

Eosinophils and the Scope of Practice in Allergy/Immunology



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As allergists/immunologists examine how our specialty fits into the continuously evolving health care system, there have been many efforts to explore how to expand our scope of practice and positive influence in broader health care systems. Our expert care of very common diseases, such as asthma and allergic rhinitis, often leads to better outcomes, improved patient quality of life, and reduced total cost of care. However, although we look to expand our scope of practice, 2 basic biological responses are essentially synonymous with our specialty and regularly evoke consultation from an allergist/immunologist. One is anaphylaxis and the other is eosinophilia and its associated diseases. Although there has been recent attention to eosinophilia in asthma, there are a number of other conditions, both common and rare, which should be within the primary expertise of our specialists. This thematic issue was produced in this context to continually educate our specialists to enhance our diagnostic and treatment skills, set us apart as authoritative experts, and further secure our future in the health care systems of the future.

This issue of *Journal of Allergy and Clinical Immunology: In Practice* brings together reviews on specific diseases as well as primary biology of the eosinophil. The most important goal was to stimulate our thinking into the many unanswered questions surrounding the role of eosinophils in human disease and health. Looking to the future of our specialty always reminds me that our mentors supply significant perspective on future directions. In 1975, Dr M. Joseph Chusid (one of my mentors) published one of the first case series of patients with the hypereosinophilic syndrome.¹ Now 43 years later, he reviews the fundamental question that we need to keep in mind as we see patients. Are the roles of the eosinophil in humans restricted to disease pathogenesis and protection from parasites?² The answer is complex, but eosinophils have been shown to strongly contribute to modulation of inflammation, tissue repair, tissue remodeling, female reproductive health, tumor surveillance, transplant rejection, autoimmune pathogenesis, and adipose tissue remodeling. The evolutionary appearance of the eosinophil hundreds of million years ago in all vertebrates is natural testimony to the need for their existence, despite unclear consequences in the rare patient devoid of eosinophils and the relative well-being of eosinophil-less mice.³

The articles on eosinophilic diseases of the esophagus,⁴ lung,⁵ skin,⁶ vasculitis,⁷ and systemic hypereosinophilic syndrome⁸ answer many fundamental questions regarding the mechanisms of eosinophil function. The authors, and their subject matter, were strategically chosen to highlight similar and contrasting effects of eosinophils within the same organ system. The circadian nature of eosinophils and basal regulation now appears to be closely linked to the identification of type 2 innate lymphoid cells that constitutively express IL-5 and are induced to express IL-13, resulting in eotaxin production and eosinophil accumulation.⁶ Allen et al's review of the eosinophilic pneumonias highlights the often variable tissue responses involved with eosinophils.⁹ In 1989,⁹ the description of acute eosinophilic pneumonia (AEP), a syndrome of rapid-onset respiratory failure with a predominance of eosinophils in bronchoalveolar lavage fluid, was a critical sentinel article demonstrating the destructive nature of eosinophils in the lung. The adult respiratory distress syndrome, with a mortality rate of 67% in 1990, was indistinguishable clinically from AEP.¹⁰ Identification and treatment of AEP with systemic corticosteroids leads to rapid reversal of respiratory failure. This observation saved lives¹¹ and was the key message of this work. The distinct contrast between this acute life-threatening immune response and chronic eosinophilic pneumonia or persistent asthma demonstrates the multiple variable mechanisms involved in eosinophilic disease. It also highlights the key need for the allergist/immunologist to be further integrated into the broad health care system. Among the adverse health effects being associated with the new epidemic of e-cigarette use is eosinophilic pneumonia, which again presents an opportunity for allergy and immunology to lead the research into this new challenge.^{12,13}

This editorial is not meant to supplant the in-depth work of the authors but strives to stimulate the reader's curiosity in reading these articles in depth. How is it that the eosinophil as a predominant participant in the pathophysiology of asthma does not induce the dramatic respiratory failure of AEP? Why does the myocardium in the hypereosinophilic syndrome, the esophagus in eosinophilic esophagitis, and the subcutaneous tissue in eosinophilic fasciitis develop fibrosis, whereas the tissues in atopic dermatitis, benign hypereosinophilia of uncertain significance, familial hypereosinophilia, insect bites, or episodic angioedema with eosinophilia do not? Complex interactions of the environment, genetics, immune system programming (T_H2), chemokines, interleukins, and unique cells in various organs (eg, type 2 innate lymphocytes in the skin) hold part of the answers. In certain situations, eosinophils may no longer be present in tissue biopsies in high quantities, but have left their long-lived intact functioning granules. The eosinophil granules appear to contribute to tissue modification in the esophagus and to pruritus of the skin in atopic dermatitis.^{4,6} Despite Ehrlich's

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discovery of the eosinophil in 1879, I suspect that we are only at the beginning of a revolution of knowledge about the eosinophils in both health and disease. It will be likely that the successes and failures of targeted biologic therapy will enhance our understanding of this unique cell.

Finally, when the clinician faces a patient for consultation of an elevated eosinophil count, a very practical case-based presentation brings the reader a well-organized, valuable algorithm for evaluating and treating these patients.¹⁴ The armamentarium of the allergy/immunology clinician includes glucocorticoids, imatinib, immunosuppressant medications, JAK inhibitors, tyrosine kinase inhibitors, and various biologic therapies depending on the target. Most studies tell us when to start such therapies and what to evaluate for their expected outcomes. As treatment continues with time, there may be variable responses and considerations always turn to the use of biologic agents. Unfortunately, the clinician is faced with unanswered but critical questions that they have to discuss with their patients.

I approached 2 additional world-renowned experts on eosinophils, Dr Amy Klion at the National Institutes of Health and Dr Gerald Gleich at the University of Utah. We asked their opinion on which critical questions are unanswered in the use of biologic therapy for eosinophilic disease. Summarized below are their top unanswered questions that require additional study (A. Klion, G. Gleich, personal communication, July 18, 2018).

- How do we choose between the many eosinophil-lowering biologics available or soon to be available for the treatment of an individual patient?
 - Does the etiology of the eosinophilia play a major role in the efficacy and/or development of resistance to the various eosinophil-lowering biologics or are other factors, such as the organ system involved, more important?
 - Are there biomarkers that predict response?
 - How will the coadministration of biologics for other indications affect the efficacy of eosinophil-lowering agents? For example, will TNF inhibitors that affect natural killer cell function impair the activity of afucosylated antibodies that rely on antibody-dependent cell-mediated cytotoxicity (ADCC)?
- Are the doses of eosinophil-lowering biologics approved for asthma sufficient to treat patients with other eosinophilic disorders? If not, which patients would benefit from higher dosing versus a different agent?
- Would coadministration of biologics with differing mechanisms of action promote even better health outcomes or increase toxicity?
- How should ongoing therapies be managed in the face of an apparently effective targeted biologic?
 - When should other therapies, including those with partial efficacy, be tapered or stopped?
 - How should patients be monitored during tapering of other therapies for reemergence of unrelated conditions that may have been treated by therapies with broader effects on inflammation, such as corticosteroids?
- Which clinical outcomes (eg, fibrosis, esophageal compliance, pruritus, neuropathy, pulmonary function, renal function, and

rash amelioration) are most valuable in measuring the effectiveness of therapy?

- Is long-term reduction or depletion of eosinophils safe?
 - What is the effect of removing eosinophils on homeostatic mechanisms in which eosinophils are believed to play a role, such as tissue remodeling, glucose metabolism, and tumor surveillance?
 - Will eosinophil depletion in patients with chronic eosinophilic disorders disrupt negative feedback loops, causing other cell types to proliferate, become more activated, or even undergo neoplastic transformation?

The “journal” hopes to have raised the clinically relevant basic science knowledge, diagnostic acumen, and treatment expertise of our specialty with this issue. Most important is that we are in our infancy of our knowledge of some of the interventions with new therapies. Keen observation by the practicing clinician will be key to safe and effective care in these disorders. We look forward to the future role of the allergy/immunology practitioner, as this expertise will help solidify our specialty’s future in the new world of health care.

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