Guidelines for the diagnosis and treatment of eosinophilia.
2ND version, September 2012

The Nordic study group on myeloproliferative disorders (NMPD) decided in 2007 to write a proposal for guidelines on hypereosinophilic states, based on already existing national and international recommendations. The aim was initially to write a document that could be used in all Nordic countries for clinical as well as educational purposes. Therefore, in the first version in April 2009 numerous illustrations were given with references, including on-line linking from the document to relevant websites, which may all be used, some with permissions as stated at the end of the document in a separate section.

Hypereosinophilia in haematology is one of the very rare conditions, and solid evidence based on large protocols or randomized trials are still very limited or lacking. This proposal for guidelines tend to give current best evidence and interpretation in making decisions, based upon the development reported in diagnostic work-up and therapy.

This revised, 2nd guideline 2012 is written for health professionals with a speciality or interest in haematology and in eosinophilia. It still incorporate the diagnostic criteria established by the World Health Organization 2008, and it has been an objective to focus on handling of the patient with eosinophilia and present the guideline in an electronic format, accessible on the PC at work or home, or by any portable device with access to the NMPN Study Group webpage (www.nordicmpd.org), using a reference index. We plan further updates on a bi-annual basis, and it is therefore recommended that colleagues use the on-line version, rather than to print and copy paper versions of the documents, and to send comments for improvements and how this electronic version works for You.

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for the Nordic MPN Study Group, September 2012.

Content

Introduction

The eosinophilic granulocyte – the eosinophil – was originally described as the acidophilic leukocyte by Paul Ehrlich in 1879. The name was given due to the coarse orange / red granulae, clearly visible by light microscopy in the cytoplasm, when stained with eosin. The name was coined after Eos, the Greek goddess of the dawn. The physiology and function of eosinophils, as well as its pathophysiological role related to is biological potential, is still a scientific fruitful topic.

Eosinophils develop in the bone marrow and IL-3, IL-5 and GM-CSF are essential for their differentiation. The eosinophilic granulocyte is able to secrete or express a wide range of receptors, cytokines, chemokines, cytotoxic enzymes, lipid mediators and neuromediators, and are normally involved in host defence against parasites, as modulators of innate and adaptive immunity, inflammatory responses and tissue repair, and affect mast cell activation and T-cell function (1 – 4).

This 2nd version of the guideline intends to bring the eosinophil in focus in a clinical spectrum of very variable disorders, where the cell is either reactive or the cause of disease itself. The most common cause of eosinophilia in the western world seems to be allergy and in the developing countries invasive parasite infections.

Blood eosinophil count above the upper reference limit (in adults $\geq 0.5 \times 10^9$/L) is the hallmark of eosinophilia. Eosinophilia is regarded as mild if blood eosinophil count is $0.5 - 1.5 \times 10^9$/L, moderate if the count is $> 1.5 - 5.0 \times 10^9$/L and severe if the count is $> 5.0 \times 10^9$/L.

Eosinophilia can be divided in three different categories (5):
I: reactive (or secondary) eosinophilia,
II: clonal (or primary) eosinophilia, and
III: idiopathic hypereosinophilic syndrome (HES).

The definition of hypereosinophilic syndrome (HES) was originally proposed in 1975, categorizing patients with moderate or severe blood eosinophilia, of unknown origin for more than six months and responsible for organ damage (6). The term in its original meaning is not useful anymore as a "working diagnosis over time," since the technical progress in diagnostic tools, in particular in genetic analysis, has increased the number of clonal haemapoietic diseases where eosinophilia has a specific cause. These disorders are very important to identify because of the availability of targeted therapy. In general, patients with moderate and severe hypereosinophilia need to receive treatment to minimize the risk of organ dysfunction.

Incidence

Neither the incidence – nor prevalence – of hypereosinophilia is well described, and depends upon the source of data. In the general practitioners clinic the incidence may be up to 7 % of patients showing eosinophilia in bloodsamples (7), whereas the age-adjusted incidence in USA has been reported to be 0.036 per 100.000 persons (8). Furthermore, the incidence of eosinophilia must be anticipated to be very different and depend upon individual hospitals and departments, routine in using differential counts etc. (9). There is a male predominance in some types of clonal eosinophilia (10). The age of onset is very variable.

Eosinophilia and clinical presentation

The combination of eosinophilia and symptoms caused by eosinophils is very important to relate and realize, in order to make the correct diagnostic work-up and give the proper treatment. It is generally accepted that there is no strict correlation between the degree of eosinophilia and the risk of organ-involvement and that various factors may be necessary to elicit the end-organ damage (11). Some clinical entities have been recognized for many years and named as specific conditions, and they will briefly be described in the diagnostic algorithm.

Clinical manifestations of eosinophilia differ very much between patients. In patients with reactive eosinophilia, the primary disease or cause also may contribute to the clinical presentation. In patients with primary, clonal haematological disorders, some patients may be asymptomatic and the clinical presentation otherwise very heterogeneous – and any comorbidity may also interact irrespective of the cause of eosinophilia. Most organ-specific symptoms may be caused by the eosinophilia, however the frequency in each specific disease is difficult to state due to the limited patient-material. More than one organ may be involved, including the bone marrow affection in primary eosinophilia. Some organs, however, are more frequently affected in hypereosinophilic conditions, and the involvement is not possible to differentiate from other, much more common causes for insufficiency or symptoms (table 1). Sometimes, tissue biopsies must be performed to demonstrate infiltration of eosinophils. The tissues most vulnerable and most frequently affected by eosinophil products or penetration are the **heart** (~ 60 %), and in decreasing frequency the **skin**, the **nervous system** and the **respiratory** and **gastrointestinal tract** (~ 20 %) in that order. The symptoms may be life-threatening and are major sources of morbidity in eosinophila. **Any symptom may be experienced in eosinophilia**, not just the one more common stated, but also eye (for instance microthrombus formation, retinal arteritis) or renal (for instance acute renal insufficiency, glomerulopathy and glomerulonephritis) manifestations (12 - 19). The hematopoietic system is (naturally) involved in every case, due to eosinophilia *per se* but neutrophilia, basophilia, dysplastic features and immature white blood cells, anemia, thrombocytopenia or thrombocytosis may also be found in blood samples (20), and depending on the cause of eosinophilia.

However, the observations of clinical symptoms cannot be related to any specific diagnose or clonal eosinophilia, since they generally represent patient populations characterized by an increased eosinophil count, but not by the same, specific diagnosis. Some characteristic features clinically have emerged in primary eosinophilia using the more precise diagnostic classification.

Table 1. Clinical manifestations due to hypereosinophilia, irrespective of cause

Organ	Symptoms	Ref.
Heart	Myocardial necrosis (weeks), valvular involvement, thrombosis (months later) and fibrosis (end stage) (Loeffler's endocarditis and myocardial fibrosis in late stages) manifesting in congestive cardiac insufficiency, hypertrophy, dilation, arrhythmias, and pericardial effusion.	12, 13
Nervous system	Cerebral thrombosis – mostly arterial, transient ischemia, embolic or local thrombus formation. Encephalopathy, in particular cognitive and / or upper neuron paresis. Peripheral neuropathies, symmetric or not, sensory or motoric or both.	12, 14
Skin	Urticaria, angioedema, pruritus, papulous or nodulous lesions, mucocutaneous ulcera.	12, 15
Pulmonary	Chronic, generally non-productive cough. Bronchial hyperactivity may be present in some, and some may have pulmonary symptoms secondary to heart affection.	12, 16
Gastrointestinal	Diarrhoea, intermittent or persistent, but various abdominal symptoms may be experienced, also depending on a more selective localization in the gastrointestinal tract	12, 17
Rheumatological	Arthralgia, mostly major joints, arthritis and myalgia. Raynaud's phenomenon. Autoimmune phenomena mostly develop in rheumatic disorders with eosinophilia,	12, 18

Eosinophilia and paraclinical procedures

Eosinophils have normal functions and they may increase in numbers in blood or accumulate in tissues due to relevant stimuli, primarily allergy and infections. This hypereosinophilic state may thus be a physiological phenomenon and cause reactive or secondary eosinophilia. However, the number of eosinophils may also increase secondary or as a reaction to a benign or malignant, haematological or non-haematological disorder, primarily due to cytokine-driven eosinophilia. Autonomous clonal proliferations of eosinophils (neoplasms associated with rearrangements of platelet derived growth factor receptors, PDGFR, or fibroblasts growth factor receptors, FGFR1 or chronic eosinophilic leukaemia (CEL) with other clonal markers) are very rare diseases. Finally, the cause of persisting symptomatic hypereosinophilia may remain unclear and then carries the name "true" idiopathic hypereosinophilic syndrome (HES). HES thus remains a diagnosis of exclusion.

Reactive eosinophilia

Reactive eosinophilia is a non-clonal disorder where the production of eosinophils is increased as a response to exogenous stimuli, such as IL-5, IL-3 and GM-CSF mainly produced by T-helper cells (1-4). The causes of reactive eosinophilia are listed in table 2 and further illustrated in fig. 1 and fig. 2. These tables, figures and algorithms are based on excellent reviews (5,7,10,19,20 – 33) and the present 2008 WHO classification (34).

Table 2. Causes of reactive eosinophilia.

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1. Infections
   a. parasites, especially tissue invasive parasites, like filariasis, ascariasis, strongyloidiasis, trichinosis, toxocarisis, schistosomiasis, hookworm (*Achylostoma, Necator*)
   b. chrocic infections
   c. HIV
   d. recovery from a bacterial infection

2. Allergy
   a. atopic diseases: bronchial asthma, allergic rhinitis, atopic eczema, urticaria
   b. food allergy

3. Drugs
   any drug, but especially seen with antibiotics, sulphonamides, antirheumatics, anticonvulsants and allopurinol, DRESS syndrome

4. Lung diseases
   a. acute and chronic idiopathic eosinophilic pneumonia (Loefflers diasese see page 15)
   b. Churg-Strauss syndrome (tissue eosinophilia, vasculitis and granulomas, see page 15)
   c. allergic bronchopulmonary aspergillosis

5. Eosinophil-associated gastrointestinal disorders
   a. primary or secondary eosinophilic esophagitis
   b. primary or secondary gastroenteritis, including celiac disease
   c. primary or secondary colitis, including inflammatory bowel disease

6. Other causes of autoimmune, inflammatory or toxic origin
   a. connective tissue diseases (scleroderma, polyarteritis nodosa, LED etc.)
   b. eosinophilic fasciitis
   c. Kimura disease (follicular hyperplasia, eosinophilic infiltrates, proliferation of venules)
   d. sarcoidosis
   e. chronic pancreatitis
   f. eosinophilia-myalgia syndrome
   g. toxic oil syndrome

7. Malignant diseases
   a. lymphoproliferative diseases where eosinophils are not part of the malignant clone (Hodgkin lymphoma, non-Hodgkin lymphomas especially T-cell lymphomas)
   b. carcinomas (especially metastatic diseases)

8. Clonal expansion of immunophenotypically aberrant T cells without overt lymphoproliferative disease (T-cell hypereosinophilic syndrome i.e. T-HES)

9. Endocrine hypofunctions (i.e. Addison disease)

Idiopathic hypereosinophilic syndrome and CEL

The traditional criteria for idiopathic hypereosinophilic syndrome consist of persistent eosinophilia ($\geq$ 1.5 x 10E9/L for > 6 months) and target organ damage. The current WHO-criteria for chronic eosinophilic leukaemia and idiopathic hypereosinophilic syndrome are shown in table 3 and 4 (34).

Table 3. Diagnosis of chronic eosinophilic leukaemia (CEL) and idiopathic hypereosinophilic syndrome (HES), modified from WHO-criteria (2008)

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Required: Persistent eosinophilia $\geq$ 1.5 x 10E9/L in blood, increased numbers of bone marrow eosinophilia, and myeloblasts < 20% in blood or marrow.

1. Exclude all causes of reactive eosinophilia secondary to:
   a. Allergy
   b. Parasitic disease
   c. Infectious disease
   d. Pulmonary diseases (hypersensitivity pneumonitis, Loeffler´s etc.)
   e. Collagen vascular disease

2. Exclude all neoplastic disorders with secondary, reactive eosinophilia:
   a. T cell lymphomas, including mycosis fungoides, Sezary syndrome
   b. Hodgkin lymphoma
   c. Acute lymphoblastic leukaemia/lymphoma

3. Exclude other neoplastic disorders in which eosinophils are part of the neoplastic clone:
   a. Chronic myelogenous leukaemia (Ph chromosome or *BCR/ABL* fusion gene positive) and other myeloproliferative neoplasms or myelodysplastic/myeloproliferative neoplasms
   b. Neoplasms with t(5;12)(q31-35;p13) or other rearrangements of *PDGFRB*
   c. Neoplasms with *FIP1L1-PDGFRA* fusion gene or other rearrangements of *PDGFRA*
   d. Neoplasms with rearrangements of *FGFR1*
   e. Acute myeloid leukaemia, including those with inv(16)(p13q22), t(16;16)(p13;q22)

4. Exclude T cell population with aberrant phenotype and abnormal cytokine production

5. If there is a clonal cytogenetic or molecular genetic abnormality, or blast cells are more than 2% in the peripheral blood (>2%) or more than 5% in the bone marrow, diagnose chronic eosinophilic leukaemia, not otherwise specified (CEL, NOS).*

6. If there is no demonstrable disease that could cause eosinophilia, no abnormal T-cell population, and no evidence of a clonal myeloid disorder, diagnose idiopathic hyper-eosinophilic syndrome (when organ-involvement) or idiopathic hypereosinophilia (without organ dysfunction)

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* The ending NOS excludes clonal eosinophilas with recurrent gene rearrangements.

Clonal eosinophilia

Eosinophilia is regarded as – and to be part of - a clonal disease when there is a positive cytogenetic or molecular genetic marker or it is very likely that eosinophils are part of otherwise diagnosed myeloid malignancy. The improved methods to reveal the clonal origin of hypereosinophilia have shifted the balance towards chronic eosinophilic leukaemia and decreased the diagnoses of idiopathic hypereosinophilic syndrome. Moreover, the 2008 WHO criteria for the diagnosis and classification of myeloproliferative neoplasms have moved towards predominantly genetic classification system with disease specific molecular markers. Thus, myeloid neoplasms with molecularly characterized eosinophilia (i.e. FIP1L1-PDGRFA fusion gene) previously classified under CEL/HES are now assembled into a new category of their own. The myeloid disorders associated with eosinophilia can according to these guidelines be divided to molecularly defined and clinicopathologically defined diseases as shown in table 4 (34).

Table 4. Classification of myeloid neoplasms associated with eosinophilia
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1. Acute myeloid leukaemia

2. Chronic myeloid disorders

    a. Molecularly defined
        i.   BCR/ABL+ chronic myeloid leukaemia
        ii.   PDGFRA-rearranged eosinophilic disorder
        iii.   PDGFRB-rearranged eosinophilic disorder
        iv.   KIT-mutated systemic mastocytosis
        v.   8p11 syndrome (FGFR1 rearrangements)

    b. Clinicopathologically assigned
        i.   Chronic myeloproliferative neoplasms (including chronic eosinophilic leukaemia not otherwise specified (NOS) and mastocytosis)
        ii.   Myelodysplastic syndromes
        iii.   Myelodysplastic / myeloproliferative syndromes

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Laboratory investigations and imaging studies in unexplained persistent eosinophilia

The diagnostic work-up of unexplained persistent eosinophilia relies on clinical history (especially allergy, drugs, and travel history) as well as symptoms and signs which may point to a reactive eosinophilia or a specific organ related eosinophilic syndrome. The

investigations that are indicated are listed in table 6 and can be focused on the basis of clinical suspicion.

Table 5. Investigations in unexplained and persistent hypereosinophilia.

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1. Blood counts and morphology to assayed for
    a. severity of eosinophilia and
    b. abnormalities in other blood cells, which might point to clonal eosinophilia

2. Serum total immunoglobulin E, and specific tests for allergy (skin prick tests and allergen specific IgE tests) if indicated.

3. Investigation of parasitic infections
    a. stool parasites
    b. serological tests for suspected parasitic infections like schistosomiasis, filariasis, toxocariasis etc.
    c. specific studies according to focal findings (imaging studies, spinal fluid, blood smear, tissue biopsy etc.)

4. Bone marrow aspiration and biopsy

5. Cytogenetic analysis on bone marrow aspirate

6. Molecular analysis on peripheral blood cells for *PDGFRA, PDGFRB and FGFR1 gene rearrangements*

7. Serum tryptase, serum erythropoietin, serum vitamin B_{12} and JAK2 mutation analysis

8. Investigation of blood T-cells (immunophenotyping and molecular analysis) for possible cytokine-driven eosinophilia (T-HES)

9. Imaging studies (CT scan, ultrasound) of chest and abdomen for underlying lymphoma or non-haematological malignancy.

10. Serum troponin and ECG / echocardiogram

11. Pulmonary function tests and bronchoalvelolar lavage if clinically indicated

12. Serum interleukin 5 concentration (if available)

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The diagnostic work-up of unexplained eosinophilia can be divided in two categories: (1) the definitive tests to diagnose clonal eosinophilia which should be performed directly if the suspicion of primary haematological disease is high and the risk of organ failure is imminent and (2) investigation of reactive causes of eosinophilia (with follow-up to confirm persistency).

The definitive tests for clonal eosinophilia include:

1. **Full blood count.** Diagnosis of persistent hypereosinophilia and suspicion of chronic eosinophilic leukaemia arises from the full blood counts including white cell differential. Absolute eosinophil count should be $\geq$ 1.5 x 10E9/L. In otherwise unexplained cases follow the counts for 6 months to confirm the persistence of eosinophilia, if possible due to disease severity.

2. **Blood cell morphology.** Examine the blood film for morphological abnormalities that may indicate other haematological diseases, like increase in monocyte count seen in chronic myelomonocytic leukaemia with eosinophilia, circulating blasts seen in acute leukaemia, dysplastic changes in neutrophils seen in myelodysplastic syndrome, atypical chronic myeloid leukaemia or chronic myelomonocytic leukaemia, abnormal lymphocytes or raised amount of lymphocytes seen in chronic lymphoproliferative diseases, leuko-erythroblastic changes seen in myelofibrosis or disorders with bone marrow infiltration etc. Abnormalities in the morphology of eosinophils have been described in hypereosinophilic syndrome and chronic eosinophilic leukaemia, like enlarged cell size, sparse granulation with clear areas of cytoplasm and nuclear hypo- or hypersegmentation, but they may also be seen in reactive conditions.

3. **Bone marrow aspiration and biopsy.** Examine bone marrow morphology to confirm excess of eosinophils and to exclude other haematological disorder or bone marrow infiltration, which may be associated with eosinophilia. If the proportion of myeloid blasts is >20%, proceed with the differential diagnostics of acute leukaemia. In case of less prominent increase of blasts (5 – 19%), proceed with differential diagnostics of myeloproliferative and myelodysplastic disorders. Bone marrow biopsy should be stain for reticulin fibres (myelofibrosis) and tryptase (mast cell disorders, where also CD117 staining or analysis by flow cytometry may be helpful). Immunocytochemistry for lymphoid malignancies should be analyzed when indicated by the morphological findings. Flow cytometry for CD52 on eosinophils may be done to demonstrate a possible sensitivity to antibody therapy.

4. **Cytogenetics on bone marrow aspirates.** Examine the karyotype on bone marrow aspirates (G-banding of at least 20 bone marrow metaphases). The translocations between chromosome 5q33 (PDGFRB) and one of its several partner chromosomes, as well as chromosome 8p11 (FGRFR1) and one of its partners can be detected by conventional cytogenetics and can be confirmed with relevant FISH-probes. Intrachromosomal deletion of chromosome 4 resulting in FIP1L1-PDGFRA fusion gene is cytogenetically occult, but can be demonstrated by interphase FISH with probes flanking the deleted part of chromosome 4 as well as upstream and downstream sequences. Samples should be tested for FIP1L1-PDGFRA fusion gene either with FISH or with molecular methods (see below).

5. **Molecular analysis for FIP1L1-PDGFRA fusion gene.** Peripheral blood sample is suitable for RT-PCR analysis of FIP1L1-PDGFRA fusion gene. The advantage of

RT-PCR over FISH is the greater sensitivity of the method which allows the detection of the fusion gene even if the proportion of positive cells is rather low. RT-PCR can also be used for the detection of minimal residual disease during treatment with kinase inhibitors.

6. **Molecular analysis for *Wilms tumor (WT)* gene.** RT-PCR on bone marrow or peripheral blood for WT1 has recently been reported to discriminate secondary or reactive eosinophilia from idiopathic hypereosinophilia (HES) and CEL, both of which shows significantly higher levels. The transcript amount in bone marrow correlated with measurements in blood, and was representative for response during treatment of HES and CEL (35).

7. **Additional tests.** Serum markers for chronic myeloproliferative disorders include elevated tryptase and decreased erythropoietin as well as demonstration of JAK2 mutation in blood cells. The clonal aspect may in female patients also be demonstrated by X-chromosome inactivation, HUMARA test (36). This analysis needs to be validated more in patients with eosinophilia.

Table 6. Examples of chromosomal rearrangements and fusion genes reported with PDGFRB (left) and FGRFR1 (right column) in conditions with eosinophilia.

Cytogenetics	Hameatological diagnosis		Cytogenetics	Fusion gene
t(1;3;5)(p36;p21;q33)	CEL		t(8;13)(p11;q12)	ZNF198-FGFR1
t(1;5)(q21;q33)	CEL		t(8;9)(p11;q33)	CEP110-FGFR1
t(1;5)(q23;q33)	MPN / MDS with eosinophilia		t(6;8)(q27;p11-12)	FGFR1OP1-FGFR1
t(5;10)(q33;q21)	aCML with eosino-philia, MPD with eosinophilia		t(8;22)(p11;q11)	BCR-FGFR1
t(5;12)(q31-33;p12-p13)	CMML with eosinophilia		t(7;8)(q34;p11)	TRIM24-FGFR1
t(5;12)(q31-q33;q24)	CEL		t(8;17)(p11;q23)	MYO18A-FGFR1
t(5;14)(q33;q32)	CMML with eosinophilia		t(8;19)(p12;q13.3)	HERVK-FGFR1
t(5;15)(q33;q22)	Ph'neg CML with pro-minent eosinophilia		ins(12;8)(p11;p11p22)	FGFR1OP2-FGFR1

Data from (34). Abbreviations: CEL Chronic Eosinophilic Leukemia, MPN Myeloproliferative Neoplasm, MDS Myelodysplasia, aCML atypical Chronic Myeloid Leukemia, CMML chronic MyeloMonocytic Leukemia. Additional data on molecular defect fusion gene or mutations is given in (24).

Tests that should be performed to diagnose (or exclude) reactive eosinophilia and / or demonstrate target organ dysfunction

1. **Tests for allergy.** As allergic conditions are the most common cause of reactive eosinophilia, examine serum total IgE. If there is any suspicion of specific allergic condition, examine skin prick tests and/or allergen specific IgE-tests.

2. **Tests for parasitic infections**. Examine repeated (fresh) stool specimen for the diagnostics of parasite infections. Specimen of duodenal aspirate, sputum, spinal fluid, urine, blood film and tissue biopsy may also be examined if clinically indicated. For suspected parasitic infections like schistosomiasis, filariasis, toxocariasis etc. examine serological blood tests.

3. **Tests for abnormal T-cells in peripheral blood.** Consider the possibility of abnormal T-cells as the cause of reactive eosinophilia (condition which is sometimes called T-HES). Analyse the immunophenotype of blood T-cells with multiparameter flow cytometry. T-cells with aberrant phenotype (CD3+/4-/8- or CD3-/4+) indicates reactive eosinophilia (T-HES). These aberrant T-cells may or may not be clonal and can be further characterised by molecular methods (rearrangement of T-cell receptor gene). Serum IL-5 measurement can also be helpful and is recommended if it is available.

4. **Tests for eosinophilia-mediated organ damage.** The evaluation of persistent eosinophilia should include tests for eosinophil-mediated organ damage, especially cardiac and pulmonary problems. These investigations include ECG, echocardiogram, serum troponin concentration or pro-BNP, chest X-ray, pulmonary function tests. Also bronchoalveolar lavage may be performed, if clinically indicated.

5. **Imaging studies.** Imaging studies (CT scan, ultrasound) of chest and abdomen should be performed for possible underlying lymphoma or non-haematological malignancy.

Handling of patients with eosinophilia, irrespective of the degree of eosinophilia – although more urgent the higher the count – therefore imply a classic clinical approach. Obtaining a sufficient and thorough anamnesis, focusing on travelling, infectious symptoms, autoimmune disease, drugs, itching and eczema or systemic symptoms like night sweats or weight loss may be clues to the diagnosis. Some clinical observations like splenomegaly or lymphoma, type of rash, affection of organ function in respiration, circulation or neurology may contribute to a possible diagnosis or in a combined fashion give a rational examination by relevant tests (above).

The diagnostic / clinical algorithm when meeting the patient with eosinophilia may be illustrated in fig. 1. This algorithm for diagnostic work-up of persistent eosinophilia is

modified from (34,37) and combined with every other differential diagnosis in eosinophilia given in this guideline (5,7,10,19,20 – 33). In addition therapy is briefly stated for eosinophilia due to clonal bone marrow disorders and hypereosinophilia (for details, see treatment section, page 18).

Fig. 1 Diagnostic algorithm (nex page) (legend): Algorithm for eosinophilia. Abbreviations and comments: BM bone marrow; CEL chronic eosinophilic leukaemia; CML chronic myeloid leukaemia; CyA cyclosporine A; FGFR fibroblast growth factor receptor; iHE idiopathic hypereosinophilia; iHES idiopathic hypereosinophilic syndrome; HU hydroxyurea; IFNα interferon-α(2a or 2b); PB peripheral blood; PDGFR platelet derived growth factor A or B; PV polycythemia vera; TKI tyrosine kinase inhibitor; s serum. When blasts exceeds 20 % in blood or bone marrow: acute leukaemia; nos not otherwise specified.

Figure 1.

Iatrogenic / drugs
-i.e. antibiotics, anti-
epileptics, allopurinol

allergy
atopy

parasitic infection
roundworm, bilharzia etc

pulmonari or gastro-intestinal
eosinophilic syndromes

morbus Addison

collagenosis, i.e. polyarteritis nodosa, rheu-
matoid arthritis, Churg-Strauss, sclerodema

paraneoplastic, i.e. morbus
Hodgkin, disseminated solid tumor

Eosinophilia > 1.5×10^9 / l
in blood

eosinophil fasciitis

inflammatory bowel disease
chronic pancreatitis

sarcoidosis

If none of the differential-diagnosis above is demonstrated following clinical history, clinical examination and diagnostic tests, e.g. microbiological, bloodsamples, tissue biopsies, imaging then measure s-tryptase and perform bone marrow examination including morphology, FISH, RT-PCR, flow cytometry and / or karyotype for clonality and examine for

FIP1L1-PDGFRA deletion	5q33 translocation	8p11 translocation	TcR positive or Th population	Eosinophilia *with* other morphology	Eosinophilia *without* other morphology
PDGFRA rearrangement myeloid neoplasi with eosinophilia	PDGFRB rearrangement myeloid neoplasi with eosinophilia	FGFR1 rearrangement myeloid neoplasi with eosinophilia	T-cell driven eosinophilia perhaps lymphoma	myelodysplasia, acute leukemia, CML, PV, a.o. with typical clonality	Blood blast > 2 % or BM blast > 5 % or non-specific clonality

yes   no

organ involvement

marrow fibrosis with mastcells high s-vitamin B_{12} and –tryptase, anaemia, splenomegaly, and risk of heart (organ) dysfunction ("myeloid phenotype")	myelodysplastic -myeloproliferative often associated with non-Hodgkin lymphoma ("stemcell leukemia/ lymphoma syndrome")	eczema, itch high S-IgE and lung symptoms ("lymphoid "phenotype")	very variabel clinical presentation, perhaps unexpected, often characteristic clonal markers, i.e. JAK2, Ph[1]

CEL
(nps)

yes   no

iHES   iHE

TKI	TKI	cytostatics in combination	prednisolone, CyA	TKI, IFN, cytostatics	TKI, HU or IFNα (or none iHE)

Eosinophilia in some non-haematological conditions.

Some clinical conditions with eosinophilia may demonstrate selective organ manifestations of chronic nature – in particular abdominal (38,39) and pulmonal (40,41). These patients may be referred to specialists in gastroenterology or lung diseases for further evaluation and treatment by colleagues in other specialties or in collaboration, using principles from treatment of eosinophilia in haematological disorders. Likewise, haematological patients with pronounced organ-related symptoms should be considered to be conferred with specialists in that particular problem. Some molecules may be critical to eosinophilic trafficking and homing in particular end-organs (19).

Some clinical conditions shows eosinophilia as part of other disorders (reactive or secondary eosinophilia), and three syndromes are described briefly here for clarification.

▪ **DRESS syndrome**: Drug Rash (or Reaction) with Eosinophilia and Systemic Symptoms. A serious condition developing one week to two months after drug exposure. Allopurinol, antiepileptics and antibiotics, but also imatinib and many other drugs have been associated with DRESS (5,26,42,43). The systemic symptoms may present as fever and involvement of one or more internal organs. Patients will often have fever, malaise, extensive exanthema, liver involvement, lymph node enlargement and pharyngitis. The patients may have signs of nephritis, arthritis or pneumonitis. Cessation of the given medication, immunosuppression by corticosteroids and (intensive) symptomatic therapy is indicated (44).

▪ **Churg-Strauss syndrome**: a small-vessel necrotizing vasculitis, considered to be a Th2 mediated disease, which may be defined by different criteria, but is characterized by marked eosinophilia, asthma, mono- or polyneuropathy, migrating pulmonary infiltrates, paranasal sinus abnormality and /or extravascular eosinophils in biopsies or samples (at least four of six criteria present in American College of Rheumatology Criteria) (5,45,46). Up to 50 % of the patients have antineutrophil cytoplasmic antibodies, and in most of these other autoantibodies may be detected, i.e. anti-myeloperoxidase. It is a chronic disease, with a risk of vasculitis symptoms in all organs, and treated by immunosuppressive agents, sometime alkylation or antibody-therapy. It may in some cases be difficult to rule out a haematological disorder without specific tests, and thus differentiate a vasculitis and a clonal blood disorder.

▪ **Loeffler syndrome**: originally a parasitic induced eosinophil pneumonia, but now also referred to in drug induced or self-limiting acute pneumonitis, with transient pulmonary infiltrates, glucocorticoid sensitive and with variable lung manifestations and given the term "Loeffler's syndrome" to any form of acute onset pulmonary eosinophilia no matter what the underlying cause (47,48) and above.

Eosinophilia in haematologic bone marrow diseases.

The symptoms in primary eosinophilia, due to a clonal bone marrow disorder (table 3, 4 and fig. 1), may be asymptomatic or have any of the symptoms given in table 1, in addition to any degree of constituent symptoms – fatigue, weight loss and nights sweats due to a hyper catabolic state in any degree. Some discomfort may be noted due to a – mostly moderate - enlarged spleen, if present. Some symptoms may be related to anaemia, or haemorrhagic diathesis due to thrombocytopenia, present to a variable extend (20).

An increasing number and variety of cytogenetic aberrations have been reported in clonal eosinophilia by banding technique, involving translocations, additions, insertions, deletions, other abnormalities and complex karyotypes in the last 20 years (5, 21, 22, 49, 50) and associated with CEL. Therefore, classic karyotypes must be performed (table 4 and 6). In addition, some specific cytogenetic abnormalities have long been associated with acute myeloid leukaemia, i.e. inv(16), t(5;16), t(8;21) and others (51).

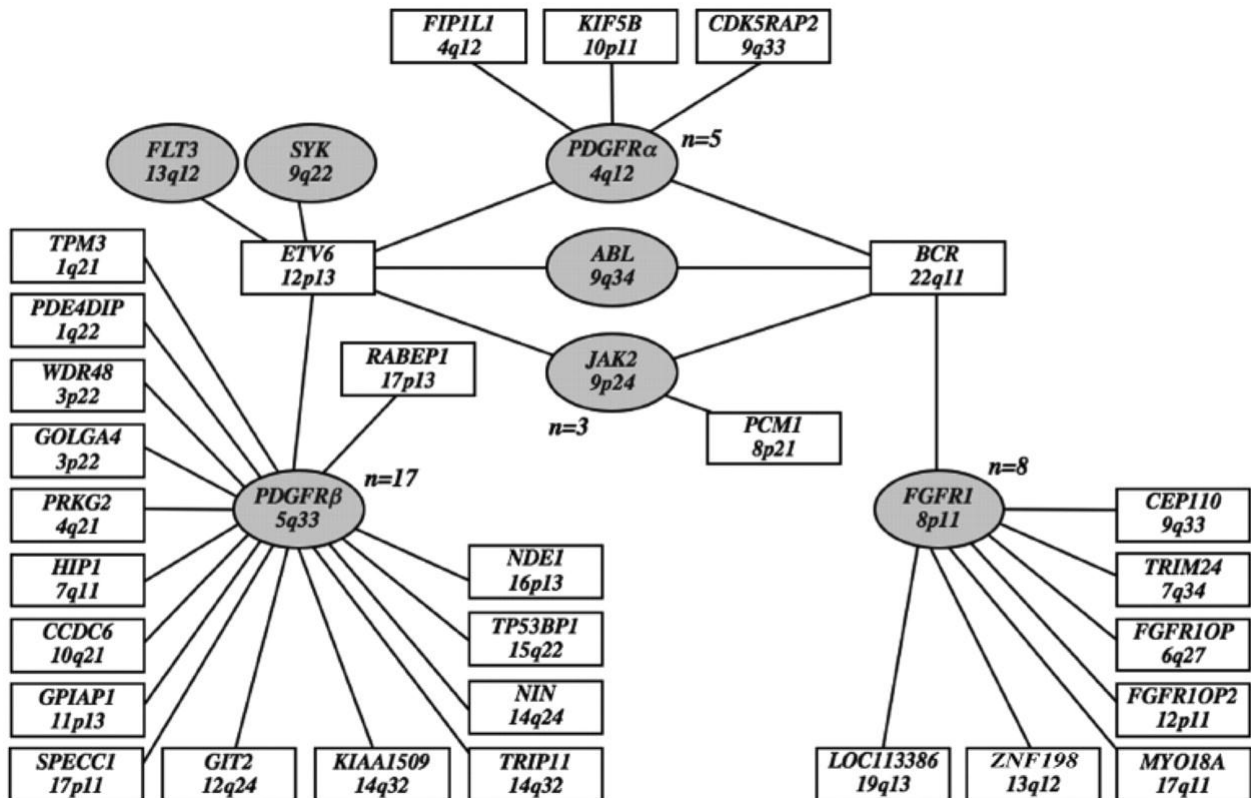**Figure 2. A network of tyrosine kinase fusion genes.**

Fig. 2. Network of tyrosine fusion genes in eosinophilic myeloproliferative disorders and related diseases (26) (reproduced with permission). PDGFR Platelet-derived Growth Factor Receptor. FGFR1: fibroblast growth factor receptor 1.

The Platelet-Derived Growth Factor Receptor (PDGFR) A and B has been identified as a partner-gene in eosinophilia (fig. 2) (5,20,22,26,27,49). In particular, a dys-regulated tyrosine kinase originating from a interstitial deletion on chromosome 4 where PDGFRA fuse with FIP1-like1 (FIP1L1) gene has been described in detail (52 - 56), and the fusion gene cooperates with IL-5 to induce a CEL-like disease in mouse models (57) and the severity of disease seems to be associated with polymorphic variations at the IL5Rα locus (58).

In recent years two phenotypes of eosinophilia have been described in primary, clonal eosinophilia – a myeloid and a lymphoid or T-variant (59 - 61), with individual variations in manifestations. The "myeloid phenotype" have a male preponderance, the "lymphoid" seems to show a higher incidence among females, and these clinical entities may now be related to specific clonal abnormalities (Table 7).

Table 7. Clinical and diagnostic differences between (so-called) "m- and l-HES."

Myeloid "m-HES"	Lymphoid "l- or T-HES"
Splenomegaly and hepatomegaly	Increased IL-5 production
Leukocytosis, immature forms	Increase S-IgE
Increase serum vitamin B_{12} & tryptase conc.	Polyclonal hypergammaglobulinemia
Anemia and thrombocytopenia	Itching, eczema
Cardiac complications	Urticaria, angioedema
Less glucocorticoid sensitive	Pulmonary symptoms
More aggressive clinical phenotype	Glucocorticoid sensitive
Association with systemic mastocytosis SM	Approximately 25 % of HES patients
PDFGR disorders	T-cell phenotype subsets

The T-cell clone may be detected by TcReceptor analysis as described in the section on diagnostic work-up or analysis for aberrant T-cell phenotypes (CD3+/4-/8- or CD3-/4+) (62 - 64), associated with eosinophilia by IL-5 production.

Eosinophilia thus represents a very heterogeneous clinical spectrum, and may be caused by another disease or the eosinophilic granulocyte is the representative of a clonal dis-order (5-35,49,65) or so-called iHES (idiopathic hypereosinophilic syndrome) when clonality is not demonstrated, but organ dysfunction is demonstrated (heart, lung etc), or (simply) idiopathic hypereosinophilia (iHE) when the patient shows no organ involvement (fig. 1) (34).

Another elegant and functional clinical-biological approach than given in fig. 1, is shown in fig. 3 (based on ref. 25), with the additional point that here idiopathic hypereosinophilic

syndrome represents non-clonal eosinophilia. Both fig. 1 and fig. 3 demonstrates the crucial importance of correct diagnosis for eosinophilia, in order to choose the right treatment.

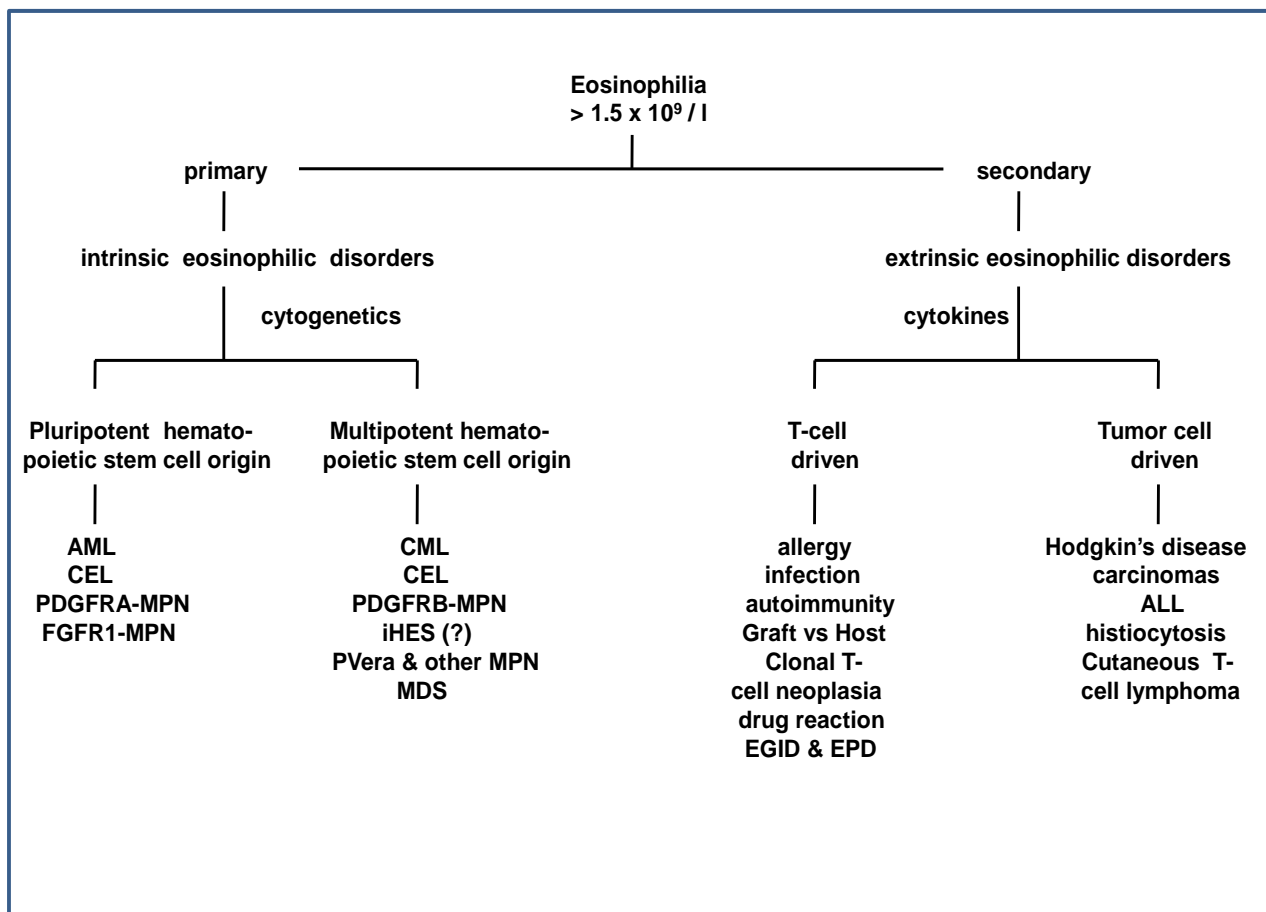**Figure 3. Classification of eosinophilic disorders based on biology**

Fig.3. Classification of eosinophilic disorders based on biology – caused by cytogenetics or cytokines. Eosinophilia is either mediated by cytokines (in particular IL-5) or a consequence of mutations, translocations or other cytogenetic abnormality in hematopoietic stem cells leading to predominant eosinophil differentiation. AML: acute myeloid leukemia; CEL chronic eosinophilic leukemia; CML chronic myeloid leukemia; MPN myeloproliferative neoplasm; MDS myelodysplastic syndrome; PDGFRA/B platelet derived growth factor A/B, PVera polycythemia vera; EGID eosinophilic gastrointestinal disorders; EPD eosinophilic pulmonary disorders; ALL acute lymphocytic leukemia. Modified from (5-35, 38-41,47,48).

The 2008 WHO classification of tumours of haematopoietic and lymphoid tissues (34) implement the identification of various clonal conditions associated with eosinophilia. The best clinical management of patients with primary eosinophilia is dependent on a correct diagnosis. It may be a goal to classify all patients by a specific pathogenesis. Still, a major part of the patients today seen in the clinical setting with primary eosinophilia do not demonstrate clonal characteristics. Therefore, some heterogeneity and overlap is evident.

The clinical course for this important group of patients remains uncertain and the management may involve a successive administration of various available treatments in order to obtain control of blood-eosinophilia and symptoms, simultaneously. The treatment may preferably be glucocorticoid sparing, but then often involving cytoreduction and immunosuppression based on individual patient decisions.

Recognizing this complex development, Simon et al. have proposed that patients with primary hypereosinophilia may be separated into myeloproliferative, lymphocytic, overlapping, undefined, associated and familial forms, and crystallized in a working definition (31).

Figure 4. A revised classification of hypereosinophilic syndromes.
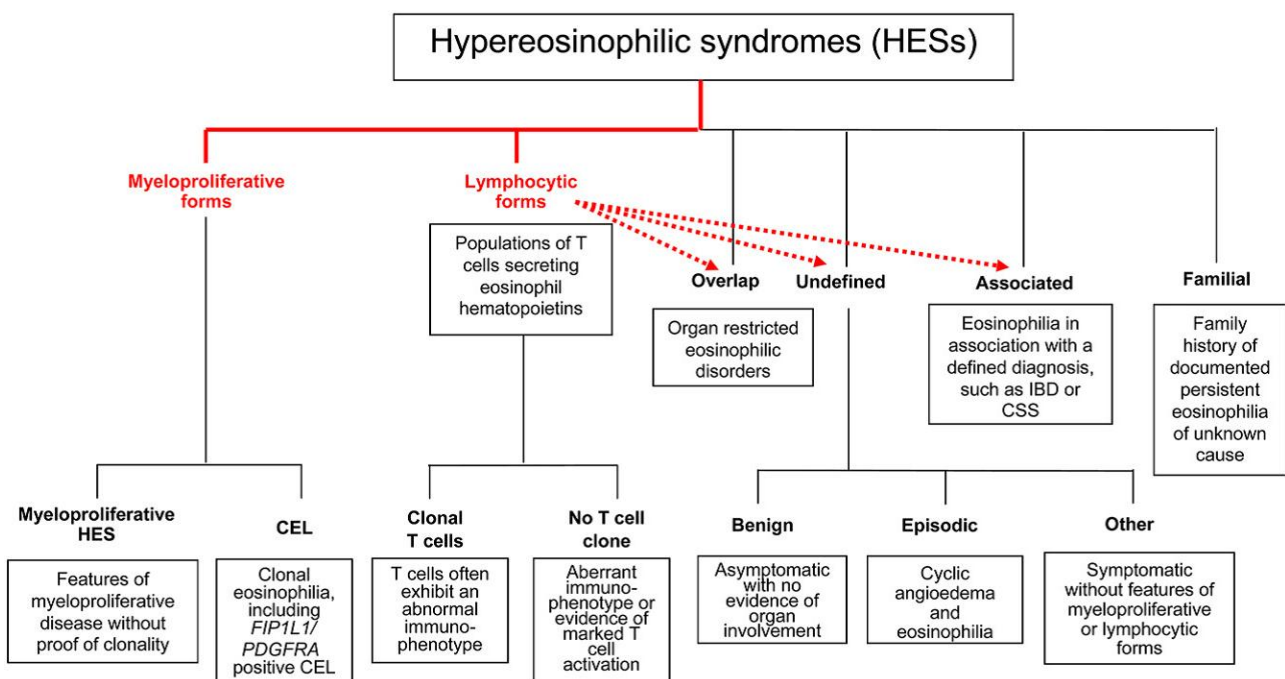

Fig. 4. The *dashed arrows* identify HES forms for which some patients have T-cell driven disease. IBD: inflammatory bowel disease. CSS: Churg-Strauss syndrome (31).

The various algorithms presented here (figs. 1,3,4 and tables 3,4) may be valuable in different situations, with different approaches for diagnostic and therapeutic purposes. They may each contribute to structure the concept of primary hypereosinophilia. They also illustrate the need for standardized tests (e.g. in PCR) in particular in optimal sensitivity, and the lack of validated, specific and (easily) reproducible assays for cytokines for routine use in order to determine if the pathogenesis is T-cell dependent (24,31,49).

Treatment of eosinophilia

Several review articles have recently been published in this field (10,20-22,24-27,29, 32,33,66,67) and including secondary / reactive causes, where anti-infective, immunosuppressive and symptomatic therapy is effective (5, 41-48). The following thoughts, recommendations and even wording have been influenced by the reviews and case reports in eosinophilia – although it may be difficult to interpret clonality in many previous, older reports (34). In the following hypereosinophilia therefore refers to conditions with clonal eosinophilia or possibly iHES and iHE.

This section focus on eosinophilic, haematological disorders, as depicted in fig. 1 lower half, fig. 3 left half, when all other causes or reactive eosinophilia have been eliminated, and a specific / clonal disorder with eosinophilia been identified, and includes the iHES and iHE (table 3).

Conditions with clonal eosinophilia are chronic disorders in which the toxicity of the treatment has to be carefully considered. Corticosteroids and hydroxyurea have been the standard treatment (12), together with interferon alpha (IFN-α) (68). With the discovery of the FIP1L1-PDGFRA fusion, PDFGRB and FGFR1 translocations with constitutive tyrosine kinase activity in subgroups of patients (5,10,22-24,26,28,34), and presence of increased IL-5 production by abnormal T-cells in others (4,69,70), the treatment recommendations have changed.

Currently the treatment of hypereosinophilia should be based on disease severity and eventual detection of pathogenic variants. For FIP1L1-PDGFRA positive patients, imatinib is the first line therapy. For others, corticosteroids are generally recommended. Hydroxyurea, INF-α, and imatinib are used for corticosteroid-resistant cases, as well as for corticosteroid-sparing purposes. Recent data suggest that mepolizumab, an anti-IL-5 antibody, is an effective corticosteroid-sparing agent for FIPL1-PDGFRA-negative patients.

The relationship between the absolute eosinophil count and organ damage is not always consistent (11,71,72). Other markers of disease progression have been proposed, but none has been validated, and no response criteria have so far been presented. One reason is lack of standardization of molecular methods, and perhaps reproducibility among different laboratories. Nevertheless, which is a problem in myeloproliferative disease in general, it might be of value to monitor the therapeutic response in FIP1L1-PDGFRA positive hypereosinophilia using RT-PCR for the transcript levels (52,73,74) or WT-1 (35) or other clonal parameters, just like BCR/ABL in CML (75) and JAK2 in Ph'-negative MPN (76). In I-HES (table 7, often T-cell driven eosinophilia) the numbers of phenotypically aberrant lymphocytes can be evaluated by FACS (62,77). However, in most cases the response to treatment are conveniently monitored by clinical symptoms and eosinophil counts. A proposal for various parameters and a simple response assessment for prospective use is given in table 8.

The specific therapeutic spectrum includes (table 9):
- Corticosteroids
- Myelosuppressive agents
- Immunomodulatory therapy
- Monoclonal antibodies
- Tyrosine kinase inhibitors
- Bone marrow transplantation

Table 8. Response criteria in patients with primary eosinophilia following treatment.

Variable	Complete response (CR)	Partial response (PR)	No response – or loss of response at any later time point
B-eosinophilia / total WBC	Normalization < 0.45 x 10^9 /l, within normal range	≥ 50 % reduction in blood eosinophilia number	< 50 % reduction
Hgb, platelets, LDH	Normalization off all (if abnormal at diagnosis)	≥ 50 % improvement of any	< 50 % improvement
Blood / plasma para-meter related to eosi-nophilia (CRP, IgE, tryptase etc.)	Normalization of all	≥ 50 % improvement of any	< 50 % improvement
Any clonal parameter (if present) (molecular or cytogenetic remission)	Not detectable when measured in the same sample type – blood or bone marrow	≥ 2-log reduction in qPCR or ≥ 50 % reduc-tion in FISH or number of metaphases in karyotype	< 2-log reduction in qPCR or < 50 % reduction in FISH or karyotype clonal aberration
Organ involvement clinically (spleno-megaly, cardiac, pulmonary etc.)	No symptoms, without symptomatic treatment and evaluated clinically	No symptoms, but trea-ted symptomatically (ACE inhibitors, inhala-tions etc.) due to eosinophilia sequelae	+ symptoms and requiring treat-ment
Organ involvement resolved by labora-tory tests (spleno-megaly, cardiac, pul-monary insuff. etc.)	Normalization, verified by X-ray, ultrasound, MUGA, lung function etc.	≥ 50 % improvement, verified by X-ray, ultrasound, MUGA, lung function etc.	< 50 % improvement
Symptoms related to eosinophilia	Disappearance of all	Improvement on (ECOG) adverse event scale	No significant im-provement – or worsening due to eosinophilia
Quality of life	Improvement defined by a scoring system	No improvement defi-ned by scoring	Worsening of QoL

A "true" complete remission should fulfill all criteria in the column, pre-defined for the individual patient (category). A so-called PR may be obtained if at least half the parameters, evaluable for the patient, actually fulfill the criteria for the individual patient. The response criteria may further be defined in time, i.e. obtained within 1-3-6 months from start of therapy – or lost during treatment as a result of disease progression or relapse. The response criteria in table 8 may be considered a proposal and they have *not* been validated. One issue is the lack of standardized PCR techniques, and the criteria, in some form modified from table 8, may therefore be useful for the time being at departmental level. Response criteria based on blood-eosinophilia and symptoms alone have been used in 2009 in a retrospective multicenter study (78).

Besides the treatments for hypereosinophilia described here, a number of other cytotoxic (methotrexate, purinethol, etoposide, fludarabine, cyclophosphamide) or immuno-suppressive therapies (azathioprine, thalidomide) have been reported in a few patients, (also) with variable results, and often discontinued albeit administered in a rational setting (78). Prospective, randomized if possible, clinical trials in primary hypereosinophilia is needed, which will necessitate multicenter collaboration (68).

Corticosteroids

Corticosteroids are first-line treatment for most patients with hypereosinophilia, except the FIP1L1-PDGFRA positive eosinophilias. Corticosteroids are also indicated, together with imatinib, in patients with FIP1L1-PDGFRA-positive eosinophilia and signs of myocarditis (79). The effect of glucocorticoids are obtained by various mechanisms on transcription of inflammatory mediators, inhibition of eosinophil survival (4), in addition to a lymphocytotoxic effect. For FIP1L1-negative patients, the usual starting dose of corticosteroid dose is ½-1 mg prednisone/kg body weight/day. Some 85% of patients will respond to this treatment (78) and the dose can be slowly tapered. Prophylaxis against osteopenia and opportunistic infection should be considered for patients requiring maintenance treatment. Rarely, patients with eosinophilia may be resistant to glucocorticoids (4).

A history of angioedema, a profound and rapid eosinopenic response to challenge with prednisone, high serum IgE levels, and no hepatosplenomegaly are favorable predictors of long-term response to corticosteroid treatment (12). However, corticosteroid toxicity is common (cataract, hyperglycemia, hypertension, weight gain, increased risk of infection, perhaps increased risk of gastritis etc.) and steroid sparing alternatives are usually needed.

In every case of oral prednisolone therapy lasting for more than a month, the risk of glucocorticoid-induced bone disease should be considered (80), and all patients should receive adequate calcium and vitamin-D supplementation. In particular in patients with risk factors for therapy elated osteoporosis, e.g.: advanced age, low BMI, concomitant diseases, smoking, alcohol consumption, frequent falls, low bone mineral density and immobilization must be considered for prophylaxis by various measures (81,82).

Myelosuppressive agents

Hydroxyurea
Hydroxyurea (1-3 g/day) is the myelosuppressive drug that is preferably used to lower the eosinophil count, and it acts synergistically with IFN-α. This combination has been used with success in several cases with eosinophilia (83). Also, a combination of hydroxyurea and imatinib has been reported to be effective. A response to treatment with hydroxyurea is commonly seen within 2 weeks and it is not effective in cases where a rapid decrease in eosinophil count is needed.

Side effects: myelosuppression, gastrointestinal toxicity, leg ulcers and skin rash (84).

Vincristine

Vincristine can be used for rapid lowering of the eosinophils in patients with extremely high eosinophil counts (> 100 × 10^9/L). It is rarely used for long-term management of eosinophilia. However, it has been used in some cases (67,85). The recommended dose for adults is 1–2 mg intravenously.

Side effects: neurotoxicity (86).

Combination regimens

A small series of patients with hypereosinophilia has been treated from 1999-2001 with a combination of 2-chlorodeoxyadenosine and cytarabine, and some 55 % obtained a complete remission, with a median overall survival of 44 mo. Dosage was 1 g / m^2 of cytarabine and 12 mg / m^2 for cladribine (87).

Side effects: febrile neutropenia and bone marrow insufficiency.

Immunomodulatory therapy

Interferon-α

Low doses of IFN-α (1-5 million U/m^2/d) are often effective but the response usually become evident after several weeks of treatment (68,81). Low-dose hydroxyurea (500 mg daily) potentiates the effect of IFN-α (88). Monotherapy with IFN-α should be avoided in L-HES; *in vitro* data have demonstrated an inhibitory effect of IFN-α on spontaneous apoptosis of clonal $CD3^-CD4^+$ T-cells (89). In this setting a corticosteroid should be added because of its proapoptotic effect on the clonal T-cells. PEG-IFN-α2b have been used effectively in a few patients with eosinophilia (90). IFN-α treatment may be used in pregnancy, as in other MPNs (91), and also in female patients with eosinophilia (92). The pegylated forms of IFN2a and α2b may both be used for long-term treatment, but solid data is lacking (68).

Side effects: myelosuppression, flu-like symptoms, depression or other mental symptoms, fatigue, increased liver transaminases, gastrointestinal discomfort, thyroid affection, etc.

Cyclosporine A

Some case reports and one study have been published demonstrating a maintenance effect of cyclosporine A therapy in adult patients, in particular with I-HES and T-cell receptor rearrangement (78,93,94). This is well explained by an inhibitory effect on the production of IL-5 (1,4,5,70). Also mycophenolate mofetil may be effective (78), perhaps with a better side-effect profile.

Side effects: hypertension, renal insufficiency, tremor, headache, hyperlipidemia, gingival hyperplasia, muscle cramps, hypertrichosis, etc.

Monoclonal antibodies

Two different humanized, monoclonal anti–IL-5 antibodies, reslizumab (SCH55700, Cephalon) and mepolizumab (GlaxoSmithKline), can markedly decrease the eosinophil count in hyper-eosinophilia, regardless of the underlying cause by binding to free IL-5 (10,95-98). These responses were in some patients sustained for up to a year, after multiple infusions of anti–IL-5. The therapy appears well tolerated, but may cause a rebound effect (99). However, these substances are currently only available in clinical (phase III) trials and has not been approved for use in any eosinophil-related disorder (100). Mepolizumab is in phase 3 protocol for hypereosinophilc syndrome (101), but it has been reported that approval might be jeopardized by the risk-benefit data (102). However, mepolizumab has been used in one of the only prospective, placebo-controlled clinical trials in hypereosinophilia including 85 FIPL1-PDGFRA negative patients, to give a corticoid-sparing effect as an end-point, reducing the eosinophil count to less than 0.6 x 10^9 /l for eight or more weeks in 95% of patients, as compared with 45 % receiving placebo (and steroids). The treatment was administered intravenously every four week during a 36-week period, and was well tolerated (103). These results demonstrate a potential clinical benefit of immunotherapy in hypereosinophilia.

The routine clinical use in treatment algoritms (fig. 1) is not settled, but antibody treatment against IL-5 may be valuable in several primary and secondary causes (fig. 3). However, the two antibodies are not currently available for compassionate use in the Nordic countries.

The monoclonal anti-CD52 antibody (Mabcampath®; alemtuzumab) has been used successfully in several cases with hypereosinophilia. It might be an alternative treatment for patients with HES refractory to other therapies, including clonal eosinophilia (10, 78, 102, 104 - 106). Most eosinophil granulocytes highly express CD52, a surface glycoprotein expressed on B- and T-lymphocytes (107). It may be speculated that anti-CD52 induces the significant effect in patients with hypereosinophilia by reducing eosinophilia not only be a direct cytotoxic effect on eosinophils, but also by a T-cell mediated mechanism. Anti-CD52 therapy seems to be a promising, and actually already available alternative in hypereosinophilia, although not *per se* approved for treatment of primary eosinophilia.

Dosage in alemtuzumab treatment for hypereosinophilia has varied, but may be used in a similar manner as for chronic lymphocytic leukemia in escalating doses, with a weekly maintenance tolerated dosage, and continued for three months – or an individual evaluation. Possibly the intravenous route may be simplified to subcutaneous administration. Cytomegalovirus prophylaxis is recommended (106,107).

Side effects: difficult to evaluate, but may be minor depending on dosages. Immunosuppressive effect and risk of (opportunistic) infections, perhaps lymphoma development and rebound effects following cessation of antibody therapy (10,101,107).

Tyrosine kinase inhibitors

Imatinib mesylate

Imatinib mesylate is active against several receptor tyrosine kinases, including the fusion kinase originating from the FIP1L1-PDGFRA mutation. A number of studies have shown a striking potency of imatinib in patients with FIP1L1-PDGFRA-positive hypereosinophilia, and no case of primary resistance to imatinib has been reported (10,19,29,30,52,108, 109). There is a general consensus for the use of imatinib as first-line therapy in patients with the FIP1L1-PDGFRA fusion gene and in cases with clinical and laboratory signs of this subtype of eosinophilia, e.g. tissue fibrosis, increased serum vitamin B_{12} and increased serum tryptase levels, and often male sex. The imatinib response rate in FIP1L1-PDGFRA-positive patients is close to 100%, with very few cases of acquired imatinib resistance. The T674I substitution in the ATP-binding domain of PDGFRA (52,102,108 - 110) is associated with imatinib resistance, similar to the T315I mutation observed in patients with CML. *In vitro* data and case reports suggest that tyrosine kinase inhibitors under development are effective even in the presence of the T674I mutation (10,102,111).

The responses to imatinib in FIP1L1-PDGFRA-positive patients are rapid, and eosinophil counts are normalized within 1 week of treatment. The clinical manifestations usually disappear within 1 month. The exception is cardiac involvement, which is irreversible unless treatment is begun before fibrosis leads to permanent damages (109). The side effects of imatinib therapy are generally mild and rarely requires to discontinuation of treatment. However, acute cardiac failure has been seen and has led to the recommendation that patients with evidence of cardiac involvement, e.g. increased s-troponin levels, should be pretreated with corticosteroids (79).

The dose required to induce and maintain remission is generally lower (100 mg/day) than for patients with CML (≥ 400 mg) (109). Influence of imatinib on clinical manifestations related to heart involvement are variable, and endomyocardial fibrosis appears to be irreversible (53, 109). Reversal of bone marrow pathology and molecular remission can be achieved in most patients with the FIP1L1-PDGFRA fusion gene (109, 112). It has been recommended that the imatinib dose should be adjusted to ensure molecular remission, in order to prevent the development of acquired resistance (67).

Imatinib has become first-line therapy for patients with FIP1L1-PDGFRA-associated eosinophilia (5,10,20-30), but the overall follow-up is short, and prospective randomized trials are limited (113). It is unclear if imatinib can be curative for clonal eosinophilia, through eradication of the leukemic clone. It has been reported that interruption of imatinib in FIP1L1-PDGFRA-positive patients in molecular remission, is followed by recurrence of the disease within months (112, 114), making maintenance therapy with imatinib necessary (115).

Durable responses have been obtained in patients with PDGFRB fusion genes and eosinophilia, but reports are still based on low number of patients (116), but the recommended dosage for patients with MDS/MPNs with eosinophilia (table 6) and tyrosine kinase activity due to rearranged PDGFRB, the recommended dosage is imatinib 400 mg daily (10). The effect of imatinib therapy in PDGFR-negative eosinophilia is unclear, although responses have been seen in some patients. Currently, there are no markers that can help identify PDGFR-negative patients with imatinib-sensitive disease. A short course of imatinib 400 mg daily has been recommended to patients with clinical and biological

findings typically seen in m-HES and those resistant to therapy with corticosteroids. A rapid haematological response support continuation of imatinib treatment. In a recent review, it was suggested that presence of splenomegaly or lung disease could be associated with a higher probability (89% and 96% respectively) of complete haematological response to imatinib (117). Imatinib is not useful in patients with I-HES.

Second generation TKI

Several alternative tyrosine kinase inhibitors have been tested *in vitro* and *in vivo* (animal models) for effects on FIP1L1-PDGFRA activity. Nilotinib (Tasigna®), is able to inhibit kinase activity of wild-type FIP1L1-PDGFRA (117). PKC412 (111), and sorafenib (119), are able to inhibit kinase activity of both wild-type FIP1L1-PDGFRA and the imatinib-resistant T674I mutant form. Likewise, emerging data on Dasatinib (Sprycel®) in these Ph[1] negative myeloproliferative disorders indicate the need for larger clinical studies (102,120).

Side effects: fluid retention, muscle cramps, diarrhea, skin rash and elevated liver enzymes, some dose dependent (121).

Bone marrow transplantation

Myeloablative and reduced-intensity conditioning allogeneic bone marrow transplantation has been used successfully in a few hypereosinophilic patients, and with disease-free survival reported for longer periods (10,122,123). But the transplantation related toxicity still remain a major problem, and the role of bone marrow transplantation in primary hypereosinophilic patients is not well established. This treatment can be considered for patients with FIP1L1-PDGFRA-positive patients, resistant or intolerant to imatinib therapy or FIP1L1-PDGFRA-negative patients, for instance FGFR1-positive eosinophilia (10,34), with progressive end-organ damage when standard therapies or any experimentel therapy have been exhausted.

Risk adaption and symptomatic treatment

No internationally recommendation is available of when to start – or wait – to treat patients with primary eosinophilia. The decision must be made by a careful diagnostic procedure, assessment of eosinophilia-related organ damage (table 1) and the eosinophil count. In case of moderate – severe eosinophilia it is not possible to predict when or how the patient may suffer eosinophilia-dependent symptoms (1-4), and a wait-and-watch policy may be hazardous. It is a complex, individually-based clinical decision, when to start and if it is possible to pause or stop at any time-point.

Treatment of eosinophilic-induced organ dysfunction is symptomatic according to the manifestations of in particular cardiac, pulmonary and skin symptoms. It may involve evaluation and assistance from other specialists in internal medicine.

Table 9. Present treatment options for eosinophilia due to a clonal haematological disorder, or iHES and iHE.

Medication and administration	Indications	Dose	Comments
Corticosteroids oral, or i.v.	First-line treatment unless FIP1L1-PDGFRA positive	Initial dose ≥40 mg prednisone q.d.	Side effects at higher dose or prolonged therapy
Hydroxyurea oral	Second-line treatment	1-3 g / day	Slow onset of action
Cladribine & cytarabine i.v.	Second-line treatment	2-CdA 12 mg /m^2 & Ara-C 1 g / m^2 / 5 d	Patient-population not characterized by clonality
Vincristine i.v.	Consider for counts >100,000/mm^3,	1-2 mg i.v.	For rapid reduction of eosinophil count
IFN-α s.c.	Second-line therapy	1-2 mU / m^2 q.d.	Slow onset of action
Cyclosporine A oral	Lymphocytic variant	100 mg maintenance / d	Induction therapy includes corticosteroids and hydroxyurea
Anti-CD52 antibody therapy (anti-IL5 antibody if approved, awaits official data)	Second line therapy, incl clonal eosinophilia	Stepwise increase (3 – 10 – 30 mg), maintenance	Immunosuppression and risk of opportunistic infections
Imatinib mesylate oral	First-line treatment for FIP1L1-PDGFRA positive. Consider for other refractory cases	100 - 400 mg q.d.	Together with corticosteroids if cardiac involvement

Closing statements.

Meeting a patient with eosinophilia represents a challenge – diagnostically and therapeutically, and the encounter will in most cases result in a multidisciplinary approach. Optimal diagnostic repertoire is important to give the best treatment, and possibly to monitor the outcome. It may be considered to centralize the patients without an obvious secondary cause for the eosinophilia to haematologic departments.

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References are listed as they appear in the text. In selected references a link is given in the first author's name to "pub-med." In some references a link is given in the Journal title directly to a "free article" if available. References in pdf format may be obtained also from
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