

NEWS & VIEWS

Algorithms in Allergy and Clinical Immunology



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Medical algorithm: Diagnosis and treatment of hypereosinophilic syndrome

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Hypereosinophilic syndrome (HES) is a group of rare disorders characterized by persistently elevated eosinophil count and eosinophil-mediated organ damage. The most frequent symptoms are cutaneous (eg, urticaria and angioedema) and respiratory (eg asthma and sinusitis).¹ HES can further cause gastrointestinal, cardiovascular, neurologic, and hematologic involvement, with cardiac manifestations having the most significant implications in terms of morbidity and mortality.² While population-based data are missing, the prevalence has been estimated between 0.3 and 6.3 per 100 000 inhabitants.³ HES needs to be differentiated from other causes of hypereosinophilia such as parasitosis or cancer.⁴

1 | DIAGNOSIS OF HES

According to a multidisciplinary consensus,⁵ the following criteria need to be fulfilled for the diagnosis of HES (Figure 1). First, (blood) hypereosinophilia, which is defined as elevation of absolute eosinophil count in peripheral blood ($>1.5 \times 10^9/L$) on two examinations at least 4 weeks apart, needs to be present in the respective patient. In case of life-threatening organ damage (eg myocardial ischemia, and respiratory failure), a preliminary diagnosis can be established without a second examination of eosinophil count in order to provide immediate care.

Second, there must be evidence of organ damage or dysfunction attributable to tissue hypereosinophilia. Tissue hypereosinophilia can be determined whether (a) the percentage of eosinophils in bone marrow is $>20\%$ of all nucleated cells and/or (b) if tissue infiltration by eosinophils is extensive, according to the opinion of an experienced pathologist and/or (c) a marked deposition of eosinophil granulate proteins is found. Organ damage is defined as at

least one of the following conditions: (a) fibrosis (lung, heart, gastrointestinal system, and skin), (b) thrombosis, (c) cutaneous or mucosal erythema, angioedema, ulceration, pruritus, or eczema, and/or (d) peripheral or central neuropathy with chronic or recurrent neurologic deficit.¹ Occasionally, damage of other organs such as pancreas, liver, and kidney can be judged as eosinophil-mediated, leading to the diagnosis HES without presence of the above mentioned conditions.⁵

Third, other disorders or conditions must be excluded as major reasons for the observed organ damage, meaning the organ damage must be eosinophil-driven. If all three criteria are met, the diagnosis of HES can be established.

Hypereosinophilic syndrome can further be classified according to the pathogenesis of eosinophilia (Figure 1).⁶ If rearrangements of PDGFRA, PDGFRB, FGFR1, or PCM-JAK2 are detected or further indicators of clonal eosinophils apply, HES is classified as neoplastic/myeloproliferative. If eosinophils are polyclonal and eosinophilia is considered mostly cytokine-driven, HES is classified as reactive. Thus, reactive HES comprises many different conditions, ranging from parasitic infections and adverse drug reactions to inflammatory diseases. As an indolent T-cell lymphoproliferative disease, also the lymphocytic variant of HES is considered a subtype of reactive HES. The diagnosis of idiopathic HES can only be established if no underlying cause for HE could be determined despite thorough clinical work-up.

2 | TREATMENT OF HES

Severe cases of HES, in particular extreme hypereosinophilia with an absolute eosinophil count of $>100 \times 10^9/L$, signs and symptoms

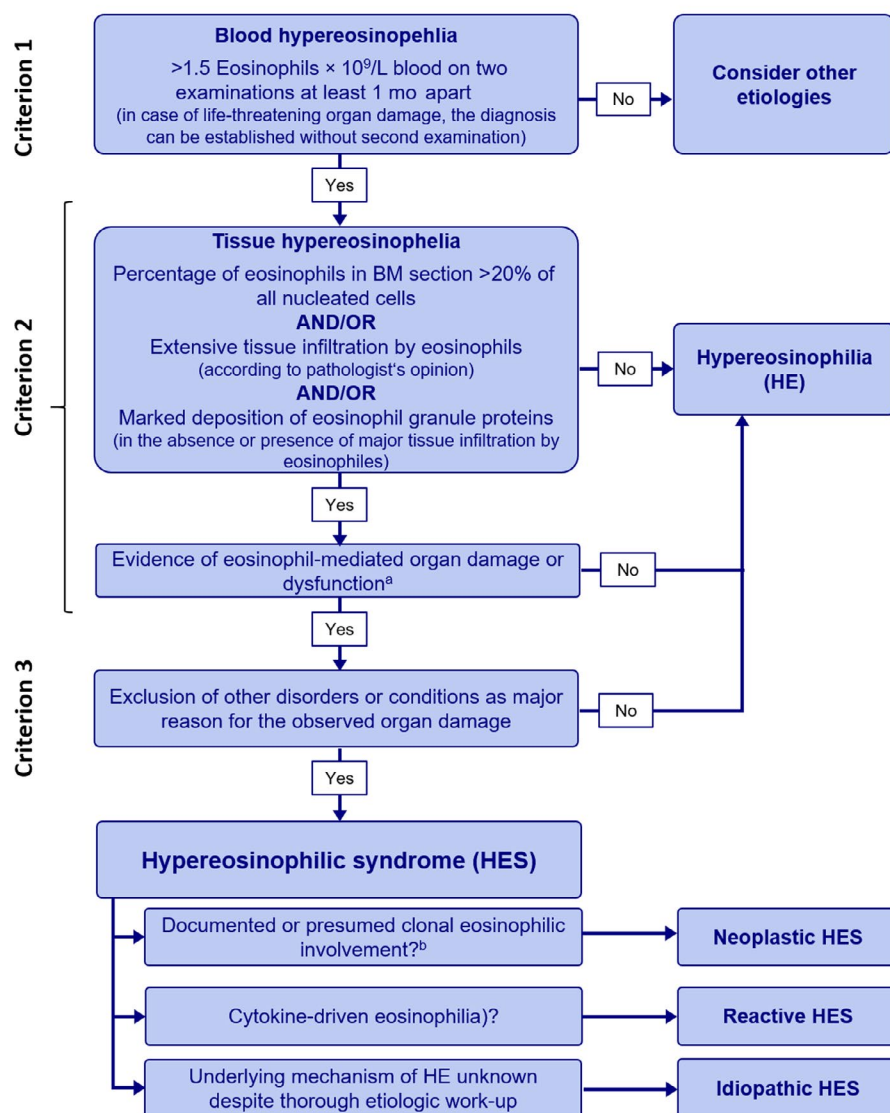
Diagnostic Algorithm for hypereosinophilic syndrome (HES)

FIGURE 1 Medical algorithm for the diagnosis of hypereosinophilic syndrome (HES). ^aAt least one of the following conditions must be present: (a) fibrosis (lung, heart, digestive tract, skin, and others), (b) thrombosis, (c) cutaneous or mucosal erythema, (angio) edema, ulceration, pruritus, or eczema, and/or (d) peripheral or central neuropathy with chronic or recurrent neurologic deficit. ^bGenetic abnormality known to cause clonal eosinophilia (eg, rearrangement of PDGFRA, PDGFRB, FGFR1, or PCM-JAK2) and/or ≥4 of the following features: dysplastic eosinophils, elevated serum vitamin B12 and/or tryptase levels, anemia and/or thrombocytopenia, splenomegaly, bone marrow cellularity >80%, myelofibrosis, atypical mastcells; and/or strong clinical suspicion of a myeloproliferative disorder

of leukostasis or other life-threatening complications require an acute intervention with single stat high-dose glucocorticoids (eg, 1 mg/kg prednisone or even 1 g methylprednisolone; Figure 2).⁷ Prior to initiating treatment, parasitic infections need to be ruled out as corticosteroid treatment can trigger, for example, a fatal strongyloidiasis hyper-infection syndrome.⁸ If parasitosis cannot be ruled out, empiric ivermectin should be administered simultaneously with steroid treatment.⁷ If hypereosinophilia and clinical symptoms did not sufficiently improve within 2 days, a second-line therapy should be added depending on clinical presentation until the absolute eosinophil count has been sufficiently reduced (eg, imatinib if myeloproliferative disease is suspected, cyclophosphamide for eosinophilic vasculitis).^{7,9}

In less severe cases, treatment decisions depend on the type of HES and the clinical symptoms. If findings such as high serum

vitamin B₁₂, anemia, thrombocytopenia, hepatosplenomegaly, or chromosomal abnormalities suggest a myeloproliferative type of HES,² imatinib should be administered. For other forms of HES, symptomatic patients should be treated with corticosteroids and underlying conditions (eg, parasitic infections) need to be managed.⁷ When hypereosinophilia and its symptoms are sufficiently suppressed, corticosteroids should be tapered and steroid-sparing treatment options should be considered where appropriate. If corticosteroid treatment does not yield sufficient results, second-line treatment, for example, with hydroxyurea, imatinib, interferon-α, or mepolizumab, can be considered.⁷ Asymptomatic patients do not require treatment.⁷ However, all patients with HES have to be closely monitored for organ damage and cardiovascular and thromboembolic complications.

Treatment Algorithm for Hypereosinophilic Syndrome

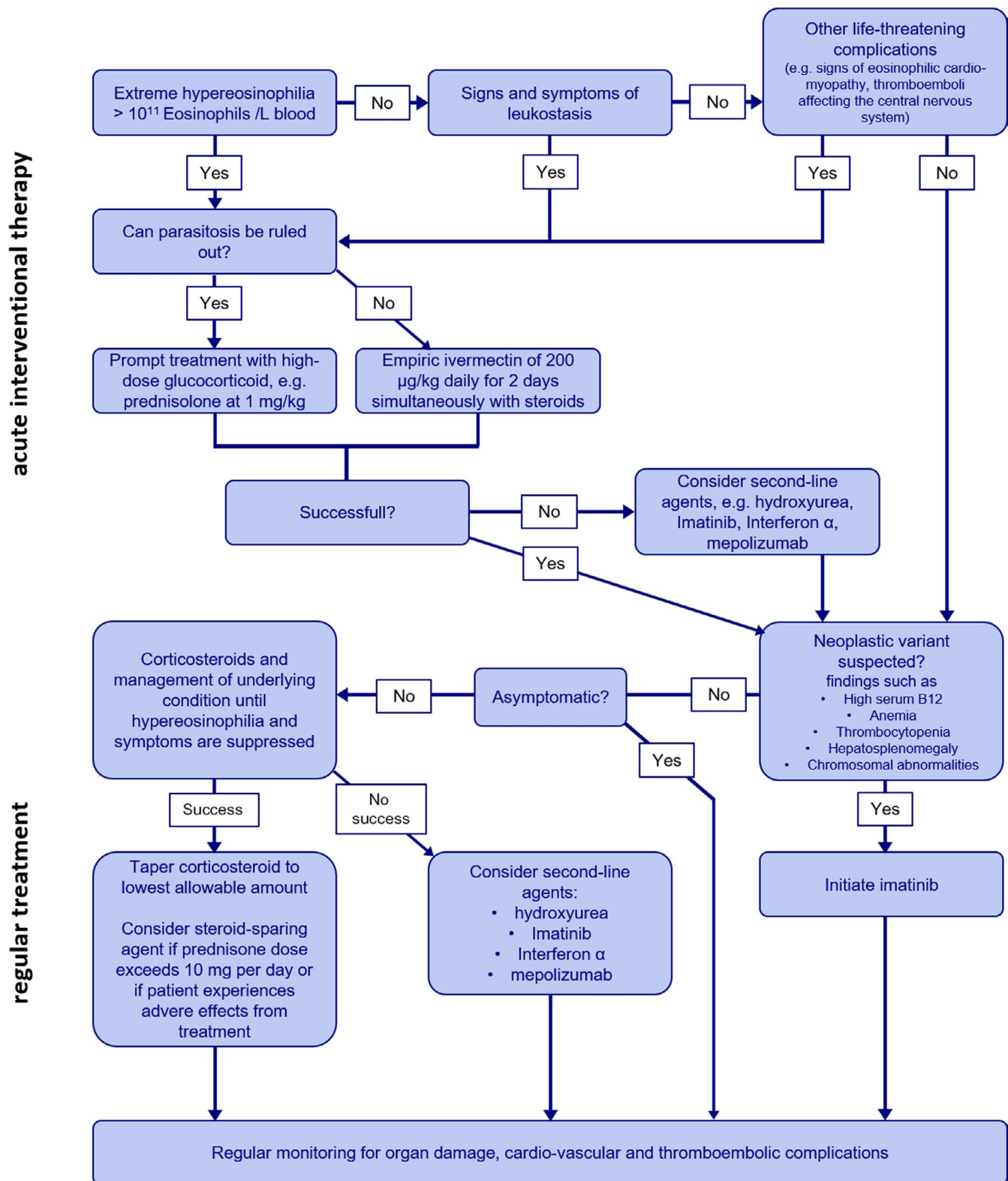


FIGURE 2 Medical algorithm for the treatment of hypereosinophilic syndrome

CONFLICT OF INTEREST

BS has received personal honoraria and grants from Novartis. A. Zink has been an advisor and/or received speaker's honoraria and/or received grants and/or participated in clinical trials of AbbVie, Amgen, Imirall, Beiersdorf Dermo Medical, Bencard Allergie, BMS, Celgene, Eli Lilly, GSK, Janssen Cilag, Miltenyi Biotec, Pfizer, Novartis, Sanofi-Aventis, Takeda Pharma. KE is member or advisory boards and receives speaker's fees from Abbvie, Almirall, BMS, Celgene, Hexal, Janssen, Novartis, Leo, Lilly, Sanofi, UCB.

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