

Eosinophilic Disorders: Best Practices for HES and EGPA at ATS 2026

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The management of hypereosinophilic syndrome (HES) and eosinophilic granulomatosis with polyangiitis (EGPA) remains complex, requiring precise diagnostic criteria and tailored therapeutic strategies to mitigate end-organ damage. ATS 2026 highlighted current best practices, emphasising the importance of early diagnosis and targeted therapies to improve patient outcomes.¹

KEY TAKEAWAYS

- The Pivot: Updated diagnostic algorithms and treatment pathways for HES and EGPA.
- The Data: Early initiation of targeted therapies, particularly biologics, demonstrates superior disease control compared to corticosteroids alone.
- The Action: Clinicians should integrate specific diagnostic markers and consider biologics earlier in the treatment paradigm for eligible patients.

Eosinophilic disorders, including hypereosinophilic syndrome (HES) and eosinophilic granulomatosis with polyangiitis (EGPA), are characterised by persistent eosinophilia and diverse organ involvement. The clinical dilemma lies in differentiating these conditions and initiating appropriate, often immunosuppressive, therapy before irreversible organ damage occurs. HES is defined by peripheral blood eosinophil counts exceeding $1.5 \times 10^9/L$ for at least six months, or for less than six months in the presence of signs or symptoms of eosinophil-related organ damage, after exclusion of secondary causes.¹ EGPA, conversely, is a systemic vasculitis characterised by asthma, eosinophilia, and extravascular granulomas.² Both conditions necessitate a nuanced diagnostic approach and a treatment strategy that balances efficacy with minimisation of adverse effects. The prevalence of HES is estimated to be approximately 0.003% to 0.005% in the general population, while EGPA affects about 10 to 14 individuals per million, highlighting their rarity and the challenges in accumulating large patient cohorts for clinical trials. Understanding the distinct pathophysiological mechanisms driving each disorder is crucial for targeted therapeutic development.

Gaining Control of Eosinophilic Disorders: Best Practices

ATS 2026 sessions on eosinophilic disorders focused on refining diagnostic pathways and optimising therapeutic interventions. For HES, the diagnostic workup typically involves excluding secondary causes such as parasitic infections, allergic reactions, and malignancies. Genetic testing for FIP1L1-PDGFR α fusion gene is critical, as its presence identifies a specific HES subtype (myeloproliferative HES) that responds dramatically to imatinib.³ In patients without this fusion gene, further subtyping into lymphocytic HES, idiopathic HES, or other variants guides treatment selection. This subtyping is often based on clinical presentation, bone marrow findings, and T-cell clonality. For EGPA, diagnosis

relies on the American College of Rheumatology (ACR) criteria, which include asthma, eosinophilia (>10% on differential white blood cell count), mononeuropathy or polyneuropathy, non-fixed pulmonary infiltrates, paranasal sinus abnormality, and extravascular eosinophils on biopsy.⁴ Anti-neutrophil cytoplasmic antibodies (ANCA), particularly anti-myeloperoxidase (MPO-ANCA), are detected in approximately 30-40% of EGPA patients and may correlate with specific clinical phenotypes.⁵ The presence of ANCA often indicates a more severe vasculitic presentation, while ANCA-negative EGPA tends to have more prominent cardiac involvement and less severe renal disease. The diagnostic process for both conditions often involves a multidisciplinary team, including pulmonologists, rheumatologists, allergists, and hematologists, to ensure comprehensive evaluation and accurate diagnosis.

Treatment strategies for both HES and EGPA typically begin with corticosteroids. For HES, prednisone at 1 mg/kg/day is a common initial approach.¹ However, long-term corticosteroid use is associated with significant adverse effects, prompting the exploration of corticosteroid-sparing agents. Mepolizumab, an anti-IL-5 monoclonal antibody, has demonstrated efficacy in reducing eosinophil counts and corticosteroid dependence in patients with HES.⁶ Reslizumab and benralizumab, also targeting IL-5 or its receptor, represent additional options. Mepolizumab works by binding to interleukin-5 (IL-5), a cytokine that plays a central role in the growth, differentiation, recruitment, activation, and survival of eosinophils. By blocking IL-5, mepolizumab reduces eosinophil levels in the blood and tissues. For EGPA, induction therapy often involves high-dose corticosteroids, sometimes combined with cyclophosphamide for severe organ-threatening disease.⁷ Maintenance therapy frequently includes azathioprine or methotrexate. Mepolizumab is approved for the treatment of EGPA and has shown significant reductions in relapse rates and corticosteroid dose.⁸ A randomised, placebo-controlled trial (N=136) demonstrated that mepolizumab, added to standard therapy, increased the accrued time in remission by 32 weeks (95% CI, 16 to 48 weeks; P8 This trial enrolled adult patients with refractory or relapsing EGPA who were receiving stable doses of oral glucocorticoids with or without other immunosuppressants. The integration of biologics into earlier lines of therapy for both HES and EGPA was a key theme. The data suggest that early initiation of targeted therapies, particularly anti-IL-5 agents, can lead to better disease control, reduced corticosteroid exposure, and improved quality of life.^{6,8} This approach moves beyond simply managing symptoms to addressing the underlying eosinophilic inflammation more directly. Limitations in current practice include the heterogeneity of these disorders, which can make a one-size-fits-all approach challenging. The rarity of these conditions also poses difficulties for conducting large-scale, well-powered clinical trials, often leading to smaller sample sizes and reliance on real-world evidence. Further research is needed to identify biomarkers that can predict response to specific therapies and to explore novel targets beyond the IL-5 pathway. The long-term safety and efficacy of newer biologics also require continued surveillance. Additionally, understanding the specific patient populations that benefit most from particular biologics remains an area of active investigation, as individual responses can vary significantly.

CLINICAL IMPLICATIONS

The emphasis at ATS 2026 on early and targeted intervention for eosinophilic disorders is a welcome, if overdue, development. For too long, clinicians have relied on broad-spectrum immunosuppression, primarily corticosteroids, which offer symptomatic relief but carry a heavy burden of adverse effects. The increasing evidence supporting biologics like mepolizumab in both HES and EGPA should prompt a re-evaluation of current prescribing patterns. It is no longer sufficient to reserve these agents for refractory cases; the data

suggest they should be considered earlier to prevent cumulative corticosteroid toxicity and irreversible organ damage.

The industry's role in developing these targeted therapies is clear, but the challenge now lies in ensuring equitable access and appropriate patient selection. Diagnostic precision, particularly in distinguishing HES subtypes and EGPA phenotypes, is paramount. Without robust diagnostic algorithms and accessible genetic testing, the full benefit of these advanced therapies will not be realised. Payers and guideline bodies must adapt to the evolving evidence, recognising that the upfront cost of biologics may be offset by reduced hospitalisations, fewer complications from corticosteroid use, and improved patient productivity.

Patients with HES and EGPA often face a protracted diagnostic journey and a significant impact on their quality of life. The shift towards more targeted, corticosteroid-sparing treatments offers a genuine improvement in their prognosis and daily experience. While the heterogeneity of these conditions means that a universal solution remains elusive, the current trajectory towards precision medicine in eosinophilic disorders is a positive step. Clinicians must remain vigilant for the subtle signs of these rare conditions and be prepared to navigate complex diagnostic pathways to ensure patients receive optimal, evidence-based care.

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