

Unmet needs and evidence gaps in hypereosinophilic syndrome and eosinophilic granulomatosis with polyangiitis



Michael E. Wechsler, MD,^a Bernhard Hellmich, MD,^b Maria C. Cid, MD,^c David Jayne, FMedSci,^d Xinping Tian, MD,^e Lee Baylis, MD,^f and Florence Roufosse, MD, PhD^g
 Denver, Colo; Kirchheim-Teck, Germany; Barcelona, Spain; Cambridge, United Kingdom; Beijing, China; Durham, NC; and Brussels, Belgium

Hypereosinophilic syndrome (HES) and eosinophilic granulomatosis with polyangiitis (EGPA) are rare systemic inflammatory disorders with overlapping symptoms, elevated eosinophil counts, and heterogenous clinical presentations. Although progress has been made in recent years, there are substantial gaps in our understanding of the pathologic mechanisms involved in these diseases, as well as numerous unmet needs relating to both diagnosis and patient management. For example, in most cases of HES, the underlying cause of hypereosinophilia is unknown, while in EGPA, although a polygenic genetic susceptibility has been found,

understanding of the pathogenic mechanisms remains largely elusive. Delineating differences between certain disease variants may be challenging, and there are no reliable predictive markers of disease course. In addition, the current diagnostic criteria for HES and classification criteria for EGPA are not easy to implement in a nonspecialist setting, and specialist referral pathways need to be signposted more clearly. Furthermore, disease-specific activity scores need to be developed to aid the assessment of treatment effects, and improved biomarkers are needed to aid with treatment stratification. In this review, we outline the limitations of our current understanding of HES and EGPA and highlight areas for future work, which ultimately should help improve patient management and outcomes. (*J Allergy Clin Immunol* 2023;151:1415-28.)

Key words: Hypereosinophilic syndrome (HES), eosinophilic granulomatosis with polyangiitis (EGPA), eosinophilic diseases, vasculitis, unmet needs, anti-IL-5, biologic

From ^athe Department of Medicine, National Jewish Health, Denver; ^bthe Department of Medicine, Medius Kliniken, Academic Teaching Hospital, University of Tübingen, Kirchheim-Teck; ^cthe Hospital Clínic de Barcelona, University of Barcelona, Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), Barcelona; ^dthe Department of Medicine, University of Cambridge, Cambridge; ^ePeking Union Medical College Hospital, Beijing; ^fGlobal Medical Affairs, GSK, Durham; and ^gthe Department of Internal Medicine, Hôpital Erasme, Université Libre de Bruxelles, Brussels.

Disclosure of potential conflict of interest: M. E. Wechsler reports research grants from the National Institute of Allergy and Infectious Diseases and the National Heart, Lung, and Blood Institute; and has acted as a consultant for GSK, Genentech, Sanofi, France Regeneron, AstraZeneca, Teva, Novartis, Boehringer Ingelheim, Sentien, and Equilibrium. B. Hellmich reports consulting fees from GSK, InflaRx, Novartis, and Vifor; honoraria for lectures from Amgen, AstraZeneca, BMS, Boehringer Ingelheim, Chugai, GSK, Janssen, MSD, Pfizer, Phadia, Roche, and Vifor; and has participated on monitoring boards or advisory boards for InflaRx. M. C. Cid has acted as consultant for GSK, AbbVie, Janssen, and Vifor; has received a research grant from Kiniksa Pharmaceuticals; has received educational fees from GSK, Vifor, and Roche; and has received meeting attendance support from Roche and Kiniksa Pharmaceuticals. D. Jayne is supported by the NIHR Cambridge Biomedical Research Centre and has received research grants from GSK, AstraZeneca, Aurinia, BMS, Boehringer Ingelheim, ChemoCentryx, Janssen, Novartis, Roche/Genentech, Takeda, and Vifor; has acted as a consultant for GSK, AstraZeneca, Aurinia, BMS, Boehringer Ingelheim, ChemoCentryx, Janssen, Novartis, Roche/Genentech, Takeda, and Vifor; has received speaker fees from Amgen, Vifor, and GSK; has participated on monitoring or advisory boards for GSK and Chinook; owns stock in Aurinia; and is president of the European Vasculitis Society. L. Baylis is an employee of GSK and owns stocks/share options in GSK. F. Roufosse reports consultancy fees from AstraZeneca, GSK, and Merck; speaking fees from AstraZeneca, GSK, and Menarini; and royalties from UpToDate. The other author declares no relevant conflicts of interest.

Received for publication November 18, 2022; revised February 17, 2023; accepted for publication March 16, 2023.

Available online April 21, 2023.

Corresponding author: Michael E. Wechsler, MD, Department of Medicine, National Jewish Health, 1400 Jackson St, Denver, CO 80206. E-mail: wechslerm@NJHealth.org.

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0091-6749

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<https://doi.org/10.1016/j.jaci.2023.03.011>

Hypereosinophilic syndrome (HES) and eosinophilic granulomatosis with polyangiitis (EGPA) are rare systemic diseases characterized by persistent elevation of blood eosinophil counts and variable patterns of eosinophilic tissue infiltration, resulting in end-organ damage and/or dysfunction.^{1,2} Both diseases have heterogenous clinical presentations; although there can be overlaps in clinical features, there are also key distinctions (Table I; Fig 1).^{1,2}

Eosinophilic infiltrates are characteristic of both HES and EGPA, and in both diseases, patients experience end-organ damage as a result of eosinophil infiltration, eosinophil-induced fibrosis, and eosinophil promotion of hypercoagulability, with some symptom patterns resembling allergic manifestations.³ In HES, the most common clinical manifestations are constitutional symptoms and manifestations affecting pulmonary, dermatologic, and gastrointestinal systems (Fig 1).^{1,4,5} Several subtypes or variants of HES have been identified on the bases of differences in disease pathophysiology.¹ EGPA is typically characterized by the combination of late-onset asthma often associated with nasal polyps and eosinophil-rich inflammation (including necrotizing granulomas), along with necrotizing vasculitis of small vessels and blood eosinophil counts of ≥ 1000 cells/ μ L.^{2,6} Common clinical manifestations in EGPA, in addition to those associated with blood or tissue eosinophilia, therefore include symptoms of underlying vasculitis, similar to other antineutrophil cytoplasmic antibody (ANCA)-associated vasculitides (AAV) (Fig 1).^{2,7} In some cases, there can be overlap in the presentation of EGPA and HES.^{7,8}

Abbreviations used

AAV:	ANCA-associated small vessel vasculitides
ACR:	American College of Rheumatology
ANCA:	Antineutrophil cytoplasmic antibody
BVAS:	Birmingham Vasculitis Activity Score
CCL:	Chemokine CC-motif ligand
CD:	Cluster of differentiation
EGPA:	Eosinophilic granulomatosis with polyangiitis
EULAR:	European Alliance of Associations for Rheumatology
FFS:	Five Factor Score
<i>FIP1L1-PDGFRα</i> :	Fip1-like 1–platelet-derived growth factor receptor α
I-HES:	Idiopathic HES
L-HES:	Lymphocytic (or lymphoid)-variant HES
mAb:	Monoclonal antibody
M-HES:	Myeloid-variant HES
MPO:	Myeloperoxidase
PR3:	Proteinase 3
SCS:	Systemic corticosteroids

Systemic corticosteroids (SCS) are the mainstay of current standard-of-care treatment for HES and EGPA, resulting in a high cumulative corticosteroid exposure that represents an additional source of morbidity.^{9–11} In both HES and EGPA, disease course can vary. Some patients with HES experience recurrent flares, while others have persistent disease that requires constant treatment.¹² For patients with EGPA, the eosinophilic, asthmatic, and vasculitic components of disease may follow different patterns. On the one hand, the course of vasculitis is usually halted by immunosuppressive treatment, although former ischemic damage may be irreversible, and some patients experience vasculitic relapse, leading to further accumulation of damage.^{13,14} On the other hand, most patients with EGPA experience exacerbations of upper and lower airway symptoms and/or recurrent hypereosinophilia during SCS tapering, despite successful induction of remission.^{7,13}

HES and EGPA are both eosinophilic diseases with serious and systemic manifestations. They also share a series of unmet needs. Because both are rare diseases with complex, overlapping pathology as well as heterogeneous systemic disease presentation and manifestations, patients face challenges to receiving timely diagnosis and effective treatment. The recent emergence of biologic eosinophil-targeting therapies for both HES and EGPA is a critical first step toward meeting the long-standing need for well-tolerated and effective treatments; however, many gaps in the understanding of the underlying diseases and optimal disease management and treatment approach remain to be addressed.

This review summarizes the gaps in understanding of pathologic mechanisms in HES and EGPA and highlights selected unmet needs in diagnosis, disease activity assessment, and treatment for both diseases.

HES AND EGPA PATHOGENESIS

Evidence gaps in HES pathogenesis

HES can be classified as idiopathic (I)-HES, myeloid (M)-HES, lymphocytic (L)-HES, or familial, according to the underlying pathogenesis (Fig 2).^{1,15} The precise prevalence of each variant is unknown, but the majority of cases are idiopathic

and have largely unknown etiologic mechanisms. While understandings of M-HES, L-HES, and familial HES are better delineated,¹⁵ many questions remain unanswered.

M-HES accounts for approximately 10% to 20% of HES cases and is characterized by the clonal expansion of eosinophils in a primary myeloid neoplasm.^{15,16} In >80% of cases, M-HES is associated with an interstitial deletion in chromosome 4, resulting in the Fip1-like 1–platelet-derived growth factor receptor α (*FIP1L1-PDGFR α*) fusion gene; this causes autonomous proliferation of hematopoietic stem cells, leading to increased eosinophil counts.¹⁵ In other M-HES cases, cytogenetic perturbations involving tyrosine kinases have been identified as the likely cause; these include other gene fusions of *PDGFR α* , as well as *PDGFRB*, *FGFR1*, and *JAK2*, or point mutations in *JAK2*.^{15,17,18} What other as-yet-unidentified somatic mutations or epigenetic imbalances drive M-HES? Could these alterations be the cause of HES in patients who have features typically encountered in myeloid disease (eg, dysplastic eosinophils, anemia or thrombocytopenia, elevated serum B₁₂, elevated serum tryptase, and/or select abnormalities discovered via bone marrow biopsy¹⁹) without a detectable mutation?

In L-HES cases, elevated eosinophil counts are caused by the overproduction of eosinophilopoietic cytokine or cytokines by immunophenotypically aberrant T-cell populations.²⁰ In the most common L-HES subvariant, clonal IL-5–producing T-cell populations have a cluster of differentiation (CD) 3⁺CD4⁺ immunophenotype.^{21,22} However, the primary pathogenic event in L-HES is unclear; additionally, other forms of L-HES have not yet been well characterized. A proportion of patients with L-HES go on to develop T-cell lymphoma,²³ but there are currently no predictive biomarkers to identify which patients have disease that will follow this course.

Familial HES is an extremely rare multigeneration autosomal-dominant condition, with only a single well-described family in the literature so far.¹⁵ This has been mapped to the type 2 cytokine cluster on chromosome 5q, but the precise mutation remains unknown.¹⁵

In I-HES cases, the underlying causes of the imbalance in eosinophil production, apoptosis, and/or activation are, by definition, unknown. IL-5 promotes the maturation and differentiation of eosinophils in bone marrow and potentiates their survival and activation in blood and tissue.²⁴ This has long been proposed as a primary driver of eosinophilia in I-HES.^{25,26}

Eosinophil dysregulation plays a central role in HES and other eosinophil-associated diseases, but gaps remain in the understanding of eosinophil pathology.²⁷ Eosinophilic inflammation is a key aspect of HES pathology (Fig 2),^{1,24,28} eosinophilic tissue infiltration, eosinophil-associated tissue fibrosis, and thrombosis can all contribute to organ damage.³ Additional cell types, including tissue lymphocytes and mast cells, may be increased in certain HES presentations, but their specific role in disease is not understood.^{15,19,21} Although HES can affect almost any organ system, some manifestations are more prevalent in certain HES variants.^{1,5} It remains unknown whether the mechanisms of organ damage vary by organ system,³ and what factors influence the development of distinct manifestations.²⁹ Along these lines, one study found that patients with HES with molecular aberrations of clonal hematopoiesis of indeterminate potential-associated genes or spliceosome genes were more likely to experience thrombotic events—one of many potential HES complications, although further

TABLE I. Key clinical features in HES and EGPA

Feature	HES	EGPA
Onset	Commonly adult onset	Commonly adult onset, but may occur in children; commonly gradual progression of disease though prodromal, eosinophilic, and vasculitic stages
Asthma/atopy history	Occasional	Most
ANCA	No association	Common (~30% to 40%)
Eosinophilia	All	All
Blood	All	All
BALF	Common with pulmonary involvement	Most of the time
Tissue	All	All
Vasculitis	No clear association; indicates EGPA (not to be confused with perivascular eosinophils in HES [common])*	Most of the time (may not be overt)
Extravascular granulomas (eosinophilic)	No association	May be observed
Multiorgan involvement	Common	Most of the time
Therapeutic requirements/response		
Responds to corticosteroids	Most of the time	Most of the time
Requires therapies other than corticosteroids	Very common	Common

Data are from the following references.^{1,2,4,7,12,105} Frequency of select key clinical features in HES and EGPA is described with increasing frequency as follows: no association; occasional; may be observed; common; very common; most of the time; all. BALF, Bronchioalveolar lavage fluid.

*This can be challenging to differentiate in practice, requiring examination of many sections by experienced pathologists. Vasculitis is segmental and may not be visible in a given section where perivascular infiltrates may be seen.

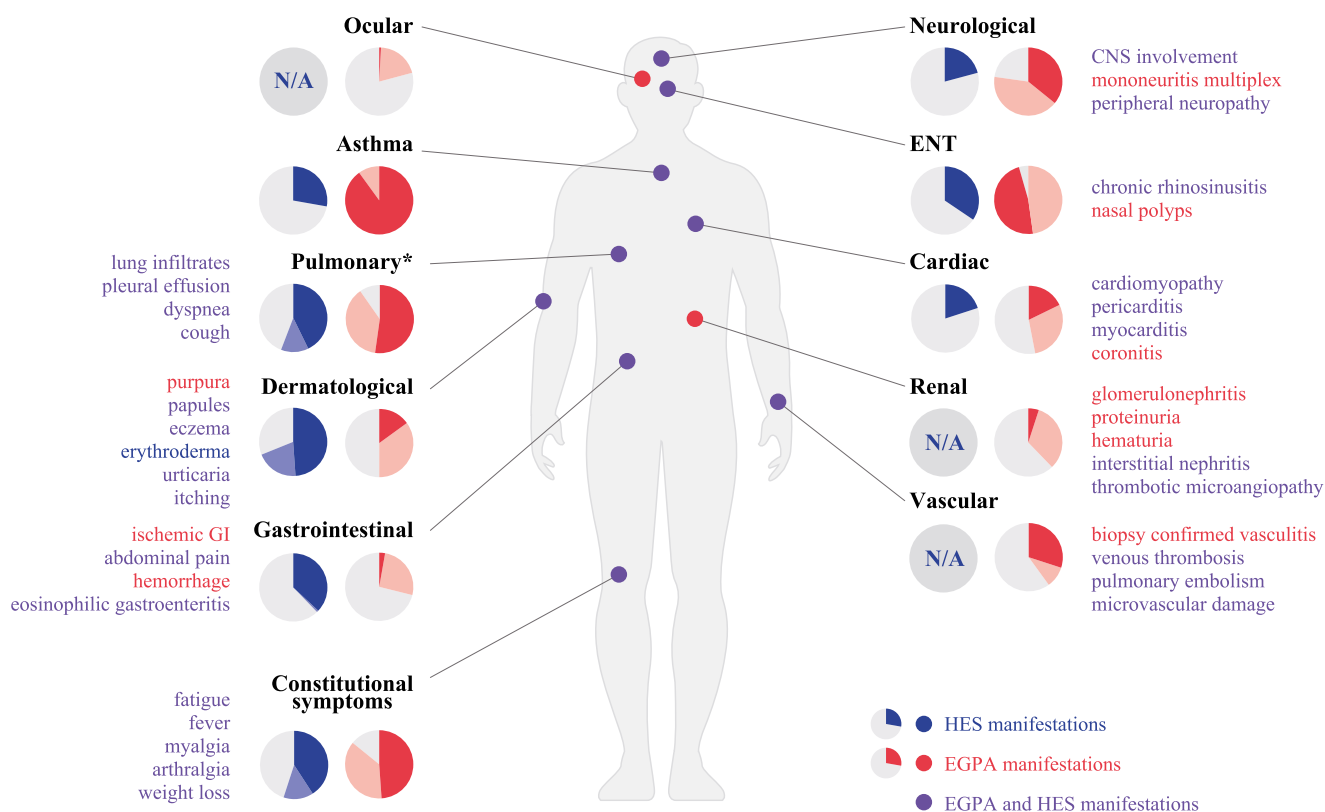


FIG 1. Clinical manifestations of HES and EGPA. Purple text indicates symptoms that may occur in HES or EGPA. Red text indicates symptoms associated with vasculitis in EGPA. Pie charts indicate range of reported percentages of patients displaying manifestations in each organ in HES (blue pie charts) or EGPA (red pie charts) from reviewed series;^{4,7,14,63,71,93,101-104} darker shades of red and blue indicate lowest reported percentage; dark plus light shading indicate highest reported percentage. Where overall percentage of manifestations in a given organ was unavailable, the percentage shown is that of the most prevalent symptom. Series used included data for manifestations at baseline through follow-up. *Pulmonary manifestations not including asthma. CNS, Central nervous system; ENT, ear, nose, and throat; GI, gastrointestinal; N/A, not available.

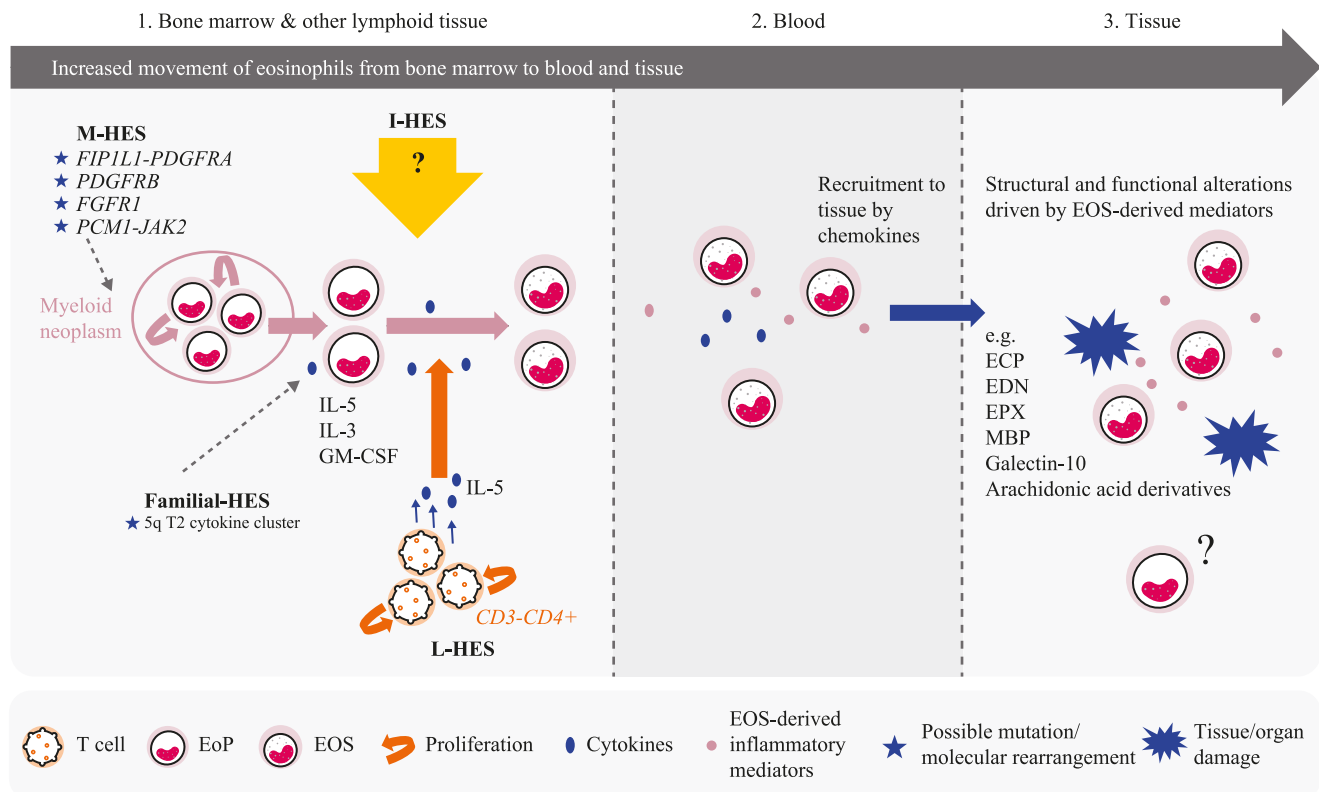


FIG 2. Mechanisms of disease pathology in HES. **(1)** HSCs mature to EoPs in bone marrow (via EoMPs) under the control of eosinophilopoietic cytokines (eg, IL-3, IL-5, GM-CSF). In HES, expansion of EoPs and increased production and maturation of EOS can result from primary myeloid neoplasm (M-HES), overproduction of eosinophilopoietic cytokines (ie, IL-5) by aberrant clonal T cells (L-HES), unknown mutation in the T2 cytokine cluster (familial HES), or unknown causes (I-HES). **(2)** In blood, cytokines promote EOS activation and chemotaxis. **(3)** EOS activation and degranulation lead to inflammation causing structural and functional alterations in tissue. The role of EoP recruitment, accumulation, and differentiation in local tissue in HES is currently unknown.^{15,18,24,27} ECP, EOS cationic protein; EDN, EOS-derived neurotoxin; EoMP, EOS/mast cell progenitor; EoP, EOS progenitor; EOS, eosinophil; EPX, EOS peroxidase; FGFR1, fibroblast growth factor receptor 1; GM-CSF, granulocyte-macrophage colony-stimulating factor; HSC, hematopoietic stem cell; MBP, major basic protein; PDGFRB, platelet-derived growth factor receptor β ; T2, type 2

corroboration of this finding is needed.³⁰ Validated biomarkers and tools are needed to predict the development of other serious complications associated with reduced survival, including cardiac involvement (Table II).³¹

Evidence gaps in EGPA pathogenesis

EGPA is a rare disease, with an estimated global prevalence of 15.27 (95% confidence interval, 11.89, 19.61) cases per million.³² Its rarity has hindered clinical investigations, and large gaps remain in our knowledge of EGPA pathogenesis. Although a subset of patients with EGPA are positive for antineutrophil cytoplasmic antibody (ANCA), it is also clear that eosinophils and IL-5 play an important role in EGPA pathogenesis (Fig 3).^{2,24} Chronic eosinophilic tissue inflammation is a central feature of both HES and EGPA pathology. In recent years, the common role of eosinophil dysregulation in the pathogenesis of both diseases has been underlined by the ability of anti-IL-5 therapy to reduce disease activity in phase 3 trials for HES and EGPA.^{33,34} IL-5 is also increased in bronchoalveolar lavage fluid of patients with active EGPA compared to patients in remission or control patients with asthma.³⁵ Furthermore, cells from

bronchoalveolar lavage fluid in patients with active disease compared to those in remission had a type 2 inflammatory profile, associated with T_H2 cell and T-regulatory cell activity, with increased expression of IL-5, IL-4, and CC motif chemokine receptor 4 (aka CCR4), among others.³⁵ The role of IL-5 in EGPA disease pathogenesis is also supported by its overproduction in cultured peripheral blood mononuclear cells from patients with EGPA compared to those from healthy controls.³⁶ Elevated expression of chemokine CC-motif ligand (CCL) 26/eotaxin-3 is also associated with active EGPA.³⁷ Direct involvement of eosinophils in EGPA pathogenesis is further supported by a genome-wide association study, which demonstrated that 7 of 8 genetic variants/polymorphisms most strongly associated with EGPA were associated with eosinophil counts in the general population.⁸ However, the role of eosinophils in the vasculitic component of disease remains unclear.

The immune response in EGPA extends beyond eosinophils, type 2, and immunoregulatory components. Studies of peripheral blood lymphocytes and cytokines in patients with EGPA suggest the involvement of T_H17 , T_H1 , and T_H0 T-cell effector subsets as well.³⁸⁻⁴⁰ Approximately 30% to 40% of patients with EGPA are ANCA positive^{8,41}—a clear indicator of B-cell and

TABLE II. Research needs to address evidence gaps in HES and EGPA pathology, diagnosis, and treatment

Research priorities	Potential impact of research in relation to evidence gaps or unmet needs
Creation of harmonized patient registries ● Development of multicenter prospective patient registries for both HES and EGPA ○ Different registries may be needed in the United States, Europe, Asia, etc, to avoid technical hurdles related to privacy/data sharing, but content of registries must be aligned so data can be pooled/compared ○ Several prospective vasculitis registries have recently been established in recent years, including GEVAS (Germany, Austria, and Switzerland), UKIVAS (United Kingdom), and POLVAS (Poland). National registries must be harmonized to allow pooled analyses ● Future HES registries should use methodology similar to existing EGPA registries to allow comparisons between HES and EGPA	● Delineate epidemiology, disease course, predictive factors for disease progression, and development of specific complications ● Provide resources for development of refined classification criteria for systemic eosinophilic diseases, in particular for idiopathic HES ● Gather data on real-world efficacy of current biologics (and other future targeted therapies), including: ○ Response to treatment across disease variants and at different disease stages ○ Impact of early initiation of treatment with biologics ○ Safety/efficacy of combination therapy with different biologics ○ Differences in response to treatment, relapse rates, and damage accrual between HES and EGPA ● Gather data on long-term effects of eosinophil depletion (as more patients are prescribed anti-IL-5 biologics) ● Identify similarities and differences in long-term outcomes and prognosis for patients with HES and EGPA
Fundamental research ● Elucidation of roles of eosinophils in human health (homeostatic/resident eosinophils)	● Impact of eosinophil targeting therapies on normal homeostatic function
Translational research ● Molecular and functional characterization of components of inflammation in different phases and severity stages of HES and EGPA	● Identify key cells and mediators involved in pathogenesis and disease manifestations ● Clarify disease heterogeneity to develop a more robust classification system of disease subsets and identify corresponding biomarkers ● Identify new therapeutic target candidates
Tools for detecting and quantifying disease activity ● Development of tools for detection and quantification of tissue eosinophilia, including presence of eosinophil activation: ○ Need for surrogates to routine stain when extensive degranulation occurs ○ Need for noninvasive tools ● Identification of other markers of disease activity and predictors of relapse in body fluids, tissue	● Create a standardized and accessible approach for quantification of eosinophilic inflammation in tissues for more accurate and early diagnosis ● Improve accuracy of disease activity assessment to help improve treatment stratification ● Early intervention to prevent relapse ● Adapt clinical trial end points accordingly
Clinical parameters to assess disease activity and prognosis ● Establish disease-specific definitions of disease activity states, including: ○ Remission ○ Relapse ○ Low/controlled disease activity ● Define consensus definition of disease stages that are meaningful in terms of response to treatment and long-term-outcomes: ○ Prognosis ○ Damage accrual ○ Need for long-term-immunosuppression ○ Refine scoring system for disease activity in diseases with multiple potential clinical complications	● Improve accuracy of patient outcome reporting ● Monitor treatment needs and accurately assess response to treatment ● Avoid irreversible organ damage ● Adapt clinical trial end points accordingly
Fast-track evaluation of efficacy of novel targeted treatment options ● Accelerated access to clinical trials and/or pilot studies with medications targeting key steps in pathogenesis (ie, biologics targeting type 2 inflammation: anti-Siglec-8, anti-IL-4R, anti-TSLP) ● Development of clinical trial designs for pilot studies in EGPA and HES that allow: ○ Sufficiently robust efficacy and safety signals from small patient cohorts ○ Comparison across clinical trials with different agents	● Identify new therapeutic options with potential to reduce disease burden, especially for patients with refractory disease: ○ Reduce corticosteroid dependence ○ Manage manifestations ○ Maintain remission ○ Reduce relapse rate ○ Reduce accrued damage
Treatment strategy studies ● Prospective studies comparing the impact of different protocols for induction treatment on long-term outcomes: ○ Is more intense induction treatment associated with lower rate of relapse?	● Optimize treatment approach with respect to both short-term and long-term patient outcomes

(Continued)

TABLE II. (Continued)

Research priorities	Potential impact of research in relation to evidence gaps or unmet needs
○ Should biologics be used in combination to target multiple aspects of disease pathology? ○ What is the effect of long-term administration of maintenance treatments (eg, biologics) with respect to dose reduction protocols and ability to stop maintenance treatment in patients with stable remission?	

Siglec-8, Sialic acid immunoglobulin-like lectin 8; *TSLP*, thymic stromal lymphopoietin.

autoimmune involvement.^{42,43} Antibodies are most commonly anti-myeloperoxidase (MPO)-ANCA (30% to 35% of patients), although anti-proteinase 3 (PR3) antibodies (PR3-ANCA) have also been detected (1% to 2% of patients).^{2,8,44-46} B-cell involvement is further supported by extensive IgG₄ plasma cell infiltrates in lung biopsy samples of patients with EGPA.⁴⁷ How B cells, T cells, and eosinophils interact in the pathogenesis of EGPA and the relative contributions of these different cell types to damage remain unknown. Are there distinct drivers of hypereosinophilia and vasculitic symptoms in ANCA-negative versus ANCA-positive disease?⁴⁵ Experimental evidence suggests a direct role for ANCA in the pathology of other AAVs (eg, microscopic polyangiitis and granulomatosis with polyangiitis). In the suggested model, ANCA activates neutrophils, which damage blood vessel walls via degranulation and formation of neutrophil extracellular traps.² Although EGPA-specific experimental evidence is currently lacking, it has been proposed that in MPO-ANCA-positive patients, MPO-ANCA-activated neutrophils produce IL-17 to promote T_H17 lymphocyte differentiation, which further encourages neutrophil activation.⁴² It remains to be determined whether the pathology of vasculitis differs in patients without detectable MPO-ANCA.⁴² While the frequency of clinical features in these patient populations differs, there is substantial overlap.^{8,45,48} Notably, ANCA-positive serum status can change with treatment and recent findings of sputum ANCA reactivity in patients with respiratory EGPA manifestations and ANCA-negative serum highlight how much remains unknown regarding the significance of ANCA in the different facets of EGPA pathology.⁴⁹

Genetic studies have shed further light on the pathology of EGPA; a genome-wide association study identified variants at thymic stromal lymphopoietin, BCL2L11, and CDK6 as risk factors for EGPA, independent of ANCA status, as well as class II HLA polymorphisms, typical of autoimmune disorders.⁸ Among patients positive for MPO-ANCA, the strongest association was with HLA-DQ, while ANCA-negative EGPA had a similar genetic risk profile to asthma, including an association with the IL-5/IRF1 loci, thymic stromal lymphopoietin, and *GPA33* genes.⁸ GPA33 codes for an epithelial glycoprotein that helps maintain barrier function in intestinal and bronchial tissue; it also appears to be associated with inflammatory bowel disease.⁸ These findings may help partially explain the development of specific organ manifestations in patients with EGPA, and ultimately in patients with other eosinophilic conditions, particularly organ-restricted forms that often occur in tissues with an epithelium. Further studies are needed to confirm the role of the identified genes. Besides the complex genetic susceptibility, environmental exposures such as silica and organic solvents are also associated with EGPA risk, with possible

differences in risk factors for ANCA-positive and -negative disease.⁵⁰ However, better understanding of the environmental triggers of disease development or relapses is needed.⁵¹ As seen in HES, patterns of organ involvement and disease course are variable, and predictors for these differences are not well understood.^{3,41}

CURRENT APPROACHES AND UNMET NEEDS IN HES AND EGPA DIAGNOSIS AND ASSESSMENT
Challenges and unmet needs in HES diagnosis

There are many barriers to patients receiving a timely HES diagnosis. Because all HES variants are rare diseases often not well known to clinicians, patients may see multiple specialists for different symptoms before their condition is recognized; this can lead to delays in diagnosis.⁵² Additionally, the significance of hypereosinophilia may be overlooked, as it is often regarded as a marker of allergic inflammation.⁵³ There is also a need to clarify referral pathways for primary care physicians via more widespread information on country-specific experts and the locations of referral centers.

The widely recognized diagnostic criteria for HES are a persistent blood eosinophil count of ≥ 1500 cells/ μ L and tissue eosinophilia directly responsible for target organ damage and/or dysfunction without a discernible secondary cause.²⁸ HES disease classification is an evolving area (Table III), and primary care providers and specialists need to be educated on the latest diagnostic recommendations. Multiple organ involvement is typical of HES, although single-organ disease forms such as chronic eosinophilic pneumonia often also meet HES definitions.²⁸ Patients are often initially treated by a specialist according to their most prominent organ manifestation. Constitutional symptoms and those affecting skin, lung, and gastrointestinal systems are some of the most common presentations in HES, but they are not present in all cases (Fig 1). A thorough patient history, laboratory assessments, and physical examination are needed to identify systemic involvement, and subsequently allow multiorgan HES to be distinguished from organ-specific eosinophilic disorders (Table I; Fig 1). Additionally, single organ involvement may be the first manifestation of disease that will progress to a multisystem disorder. A multidisciplinary approach is necessary to identify critical multiorgan involvement, such as asymptomatic cardiac involvement, which can be overlooked if the initial assessment is excessively specialty focused. Treatment may prevent the development of further organ-based complications.

Differential diagnosis of HES should first include investigations into common underlying causes of hypereosinophilia, such as adverse drug reactions or parasitic infections (helminthiasis),

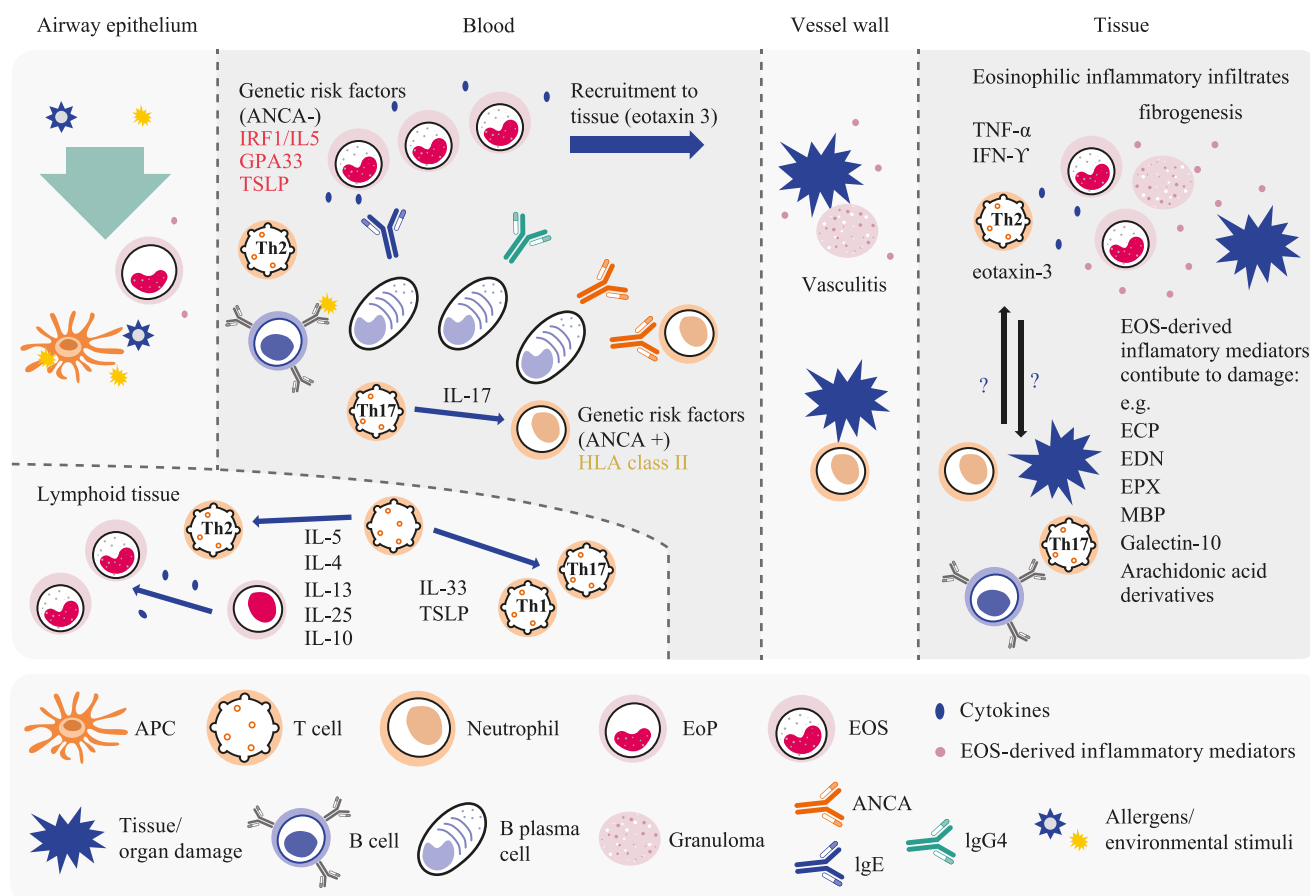


FIG 3. Mechanisms of disease pathology in EGPA. Both innate and adaptive immune response pathways contribute to EGPA pathology. T_H2 cytokines promote eosinophilic inflammation in blood, tissue, and extravascular granulomas. B cells produce ANCA, IgE, and IgG4, which are all implicated in EGPA pathology. ANCA, B cells, and T_H17 cells contribute to vasculitis by activation of neutrophils. IgE- and T-cell-derived cytokines (eg, IL-5) stimulate EOS. The interaction between, and relative contributions of, these pathways in EGPA pathology remains poorly understood (indicated by question marks).^{2,8,35-37,42,43,51} APC, Antigen-presenting cell; EoP, EOS progenitor; EOS, eosinophil; HPC, hematopoietic progenitor cell; TSLP, thymic stromal lymphopoietin.

followed by evaluation for specific HES variants,²⁰ although the current classification system for HES variants is not easy to implement in routine clinical practice. Evidence-based recommendations that guide the diagnostic assessment of HES are lacking, and not all routine laboratories are equipped to detect less common subvariants of both M-HES and L-HES. The first identified molecular cause of M-HES, the *FIP1L1-PDGfra* gene fusion,⁵⁴ can be detected by PCR or by fluorescence *in situ* hybridization using widely available probes.^{18,20} However, a variety of less common mutations and rearrangements have been reported in M-HES and may be difficult to detect in a routine clinical setting.²⁰

Diagnosis of L-HES is challenging and complicated by its clinical heterogeneity.²¹ A recent evidence-based evaluation of diagnostic tools for L-HES recommends the initial use of lymphocyte phenotyping by flow cytometry to detect aberrant clonal T cells that most commonly have a $CD3^+CD4^+$ immunophenotype.⁵⁵ Furthermore, there is a lack of consensus on the criteria that need to be fulfilled for L-HES diagnosis in the absence of $CD3^+CD4^+$ T cells.¹⁸ Finally, a diagnosis of I-HES is reached once other HES variants (M-HES and L-HES) have been assessed and excluded.¹⁸

Measures of HES activity, severity, and manifestations

The variation in patterns of disease activity (ie, episodic vs chronic/progressive) and range of possible organ manifestations in HES complicates accurate assessment of overall disease activity; there are no specialized assessment tools currently available. Blood eosinophil counts are a limited measure of HES activity. Assessing tissue eosinophil infiltration is crucial, but there are limitations to the methods commonly used in routine practice, and no validated thresholds are available for tissue eosinophilia for most organs.²⁷ A recent study investigated serum, plasma, and urine concentrations of the eosinophil granule proteins in patients with HES, EGPA, and eosinophilic asthma and identified urine eosinophil-derived neurotoxin concentration as a potential marker of disease activity.⁵⁶ Although further studies are needed to validate the results, urine neurotoxin concentration was independent of SCS dose but responsive to biologic treatment and increased before relapse in both patients with HES and EGPA.⁵⁶ Assessment of disease severity is further complicated by the involvement of a mix of critical organ manifestations, with potentially life-threatening complications, and less serious manifestations (such as itching and fatigue),

TABLE III. Definition or classification criteria for HES and EGPA

Disease	Study or publication	Criteria type	Criteria	Subclassifications
HES	Valent ²⁸	Diagnostic and classification	1. Blood eosinophil count ≥ 1500 cells/μL on 2 examinations (interval ≥ 2 weeks) 2. Organ damage and/or dysfunction attributable to tissue HE (with marked tissue eosinophil infiltrates or/and extensive deposition of eosinophil-derived proteins such as eMBP1 or EPX and typical clinical, histopathologic, and laboratory-based signs of HE-induced organ damage) 3. Exclusion of other disorders or conditions as a major reason for organ damage	● Idiopathic ● Primary (neoplastic) ● Secondary (reactive) ● Familial
HES	Shomali ¹⁸	Classification (of idiopathic HES)	1. Blood eosinophil count > 1500 cells/μL 2. Tissue damage or end-organ damage 3. Exclusion of all primary and secondary causes of hypereosinophilia as well as its lymphocyte variant	
HES	Simon ¹⁰⁶	Definition	1. Blood eosinophilia ≥ 1500 cells/μL on at least 2 occasions or evidence of prominent tissue eosinophilia associated with symptoms and marked blood eosinophilia 2. Exclusion of secondary causes of eosinophilia, such as parasitic or viral infections, allergic diseases, drug-induced or chemical-induced eosinophilia, hypoadrenalism, and neoplasms	
HES	Klion ⁵⁹	Classification	1. Eosinophils ≥ 1500 cells/μL 2. Persistent eosinophilia and/or end-organ damage/dysfunction 3. Exclusion of secondary causes of eosinophilia	● Myeloproliferative variant ● Lymphocytic variant ● Familial ● Undefined ● Overlap* ● Associated†
HES	Chusid ¹⁰⁷	Classification	1. Persistent eosinophilia ≥ 1500 cells/μL for 6 months 2. Lack of evidence of parasitic, allergic, or other known cause for eosinophilia 3. Presumptive signs and symptoms of organ involvement including hepatosplenomegaly, organic heart murmur, congestive heart failure, diffuse or focal CNS abnormalities, pulmonary fibrosis, weight loss, anemia	
EGPA	Grayson ⁵⁸	Classification (ACR/EULAR criteria)	When a diagnosis of small or medium vessel vasculitis has been made a cumulative score of ≥ 6 points across the 7 items is needed for a classification of EGPA: 1. Blood eosinophil count ≥ 1000 cells/μL (+5 points) 2. Obstructive airway disease (+3 points) 3. Nasal polyps (+3 points) 4. Positive test for cytoplasmic ANCA or anti-PR3 antibodies (−3 points) 5. Extravascular eosinophil-predominant inflammation on biopsy (+2 points) 6. Mononeuritis multiplex (+1 point) 7. Hematuria (−1 point)	

(Continued)

TABLE III. (Continued)

Disease	Study or publication	Criteria type	Criteria	Subclassifications
EGPA	Wechsler ³⁴	Clinical trial inclusion criteria (MIRRA)	1. History or presence of asthma 2. Blood eosinophil count $\geq 10\%$ or 1000 cells/μL 3. Two or more of the following: ● Histopathologic evidence of eosinophilic vasculitis, perivascular eosinophilic infiltration, or eosinophil-rich granulomatous inflammation ● Neuropathy ● Pulmonary infiltrates ● Sinonasal abnormality ● Cardiomyopathy ● Glomerulonephritis ● Alveolar hemorrhage ● Palpable purpura ● ANCA positivity	
EGPA	Jennette ⁶	Nomenclature/definitions	Eosinophil-rich and granulomatous inflammation involving the respiratory tract, and necrotizing vasculitis predominantly affecting small to medium-size vessels, and associated with asthma and eosinophilia ● ANCA is more frequent when glomerulonephritis is present	
EGPA	Lanham ¹⁰⁸	Case review inclusion criteria	1. Asthma 2. Peak peripheral blood eosinophil count >1500 cells/μL 3. Systemic vasculitis involving 2 or more extrapulmonary organs	
EGPA	Churg ¹⁰⁹	Case review and definition	● Severe asthma ● Fever ● Hypereosinophilia ● Extravascular granulomatous lesions ● Necrotizing inflammatory, and granulomatous vascular changes	

CNS, Central nervous system; *eMBPI*, eosinophil major basic protein 1; *EPX*, eosinophil peroxidase; *WHO*, World Health Organization.

*Incomplete criteria; apparent restriction to specific tissues/organs.

†Peripheral eosinophilia (1500 cells/ μL) in association with a defined diagnosis.

which can still have a severe impact on quality of life. Tools are needed for the stratification of disease severity, including assessment of cardiovascular threat and thrombophilia, both serious disease complications.¹ It can also be challenging to distinguish active disease from prior irreversible organ damage. Finally, there is currently a lack of patient-reported outcome tools validated for use in HES, limiting the assessment of health-related quality of life in this patient population.⁵⁷

Challenges and unmet needs in EGPA diagnosis

EGPA is classified among the ANCA-associated small vessel vasculitides, with microscopic polyangiitis and granulomatosis with polyangiitis.⁶ The recently revised American College of Rheumatology (ACR)/European Alliance of Associations for Rheumatology (EULAR) classification criteria for EGPA can be used to classify a patient as having EGPA when a diagnosis of small or medium vessel vasculitis has already been made.⁵⁸ However, the criteria were not developed to differentiate patients with EGPA from those with other eosinophilic diseases.⁵⁸ Like

HES, differential EGPA diagnosis includes assessment for other causes of hypereosinophilia, especially localized eosinophilic diseases involving the airways (eg, allergic bronchopulmonary aspergillosis and chronic eosinophilic pneumonia); in addition, gastrointestinal symptoms like eosinophilic gastroenteritis should not be overlooked.^{2,28,43} Distinguishing EGPA from HES can be challenging, particularly in cases without overt vasculitis manifestations and without detectable ANCA; similarities in presentation mean that exclusion of HES variants or identification of overlap HES must be carefully considered.⁵⁹ Indeed, some patients will meet the diagnostic criteria for both HES and EGPA, and in some classification criteria, EGPA is included as a special variant of HES.²⁸

The presence of vasculitis (histologic evidence or surrogate markers) is an obligatory feature of EGPA in most classification criteria and disease definitions (Table III), and it is a key distinction between HES and EGPA. Detection of vasculitis or perivascular granulomatous involvement is not always straightforward, depending on the affected organ, and is complemented by thoroughly searching for vasculitis surrogates (ie, mononeuritis

multiplex, abnormal urinary sediment, purpura). Specific disease features that are more typical of EGPA compared to HES should also be considered; asthma and nasal polyps are very common clinical features in patients with EGPA, and manifestations such as glomerulonephritis and mononeuritis multiplex are fairly common in EGPA but are not typical of HES (Table 1; Fig 1). In patients with asthma and hypereosinophilia, identification of anti-MPO (or, less frequently, anti-PR3 antibodies by antigen-specific immunoassays) further supports an EGPA diagnosis.^{2,8,45} Future research should aim to identify tools and biomarkers to help distinguish EGPA from other eosinophilic diseases like HES. A range of cytokines have been investigated as potential biomarkers of HES and EGPA (including serum IL-8, IL-5, IL-10, TARC/CCL17) but are unable to clearly distinguish between the diseases.⁶⁰ Another study demonstrated that nonelevated pretreatment C-reactive protein levels were suggestive of HES over EGPA in patients with asthma, eosinophilia, and systemic manifestations of tissue hypereosinophilia.⁶¹ Potential biomarkers implicated in eosinophil, T-cell, or B-cell biology could be of particular interest.

Patients in the prodromal phase, before EGPA can be confirmed, typically present with late-onset severe asthma and rhinosinusitis.¹³ In the typical clinical course, many years may pass between initiation of respiratory symptoms, frank blood hypereosinophilia, and overt vasculitis.¹³ On average, 9 years elapse between development of asthma symptoms and EGPA diagnosis;^{7,14} however, other patients develop eosinophilia and vasculitis simultaneously, and some patients receive an asthma diagnosis after EGPA.¹³ Treatment with SCS during the prodromal phase may halt or delay the development of vasculitis.⁶² Asthma and chronic rhinosinusitis are common airway disorders, and improved methods are needed to identify patients with disease most likely to progress to EGPA in order to adapt monitoring for early detection and treatment of progression. A better understanding of any environmental triggers that may be responsible for disease progression is also required.

Measures of EGPA severity, activity, and manifestations

The Five Factor Score (FFS) and the Birmingham Vasculitis Activity Score (BVAS) are useful tools for assessing EGPA prognosis and disease activity.⁶³ The FFS score (based on the presence or absence of 5 items) predicts mortality risk, with FFS ≥ 1 associated with increasingly poor prognosis compared to FFS = 0.⁶⁴ BVAS is validated for use in AAV but does not accurately capture all aspects of EGPA.⁶⁵ There is a need for a more specific EGPA assessment tool that captures all components of the disease, including vasculitis; ear, nose, and throat; asthma; and manifestations attributed to tissue eosinophilia. However, because not all symptoms will present at the same time during the disease course, it may also be necessary to evaluate these components separately. A specific patient-reported outcome tool for AAV has also recently been developed and was validated using a cohort including patients with EGPA.⁶⁶ This tool includes organ-specific domains that account for ear, nose, and throat and pulmonary manifestations and should be integrated into future clinical trials for EGPA.

Although FFS can assess current prognosis, tools that predict cardiac involvement, disease relapse, and progression would likely be of great value for clinical practice. Most potential

biomarkers of disease activity and relapse investigated to date, including serum levels of thymus and activation-regulated chemokine (TARC/CCL17), eotaxin-3 (CCL26), IgG₄, and absolute eosinophil count, do not accurately differentiate inactive from active EGPA.^{67,68} However, as previously discussed, recent findings suggest urine eosinophil-derived neurotoxin concentration may predict EGPA relapse.⁵⁶ Cardiac involvement (including cardiomyopathy and coronary artery disease) has long been described as a major contributor to EGPA-associated mortality, and in the absence of tools to predict cardiac involvement, sensitive and specific methods to detect involvement early are required.^{69,70} Recent work has aimed to identify the best approach to diagnosing cardiomyopathy associated with increased risk of cardiac events in patients with EGPA.⁷¹

CURRENT ADVANCES AND UNMET NEEDS IN HES AND EGPA TREATMENT

Treatment of HES and EGPA is frequently driven by disease severity and aims to alleviate symptoms and limit organ damage caused by eosinophilic tissue infiltration or necrotizing vasculitis (EGPA only).^{18,72} SCS are a mainstay of treatment in many cases.^{1,2,73} However, because long-term SCS and/or immunosuppressant/cytotoxic use is toxic,^{10,11,74} alternative steroid-sparing therapies for HES and EGPA are needed. Several novel biologic therapies have been developed that are either approved or are undergoing clinical trials for the treatment of HES or EGPA, as outlined below.^{33,34,75-79}

Current advances and unmet needs in HES treatment

Treatment approaches for HES should be guided by the type and severity of manifestations and HES variant (detailed recommendations are provided elsewhere^{18,20}), but in most cases, the first-line treatment for HES is typically SCS.¹⁸ An exception is the use of the tyrosine kinase inhibitor imatinib as first-line therapy for *FIP1L1-PDGFR α* -positive disease (and other M-HES variants with PDGFR signaling abnormalities).^{18,54} Second-line HES therapy is often necessary in patients with disease that responds poorly to or requires high-dose SCS; it relies on various cytotoxic or immunomodulatory/suppressive drugs, such as hydroxyurea or IFN- α .^{1,73} Although the disease of most patients responds to SCS, some cases require moderate-to-high doses to control symptoms. In addition, resistance to SCS is more frequent among patients with M-HES or L-HES than I-HES.⁸⁰ Among patients with PDGFR α -negative HES, steroid resistance does not correlate with changes in glucocorticoid receptor expression and may be linked with elevated serum IL-5 levels.⁸¹ In cases of suspected M-HES and cases of I-HES, where SCS response is insufficient, imatinib treatment may be tried as a second-line therapy and is occasionally effective.^{19,82}

Novel biologic therapies targeting eosinophils may also be considered in patients whose disease remains poorly controlled despite standard-of-care treatment or who experience therapy-related toxicity. Mepolizumab is a humanized monoclonal antibody (mAb) that targets IL-5 and is approved for the treatment of severe eosinophilic asthma, EGPA, HES, and chronic rhinosinusitis with nasal polyps in multiple regions worldwide.⁸³⁻⁸⁵ Several clinical studies of patients with HES, including the

pivotal phase 3 200622 study (NCT02836496) and open-label extension, demonstrated reduced disease flares, decreased SCS use, and improved fatigue with mepolizumab compared to placebo.^{33,86-88} Mepolizumab treatment is also associated with improved health-related quality of life as well as work productivity and activity in patients with HES.⁸⁹ Recent *post hoc* analyses of the 200622 study have also demonstrated that reductions in HES flares seen with mepolizumab compared to placebo were independent of baseline blood eosinophil count and concomitant therapies.^{90,91} Two other humanized mAbs targeting IL-5 signaling have been or are under investigation for HES.^{76,79,92} These are reslizumab, which targets IL-5 directly and was evaluated in a small pilot study,⁹² and benralizumab, which targets the IL-5 receptor α subunit to reduce IL-5 signaling while inducing antibody-dependent cell-mediated cytotoxicity.⁷⁶ The phase 3 NATRON study (NCT04191304) with benralizumab in patients with HES is ongoing and follows promising results from a small phase 2 study.^{76,79} As understanding of other mechanisms driving hypereosinophilia improves, mAbs against a broader range of targets are being considered, including anti-sialic acid immunoglobulin-like lectin (aka Siglec)-8.²⁰

The previously discussed unmet needs in HES pathogenesis and disease assessment also limit treatment development (Table II). There are no validated measures of disease activity to measure treatment response in patients with HES.^{7,93} The proportion of patients displaying a relapsing–remitting disease course and risk factors for relapse are also not well characterized, making it difficult to differentiate between spontaneous improvement versus treatment response and to judge whether relapse is likely as treatment is tapered. There are also only limited data available to help guide the duration of treatment and tapering strategies.

In addition, there is a need to understand why some patients continue to experience symptoms and active disease complications despite normalization of eosinophil counts with therapy, and why there are patients whose blood eosinophil counts remain elevated despite standard-of-care treatment. There is also a need to identify lymphocyte-specific treatment targets, particularly for patients with L-HES, whose disease is less responsive to SCS and second-line agents.^{21,80} Likewise, understanding the pathogenesis of I-HES, including organ-restricted disease forms, may lead to the identification of new treatment targets. Importantly, improved methods for identifying critical organ involvement are needed to treat serious complications early and to monitor whether treatments are effectively controlling complications.

Current advances and unmet needs in EGPA treatment

First-line treatment of EGPA frequently involves treatment with SCS to achieve remission, in combination with cyclophosphamide or rituximab in patients with severe manifestations (FFS ≥ 1).^{2,72,74} Additionally, immunosuppressive therapies such as azathioprine, methotrexate, or mycophenolate mofetil are also used in patients with severe disease manifestations to maintain remission and as steroid-sparing agents, although efficacy remains unclear.^{2,72} A number of novel biologics may offer benefits as SCS-sparing treatments, in addition or as an alternative to traditional immunosuppressive therapies.⁹⁴ Recent ACR guidelines describe the treatment recommendations for patients with nonsevere/severe EGPA and different stages of remission

and relapse, but also highlight the lack of high-quality evidence to support such recommendations.⁷²

Rituximab is an anti-CD20 mAb that targets B cells and is approved for the treatment of AAV granulomatosis with polyangiitis and microscopic polyangiitis.⁹⁵ Observational studies of rituximab-treated patients with EGPA demonstrate treatment benefit, in particular for patients with ANCA-positive disease.^{95,96} Recent data from a randomized clinical trial showed similar efficacy of rituximab added to SCS compared to standard clinical care including cyclophosphamide for patients with FFS > 0 .⁹⁷

Several mAbs targeting IL-5 signaling have been studied in relation to EGPA treatment. In the phase 3 MIRRA study, patients treated with mepolizumab compared to placebo spent more time in remission, had reduced relapse rates, and had reduced SCS use.^{34,98} *Post hoc* analyses further demonstrated that patients treated with mepolizumab compared to placebo were more likely to experience 1 or more clinical benefits (defined as experiencing remission, $\geq 50\%$ reduction in SCS dose, or remaining relapse-free).⁹⁸ In addition, a small open-label study for benralizumab in patients with EGPA demonstrated steroid-sparing effects,⁷⁷ and a phase 3 noninferiority study of benralizumab versus mepolizumab (NCT04157348, MANDARA) is currently recruiting patients.⁷⁸ Finally, a small open-label study of reslizumab in patients with EGPA demonstrated reductions in SCS use.⁷⁵

As more therapeutic options become available, identifying appropriate biomarkers to define EGPA variants and inform treatment choices will be important. It remains to be determined whether treatment outcomes are influenced by specific disease features, such as ANCA status or the presence of clear-cut vasculitic manifestations. Current international consensus statements recommended that the ANCA status itself should not guide treatment decisions in EGPA.⁴⁵ In this regard, available data suggest treatment benefits of mepolizumab are irrespective of ANCA status.^{34,44} Additionally, as is also seen in patients with HES, the response to mepolizumab for different disease manifestations can be variable; it is therefore important to understand the reasons for differences in response to further uncover predictive treatment response biomarkers.⁹⁹ The use of a vasculitis score (eg, BVAS) may help with the classification of EGPA subgroups beyond ANCA status. It is also worth noting that large, double-blind, controlled studies in patients with EGPA are needed to verify the initial findings of efficacy of reslizumab and benralizumab.

Further questions around the use of biologics for EGPA remain, including around the impact of reduced eosinophil counts on the vasculitic component of disease. In addition, because patients with organ- and life-threatening manifestations within 3 months of screening were excluded in the MIRRA trial, investigation of the efficacy of mepolizumab in this subgroup is warranted.³⁴ Conversely, whether anti-IL-5 treatment offers benefits (eg, oral corticosteroid sparing) and potentially disease-modifying effects (eg, prevention of further organ and vasculitic damage) if initiated early in the disease course of EGPA also requires investigation. Further studies of the potential for long-term oral corticosteroid sparing effects of anti-IL-5 biologics after remission induction are also needed. Additionally, whether combination use of biologics with different targets, such as anti-IL-5 and B-cell depleting therapies, is appropriate is not yet known and should be assessed.¹⁰⁰

FUTURE DIRECTIONS

Although our understanding of HES and EGPA has improved substantially over the past few years, many areas still require further research (Table II).²⁷ The creation of international patient registries with associated biobanking of samples may aid research into pathogenic differences between disease variants and act as a resource for future genome-wide association or next-generation sequencing studies. Such registries could also be valuable for studies investigating disease course, organ involvement, and long-term relapse rates. A more complete understanding of pathogenesis may also lead to the identification of new therapeutic targets and much-needed biomarkers to aid in both the definitive diagnosis of HES and EGPA variants and to aid in treatment stratification.

The availability of clear clinical guidelines for diagnosis, management, and treatment is essential for both HES and EGPA. ACR recommendations for EGPA management have been recently published;⁷² however, there is a lack of comprehensive guidelines for the treatment of HES. The stratification of treatment options for HES has not been well studied, and further trials are needed to assess treatment responses in patient subgroups. For EGPA, the existing treatment guidelines are limited by the sparsity of phase 3 studies in patients with this disease. Although patients with EGPA have been included in some clinical trials for necrotizing vasculitis/AAV, this requires treatment recommendations to be extrapolated from the outcomes of a heterogeneous study population with vasculitides.

As more therapeutic options for patients with HES and EGPA become available, it will also be important to establish which treatment is most appropriate for which patient, and at which stage of the disease course.^{15,68} Currently studies of biologics have focused on their use as second-line therapies in patients with refractory or relapsing disease. However, the potential benefit of early treatment initiation, such as in the remission induction phase, remains to be established. This will be aided by more double-blind clinical trials to provide high-quality evidence of treatment benefits, as well as long-term observational studies.

Future studies would be aided by the establishment of consensus remission criteria. In clinical practice, the goal of treatment may need to be downgraded to compromise between SCS-related risks and tolerable symptoms. The glucocorticoid toxicity index may be useful to determine SCS-associated morbidity on an individual level, although further validation is warranted.⁹ Current definitions of EGPA remission (EULAR, ACR) focus on the systemic vasculitic components; there is no consensus on whether the asthma and ear, nose, and throat components should be included in the definition of remission in EGPA.⁷² In addition, the assessment of overall disease activity and severity are challenging with currently available tools. This is especially difficult in patients with HES, where the development of a range of validated disease activity and patient-reported outcome tools to better assess symptoms and impacts should be a focus of future research.

Conclusion

The mechanisms of HES and EGPA remain poorly understood. There is limited understanding of what determines the variation in organ involvement and disease severity seen in patients. In addition, the diagnosis of HES and EGPA remains challenging in routine clinical settings. The identification of improved

diagnostic tools and ways to measure disease activity, as well as improved understanding of the pathologic mechanisms leading to different disease subtypes, remain important topics for future research. Developments in these areas should ultimately help improve patient management and outcomes.

Editorial support (in the form of writing assistance, including preparation of the draft manuscript under the direction and guidance of the authors, collating and incorporating authors' comments for each draft, assembling tables and figures, grammatical editing and referencing) was provided by Alice Rees, PhD, at Fishawack Indicia Ltd, UK, part of Fishawack Health, and was funded by GSK.

REFERENCES

- Curtis C, Ogbogu P. Hypereosinophilic syndrome. *Clin Rev Allergy Immunol* 2016;50:240-51.
- Furuta S, Iwamoto T, Nakajima H. Update on eosinophilic granulomatosis with polyangiitis. *Allergol Int* 2019;68:430-6.
- Akuthota P, Weller PF. Spectrum of eosinophilic end-organ manifestations. *Immunol Allergy Clin North Am* 2015;35:403-11.
- 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;124:1319-25.e3.
- Requena G, van den Bosch J, Akuthota P, Kovalszki A, Steinfeld J, Kwon N, et al. Clinical profile and treatment in hypereosinophilic syndrome variants: a pragmatic review. *J Allergy Clin Immunol* 2022;10:2125-34.
- Jennette JC, Falk RJ, Bacon PA, Basu N, Cid MC, Ferrario F, et al. 2012 revised International Chapel Hill consensus conference nomenclature of vasculitides. *Arthritis Rheum* 2013;65:1-11.
- Comarmond C, Pagnoux C, Khellaf M, Cordier JF, Hamidou M, Viallard JF, et al. Eosinophilic granulomatosis with polyangiitis (Churg-Strauss): clinical characteristics and long-term followup of the 383 patients enrolled in the French Vasculitis Study Group cohort. *Arthritis Rheum* 2013;65:270-81.
- Lyons PA, Peters JE, Alberici F, Liley J, Coulson RMR, Astle W, et al. Genome-wide association study of eosinophilic granulomatosis with polyangiitis reveals genomic loci stratified by ANCA status. *Nat Commun* 2019;10:5120.
- Floyd L, Morris A, Joshi M, Dhaygude A. Glucocorticoid therapy in ANCA vasculitis: using the glucocorticoid toxicity index as an outcome measure. *Kidney360* 2021;2:1002-10.
- Sarnes E, Crofford L, Watson M, Dennis G, Kan H, Bass D. Incidence and US costs of corticosteroid-associated adverse events: a systematic literature review. *Clin Ther* 2011;33:1413-32.
- Strehl C, Bijlsma JW, de Wit M, Boers M, Caeyers N, Cutolo M, et al. Defining conditions where long-term glucocorticoid treatment has an acceptably low level of harm to facilitate implementation of existing recommendations: viewpoints from an EULAR task force. *Ann Rheum Dis* 2016;75:952-7.
- Kahn JE, Groh M, Lefèvre G. (A critical appraisal of) classification of hypereosinophilic disorders. *Front Med (Lausanne)* 2017;4:216.
- Berti A, Boukhalal S, Groh M, Cornec D. Eosinophilic granulomatosis with polyangiitis: the multifaceted spectrum of clinical manifestations at different stages of the disease. *Expert Rev Clin Immunol* 2020;16:51-61.
- Doubelt I, Cuthbertson D, Carette S, Chung SA, Forbess LJ, Khalidi NA, et al. Clinical manifestations and long-term outcomes of eosinophilic granulomatosis with polyangiitis in North America. *ACR Open Rheumatol* 2021;3:404-12.
- Klion AD, Ackerman SJ, Bochner BS. Contributions of eosinophils to human health and disease. *Annu Rev Pathol* 2020;15:179-209.
- Gotlib J, Cools J. Five years since the discovery of FIP1L1-PDGFR α : what we have learned about the fusion and other molecularly defined eosinophilias. *Leukemia* 2008;22:1999-2010.
- Bain BJ. Myeloid and lymphoid neoplasms with eosinophilia and abnormalities of PDGFR α , PDGFR β or FGFR1. *Haematologica* 2010;95:696-8.
- Shomali W, Gotlib J. World Health Organization-defined eosinophilic disorders: 2022 update on diagnosis, risk stratification, and management. *Am J Hematol* 2022;97:129-48.
- Khouri P, Desmond R, Pabon A, Holland-Thomas N, Ware JM, Arthur DC, et al. Clinical features predict responsiveness to imatinib in platelet-derived growth factor receptor- α -negative hypereosinophilic syndrome. *Allergy* 2016;71:803-10.

20. Helbig G, Klion AD. Hypereosinophilic syndromes—an enigmatic group of disorders with an intriguing clinical spectrum and challenging treatment. *Blood Rev* 2021;49:100809.
21. Carpentier C, Verbanck S, Schandené L, Heimann P, Trépan AL, Cogan E, et al. Eosinophilia associated with CD3⁺CD4⁺ T cells: characterization and outcome of a single-center cohort of 26 patients. *Front Immunol* 2020;11:1765.
22. Lefèvre G, Copin MC, Roumier C, Aubert H, Avenel-Audran M, Grardel N, et al. CD3⁺CD4⁺ lymphoid variant of hypereosinophilic syndrome: nodal and extranodal histopathological and immunophenotypic features of a peripheral indolent clonal T-cell lymphoproliferative disorder. *Haematologica* 2015;100:1086-95.
23. Roufosse F, Cogan E, Goldman M. Lymphocytic variant hypereosinophilic syndromes. *Immunol Allergy Clin North Am* 2007;27:389-413.
24. Ramirez GA, Yacoub MR, Ripa M, Mannina D, Cariddi A, Sapori N, et al. Eosinophils from physiology to disease: a comprehensive review. *Biomed Res Int* 2018;2018:9095275.
25. Owen WF, Rothenberg ME, Petersen J, Weller PF, Silberstein D, Sheffer AL, et al. Interleukin 5 and phenotypically altered eosinophils in the blood of patients with the idiopathic hypereosinophilic syndrome. *J Exp Med* 1989;170:343-8.
26. Raghavachar A, Fleischer S, Frickhofen N, Heimpel H, Fleischer B. T lymphocyte control of human eosinophilic granulopoiesis. Clonal analysis in an idiopathic hypereosinophilic syndrome. *J Immunol* 1987;139:3753-8.
27. Khoury P, Akuthota P, Ackerman SJ, Arron JR, Bochner BS, Collins MH, et al. Revisiting the NIH Taskforce on the Research needs of Eosinophil-Associated Diseases (RE-TREAD). *J Leukoc Biol* 2018;104:69-83.
28. Valent P, Klion AD, Roufosse F, Simon D, Metzgeroth G, Leiferman KM, et al. Proposed refined diagnostic criteria and classification of eosinophil disorders and related syndromes. *Allergy* 2022.
29. Mankad R, Bonnichsen C, Mankad S. Hypereosinophilic syndrome: cardiac diagnosis and management. *Heart* 2016;102:100-6.
30. Leiva O, Baker O, Jenkins A, Brunner AM, Al-Samkari H, Leaf RK, et al. Association of thrombosis with hypereosinophilic syndrome in patients with genetic alterations. *JAMA Netw Open* 2021;4:e2119812-e.
31. Pardanani A, Lasho T, Wassie E, Finke C, Zblewski D, Hanson CA, et al. Predictors of survival in WHO-defined hypereosinophilic syndrome and idiopathic hypereosinophilia and the role of next-generation sequencing. *Leukemia* 2016;30:1924-6.
32. Jakes RW, Kwon N, Nordstrom B, Goulding R, Fahrback K, Tarpey J, et al. Burden of illness associated with eosinophilic granulomatosis with polyangiitis: a systematic literature review and meta-analysis. *Clin Rheumatol* 2021;40:4829-36.
33. Roufosse F, Kahn JE, Rothenberg ME, Wardlaw AJ, Klion AD, Kirby SY, et al. Efficacy and safety of mepolizumab in hypereosinophilic syndrome: a phase III, randomized, placebo-controlled trial. *J Allergy Clin Immunol* 2020;146:1397-405.
34. Wechsler ME, Akuthota P, Jayne D, Khoury P, Klion A, Langford CA, et al. Mepolizumab or placebo for eosinophilic granulomatosis with polyangiitis. *N Engl J Med* 2017;376:1921-32.
35. Jakiela B, Szczeklik W, Plutecka H, Sokolowska B, Mastalerz L, Sanak M, et al. Increased production of IL-5 and dominant Th2-type response in airways of Churg-Strauss syndrome patients. *Rheumatology (Oxford)* 2012;51:1887-93.
36. Hellmich B, Csernok E, Gross WL. Proinflammatory cytokines and autoimmunity in Churg-Strauss syndrome. *Ann N Y Acad Sci* 2005;1051:121-31.
37. Zwerina J, Bach C, Martorana D, Jatzwauk M, Hegasy G, Moosig F, et al. Eotaxin-3 in Churg-Strauss syndrome: a clinical and immunogenetic study. *Rheumatology* 2011;50:1823-7.
38. Bello F, Emmi G, Tamburini C, Maggi L, Annunziato F, Cosmi L, et al. Eosinophilic granulomatosis with polyangiitis-related myocarditis during mepolizumab therapy reveals a Th1/Th17-mediated vasculitic response. *Clin Exp Rheumatol* 2022;40:863-4.
39. Kiene M, Csernok E, Müller A, Metzler C, Trabandt A, Gross WL. Elevated interleukin-4 and interleukin-13 production by T cell lines from patients with Churg-Strauss syndrome. *Arthritis Rheum* 2001;44:469-73.
40. Jakiela B, Sanak M, Szczeklik W, Sokolowska B, Plutecka H, Mastalerz L, et al. Both Th2 and Th17 responses are involved in the pathogenesis of Churg-Strauss syndrome. *Clin Exp Rheumatol* 2011;29:S23-34.
41. Chang HC, Chou PC, Lai CY, Tsai HH. Antineutrophil cytoplasmic antibodies and organ-specific manifestations in eosinophilic granulomatosis with polyangiitis: a systematic review and meta-analysis. *J Allergy Clin Immunol* 2021;9:445-52.e6.
42. Fagni F, Bello F, Emmi G. Eosinophilic granulomatosis with polyangiitis: dissecting the pathophysiology. *Front Med (Lausanne)* 2021;8:627776.
43. Trivioli G, Terrier B, Vaglio A. Eosinophilic granulomatosis with polyangiitis: understanding the disease and its management. *Rheumatology (Oxford)* 2020;59:iii84-94.
44. Fujii T, Atsumi T, Okamoto N, Takahashi N, Tamura N, Nakajima A, et al. Post-marketing surveillance of mepolizumab use in patients with eosinophilic granulomatosis with polyangiitis in Japan: interim analysis. *Ther Res* 2021;42:403-22.
45. Moiseev S, Bossuyt X, Arimura Y, Blockmans D, Csernok E, Damoiseaux J, et al. International consensus on ANCA testing in eosinophilic granulomatosis with polyangiitis. *Am J Respir Crit Care Med* 2020.
46. Papo M, Sinico RA, Teixeira V, Venhoff N, Urban ML, Iudici M, et al. Significance of PR3-ANCA positivity in eosinophilic granulomatosis with polyangiitis (Churg-Strauss). *Rheumatology* 2020;60:4355-60.
47. Dong ZM, Lin E, Wechsler ME, Weller PF, Klion AD, Bochner BS, et al. Pulmonary eosinophilic granulomatosis with polyangiitis has IgG₄ plasma cells and immunoregulatory features. *Am J Pathol* 2020;190:1438-48.
48. Mahr A, Moosig F, Neumann T, Szczeklik W, Taillé C, Vaglio A, et al. Eosinophilic granulomatosis with polyangiitis (Churg-Strauss): evolutions in classification, etiopathogenesis, assessment and management. *Curr Opin Rheumatol* 2014;26:16-23.
49. Mukherjee M, Thomas SR, Radford K, Dvorkin-Gheva A, Davydchenko S, Kjarsgaard M, et al. Sputum antineutrophil cytoplasmic antibodies in serum antineutrophil cytoplasmic antibody-negative eosinophilic granulomatosis with polyangiitis. *Am J Respir Crit Care Med* 2019;199:158-70.
50. Maritati F, Peyronel F, Fenaroli P, Pegoraro F, Benigno GD, et al. Occupational exposures and smoking in eosinophilic granulomatosis with polyangiitis: a case-control study. *Arthritis Rheum* 2021;73:1694-702.
51. Wu EY, Hernandez ML, Jennette JC, Falk RJ. Eosinophilic granulomatosis with polyangiitis: clinical pathology conference and review. *J Allergy Clin Immunol* 2018;6:1496-504.
52. Stoller JK. The challenge of rare diseases. *Chest* 2018;153:1309-14.
53. Akuthota P, Xenakis JJ, Weller PF. Eosinophils: offenders or general bystanders in allergic airway disease and pulmonary immunity? *Arthritis Rheum* 2011;3:113-9.
54. 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;348:1201-14.
55. Carpentier C, Schandené L, Dewispelaere L, Heimann P, Cogan E, Roufosse F. CD3⁺CD4⁺ lymphocytic variant hypereosinophilic syndrome: diagnostic tools revisited. *J Allergy Clin Immunol* 2021;9:2426-39.e7.
56. Makiya MA, Khoury P, Kuang FL, Mata AD, Mahmood S, Bowman A, et al. Urine eosinophil-derived neurotoxin: a potential marker of activity in select eosinophilic disorders. *Allergy* 2022.
57. Kovacs N, Benjamin K, Holland-Thomas N, Moshkovich O, Nelsen LM, Ortega H, et al. Symptom assessment in hypereosinophilic syndrome: toward development of a patient-reported outcomes tool. *J Allergy Clin Immunol Pract* 2020;8:3209-12.e8.
58. Grayson PC, Ponte C, Suppiah R, Robson JC, Craven A, Judge A, et al. 2022 American College of Rheumatology/European Alliance of Associations for Rheumatology classification criteria for eosinophilic granulomatosis with polyangiitis. *Ann Rheum Dis* 2022;81:309-14.
59. 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;117:1292-302.
60. Khoury P, Zagallo P, Talar-Williams C, Santos CS, Dinerman E, Holland NC, et al. Serum biomarkers are similar in Churg-Strauss syndrome and hypereosinophilic syndrome. *Allergy* 2012;67:1149-56.
61. Leurs A, Chenivesse C, Lopez B, Gibier JB, Clément G, Groh M, et al. C-reactive protein as a diagnostic tool in differential diagnosis of hypereosinophilic syndrome and antineutrophil cytoplasmic antibody-negative eosinophilic granulomatosis with polyangiitis. *J Allergy Clin Immunol Pract* 2019;7:1347-51.e3.
62. Churg A, Brallas M, Cronin SR, Churg J. Formes frustes of Churg-Strauss syndrome. *Chest* 1995;108:320-3.
63. Solans-Laqué R, Rodríguez-Carballeira M, Rios-Blanco JJ, Fraile G, Sáez-Comet L, Martínez-Zapico A, et al. Comparison of the Birmingham Vasculitis Activity Score and the Five-Factor Score to assess survival in antineutrophil cytoplasmic antibody-associated vasculitis: a study of 550 patients from Spain (REVAS registry). *Arthritis Care Res* 2020;72:1001-10.
64. Guillevin L, Pagnoux C, Seror R, Mahr A, Mouthon L, Toumeline PL. The Five-Factor Score revisited: assessment of prognoses of systemic necrotizing vasculitides based on the French Vasculitis Study Group (FVSG) cohort. *Medicine* 2011;90:19-27.
65. Mukhtyar C, Lee R, Brown D, Carruthers D, Dasgupta B, Dubey S, et al. Modification and validation of the Birmingham Vasculitis Activity Score (version 3). *Ann Rheum Dis* 2009;68:1827-32.
66. Robson JC, Dawson J, Doll H, Cronholm PF, Milman N, Kellom K, et al. Validation of the ANCA-associated vasculitis patient-reported outcomes (AAV-PRO) questionnaire. *Ann Rheum Dis* 2018;77:1157-64.

67. DeJaco C, Oppl B, Monach P, Cuthbertson D, Carette S, Hoffman G, et al. Serum biomarkers in patients with relapsing eosinophilic granulomatosis with polyangiitis (Churg-Strauss). *PLoS One* 2015;10:e0121737.
68. Grayson PC, Monach PA, Pagnoux C, Cuthbertson D, Carette S, Hoffman GS, et al. Value of commonly measured laboratory tests as biomarkers of disease activity and predictors of relapse in eosinophilic granulomatosis with polyangiitis. *Rheumatology (Oxford)* 2015;54:1351-9.
69. Groh M, Masciocco G, Kirchner E, Kristen A, Pellegrini C, Varnous S, et al. Heart transplantation in patients with eosinophilic granulomatosis with polyangiitis (Churg-Strauss syndrome). *J Heart Lung Transplant* 2014;33:842-50.
70. Pakbaz M, Pakbaz M. Cardiac involvement in eosinophilic granulomatosis with polyangiitis: a meta-analysis of 62 case reports. *J Tehran Heart Center* 2020;15:18-26.
71. Sartorelli S, Chassagnon G, Cohen P, Dunogué B, Puéchal X, Régent A, et al. Revisiting characteristics, treatment and outcome of cardiomyopathy in eosinophilic granulomatosis with polyangiitis (formerly Churg-Strauss). *Rheumatology (Oxford)* 2022;61:1175-84.
72. Chung SA, Langford CA, Maz M, Abril A, Gorelik M, Guyatt G, et al. 2021 American College of Rheumatology/Vasculitis Foundation guideline for the management of antineutrophil cytoplasmic antibody-associated vasculitis. *Arthritis Rheum* 2021;73:1366-83.
73. Klion AD. How I treat hypereosinophilic syndromes. *Blood* 2015;126:1069-77.
74. Groh M, Pagnoux C, Baldini C, Bel E, Bottero P, Cottin V, et al. Eosinophilic granulomatosis with polyangiitis (Churg-Strauss) (EGPA) Consensus Task Force recommendations for evaluation and management. *Eur J Intern Med* 2015;26:545-53.
75. Manka LA, Guntur VP, Denson JL, Dunn RM, Dollin YT, Strand MJ, et al. Efficacy and safety of reslizumab in the treatment of eosinophilic granulomatosis with polyangiitis. *Ann Allergy Asthma Immunol* 2021;126:696-701.e1.
76. Kuang FL, Legrand F, Makiya M, Ware J, Wetzler L, Brown T, et al. Benralizumab for PDGFRA-negative hypereosinophilic syndrome. *N Engl J Med* 2019;380:1336-46.
77. Guntur VP, Manka LA, Denson JL, Dunn RM, Dollin YT, Gill M, et al. Benralizumab as a steroid-sparing treatment option in eosinophilic granulomatosis with polyangiitis. *J Allergy Clin Immunol Pract* 2021;9:1186-93.e1.
78. Efficacy and safety of benralizumab in EGPA compared to mepolizumab (MAN-DARA). *ClinicalTrials.gov*. Available at: <https://clinicaltrials.gov/ct2/show/NCT04157348>. Accessed September 2, 2021.
79. A phase 3 study to evaluate the efficacy and safety of benralizumab in patients with hypereosinophilic syndrome (HES) (NATRON). *ClinicalTrials.gov*. Available at: <https://clinicaltrials.gov/ct2/show/NCT04191304>. Accessed September 28, 2022.
80. Khoury P, Abiodun AO, Holland-Thomas N, Fay MP, Klion AD. Hypereosinophilic syndrome subtype predicts responsiveness to glucocorticoids. *J Allergy Clin Immunol Pract* 2018;6:190-5.
81. Stokes K, Yoon P, Makiya M, Gebreegziabher M, Holland-Thomas N, Ware J, et al. Mechanisms of glucocorticoid resistance in hypereosinophilic syndromes. *Clin Exp Allergy* 2019;49:1598-604.
82. Klion A. Hypereosinophilic syndrome: approach to treatment in the era of precision medicine. *Hematology Am Soc Hematol Educ Program* 2018;2018:326-31.
83. European Medicines Agency (EMA). Nucala (mepolizumab) summary of product characteristics. Available at: https://www.ema.europa.eu/en/documents/product-information/nucala-epar-product-information_en.pdf. Accessed September 30, 2022.
84. GSK. Nucala (mepolizumab). Highlights of prescribing information. Available at: https://gskpro.com/content/dam/global/hcpportal/en_US/Prescribing_Information/Nucala/pdf/NUCALA-PI-PIL-IFU-COMBINED.PDF. Accessed September 30, 2022.
85. GSK. Nucala (mepolizumab) prescribing information, Japan. Available at: <https://gskpro.com/ja-jp/products-info/nucala/index/>. Accessed July 2021.
86. 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;131:461-7.e1-5.
87. 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;358:1215-28.
88. Gleich GJ, Roufosse F, Chupp G, Faguer S, Walz B, Reiter A, et al. Safety and efficacy of mepolizumab in hypereosinophilic syndrome: an open-label extension study. *J Allergy Clin Immunol Pract* 2021;9:4431-40.e1.
89. von Maltzahn R, Nelsen L, Bentley JH, Kwon N, Steinfeld J. PSY2 Impact of mepolizumab on health-related quality of life in patients with hypereosinophilic syndrome. *Value Health* 2021;24:S229.
90. Reiter A, Lefevre G, Cid MC, Kwon N, Mavropoulou E, Yancey SW, et al. Association between baseline therapy and flare reduction in mepolizumab-treated patients with hypereosinophilic syndrome. *Front Immunol* 2022;13:840974.
91. Rothenberg ME, Roufosse F, Faguer S, Gleich GJ, Steinfeld J, Yancey SW, et al. Mepolizumab reduces hypereosinophilic syndrome flares irrespective of blood eosinophil count and interleukin-5. *J Allergy Clin Immunol Pract* 2022;10:2367-74.e3.
92. 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;103:2939-41.
93. Samson M, Puéchal X, Devilliers H, Ribé C, Cohen P, Stern M, et al. Long-term outcomes of 118 patients with eosinophilic granulomatosis with polyangiitis (Churg-Strauss syndrome) enrolled in two prospective trials. *J Autoimmun* 2013;43:60-9.
94. Uzzo M, Regola F, Trezzi B, Toniati P, Franceschini F, Sinico RA. Novel targets for drug use in eosinophilic granulomatosis with polyangiitis. *Front Med (Lausanne)* 2021;8:754434.
95. Mohammad AJ, Hot A, Arndt F, Moosig F, Guerry MJ, Amudala N, et al. Rituximab for the treatment of eosinophilic granulomatosis with polyangiitis (Churg-Strauss). *Ann Rheum Dis* 2016;75:396-401.
96. Teixeira V, Mohammad AJ, Jones RB, Smith R, Jayne D. Efficacy and safety of rituximab in the treatment of eosinophilic granulomatosis with polyangiitis. *RMD Open* 2019;5:e000905.
97. Terrier B, Pugnet G, de Moreuil C, Bonnotte B, Benhamou Y, Diot E, et al. Rituximab versus conventional therapeutic strategy for remission induction in eosinophilic granulomatosis with polyangiitis: a double-blind, randomized, controlled trial. *Arthritis Rheum* 2021;73(suppl 10): abstract L21.
98. Steinfeld J, Bradford ES, Brown J, Mallett S, Yancey SW, Akuthota P, et al. Evaluation of clinical benefit from treatment with mepolizumab for patients with eosinophilic granulomatosis with polyangiitis. *J Allergy Clin Immunol* 2019;143:2170-7.
99. Ríos-Garcés R, Prieto-González S, Hernández-Rodríguez J, Arismendi E, Alobid I, Penati AE, et al. Response to mepolizumab according to disease manifestations in patients with eosinophilic granulomatosis with polyangiitis. *Eur J Intern Med* 2022;95:61-6.
100. Higashitani K, Yoshimi R, Sato Y, Watanabe T, Ihata A. Rituximab and mepolizumab combination therapy for glucocorticoid-resistant myocarditis related to eosinophilic granulomatosis with polyangiitis. *Mod Rheumatol Case Rep* 2022;6:87-92.
101. Dulohery MM, Patel RR, Schneider F, Ryu JH. Lung involvement in hypereosinophilic syndromes. *Respir Med* 2011;105:114-21.
102. Moosig F, Bremer JP, Hellmich B, Holle JU, Holl-Ulrich K, Laudien M, et al. A vasculitis centre based management strategy leads to improved outcome in eosinophilic granulomatosis and polyangiitis (Churg-Strauss, EGPA): monocentric experiences in 150 patients. *Ann Rheum Dis* 2013;72:1011.
103. Cottin V, Bel E, Bottero P, Dalhoff K, Humbert M, Lazor R, et al. Respiratory manifestations of eosinophilic granulomatosis with polyangiitis (Churg-Strauss). *Eur Respir J* 2016;48:1429-41.
104. Durel CA, Berthiller J, Caboni S, Jayne D, Ninet J, Hot A. Long-term followup of a multicenter cohort of 101 patients with eosinophilic granulomatosis with polyangiitis (Churg-Strauss). *Arthritis Care Res* 2016;68:374-87.
105. Wechsler ME. Pulmonary eosinophilic syndromes. *Immunol Allergy Clin North Am* 2007;27:477-92.
106. Simon HU, Rothenberg ME, Bochner BS, Weller PF, Wardlaw AJ, Wechsler ME, et al. Refining the definition of hypereosinophilic syndrome. *J Allergy Clin Immunol* 2010;126:45-9.
107. Chusid MJ, Dale DC, West BC, Wolff SM. The hypereosinophilic syndrome: analysis of fourteen cases with review of the literature. *Medicine* 1975;54:1-27.
108. Lanham JG, Elkon KB, Pusey CD, Hughes GR. Systemic vasculitis with asthma and eosinophilia: a clinical approach to the Churg-Strauss syndrome. *Medicine* 1984;63:65-81.
109. Churg J, Strauss L. Allergic granulomatosis, allergic angiitis, and periarteritis nodosa. *Am J Pathol* 1951;27:277-301.