

Guideline for the investigation and management of eosinophilia

A British Society for Haematology Guideline

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Keywords: eosinophilia, hypereosinophilia, eosinophilic leukaemia, HES

Introduction

The guideline group was selected to be representative of UK-based medical experts with an interest in myeloproliferative neoplasms and eosinophilia. PubMed and EMBASE were searched systematically for publications in English until August 2015 using the key words eosinophilia, hypereosinophilia, eosinophilic leukaemia and HES. The writing group produced the draft guideline which was subsequently revised by consensus by members of the General Haematology and Haemato-oncology Task Forces of the British Committee for Standards in Haematology. The guideline was then reviewed by a sounding board of UK haematologists and representatives from the Nordic MPN Study Group, the British Committee for Standards in Haematology (BCSH) and the British Society for Haematology (BSH) Committee and comments were incorporated where appropriate. The 'GRADE' system was used to quote levels and grades of evidence, details of which can be found in Table I. The objective of this guideline is to provide healthcare professionals with clear guidance on the investigation and management of eosinophilia.

Guideline Update

There is no previous BCSH guideline for this topic.

Aim

The purpose of this guideline is to provide a practical approach to the investigation and management of eosinophilia.

Key recommendations

- The underlying cause of eosinophilia should be sought and possible eosinophil-associated end-organ damage should be evaluated (Grade 1B)

Assessment of underlying cause

- A detailed medical history should be taken and a thorough physical examination should be performed (Grade 1C).

The history should include:

- assessment for allergic disorders, skin rashes and cardiorespiratory, gastrointestinal and constitutional symptoms.
- a detailed travel history, particularly for tropical travel; travel even in the remote past may be relevant.
- a detailed drug history.
- All patients should have a full blood count, blood film examination and routine tests of renal and liver function, a bone profile, lactate dehydrogenase, erythrocyte sedimentation rate and/or C-reactive protein and vitamin B12 assay (Grade 1C)
- Patients who are otherwise well with mild to moderate eosinophilia between 0.5 and $1.5 \times 10^9/l$ may not require further testing. Patients with systemic

symptoms and those with persistent eosinophilia (at least $1.5 \times 10^9/l$), irrespective of suspected organ damage, should be considered for additional testing for an underlying cause

- Specific causes of reactive eosinophilia, based on clinical suspicion, should be confirmed or excluded at an early stage by appropriate testing (Grade 1C).
- Patients with an eosinophil count of at least $1.5 \times 10^9/l$ with no obvious cause should be investigated for a possible haematological neoplasm with clonal eosinophilia, initially by peripheral blood analysis for *FIP1L1-PDGFR*A by fluorescence *in situ* hybridisation (FISH) or nested reverse transcriptase polymerase chain reaction (RT-PCR) (Grade 1C).
- Serum tryptase estimation should be performed if the differential diagnosis includes chronic eosinophilic leukaemia or systemic mastocytosis (Grade 1B).
- In the absence of an identifiable cause and with negative peripheral blood analysis for *FIP1L1-PDGFR*A by FISH or nested RT-PCR, a bone marrow aspirate, trephine biopsy and cytogenetic analysis should be performed; the possibility of an underlying lymphoma or of the lymphocytic variant of hypereosinophilic syndrome should be evaluated, including consideration of immunophenotyping of peripheral blood and bone marrow lymphocytes and analysis for T-cell receptor gene rearrangement (Grade 1C). The possibility of systemic mastocytosis or other myeloid neoplasm should be considered.

Assessment for possible eosinophil-associated end-organ damage

- End-organ damage should be assessed using chest radiography and/or computed tomography (CT) of the thorax, echocardiography, serum troponin T and pulmonary function testing. (Grade 1C).
- An unprovoked thromboembolic event should be recognised as a possible manifestation of eosinophil-associated tissue damage (Grade 2C).
- In patients with end-organ damage, the frequency of further serial evaluations of organ function should be determined by the severity and extent of organ compromise and/or by worsening of the eosinophilia (Grade 2C).

Emergency treatment

- Patients requiring emergency treatment for severe or life-threatening eosinophilia should receive high-dose corticosteroids (Grade 1B).
- Patients receiving corticosteroids, in whom there is a risk of strongyloides infection, should receive concomitant ivermectin to prevent potentially fatal hyperinfection (Grade 1B)

Treatment of clonal eosinophilia

- Patients with clonal eosinophilia with *FIP1L1-PDGFR*A (including patients presenting with acute leukaemia), should be treated with low dose imatinib (Grade 1B).
- Patients with clonal eosinophilia with *PDGFR*B rearrangement or *ETV6-ABL1* fusion should receive standard dose imatinib (Grade 1B).

- Patients with clonal eosinophilia with *ETV6-FLT3* fusion should be considered for sunitinib or sorafenib therapy (Grade 2B)
- Patients with clonal eosinophilia with *JAK2* rearrangement should be considered for ruxolitinib therapy (Grade 2B)
- Patients with acute myeloid leukaemia (AML) with clonal eosinophilia and no molecular or cytogenetic abnormality suggesting likely response to a tyrosine kinase inhibitor should be offered standard AML induction therapy (Grade 1A).
- Patients with other haematological neoplasms with clonal eosinophilia should have treatment directed at management of the neoplasm. If there is organ damage or dysfunction relating to the eosinophilia, treatment with corticosteroids should also be given (Grade 1C).

Treatment of lymphocytic variant of hypereosinophilic syndrome

- Patients with the lymphocytic variant of hypereosinophilic syndrome (HES) can be managed in the same manner as idiopathic HES (grade 2B)

Treatment of idiopathic hypereosinophilic syndrome

- Patients with idiopathic HES should be treated in the first instance with corticosteroids (see emergency treatment above).

- Patients with idiopathic HES who do not respond adequately to corticosteroids, or who require prolonged corticosteroid therapy, or who are intolerant of corticosteroids, should be considered for a short trial (4–6 weeks) of imatinib, immunomodulatory agents (interferon alpha, ciclosporin or azathioprine), myelosuppressive therapy (hydroxycarbamide) or monoclonal antibody therapy with mepolizumab (anti-interleukin 5), the latter preferably as part of a clinical trial (Grade 2B).
- Alemtuzumab, an anti-CD52 monoclonal antibody, should be considered for patients with severe idiopathic HES unresponsive to other therapies, and may be useful in patients with idiopathic HES-associated cardiac and cerebral dysfunction. (Grade 2B)

Role of haemopoietic stem cell transplantation (HSCT)

- HSCT should be considered for cases with clonal eosinophilia with *FGFR1* rearrangement, patients with chronic eosinophilic leukaemia, not otherwise specified and those HES patients refractory to or intolerant of both conventional tyrosine kinase inhibitor (TKI) therapy and experimental medical therapy, where available, or who display progressive end-organ damage. (Grade 2C)

Definitions

Eosinophilia is defined as an elevation of the eosinophil count above levels observed in healthy subjects, usually taken as above $0.5 \times 10^9/l$. Eosinophil counts are higher in neonates than in adults and the values gradually fall in the elderly. There is no sex or ethnic variation in the eosinophil count. Definitions of hypereosinophilia (HE) and the hypereosinophilic syndrome (HES) are based on the proposal by Chusid *et al* (Chusid *et al*, 1975) of an eosinophil count of $1.5 \times 10^9/l$ or greater persisting for at least 6 months, for which no underlying cause can be found and which is associated with signs of organ involvement and dysfunction. This criterion was subsequently accepted in the World Health Organization (WHO) classification of chronic eosinophilic leukaemia, not otherwise specified (CEL, NOS) (Bain *et al*, 2008). However treatment should not be withheld in patients with hypereosinophilia of less than 6 months duration who have evidence of end-organ damage (See Emergency treatment).

Biology

The normal bone marrow contains between 1% and 6% eosinophils and these produce an eosinophil count in the peripheral blood of $0.05\text{--}0.5 \times 10^9/l$ (Valent *et al*, 2012). Eosinophil production in the marrow is tightly controlled by a network of transcription factors (McNagny & Graf 2002) and is driven by various cytokines, principally interleukin (IL)-5, IL-3 and granulocyte-macrophage colony-stimulating factor (GM-CSF) produced by activated T lymphocytes, stromal cells and mast cells, triggering differentiation and activation (Ackerman & Bochner 2007). Such cytokines are also the

main drivers in reactive eosinophilia in contrast to clonal eosinophilia where tyrosine kinase gene fusions are common, typically involving the genes coding for platelet-derived growth factor receptor alpha (*PDGFRA*), platelet-derived growth factor receptor beta (*PDGFRB*) or fibroblast growth factor receptor 1 (*FGFR1*) (Gotlib et al, 2006).

Under normal conditions, eosinophils may also be found in lymphoid organs and the mucosa of the gastrointestinal tract and uterus but very rarely in other tissues. However, prolonged or marked activation of eosinophils may cause migration into non-native tissues such as the skin, heart and lung where they may cause end-organ damage principally through the induction of thrombosis and fibrosis (Gleich 2000).

Epidemiology

Primary and idiopathic eosinophil disorders are rare and probably under-diagnosed conditions. A large population based study in a general practice setting from Copenhagen demonstrated an incidence of eosinophilia (defined as a count of at least $0.5 \times 10^9/l$) of 4% (Andersen *et al*, 2015).

Causes of Eosinophilia

The causes of eosinophilia are numerous and are conventionally divided into three main categories – secondary (reactive), primary and idiopathic – as indicated in Table II. These are discussed below. HES predominantly affects males, with an estimated male-to-female ratio ranging up to 9 : 1 (Weller & Bubley 1994). This is largely explained by the fact that the *FIP1L1-PDGFR* fusion gene occurs almost exclusively in males. In a case

series of 188 subjects with HES, once confirmed *FIP1L1-PDGFR*A-positive patients were removed from the cohort, the difference in male-to-female prevalence was not statistically significant (Ogbogu *et al*, 2009).

Secondary (reactive) eosinophilia

These form the majority of cases of eosinophilia.

Allergic Disorders

Allergic disorders such as atopic dermatitis, asthma and seasonal allergic disorders (rhinitis/hayfever) can result in a cytokine-driven non-clonal eosinophilia which is usually mild (less than $1.5 \times 10^9/l$) with the degree of blood eosinophilia and tissue infiltration generally correlating with the severity of the disease (Horn *et al*, 1975). The eosinophilia usually resolves with control of the underlying condition.

Dermatological causes (non-allergic)

Wells syndrome (eosinophilic cellulitis) is a recurring granulomatous dermatitis with eosinophilia (Wells 1971) characterised by (i) sudden onset annular or circinate erythematous-oedematous patches that rapidly evolve to morphea-like slate-blue plaques, (ii) a histological appearance characterized by the presence of 'flame figures' and (iii) an inconstant blood eosinophilia. Similar histological appearances can be seen in other dermatological conditions but these can often be discriminated clinically. Wells

variants have been described (El-Khalawany *et al*, 2013) as well as associations with other disorders affecting the skin including connective tissue disease (Yin & Xie 2012).

Drug-induced eosinophilia

Drug hypersensitivity should always be considered as a cause for unexplained eosinophilia. The list of agents is extensive and includes dietary supplements and herbal remedies (Klion 2009). The clinical manifestations associated with drug-induced eosinophilia range from asymptomatic to life-threatening (Klion 2009). Rarely a drug reaction with eosinophilia and systemic symptoms (DRESS syndrome) occurs 3–6 weeks after the introduction of a new drug. This syndrome is characterised by a triad of a skin eruption, fever and internal organ involvement (lung, liver, kidneys, lymph nodes or heart) (Dong *et al*, 2014; Sultan *et al*, 2015). Drug-induced vasculitis and eosinophilia is also reported, manifesting with purpura, arthralgia and myalgia with possible kidney and lung involvement (Roujeau *et al*, 2014).

Infectious diseases

A detailed review of infectious causes of eosinophilia has recently been published (O'Connell & Nutman 2015). Important infective agents and their diagnostic tests are outlined in Table III. The British Infection Society and the Hospital for Tropical Diseases have published UK recommendations for the investigation of eosinophilia in patients with a tropical travel history (Checkley *et al*, 2010).

Gastrointestinal disorders

Primary gastrointestinal disorders are rarely associated with gastrointestinal tissue eosinophilia with or without peripheral blood eosinophilia. Table IV highlights the main disorders that need to be considered in the differential diagnosis.

Vasculitides

Polyarteritis nodosa (PAN) results in inflammation and injury to medium-sized and small arteries leading to ischaemia or haemorrhage in a variety of tissues and organs, though the kidneys are usually spared. Renal sparing and negative antineutrophil cytoplasmic antibodies (ANCA) are useful in differentiating PAN from other systemic necrotizing vasculitides (Hernandez-Rodriguez *et al*, 2014). Eosinophilia is occasionally seen but, when present, eosinophilic granulomatosis with polyangiitis must be considered (Watts *et al*, 2007).

Eosinophilic granulomatosis with polyangiitis (EGPA/Churg-Strauss syndrome): EGPA can present with a variety of clinicopathological features depending on the organs involved: allergic rhinitis, acute hepatitis, diarrhoea (mesenteric ischaemia), restrictive cardiomyopathy, peripheral neuropathy, skin lesions and, rarely, renal disease. ANCA is useful to support the diagnosis – mostly perinuclear ANCA (p-ANCA) against myeloperoxidase (MPO); however ANCA is positive in less than 50% of subjects (Sable-Fourtassou *et al*. *Ann Intern Med* 2005; Sinico *et al*. *Arthritis Rheum* 2005). The diagnosis is confirmed by tissue biopsy.

Rheumatological Diseases

Systemic lupus erythematosus (SLE): eosinophilia is not uncommonly described in individual case reports but there are no systematic studies on the incidence and severity of eosinophilia in SLE and eosinophilia does not form one of the diagnostic criteria for the condition (Petri *et al*, 2012).

Eosinophilic fasciitis (Shulman disease): this is a rare scleroderma-like syndrome of unknown cause, thought to be immune mediated with resultant painful swelling and progressive induration and thickening of skin/soft tissues of limbs and trunk. Laboratory findings are those of a peripheral blood eosinophilia, hypergammaglobulinaemia and elevated erythrocyte sedimentation rate (ESR). There are no universally accepted diagnostic criteria but in a recent review (Pinal-Fernandez *et al*, 2014) peripheral blood eosinophilia formed one of four minor criteria for the diagnosis. There is an association with aplastic anaemia (De Masson *et al*, 2013).

Rheumatoid arthritis (RA): a recent prospective French study showed that approximately 3% of patients with RA have an eosinophilia, which is usually mild and transient (Guellec *et al*, 2015). Although this prevalence does not differ from that of the Danish population study, defined in the same manner (Andersen *et al*, 2015), eosinophilia did appear to predict a poorer response to disease-modifying antirheumatic drug use after 3 years (Guellec *et al*, 2015). A smaller Argentinian study demonstrated a 7% prevalence of eosinophilia amongst RA patients, but in all these cases a parasitic cause for the eosinophilia was subsequently demonstrated (Chiardola *et al*, 2008).

Respiratory disease

There are a number of conditions associated with acute and chronic eosinophilic pneumonias. These have recently been extensively reviewed (Cottin 2016). Their diagnosis is based on characteristic radiological appearances and the demonstration of alveolar eosinophilia, defined as at least 25% eosinophils on broncho-alveolar lavage. Peripheral blood eosinophilia may be a feature of several of these conditions including Löffler disease, Allergic bronchopulmonary aspergillosis and sarcoidosis.

Löffler disease: Löffler first described this transient pulmonary reaction with reticulonodular shadowing on chest radiology associated with a peripheral blood eosinophilia in 1932. Patients present with a low grade fever and a cough for 7–10 days, which is usually due to an allergic reaction in the alveoli as a result of a parasitic infection (see Infectious disease) or medications (See Drug-Induced). Occasionally patients present with skin lesions. The onset of symptoms is typically 2–3 weeks following exposure to parasites and 3–4 days following ingestion of medication. This is usually a self limiting disease with symptoms subsiding within 3–4 weeks of eliminating the causal agent. The differential diagnosis is allergic bronchopulmonary aspergillosis.

Allergic bronchopulmonary aspergillosis is caused by hypersensitivity to *Aspergillus fumigatus* and results in uncontrolled asthma and recurrent pulmonary infiltrates which can progress to bronchiectasis and pulmonary fibrosis (Agarwal *et al*, 2013). Diagnostic criteria include a history of asthma or cystic fibrosis, elevated aspergillus-specific immunoglobulin (Ig) E and IgG, elevated serum IgE (1000 ng/ml or > 417 iu/ml), wheal-

and-flare skin reaction to aspergillus antigen and an eosinophil count greater than $1.0 \times 10^9/l$.

Sarcoidosis: there is no diagnostic test for sarcoidosis though a mild peripheral blood eosinophilia, raised serum angiotensin converting enzyme (ACE) level and a tissue biopsy demonstrating the presence of non-caseating granulomas in affected organs suggests the diagnosis.

Neoplastic disorders with secondary non-clonal eosinophilia

Solid tumours: a range of non-haematological neoplasms have been reported to cause reactive eosinophilia, with a prevalence of 0.5% to 7% (Montgomery *et al*, 2013). The presence of eosinophilia is often associated with more advanced metastatic disease. In cases of unexplained eosinophilia, careful clinical evaluation and radiological studies should be carried out to exclude underlying occult malignancy (Klion 2009).

Lymphoproliferative disorders: reactive eosinophilia occurs in a broad spectrum of B- and T-cell lymphoproliferative disorders. In Hodgkin lymphoma the prevalence of eosinophilia is 15% (Vaughan Hudson *et al*, 1987) and in non-Hodgkin lymphoma prevalence ranges from 2% to 20% (Montgomery *et al*, 2013) with a higher prevalence in T-cell than B-cell lymphomas. Reactive eosinophilia can occur in acute lymphoblastic leukaemia/lymphoma (Grimaldi & Meeker 1989). In the case of B-lineage acute lymphoblastic leukaemia (ALL) with t(5;14)(q31.1;q32.1), it results from dysregulation

of the *IL3* gene by proximity to the *IGH* locus. When eosinophils are part of the neoplastic clone the eosinophilia is primary rather than reactive and the case falls into the group of haematological neoplasms with clonal eosinophilia.

Lymphocytic variant HES (L-HES)

L-HES is caused by an expansion of demonstrably clonal or phenotypically aberrant T-lymphoid cells in the peripheral blood with a secondary, reactive eosinophilia (Simon *et al*, 1999), without overt lymphoproliferative disease. Such abnormal T-cell populations have been reported to be present in 17% to 27% of otherwise unexplained HES (Ogbogu *et al*, 2009; Simon *et al*, 1999). There are no current consensus diagnostic criteria and diagnosis rests on demonstration of an abnormal T-cell population by flow cytometry, with a broad range of phenotypes reported including CD3⁺CD4⁺, CD3⁺CD4⁺CD8⁻ and CD3⁺CD4⁺CD7⁻ (Roufosse 2009). Some cases of *L-HES* harbour T-cell receptor gene rearrangement (Simon *et al*, 1999), but this alone is insufficient to make the diagnosis of *L-HES* in the absence of phenotypically abnormal T cells (Roufosse 2009). Clinical manifestations of disease in *L-HES* are typically cutaneous (Simon *et al*, 1999) though patients can have more severe end-organ manifestations including cardiac and neurological involvement.

Miscellaneous Causes

Atheroembolic disease: cholesterol atheroembolic disease develops as a consequence of cholesterol microembolisation following rupture of atheromatous aortic plaques after

arterial catheterisation procedures, vascular surgery or following anticoagulant or thrombolytic therapy. A transient eosinophilia has been reported in the acute phase of the illness (Kasinath & Lewis 1987; Scolari *et al*, 2007), thought to be driven by increased IL-5 production by activated T cells at the surface of emboli (Cogan *et al*, 1995). The diagnosis is usually confirmed by biopsy of an affected organ.

Graft-Versus-Host Disease: eosinophilia can be a feature of both acute and chronic graft-versus-host disease (GVHD) following allogeneic haematopoietic stem cell transplantation (HSCT) (Ahmad *et al*, 2011; Imahashi *et al*, 2010; Jacobsohn *et al*, 2004) although the mechanisms underlying this are unclear. Conflicting data exist regarding the prognostic significance of the eosinophilia (Ahmad *et al*, 2011; Imahashi *et al*, 2010).

Gleich's syndrome: this rare disease was first described in 1984 (Gleich *et al*, 1984) and is characterised by episodic angio-oedema with eosinophilia that occurs at monthly intervals and resolves spontaneously without therapy. Cyclic variation in eosinophil, neutrophil and lymphocyte counts has been seen. (Khoury *et al*, 2014). It is associated with raised IgM and C1 esterase levels are normal. It was previously believed that this syndrome did not lead to end organ damage but a recent report highlights a case that progressed to endomyocardial fibrosis (Wright *et al*, 2016). Corticosteroids may reduce the severity of attacks.

Disorders of immune regulation: Hypereosinophilia is associated with a number of disorders of immune deficiency or immune dysregulation. These often present in the paediatric age group and often have common features including dermatological manifestations, atopic features, recurrent infections and, in some cases, predisposition to malignancy. A detailed description of these conditions is beyond the scope of this guideline but these have been outlined in a recent extensive review article (Williams *et al*, 2015). However, autosomal dominant hyper-IgE syndrome, DOCK8 deficiency, PGM3 deficiency have similar clinical features and are particularly notable due to the presence of markedly elevated IgE levels.

Clonal eosinophilia

A number of haematological neoplasms may be accompanied by an eosinophilia in which the eosinophils are part of the neoplastic clone, and the eosinophilia is thus primary. These are listed in Table II.

Clonal eosinophilia should be suspected in patients who present with unexplained isolated eosinophilia, possibly representing chronic eosinophilic leukaemia (CEL), or with haematological features consistent with chronic myelomonocytic leukaemia with eosinophilia (CMML-Eo) or atypical chronic myeloid leukaemia with eosinophilia (aCML-Eo). The neoplastic disorders to be considered in these patients include those with *JAK2*^{V617}, *KIT*^{D816V} or rearrangement of *PDGFRA*, *PDGFRB* or *FGFR1* (Bain 2008), *PCM1-JAK2* (Bain & Ahmad 2014) and, rarely, *BCR-JAK2* (Bain & Ahmad

2014), *ETV6-JAK2* (Bain & Ahmad 2014), *ETV6-ABL1* (Nand *et al*, 2009) or *ETV6-FLT3* (Walz *et al*, 2011). Patients with *BCR-ABL1*-positive chronic myelogenous leukaemia in chronic phase do not have disproportionate eosinophilia, although the eosinophils are clonal; however predominant eosinophilia can occur at the time of disease acceleration or blast transformation.

Rarely patients with acute myeloid leukaemia associated with t(8;21)(q22;q22.1) or inv(16)(p13.1q22) present with prominent peripheral blood eosinophilia (AML-Eo). Apparent AML-Eo can also represent transformation of a myeloproliferative neoplasm (MPN) with rearrangement of *PDGFRA*, *PDGFRB* or *FGFR1*.

Patients who present with ALL with eosinophilia may have either reactive eosinophilia or a leukaemia arising in a pluripotent lymphoid-myeloid stem cell in which the eosinophils are clonal. T-ALL/T lymphoblastic lymphoma with associated clonal eosinophilia can occur with *PDGFRA* and *FGFR1* rearrangements and with *ETV6-FLT3*; a small number of cases of T lymphoblastic lymphoma (Chmielecki *et al*, 2012; Ondrejka *et al*, 2014) or unspecified lymphoid blast phase (Metzgeroth *et al*, 2013) have also been reported in MPNs with *PDGFRB* rearrangement. Rarely B-ALL/B lymphoblastic lymphoma transformation is seen in association with *PDGFRA* rearrangement (Tremat *et al*, 2003). B-ALL/B lymphoblastic lymphoma occurs more often in association with *FGFR1* rearrangement and mixed phenotype acute monoblastic/precursor-B ALL (Yamamoto *et al*, 2006) has also been reported in this context. Cases with *PCM1-JAK2* can suffer a B lymphoblastic transformation.

Eosinophilia can be a feature of systemic mastocytosis when it can be postulated that the eosinophilia may be either cytokine driven, clonal or a combination of the two.

Chronic eosinophilic leukaemia, not otherwise specified is, by definition, *BCR-ABL1*-negative without rearrangement of *PDGFRA*, *PDGFRB* or *FGFR1* (Bain *et al*, 2008). Cases with *PCM1-JAK2*, *ETV6-JAK2* or *BCR-JAK2* should also be excluded. The eosinophil count must be at least $1.5 \times 10^9/l$ and, to make a distinction from AML-Eo, blast cells must be less than 20% in both the peripheral blood and bone marrow and *t*(8;21) and *inv*(16) must be absent. There may be some increase in neutrophils and monocytes or, occasionally, basophils. For the condition to be recognised as leukaemic in nature there must be an increase of blast cells in the blood or marrow or cytogenetic or other evidence of clonality. Cytogenetic abnormalities observed have included trisomy 8 and *i*(17q). CEL, NOS is a rare and aggressive disorder associated with a median survival of 20 months and a high rate of acute transformation (Helbig *et al*, 2012; Klion 2011).

Idiopathic hypereosinophilia and the idiopathic hypereosinophilic syndrome

Idiopathic HE and idiopathic HES are diagnoses of exclusion in patients who have been appropriately assessed with a detailed history, physical examination and thorough investigation without any cause being found. Both are defined by an eosinophil count of $1.5 \times 10^9/l$ or more (Chusid *et al*, 1975) with, in the case of idiopathic HES, there also being tissue damage. Organ systems involved include the heart, lungs, skin, peripheral and central nervous systems and gastrointestinal tract. Thromboembolic complications are common. Some cases are likely to represent a reactive condition consequent on an

unrecognised underlying cause. Others cases may represent eosinophilic leukaemia which is sometimes confirmed on follow up when blast transformation occurs.

Evaluation of patients presenting with eosinophilia

The evaluation of eosinophilia is centred on investigating for a possible underlying cause and assessing possible eosinophil-associated end organ damage or dysfunction. These investigations are usually performed in parallel.

The diagnostic process begins with a detailed medical history including an assessment for allergic disorders such as asthma, eczema, urticaria and hay fever. A history of skin rashes or lymphadenopathy should be sought. Cardiorespiratory and gastrointestinal symptoms should be evaluated. Constitutional symptoms should be noted including fever, drenching night sweats, weight loss, pruritus and alcohol-induced pain. A detailed travel history, particularly of tropical travel, should be taken; even travel in the remote past may be relevant. A detailed drug history should be taken.

A thorough physical examination should be performed.

Initially, all patients should have a full blood count performed and a blood film examined. This is to verify the eosinophil count as hypogranular eosinophils may not be counted accurately by automated counters. The arbitrary eosinophil count accepted for a diagnosis of CEL, NOS (Bain *et al*, 2008) and idiopathic HES (Chusid *et al*, 1975) is a count of at least $1.5 \times 10^9/l$ (but molecular analysis permits certain entities to be

diagnosed with a lower count). The blood film may indicate an alternative cause for the eosinophilia, such as parasitic disease, or may show morphological evidence of an underlying haematological neoplasm including blast cells, neutrophilia and left shift, monocytosis, basophilia, dysplastic features or circulating lymphoma cells or mast cells. The cytological features of eosinophils are not helpful in the differential diagnosis since striking abnormalities can occur in reactive eosinophilia and sometimes clonal eosinophils are cytologically fairly normal.

Routine tests should be performed for renal, liver and bone profile, lactate dehydrogenase and ESR and/or C-reactive protein (CRP). The latter tests may be helpful in excluding an inflammatory or reactive process associated with eosinophilia. Vitamin B12 should be assayed since an elevated level may point to a myeloid disorder.

Further testing is dependent on the suspected diagnosis based on the history, examination and the results of these initial investigations, and on the degree of clinical urgency. Suggested investigations are outlined in Table V. In patients who are otherwise well with mild to moderate eosinophilia between 0.5 and $1.5 \times 10^9/l$, further testing may not be indicated. Patients with systemic symptoms or those with persistent eosinophilia (at least $1.5 \times 10^9/l$), with or without suspected organ damage, should be considered for additional testing for primary and secondary causes of eosinophilia and for evaluation of organ damage.

Secondary (reactive) eosinophilia should be confirmed or excluded at an early stage. In patients with an eosinophilia of at least $1.5 \times 10^9/l$ with no obvious underlying cause, a

haematological neoplasm with clonal eosinophilia should be considered. In a non-urgent situation, it is prudent to do the least invasive tests first with peripheral blood analysis for *FIP1L1-PDGFRA* by fluorescence *in situ* hybridisation (FISH) or nested reverse transcriptase polymerase chain reaction (RT-PCR). Serum tryptase estimation is indicated if the differential diagnosis includes CEL or systemic mastocytosis. Otherwise, a bone marrow aspirate, trephine biopsy and cytogenetic analysis should be performed. Morphological assessment of the marrow is vital for exclusion of haematological and non-haematological malignancy. If serum tryptase is elevated, a diagnosis of systemic mastocytosis should be considered and molecular analysis for *KIT* on a bone marrow aspirate should be performed. However it should be noted that serum tryptase is also often elevated in patients with CEL with *FIP1L1-PDGFRA* who may also have increased bone marrow mast cells; because of their sensitivity to imatinib, it is very important that such cases are not misdiagnosed as systemic mastocytosis. In addition, occasional cases of unexplained eosinophilia may test positive for *JAK2*^{V617F} (Schwaab *et al*, 2015). Abnormalities that are particularly sought on cytogenetic and molecular analysis and their clinical significance are summarised in Table VI. It is important to stress that almost all tyrosine kinase fusions apart from *FIP1L1-PDGFRA* are associated with visible cytogenetic rearrangements and therefore we recommend bone marrow cytogenetic analysis for cases with a suspected underlying MPN. Break-apart FISH analysis for specific loci may be used as an alternative but may be a relatively expensive approach. Any suspected fusion should be confirmed by RT-PCR and sequencing to ensure that targeted therapy is used appropriately and to facilitate subsequent molecular monitoring.

Key recommendations

- **The underlying cause of eosinophilia should be sought and possible eosinophil-associated end-organ damage should be evaluated (Grade 1B)**

Assessment of underlying cause

- **A detailed medical history should be taken and a thorough physical examination should be performed (Grade 1C).**

The history should include:

- **assessment for allergic disorders, skin rashes and cardiorespiratory, gastrointestinal and constitutional symptoms.**
- **a detailed travel history, particularly for tropical travel; travel even in the remote past may be relevant.**
- **a detailed drug history.**
- **All patients should have a full blood count, blood film examination and routine tests of renal and liver function, a bone profile, lactate dehydrogenase, erythrocyte sedimentation rate and/or C-reactive protein and vitamin B12 assay (Grade 1C)**
- **Patients who are otherwise well with mild to moderate eosinophilia between 0.5 and $1.5 \times 10^9/l$ may not require further testing. Patients with systemic symptoms and those with persistent eosinophilia (at least $1.5 \times 10^9/l$), irrespective of suspected organ damage, should be considered for additional testing for an underlying cause**

- Specific causes of reactive eosinophilia, based on clinical suspicion, should be confirmed or excluded at an early stage by appropriate testing (Grade 1C).
- Patients with an eosinophil count of at least $1.5 \times 10^9/l$ with no obvious cause should be investigated for a possible haematological neoplasm with clonal eosinophilia, initially by peripheral blood analysis for *FIP1L1-PDGFR*A by fluorescence *in situ* hybridisation (FISH) or nested reverse transcriptase polymerase chain reaction (RT-PCR) (Grade 1C).
- Serum tryptase estimation should be performed if the differential diagnosis includes chronic eosinophilic leukaemia or systemic mastocytosis (Grade 1B).
- In the absence of an identifiable cause and with negative peripheral blood analysis for *FIP1L1-PDGFR*A by FISH or nested RT-PCR, a bone marrow aspirate, trephine biopsy and cytogenetic analysis should be performed; the possibility of an underlying lymphoma or of the lymphocytic variant of hypereosinophilic syndrome should be evaluated, including consideration of immunophenotyping of peripheral blood and bone marrow lymphocytes and analysis for T-cell receptor gene rearrangement (Grade 1C). The possibility of systemic mastocytosis or other myeloid neoplasm should be considered.

Assessment of tissue damage

In patients with suspected tissue damage as a consequence of eosinophilia, investigations are directed at assessment of organ involvement including chest radiography and/or computed tomography (CT) of the thorax, echocardiography, serum troponin T and

pulmonary function testing (see Table VII). An unprovoked thromboembolic event is a recognised consequence of hypereosinophilia and is a manifestation of tissue damage.

In patients found to have tissue damage, the frequency of further serial evaluations of organ function is determined by the severity and extent of organ compromise and/or by worsening of the eosinophilia

Key recommendations

Assessment for possible eosinophil-associated end organ damage

- **End organ damage should be assessed using chest radiography and/or computed tomography of the thorax, echocardiography, serum troponin T and pulmonary function testing. (Grade 1C).**
- **An unprovoked thromboembolic event should be recognised as a possible manifestation of eosinophil-associated tissue damage (Grade 2C).**
- **In patients with end-organ damage, the frequency of further serial evaluations of organ function should be determined by the severity and extent of organ compromise and/or by worsening of the eosinophilia (Grade 2C).**

Treatment of patients with eosinophilia

The treatment of eosinophilia should be directed at the underlying cause. Specific treatment of secondary (reactive) eosinophilia is outside of the scope of this guideline and specialist referral should be made where indicated. Some patients with chronic marked

eosinophilia may never experience end-organ damage and treatment of eosinophilia in this circumstance is not merited. Emergency treatment, treatment of clonal eosinophilia and treatment of idiopathic HES are dealt with below and summarised in Figure 2.

Emergency treatment

There is no consensus on the absolute eosinophil level in the peripheral blood at which treatment is deemed necessary in completely asymptomatic patients (Gotlib 2014). The absolute eosinophil count does not correlate well with the degree or risk of organ damage (Brito-Babapulle 2003; Flaum *et al*, 1981; Schooley *et al*, 1981). There is some evidence for urgent treatment in cases with a high count of degranulated eosinophils since cardiac damage has been found to correlate with a degranulated eosinophil count of $1 \times 10^9/l$ or more (Spry *et al*, 1983). In the absence of identified organ damage, there is no evidence to indicate when or if treatment should be initiated. However in cases with significant organ dysfunction, particularly cardiac or pulmonary, emergency treatment is required.

The aim of therapy is to reduce the absolute eosinophil count and reduce tissue infiltration and eosinophil-mediated tissue damage (Klion 2009). A response assessment has been proposed by the Nordic study group based on (i) normalisation of eosinophil count, other haematological parameters and biochemical indicators such as IgE and serum tryptase; (ii) no evidence of organ involvement or symptoms; (iii) quality of life assessment (Bjerrum *et al*, 2012). This has yet to be validated.

Corticosteroids

High dose corticosteroids are the mainstay of emergency treatment and may be indicated whilst awaiting the results of initial investigations. The evidence for their use is limited and largely restricted to numerous case reports and small case series, many of which were published prior to the understanding of the molecular characterisation of hypereosinophilic syndromes (Klion *et al*, 2006; Roufosse & Weller 2010; Simon & Klion 2012; Weller & Bubley 1994). Although there is no evidence for the use of corticosteroids in combination with other immunosuppressive or myelosuppressive agents as first line therapy, this may be prudent to lessen eosinophil-mediated tissue damage.

Where there is evidence of life-threatening organ involvement treatment should start with the equivalent of 1 mg/kg/day of methylprednisolone intravenously. Otherwise, oral prednisolone is generally used at a dose of 0.5–1 mg/kg/day for 1–2 weeks. In extreme eosinophilia, consideration could be given to the concomitant administration of allopurinol for a short period. Corticosteroids can be slowly tapered over a period of 2–3 months to the lowest possible maintenance dose to retain response. Complete and partial response rates vary, typically between 64 and 85% (Helbig *et al*, 2013; Helbig *et al*, 2014; Ogbogu *et al*, 2009) with reported maintenance doses of prednisone (or equivalent) ranging widely between 1 mg and 60 mg daily for periods between 2 months and 20 years. The toxicity of long-term corticosteroids needs to be considered, and measures should be taken to limit the risk. In patients with a strong possibility of strongyloides exposure (see Table III), concomitant empirical ivermectin therapy should be given (200

µg/kg/day for 2 days) to prevent potentially fatal hyperinfection (Ramanathan & Nutman 2008).

Steroid-unresponsive cases may require alternative therapeutic approaches and it has been proposed that in cases where the eosinophil count remains greater than $1.5 \times 10^9/l$ after one month of therapy or if a patient requires a maintenance dose of prednisolone (or equivalent) of greater than 10 mg daily, a second-line agent should be considered (see Treatment of idiopathic hypereosinophilic syndrome).

Key recommendations

Emergency treatment

- **Patients requiring emergency treatment for severe or life-threatening eosinophilia should receive high-dose corticosteroids (Grade 1B).**
- **Patients receiving corticosteroids, in whom there is a risk of strongyloides infection, should receive concomitant ivermectin to prevent potentially fatal hyperinfection (Grade 1B)**

Treatment of primary (clonal) eosinophilic disorders

Chronic leukaemias with clonal eosinophilia and a specific molecular target

In clonal eosinophilia the highest priorities are to provide emergency treatment when required and to recognise entities in which specific therapy with a tyrosine kinase

inhibitor (TKI) is indicated as highlighted in Table VI. Patients with significant organ dysfunction, particularly cardiac or pulmonary, require emergency corticosteroid treatment alongside specific TKI therapy when appropriate.

Cases associated with *FIP1L1-PDGFR*A are highly sensitive to imatinib and a starting dose of 100 mg daily should be commenced (Baccarani *et al*, 2007). Dose titration, up to 400 mg daily, is dependent on eosinophil count and molecular response. Imatinib should also be commenced in patients presenting in acute leukaemic transformation as they may enter remission with imatinib even in the absence of chemotherapy (Barraco *et al*, 2014). Acquired imatinib resistance is uncommon but a T674I mutation, and less commonly a D842V mutation, leading to multi-TKI resistance has been observed in some cases.

Cases associated with *PDGFRB* rearrangement or an *ETV6-ABL1* fusion gene are responsive to imatinib at a dose of 400 mg daily. Molecular monitoring is indicated. Neoplasms associated with *ETV6-FLT3* may be responsive to sunitinib or sorafenib (Walz *et al*, 2011).

Ruxolitinib has demonstrated activity in cases with *PCM1-JAK2* or other *JAK2* rearrangement. Doses are adapted to platelet counts in line with the summary of product characteristics for ruxolitinib. Although a complete remission may be achieved, this is often of limited duration (Schwaab *et al*, 2014).

Chronic leukaemias with clonal eosinophilia without a specific molecular target

Clonal disorders without a specific molecular targeted therapy can be treated as for idiopathic HES as described below. Some patients may respond to imatinib though they often require higher doses of this agent and seem to respond more slowly (Metzgeroth *et al*, 2008; Butterfield *et al*, 2009). In view of the good safety profile of this agent, a short trial of imatinib 400 mg daily for 4–6 weeks is justified. Patients with at least four features of an MPN are more likely to respond to imatinib (Khoury *et al*, 2016). Cases associated with *FGFR1* rearrangement have a poor prognosis and intensive AML-type induction treatment followed by haematopoietic stem cell transplantation (HSCT) may be the best option. Because of the poor prognosis of CEL, NOS (Helbig 2012) this approach could also be justified in these cases. Response is assessed by monitoring a clonal marker when possible and by the eosinophil count.

Other haematological malignancies with an associated clonal eosinophilia

Patients with AML with clonal eosinophilia and no identifiable molecular or cytogenetic abnormality should be offered standard AML induction therapy. In patients with other haematological neoplasms with an associated clonal eosinophilia, treatment should be directed towards management of the underlying cause. If there is organ damage or dysfunction relating to the eosinophilia, addition of corticosteroids is indicated.

Key recommendations

Treatment of clonal eosinophilia

- Patients with clonal eosinophilia with *FIP1L1-PDGFR*A (including patients presenting with acute leukaemia), should be treated with low dose imatinib (Grade 1B).
- Patients with clonal eosinophilia with *PDGFRB* rearrangement or *ETV6-ABL1* fusion should receive standard dose imatinib (Grade 1B).
- Patients with clonal eosinophilia with *ETV6-FLT3* fusion should be considered for sunitinib or sorafenib therapy (Grade 2B)
- Patients with clonal eosinophilia with *JAK2* rearrangement should be considered for ruxolitinib therapy (Grade 2B)
- Patients with acute myeloid leukaemia with clonal eosinophilia and no molecular or cytogenetic abnormality suggesting likely response to a tyrosine kinase inhibitor should be offered standard AML induction therapy (Grade 1A).
- Patients with other haematological neoplasms with clonal eosinophilia should have treatment directed at management of the neoplasm. If there is organ damage or dysfunction relating to the eosinophilia, treatment with corticosteroids should also be given (Grade 1C).

Treatment of Lymphocytic variant HES

Appropriate management is similar to that of idiopathic HES (see under relevant heading). Corticosteroids are indicated for primary management. Ciclosporin may be useful as a steroid-sparing agent and mepolizumab has shown efficacy in this setting (Ogbogu *et al*, 2009; Rothenberg *et al*, 2008).

Key recommendations

Treatment of lymphocytic variant of hypereosinophilic syndrome

- **Patients with the lymphocytic variant of HES can be managed in the same manner as idiopathic HES (grade 2B)**

Treatment of idiopathic hypereosinophilic syndrome

Corticosteroids

In general, corticosteroids are the first-line therapy for idiopathic HES, and immunomodulatory and myelosuppressive agents are reserved for steroid-unresponsive disease or are used as adjuvant steroid-sparing therapy.

Imatinib

As in cases of clonal eosinophilia without a specific molecular target, patients with idiopathic HES failing first line corticosteroids should be considered for a short trial (4–6 weeks) of imatinib 400 mg daily given the good safety profile of this agent.

Immunomodulatory agents

Interferon-alpha: Interferon-alpha targets both eosinophils and T cells making it a rational therapy for many hypereosinophilic disorders. Its mechanism of action and role in the treatment of hypereosinophilic syndromes including idiopathic HES have been extensively reviewed (Butterfield 2005).

Improvement in the eosinophil count is associated with improvement in organ dysfunction including clinical symptoms and organomegaly (hepatomegaly, splenomegaly or both) (Fruehauf *et al*, 1993; Murphy *et al*, 1990; Zielinski & Lawrence 1990), cardiopulmonary effects (Yamada *et al*, 1998), mucosal ulcers (Barouky *et al*, 2003) and cutaneous manifestations (Mohr *et al*, 1995). It may take several weeks to achieve a response.

The optimal starting dose of interferon-alpha in hypereosinophilic disorders has yet to be defined. A wide variety of effective doses have been reported between 1 and 5 million units/m²/day (Butterfield 2005). The side effects are usually dose dependent and frequently dose limiting (Ogbogu *et al*, 2009). Maintenance doses may be lower than initiation doses (Busch, *et al*, 1991; Canonica *et al*, 1995). There are limited data on the efficacy of once weekly pegylated-interferon as an alternative to conventional interferon-alpha (Butterfield & Weiler 2012).

Ciclosporin: ciclosporin is a calcineurin inhibitor, is used primarily in HES as a steroid-sparing immunosuppressive agent despite a relative paucity of published information, largely limited to case reports. Ciclosporin impairs T-cell activation hence its value in lymphocytic-variant HES. There are also reports of sustained clinical responses when ciclosporin is added to prednisolone in previously steroid-resistant idiopathic HES (Akiyama *et al*, 1997; Fukuta *et al*, 2001, Zabel & Schlaak 1991) and when used as a steroid-sparing agent in idiopathic paediatric HES (Hosoki *et al*, 2011; Nadarajah *et al*, 1997) (and also in cases of eosinophilic cellulitis and fasciitis (Kim *et al*, 2013, Tahara *et al*, 2008)).

A variety of effective ciclosporin doses have been reported, generally with gradual tapering following clinical response. The largest published experience in HES is that of 11 patients (within a 188-patient retrospective case series) who received ciclosporin at doses of 150 to 500 mg/24 hrs (median 200 mg); of the 5 patients who received ciclosporin monotherapy, 1 patient achieved a complete response with 2 partial responders although, notably, ciclosporin was discontinued early in 9 of the 11 patients, due to either lack of efficacy or poor tolerance (Ogbogu *et al*, 2009).

Azathioprine: azathioprine is a purine analogue used commonly in combination with corticosteroids as a steroid-sparing agent. There are case reports of its use in hypereosinophilic syndromes particularly in those presenting with cardiological complications including endomyocardial fibrosis (Pineton de Chambrun *et al*, 2015) and eosinophilic myositis (Aggarwal *et al*, 2001; Fozing *et al*, 2014). The recommended starting dose is 1–3 mg/kg/day and this should be adjusted, within these limits, depending on the clinical and haematological response. This may not be evident for weeks or

months. Lower starting doses should be considered in patients with renal and/or hepatic insufficiency or those receiving concomitant allopurinol.

Myelosuppressive therapy

Hydroxycarbamide: hydroxycarbamide is a non-alkylating ribonucleotide reductase inhibitor, which has been used as a myelosuppressive agent at dose of 0.5 to 3 g daily to lower the eosinophil count as a corticosteroid-sparing agent either alone (Ogbogu *et al*, 2009) or in combination with interferon alpha (Butterfield 2005).

Other myelosuppressive therapy: haematological benefit has been observed with other agents such as vincristine, cyclophosphamide, etoposide, cladribine and cytarabine but the evidence for their use is limited (Gotlib 2014).

Monoclonal antibodies

Anti-interleukin 5 monoclonal antibodies: interleukin 5 is the primary cytokine involved in eosinophil development and is frequently elevated in patients with HES (Owen *et al*, 1989). Two monoclonal anti-IL5 antibodies have shown promising efficacy: mepolizumab, a fully humanised murine antibody, and reslizumab, a humanised rat antibody.

Mepolizumab has shown efficacy in steroid-refractory (Plotz *et al*, 2003) and steroid-dependent HES (Ogbu *et al*, 2009; Rothenberg *et al*, 2008). Roufosse *et al* (Roufosse *et al*, 2010; Roufosse *et al*, 2013) reported that patients receiving the highest doses of prednisolone at the outset responded better to mepolizumab than those on lower doses. However patients with the greatest fall in eosinophil counts did not experience fewer HES-related symptoms. The drug was well tolerated. There is currently no evidence on its effectiveness in improving end-organ damage in HES. It should be noted that mepolizumab has recently been approved for use in refractory asthma in Europe and the USA but the approved dose in this setting is significantly lower than that used in published HES studies and is unlikely to be effective for patients with HES.

There are fewer data on reslizumab. Klion *et al* (Klion *et al*, 2004) found that two of four HES patients responded to monthly reslizumab infusions but relapsed following cessation of therapy. Response was not predicted by *FIP1L1-PDGFR*A status or baseline IL5 levels.

Alemtuzumab: two initial reports indicate that alemtuzumab may induce clinical and haematological remissions in patients with HES unresponsive to corticosteroids, hydroxycarbamide, interferon and imatinib (Pitini *et al*, 2004; Sefcick *et al*, 2004; Strati, *et al*, 2013). Patients relapsing after therapy may achieve durable responses following re-treatment with alemtuzumab. The principal complications were infections (including cytomegalovirus reactivation) and infusion reactions. Two case reports suggest that alemtuzumab can reverse established cardiac and cerebral dysfunction in patients with *FIP1L1-PDGFR*A-negative HES (Perini *et al*, 2009; Sye *et al*, 2012).

Key recommendations

Treatment of idiopathic hypereosinophilic syndrome

- **Patients with idiopathic HES should be treated in the first instance with corticosteroids (see emergency treatment above).**
- **Patients with idiopathic HES who do not respond adequately to corticosteroids, or who require prolonged corticosteroid therapy, or who are intolerant of corticosteroids, should be considered for a short trial (4–6 weeks) of imatinib, immunomodulatory agents (interferon alpha, ciclosporin or azathioprine), myelosuppressive therapy (hydroxycarbamide) or monoclonal antibody therapy with mepolizumab (anti-interleukin 5), the latter preferably as part of a clinical trial (Grade 2B).**
- **Alemtuzumab, an anti-CD52 monoclonal antibody, should be considered for patients with severe idiopathic HES unresponsive to other therapies, and may be useful in patients with idiopathic HES-associated cardiac and cerebral dysfunction. (Grade 2B)**

Role of haematopoietic stem cell transplantation

Allogeneic HSCT has been performed in a small number of patients with refractory or debilitating HES that was idiopathic or ill-defined and prolonged remissions have been

reported (Cooper *et al*, 2005; Ueno *et al*, 2002). A lack of clinical trials, small numbers reported and clinical heterogeneity make it impossible to offer definitive recommendations. Although both myeloablative and reduced intensity conditioning regimens have been used, there remains insufficient evidence to give recommendations on conditioning regimen or intensity (Cooper *et al*, 2005; Halaburda *et al*, 2006; Juvonen *et al*, 2002; Ueno *et al*, 2002).

Cases of eosinophilia associated with *FGFR1* rearrangement have a poor prognosis and intensive AML-type induction treatment followed by HSCT may be the best option. Because of the poor prognosis of CEL, NOS (Helbig 2012) this approach could also be justified in these cases.

HSCT should also be considered for those HES patients refractory to or intolerant of both conventional TKI therapy and experimental medical therapy, where available, or who display progressive end organ damage (Fathi *et al*, 2014).

Key recommendations

Role of haemopoietic stem cell transplantation

- **HSCT should be considered for cases with clonal eosinophilia with *FGFR1* rearrangement, patients with chronic eosinophilic leukaemia, not otherwise specified and those HES patients refractory to or intolerant of both**

conventional TKI therapy and experimental medical therapy, where available, or who display progressive end organ damage. (Grade 2C)

Declarations of conflicts of interest

None of the authors have any competing financial interest or conflict of interest associated with these guidelines.

Acknowledgements

We would like to thank Dr Mike Brown, Consultant in Infectious Diseases and Tropical Medicine (The Hospital for Tropical Diseases, London, UK) for his comments on the infectious causes of eosinophilia. Professor Elizabeth Soilleux, Consultant Histopathologist (Oxford University Hospitals NHS Trust, Oxford, UK.) kindly reviewed the classification sections and dermatological causes of eosinophilia. We are grateful to Dr Ole Weis Bjerrum of the Nordic MPN Study Group (Department of Hematology, Rigshospitalet, University Hospital of Copenhagen, Denmark) for his comprehensive review of the manuscript and helpful suggestions.

Table I. Evidence statements and grades of recommendations.

GRADE nomenclature

STRENGTH OF RECOMMENDATIONS:

Strong (grade 1): Strong recommendations (grade 1) are made when there is confidence that the benefits do or do not outweigh harm and burden. Grade 1 recommendations can be applied uniformly to most patients. Regard as 'recommend'.

Weak (grade 2): Where the magnitude of benefit or not is less certain a weaker grade 2 recommendation is made. Grade 2 recommendations require judicious application to individual patients. Regard as 'suggest'.

QUALITY OF EVIDENCE

The quality of evidence is graded as high (A), moderate (B) or low (C). To put this in context it is useful to consider the uncertainty of knowledge and whether further research could change what we know or our certainty.

(A) High Further research is very unlikely to change confidence in the estimate of effect. Current evidence derived from randomised clinical trials without important limitations.

(B) Moderate Further research may well have an important impact on confidence in the estimate of effect and may change the estimate. Current evidence derived from randomised clinical trials with important limitations (e.g. inconsistent results, imprecision wide confidence intervals or methodological flaws e.g. lack of blinding, large losses to follow up, failure to adhere to intention to treat analysis), or very strong evidence from observational studies or case series (e.g. large or very large and consistent estimates of the magnitude of a treatment effect or demonstration of a dose-response gradient).

(C) Low Further research is likely to have an important impact on confidence in the estimate of effect and is likely to change the estimate. Current evidence from observational studies, case series or just opinion.

Table II Causes of eosinophilia

A. Secondary (reactive) eosinophilia

- *Allergic disorders*
 - Asthma
 - Atopic dermatitis/eczema
 - Seasonal allergic disorders (rhinitis syndromes/hayfever)
- *Dermatological disorders (non-allergic)*
 - Wells syndrome
- *Drugs*
 - Including antibiotics, anticonvulsants
- *Infectious diseases*
 - Parasitic infections*
 - Fungal infections*
- *Gastrointestinal disorders*
 - Primary gastrointestinal eosinophilic disorders including eosinophilic oesophagitis
 - Chronic pancreatitis
 - Inflammatory bowel disease
 - Coeliac disease
- *Vasculitides*
 - Polyarteritis nodosa
 - Eosinophilic granulomatosis with polyangiitis (Churg-Strauss syndrome)
- *Rheumatological disease*
 - Systemic lupus erythematosus
 - Eosinophilic fasciitis (Shulman disease)
 - Rheumatoid arthritis

- *Respiratory disease*
 - Acute and chronic eosinophilic pneumonias (including Löffler syndrome, Allergic bronchopulmonary aspergillosis and sarcoidosis)
- *Neoplasms (non-haematological and haematological in which the eosinophils are not part of the neoplastic clone)*
 - Solid tumours
 - Lymphomas and acute lymphoblastic leukaemia (the majority of cases in which the eosinophils are non-clonal)
 - Systemic mastocytosis†
- *Lymphocytic variant hypereosinophilic syndrome*
- *Miscellaneous causes*
 - Atheroembolic disease
 - Chronic graft-versus-host disease
 - Gleich's syndrome (episodic angio-oedema with eosinophilia)
 - Disorders of immune regulation (including hyper IgE syndrome, DOCK8 deficiency, PGM3 deficiency)

B Primary (clonal) eosinophilia

- *Haematological neoplasms with clonal eosinophilia (i.e. neoplasms where the eosinophils form part of the neoplastic clone)*
 - Myeloid and lymphoid neoplasms with rearrangement of *PDGFRA*, *PDGFRB* or *FGFR1* or with *PCM1-JAK2*, *ETV6-JAK2* or *BCR-JAK2*
 - Chronic eosinophilic leukaemia, not otherwise specified (CEL, NOS) including cases with *ETV6-ABL1*, *ETV6-FLT3* or other tyrosine kinase fusion genes
 - Atypical chronic myeloid leukaemia with eosinophilia (aCML-Eo)
 - Chronic myelomonocytic leukaemia with eosinophilia (CMML-Eo)
 - Chronic myelogenous leukaemia in accelerated phase or transformation (occasional cases)
 - Other myeloproliferative neoplasm in transformation (occasional cases)
 - Acute myeloid leukaemia with eosinophilia, particularly with *t(8;21)(q22;q22.1)* or *inv(16)(p13.1q22)* (occasional cases only) (AML-Eo)
 - Acute lymphoblastic leukaemia, only if eosinophils demonstrated to be part of the neoplastic clone
 - Systemic mastocytosis†

C Idiopathic eosinophilia

- *No detectable primary or secondary causes for eosinophilia*

Footnote

This table outlines the important and commonest causes of eosinophilia – it should not be considered to be an exhaustive list of possible causes.

* In the presence of opportunistic or unusual infections, concomitant HIV infection should be considered.

† Systemic mastocytosis – the eosinophilia may be clonal, cytokine driven or a combination of both

Table III. Infectious diseases associated with eosinophilia*

Cause	Suggestive clinical features	Key investigations
Strongyloidiasis <i>(Strongyloides stercoralis)</i>	Travel to the tropics: South, Southeastern and Central America, rural areas of Europe, sub-Saharan Africa, South Asia, Southeast Asia. Skin: localized, pruritic, erythematous papular rash at site of skin penetration; or rapidly migrating pruritic rash (cutaneous larva migrans); or generalised rash GI: abdominal pain, weight loss, diarrhoea, vomiting Lung: cough, wheeze, dyspnoea, haemoptysis Usually asymptomatic. A raised absolute eosinophil count may be the only feature (but immunosuppression can make the eosinophil count falsely normal)	Serology (ELISA): generally sensitive and specific, but false negatives possible in immunocompromised patients. Fresh stool microscopy: relatively insensitive as parasitic larvae are only present intermittently. In rare cases, microscopy of sputum or bronchoalveolar lavage fluid may be useful. Check serology in all travellers with suggestive clinical features arriving from an endemic region. Check serology before starting corticosteroids or immunosuppression in all patients with a history of living in an endemic region. If positive, treat strongyloidiasis before starting steroids to minimise risk of hyperinfection syndrome.
Hookworm <i>(Ancylostoma duodenale and Necator americanus)</i>	Travel to endemic area (mostly rural tropical and subtropical areas of Asia, sub-Saharan Africa, and Latin America) Often asymptomatic. Symptoms usually only present in heavily infected migrants; Löffler's pneumonia can occur in travellers GI: diarrhoea, vomiting, abdominal pain, iron-deficiency,	Fresh stool microscopy for eggs (may need repeating if negative)

	malnutrition	
Filariasis <i>(Loa loa, Wuchereria bancrofti, Mansonella perstans, Brugia malayi, onchocerca spp.)</i>	Travel to endemic area (tropics) Severe pruritus and /or corneal precipitates (onchocerca spp.) Transient subcutaneous swellings (<i>Loa loa</i>) Lymphoedema (<i>W. bancrofti</i> or <i>B. malayi</i>) Eosinophilia may be only feature.	Filaria serology (ELISA) Day/night blood smears for microfilariae – timing depends on species Skin snips and slit lamp examination (<i>Onchocerca volvulus</i>)
Ascariasis <i>(Ascaris lumbricoides)</i>	Travel to endemic area (tropics), more common in children GI: ascending cholangitis, obstructive jaundice, bile duct perforation, bowel obstruction (all rare) Lung: cough, wheeze, dyspnoea, haemoptysis	Fresh stool microscopy for eggs and larvae Ultrasonography may demonstrate hepatobiliary or pancreatic ascariasis
Toxocariasis <i>(Toxocara canis or, less commonly, Toxocara cati)</i>	Contact with domestic dogs or cats Usually asymptomatic; may cause fever and anorexia Rarely causes visceral larva migrans (hepatitis and pneumonitis), or ocular, neurological and cardiac symptoms	Serology (ELISA)
Trichinosis <i>(trichinella spp.)</i>	Ingestion of undercooked pork (or rarely other meats) several days before onset of symptoms May be asymptomatic, or cause fever, headache, vomiting and	Serology (ELISA, latex agglutination) – may be false negative in first 3-4 weeks of infection Occasionally Western blot on blood

	diarrhoea. Musculoskeletal (due to invasion of muscle by parasite): myositis, weakness, muscle swelling including peri-orbital oedema. May affect heart and respiratory muscles or, rarely, lungs and CNS.	or muscle biopsy may be needed.
Schistosomiasis (<i>Schistosoma</i> spp.)	Travel to endemic area (typically sub-Saharan Africa, but rarely South America and east Asia), with history of freshwater swimming Acute symptoms: localised dermatitis ('swimmer's itch'), fever, myalgia, headache, dry cough, diarrhoea, and abdominal pain <i>S. mansoni</i>: hepatosplenomegaly and portal hypertension <i>S. haematobium</i>: genitourinary – haematuria, squamous cell carcinoma, obstructive uropathy Rarely neurological symptoms due to ectopic eggs in brain or spinal cord Eosinophilia may be only manifestation.	Urine and fresh stool microscopy (low sensitivity in low-level disease or in early infection) Serology Abdominal imaging (ultrasound or CT)
Invasive aspergillosis and allergic bronchopulmonary aspergillosis (<i>aspergillus</i> spp.)	Background of asthma or cystic fibrosis Lung: cough, wheeze, fever, dyspnoea, expectoration of brown mucus plugs, haemoptysis, lobar consolidation Wide range of other symptoms in invasive aspergillosis, especially	CT of lungs: bronchiectasis or lung infiltrates in ABPA; classically cavitating nodules surrounded by ground-glass infiltrates or lobar consolidation in invasive aspergillosis ABPA: skin prick test reactivity to <i>aspergillus</i> antigens and serum

	in immunocompromised patients	antibodies to aspergillus spp, serum total IgE Invasive aspergillosis: fungal culture of respiratory samples; tissue biopsy stained with Grocott's methenamine silver
Coccidioidomycosis (<i>coccidioides</i> spp.)	May be asymptomatic. Travel to desert areas, especially in northern and central America Symptoms of pneumonia, followed by prolonged arthralgia, fever, erythema nodosum	Serology. Culture of respiratory specimens, or lung biopsy, +/- PCR.
Fascioliasis (<i>Fasciola hepatica</i>)	Usually follows ingestion of watercress grown in sheep-raising areas, but may also be transmitted via water lettuce, mint and khat (common in some Somali communities). GI: right upper quadrant pain, vomiting, jaundice (may be mild initially, with extreme eosinophilia)	Serology Abdominal ultrasound or CT may show liver tracks or abscesses
Scabies (<i>Sarcoptes scabiei</i>)	Widespread, intensely pruritic rash, often worse at night Erythematous papules Other family members may be affected	Skin scrapings or dermoscopic examination

Footnote

This table outlines the important and commonest infectious diseases associated with eosinophilia – it should not be considered to be an exhaustive list of all possible causes.

* Consider the need to test for human immunodeficiency virus (HIV) or human lymphotropic virus 1 (HTLV-1) in patients with probable opportunistic infections

Abbreviations: ABPA, allergic bronchopulmonary aspergillosis; CNS, central nervous system; CT, computed tomography; ELISA, enzyme-linked immunosorbent assay; GI, gastrointestinal; PCR, polymerase chain reaction

Table IV. Primary gastrointestinal disorders associated with gastrointestinal tissue eosinophilia with or without peripheral blood eosinophilia

Disorder	General Comments
Primary gastrointestinal eosinophilic disorders 1) Primary eosinophilic oesophagitis 2) Primary eosinophilic gastritis 3) Primary eosinophilic colitis	A myriad of clinical symptoms may be present depending on which segment of the gastrointestinal tract is involved. These may include fatigue, dysphagia, weight loss, vomiting, gastric dysmotility or diarrhoea. The peripheral blood eosinophil count is not always abnormal. Diagnosis involves comprehensive history and examination, evaluation of secondary causes of gastrointestinal eosinophilia and biopsy findings (Prussin 2014; Zuo & Rothenburg 2007).
Chronic Pancreatitis	Can be associated with peripheral blood eosinophilia. Incidence is higher in autoimmune pancreatitis than in non-autoimmune causes (Wang <i>et al</i> , 2009).
Inflammatory Bowel Disease	Both ulcerative colitis and Crohn disease can be associated with peripheral blood eosinophilia. Ulcerative colitis with eosinophilia may be associated with a more severe clinical phenotype, including associated primary sclerosing cholangitis (Barrie <i>et al</i> , 2013; Suttor <i>et al</i> , 2009).
Coeliac Disease	Can be associated with eosinophilic oesophagitis (Thompson <i>et al</i> , 2012).

Footnote:

This table outlines the important and commonest primary gastrointestinal disorders associated with eosinophilia – it should not be considered to be an exhaustive list of all possible causes.

Table V. Suggested investigations to evaluate the cause of eosinophilia

In all cases of eosinophilia:

- Full blood count and blood film
- Routine biochemical tests including renal and liver function tests, bone profile, lactate dehydrogenase
- Erythrocyte sedimentation rate and/or C-reactive protein
- Vitamin B12 assay

In patients who are otherwise well with mild to moderate eosinophilia between 0.5 and $1.5 \times 10^9/l$, further testing may not be indicated.

Patients with systemic symptoms or those with persistent eosinophilia (at least $1.5 \times 10^9/l$), with or without suspected organ damage, should be investigated for possible secondary causes with the following:

In those with a suspected allergic aetiology:

- Serum total immunoglobulin E (IgE)
- Allergen-specific IgE tests
- Skin-prick testing for specific allergies.

In those with a suspected non-allergic dermatological cause:

- Skin biopsy

In those with a suspected infectious cause:

- Fresh stool microscopy for ova, cysts and parasites
- Serological tests for suspected parasitic infections e.g. strongyloidiasis, schistosomiasis, filariasis, toxocariasis where appropriate. (see table III)
- Consider the need to test for human immunodeficiency virus (HIV) or human lymphotropic virus 1 (HTLV-1) in patients with probable opportunistic infections

In those with a suspected gastrointestinal cause:

- Upper gastrointestinal endoscopy, small bowel endoscopy and/or colonoscopy/sigmoidoscopy
- Serum amylase
- Serology for coeliac disease-related autoantibodies (anti-tissue transglutaminase)

In those with a suspected connective tissue disorder

- Antinuclear activity (ANA) or anti-double stranded DNA (dsDNA) antibodies
- Antibodies to cyclic citrullinated peptide (CCP)

In those with a suspected vasculitis:

- Antineutrophil cytoplasmic antibodies (ANCA)
- Serology for hepatitis B virus (HBV), hepatitis C virus (HCV), human immunodeficiency virus (HIV), cytomegalovirus (CMV) and parvovirus B19

In those with suspected respiratory disease:

- Appropriate imaging
- Bronchoscopy with bronchoalveolar lavage/endobronchial ultrasonography

In those with a suspected lymphoma, non-haematological malignancy or T-cell driven eosinophilia:

- Appropriate imaging and tissue biopsy
- Peripheral blood T-cell immunophenotyping and T-cell receptor gene rearrangement studies

Miscellaneous:

- Tests for atheroembolic disease.
- Immunoglobulins and C1 esterase levels*

* If the differential diagnosis includes Gleich's syndrome

Table VI. Cytogenetic and molecular abnormalities associated with primary eosinophilias

Cytogenetic abnormality	Molecular abnormality	Clinical significance
Usually none but rarely a translocation with a 4q12 breakpoint or a cytogenetic abnormality unrelated to the causative molecular lesion	<i>FIP1L1-PDGFR</i> A or other rearrangement of <i>PDGFR</i> A	Imatinib sensitive
t(5;12)(q31-q33;p12) or other translocation with a 5q31-q33 breakpoint	<i>ETV6-PDGFR</i> B* fusion or other rearrangement of <i>PDGFR</i> B	Imatinib sensitive
t(8;13)(p11;q12) or other translocation with an 8p11-12 breakpoint	<i>ZMYM2-FGFR</i> 1 (previously known as <i>ZNF198-FGFR</i> 1) or other rearrangement of <i>FGFR</i> 1	Poor prognosis, investigational drugs or haematopoietic cell transplantation to be considered
t(8;9)(p22;p24) or other translocation with an 9p24 breakpoint	<i>PCM1-JAK</i> 2 or other rearrangement of <i>JAK</i> 2	Ruxolitinib sensitive
t(12;13)(p13;q12)	<i>ETV6-FLT</i> 3	Sunitinib and sorafenib sensitive
t(9;12)(q34;p13)	<i>ETV6-ABL</i> 1	Imatinib sensitive

* some cases with a t(5;12)(q31-q33;p12) have an out of frame fusion between *ETV6* and *ACSL6* (formerly known as *ACS2*) that is not responsive to imatinib (Cools *et al*, 2002).

Table VII. Assessment of End-Organ Damage

Cardiac assessment: chest radiography, electrocardiogram, echocardiogram, serum troponin T

Pulmonary assessment: pulmonary function tests including spirometry, O₂ saturation and transfer factor of the lung for carbon monoxide (TLCO)

Footnote:

If there is a strong suspicion of cardiac dysfunction in the absence of obvious echocardiographic abnormalities, a specialist cardiology review should be sought.

Figure 1. Testing algorithm for possible haematological neoplasms with clonal eosinophilia

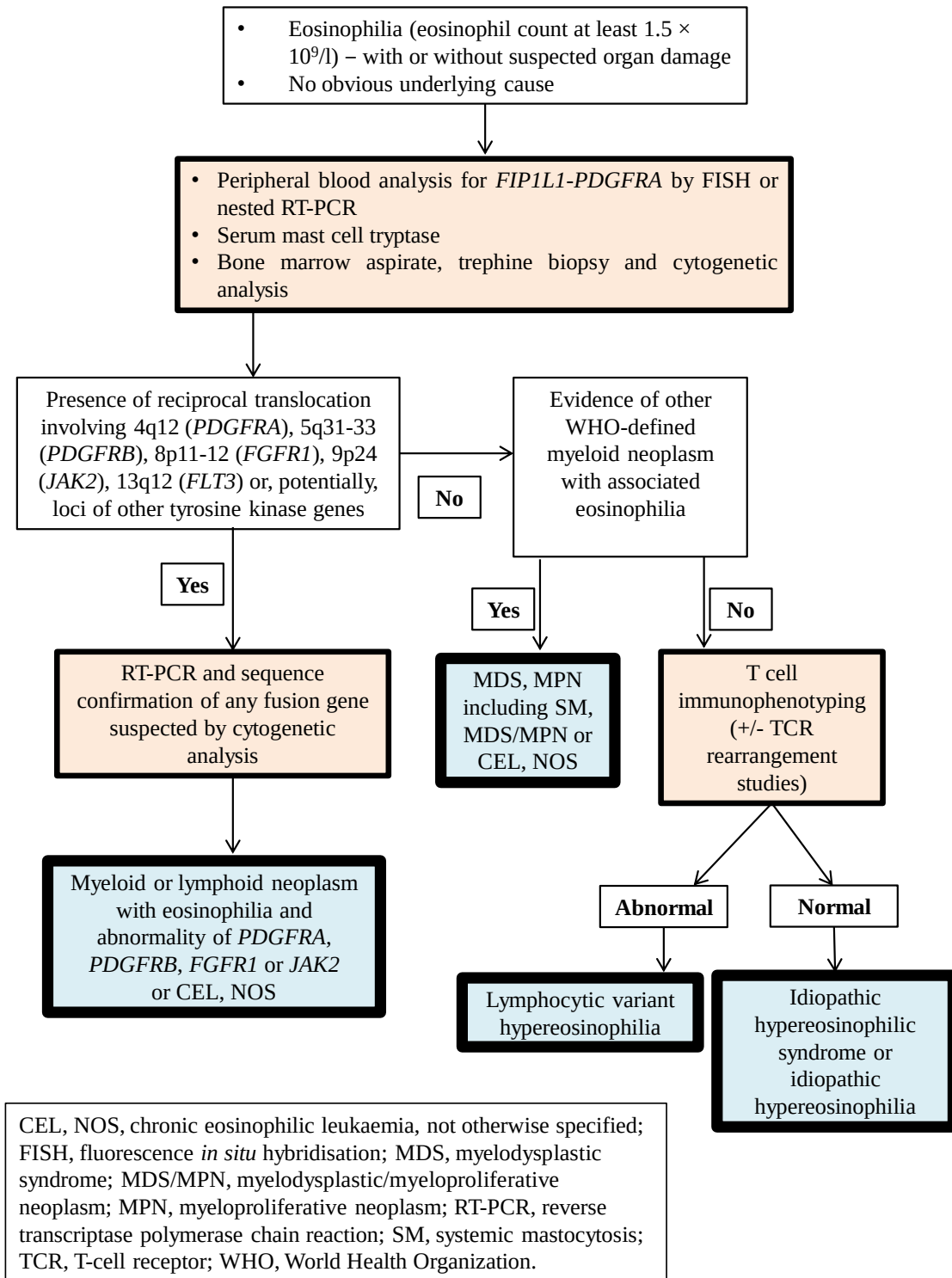
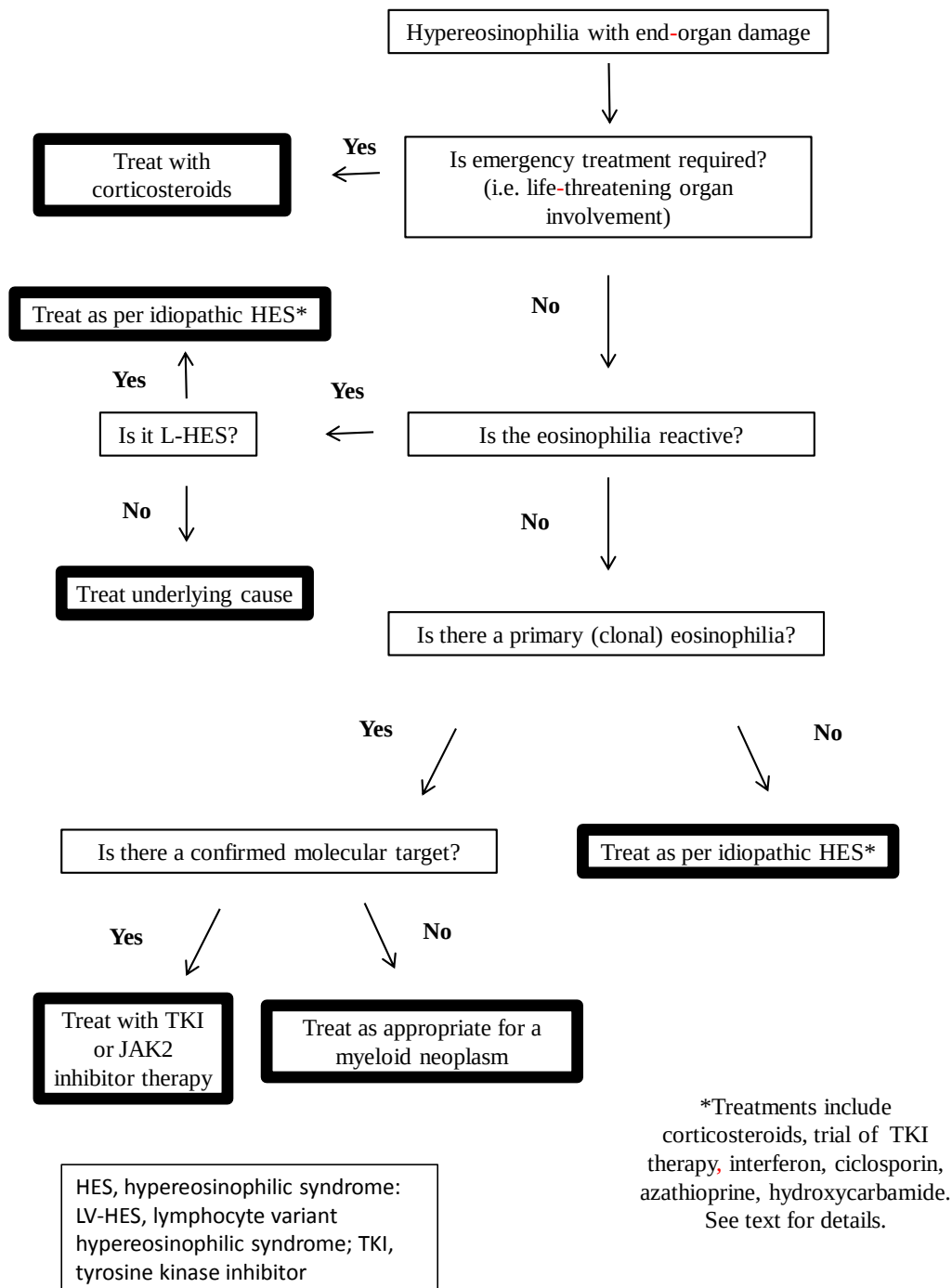


Figure 2. Algorithm for the treatment of eosinophilia



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