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## Contemporary consensus proposal on criteria and classification of eosinophilic disorders and related syndromes

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## Abstract

Eosinophilia is an important indicator of various neoplastic and nonneoplastic conditions. Depending on the underlying disease and mechanisms, eosinophil infiltration can lead to organ dysfunction, clinical symptoms, or both. During the past 2 decades, several different classifications of eosinophilic disorders and related syndromes have been proposed in various fields of medicine. Although criteria and definitions are, in part, overlapping, no global consensus has been presented to date. The Year 2011 Working Conference on Eosinophil Disorders and Syndromes was organized to update and refine the criteria and definitions for eosinophilic disorders and to merge prior classifications in a contemporary multidisciplinary schema. A panel of experts from the fields of immunology, allergy, hematology, and pathology contributed to this project. The expert group agreed on unifying terminologies and criteria and a classification that delineates various forms of hypereosinophilia, including primary and secondary variants based on specific hematologic and immunologic conditions, and various forms of the hypereosinophilic syndrome. For patients in whom no underlying disease or hypereosinophilic syndrome is found, the term hypereosinophilia of undetermined significance is introduced. The proposed novel criteria, definitions, and terminologies should assist in daily practice, as well as in the preparation and conduct of clinical trials.

## Keywords

Hypereosinophilic syndrome; eosinophilic leukemia; criteria; classification; hypereosinophilia of undetermined significance

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Eosinophilia is observed in patients with various inflammatory and allergic conditions, as well as diverse hematologic malignancies.<sup>1–3</sup> In hematopoietic stem cell and myeloid neoplasms, eosinophils originate from a malignant clone, whereas in other conditions and disorders, (hyper)eosinophilia is considered a nonneoplastic process triggered by eosinophilopoietic cytokines or by other as yet unknown processes.<sup>1–3</sup> Peripheral blood eosinophilia can be transient, episodic, or persistent. In patients with chronic (persistent) eosinophilia, tissue infiltration and the effects of eosinophil-derived effector molecules might result in clinically relevant organ pathology or even in (irreversible) organ damage.<sup>4–6</sup> Notably, among a range of effects on multiple organs, endomyocardial fibrosis, thrombosis, or both might be life-threatening consequences in patients with sustained eosinophilia. In other patients eosinophilia can be persistent but does not lead to measurable organ dysfunction. In these patients the clinical course and outcome remain uncertain; therefore they should be followed for potential disease progression.

Several neoplastic conditions are associated with eosinophilia. Myeloid neoplasms variably accompanied by eosinophilia are chronic myeloid leukemia (CML), other myeloproliferative neoplasms (MPNs), distinct variants of acute myeloid leukemia, rare forms of myelodysplastic syndromes (MDSs), some MDS/MPN overlap disorders, and a subset of patients with (advanced) systemic mastocytosis (SM).<sup>7–9</sup> These differential diagnoses have

to be considered in cases of unexplained eosinophilia, especially when signs of myeloproliferation are present. In such patients a thorough hematologic workup, including bone marrow (BM) cytology, histology and immunohistochemistry, cytogenetics, molecular analyses, and staging of potentially affected organ systems, should be initiated. In patients with eosinophilic leukemia, hypereosinophilia (HE) is a consistent and predominant feature. Most serious complications of HE (ie, endomyocardial fibrosis, thrombosis, or both) are particularly prone to develop in these patients, especially in the setting of fusion genes involving platelet-derived growth factor receptor  $\alpha$  (*PDGFRA*). This is important clinically because imatinib is usually an effective therapy in patients with *PDGFRA* fusion genes and leads to complete hematologic and molecular remission in a high proportion of cases.<sup>2,3,8–10</sup>

During the past 2 decades, several different classifications of eosinophilic disorders have been proposed in various fields of medicine.<sup>11–14</sup> Although respective criteria and definitions partially overlap, no multidisciplinary global consensus has been developed. In addition, the recent identification of several new molecular and immunologic mechanisms lends greater understanding to the disorders and therefore to logical taxonomy.

To update and refine the criteria and definitions for eosinophilic disorders and to merge classifications in a multidisciplinary consensus, we organized the Year 2011 Working Conference on Eosinophil Disorders and Syndromes (Vienna, Austria; May 27–28, 2011). Experts from the fields of immunology, allergy, hematology, pathology, and molecular medicine contributed to this project. All faculty members actively participated in preconference and postconference discussions (from October 2010 to August 2011). The final outcomes of these discussions were formulated into consensus statements and into a contemporary multidisciplinary classification of eosinophilic disorders and related syndromes together with proposed criteria that are summarized in this article.

## BIOLOGY OF EOSINOPHILS AND NORMAL LABORATORY VALUES

Under normal physiologic conditions, eosinophil production is tightly controlled by the cytokine network.<sup>4,5,8</sup> The normal eosinophil count in peripheral blood ranges between 0.05 and  $0.5 \times 10^9/L$ . Normal values for BM eosinophils also have been proposed, and in textbooks normal values of eosinophils in BM aspirates commonly range between 1% and 6%. Eosinophils are not normally present in other human tissues and organs, with the exception of the thymus, spleen, lymph nodes, uterus, and gastrointestinal tract from the stomach through the large intestine. The normal physiologic range of eosinophils in these organs is less well defined.<sup>4–6,15</sup>

Similar to other leukocytes, eosinophils originate from CD34<sup>+</sup> hematopoietic precursor cells.<sup>4,5,8</sup> The most potent growth factors for eosinophils are IL-5, GM-CSF, and IL-3.<sup>4,5,8</sup> These eosinophilopoietic cytokines are primarily produced by activated T lymphocytes, mast cells, and stromal cells and trigger not only growth but also activation of normal and neoplastic eosinophils.<sup>4–6</sup> Apart from these classical growth regulators, several other cytokines and chemokines also trigger eosinophil growth and/or function. Reactive eosinophilia is mainly caused by eosinophilopoietic cytokines (IL-3, IL-5, and GM-CSF), whereas clonal eosinophils typically are derived from progenitors containing mutations in

oncogenic tyrosine kinase receptors, such as *PDGFRA*, platelet-derived growth factor receptor  $\beta$  (*PDGFRB*), or fibroblast growth factor receptor 1 (*FGFR1*), or other acquired (cyto)genetic lesions.<sup>7–10</sup> Eosinophils produce and store a number of biologically active molecules in their granules, such as eosinophil peroxidase, eosinophil cationic protein, major basic protein, and numerous cytokines, including TGF- $\beta$ .<sup>4–6</sup> Under various conditions, eosinophils are activated to release their mediators and thereby influence tissue homeostasis and integrity. In the setting of massive and persistent activation, eosinophils cause profound changes in the microenvironment, often with resultant fibrosis, thrombosis, or both and thus severe organ damage.<sup>4–6</sup> In patients with such persistent eosinophil activation, tissue specimens might show marked deposition of eosinophil granule proteins, even in the absence of a massive eosinophil infiltrate.<sup>4–6</sup> Recommended stains for visualization and enumeration of eosinophils in organ sections are May-Grunwald-Giemsa and Wright-Giemsa. In the normal BM the eosinophil count ranges between 1% and 6%. Eosinophils are also detectable in the normal mucosal layers of the stomach, small and large bowels, uterus, thymus, spleen, and lymph nodes, but only a few robust studies comparing eosinophil numbers in normal and inflamed organs are available. Other healthy tissues do not contain eosinophils, and no eosinophil-derived proteins can be detected.<sup>15</sup>

## DEFINITION AND CLASSIFICATION OF HE

Traditionally, peripheral blood eosinophilia has been divided into mild ( $0.5\text{--}1.5 \times 10^9/\text{L}$ ), marked ( $>1.5 \times 10^9/\text{L}$ ), and massive ( $>5.0 \times 10^9/\text{L}$ ) eosinophilia. As noted previously, eosinophilia can be transient, episodic, or persistent (chronic). The proposal of this expert panel is that the term HE should be used when marked and persistent eosinophilia has been documented or marked tissue eosinophilia is observed (Table I). The faculty also agreed that the term persistent applies to peripheral blood eosinophilia recorded on at least 2 occasions with a minimum time interval of 4 weeks (except when immediate therapy is required because of HE-related organ dysfunction). Because no data from clinical trials are available, further studies will be required to validate this time point against other (traditional) time points regarding duration of eosinophilia. Similarly, further investigations will be required to validate the proposed cutoff level to define blood HE ( $1.5 \times 10^9/\text{L}$ ). Tissue HE should apply when 1 or more of the following is fulfilled: (1) the percentage of eosinophils exceeds 20% of all nucleated cells in BM sections; (2) a pathologist is of the opinion that tissue infiltration by eosinophils is extensive (massive) when compared with the normal physiologic range, compared with other inflammatory cells, or both; or (3) a specific stain directed against an established eosinophil granule protein (eg, major basic protein) reveals extensive extracellular deposition of eosinophil-derived proteins indicative of local eosinophil activation (Table I). This third criterion applies even in the absence of massive local eosinophil infiltration and can be regarded as a sign of marked and persistent eosinophil activation in local tissue sites. However, because the proposed criteria of tissue HE are not based on robust quantitative markers, additional studies will be required to improve the definition and criteria of HE by introducing more quantitative measures and objective parameters in the future. Tissue HE can occur in the absence of blood HE, although in most instances blood HE, or at least eosinophilia, is also present.

On the basis of the initial patient evaluation, HE can be divided into variant types: a hereditary (familial) HE variant,<sup>16</sup> HE of undetermined significance (HE<sub>US</sub>), primary (clonal/neoplastic) HE produced by apparently clonal (neoplastic) eosinophils (HE<sub>N</sub>), and secondary (reactive) HE (HE<sub>R</sub>, Table II). It is important to note that some of these variants (ie, HE<sub>N</sub> and HE<sub>R</sub>) do not represent final diagnoses but are meant as secondary decision points to guide further diagnostic evaluation. For example, a patient with HE<sub>N</sub> might have a *PDGFRA*-mutated MPN-eo or an overt chronic eosinophilic leukemia (CEL). The other HE variants (hereditary [familial] HE variant and HE<sub>US</sub>) are provisional diagnoses but (as is the case for all HE variants) need follow-up investigations to exclude the development of hypereosinophilic syndrome (HES) or an underlying neoplastic or nonneoplastic disorder. The faculty agreed that the term HES should be used for subjects with any HE variant (with blood eosinophilia) and clear evidence of HE-related organ damage, with the exception of certain diseases exemplified by eosinophilic gastroenteritis and eosinophilic pneumonia in which the single-organ involvement is often associated with blood eosinophilia (HE) but the role of eosinophilia in organ damage remains uncertain (see sections below and Table I).

## HE<sub>US</sub>

In addition to patients with HES, who typically require treatment to prevent disease progression, there are patients with unexplained persistent asymptomatic HE. These patients have an uncertain prognosis. For such cases, the term HE<sub>US</sub> is most appropriate. In these patients the criteria for HE are met, but there are no clinical or laboratory signs or symptoms indicative of a hereditary condition, reactive process, underlying immunologic disease, or hematopoietic neoplasm that could lead to and thus explain HE. Furthermore, no signs, symptoms, or other evidence of eosinophil-related organ damage are identified. It is important to state that the designation HE<sub>US</sub> is a proposed provisional term and that the clinical implication and value of this new terminology will require validation in forthcoming studies. If clinical manifestations develop in a patient with HE<sub>US</sub>, the diagnosis will change to idiopathic HES by definition or to single-organ involvement, depending on the identification of an underlying cause found during re-evaluation. An important observation is that patients with HE<sub>US</sub> can remain asymptomatic for some time (maybe even years) in the absence of treatment without evolution to HES or a hematologic or immunologic disorder. Further understanding is required to clarify the pathogenesis of HE<sub>US</sub> and to define risk factors predicting evolution to HES or an overt (eosinophil) neoplasm. The faculty agreed that the proposed term HE<sub>US</sub> might be preferable over older terms, such as unexplained eosinophilia, idiopathic eosinophilia, or chronic idiopathic eosinophilia, for several reasons. First, the term HE defines a (distinct) threshold eosinophil count ( $1.5 \times 10^9/L$ ). Second, unlike the terms “unexplained” or “idiopathic,” the term “of unknown significance” encompasses both the (uncertainty of) pathogenesis and the clinical relevance of the condition. Finally, a diagnosis of HE<sub>US</sub> requires a comprehensive evaluation to exclude HES, an underlying condition responsible for HE, or both. It is also important to examine these patients carefully during follow-up to exclude or document the development of an underlying (neoplastic or reactive) condition (disease), HES, or both. Clinical and laboratory parameters consistent with HE<sub>US</sub> are described in Table E1 in this article’s Online Repository at [www.jacionline.org](http://www.jacionline.org). Finally, it should be stated that blood eosinophilia



not meeting the criteria for HE must also be investigated and followed by the physicians, especially when the condition is persistent and unexplained and accompanied by signs and symptoms suggesting the presence of an underlying disease or organ damage.

## REACTIVE HYPEREOSINOPHILIA (HE<sub>R</sub>)

Patients with HE<sub>R</sub> have an underlying inflammatory, neoplastic, or other disease or condition known to produce HE (see Table E2 in this article's Online Repository at [www.jacionline.org](http://www.jacionline.org)). Eosinophils in patients with HE<sub>R</sub> are considered nonclonal cells. In these patients an underlying hematopoietic neoplasm producing clonal eosinophils has to be excluded by means of histopathologic, cytogenetic, and molecular analyses. Note, however, that HE can also be reactive in hematopoietic neoplasms, such as in Hodgkin lymphoma, T-cell lymphoma, or B-lymphoblastic leukemia/lymphoma with certain molecular defects, such as the translocation t(5;14)(q31;q32) that induces activation of the IL-3 gene. In most patients with HE<sub>R</sub>, eosinophilopoietic cytokines are primary inducers of HE, and overproduction of IL-5 can be documented in many cases.<sup>1-5</sup> However, although IL-5 levels are often measured to confirm the presence of HE<sub>R</sub>, one should be aware that neoplastic eosinophils are sometimes also triggered by (or even produce) such cytokines. Underlying conditions and disorders typically found in patients with HE<sub>R</sub> are listed in Table E2. The faculty concluded that an increase in certain T-cell subsets (by means of flow cytometry) or even clonal T cells (clonal T-cell receptor gene rearrangement) are occasionally found in patients with eosinophilic neoplasms but can also be detected in patients with HE<sub>R</sub>. If such patients have HE-related organ damage and lymphoid cells bear certain phenotypic alterations,<sup>17</sup> the lymphoid variant of HES, which is regarded as a special variant of reactive HES (HES<sub>R</sub>) by several experts, can be diagnosed (Table III). These cases have to be differentiated from patients with hematopoietic stem cell disorders in which both the eosinophils and lymphocytes belong to the neoplastic clone (HE<sub>N</sub>). However, in daily practice clonality of eosinophils is usually not determined directly (ie, in purified eosinophils). The faculty agreed that, for these patients, at least molecular and cytogenetic studies revealing or excluding fusion genes involving *PDGFRA*, *PDGFRB*, *FGFR1*, mutation analysis of Janus kinase 2 (*JAK2*), *BCR/ ABL1*, or other clonal markers (depending on clinical findings) should be applied and used as indirect evidence or for exclusion of a myeloid neoplasm and thus "eosinophil clonality." In addition, mutation analysis of *KIT* (codon 816) and a serum tryptase level should be performed in all patients to exclude (or reveal an) underlying SM.

## HES AND OTHER CONDITIONS ACCOMPANIED BY HE

The faculty agreed that HES is defined by (1) HE with blood eosinophilia, (2) HE-related organ damage, and (3) the absence of an alternative explanation for the observed organ damage (Table I). All 3 criteria must be fulfilled to establish a diagnosis of HES. All experts agreed that these previously established criteria for HES<sup>13,18</sup> remain valid, although the criteria will need refinement and better definition as new pathophysiologic markers emerge. The expert panel supplemented the HES diagnostic criteria by defining eosinophil-related organ damage to consist of eosinophil infiltrates associated with organ dysfunction, which can be associated with 1 or more of the following: (1) fibrosis (eg, lung, heart, digestive

tract, skin, and others); (2) thrombosis with or without thromboembolism; (3) cutaneous (including mucosal) erythema, edema/angioedema, ulceration, or eczema; (4) peripheral or central neuropathy with chronic or recurrent neurologic deficit; and (5) other less common organ manifestations of HES (liver, pancreas, kidney, and others; Table I). In some instances it might be difficult to establish a definite causal relationship between HE and clinical manifestations. For example, central nervous system dysfunction can occur in the absence of overt abnormalities in imaging studies. Moreover, patients might experience nonspecific constitutional symptoms, such as recurrent fever or myalgia, which might be severe. Regression of clinical manifestations with control of HE (during therapy) can provide indirect evidence for the pathogenic role of the eosinophils in such cases.

The term HES applies to all clinical presentations in which blood HE can be documented and HE is directly linked to organ damage, regardless of whether HE can be ascribed to a reactive process, neoplastic process, or another underlying disease. In fact, varied clinical manifestations, such as endomyocardial fibrosis, thrombosis, or thromboembolism, resembling those described in “historically defined HES,” can occur in patients with HE, and if HE-induced organ damage is noted and is attributable to eosinophilia, the diagnosis changes from HE to HES. It is important to recognize that HE-related organ damage in a single organ system is sufficient to call the condition HES, although differentiation of single-organ HES from other disorders in which tissue eosinophilia involves a single organ (ie, allergic sinusitis or eosinophilic esophagitis) and peripheral eosinophilia (blood HE) might also be present, can be challenging. A proposed classification of HES and other conditions and syndromes accompanied by HE is shown in Table III. When HE with associated organ damage (HES) is detected and no underlying disease or syndrome is apparent, the term idiopathic HES should be applied (Table III).

In certain specific conditions and defined syndromes, HE is present, but the cause of the eosinophilia, the role and effect of eosinophils, or both remain uncertain. Table E3 in this article’s Online Repository at [www.jacionline.org](http://www.jacionline.org) provides an overview of selected syndromes accompanied by HE. These conditions should be differentiated from true HES, HE<sub>R</sub>, HE<sub>N</sub>, and organ-restricted specific conditions accompanied by HE (see Tables E4 and E5 in this article’s Online Repository at [www.jacionline.org](http://www.jacionline.org)). In this regard it should also be mentioned that various hematopoietic and nonhematopoietic disorders can cause HE<sub>R</sub> and clinical manifestations that are not necessarily triggered by the accompanying eosinophilia (HE). Distinguishing these conditions from HES and other specific syndromes and conditions accompanied by HE can be a diagnostic challenge. Finally, it should be stated that some patients with HE<sub>R</sub> and HE<sub>N</sub> do not have clinical or laboratory signs of organ damage (HES), even if HE is marked and persistent over many years.

## CLASSIFICATION OF CLONAL (NEOPLASTIC) HYPEREOSINOPHILIA (HE<sub>N</sub>)

The faculty agreed that the criteria and definitions of the World Health Organization (WHO)<sup>12</sup> should provide the basis for classification of hematopoietic neoplasms producing HE (see Table E6 in this article’s Online Repository at [www.jacionline.org](http://www.jacionline.org)), with recognition that refinements and adaptations will be required in the future as new information becomes available. After extensive discussions, experts concluded that the



WHO classification<sup>12</sup> exhibits weaknesses because cytogenetic and molecular variables are listed as primary criteria and that subsequent histologic sub-classification is problematic because both lymphoid and myeloid neoplasms must be lumped together as subvariants into 1 molecular category. In addition, hematopoietic neoplasms can be triggered by more than 1 driver mutation in the same patient, resulting in further subcategorization of myeloid and lymphoid neoplasms (with HE). No diagnostic hierarchy of marker lesions is provided for such cases. The faculty also emphasized that in many WHO-defined neoplasms with eosinophilia, eosinophils are not a major pathogenetic factor. After thorough discussion, the faculty agreed that, in addition to a WHO-related molecular and cytogenetic-based delineation of disease variants, it is important to define robust histopathologic and morphologic criteria for the final hematologic diagnosis, such as acute eosinophilic leukemia or CEL. This is especially important for cases without a molecular or cytogenetic marker (as proof of clonality), in which the diagnosis of CEL can be challenging. A provisional working definition and first proposal is presented in Table E6. The faculty is of the opinion that further discussions will be necessary to merge these provisional working definitions with cytogenetic and molecular parameters.

The following important principles should be considered when creating such definitions and criteria in the future: (1) clonality of eosinophils cannot be documented easily in practice; (2) in many cases the involvement of eosinophils in disease pathology will remain hypothetical; (3) rearranged *PDGFRA*, *PDGFRB*, or *FGFR* genes are not specific for CEL but are also detectable in other hematopoietic neoplasms<sup>19</sup>; and (4) the presence of one WHO-defined neoplasm (one somatic gene defect) does not exclude the coexistence of another myeloid neoplasm, such as CEL, and therefore cannot serve as an exclusion criterion for the other neoplasm. In fact, in some cases both somatic gene defects might be produced by the same clone (subclone formation). In other circumstances a single molecular lesion is detected, but morphologic and immunologic criteria are sufficient to confirm the coexistence of 2 separate neoplasms. One example is SM with coexisting CEL (SM-CEL). In fact, in *KIT D816V*<sup>+</sup> SM, the prediagnostic checkpoint, “SM-eo,” might or might not lead to the final diagnosis of SM-CEL. Conversely, in rare cases of *FIP1L1/PDGFR*<sup>+</sup> CEL, a coexisting SM can be diagnosed. Finally, it should be mentioned that in most myeloid neoplasms (MPN/MDS, MDS, and SM) eosinophilia is of prognostic significance concerning survival.<sup>8</sup> Therefore we believe that eosinophilia, when present, should always be disclosed, preferably by the appendix “-eo” (eg, MDS-eo or SM-eo).

## CONCLUSIONS AND FUTURE PERSPECTIVES

The Year 2011 Working Conference on Eosinophil Disorders and Syndromes was organized with the intent to merge current definitions, criteria, and classifications on eosinophilia and eosinophil-related disorders. Refinements and new definitions, criteria, and terminology proposed by the faculty are based on a multidisciplinary consensus and should assist in daily practice, as well as in the preparation and conduct of clinical trials. In addition, the current proposal might assist in refining the current WHO classification in the near future. Future efforts should also be directed toward defining more accurate minimal diagnostic criteria for tissue HE, for HES-related organ involvement, and for the lymphoid variant of HES. In addition, there is a need to establish flow cytometric and immunohistochemical markers for

immature eosinophils and to study the pathophysiology and natural course of HE<sub>US</sub> and other HE-related conditions. Finally, a consensus on treatment response criteria and follow-up parameters needs to be established. The faculty agreed that the Year 2011 Conference was an important starting point for these initiatives and that a multidisciplinary approach is the key element in a successful classification system and will be essential for continued clinical progress in understanding eosinophilic disorders.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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## Abbreviations used

|                        |  |
|------------------------|--|
| <b>BM</b>              | Bone marrow  |
| <b>CEL</b>             | Chronic eosinophilic leukemia  |
| <b>FGFR</b>            | Fibroblast growth factor receptor  |
| <b>HE</b>              | Hypereosinophilia  |
| <b>HE<sub>N</sub></b>  | Primary (clonal/neoplastic) hypereosinophilia produced by apparently clonal (neoplastic) eosinophils |
| <b>HE<sub>R</sub></b>  | Secondary (reactive) hypereosinophilia   |
| <b>HES</b>             | Hypereosinophilic syndrome   |
| <b>HE<sub>US</sub></b> | Hypereosinophilia of undetermined significance   |
| <b>ICOG-EO</b>         | International Cooperative Working Group on Eosinophil Disorders                                      |
| <b>MDS</b>             | Myelodysplastic syndrome   |
| <b>MPN</b>             | Myeloproliferative neoplasm  |
| <b>PDGFR</b>           | Platelet-derived growth factor receptor  |
| <b>PDGFRA</b>          | Platelet-derived growth factor receptor $\alpha$   |
| <b>PDGFRB</b>          | Platelet-derived growth factor receptor $\beta$  |
| <b>SM</b>              | Systemic mastocytosis  |
| <b>WHO</b>             | World Health Organization  |

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TABLE I

## Definition of HE and HES

| Proposed term                               | Proposed abbreviation | Definition and criteria   |
|---|-----------------------|---|
| Blood eosinophilia                          | —                     | >0.5 Eosinophils $\times 10^9/L$ blood  |
| Hypereosinophilia                           | HE                    | <p>&gt;1.5 Eosinophils <math>\times 10^9/L</math> blood on 2 examinations (interval 1 month<sup>*</sup>) and/or tissue HE defined by the following<sup>†</sup>:</p> <ol style="list-style-type: none"> <li>1 Percentage of eosinophils in BM section exceeds 20% of all nucleated cells and/or</li> <li>2 Pathologist is of the opinion that tissue infiltration by eosinophils is extensive and/or</li> <li>3 Marked deposition of eosinophil granule proteins is found (in the absence or presence of major tissue infiltration by eosinophils).</li> </ol> |
| Hypereosinophilic syndrome                  | HES                   | <ol style="list-style-type: none"> <li>1 Criteria for peripheral blood HE fulfilled<sup>*</sup> and</li> <li>2 Organ damage and/or dysfunction attributable to tissue HE<sup>‡</sup> and</li> <li>3 Exclusion of other disorders or conditions as major reason for organ damage.</li> </ol>   |
| Eosinophil-associated single-organ diseases |                       | <ol style="list-style-type: none"> <li>1 Criteria of HE fulfilled and</li> <li>2 Single-organ disease (see Table III and Tables E4 and E5 for specific entities)</li> </ol>   |

<sup>\*</sup> In the case of evolving life-threatening end-organ damage, the diagnosis can be made immediately to avoid delay in therapy.

<sup>†</sup> Validated quantitative criteria for tissue HE do not exist for most tissues at the present time. Consequently, tissue HES is defined by a combination of qualitative and semiquantitative findings that will require revision as new information becomes available.

<sup>‡</sup> HE-related organ damage (damage attributable to HE): organ dysfunction with marked tissue eosinophil infiltrates and/or extensive deposition of eosinophil-derived proteins (in the presence or absence of marked tissue eosinophils) and 1 or more of the following: (1) fibrosis (lung, heart, digestive tract, skin, and others); (2) thrombosis with or without thromboembolism; (3) cutaneous (including mucosal) erythema, edema/angioedema, ulceration, pruritus, and eczema; and (4) peripheral or central neuropathy with chronic or recurrent neurologic deficit. Less commonly, other organ system involvement (liver, pancreas, kidney, and other organs) and the resulting organ damage can be judged as HE-related pathology, so that the clinician concludes the clinical situation resembles HES. Note that HES can manifest in 1 or more organ systems.

TABLE II

## Classification of HE

| Proposed terminology                        | Proposed abbreviation | Pathogenesis/definition  |
|---|-----------------------|--|
| Hereditary (familial) HE                    | HE <sub>FA</sub>      | Pathogenesis unknown; familial clustering, no signs or symptoms of hereditary immunodeficiency, and no evidence of a reactive or neoplastic condition/disorder underlying HE |
| HE of undetermined significance             | HE <sub>US</sub>      | No underlying cause of HE, no family history, no evidence of a reactive or neoplastic condition/disorder underlying HE, and no end-organ damage attributable to HE           |
| Primary (clonal/neoplastic) HE <sup>†</sup> | HE <sub>N</sub>       | Underlying stem cell, myeloid, or eosinophilic neoplasm, as classified by WHO criteria; eosinophils considered neoplastic cells <sup>*</sup>                                 |
| Secondary (reactive) HE <sup>‡</sup>        | HE <sub>R</sub>       | Underlying condition/disease in which eosinophils are considered nonclonal cells <sup>*</sup> ; HE considered cytokine driven in most cases <sup>‡</sup>                     |

\* Clonality of eosinophils is often difficult to demonstrate or is not examined. However, if a myeloid or stem cell neoplasm known to present typically with clonal HE is present or a typical molecular defect is demonstrable (eg, *PDGFR* or *FGFR* mutations or *BCR/ABL1*), eosinophilia should be considered clonal.

<sup>†</sup> HE<sub>N</sub> and HE<sub>R</sub> are prediagnostic checkpoints that should guide further diagnostic evaluations but cannot serve as final diagnoses.

<sup>‡</sup> In a group of patients, HE<sub>R</sub> might be caused/triggered by other as yet unknown processes because no increase in eosinophilopoietic cytokine levels can be documented.

TABLE III

Classification of syndromes and conditions accompanied by HE

| Variant                                      | Typical findings   |
|--|--|
| HES <sup>*</sup>                             |  |
| Idiopathic HES                               | No underlying cause of HE, no evidence of a reactive or neoplastic condition/disorder underlying HE and end-organ damage attributable to HE  |
| Primary (neoplastic) HES (HES <sub>N</sub> ) |  |
| Secondary (reactive) HES (HES <sub>R</sub> ) | Underlying stem cell, myeloid, or eosinophilic neoplasm classified according to WHO guidelines and end-organ damage attributable to HE, and eosinophils are considered (or shown) neoplastic (clonal) cells. <sup>†</sup>                                |
|  | Underlying condition/disease in which eosinophils are considered nonclonal cells; HE is considered cytokine driven, and end-organ damage is attributable to HE.  |
|  | Subvariant: lymphoid variant HES (clonal T cells identified as the only potential cause) <sup>‡</sup>  |
| Other conditions and syndromes               |  |
| Specific syndromes accompanied by HE         | Specific syndromes in which the effect of eosinophilia remains unclear but the clinical presentation is distinct and accompanied by HE; specific syndromes are listed in Table E3.   |
| Other conditions accompanied by HE           | Mostly organ-restricted conditions in which the effect of eosinophilia remains unclear; an overview of organ-restricted pathologies accompanied by HE is shown in Table E4, and that of skin disorders accompanied by eosinophilia is shown in Table E5. |

<sup>\*</sup> HES is defined as blood HE with (plus) end-organ damage attributable to tissue HE.

<sup>†</sup> Clonality of eosinophils is often difficult to demonstrate or is not examined. However, if a myeloid or stem cell neoplasm known to present typically with clonal HE is present or a typical molecular defect is demonstrable (eg, *PDGFR* or *FGFR* mutations or *BCR/ABL1*), eosinophilia should be considered clonal.

<sup>‡</sup> The lymphoid variant of HES is regarded as a special form of secondary HES by several experts, although its exact nature and pathogenesis remain controversial.