast cell proliferations	Excellent response to TKI
FGFR1	t(8;13)(p11.2;q12.1)/ *ZMYM2::FGFR1*	15 other partners including *BCR*	Common: Extramedullary T-ALL/ LL with BM MPN-like or blast phase of MPN; Others: B-ALL/LL, myeloid sarcoma, AML or MPAL	High rate of response to FGFR inhibitor such as pemigatinib, especially for cases in chronic phase
JAK2	t(8;9)(p22;p24.1)/ *PCM1::JAK2*	*ETV6* and *BCR*	Common: MPN or MDS/MPN-like BM with eosinophilia Others: B- and T-ALL/LL with BM MPN	Limited responses to ruxolitinib
FLT3	t(12;13)(p13.2;q12.2)/ *ETV6::FLT3*	*ZMYM2, TRIP11, SPTBN1, GOLGB1, CCDC88C, MYO18A, BCR*	T-ALL/LL or myeloid sarcoma with CEL-like or MDS/MPN BM features	Various responses to specific FLT3 inhibitors
ETV6::ABL1	t(9;12)(q34.1;p13.2)/ *ETV6::ABL1*	Unknown	CML-like with frequent eosinophilia in chronic or blast phase	Various responses to second generation TKI

Chronic Eosinophilic Leukemia

- CEL is an ***MPN***, which is due to clonal proliferation of eosinophil precursors, Blast count in BM is 5-20%.

- No rearrangement of PDGFRA, PDGFRB, or FGFR1; no PCM1-JAK2, ETV6-JAK2, or BCR-JAK2 fusion gene. No Ph chromosome.

- No Inv (16)(p13.1q22), t(16;16) and other diagnostic features of AML.

- Nonspecific cytogenetic or molecular abnormality has been identified in CEL.

Chronic Eosinophilic Leukemia

- **CEL is considered:**

- either myeloblast excess (either >2% in the peripheral blood or 5–20 % in the bone marrow)

- **Cytogenetic abnormalities in CEL include:**

- trisomy 8 (the most frequent)
- t(10;11)
- t(7;12)
- deletion of 7/ 7q-, isochromosome 17q

- NGS studies have suggested the possibility of re-classifying some cases of “HES” as CEL.

Chronic Eosinophilic Leukemia

- CEL is a rare and aggressive disease with high rate of transformation to acute leukemia and resistant to conventional treatment, **most cases were previously classified within HES population.**

- Patients with CEL were predominantly male (70%), and splenomegaly was the most frequent clinical manifestation.

- ASCT remains the only curative option for younger patients with CEL.

Clonal Eosinophilia

Molecularly-defined primary eosinophilia

- PDGFRA
- PDGFRB
- FGFR1
- PCM1-JAK2

(CEL) Myeloproliferative neoplasms

- Absence of rearrangements of PDGFRA/*PDGFRB* and FGFR1, absence of Ph chromosome.
- Absence of other marrow neoplasms associated with eosinophilia [AML, MDS, systemic mastocytosis, and MDS/MPN overlap disorders].
- CEL is morphologically characterized by an increase in blasts in BM or blood (fewer than 20%)

Lymphocyte-variant hypereosinophilia

- Consensus criteria for the diagnosis of "*lymphocyte-variant hypereosinophilia*" has not been established yet.

- T-cell immunophenotypic abnormalities (flowcytometry) or demonstration of Th-2 cytokine production is required for diagnosis of **Lymphocyte-derived eosinophilia** and finding of "T-cell clonality" by PCR, is not sufficient to make a diagnosis.

- Increased production of cytokines from T-cells (TARC), a chemokine produced by Th-2 may provide additional support for a diagnosis of lymphocyte-variant hypereosinophilia.

Lymphocyte-variant hypereosinophilia (reactive hypereosinophilia)

- A mixture of clonal and reactive processes: clonal production of abnormal T lymphocytes; but eosinophilia is reactive to growth factors elaborated by the T cells (IL-5 or TARC).

- Immunophenotyping of these lymphocytes include absence of CD3 (CD3-,CD4+) or double negative T-cells (CD3+ CD4-CD8-), elevated CD5 expression on CD3-CD4+ cells, loss of surface CD7. Regardless of immunophenotype, these T-cells typically express CD45RO plus HLA-DR and/or CD25.

- These patients typically have **cutaneous manifestations**. However, superficial adenopathy, rheumatologic, gastrointestinal, pulmonary, neurologic and cardiovascular involvement was also observed.

When evaluating a patient with hypereosinophilia that is not to be secondary, the following causes should be considered

(1) Myeloid or lymphoid neoplasms associated with eosinophilia (TK fusion genes)

(2) Marrow neoplasms associated with MPN, MDS, or ALL/AML

(3) CEL

(4) Lymphocytic variant of hypereosinophilia

(5) Idiopathic Hypereosinophilia including HES, without evidence for clonal proliferation

Idiopathic HES

- Any kind of HE associated with organ damage is referred to as “HES” (not just idiopathic)

- Idiopathic HES is a diagnosis of exclusion when secondary and clonal causes of eosinophilia are ruled out.

Idiopathic hypereosinophilic syndrome (IHES)

- If clonality of eosinophils cannot be proven and there is no increase in myleoblasts, then the diagnosis is idiopathic HES (Bain et al, 2016).

- Advances in molecular technology have demonstrated that many patients who previously had been considered as “idiopathic HES” now, can be found to have “CEL” since clonal molecular genetic abnormality can be demonstrated. (Gotlib and Cools 2008).

- Transformation to AML in some patients with idiopathic HES provides clue that the disorder from the start was likely a clonal CEL (Wang et al, 2016).

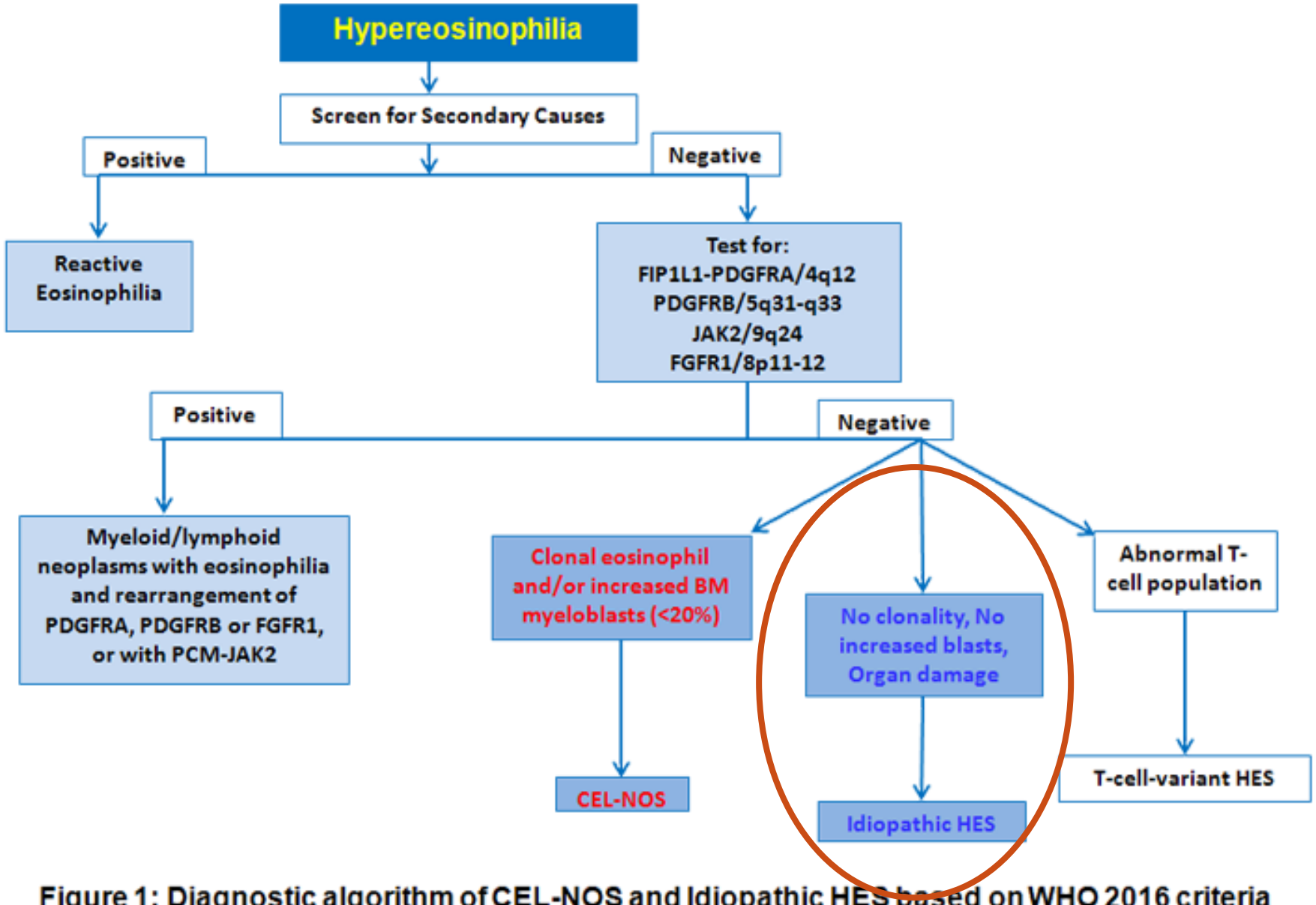
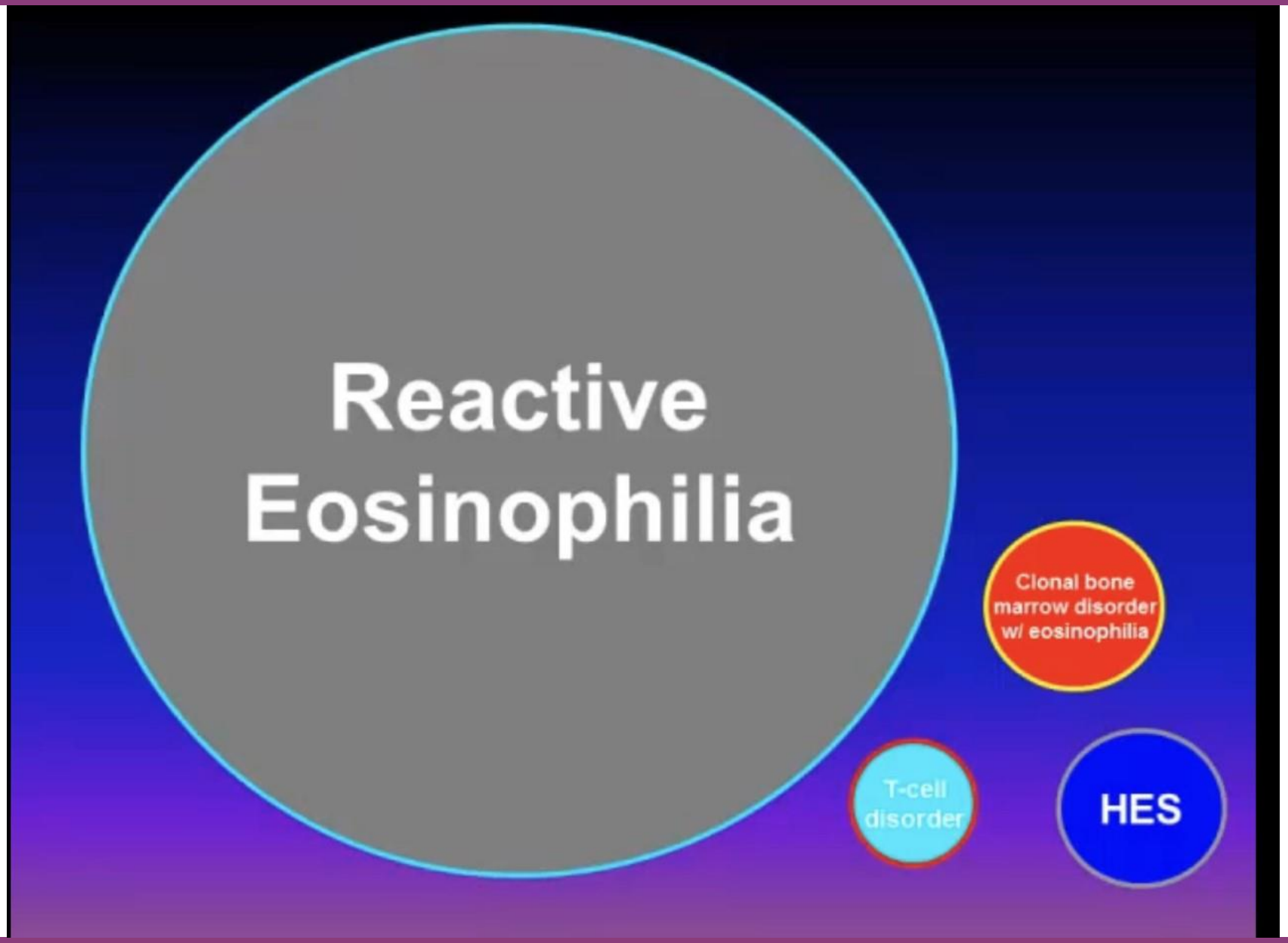


Figure 1; Diagnostic algorithm of CEL-NOS and Idiopathic HES based on WHO 2016 criteria


Reactive Eosinophilia
Clonal bone marrow disorder w/ eosinophilia
T-cell disorder
HES

frontiers in Immunology

MINI REVIEW
published: 03 September 2018
doi: 10.3389/fimmu.2018.01944

Check for updates

An Approach to the Evaluation of Persistent Hypereosinophilia in Pediatric Patients

Clinical and lab presentation of hypereosinophilia

- The most common signs and symptoms: weakness and fatigue, cough, dyspnea, myalgias or angioedema, rash or fever.
- In HES, leukocytosis (20,000-30,000 or higher) with peripheral eosinophilia (30%-70%) may be a common finding.
- Other hematologic findings may be observed: blood or BM neutrophilia, basophilia, myeloid immaturity, mature and immature eosinophils with varying degrees of dysplasia, increased blasts and marrow fibrosis.

Clinical presentation and diagnosis of HES

- Essentially all organ systems may be susceptible to the effects of sustained hypereosinophilia.
- Skin involvement was the most common in 70% of patients, followed by pulmonary and gastrointestinal manifestations.
- Cardiac disease was eventually identified in 20% of patients (only 6% at time of initial presentation). Progressive heart failure is prototype of eosinophil-mediated organ injury.

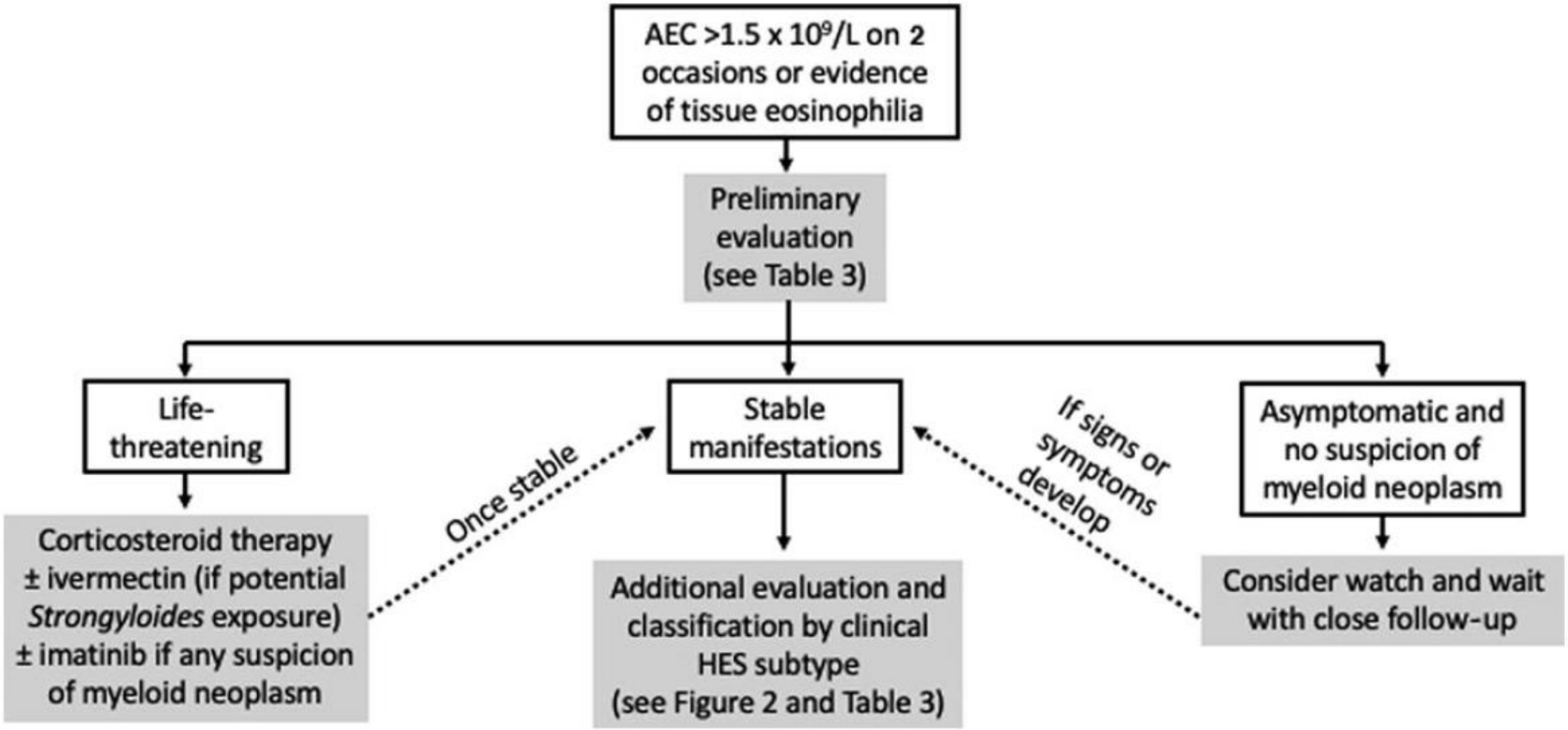


Figure 1. Initial approach to the patient with hypereosinophilic syndrome.

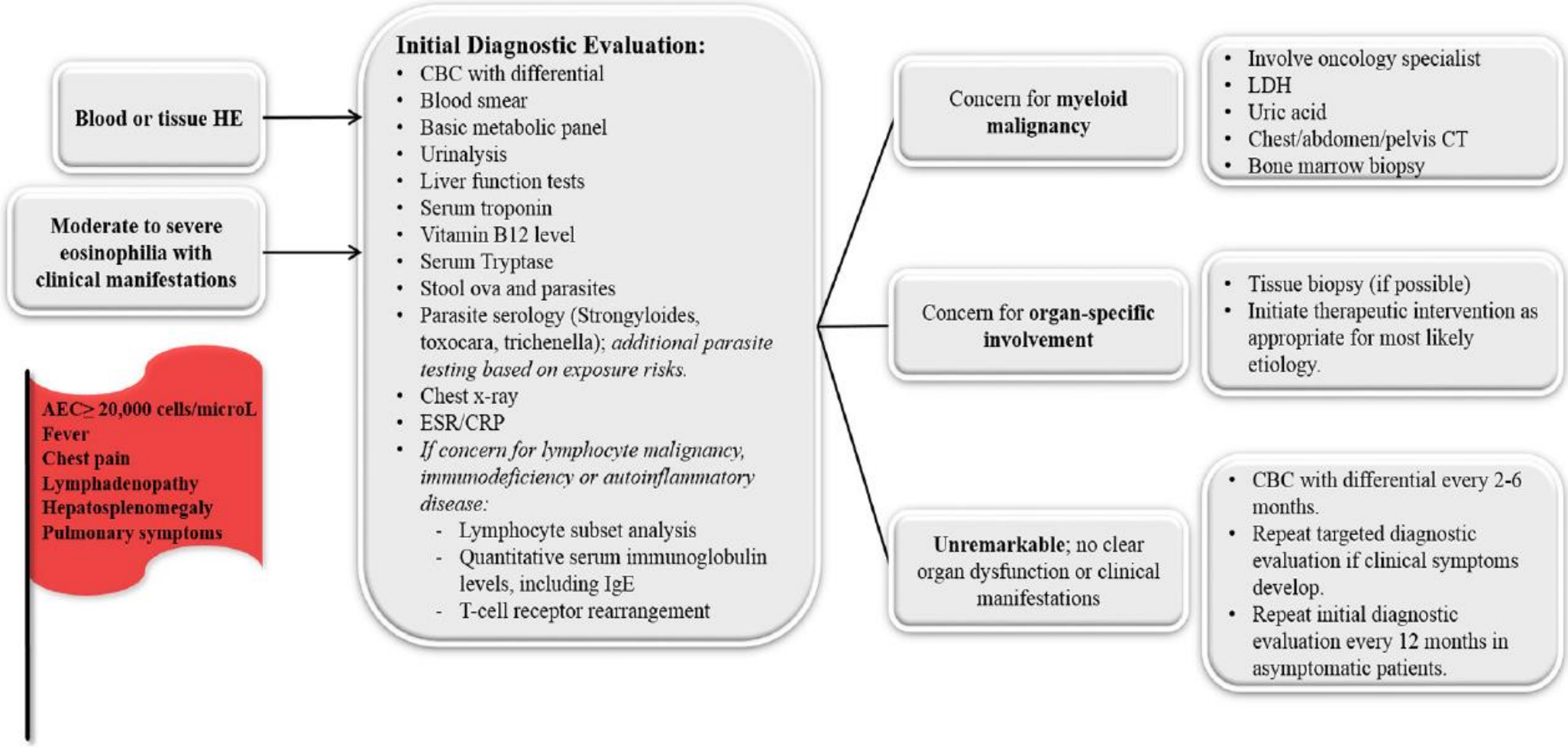
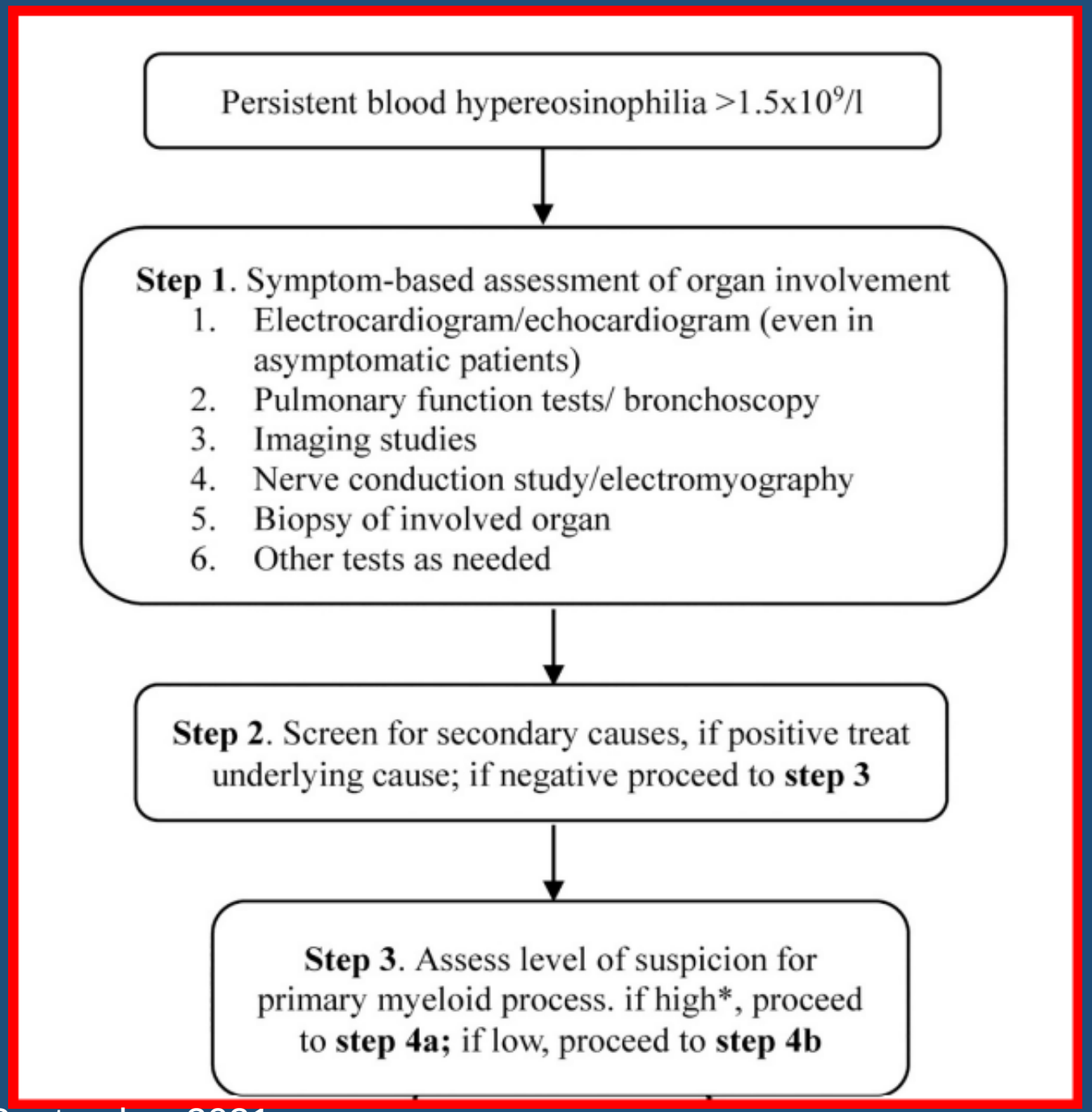


FIGURE 2 | Diagnostic approach for the child who presents with unexplained hypereosinophilia (HE) and/or moderate-to-severe eosinophilia with clinical manifestations. Concerning symptoms/laboratory findings that should prompt medical providers to pursue more intensive evaluation are noted in the red flag. ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; LDH, lactate dehydrogenase.

All patients with HES	
Complete blood count*	
Routine chemistries, including liver function tests*	
Quantitative serum immunoglobulin levels, including IgE	
Serum troponin*, echocardiogram	If abnormal, cardiac MRI should be considered as this may show characteristic features of eosinophilic involvement; tissue involvement may be patchy limiting the utility of biopsy
Pulmonary function tests*	
Chest/abdomen/pelvis CT*	To assess for splenomegaly, lymphadenopathy, and occult neoplasms
Bone marrow biopsy, including cytogenetics*	Recommended in all patients with AEC $> 5.0 \times 10^9$/L and features of M-HES or L-HES. Should be considered in other patients
Biopsies of affected tissues (if possible)*	
Other testing as indicated by history, signs, and symptoms	Including parasitic serologies, anti-neutrophil cytoplasmic antibodies, and HIV
Serum tryptase and B_{12} levels	
FIP1L1/PDGFRA analysis by FISH or RT-PCR	Testing of peripheral blood is sufficient
T- and B-cell receptor rearrangement studies	
Lymphocyte phenotyping by flow cytometry*	At a minimum CD3, CD4, and CD8 and CD19 or 20 staining should be performed to assess for aberrant $CD3^-CD4^+$, $CD3^+CD4^+CD8^+$, and $CD3^+CD4^-CD8^-$ populations and B-cell lymphoproliferative disorders



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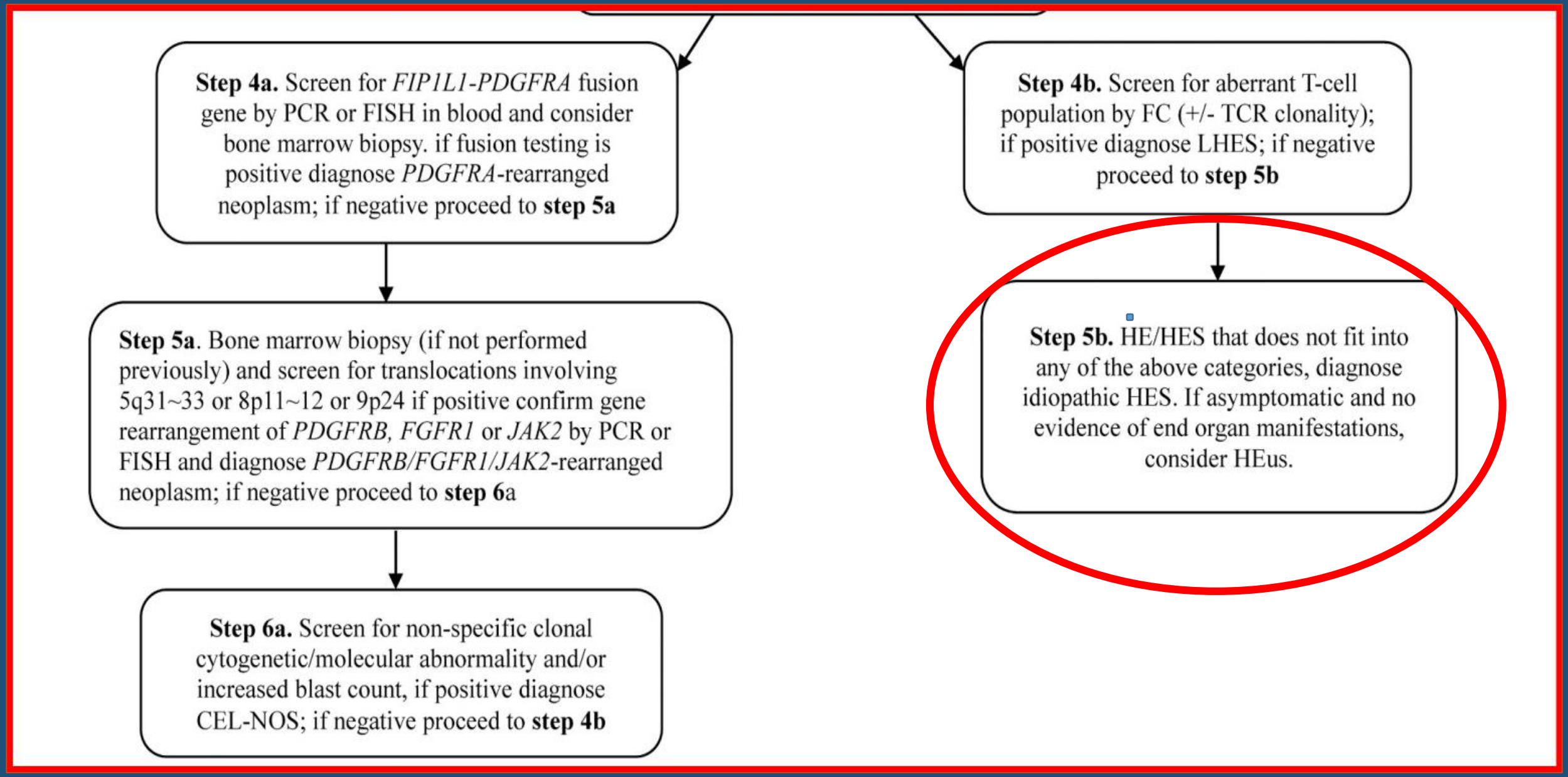

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Table 3. Initial assessment of the patient with hypereosinophilia

All patients with confirmed HE	Comments
Comprehensive history and physical examination	Including prior eosinophil counts, medications, travel/exposure history
Complete blood count with differential and smear*	Dysplastic eosinophils, other lineage involvement, and/or presence of myeloid precursors are suggestive of (but not diagnostic for) MHES
Routine chemistries, including liver function tests*	To assess end organ involvement
Quantitative serum immunoglobulin levels	IgE levels are typically elevated in a variety of conditions (ie, LHES, EGPA, parasitic infections, and some immunodeficiencies); IgM levels are elevated in LHES and episodic angioedema and eosinophilia
Serum tryptase and B12 levels	Elevated serum B12 levels can be seen in many myeloid neoplasms; elevated serum tryptase is near universal in *PDGFRA* and *KIT*-associated disease
T- and B-cell receptor rearrangement studies*; lymphocyte phenotyping by flow cytometry* (see Carpentier et al[11])†	Clonal and/or aberrant T-cell populations are characteristic of LHES and some types of lymphoma. Clonal B cells are suspicious for B-cell neoplasm, including pre–B-cell acute lymphoblastic leukemia in children/adolescents.
Serum troponin,* electrocardiogram, and echocardiogram	If abnormal, cardiac MRI should be considered
Chest/abdomen/pelvis CT*	To assess for splenomegaly, lymphadenopathy, asymptomatic pulmonary involvement, and occult neoplasms
Biopsy of affected tissues (if possible)*	Cardiac tissue involvement can be patchy, limiting the utility of cardiac biopsy
Selected patients with HE/HES	
Pulmonary function tests*	Any patient with suspected pulmonary involvement or abnormal findings on chest CT
Bone marrow aspirate and biopsy*	All patients with AEC >5.0×10⁹/L and/or features suggestive of LHES or MHES; patients with clear diagnoses, such as EGPA or parasitic infection, may not need bone marrow testing despite AEC >5.0×10⁹/L
Testing for *BCR::ABL1*, *FIP1L1::PDGFRA*, and translocations/mutations involving *PDGFRB*, *JAK2*, *FGFR1*, and *KIT*	Testing should be guided by results of initial testing and bone marrow examination; all patients with elevated serum tryptase and/or B12 levels should be tested for *FIP1L1::PDGFRA*
NGS myeloid panel; targeted or whole-exome sequencing; other genetic testing	Depending on initial evaluation
PET scan,* EBV viral load	Particularly in patients with suspected LHES
Other testing for secondary causes	As indicated by clinical history and physical examination

The decision to initiate urgent therapy depends on AEC, severity of the clinical presentation and risk of rapid progression

Clinical and lab findings associated with aggressive disease and poor prognosis include:

- AEC > 100,000/mm3,
- signs of congestive heart failure,
- splenomegaly,
- presence of early myeloid precursors on the peripheral smear,
- elevated serum B12, and/or tryptase levels,

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How I treat hypereosinophilic syndromes

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Hypereosinophilic syndromes (HESs) are a group of rare disorders characterized by peripheral blood eosinophilia of 1.5×10^9/L or higher and evidence of end organ manifestations attributable to the eosinophilia and not otherwise explained in the clinical setting. HESs are pleomorphic in clinical presentation and can be idiopathic or associated with a variety of underlying conditions, including allergic, rheumatologic, infectious, and neoplastic disorders. Moreover, the etiology of the eosinophilia in HESs can be primary (myeloid), secondary (lymphocyte-driven), or unknown. Although corticosteroids remain the first-line therapy for most forms of HESs, the availability of an increasing number of novel therapeutic agents, including tyrosine kinase inhibitors and monoclonal antibodies, has necessarily altered the approach to treatment of HESs. This review presents an updated treatment-based approach to the classification of patients with presumed HES and discusses the roles of conventional and novel agents in the management of these patients. (*Blood*. 2015;126(9):1069-1077)

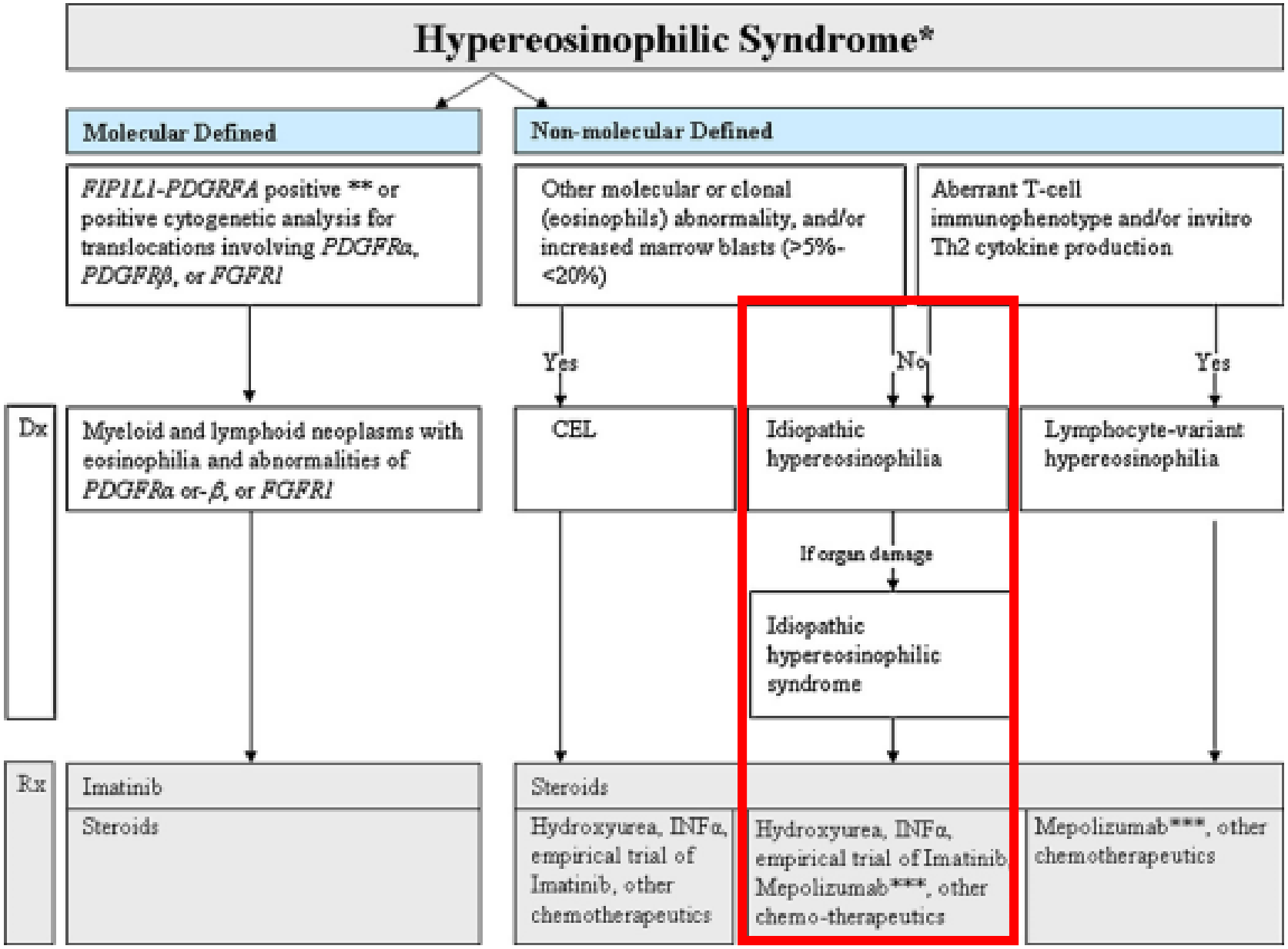
Decision to treat

- The first step is to assess the need for urgent intervention ?? Biomarkers are lacking !! I

- All patients with FIP1L1-PDGFRA and features suggestive of M-HES require treatment to prevent disease progression.

- Patients with HE_{US} who select to hold treatment should be monitored closely (every 3 months for the first 1 to 2 years) for the development of clinical manifestations of HES.

- When life-threatening manifestations are present or imminent, high-dose corticosteroid therapy should be initiated immediately.
- Recommended dosing ranges from 1 mg/kg prednisone to 1 g methylprednisolone depending on the severity of the clinical manifestations.
- If the eosinophil count and symptoms do not improve after 1 to 2 days of high-dose corticosteroid therapy, a second agent should be added to rapidly lower the eosinophil count.
- Imatinib mesylate is most appropriate if MPN is suspected but is unlikely to be effective in a patient with lymphocyte- HES.
- Additional agents that have been used to rapidly lower eosinophils in steroid-refractory patients include: high-dose hydroxyurea, vincristine, and mepolizumab (humanized anti-interleukin -5 antibody).


Hypereosinophilic Syndrome*
Molecular Defined
Non-molecular Defined
FIP1L1-PDGRFA positive ** or positive cytogenetic analysis for translocations involving PDGFRα, PDGFRβ, or FGFR1
Other molecular or clonal (eosinophils) abnormality, and/or increased marrow blasts (>5%-<20%)
Aberrant T-cell immunophenotype and/or invitro Th2 cytokine production
Yes
No
Yes
Dx
Myeloid and lymphoid neoplasms with eosinophilia and abnormalities of PDGFRα or-β, or FGFR1
CEL
Idiopathic hypereosinophilia
Lymphocyte-variant hypereosinophilia
If organ damage
Idiopathic hypereosinophilic syndrome
Rx
Imatinib
Steroids
Steroids
Hydroxyurea, INFα, empirical trial of Imatinib, other chemotherapeutics
Hydroxyurea, INFα, empirical trial of Imatinib Mepolizumab***, other chemo-therapeutics
Mepolizumab***, other chemotherapeutics

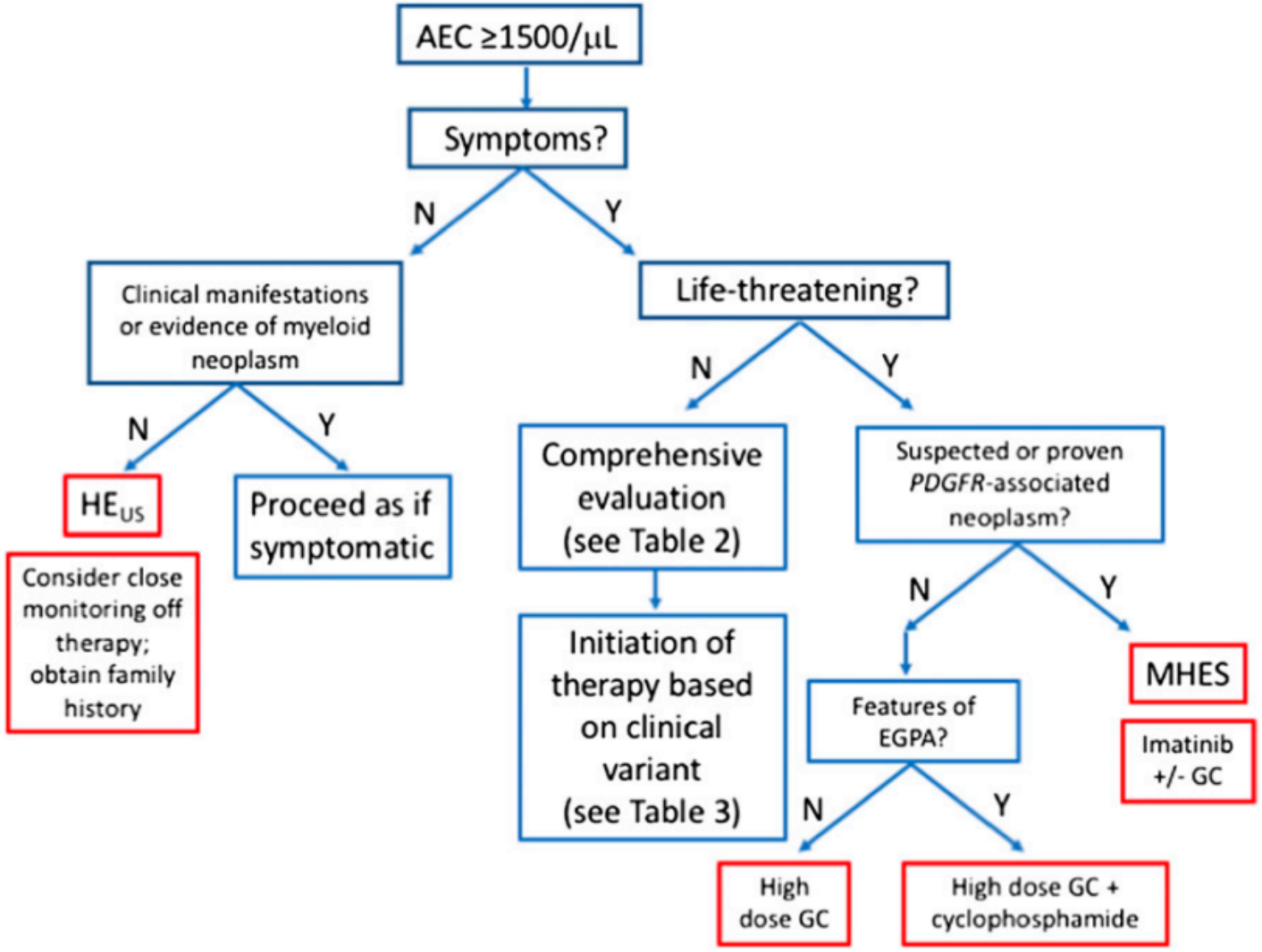
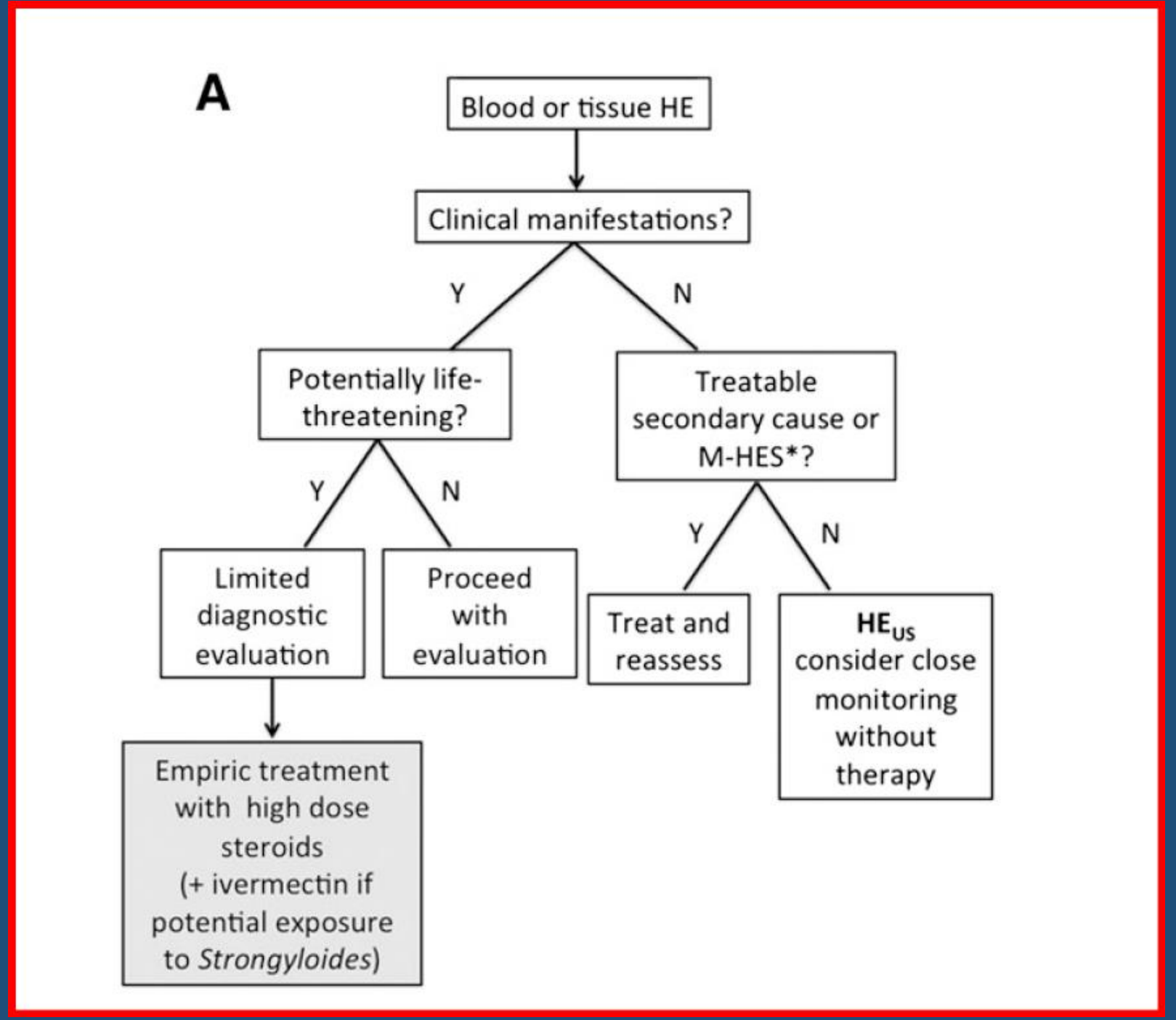


Figure 1. Initial approach to the treatment of a patient presenting with hypereosinophilia. GC, glucocorticoid; HE$_{US}$, hypereosinophilia of unknown significance; N, no; Y, yes.



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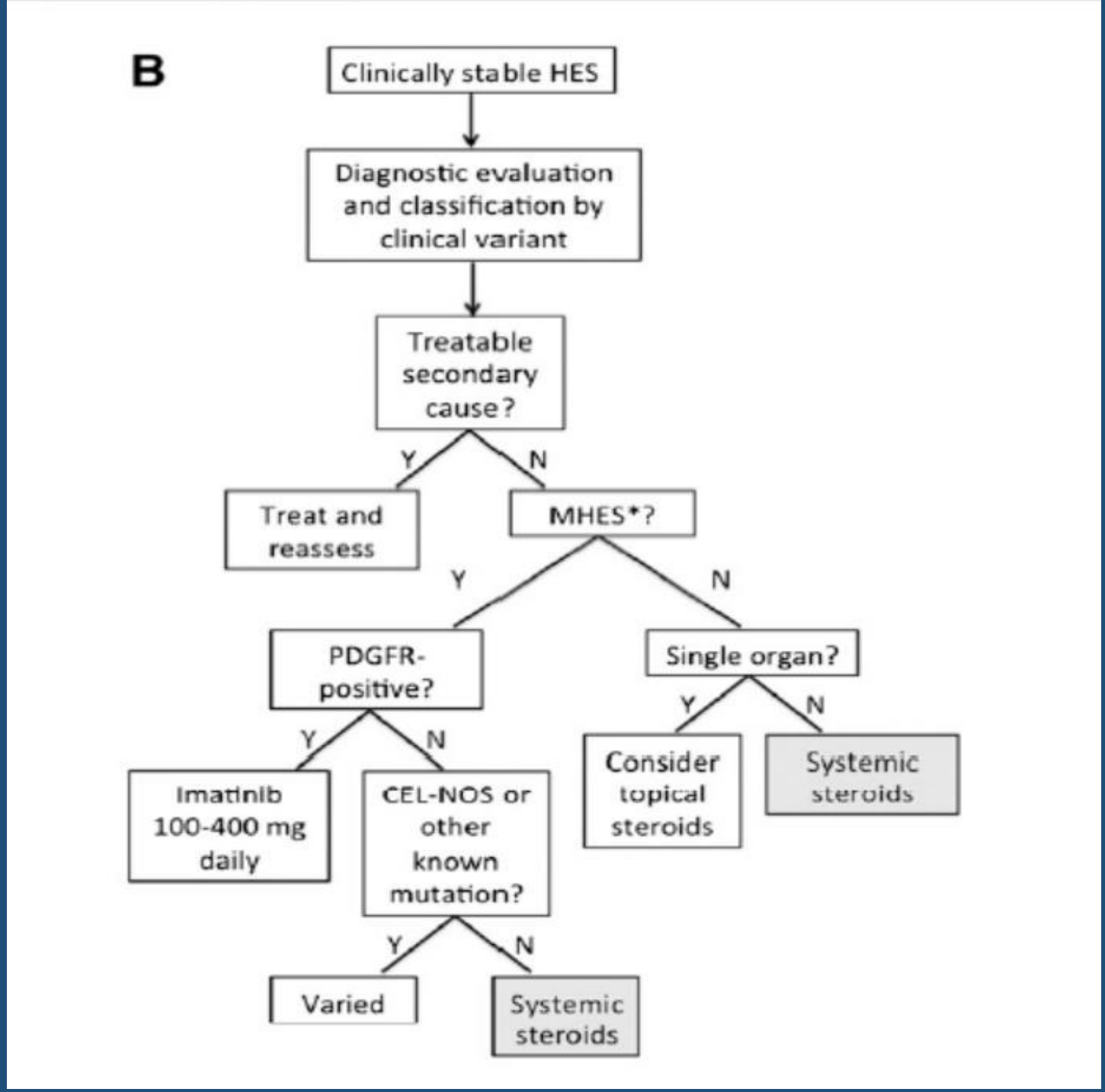
(A) presumed HES



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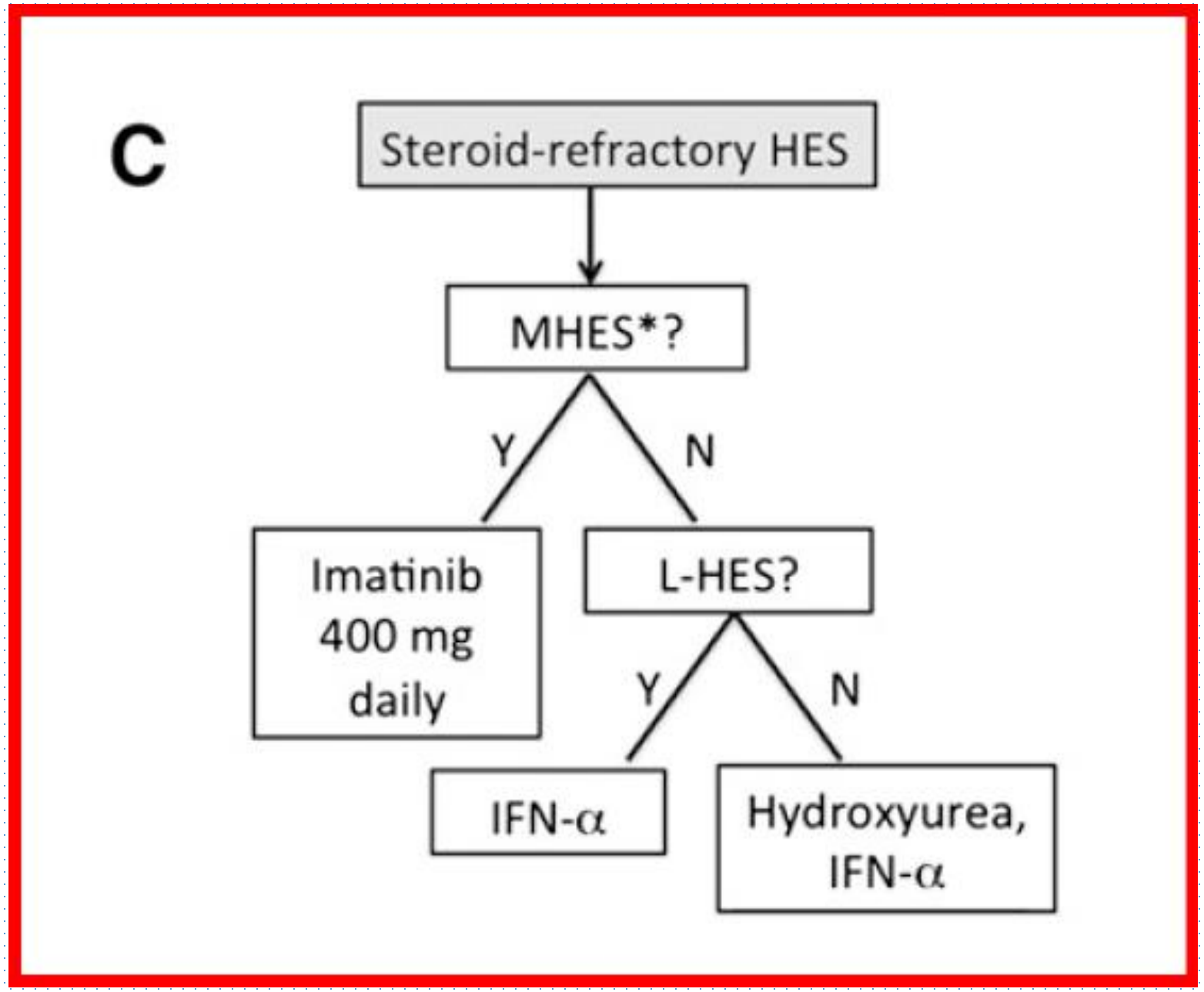
(B) clinically stable HES



(C) steroid-resistant HES

Table 3. HES therapy

Drug	Usual dosing	Side effects*	Comments
Imatinib	100-400 mg orally	Cytopenias, hepatitis, diarrhea, edema, necrotizing myocarditis	First line for *PDGFR*-associated myeloid neoplasms, second line for other forms of MHES
Prednisone	Varied, oral, swallowed, or intravenous	Weight gain, osteopenia, diabetes, mood disturbance	First line for most *PDGFR*-negative HES; adjunct for *PDGFRA* positive with cardiac involvement
Hydroxyurea	1-2 g/d, oral	Cytopenias, diarrhea	Second line for idiopathic HES and *PDGFRA*-negative MHES; low dose may potentiate activity of interferon-α
Interferon-α	1-3 mU subcutaneously daily or 3 times per week; varied (pegylated)	Flu-like symptoms, depression, cytopenias, hypothyroidism, neuropathy, liver toxicity	Second line for all forms of HES; preferred second line for LHES
Methotrexate	7.5-20 mg weekly, orally or subcutaneously	Cytopenias, liver toxicity, pneumonitis, desquamative skin rash, encephalopathy, secondary malignancy	Alternative second-line agent for EGPA, HES with pulmonary involvement
Cyclosporine	150 mg daily orally	Nephrotoxicity, hypertension, neurotoxicity, secondary malignancy	Little data to support use in HES, although anecdotal reports of efficacy in LHES

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NEWS & VIEWS

Algorithms in Allergy and Clinical Immunology

Medical algorithm: Diagnosis and treatment of hypereosinophilic syndrome

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Keywords: allergy diagnosis, allergy treament, eosinophils, hypereosinophilic syndrome

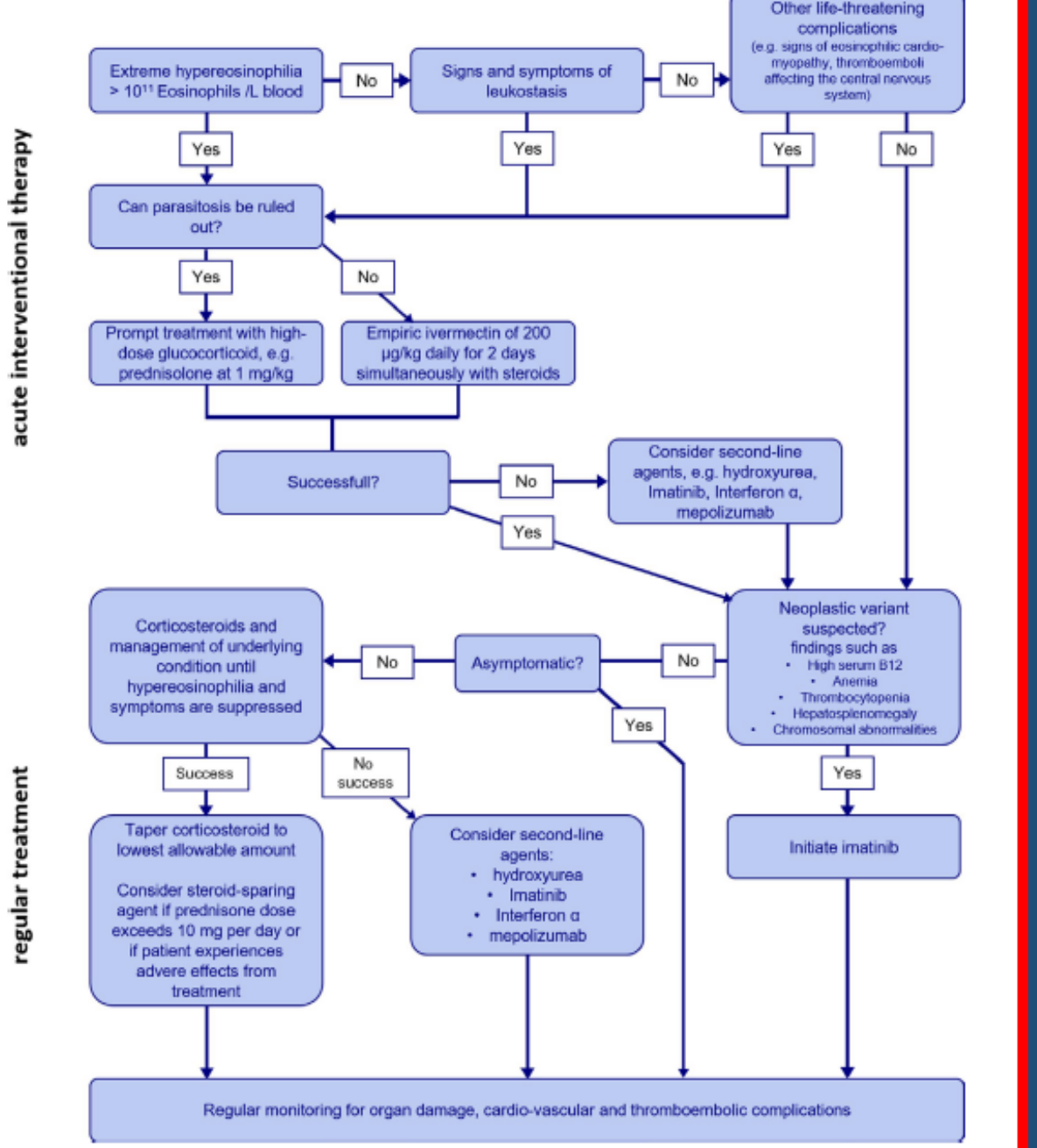
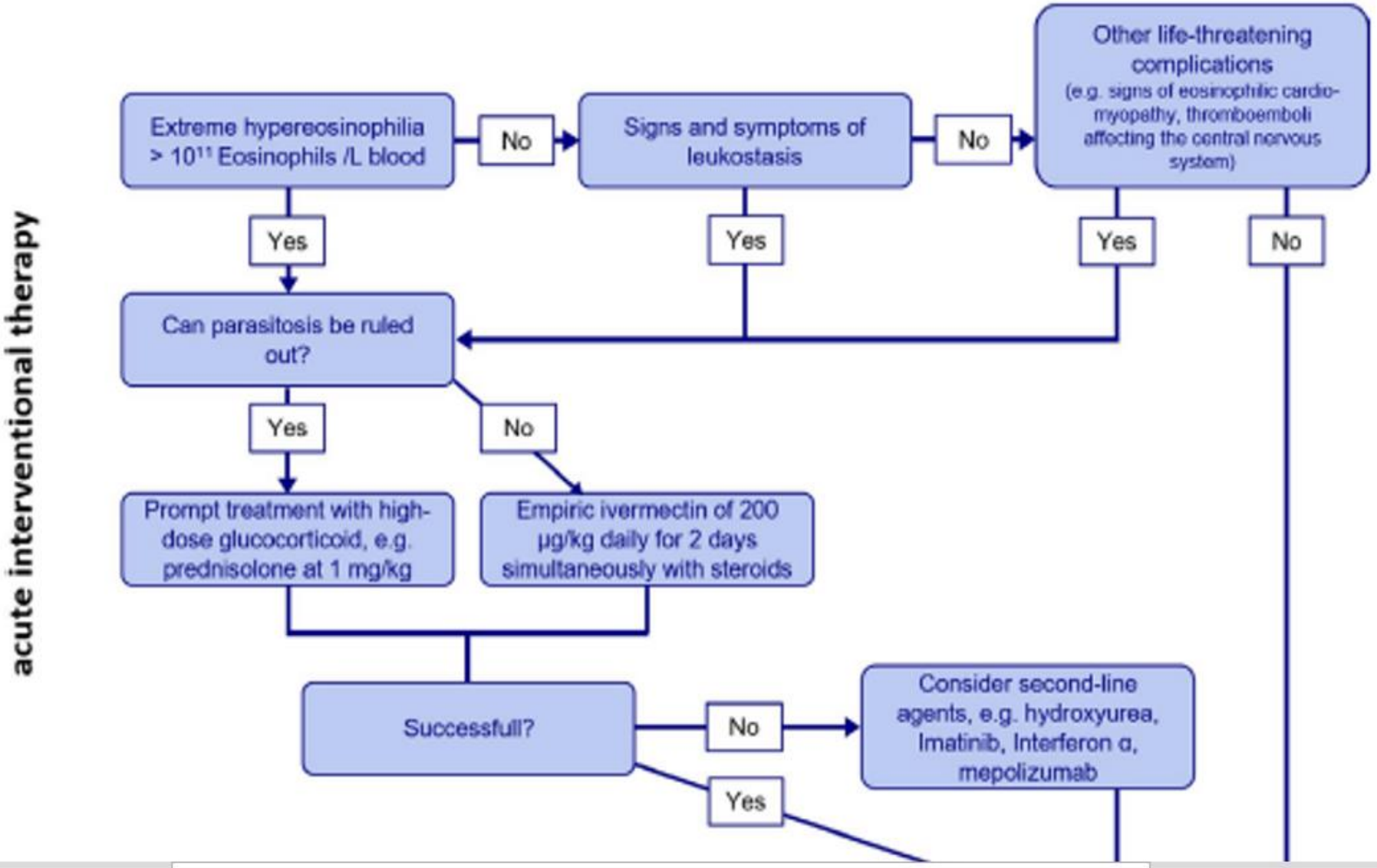
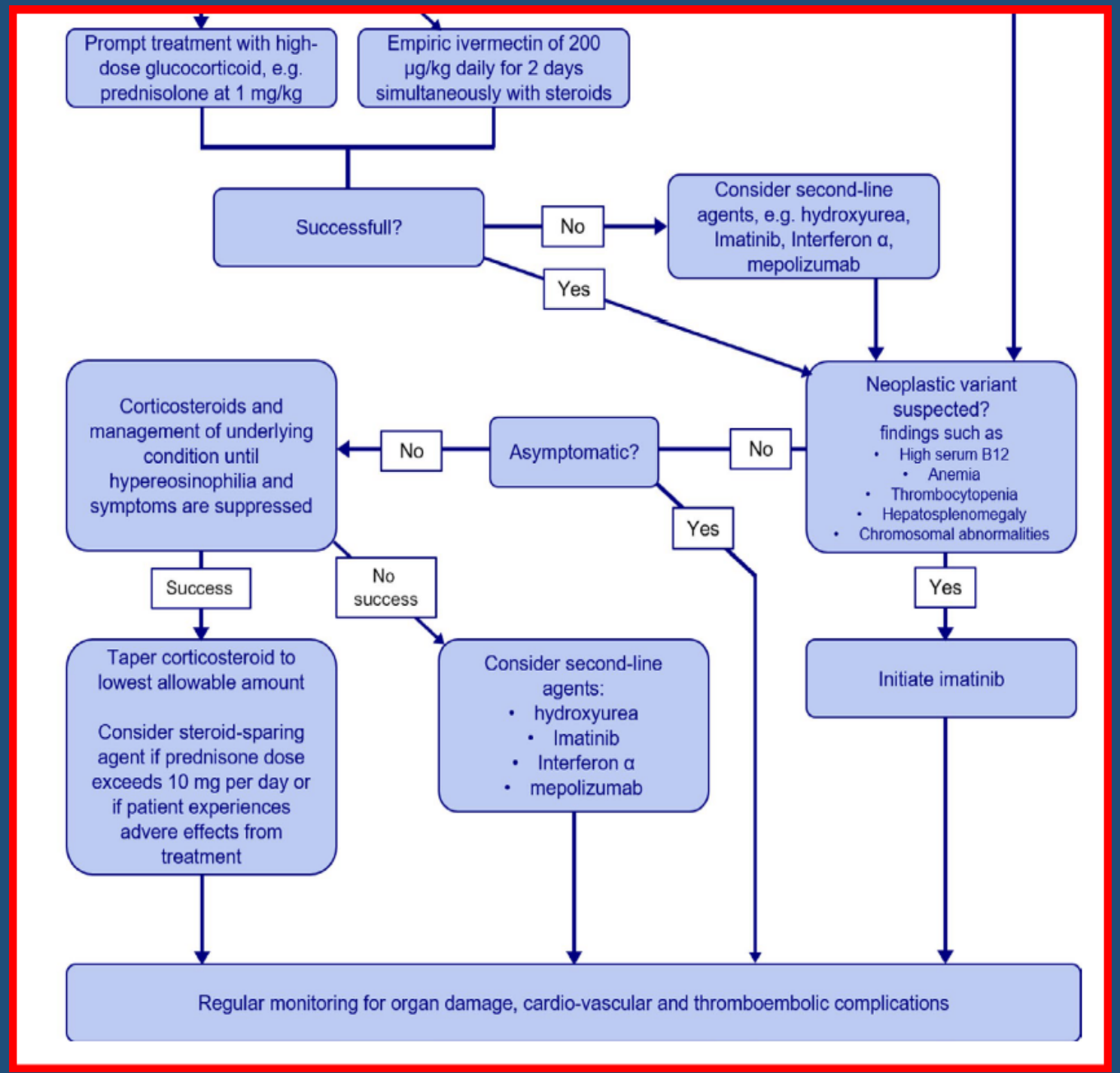


FIGURE 2 Medical algorithm for the treatment of hypereosinophilic syndrome

Treatment Algorithm for Hypereosinophilic Syndrome





Allergy. 2020;75:3003–3006.

Therapy for eosinophil-related disorders.

Disease category	Most common therapies	Suggested doses
PDGFRA-rearranged neoplasm	Imatinib	100–400 mg daily
PDGFRB-rearranged neoplasm	Imatinib	400 mg daily
FGFR1-rearranged neoplasm	Chemotherapy followed by allo-SCT	varied
JAK2-rearranged neoplasm	Ruxolitinib followed by allo-SCT	varied
Chronic eosinophilic leukemia-not otherwise specified	Hydroxyurea	500–1000 mg daily
	Interferon-α	3–4 mU thrice a week
	Pegylated interferon	90 μg weekly
	Chemotherapy followed by allo-SCT[a]	varied
Idiopathic hypereosinophilic syndrome	Prednisone	varied
	Hydroxyurea	500–2000 mg daily
	Interferon-α	1 mU daily – 3 mU thrice a week
	Pegylated interferon-α-2b	45–90 μg weekly
	Imatinib[a]	400–800 mg daily
	Mepolizumab[b]	300 mg iv/sc monthly
	Chemotherapy followed by allo-SCT[c]	varied
Lymphocytic variant hypereosinophilic syndrome	Prednisone	1 mg/kg daily
	Interferon-α	3–4 mU thrice a week
	Pegylated interferon-α-2b	45–90 μg weekly
	Mepolizumab	300 mg-700 mg iv/sc monthly
	Alemtuzumab	5-30g iv thrice a week

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PDGFR-Associated eosinophilia

- Patients with rearrangements or mutations involving PDGFRA should be treated with imatinib mesylate (100-400 mg daily).

- Corticosteroids (>1 mg/kg prednisone or equivalent) should be administered during the first few days of imatinib therapy in patients with a history of cardiac involvement and/or elevated serum troponin.

- The response to imatinib is typically within days to a few weeks, and complete hematologic and molecular remission is almost universal.

- Although studies demonstrated relapse in PDGFRA-positive patients within 2-3 months of imatinib discontinuation, recent data suggests that cure may be possible in some cases, especially after prolonged molecular remission.

- Molecular relapse typically precedes recurrence of eosinophilia, So testing for the presence of FIP1L1- PDGFRA is recommended every 3-6 months in patients on a stable imatinib dose and every 3 months after drug discontinuation.

- Imatinib resistance is uncommon in PDGFRA-associated MPN but has been reported.

- Newer TKIs, including sorafenib and midostaurin, have in vitro activity against imatinib-resistant mutation (T674I) FIP1L1-PDGFRA fusion with the most common imatinib-resistant mutation (T674I), although only ponatinib has activity against the clinically relevant D842V mutation.

- Successful use of nilotinib as primary therapy for M-HES has been reported in one case series, and both nilotinib and dasatinib have been used as salvage therapy in patients with PDGFRA associated MPN who were intolerant to imatinib.

- Sorafenib has been used in 2 patients with the imatinib-resistant T674I mutation with transient response.

- The use of other TKIs for imatinib resistant M-HES has not been reported to date.

- Patients with aggressive disease who progress despite TKI therapy should be considered for ASCT.

- Imatinib is also first-line therapy for patients presenting with MPN due to rearrangements of PDGFRB, regardless of the fusion partner.

PDGFR-negative M-HES

- High-dose corticosteroids are often effective in the short-term reduction of eosinophilia and clinical manifestations in patients with PDGFR negative M-HES and are useful in the initial management of such patients.

- Unfortunately, many patients show only a transient or partial response and require treatment with additional agents. Although imatinib response rates in PDGFRA-negative HES vary widely (9-60%), PDGFR-negative patients often require higher doses of imatinib and appear to respond more slowly.

- Consequently, imatinib (400 mg daily for > 4 weeks) is recommended. Patients experiencing a suboptimal or partial response should undergo repeat bone marrow examination, because unmasking of pre-B-cell acute lymphocytic leukemia has been reported in patient with a partial response to imatinib.

- The most appropriate therapy for patients who fail steroid and imatinib therapy depends on the severity of the clinical manifestations. Possibilities include hydroxyurea, interferon-a, second- and third-generation TKIs, and allogeneic transplantation.

- Patients with aggressive disease and molecular or cytogenetic abnormalities that are typically resistant to steroid and imatinib therapy, including FGFR1 mutations, represent a special category of PDGFR-negative M-HES and should be considered early for alternative therapies.

- Corticosteroids remain the mainstay of therapy for idiopathic HES. Although high doses are effective in most patients, dosing and duration should be individualized based on the clinical manifestations and risk of end organ damage. Once the eosinophil count has normalized and symptoms have improved, the steroid dose should be tapered slowly with a goal of 10 mg prednisone equivalent or less daily.

- In patients who experience significant steroid side effects or who fail to respond adequately to therapy, a second agent should be added. The most commonly used second-line therapies are hydroxyurea and Interferon a (1-3 mU subcutaneously daily), each of which is effective in 30% of patients.

- Low-dose hydroxyurea (500 mg daily) has been reported to potentiate the effects of interferon-a without increasing toxicity in M-HES and is a reasonable alternative to escalating the interferon dose in HES patients who demonstrate partial response to interferon-a alone.

- Cyclosporine, alemtuzumab, and 2-CDA have been used to treat small numbers of HES patients with some success but with considerable toxicity and are additional options for treatment-refractory patients.

L-HES

- Although corticosteroids are also first-line treatment of L-HES, many patients require moderate to high doses (30-60 mg prednisone daily) to induce and maintain clinical remission.

- When significant steroid side effects develop or eosinophilia and symptoms persist despite corticosteroid therapy, interferon-a is the preferred second-line agent.

- Although in vitro data suggest that interferon-a monotherapy may cause outgrowth of abnormal lymphocyte populations, the utility of concomitant low-dose corticosteroid therapy to enhance apoptosis of these cells in patients with L-HES treated with interferon-a is controversial.

- As in idiopathic HES, other agents, including methotrexate, cyclophosphamide, cyclosporine, and alemtuzumab, have been used as steroid-sparing agents in L-HES with variable success.

Novel therapies and clinical trials

- Mepolizumab, a humanized monoclonal anti-IL-5 antibody, has been the best studied in HES. Monthly mepolizumab was safe and effective in PDGFRA negative patients as a steroid-sparing agent, and also in L-HES.

- Mepolizumab is currently available on clinical protocols for patients with life-threatening HES, refractory to standard therapies.

- Additional novel agents currently in trials for the treatment of HES include: Benralizumab (an monoclonal antibody to IL-5 receptor that has shown efficacy in eosinophilic asthma).

Familial HE/HES

- Familial forms of some eosinophilic disorders, such as EGID, are relatively common and involve environmental and genetic factors.

- In contrast, familial multisystem HES appears to be extremely rare. Autosomal dominant transmission of HE has been mapped to chromosome 5q31-33 in one extended family.

- Of note, although 2 members of the family developed HES with fatal endomyocardial fibrosis and neuropathy, most affected family members have remained asymptomatic despite lifelong HE.

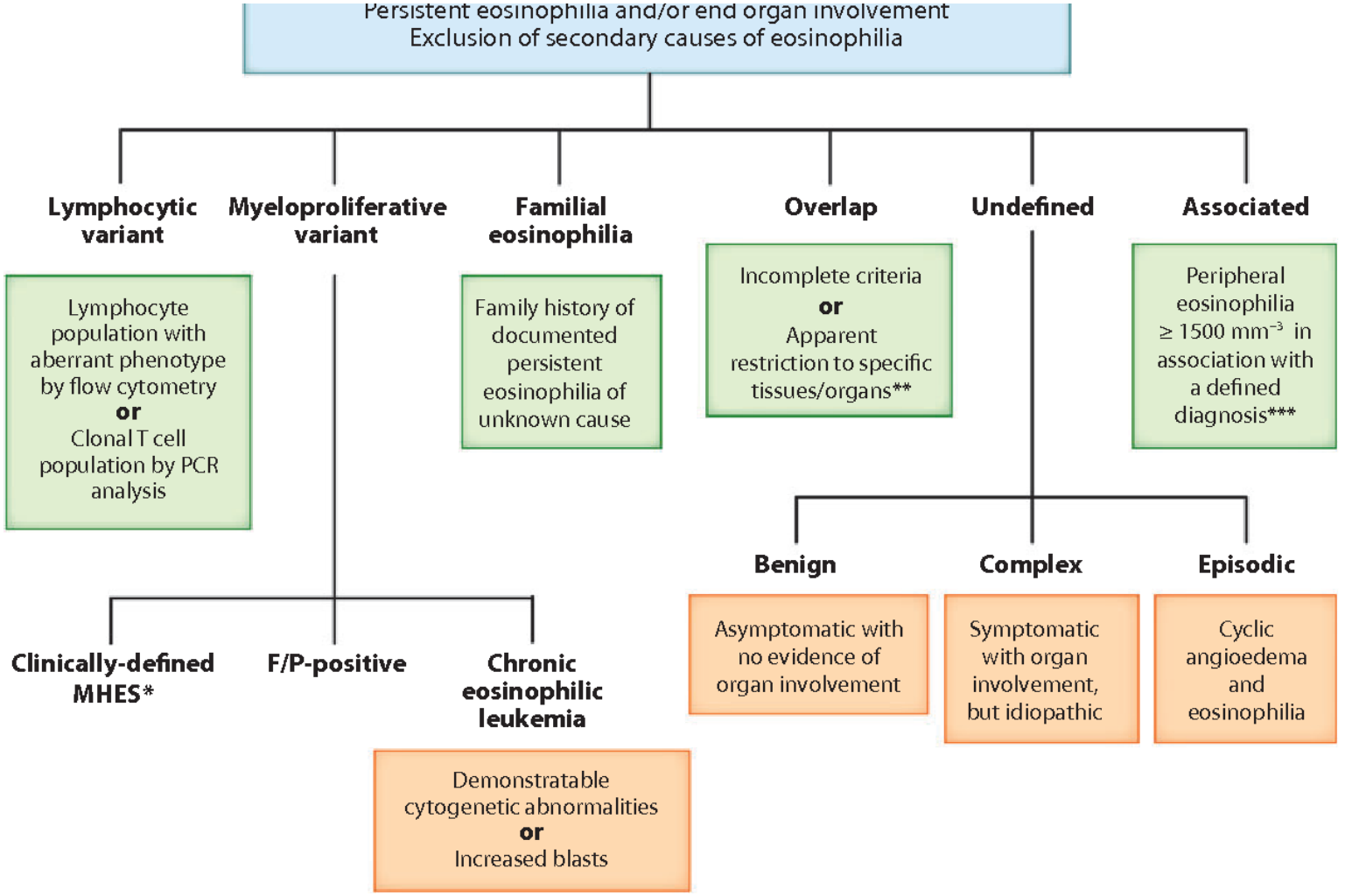

Figure 1

Classification of hypereosinophilic syndrome (HES) variants. *M-HES is clinically defined as peripheral eosinophilia ≥1500 mm^{-3} and at least four of the following features: dysplastic eosinophils on peripheral smear, serum B12 level >1000 pg ml^{-1}, serum tryptase level