NORDIC MPN STUDY GROUP

Care program for the diagnosis and treatment of eosinophilia

3rd version, May 2018

The Nordic study group on myeloproliferative neoplasms (NMPN) 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. The first version was available online in April 2009.

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. The second version of guidelines published in September 2012 intended to give current best evidence, aid in interpretation in order to make decisions and was based upon the development reported in diagnostic work-up and therapy. The 2nd version has been viewed or downloaded more than 50,000 times from the Nordic and National homepages. The Nordic group appreciates this interest and hopes that the content of this 3rd version may be as useful in the coming years.

This revised, 3rd guideline 2018 is written for health professionals with a speciality or interest in haematology and in eosinophilia. It incorporates the diagnostic criteria established by the World Health Organization 2016, 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 (http://www.nmpn.org/), using a reference index. An algorithm which may be valuable meeting a patient is presented in addition to a detailed flow-schedule as previously. We thank publishers for accept to bring illustrations from published papers. We urge colleagues to send comments for improvements and how this electronic version works for you.

For the Nordic MPN Study Group, May 2018 - Writing committee:

Sakari Kakko, Oulu (SF)	e-mail: sakari.kakko@ppshp.fi
Gunhild Thomsen; Odense (DK)	e-mail: gunhild.nynke.thomsen@rsyd.dk
Kristina Carlson, Uppsala (S)	e-mail: kristina.carlson@akademiska.se
Henrik Hjorth-Hansen, Trondheim (N)	e-mail: henrik.hjorth-hansen@ntnu.no
Ole Weis Bjerrum, Copenhagen (DK)	e-mail: ole.weis.bjerrum@regionh.dk
Veli Kairisto, Turku (SF)	e-mail: velkai@utu.fi
Dia Issa Hassaf, Ringerike (N)	e-mail: issdia@vestreviken.no
Hans Wadenvik, Gothenburg (S)	e-mail: hans.wadenvik@telia.com
Christen Lykkegaard Andersen, Roskilde (DK)	e-mail: christen.andersen@sund.ku.dk

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Algorithm for your coat! – incl LINKS to key information

B-eosinophil granulocytes > 0.5 x10^9/l
in most patients > 1.5 x 10^9/l -> Definitions

Symptoms related to eosinophilia ->
Table 1 and Figure 2

Exclude the common causes of eosinophilia:
Drugs, allergic reactions, parasitic infestation
Take history for previous diseases, immigration, travel and clinical course. If no obvious reasons consider options below

URGENT: cardiovascular, pulmonary, neurological symptoms developed within weeks or hospitalized for whatever reason -> Table 1 and Figure 2 and Figure 6.
Decision: to initiate glucocorticoids

NOT urgent: minimal and no critical symptoms, manifestations and B-eosinophilia present for months and not progressing within weeks.
Decision: when to see patient again

Consider a probable diagnosis:
Primary (haematological, cytogenetic, rare) OR
Secondary (reactive, cytokine-driven, common) ->
Table 2, Table 3 and Table 4

Initial work-up in all patients:

1. basic laboratory organ-functions (haematology, kidney, liver, CRP, glucose)
2. symptomatic therapy for any manifestation in particular vital organ symptoms
3. consider conf. specialist in another discipline or national reference center
4. prioritize diagnostic tests according to probable causes and the severity of the condition – it may be necessary to initiate multiple tests simultaneously. If urgent (try to) obtain samples for cytogenetic tests before a specific treatment

Primary eosinophilia (cytogenetics):
Table 3, and Figure 3

Specific tests (rare causes):
Blood and bone marrow for morphology, cytogenetic and molecular biology (p 17–19) and Table 5
– per regional or national practice

Secondary eosinophilia (cytokines):
Table 2, Table 3 and Figure 3

Iatrogenic eosinophilia? Medicine list

Specific tests (common causes):
Biopsy, imaging, titers, quantitative parameters microbiological, functional organ status (particular heart and lung in "all patients") Table 5

1. prioritize samples as urgent when necessary, and ascertain receipt of material
2. perform analysis for both primary and secondary causes if necessary
3. consider secondary causes before primary causes
4. commence glucocorticoids if urgent manifestations (½-1 mg prednisolone / kg / day)
5. commence anti-microbial treatment when relevant
6. assess the need for supportive treatment (organ, allopurinol, diabetic)
7. cytoreduction with hydroxurea 1 – 2 gr /day or Ara-C (->Treatment) if clonal cause cannot be ruled out or severe eosinophilia and urgent symptoms, until clarification
8. plan for follow-up of effect, results of analysis and side-effects

Introduction

The eosinophilic granulocyte – the eosinophil – was described by Paul Ehrlich in 1879 examining cells in the blood smear. The name was given due to the coarse red granules, 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 the biological potential, is still a scientific fruitful topic. It is easy to identify an eosinophil in a smear or tissue sample due to the characteristic granules and the bilobar nuclei. It is a challenge, however, to disentangle the differential diagnosis in a clinical work-up and provide the patient the optimal treatment.

This 3rd version of the guideline maintains 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 is due to allergic conditions and in the developing countries invasive parasitic infections. A major development has been achieved in information on the pathophysiology of eosinophils in diseases, the diagnostic tools in particular in haematology and a translation to therapeutic improvements [1-11].

The Eosinophil Granulocyte

Eosinophils develop in the bone marrow from myeloid stem cells. The normal balance in production, trafficking through the blood stream, extravasation until cell-death in the tissues is regulated by cytokines. Feedback-systems involving IL-3, GM-CSF and in particular IL-5 are essential for eosinopoiesis and activation, interacting with transcription factors like GATA1 and PU.1 [3, 12-16]. Results from mice models have demonstrated that protein tyrosine phosphatase SHP2, which participates in signaling events by mediating T-cell development and function, regulates cytokine-dependent granulopoiesis and is a critical regulator of eosinophil differentiation [17].

The eosinophilic granulocytes circulate between 8 – 18 hours in the blood [18]. Then they egress to tissues, particularly the gastrointestinal tract, spleen, lymph nodes, thymus, uterus, guided by multiple factors, including cytokines, chemokines and adhesion molecules and may live for days to weeks, where mechanisms of enhanced survival in inflammation are described [5, 15, 19, 20]. In this way it is different from the neutrophil, which has a shorter life-span, but otherwise the two granulocytes share common features in development and function. The neutrophil is a bit smaller than the eosinophil (Fig. 1). The eosinophilic granulocyte is mobile and a highly interactive player, which influences the neighbouring tissue. The cell has an extensive collection of receptors and signals itself. It is able to secrete or express a wide range of receptors, cytokines, chemokines, cytotoxic enzymes, lipid mediators and neuromediators (Fig. 1). Eosinophils may assemble an NAPDH oxidase in the plasma membrane upon activation and produce toxic oxygen species, may be involved in antigen presentation and nuclear chromatolysis that cause the release of DNA neutrophil extracellular traps [15, 19, 21-23].

Figure 1. The ultrastructure of the human eosinophil granulocyte. From (23) with permision. A microscopic view in routine staining of a blood smear.

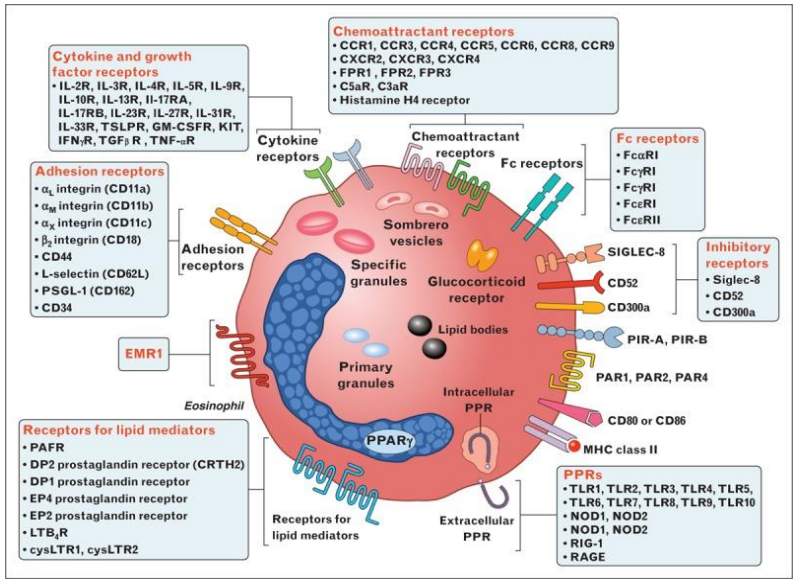


Illustration left. Human eosinophils display a wide spectrum of cell-surface receptors for cytokines and growth factors (e.g. IL5), chemokines, adhesion molecules, lipid mediators, chemoattractants, complement, immunoglobulins, Siglecs, histamine, PIRs, PARs, PPRs, CD40, CD80/CD86, and MHC class II. The epidermal growth factor-like module containing mucin-like hormone receptor 1 (EMR1) appears truly eosinophil specific. Eosinophils contain the glucocorticoid receptor in high copy number. The α variant of the glucocorticoid receptor is five-fold higher in eosinophils than in neutrophils making these cells highly susceptible to the therapeutic effects of glucocorticoids. Eosinophils contain specific granules containing several cationic proteins, primary granules, lipid bodies, and sombrero vesicles. CC, chemokine ligand; CCR, CC-chemokine receptor; CXCL, CXC-chemokine ligand; CXCR, CXC-chemokine receptor; PIRs, paired immuno-globulin-like receptors; PARs, proteinase-activated receptors; PPRs, pattern-recognition receptors.

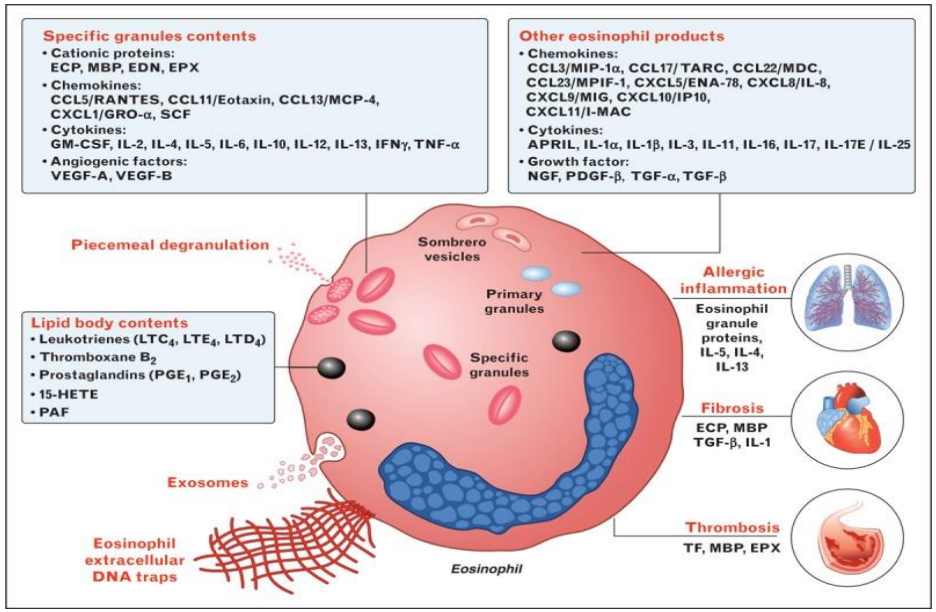
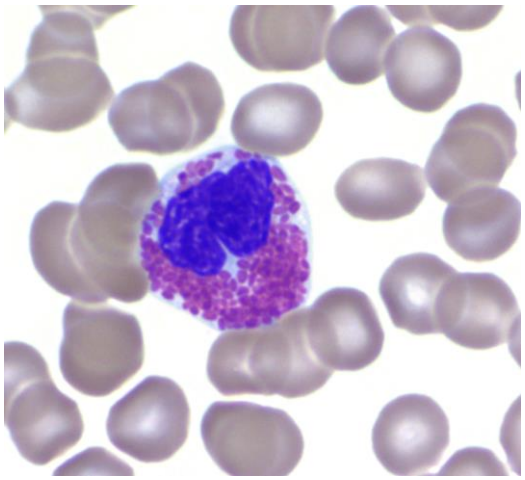


Illustration right. Eosinophils contain and/or release a wide array of preformed and de novo synthesized mediators important for their effector functions. Specific granules contain several cationic proteins, including MBP, ECP, EDN, and EPX. Eosinophils can degranulate by exocytosis or by piecemeal degranulation whereby individual granule contents are differentially secreted by activated eosinophils without disruption of the cell membrane. Sombrero vesicles are morphologi-cally distinct vesicles that carry granules to the plasma membrane. Lipid bodies are structurally distinct sites within eosinophils that are responsible for synthesis of eicosanoid mediators of inflammation. Eosinophils produce numerous chemokines, cytokines, growth and angiogenic factors that mediate allergic inflammation, fibrosis, and thrombosis. Eosinophils generate extracellular DNA traps and secrete exosomes. A non-exhaustive list of these products is shown in boxes. ECP, eosinophil cationic protein; EDN, eosinophil-derived neurotoxin; EPX, eosinophil peroxidase; MBP, major basic protein; PAF, platelet activating factor; PDGF, platelet-derived growth factor; SCF, stem cell factor; TF, tissue factor; TGF, transforming growth factor; VEGF, vascular endothelial growth factor.



Peripheral blood smear. The characteristic bilobar eosinophil with coarse orange / red granula is shown together with red blood cells. Oil immersion x100 © Henrik Hjorth-Hansen

The eosinophils are normally involved in modulation of innate and adaptive immunity, and affect mast cell activation, T-cell function, inflammatory responses and tissue repair and defence against helminths. All functions appear to be more complex than anticipated previously [15, 19, 21-24]. The eosinophils are involved in human health and disease states, but not consequently with concomitant blood eosinophilia. Accumulating data associates the human eosinophil with metabolic homeostasis (diabetes mellitus type 2), reproductive homeostasis (female fertility), inflammation (bowl disease). asthma and idiopathic lung fibrosis, demyelination (multiple sclerosis), cancer pathophysiology and more [15, 19, 23, 25-27]. The detailed understanding in eosinopoiesis, survival and functions may pave the way for improvements in therapy.

The gene expression, methylation patterns and profile of activation have been studied in humans, and more details may still be demonstrated in various disease states. Specific gene upregulation and identification of previously unidentified genes in eosinophils have been reported after *in vivo* allergen challenge, thus potential new candidates to elucidate contributions by eosinophil activity to airway biology, including asthma [28, 29]. Circulating human eosinophils have been reported to share a similar transcriptional profile in asthma, and conditions associated with eosinophilia, like prurigo, bullous pemphigoid, drug reactions, giardiasis, ascaridiosis, scabies and pulmonary aspergillosis [30]. Finally, a DNA methylation signature may distinguish eosinophilia in benign and malignant conditions [31]. The results achieved by molecular biological studies of eosinophils in various disease states may be an additional and rational way forward to differentiate the conditions and to develop more specific treatments.

Definitions and incidence

The upper reference limit in adults is (in most laboratories) 0.5 x 10^9/L. There is no sex difference or strict age correlation in adults. A number of eosinophils above this value is the hallmark of eosinophilia. Eosinophilia is regarded as mild if blood eosinophil count is 0.5 – 1.5 x 10^9/L, moderate if the count is > 1.5 – 5.0 and severe if the count is > 5.0 x 10^9/L [1, 4]. Routinely, a blood-eosinophil count above 1.5 x10^9/l is associated with hypereosinophilia, but symptoms may manifestate with mild eosinophilia.

Eosinopenia with absence of eosinophils may be associated with immune deficiencies and during treatment of allergic diseases, like asthma and urticaria [32]. Apparently, the "chronic" absence of eosinophils does not have any clinically impact. Studies in the pathophysiology of disorders, which have been associated with a contribution by eosinophil activity [26] have not been performed, the follow-up may be too short during eosinopenia, and the consequence of a helminthic infection is not clarified in patients with eosinopenia.

Eosinophilia is practically divided in three different categories [1, 4, 5, 31, 32] with different terms, relating to the causative state:

1. primary, (clonally eosinophilia),
2. secondary, (reactive/secondary or cytokine-driven eosinophilia to a likely causing condition), and
3. idiopathic hypereosinophilia (iHE).

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 [1, 2, 4-10, 33, 34]. The term in its original meaning is not useful anymore as a "working diagnosis over time," since the technical progress in diagnostic tools has reduced the time needed to perform and increased the number of clonal haemapoietic diseases where eosinophilia has a specific cause, and due to the risk of untreated eosinophilia.

The iHE is a situation with eosinophilia, but without a manifestation of organ damage of the eosinophils and without a specific primary or secondary cause after thorough diagnostic work-up [1, 2, 4-10, 33, 34]. The iHE with clinical manifestations is called a syndrome (iHES) provided no specific diagnosis is demonstrated, but the patient has symptoms attributable to the eosinophilia.

In primary eosinophilia it is the eosinophil granulocyte and precursors, which harbour a clonal aberration and represent the disease. In secondary eosinophilia it is another condition involving either infection, infestation, inflammation or malignancy which induce eosinophilia due to cytokines or inflammatory mediators, which affect eosinophils and precursors and reflect the disease. Familial presentation of eosinophilia is very rare.

The incidence of eosinophilia varies worldwide and is probably more likely to be due to infection in tropical regions, and to inflammation in industrialized regions. During a ten-year period an incidence of four to five percentage has been reported in individual persons who had a blood sample at the general practitioner in Copenhagen [35, 36]. The presence of eosinophilia is in almost all patients transient and therefore a low prevalence, but eosinophilia is as common as the incidence of the major diagnoses like diabetes or ischaemic heart disease in the Western world. Eosinophilia in routine blood samples is associated with an increased risk of bladder cancer, but not with other solid cancers [37]. The age-adjusted incidence of eosinophilia in USA has been reported to be 0.35 per million persons [38]. The incidence of eosinophilia in hospital patient populations has been reported to be above ten percentage in a Korean [39] and in an Indian university hospital [40]. The distribution of causes reflects the various specialties and routine in requesting differential counts [41]. The age of onset is very variable and this document addresses adult patients with primary eosinophilia in particular. However, the observation of eosinophilia should always merit a reflection as to why.

Eosinophilia and clinical presentation

The clinical challenge is to identify the cause of eosinophilia. The circumstances may vary from a completely unaffected person to a patient suffering acute and life-threatening (e.g. heart-manifestations) or chronic and disabling symptoms (e.g. itching). The combination of eosinophilia and symptoms caused by eosinophils is very important to relate and realize, in order to institute the correct diagnostic work-up and initiate 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 inflict the end-organ damage [15, 19, 42]. Some benign, clinical entities, most likely due to multifactorial causes have been recognized for many years and named as specific conditions, and they will briefly be described in the diagnostic algorithm.

Clinical manifestations differ very much between patients with eosinophilia. In patients with reactive eosinophilia, the primary disease or cause may also contribute to and dominate 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, and therefore be difficult to separate from each other. 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 and the access during the years to specific diagnostic, sensitive clonal tests. More than one organ may be involved in the individual patient, 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 of insufficiency or symptoms. Tissue biopsies should be performed in order to demonstrate infiltration of eosinophils and substantiate infiltration of eosinophils and establish the causative relation. In some cases, a biopsy is difficult to perform and other methods such as assessment of the clinical course, imaging, exclusion of other causes and response to

treatment for eosinophilia may be useful to estimate likelihood of diagnosis or end-organ damage. It is important to consider that the interpretation of biopsies and biochemical or imaging assessment may be blurred by glucocorticoid treatment, which frequently has a rapid effect.

The tissues most vulnerable and frequently affected by eosinophil products or penetration are the heart, respiratory system, gastrointestinal tract, the skin or the nervous system (Table 1) [1, 2, 4, 42, 43]. The most detailed retrospective, recent study on the initial clinical presentation in hypereosinophilic syndrome showed skin to be most and haematological manifestations to be least common as the clinical presentation. The study was based on data from 188 patients, who included clonal eosinophilia and iHES (fig. 2) [44].

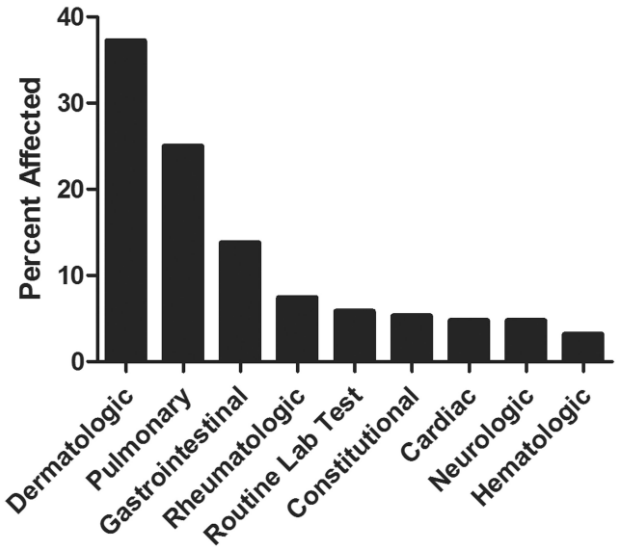


Figure 2. Initial clinical presentation by symptom in HES [44] with permission.

Although only 5% had cardiac complications at presentation of HES, including clonal eosinophilia, it is very important to emphasize that the incidence of cardiac symptoms develop later in 20% [8, 44], illustrating the need to perform status for vital organ functions (such as spirometry and echocardiography) at diagnosis of iHES and clonal eosinophilia.

The symptoms may all be a major source of morbidity in eosinophilia. Any symptom may be experienced in eosinophilia, for instance also in the eye: microthrombus formation, retinal arteritis [45] or renal: acute renal insufficiency, glomerulopathy and glomerulonephritis [46]. The hematopoietic system is involved in every case of primary eosinophilia, due to eosinophilia *per se* but depending on aetiology neutrophilia, basophilia, dysplastic features and immature white blood cells, anemia, thrombocytopenia or thrombocytosis may also be found in blood samples [47], but rarely manifest as the dominating manifestation (Fig. 2) [44].

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

Table 1. Clinical manifestations due to primary hypereosinophilia [1, 2, 4, 42, 43, 47].

Organ	Symptoms	Ref.
Heart	Myocardial necrosis (first stage), valvular involvement with insufficiency, mural thrombosis (in particular atrioventricular) and fibrosis (end stage) (Loeffler's endocarditis) manifesting in congestive (restrictive) cardiac insufficiency (both right and left), hypertrophy, dilation, arrhythmias, and pericardial effusion. Perhaps an increased risk in thrombotic events.	[48-52]
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.	[53-55]
Skin	Urticaria, (episodic) angioedema mostly in face or may be systemic, including pronounced weight changes. Pruritus, vesicles, papulous or nodulous lesions, mucocutaneous ulcers.	[56, 57]
Pulmonary	Chronic, generally non-productive cough. Bronchial hyper-activity may be present in some, and some may have pulmonary symptoms secondary to heart affection. Dyspnoea, pleural effusion, pleuritic pain.	[58, 59]
Gastrointestinal	Diarrhoea, intermittent or persistent, but various abdominal symptoms may be experienced, also depending on a more selective localization in the gastrointestinal tract – esophagus or (large) intestine.	[60-62]
Rheumatological	Arthralgia, mostly major joints, arthritis and myalgia, bursitis. Raynaud's phenomenon. Autoimmune or systemic phenomena mostly develop in rheumatic disorders with eosinophilia, e.g. polyangitis.	[63, 64]
Haematologic	Night sweats, weight loss, symptoms due to (hepato-) splenomegaly, and symptoms due to anemia.	[4, 44, 47]

Eosinophilia and paraclinical procedures

Eosinophils have normal functions and they increase in numbers in blood or accumulate in tissues due to relevant stimuli, primarily allergy and infections. This reactive and secondary hypereosinophilic state may thus be a physiological phenomenon. 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 mechanism. An eosinophilia may vary from mild to severe, irrespective of the condition, which vary from very rare to common prevalences.

Autonomous, primary and clonal proliferation of eosinophils are defined by the WHO 2016 classification update as myeloid or lymphoid neoplasms with eosinophilia and rearrangement of a number of specific genes: *PDGFRA*, *PDGFRB*, or *FGFR1*, or with *PCM1-JAK2*, although it is noted that eosinophilia may be absent in a subset cases [65]. These are all very rare diseases. Finally, the cause of persisting symptomatic hypereosinophilia may remain unclear and then carries the name “true” idiopathic hypereosinophilia (iHE) or with symptoms in a syndrome (iHES) [1, 7-10, 33, 34]. Both conditions remain a diagnosis *per exclusionem*, and it is recommended to perform a full diagnostic work-up because even infectious conditions may be subclinical [5].

Paraclinical procedures should be guided by the clinical circumstances, based on patient history, any manifestations interpreted as eosinophilia-related, and not primarily by number of eosinophil granulocytes in blood-samples. Differential diagnostic assessment is not determined by blood eosinophil count, because there is no correlation between the eosinophil count and organ involvement. The relevant analysis for primary and secondary eosinophilia may be performed in parallel depending on the severity of the clinical presentation.

Reactive eosinophilia

Reactive eosinophilia is *per se* a non-clonal disorder of the eosinophil where the production of eosinophils is increased as a response to exogenous stimuli, such as IL-5, IL-2, IL-3 and GM-CSF mainly produced by T-helper cells [12-16]. The causes of reactive eosinophilia are listed in Table 2 and 3 and further illustrated in Fig. 3 (diagnostic algorithm). These tables and the algorithm are based on excellent reviews [1-11, 47, 66] and the present 2016 WHO classification [65] (Table 4). The list in not complete, and many diagnoses are rarely associated with eosinophilia. The eosinophilia varies in intensity and is not consistently observed in the conditions.

Table 2. Causes of reactive eosinophilia.

1. Infections
    a. parasites, especially tissue invasive parasites, like filariasis, ascariasis, strongyloidiasis, trichinosis, toxocarisis, schistosomiasis, hookworm, giardia
    b. pathogenic gut infections: salmonella, campylobacter, Yersinia, amoeba
    c. chronic infections, in particular tuberculosis
    d. HIV, CMV, EBV, hepatitis
    e. scabies
    f. recovery from a bacterial infection

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

3. Drugs
    a. any drug, but especially seen with antibiotics, sulphonamides, antirheumatics, anticonvulsants and allopurinol, including DRESS syndrome (idiosyncratic reaction)

4. Lung diseases
    a. acute and chronic idiopathic eosinophilic pneumonia (Loefflers disease)
    b. eosinophilic asthma
    c. eosinophilic granulomatosis with polyangiitis (previously Churg-Strauss syndrome)
    d. 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, RA etc.)
    b. eosinophilic fasciitis
    c. sarcoidosis
    d. chronic pancreatitis
    e. Wells syndrome (eosinophil cellulitis)
    f. Kimuras syndrome
    g. eosinophilia-myalgia syndrome
    h. dermato-myositis
    i. hyper IgG4 syndrome
    j. graft versus host disease (GvH)
    k. congenital immune deficiency (e.g. Job hyper IgE syndrome, Wiskott-Aldrich)
    l. 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), systemic mastocytosis
    b. carcinomas (especially metastatic diseases)

8. Endocrine hypofunctions (i.e. Addison disease, hypothyroid conditions)

9. Clonal expansion of immunophenotypically aberrant T cells without overt lymphoproliferative disease (Gleich syndrome, episodic angioedema)

Idiopathic hypereosinophilia and neoplasms associated with eosinophilia

The traditional criteria for idiopathic hypereosinophilic syndrome consist of persistent eosinophilia $\geq$ 1.5 x 10^9/L (*per definition* for > 6 months, in practice in repeated blood samples over days to weeks) and target organ damage. The current WHO-criteria defines myeloid / lymphoid neoplasms with eosinophilia by specific clonality, although it is noted that eosinophilia may be absent in a subset of cases [65]. The term chronic eosinophilic leukaemia (CEL), which was used in the WHO 2008 classification, and idiopathic hypereosinophilic syndrome (iHES) are not included in the 2016 classification (Table 3 & 4), but it still is meaningful clinically to consider a condition with eosinophilia and a myeloproliferative phenotype with a clonal abnormality or blast cells account for >= 2 % of cells in the peripheral blood or >= 5% in the bone marrow as a chronic eosinophil leukemia (Not otherwise specified, CEL (NOS)) provided no other specific diagnostic criteria are met. Familial cases of eosinophilia have been reported [5, 33, 66].

Table 3. Diagnosis of neoplasms associated with eosinophilia and idiopathic hypereosinophilia, modified from WHO-criteria 2016 [65]

Required: Persistent eosinophilia $\geq$ 1.5 x 10^9/L in blood, increased numbers of bone marrow eosinophils, and myeloblasts < 20% in blood or marrow.

1. Exclude all causes of reactive eosinophilia secondary to:
    a. Drug induced (iatrogenic)
    b. Allergy
    c. Parasitic and other infections
    d. Inflammatory conditions, including solid cancer
    e. Pulmonary diseases (hypersensitivity pneumonitis, Loeffler´s etc.)
    f. Autoimmune conditions
2. Exclude all neoplastic disorders with secondary, reactive eosinophilia:
    a. T cell lymphomas, including mycosis fungoides, Sezary syndrome
    b. Hodgkin lymphoma
    c. Systemic mastocytosis
    d. Acute lymphoblastic leukaemia
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)
    b. Ph' negative myeloproliferative neoplasms (PV, ET, MF)
    c. Myelodysplastic / myeloproliferative neoplasms
    d. Myelodysplastic syndrome
4. Acute myeloid leukaemia, including those with inv(16)(p13q22), t(16;16)(p13;q22)
5. Exclude T cell population with aberrant phenotype and abnormal cytokine production (Gleich Syndrome)
6. Demonstrate a myeloid / lymphoid neoplasm with eosinophilia (WHO 2016)
    a. Neoplasms with *FIP1L1-PDGFRA* fusion gene or other rearrangements of *PDGFRA*
    b. Neoplasms with t(5;12)(q31-35;p13) or other rearrangements of *PDGFRB*
    c. Neoplasms with rearrangements of *FGFR1*
    d. Myeloid neoplasm with t(8;9)(p22;p24.1);*PCM1-JAK2*
7. Demonstration of a clonal cytogenetic or molecular genetic abnormality, or blast cells are more than 2% in the peripheral blood or more than 5% in the bone marrow, diagnosis chronic eosinophilic leukaemia, not otherwise specified (CEL, NOS).

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)

Primary 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 myeloid/lymphoid neoplasms with eosinophilia, which often has the phenotype of a chronic eosinophilic leukaemia (CEL) and decreased the number of idiopathic hypereosinophilic syndrome (iHES) diagnosis.

The 2016 WHO criteria for the diagnosis and classification of myeloproliferative neoplasms have moved towards predominantly genetic classification system with disease specific molecular markers [65] (Table 4). Thus, myeloid neoplasms with molecularly characterized eosinophilia (i.e. *FIP1L1-PDGRFA* fusion gene) previously classified under CEL/HES are now assembled into a 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 Tables 3 and 4.

Table 4. Myeloid / lymphoid neoplasms associated with eosinophilia WHO 2016 [65]

NEOPLASMA	PRESENTATION	GENETICS
PDGFRA	Eosinophilia ↑Serum tryptase ↑bone marrow mast cells	Cryptic deletion 4q12 FIP1L1-PDGFRA and more than 66 other partners
PDGFRB	Eosinophilia CMML with eosinophilia	t(5;12)(q32;p13.2) ETV6-PDGFRB and more than 25 other partners
FGFR1	Eosinophilia Often presents like T-ALL or AML, previously termed stemcell leukaemia/ lymphoma syndrome	Translocations with 8p11.2 FGFR1-multiple partners
PCM1-JAK2	Characterized by eosinophilia, BM of left-shifted erythroid predominance, lymphoid aggregates, and often myelofibrosis, mimicking PMF. Rarely present as T- or B-lymphoblastic leukemia (ALL)	t(8;9)(p22;p24.1) *PCM1-JAK-2*

Laboratory investigations and imaging studies in unexplained persistent eosinophilia

The diagnostic work-up of unexplained persistent eosinophilia relies on clinical history, including allergy, drug exposure, immigration and social background, and travel history, as well as symptoms and signs which may indicate a reactive eosinophilia or a specific organ related eosinophilic syndrome. The investigations that are indicated are listed in Table 5 [1-11, 44, 47, 66] and can be focused by relevant information and careful evaluation, in particular on exposures, symptoms, results of available lab data, thorough clinical examination and on the basis of the working diagnosis. Most patients have a transient and reactive eosinophilia.

Table 5. Investigations in unexplained and persistent blood eosinophilia.

1. Consider pause or change in medication, if relevant
2. Blood counts and morphology to be assessed for
    a. severity of eosinophilia and
    b. abnormalities in other blood cells, which might point to clonal eosinophilia
3. Plasma total immunoglobulin E, and specific tests for allergy (skin prick tests and allergen specific IgE tests) if indicated.
4. Investigation of microbiological diseases
    a. stool (x 3) for microscopy and / or cultures for pathogens, by PCR when available
    b. serological tests for suspected parasitic, bacterial or viral infections
    c. specific studies according to focal findings (imaging studies, spinal fluid, urine, blood smear, tissue biopsy etc.)
5. Blood and bone marrow aspiration and biopsy from the iliac crest
6. Cytogenetic analysis on bone marrow aspirate
7. Molecular biological or FISH analysis on bone marrow aspirate or peripheral blood cells specifically for *PDGFRA, PDGFRB, FGFR1 and PCM1 gene rearrangements*, or NGS for myeloid panel when available
8. Assessment of relevant tissue biopsies (malignant, infection, inflammation)
9. Plasma tryptase (mast cell activity), erythropoietin (myeloproliferation), IgG total and IgG4
10. Investigation of blood T-cells by immunophenotyping and molecular analysis for T-cell receptor status for possible cytokine-driven eosinophilia
11. Imaging studies using HR or CT scan, prioritizing PET technique, ultrasound of chest and abdomen for underlying lymphoma or non-haematological malignancy
12. Plasma troponin and pro-BNP and ECG / echocardiogram, using CT or MR scan (incl. gadolinium if available) if symptomatic
13. Pulmonary function tests, and bronchoalveolar lavage if clinically indicated
14. Serum interleukin 5 concentration (if available)

The diagnostic work-up of unexplained eosinophilia can be divided in two categories It is sometimes necessary to do both categories of evaluation at the same time.:

I. tests to diagnose clonal eosinophilia should be performed directly if the suspicion of primary haematological disease is high and if signs of affected end organsare present.
II. investigation of reactive causes of eosinophilia (with follow-up to confirm persistency). Analysis should be performed on samples taken before the initiation of treatment, in particular if glucocorticoids are used.

Use of the diagnostic armamentarium for the numerous causes of eosinophilia (Tables 2-5) may include costly procedures, in particular involving molecular analysis principles (PCR, NGS) or some imaging techniques (PET-CT or MR scanning). No doubt, the number of tests required from specialised laboratories is sometimes higher than necessary. The special tests should be used e.g. in case of a relevant travel exposure for helminth infections and relevant symptoms. The severity and development of eosinophilia may be indicative of a clonal condition [67], and thus support when to use tests for diagnostic aberrations (Table 4). Still, the overlapping clinical presentations and symptoms make it difficult to draw conclusions with certainty and exclude tests in many patients. Analysis by molecular biology methods are often performed in “packages,” decided by the laboratory, which may be more economic than sequential analysis and less time consuming.

It is recommended to use the special analysis carefully, and it may be necessary in the local/regional laboratories to decide how to use the NGS tests, including both DNA- and RNA-based analysis, and then replace other tests previously used (like cytogenetics or specific PCR analysis). NGS is still not routine at all institutions, and the data also need clarification for most clinicians in order to interpret the result correctly.

The definitive tests for clonal eosinophilia include methods, which are performed routinely (counts and morphology) and specific analysis (all other) which may be performed in a prioritized succession depending on the clinical circumstance (the patient status). Treatment by corticosteroid, a tyrosine kinase inhibitor or cytostatic therapy (e.g. hydroxyurea) may be initiated separately or in combination in urgent situations with close monitoring. Urgent situations include: cardiovascular (reduced EF, thrombosis), pulmonary (reduced functional activity) and neurologic (central or peripheral functional symptoms) symptoms, which have developed within weeks or for any reason leads to hospitalization.

1. **Full blood count.** Diagnosis of persistent hypereosinophilia and suspicion of acute or chronic eosinophilic haematological disorders arises from the patient history and full blood counts including white cell differential. Absolute eosinophil count should be $\geq 1.5 \times 10^9$/L, but the number of eosinophils is not crucial.

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. Eosinophils may disintegrate performing the smear, and be visible like smudge cells, with the coarse granules visible in the vicinity.

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 analysed when indicated by the morphological findings. Abnormal bone marrow morphology has been reported to be a tool, used carefully [68] by e.g. cellularity, megakaryocyte numbers and morphology, fibrosis, dyspoiesis and eosinophil pathology to discriminate chronic eosinophilic conditions without specific clonality from iHES [69].

4. **FISH on blood or bone marrow aspirate.** No specific CD-pattern is useful in the analysis of eosinophils *per se*, because the cell has no unique marker or profile. It has been considered that EMR1 only may be expressed on the surface of eosinophil granulocytes [70]. Other surface markers and potential targets for treatment like CD52 may be demonstrated prior to treatment (Figure 1). Specific fusion genes, like the FIP1L1-PDGFRA 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 [47]. FISH analysis may be false negative and follow-up examination by a PCR technique is recommended if the clinical interpretation needs to be thoroughly substantiated.

5. **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. The clonal aspect may in female patients be demonstrated by X-chromosome inactivation, HUMARA test [71]. This analysis needs to be validated

more in patients with eosinophilia, but may characterize a clonal state in idiopathic hypereosinophilia.

6. **Molecular analysis for PDGFRA, PDGFRB, FGFR1 and PCM1, ideally by NGS technique using a panel of markers for fusion genes.** Peripheral blood sample is suitable for RT-PCR analysis in most cases. 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. The number of potential myeloid/lymphoid fusion genes is very high [10].

7. **Molecular analysis for other genes.** RT-PCR on bone marrow or peripheral blood for WT1 gene has been reported to discriminate secondary or reactive eosinophilia from idiopathic hypereosinophilia and neoplasms with eosinophilia, both of which show significantly higher levels. The transcript amount in bone marrow correlated with measurements in blood, and was representative for response during treatment of the disease [72]. However, the method is not used routinely due to the increasing number of identified clonal markers. WT1 and the HUMARA (in female patients only) test may be considered to be of experimental character to demonstrate clonality. More mutations may be identified in the coming years by gene expression profile analysis, which in the same way may represent a clonal marker for diagnosis and monitoring [31].

8. **Additional tests.** Plasma (or serum) markers for chronic myeloproliferative disorders include elevated tryptase and decreased erythropoietin as well as demonstration of mutation in blood cells, typical for Ph'negative neoplasms. Measurement of eosinophil components, like major basic protein, eosinophil peroxidase or eosinophil-derived neurotoxin (Fig. 1), if available may reflect an eosinophil activity and may contribute to explain e.g. cardiac involvement. The eosinophil parameters are used in some institutions, may in addition serve for monitoring during treatment, but the results are not part of any diagnostic criteria, and do not seem to offer added value compared to other, more specific tests.

Tests that should be performed to diagnose (or exclude) reactive eosinophilia and / or demonstrate target organ dysfunction includes (Tables 1,2):

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, or by PCR tests when available.

3. **Tests for abnormal T-cells in peripheral blood.** Consider the possibility of abnormal T-cells as the cause of reactive eosinophilia (Gleich syndrome). Analyze the immunophenotype of blood T-cells with multiparameter flow cytometry. T-cells with aberrant phenotype (CD3+/4-/8- or CD3-/4+) indicate reactive eosinophilia. 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 / plasma IL-5 measurement can also be helpful and is recommended if 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 complications. These investigations include ECG, echocardiogram – or CT / MR scan (including gadolinium when relevant with more details), plasma / serum troponin concentration or pro-BNP, chest X-ray, pulmonary function tests including reversibility. Also bronchoalveolar lavage may be performed, if clinically indicated.

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

Approaching the patient with eosinophilia

Handling of patients with eosinophilia, irrespective of the degree of eosinophilia – although in principle more urgent the higher the count at diagnosis – therefore imply a classical clinical approach. Obtaining a sufficient and thorough disease history, focusing on travelling, previous and present social circumstances, infectious exposures and symptoms, autoimmune disease, drugs, dyspnea, wheezing, 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 (Tables 1-5).

One diagnostic / clinical algorithm when meeting the patient with eosinophilia is illustrated in Fig. 3. This algorithm for diagnostic work-up is combined with every other differential diagnosis in eosinophilia given in this guideline and previous reviews [1-11, 44, 47, 66]. Often, the initial diagnostic work-up, and therapy, involve a multidisciplinary collaboration of diagnostic and clinical departments. Ideally, the collaboration is established as a highly specialised centre, in the same hospital, or a collaboration established between relevant departments in a few hospitals, preferably in a close proximity geographically. The collaboration also includes named colleagues within the center and a regular mode-of-collaboration, e.g. by conferences. A list of contacts is given at the end of this care program.

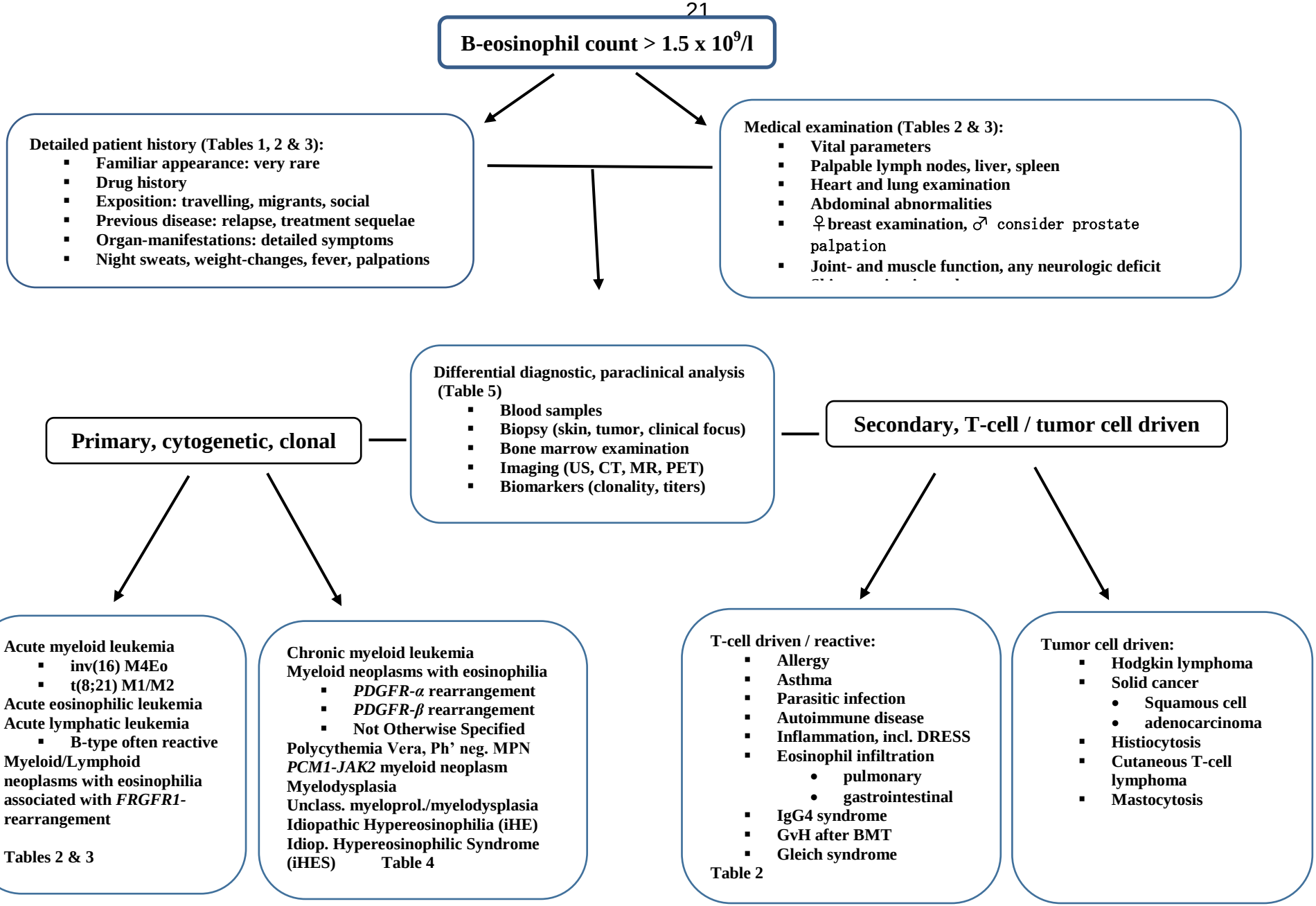

B-eosinophil count > 1.5 x 10^9/l
Detailed patient history (Tables 1, 2 & 3):
Familiar appearance: very rare
Drug history
Exposition: travelling, migrants, social
Previous disease: relapse, treatment sequelae
Organ-manifestations: detailed symptoms
Night sweats, weight-changes, fever, palpations
Medical examination (Tables 2 & 3):
Vital parameters
Palpable lymph nodes, liver, spleen
Heart and lung examination
Abdominal abnormalities
♀ breast examination, ♂ consider prostate palpation
Joint- and muscle function, any neurologic deficit
Differential diagnostic, paraclinical analysis (Table 5)
Blood samples
Biopsy (skin, tumor, clinical focus)
Bone marrow examination
Imaging (US, CT, MR, PET)
Biomarkers (clonality, titers)
Primary, cytogenetic, clonal
Secondary, T-cell / tumor cell driven
Acute myeloid leukemia
inv(16) M4Eo
t(8;21) M1/M2
Acute eosinophilic leukemia
Acute lymphatic leukemia
B-type often reactive
Myeloid/Lymphoid neoplasms with eosinophilia associated with FRGFR1-rearrangement
Tables 2 & 3
Chronic myeloid leukemia
Myeloid neoplasms with eosinophilia
PDGFR-α rearrangement
PDGFR-β rearrangement
Not Otherwise Specified
Polycythemia Vera, Ph' neg. MPN
PCM1-JAK2 myeloid neoplasm
Myelodysplasia
Unclass. myeloprol./myelodysplasia
Idiopathic Hypereosinophilia (iHE)
Idiop. Hypereosinophilic Syndrome (iHES) Table 4
T-cell driven / reactive:
Allergy
Asthma
Parasitic infection
Autoimmune disease
Inflammation, incl. DRESS
Eosinophil infiltration
pulmonary
gastrointestinal
IgG4 syndrome
GvH after BMT
Gleich syndrome
Table 2
Tumor cell driven:
Hodgkin lymphoma
Solid cancer
Squamous cell
adenocarcinoma
Histiocytosis
Cutaneous T-cell lymphoma
Mastocytosis

Figure 3. Diagnostic approach in eosinophilia. M1, M2, M4 FAB classification acute myeloid leukaemia, FGFR fibroblast growth factor receptor, PDGFR platelet derived growth factor, NOS not otherwise specified, PCM pericentriolar material, JAK Janus kinase, MPN myeloproliferative neoplasm, MDS myelodysplasia, GvH graft versus host, BMT allogeneic bone marrow transplantation, HES hypereosinophilic syndrome

Eosinophilia in haematologic bone marrow diseases

Reactive eosinophilia thus accounts for the majority of cases of eosinophilia, whereas more rare cases of eosinophilia are the results of inherent defects in the eosinophil itself.
In recent years two clinical phenotypes of eosinophilia have been described in primary eosinophilia – a myeloid and a lymphoid (or T- [73-75]) variant with individual variations in manifestations. (Table 6). The term “myeloid variant” has been implemented because of clinicopathologic similarity to CML and the MPNs [4]. The lymphoid variant is characterized by an abnormal T-cell population as demonstrated by lymphocyte immunophenotyping or T cell receptor gene rearrangement studies which associates with excessive eosinophilopoietic cytokine production. Hence the eosinophils themselves are without inherent pathology. Consensus criteria for the diagnosis of lymphocyte-variant hypereosinophilia have not been established [4, 47, 76].

Table 6. 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	Increased S-IgE
Increased serum vitamin B12 & tryptase	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	Approximately 25% of HES patients
PDFGR disorders	T-cell phenotype subsets
A T-cell clone may be detected by T cell receptor analysis as described in the section on diagnostic work-up or analysis for aberrant T-cell phenotypes (CD3+/4-/8- or CD3-/4+), associated with eosinophilia by IL-5 production.	

The initiating examinations of the blood smear, standard laboratory workup, bone marrow morphologic, cytogenetic, and immunophenoytpic assessment will most likely determine the cause of eosinophilia by a WHO-defined myeloid neoplasm such as systemic mastocytosis, CML, AML, MDS, or MDS/MPN overlap disorder (e.g. CMML) [4]. In addition, an extensive number of cytogenetic aberrations associated with CEL have been reported in clonal eosinophilia by the use of conventional
banding techniques involving translocations, additions, insertions, deletions with the identification of some 60 different fusion genes which has emphasized the pivotal role of constitutively activated tyrosine kinases (TK) in the pathogenesis of these disorders [66, 77-80].

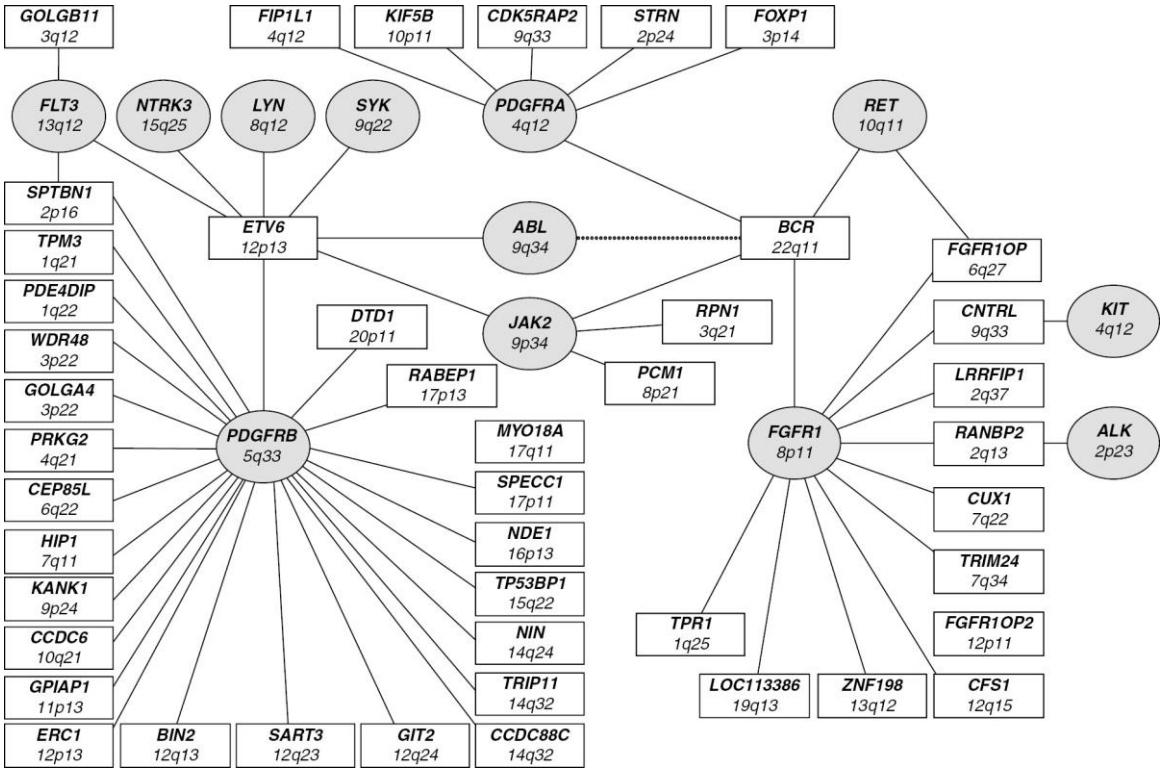


Figure 4. Network of tyrosine kinase fusion genes in myeloid and lymphoid neoplasms with eosinophilia and related disorders From [81] with permission.

Molecular evidence of PDGFRA or -B, or FGFR1 fusion gene products is often accompanied by its karyotype counterpart such as rearrangement of 4q12 (PDGFRA fusion partners besides FIP1L1 which is cytogenetically occult), 5q31-33 (PDGFRB) or 8p11-13 (FGFR1) [4, 82]. Importantly, laboratory evaluation of the FIP1L1-PDGFRA gene fusion involves RT-PCR or FISH and is an important analysis due to the excellent prognosis of this particular condition (see treatment). This dysregulation of tyrosine kinase function originates from the interstitial deletion on chromosome 4 where PDGFRA fuses with the FIP1like1 (FIP1L1) gene and is by far the most common fusion gene in primary eosinophilia and has been described in detail [76, 83-86]. The FIP1L1-PDGFRA fusion is not entirely unique for CEL and has also demonstrated in cases of AML and T-cell lymphoblastic lymphoma associated with eosinophilia [87]. In addition, there are several rare and structurally similar fusions involving other TK, e.g., ETV6-ABL1 or ETV6-FLT3, but these are exceedingly rare [81]. Another elegant and functional clinical-biological approach is shown in Fig. 5.

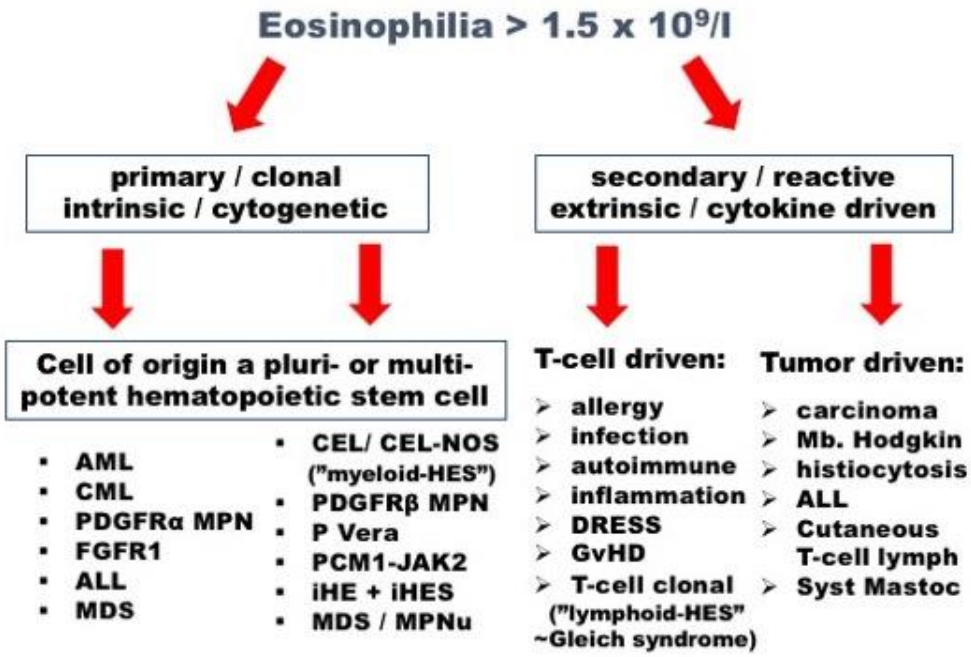


Figure 5. Classification of eosinophilic disorders based on biology – caused by cytogenetics or cytokines. Eosinophilia is either mediated by cytokines (in particular IL-5) or a consequence of mutations, translocations or other cytogenetic abnormality in hematopoietic stem cells leading to predominant eosinophil differentiation. ALL acute lymphocytic leukemia, AML acute myeloid leukemia; CEL chronic eosinophilic leukemia; CML chronic myeloid leukemia; DRESS drug reaction eosinophilia systemic symptoms; FGFR1 fibroblast growth factor receptor 1 driven; GvHD graft versus host disease; iHE idiopathic hypereosinophilia, iHES idiopathic hypereosinophilic syndrome; MDS myelodysplastic syndrome; MPN(u) myeloproliferative neoplasm (unclassified); PDGFRA/B platelet derived growth factor A/B, P Vera polycythemia vera; Syst Mastoc systemic mastocytosis [88, 89].

Optimal management of patients with primary eosinophilia is dependent on the correct diagnosis, but since a substantial part of patients do not demonstrate aberrant clonal characteristics diagnostic workup may still be challenging in spite of the last decades´ improved molecular understanding.

Treatment of eosinophilia

Several reviews have been published in the field of eosinophilia [1, 4, 6, 34, 47, 79, 88, 90-96]. In patients with reactive causes antibacterial, immunosuppressive, cytoreductive or symptomatic therapy is recommended [66, 97, 98]. The following recommendations have been influenced by the reviews and case reports published in eosinophilia, although it may be difficult to interpret clonality in many, older reports [93]. Therefore, in the following hypereosinophilia refers to conditions with clonal eosinophilia or to iHES or to iHe, and reflects current treatment principles. Novel targeted treatment options may become available within a few years [99], and patients with primary eosinophilia must be considered for clinical trials whenever possible.

The aim of the therapy is to reduce the eosinophil count in the blood and to reduce symptoms and tissue damage caused by eosinophilic infiltration. The urgency of the treatment depends on the severity of the symptoms. Immediate treatment should be started in rare patients with signs of leucostasis (leucocytes, i.e. eosinophils, over 50-100 x 10^9/l) and in patients with suspected thromboembolic complications or severe pulmonary or cardiac involvement due to hypereosinophilia. Some patients with marked and sustained eosinophilia may never experience end-organ damage and therefore require no treatment. However asymptomatic patients with rearrangements of PDGFRA or PDGFRB should be treated. As always, treatment principles include the most effective therapy, with few adverse events and risk of long-term toxicity, to achieve and maintain a clinical remission and improve QoL. However, many treatments are used off-label, based on a rational mode-of-actions and treatment in similar myeloproliferative or lymphoproliferative conditions.

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, Figure 2) 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 [15, 16, 100, 101], 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. Asymptomatic patients requiring no therapy should be monitored regularly to detect new symptoms and signs. Asymptomatic cardiac (troponin levels, echocardiography) and pulmonary (pulmonary function tests and thorax x-ray) complications should be ruled out in patients that are to be followed. Treatment of eosinophilic-induced organ dysfunction is symptomatic according to the manifestations of in particular cardiac, pulmonary and skin symptoms. Diagnosis and treatment of patients with primary eosinophilia represents a multi-disciplinary challenge.

Currently, the treatment of hypereosinophilia should be based on disease severity and detection of pathogenic genetic variants. For FIP1L1-PDGFRA-positive patients, imatinib is first line therapy. For others, corticosteroids are generally recommended firstly. Hydroxyurea, INFα, 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. For patients with an eosinophilia-associated WHO-defined myeloid malignancy (e.g. AML, MDS, systemic mastocytosis, CML and MPNs) therapy follows disease-specific guidelines and if organ damage is suspected to be related to eosinophilia, corticosteroids should added to the therapy, until symptom-control and haematological remission is obtained, and then tapered.

Rarely, leukapheresis may be considered at presentation in cases with extreme eosinophilia and life-threatening organ manifestations. Some experiences have recently been reported [102].

A similar risk-stratification and -adapted therapeutic approach to patients with HES has been introduced [4]. The concept is based on an upfront identification of subtype of eosinophilia by specific diagnostic tests for the clonal markers and characterization in

accordance with current WHO classification. It is not possible to foresee what duration and severity of eosinophilia causes tissue damage. The purpose of treatment in primary eosinophilia is to mitigate eosinophilia-dependent organ damage [4]. When to commence cytoreductive therapy is based on an individual assessment and should include comorbidity and in particular cardiac, pulmonary diagnosis, treated in accordance with guidelines, and therefore may be in collaboration with a colleague in the relevant specialty.

The relationship between the absolute eosinophil count and organ damage is not consistent [103-105]. Other markers of disease progression have been proposed, but none have been validated, and no response criteria have so far been presented. One reason is the lack of standardization of molecular methods, and perhaps reproducibility among different laboratories. Nevertheless, as 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 [76, 106, 107], perhaps in rare cases WT-1 [72] or other clonal parameters, just like BCR-ABL in CML. In HES the numbers of phenotypically aberrant lymphocytes can be evaluated by FACS [108, 109]. 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 studies is given in Table 7.

Table 7. 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-eosinophils / total WBC	Normalization < 0.5 x 10^9/l, within normal range	≥ 50 % reduction in blood eosinophil number	< 50 % reduction
Hgb, platelets, LDH	Normalization of all (if abnormal at diagnosis)	≥ 50 % improvement of any	< 50 % improvement
Blood / plasma parameter related to eosinophilia (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 % reduction 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 (splenomegaly, cardiac, pulmonary etc.)	No symptoms, without symptomatic treatment and evaluated clinically	No symptoms, but treated symptomatically (ACE inhibitors, inhalations etc.) due to eosinophilia sequelae	+ symptoms and requiring treatment
Organ involvement resolved by laboratory tests (splenomegaly, cardiac, pulmonary 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 improvement – or worsening due to eosinophilia
Quality of life	Improvement defined by a scoring system	No improvement defined by scoring	Worsening of QoL

A “true” complete remission should fulfil all criteria in the column. A so-called PR may be obtained if at least half the parameters, evaluable for the patient, actually fulfil 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 7 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 7, 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 [44].

The principles in the treatment algorithm is given in Fig. 6 and the most common treatments described in more detail in paragraphs below and summarized in Table 8.

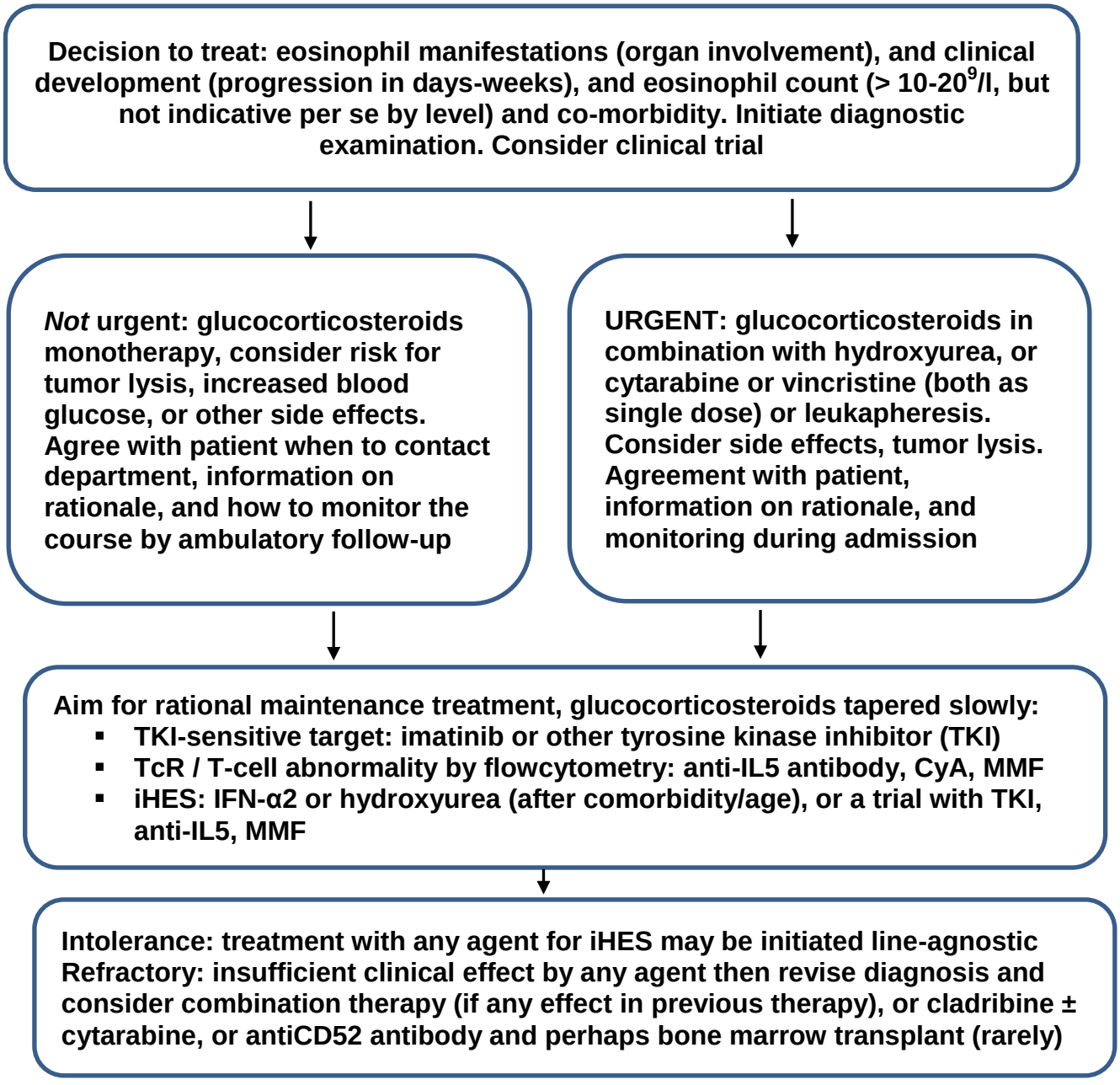


Fig. 6 Treatment principles in primary eosinophilia (overview).

The figure illustrates the options of therapy, based on specific targets and in (true) iHES. A trial with TKI, anti-IL5 antibody and other agents should be for at least 6-12 weeks in relevant dosage, and with pre-defined criteria for success (symptoms, eosinophil count, side-effects). Abbreviations: CyA cyclosporine A; HU Hydroxyurea; INF interferon; MMF mycomofetil; TKI tyorine Kinase Inhibitor. Related information in the quick clinical guide, table 1, table 5, fig. 3, table 6, and table 8.

Besides the treatments described here, a number of other cytotoxic (methotrexate, purinethol, etoposide, fludarabine, cyclophosphamide) or immunosuppressive (azathioprine, thalidomide) therapies have been reported in few patients with variable results, and often discontinued albeit administered in a rational setting [1, 4, 6, 34, 44, 47, 79, 88, 90-96]. Prospective, randomized clinical trials in primary hypereosinophilia are needed with multicentre collaboration [110].

Glucocorticosteroids

Glucocorticosteroids are first-line treatment for most patients with hypereosinophilia, except the FIP1L1-PDGFRA positive eosinophilias. Glucocorticosteroids are also indicated, together with imatinib, in patients with FIP1L1-PDGFRA-positive eosinophilia and signs of myocarditis [111]. For FIP1L1-negative patients the usual starting dose is ½-1 mg oral prednisone/kg body weight/day. When there is s suspicion of life-threating organ involvement, 1 mg/kg/day of intravenously methylprednisolone even to initially 1 g pulse/day for one to two days is recommended. Up to 85 % of patients will respond to this treatment [44] and in that case, the dose can be slowly tapered over 2-3 months to the lowest possible maintenance dose, that controls the symptoms and blood eosinophil levels (to less than 1.5). If eosinophilic levels are not decreased within one week of treatment, the dose should be increased, and in patients with eosinophils over 1.5 after one month of corticosteroid therapy, other therapies should be considered. Prophylaxis against osteoporosis must be considered, and also against opportunistic infections for patients requiring maintenance treatment and depending on concomitant treatment and conditions. Rarely, patients with eosinophilia are resistant to glucocorticoids.

A history of angioedema, a profound and rapid eosinopenic response to challenge with prednisone, high serum IgE levels, and no hepatosplenomegaly have been considered to be favourable predictors of long-term response to corticosteroid treatment [43]. Due to the current more specific diagnostic tools and classification, these parameters may not be applicable as prognostic factors in all patients anymore. However, corticosteroid toxicity is common (cataract, hyperglycemia, hypertension, weight gain, increased risk of infection, increased risk of gastritis etc.) and steroid sparing alternatives are usually needed, especially if the maintenance dose of prednisolone is over 10 mg/day or significant side effects during therapy develop.

Myelosuppressive agents

Hydroxyurea

Hydroxyurea (1-3 g/day) is the myelosuppressive drug that is preferably used to lower the eosinophil count, as monotherapy or as a combination with corticosteroids, IFN-α or imatinib. A response to treatment with hydroxyurea is commonly seen within 2 weeks and it is not always effective as a single agent in cases where a rapid decrease in (very high) eosinophil count is needed.

Side effects: myelosuppression, potential carcinogenic and teratogenic, gastrointestinal toxicity, (irreversible) leg ulcers, skin malignancy, (rarely) hair loss, nail problems and skin rash [112]. Consider age of patients when used as maintenance.

Vincristine

Vincristine can be considered as an additional, single-dose treatment to lower the eosinophils in patients with extremely high eosinophil counts (>50-100 x 10^9/l). It should not be used for long term management of eosinophilia. However, it has been used in some cases [95, 113]. The recommended dose for adults is 1-2 mg intravenously as a single dose, with days-weeks interval, but the treatment must not be used for maintenance.

Side effects: neurotoxicity, including obstipation [114].

Immunomodulatory therapy

Interferon-α

Low doses of IFN-α are often effective in patients refractory to other therapies or as corticosteroid-sparing agent, but the response usually first becomes evident after several weeks of treatment [110, 115]. The treatment depends which interferon medication is available. Most convenient for patients is to administer interferon-α treatment in a pegylated formulation where adverse events may be less manifest. The initial dose could

be 1 MU subcutaneously three times a week and increased to 3-4 MU three times a week, if tolerated. Low-dose hydroxyurea (500 mg daily) potentiates the effect of IFN-α [116]. PEG-IFN-α is given in doses similar to (other) myeloproliferative disorders, and it is considerate to initiate treatment in low doses, like 45 microgr. subcutaneously (Pegasys®) once weekly in order to reduce side effects, and concomitantly taper any other treatment. The proper dose is then identified during follow-up by eosinophil count, any organ symptoms and the presence of side effects. Treatment dose and interval, which may be 7–14 days, is individual when treating with interferon-α2.

Monotherapy with IFN-α should be avoided or used with caution in L-HES; in vitro data have demonstrated an inhibitory effect of IFN-α on spontaneous apoptosis of clonal CD3−CD4+ T- cells [117]. In this setting a corticosteroid should be added because of its proapoptotic effect on the clonal T-cells. IFN-treatment may be used in pregnancy, as in other MPNs [118], and also in female patients with eosinophilia during pregnancy [119]. The pegylated forms of IFN2a and α2b may both be used for long-term treatment, which is considered to be safe in myeloproliferative disease, but solid data is lacking in eosinophilia [110].

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

Cyclosporine A and mycomofetil

Some case reports and one study have been published demonstrating a maintenance effect of cyclosporine A therapy in adult patients, in particular with L-HES and T-cell receptor rearrangements [44, 111, 120]. This is well explained by an inhibitory effect on the production of IL-5 [15, 66, 101, 121]. Also, mycophenolate mofetil may be effective [44], perhaps with a better side-effect profile.

Side-effects: hypertension, renal insufficiency, tremor, headache, hyperlipidemia, gingival hyperplasia, muscle cramps, hypertrichosis etc. A possible increased risk for secondary (incl. lymphoproliferative) malignancies must be considered.

Monoclonal antibodies

Two different humanized, monoclonal anti–IL-5 antibodies, reslizumab (SCH55700, Cephalon) and mepolizumab (GlaxoSmithKline), can markedly decrease the eosinophil count in hypereosinophilia, regardless of the underlying cause by binding to free IL-5 [4, 122-125]. These responses were in some patients sustained for up to a year, after multiple infusions of anti–IL-5. In HES patients, regression of constitutional symptoms, eosinophilic dermatologic lesions and improvements in pulmonary function in patients with pulmonary disease, have been observed with anti-IL-5 therapy [123-125]. The therapy appears well tolerated, but may cause a rebound effect [126]. Also, tachyphylaxis has been observed without development of neutralizing antibodies with repeated doses [124], but it may not pose a problem with the subcutaneous formulation. Mepolizumab is currently approved for severe eosinophilic asthma, and not for HES, but EMA has granted an orphan status, and the treatment has a place in HES [127].

Anti-IL5 treatment by mepolizumab may be considered to be a rational treatment in Gleich syndrome, characterized by aberrant T-lymphocyte subclones, TcR clonality, increased IgM and cyclic angioedemea and eosinophilia accompanied by cytopenias [128]. IL-5 plays a key role in the pathogenesis. Measurements of IL-5 in plasma is not routinely available in hospitals, and the treatment is decided by the clinical presentation. IL-5 was not correlated to the outcome in the original study [129]. New clinical studies are ongoing in HES, and data may be awaited in 2019-2020. Very few, casuistic data are available by reslizumab [130]. Anti-IL5receptor antibody may become available as a treatment of primary eosinophilia without another, demonstrable sensitive target for treatment.

The monoclonal anti-CD52 antibody (alemtuzumab) has been used successfully in several cases with hypereosinophilia. It may be an alternative treatment for patients with HES refractory to other therapies, including clonal eosinophilia [44, 96, 131-134]. Most eosinophil granulocytes highly express CD52, a surface glycoprotein expressed on B- and T-lymphocytes [135]. 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 is an available alternative in hypereosinophilia, although not *per se* approved for treatment of primary eosinophilia. The treatment with alemtuzumab is not curative and in some cases, the disease recurs after the treatment is stopped without any maintenance therapy.

Alemtuzumab may be beneficial in HES patients with cardiac and cerebral dysfunction [136, 137]. 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 [134, 135].

Side effects: depends on the antibody. Favourable for mepoilizumab. Significant risk for immunosuppressive effect and opportunistic infections with alemtuzumab (i.e. CMV, pneumocystis, fungal), perhaps lymphoma development and rebound effects following cessation of antibody therapy [96, 135, 138].

Tyrosine kinase inhibitors

Imatinib

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 striking potency of imatinib in patients with FIP1L1-PDGFRA-positive hypereosinophilia, and no case of primary resistance to imatinib has been reported [6, 66, 76, 96, 139-141]. There is a general consensus for the use of imatinib as first-line therapy in patients (asymptomactic or symptomatic) with the FIP1L1-PDGFRA fusion gene and in cases without this fusion gene, but with clinical and laboratory signs of this subtype of eosinophilia, e.g. tissue fibrosis, extremely high eosinophil levels, dysplastic eosinophils in blood, splenomegaly, increased serum vitamin B12 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 have been reported. The T674I substitution in the ATP-binding domain of PDGFRA [76, 131, 140-142] is associated with acquired imatinib- and other TKI resistance, similar to the T315I mutation observed in patients with CML. In addition, patients with iHES failing corticosteroid and/or hydroxyurea therapy should be considered for a short trial (4-6 weeks) of imatinib 400 mg daily.

The responses to imatinib (initially 100 mg/day) in FIP1L1-PDGFRA-positive patients are rapid, and eosinophil counts are normalized within one to two weeks of treatment. The

clinical manifestations usually disappear within 1 month. In patients, who do not respond in two to four weeks, imatinib should be increased to dose 400 mg/day and if that is failed, other therapies considered. The exception is cardiac involvement, which is irreversible unless treatment is begun before fibrosis leads to permanent damages [141]. 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 or abnormalities in echocardiography, should be concomitantly treated with corticosteroids (1 to 2 mg Prednisolone per kg for the first one to two weeks) [111].

The dose required to induce and maintain remission is generally lower (100 mg/day or even lower down to 100-200 mg weekly) than for patients with CML (≥ 400 mg) [141]. Influence of imatinib on clinical manifestations related to heart involvement are variable, and endomyocardial fibrosis appears to be irreversible [83, 141]. Reversal of bone marrow pathology and molecular remission can be achieved in most patients with the FIP1L1-PDGFRA fusion gene [141, 143]. Imatinib dose should be adjusted to ensure molecular remission (i.e. no detectable FIP1L1-PDGFRA by PCR or FISH), in order to prevent the development of acquired resistance [95]. Imatinib has become first-line therapy for patients with FIP1L1-PDGFRA-associated eosinophilia [6, 47, 66, 78, 79, 88, 90-92, 96, 144, 145], but prospective randomized trials are limited [146]. 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 [84, 143, 146]. making maintenance therapy with imatinib necessary [147]. However, long term disease-free remissions – like in CML after long-term TKI treatment and optimal, molecular responses – are accumulating in a minor group of patients [148, 149]. Some patients with TKI-sensitive disease may be considered for treatment cessation and close monitoring, like in CML post-TKI therapy, using FISH or PCR for the transcript detection instead of BCR-abl [150].

Durable responses have been obtained with imatinib in eosinophilic patients with PDGFRB, PDGFRA (other than PDGFRA-FIPIl1) rearrangements and ETV&-ABL1 -fusion genes [151, 152], and the recommended dosage is imatinib 400 mg daily [96]. Cytogenetic abnormalities causing demonstrable abnormalities in ETV6-FLT3 may be sensitive to sunitinib and sorafenib (1).

Even, in the blast phase of PDGFRA- or PDGFRB- associated eosinophilias, imatinib as monotherapy could be effective, since in a series of 17 blast phase or sarcoma patients, 15 achieved durable complete hematologic and molecular remissions [153].

The effect of imatinib therapy in PDGFR-negative eosinophilia is unclear, although responses have been seen in some patients [154]. Currently, there are no markers that can help identify PDGFR-negative patients with imatinib-sensitive (possibly tyrosine kinase driven) 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 [155]. Imatinib is not useful in patients with clinical l-HES.

Ruxolitinib

Ruxolitinib is suggested therapy for patients with JAK2 rearrangements and have been reported efficacious in the entity with PCM1-JAK2 fusion gene [156]. Casuistic reports of beneficial effect of ruxolitinib in non-clonal HES have been presented [157]. Sunitinib or sorafenib is suggested for clonal eosinophilia patients with ETV6-FLT3-fusion gene. Cases with FGFR1 rearrangement and CEL, NOS have a poor prognosis and intensive AML-type induction therapy followed by HSCT is suggested.

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 is able to inhibit kinase activity of wild-type FIP1L1-PDGFRA [155]. PKC412 and sorafenib are able to inhibit kinase activity of both wild type FIP1L1-PDGFRA and the imatinib-resistant T641I mutant form. Likewise, emerging data on dasatinib in the Ph-negative myeloproliferative disorders indicate a clinical efficacy [131, 158], and dasatinib should be considered in imatinib-resistant cases [159].

Side effects: fluid retention, muscle cramps, diarrhea, skin rash and elevated liver enzymes, some dose dependent [160].

Bone marrow transplantation

Myeloablative and reduced-intensity conditioning allogeneic bone marrow transplantation have been used successfully in a few hypereosinophilic patients, and with disease-free survival reported for longer periods [96, 161, 162]. But the transplantation-related toxicity still remains a major problem, and the role of bone marrow transplantation in primary hypereosinophilic patients is not well established. This treatment can be considered for FIP1L1-PDGFRA-positive patients, who are resistant or intolerant to imatinib therapy and HES patients, with progressive end-organ damage when standard therapies or any experimental therapy have failed. Cases with FGRFR1 and CEL, NOS, have a poor prognosis and are candidates for bone marrow transplantation.

Table 8. Present treatment options for eosinophilia due to a clonal haematological disorder, or iHES Additional details in text.

Medication and administration	**Indications and practical comments on line of therapy**	**Dose**	**Comments**
Glucocorticosteroids oral, or i.v.	First-line treatment, to reduce eosinophil count and avoid inflammation in combination with other treatments the first weeks	Initial dose ≥40 mg prednisone or 40 – 80 mg solumedrol i.v. once daily	Various side effects. Consider allopurinol initially. Consider osteoporosis prophylaxis in prolonged or repeated therapy
Hydroxyurea oral	First line: eosinophil counts > 10-20^{9}/l and symptoms until diagnostic clarification second-line: m_HES, iHES, targeted therapy not rational,	1-3 g / day	Chemotherapy, dose may be divided. A principal risk of long-term toxicity (skin, malignancy), therefore consider age when treating, caution as maintenance therapy < 60 years of age, tapering of dose and pausing of therapy may be possible
Interferon IFN-α2 s.c.	Second-line therapy as maintenance in particular in younger patients, mHES clinically, without TKI sensitive clone	1-2 mU / m2 q.d.- or IFN-α pegylated, commence low dose e.g. 25-45 microgr s.c. once weekly	Slow onset of action, risk of numerous side effects, may be mitigated by low dose initially. IFN-α may be used during pregnancy. In principle to be avoided in l-HES due to interaction with lymphocyte subsets
Imatinib mesylate oral Tyrosine Kinase Inhibitor (TKI)	First-line: for FIP1L1-PDGFRA, and maintenance. r Third+ line: refractory cases, without available targeted therapy	100 - 400 mg Once daily	Together with glucocorticosteroids if cardiac / organ involvement at diagnosis. Consider risk for tumourlysis. May be effective in iHES with TKI-sensitive, but not demonstrable clonal driven eosinophilia. Second generation TKI may then also be effective, instead of imatinib. A response to TKI may be of short duration in this patient population
Mepolizumab (anti-IL5 monoclonal antibody) s.c.	Second/third line, but may be used as maintenance treatment in Gleich syndrome and l-HES	100 mg up to 300 mg s.c. / 4 weeks	In principle at risk of parasitic infections. Experience is accumulating with treatment of iHES with anti-IL5 treatment,
Cyclosporine A oral	Third-line therapy	100 mg maintenance / day	Induction therapy includes glucocosteroids and hydroxyurea, and may be started in higher doses, but P-concentration monitoring should not be necessary
Mycomofetil oral	Third-line therapy	1 – 2 gr / day in two doses	No need P-conc monitoring. In principle a risk for secondary. Malignancy as in CyA treatment, but may involve less side effects
Cladribine & cytarabine i.v.	Third/fourth line treatment for resistant cases	2-CdA 12 mg / m2 & Ara-C 1g/m2 /5 days in cycles	Patient-population not characterized by clonality or refractory to previous therapy. Cytarabin may be used for cytoreduction at diagnosis as single-dose (1-2 gr i.v.) in urgent situations. Cladribine may be given as monotherapy in refractory cases
Vincristine i.v.	Consider for counts at presentation >50-100 x 10^{9}/l. For resistant cases	1-2 mg i.v. e.g. weekly	May be valuable in initial therapy, must not be used for maintenance due to neurotoxic side effects
Anti-CD52 antibody i.v. or s.c.	Fourth line therapy. For resistant cases, as maintenance, but pausing of therapy must be sought	Stepwise increase (3 –10 – 30 mgweekly) , maintenance	Pronounced immunosuppression and high risk of opportunistic infections. Need for prophylactic treatment and close clinical monitoring

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.

References

1. Butt NM, Lambert J, Ali S, Beer PA, Cross NC, Duncombe A*, et al.* Guideline for the investigation and management of eosinophilia. *Br J Haematol* 2017; **176**:553-572.
2. Curtis C, Ogbogu P. Hypereosinophilic Syndrome. *Clin Rev Allergy Immunol* 2016; **50**:240-251.
3. Curtis C, Ogbogu PU. Evaluation and Differential Diagnosis of Persistent Marked Eosinophilia. *Immunol Allergy Clin North Am* 2015; **35**:387-402.
4. Gotlib J. World Health Organization-defined eosinophilic disorders: 2015 update on diagnosis, risk stratification, and management. *Am J Hematol* 2015; **90**:1077-1089.
5. Klion AD. Eosinophilia: a pragmatic approach to diagnosis and treatment. *Hematology Am Soc Hematol Educ Program* 2015; **2015**:92-97.
6. Klion AD. How I treat hypereosinophilic syndromes. *Blood* 2015; **126**:1069-1077.
7. Kovalszki A, Weller PF. Eosinophilia. *Prim Care* 2016; **43**:607-617.
8. Leru PM. Eosinophilia and Hypereosinophilic Disorders - Update on Etiopathogeny, Classification and Clinical Approach. *Rom J Intern Med* 2015; **53**:289-295.
9. Noh HR, Magpantay GG. Hypereosinophilic syndrome. *Allergy Asthma Proc* 2017; **38**:78-81.
10. Reiter A, Gotlib J. Myeloid neoplasms with eosinophilia. *Blood* 2017; **129**:704-714.
11. Roufosse F. Management of Hypereosinophilic Syndromes. *Immunol Allergy Clin North Am* 2015; **35**:561-575.
12. Nussbaum JC, Van Dyken SJ, von Moltke J, Cheng LE, Mohapatra A, Molofsky AB*, et al.* Type 2 innate lymphoid cells control eosinophil homeostasis. *Nature* 2013; **502**:245-248.
13. Esnault S, Kelly EA. Essential Mechanisms of Differential Activation of Eosinophils by IL-3 Compared to GM-CSF and IL-5. *Crit Rev Immunol* 2016; **36**:429-444.
14. Fulkerson PC, Schollaert KL, Bouffi C, Rothenberg ME. IL-5 triggers a cooperative cytokine network that promotes eosinophil precursor maturation. *J Immunol* 2014; **193**:4043-4052.
15. Blanchard C, Rothenberg ME. Biology of the eosinophil. *Adv Immunol* 2009; **101**:81-121.
16. Elsas PX, Elsas MI. Eosinophilopoiesis at the cross-roads of research on development, immunity and drug discovery. *Curr Med Chem* 2007; **14**:1925-1939.
17. Xia LX, Hua W, Jin Y, Tian BP, Qiu ZW, Zhang C*, et al.* Eosinophil differentiation in the bone marrow is promoted by protein tyrosine phosphatase SHP2. *Cell Death Dis* 2016; **7**:e2175.
18. Kovalszki A, Sheikh J, Weller P. Eosinophils and Eosinophilia. *In: Rich RR, editor* 2013; C**linical immunology principles and practice. 4th. London: Elsevier Saunders**:298-309.
19. Park YM, Bochner BS. Eosinophil survival and apoptosis in health and disease. *Allergy Asthma Immunol Res* 2010; **2**:87-101.
20. Schwartz C, Willebrand R, Huber S, Rupec RA, Wu D, Locksley R*, et al.* Eosinophil-specific deletion of IkappaBalpha in mice reveals a critical role of NF-kappaB-induced Bcl-xL for inhibition of apoptosis. *Blood* 2015; **125**:3896-3904.
21. Shamri R, Xenakis JJ, Spencer LA. Eosinophils in innate immunity: an evolving story. *Cell Tissue Res* 2011; **343**:57-83.

22. Ueki S, Konno Y, Takeda M, Moritoki Y, Hirokawa M, Matsuwaki Y*, et al.* Eosinophil extracellular trap cell death-derived DNA traps: Their presence in secretions and functional attributes. *J Allergy Clin Immunol* 2016; **137**:258-267.
23. Varricchi G, Bagnasco D, Borriello F, Heffler E, Canonica GW. Interleukin-5 pathway inhibition in the treatment of eosinophilic respiratory disorders: evidence and unmet needs. *Curr Opin Allergy Clin Immunol* 2016; **16**:186-200.
24. Huang L, Appleton JA. Eosinophils in Helminth Infection: Defenders and Dupes. *Trends Parasitol* 2016; **32**:798-807.
25. Davis BP, Rothenberg ME. Eosinophils and cancer. *Cancer Immunol Res* 2014; **2**:1-8.
26. Jacobsen EA, Helmers RA, Lee JJ, Lee NA. The expanding role(s) of eosinophils in health and disease. *Blood* 2012; **120**:3882-3890.
27. Sakkal S, Miller S, Apostolopoulos V, Nurgali K. Eosinophils in Cancer: Favourable or Unfavourable? *Curr Med Chem* 2016; **23**:650-666.
28. Uhm TG, Kim BS, Chung IY. Eosinophil development, regulation of eosinophil-specific genes, and role of eosinophils in the pathogenesis of asthma. *Allergy Asthma Immunol Res* 2012; **4**:68-79.
29. Esnault S, Kelly EA, Schwantes EA, Liu LY, DeLain LP, Hauer JA*, et al.* Identification of genes expressed by human airway eosinophils after an in vivo allergen challenge. *PLoS One* 2013; **8**:e67560.
30. Barnig C, Alsaleh G, Jung N, Dembele D, Paul N, Poirot A*, et al.* Circulating Human Eosinophils Share a Similar Transcriptional Profile in Asthma and Other Hypereosinophilic Disorders. *PLoS One* 2015; **10**:e0141740.
31. Andersen CL, Nielsen HM, Kristensen LS, Sogaard A, Vikesa J, Jonson L*, et al.* Whole-exome sequencing and genome-wide methylation analyses identify novel disease associated mutations and methylation patterns in idiopathic hypereosinophilic syndrome. *Oncotarget* 2015; **6**:40588-40597.
32. Gleich GJ, Klion AD, Lee JJ, Weller PF. The consequences of not having eosinophils. *Allergy* 2013; **68**:829-835.
33. Valent P, Klion AD, Horny HP, Roufosse F, Gotlib J, Weller PF*, et al.* Contemporary consensus proposal on criteria and classification of eosinophilic disorders and related syndromes. *J Allergy Clin Immunol* 2012; **130**:607-612 e609.
34. Valent P, Klion AD, Rosenwasser LJ, Arock M, Bochner BS, Butterfield JH*, et al.* ICON: Eosinophil Disorders. *World Allergy Organ J* 2012; **5**:174-181.
35. Andersen CL, Lindegaard H, Vestergaard H, Siersma VD, Hasselbalch HC, de Fine Olivarius N*, et al.* Risk of lymphoma and solid cancer among patients with rheumatoid arthritis in a primary care setting. *PLoS One* 2014; **9**:e99388.
36. Andersen CL, Siersma VD, Hasselbalch HC, Lindegaard H, Vestergaard H, Felding P*, et al.* Eosinophilia in routine blood samples as a biomarker for solid tumor development - A study based on The Copenhagen Primary Care Differential Count (CopDiff) Database. *Acta Oncol* 2013.
37. Andersen CL, Siersma VD, Hasselbalch HC, Lindegaard H, Vestergaard H, Felding P*, et al.* Eosinophilia in routine blood samples as a biomarker for solid tumor development - A study based on the Copenhagen Primary Care Differential Count (CopDiff) Database. *Acta Oncol* 2014; **53**:1245-1250.
38. Crane MM, Chang CM, Kobayashi MG, Weller PF. Incidence of myeloproliferative hypereosinophilic syndrome in the United States and an estimate of all hypereosinophilic syndrome incidence. *J Allergy Clin Immunol* 2010; **126**:179-181.
39. Kim DW, Shin MG, Yun HK, Kim SH, Shin JH, Suh SP*, et al.* [Incidence and causes of hypereosinophilia (corrected) in the patients of a university hospital]. *Korean J Lab Med* 2009; **29**:185-193.

40. Bansal R, Kaur A. Incidence of Eosinophilia in Rural Population in North India: A Study at Tertiary Care Hospital. *Ann Pathol Lab Med* 2017:A43 – 47
41. Sade K, Mysels A, Levo Y, Kivity S. Eosinophilia: A study of 100 hospitalized patients. *Eur J Intern Med* 2007; **18**:196-201.
42. Akuthota P, Weller PF. Spectrum of Eosinophilic End-Organ Manifestations. *Immunol Allergy Clin North Am* 2015; **35**:403-411.
43. Weller PF, Bubley GJ. The idiopathic hypereosinophilic syndrome. *Blood* 1994; **83**:2759-2779.
44. Ogbogu PU, Bochner BS, Butterfield JH, Gleich GJ, Huss-Marp J, Kahn JE*, et al.* Hypereosinophilic syndrome: a multicenter, retrospective analysis of clinical characteristics and response to therapy. *J Allergy Clin Immunol* 2009; **124**:1319-1325 e1313.
45. Chaine G, Davies J, Kohner EM, Hawarth S, Spry CJ. Ophthalmologic abnormalities in the hypereosinophilic syndrome. *Ophthalmology* 1982; **89**:1348-1356.
46. Liapis H, Ho AK, Brown D, Mindel G, Gleich G. Thrombotic microangiopathy associated with the hypereosinophilic syndrome. *Kidney Int* 2005; **67**:1806-1811.
47. Gotlib J, Cools J, Malone JM, 3rd, Schrier SL, Gilliland DG, Coutre SE. The FIP1L1-PDGFRalpha fusion tyrosine kinase in hypereosinophilic syndrome and chronic eosinophilic leukemia: implications for diagnosis, classification, and management. *Blood* 2004; **103**:2879-2891.
48. Ommen SR, Seward JB, Tajik AJ. Clinical and echocardiographic features of hypereosinophilic syndromes. *Am J Cardiol* 2000; **86**:110-113.
49. Mankad R, Bonnichsen C, Mankad S. Hypereosinophilic syndrome: cardiac diagnosis and management. *Heart* 2016; **102**:100-106.
50. Helbig G, Hus M, Brzezniakiewicz-Janus K, Woszczyk D, Lewandowski K, Kyrcz-Krzemien S. Cardiovascular dysfunction as a common cause of mortality in hypereosinophilic syndromes. *Pol Arch Med Wewn* 2015; **125**:692-694.
51. Li H, Dai Z, Wang B, Huang W. A case report of eosinophilic myocarditis and a review of the relevant literature. *BMC Cardiovasc Disord* 2015; **15**:15.
52. Seguela PE, Iriart X, Acar P, Montaudon M, Roudaut R, Thambo JB. Eosinophilic cardiac disease: Molecular, clinical and imaging aspects. *Arch Cardiovasc Dis* 2015; **108**:258-268.
53. Rice CM, Kurian KM, Renowden S, Whiteway A, Price C, Scolding NJ. Idiopathic hypereosinophilic syndrome: a new cause of vasculitis of the central nervous system. *J Neurol* 2015; **262**:1354-1359.
54. Williams C, Kalra S, Nath U, Bown N, Wilson V, Wilkins BS*, et al.* FIP1L1-PDGFRA positive chronic eosinophilic leukaemia and associated central nervous system involvement. *J Clin Pathol* 2008; **61**:677-680.
55. Lee D, Ahn TB. Central nervous system involvement of hypereosinophilic syndrome: a report of 10 cases and a literature review. *J Neurol Sci* 2014; **347**:281-287.
56. Leiferman KM, Gleich GJ, Peters MS. Dermatologic manifestations of the hypereosinophilic syndromes. *Immunol Allergy Clin North Am* 2007; **27**:415-441.
57. Plotz SG, Huttig B, Aigner B, Merkel C, Brockow K, Akdis C*, et al.* Clinical overview of cutaneous features in hypereosinophilic syndrome. *Curr Allergy Asthma Rep* 2012; **12**:85-98.
58. Kang EY, Shim JJ, Kim JS, Kim KI. Pulmonary involvement of idiopathic hypereosinophilic syndrome: CT findings in five patients. *J Comput Assist Tomogr* 1997; **21**:612-615.
59. Dulohery MM, Patel RR, Schneider F, Ryu JH. Lung involvement in hypereosinophilic syndromes. *Respir Med* 2011; **105**:114-121.
60. Katre RS, Sunnapwar A, Restrepo CS, Katabathina VS, Mumbower A, Baxi A*, et al.* Cardiopulmonary and Gastrointestinal Manifestations of Eosinophil- associated

Diseases and Idiopathic Hypereosinophilic Syndromes: Multimodality Imaging Approach. *Radiographics* 2016; **36**:433-451.
61. Inayat F, Hurairah A. Gastrointestinal and Hepatic Involvement in Hypereosinophilic Syndrome. *Cureus* 2016; **8**:e760.
62. Zuo L, Rothenberg ME. Gastrointestinal eosinophilia. *Immunol Allergy Clin North Am* 2007; **27**:443-455.
63. Brogadir SP, Goldwein MI, Schumacher HR. A hypereosinophilic syndrome mimicking rheumatoid arthritis. *Am J Med* 1980; **69**:799-802.
64. Prattichizzo FA, Bernini L. An idiopathic hypereosinophilic syndrome mimicking seronegative rheumatoid arthritis: 20-year follow-up with clinical and laboratory findings. *Clin Exp Rheumatol* 1992; **10**:79-81.
65. Arber DA, Orazi A, Hasserjian R, Thiele J, Borowitz MJ, Le Beau MM*, et al.* The 2016 revision to the World Health Organization classification of myeloid neoplasms and acute leukemia. *Blood* 2016; **127**:2391-2405.
66. Tefferi A, Patnaik MM, Pardanani A. Eosinophilia: secondary, clonal and idiopathic. *Br J Haematol* 2006; **133**:468-492.
67. Okada R, Nakachi S, Inokuma S. The severity of peripheral blood eosinophilia indicates an eosinophilia-associated disease corresponding to its level. *Allergol Int* 2016; **65**:112-114.
68. Schwaab J, Jawhar M, Naumann N, Schmitt-Graeff A, Fabarius A, Horny HP*, et al.* Diagnostic challenges in the work up of hypereosinophilia: pitfalls in bone marrow core biopsy interpretation. *Ann Hematol* 2016; **95**:557-562.
69. Wang SA, Hasserjian RP, Tam W, Tsai AG, Geyer JT, George TI*, et al.* Bone marrow morphology is a strong discriminator between chronic eosinophilic leukemia, not otherwise specified and reactive idiopathic hypereosinophilic syndrome. *Haematologica* 2017; **102**:1352-1360.
70. Hamann J, Koning N, Pouwels W, Ulfman LH, van Eijk M, Stacey M*, et al.* EMR1, the human homolog of F4/80, is an eosinophil-specific receptor. *Eur J Immunol* 2007; **37**:2797-2802.
71. Chang HW, Leong KH, Koh DR, Lee SH. Clonality of isolated eosinophils in the hypereosinophilic syndrome. *Blood* 1999; **93**:1651-1657.
72. Cilloni D, Messa F, Martinelli G, Gottardi E, Arruga F, Defilippi I*, et al.* WT1 transcript amount discriminates secondary or reactive eosinophilia from idiopathic hypereosinophilic syndrome or chronic eosinophilic leukemia. *Leukemia* 2007; **21**:1442-1450.
73. Roufosse F, Cogan E, Goldman M. The hypereosinophilic syndrome revisited. *Annu Rev Med* 2003; **54**:169-184.
74. Roufosse F, Cogan E, Goldman M. Recent advances in pathogenesis and management of hypereosinophilic syndromes. *Allergy* 2004; **59**:673-689.
75. Roufosse FE, Goldman M, Cogan E. Hypereosinophilic syndromes. *Orphanet J Rare Dis* 2007; **2**:37.
76. Cools J, DeAngelo DJ, Gotlib J, Stover EH, Legare RD, Cortes J*, et al.* A tyrosine kinase created by fusion of the PDGFRA and FIP1L1 genes as a therapeutic target of imatinib in idiopathic hypereosinophilic syndrome. *N Engl J Med* 2003; **348**:1201-1214.
77. Bain BJ. Cytogenetic and molecular genetic aspects of eosinophilic leukaemias. *Br J Haematol* 2003; **122**:173-179.
78. Gotlib J. Molecular classification and pathogenesis of eosinophilic disorders: 2005 update. *Acta Haematol* 2005; **114**:7-25.
79. Gotlib J, Cross NC, Gilliland DG. Eosinophilic disorders: molecular pathogenesis, new classification, and modern therapy. *Best Pract Res Clin Haematol* 2006; **19**:535-569.

80. Klion AD. Eosinophilic myeloproliferative disorders. *Hematology Am Soc Hematol Educ Program* 2011; **2011**:257-263.
81. C.P. Cross, Dimitra Koumaki, Georgia Metzgeroth, Reiter A. Managing Myeloproliferative Neoplasms. A Case-Based Approach. *Online publication* 2016.
82. Bain BJ. Myeloid and lymphoid neoplasms with eosinophilia and abnormalities of PDGFRA, PDGFRB or FGFR1. *Haematologica* 2010; **95**:696-698.
83. Vandenberghe P, Wlodarska I, Michaux L, Zachee P, Boogaerts M, Vanstraelen D*, et al.* Clinical and molecular features of FIP1L1-PDFGRA (+) chronic eosinophilic leukemias. *Leukemia* 2004; **18**:734-742.
84. Pardanani A, Brockman SR, Paternoster SF, Flynn HC, Ketterling RP, Lasho TL*, et al.* FIP1L1-PDGFRA fusion: prevalence and clinicopathologic correlates in 89 consecutive patients with moderate to severe eosinophilia. *Blood* 2004; **104**:3038-3045.
85. Gilliland G, Cools J, Stover EH, Wlodarska I, Marynen P. FIP1L1-PDGFRalpha in hypereosinophilic syndrome and mastocytosis. *Hematol J* 2004; **5 Suppl 3**:S133-137.
86. Buitenhuis M, Verhagen LP, Cools J, Coffer PJ. Molecular mechanisms underlying FIP1L1-PDGFRA-mediated myeloproliferation. *Cancer Res* 2007; **67**:3759-3766.
87. Metzgeroth G, Walz C, Score J, Siebert R, Schnittger S, Haferlach C*, et al.* Recurrent finding of the FIP1L1-PDGFRA fusion gene in eosinophilia-associated acute myeloid leukemia and lymphoblastic T-cell lymphoma. *Leukemia* 2007; **21**:1183-1188.
88. Simon D, Simon HU. Eosinophilic disorders. *J Allergy Clin Immunol* 2007; **119**:1291-1300; quiz 1301-1292.
89. Andersen CL, Vestergaard H, Norgaard P, Felding P, Pallisgaard N, Rasmussen IH*, et al.* [Eosinophilia--pathogenesis, classification and therapy]. *Ugeskr Laeger* 2009; **171**:3256-3262.
90. Valent P, Gleich GJ, Reiter A, Roufosse F, Weller PF, Hellmann A*, et al.* Pathogenesis and classification of eosinophil disorders: a review of recent developments in the field. *Expert Rev Hematol* 2012; **5**:157-176.
91. Fletcher S, Bain B. Eosinophilic leukaemia. *Br Med Bull* 2007; **81-82**:115-127.
92. Reiter A, Grimwade D, Cross NC. Diagnostic and therapeutic management of eosinophilia-associated chronic myeloproliferative disorders. *Haematologica* 2007; **92**:1153-1158.
93. Roufosse F, Weller PF. Practical approach to the patient with hypereosinophilia. *J Allergy Clin Immunol* 2010; **126**:39-44.
94. Kalac M, Quintas-Cardama A, Vrhovac R, Kantarjian H, Verstovsek S. A critical appraisal of conventional and investigational drug therapy in patients with hypereosinophilic syndrome and clonal eosinophilia. *Cancer* 2007; **110**:955-964.
95. Klion AD, Bochner BS, Gleich GJ, Nutman TB, Rothenberg ME, Simon HU*, et al.* Approaches to the treatment of hypereosinophilic syndromes: a workshop summary report. *J Allergy Clin Immunol* 2006; **117**:1292-1302.
96. Gotlib J. World Health Organization-defined eosinophilic disorders: 2017 update on diagnosis, risk stratification, and management. *Am J Hematol* 2017; **92**:1243-1259.
97. Marchand E, Cordier JF. Idiopathic chronic eosinophilic pneumonia. *Semin Respir Crit Care Med* 2006; **27**:134-141.
98. Fernandez Perez ER, Olson AL, Frankel SK. Eosinophilic lung diseases. *Med Clin North Am* 2011; **95**:1163-1187.
99. Bochner BS. Novel Therapies for Eosinophilic Disorders. *Immunol Allergy Clin North Am* 2015; **35**:577-598.
100. Kariyawasam HH, Robinson DS. The eosinophil: the cell and its weapons, the cytokines, its locations. *Semin Respir Crit Care Med* 2006; **27**:117-127.

101. Rothenberg ME, Hogan SP. The eosinophil. *Annu Rev Immunol* 2006; **24**:147-174.
102. Wang ML, Davenport RD, Yamada C. Comparison of two leukocytapheresis protocols in a case of idiopathic hypereosinophilic syndrome. *J Clin Apher* 2016; **31**:481-489.
103. Brito-Babapulle F. The eosinophilias, including the idiopathic hypereosinophilic syndrome. *Br J Haematol* 2003; **121**:203-223.
104. Flaum MA, Schooley RT, Fauci AS, Gralnick HR. A clinicopathologic correlation of the idiopathic hypereosinophilic syndrome. I. Hematologic manifestations. *Blood* 1981; **58**:1012-1020.
105. Schooley RT, Flaum MA, Gralnick HR, Fauci AS. A clinicopathologic correlation of the idiopathic hypereosinophilic syndrome. II. Clinical manifestations. *Blood* 1981; **58**:1021-1026.
106. Klion AD, Noel P, Akin C, Law MA, Gilliland DG, Cools J*, et al.* Elevated serum tryptase levels identify a subset of patients with a myeloproliferative variant of idiopathic hypereosinophilic syndrome associated with tissue fibrosis, poor prognosis, and imatinib responsiveness. *Blood* 2003; **101**:4660-4666.
107. Pardanani A, Ketterling RP, Brockman SR, Flynn HC, Paternoster SF, Shearer BM*, et al.* CHIC2 deletion, a surrogate for FIP1L1-PDGFRA fusion, occurs in systemic mastocytosis associated with eosinophilia and predicts response to imatinib mesylate therapy. *Blood* 2003; **102**:3093-3096.
108. Roufosse F, Schandene L, Sibille C, Willard-Gallo K, Kennes B, Efira A*, et al.* Clonal Th2 lymphocytes in patients with the idiopathic hypereosinophilic syndrome. *Br J Haematol* 2000; **109**:540-548.
109. Butterfield JH, Gleich GJ. Interferon-alpha treatment of six patients with the idiopathic hypereosinophilic syndrome. *Ann Intern Med* 1994; **121**:648-653.
110. Bjerrum OW. Interferon treatment in patients with hypereosinophilia. *Curr Drug Targets* 2011; **12**:429-432.
111. Pitini V, Arrigo C, Azzarello D, La Gattuta G, Amata C, Righi M*, et al.* Serum concentration of cardiac Troponin T in patients with hypereosinophilic syndrome treated with imatinib is predictive of adverse outcomes. *Blood* 2003; **102**:3456-3457; author reply 3457.
112. Spivak JL, Hasselbalch H. Hydroxycarbamide: a user's guide for chronic myeloproliferative disorders. *Expert Rev Anticancer Ther* 2011; **11**:403-414.
113. Sakamoto K, Erdreich-Epstein A, deClerck Y, Coates T. Prolonged clinical response to vincristine treatment in two patients with idiopathic hypereosinophilic syndrome. *Am J Pediatr Hematol Oncol* 1992; **14**:348-351.
114. Sioka C, Kyritsis AP. Central and peripheral nervous system toxicity of common chemotherapeutic agents. *Cancer Chemother Pharmacol* 2009; **63**:761-767.
115. Dore RK. How to prevent glucocorticoid-induced osteoporosis. *Cleve Clin J Med* 2010; **77**:529-536.
116. Coutant G, Bletry O, Prin L, Hauteville D, de Puyfontaine O, Abgrall JF*, et al.* [Treatment of hypereosinophilic syndromes of myeloproliferative expression with the combination of hydroxyurea and interferon alpha. Apropos of 7 cases]. *Ann Med Interne (Paris)* 1993; **144**:243-250.
117. Schandene L, Roufosse F, de Lavareille A, Stordeur P, Efira A, Kennes B*, et al.* Interferon alpha prevents spontaneous apoptosis of clonal Th2 cells associated with chronic hypereosinophilia. *Blood* 2000; **96**:4285-4292.
118. Griesshammer M, Struve S, Barbui T. Management of Philadelphia negative chronic myeloproliferative disorders in pregnancy. *Blood Rev* 2008; **22**:235-245.

119. Kanthawatana. Recombinant interferon-alpha (IFN) and pregnancy in a patient with hypereosinophilic syndrome. *J Allergy Clin Immunol* 1998; **101: S20 (abstract 88)**.
120. Zaheri S, Alam A, Marks AJ, Wakelin S. Lymphocytic variant of hypereosinophilic syndrome. *Clin Exp Dermatol* 2010; **35**:634-636.
121. Helbig G, Wieczorkiewicz A, Dziaczkowska-Suszek J, Majewski M, Kyrcz-Krzemien S. T-cell abnormalities are present at high frequencies in patients with hypereosinophilic syndrome. *Haematologica* 2009; **94**:1236-1241.
122. Menzies-Gow A, Flood-Page P, Sehmi R, Burman J, Hamid Q, Robinson DS*, et al.* Anti-IL-5 (mepolizumab) therapy induces bone marrow eosinophil maturational arrest and decreases eosinophil progenitors in the bronchial mucosa of atopic asthmatics. *J Allergy Clin Immunol* 2003; **111**:714-719.
123. Garrett JK, Jameson SC, Thomson B, Collins MH, Wagoner LE, Freese DK*, et al.* Anti-interleukin-5 (mepolizumab) therapy for hypereosinophilic syndromes. *J Allergy Clin Immunol* 2004; **113**:115-119.
124. Klion AD, Law MA, Noel P, Kim YJ, Haverty TP, Nutman TB. Safety and efficacy of the monoclonal anti-interleukin-5 antibody SCH55700 in the treatment of patients with hypereosinophilic syndrome. *Blood* 2004; **103**:2939-2941.
125. Plotz SG, Simon HU, Darsow U, Simon D, Vassina E, Yousefi S*, et al.* Use of an anti-interleukin-5 antibody in the hypereosinophilic syndrome with eosinophilic dermatitis. *N Engl J Med* 2003; **349**:2334-2339.
126. Kim YJ, Prussin C, Martin B, Law MA, Haverty TP, Nutman TB*, et al.* Rebound eosinophilia after treatment of hypereosinophilic syndrome and eosinophilic gastroenteritis with monoclonal anti-IL-5 antibody SCH55700. *J Allergy Clin Immunol* 2004; **114**:1449-1455.
127. Roufosse FE, Kahn JE, Gleich GJ, Schwartz LB, Singh AD, Rosenwasser LJ*, et al.* Long-term safety of mepolizumab for the treatment of hypereosinophilic syndromes. *J Allergy Clin Immunol* 2013; **131**:461-467 e461-465.
128. Khoury P, Herold J, Alpaugh A, Dinerman E, Holland-Thomas N, Stoddard J*, et al.* Episodic angioedema with eosinophilia (Gleich syndrome) is a multilineage cell cycling disorder. *Haematologica* 2015; **100**:300-307.
129. Rothenberg ME, Klion AD, Roufosse FE, Kahn JE, Weller PF, Simon HU*, et al.* Treatment of patients with the hypereosinophilic syndrome with mepolizumab. *N Engl J Med* 2008; **358**:1215-1228.
130. Walsh GM. Profile of reslizumab in eosinophilic disease and its potential in the treatment of poorly controlled eosinophilic asthma. *Biologics* 2013; **7**:7-11.
131. Antoniu SA. Novel therapies for hypereosinophilic syndromes. *Neth J Med* 2010; **68**:304-310.
132. Pitini V, Teti D, Arrigo C, Righi M. Alemtuzumab therapy for refractory idiopathic hypereosinophilic syndrome with abnormal T cells: a case report. *Br J Haematol* 2004; **127**:477.
133. Sefcick A, Sowter D, DasGupta E, Russell NH, Byrne JL. Alemtuzumab therapy for refractory idiopathic hypereosinophilic syndrome. *Br J Haematol* 2004; **124**:558-559.
134. Verstovsek S, Tefferi A, Kantarjian H, Manshouri T, Luthra R, Pardanani A*, et al.* Alemtuzumab therapy for hypereosinophilic syndrome and chronic eosinophilic leukemia. *Clin Cancer Res* 2009; **15**:368-373.
135. Gribben JG, Hallek M. Rediscovering alemtuzumab: current and emerging therapeutic roles. *Br J Haematol* 2009; **144**:818-831.
136. Perini GF, Santos FP, Hamerschlak N. Alemtuzumab in the reversal of encephalopathy associated with hypereosinophilic syndrome. *Br J Haematol* 2009; **147**:592.

137. Syed FF, Bleeker JS, Glockner J, Pardanani A, Cooper LT, Jr. Response to alemtuzumab in FIP1L1/PDGFRA-negative hypereosinophilic myocarditis on serial cardiac magnetic resonance imaging. *J Am Coll Cardiol* 2012; **59**:430.
138. Reichert JM. Which are the antibodies to watch in 2012? *MAbs* 2012; **4**:1-3.
139. Bochner BS, Gleich GJ. What targeting eosinophils has taught us about their role in diseases. *J Allergy Clin Immunol* 2010; **126**:16-25; quiz 26-17.
140. Gleich GJ, Leiferman KM, Pardanani A, Tefferi A, Butterfield JH. Treatment of hypereosinophilic syndrome with imatinib mesilate. *Lancet* 2002; **359**:1577-1578.
141. Klion AD, Robyn J, Akin C, Noel P, Brown M, Law M*, et al.* Molecular remission and reversal of myelofibrosis in response to imatinib mesylate treatment in patients with the myeloproliferative variant of hypereosinophilic syndrome. *Blood* 2004; **103**:473-478.
142. Pardanani A, Reeder T, Porrata LF, Li CY, Tazelaar HD, Baxter EJ*, et al.* Imatinib therapy for hypereosinophilic syndrome and other eosinophilic disorders. *Blood* 2003; **101**:3391-3397.
143. Jovanovic JV, Score J, Waghorn K, Cilloni D, Gottardi E, Metzgeroth G*, et al.* Low-dose imatinib mesylate leads to rapid induction of major molecular responses and achievement of complete molecular remission in FIP1L1-PDGFRA-positive chronic eosinophilic leukemia. *Blood* 2007; **109**:4635-4640.
144. Haferlach T, Bacher U, Kern W, Schnittger S, Haferlach C. The diagnosis of BCR/ABL-negative chronic myeloproliferative diseases (CMPD): a comprehensive approach based on morphology, cytogenetics, and molecular markers. *Ann Hematol* 2008; **87**:1-10.
145. Roche-Lestienne C, Lepers S, Soenen-Cornu V, Kahn JE, Lai JL, Hachulla E*, et al.* Molecular characterization of the idiopathic hypereosinophilic syndrome (HES) in 35 French patients with normal conventional cytogenetics. *Leukemia* 2005; **19**:792-798.
146. Baccarani M, Cilloni D, Rondoni M, Ottaviani E, Messa F, Merante S*, et al.* The efficacy of imatinib mesylate in patients with FIP1L1-PDGFRalpha-positive hypereosinophilic syndrome. Results of a multicenter prospective study. *Haematologica* 2007; **92**:1173-1179.
147. Ng HJ, Tan DC, Yiu RC, How GF. Maintenance therapy with imatinib appears necessary despite molecular remission in FIP1L1-PDGFRA fusion gene positive hypereosinophilic disorder. *Leuk Res* 2008; **32**:169-171.
148. Helbig G, Kyrcz-Krzemien S. Cessation of imatinib mesylate may lead to sustained hematologic and molecular remission in FIP1L1-PDGFRA-mutated hypereosinophilic syndrome. *Am J Hematol* 2014; **89**:115.
149. Qu SQ, Qin TJ, Xu ZF, Zhang Y, Ai XF, Li B*, et al.* Long-term outcomes of imatinib in patients with FIP1L1/ PDGFRA associated chronic eosinophilic leukemia: experience of a single center in China. *Oncotarget* 2016; **7**:33229-33236.
150. Saussele S, Richter J, Hochhaus A, Mahon FX. The concept of treatment-free remission in chronic myeloid leukemia. *Leukemia* 2016; **30**:1638-1647.
151. Jawhar M, Naumann N, Schwaab J, Baurmann H, Casper J, Dang TA*, et al.* Imatinib in myeloid/lymphoid neoplasms with eosinophilia and rearrangement of PDGFRB in chronic or blast phase. *Ann Hematol* 2017; **96**:1463-1470.
152. David M, Cross NC, Burgstaller S, Chase A, Curtis C, Dang R*, et al.* Durable responses to imatinib in patients with PDGFRB fusion gene-positive and BCR-ABL-negative chronic myeloproliferative disorders. *Blood* 2007; **109**:61-64.
153. Metzgeroth G, Schwaab J, Gosenca D, Fabarius A, Haferlach C, Hochhaus A*, et al.* Long-term follow-up of treatment with imatinib in eosinophilia-associated myeloid/lymphoid neoplasms with PDGFR rearrangements in blast phase. *Leukemia* 2013; **27**:2254-2256.

154. Fraticelli P, Kafyeke A, Mattioli M, Martino GP, Murri M, Gabrielli A. Idiopathic hypereosinophilic syndrome presenting with severe vasculitis successfully treated with imatinib. *World J Clin Cases* 2016; **4**:328-332.
155. Muller AM, Martens UM, Hofmann SC, Bruckner-Tuderman L, Mertelsmann R, Lubbert M. Imatinib mesylate as a novel treatment option for hypereosinophilic syndrome: two case reports and a comprehensive review of the literature. *Ann Hematol* 2006; **85**:1-16.
156. Rumi E, Milosevic JD, Selleslag D, Casetti I, Lierman E, Pietra D*, et al.* Efficacy of ruxolitinib in myeloid neoplasms with PCM1-JAK2 fusion gene. *Ann Hematol* 2015; **94**:1927-1928.
157. Lee s, Palmares C. Ruxolitinib Used to Treat Hypereosinophilic Syndrome. *Blood* 2016; **128:5500**.
158. Verstovsek S. Preclinical and clinical experience with dasatinib in Philadelphia chromosome-negative leukemias and myeloid disorders. *Leuk Res* 2009; **33**:617-623.
159. Chang M. Salvage Therapy of Imatinib-resistant Hypereosinophilic Syndrome with PDGFRB Rearrangement: A Case Report. *Journal of Cancer Research and Practice* 2016; **10.1016/j.jcrpr.2015.10.003.**
160. Hartmann JT, Haap M, Kopp HG, Lipp HP. Tyrosine kinase inhibitors - a review on pharmacology, metabolism and side effects. *Curr Drug Metab* 2009; **10**:470-481.
161. Ueno NT, Anagnostopoulos A, Rondon G, Champlin RE, Mikhailova N, Pankratova OS*, et al.* Successful non-myeloablative allogeneic transplantation for treatment of idiopathic hypereosinophilic syndrome. *Br J Haematol* 2002; **119**:131-134.
162. Halaburda K, Prejzner W, Szatkowski D, Limon J, Hellmann A. Allogeneic bone marrow transplantation for hypereosinophilic syndrome: long-term follow-up with eradication of FIP1L1-PDGFRA fusion transcript. *Bone Marrow Transplant* 2006; **38**:319-320.