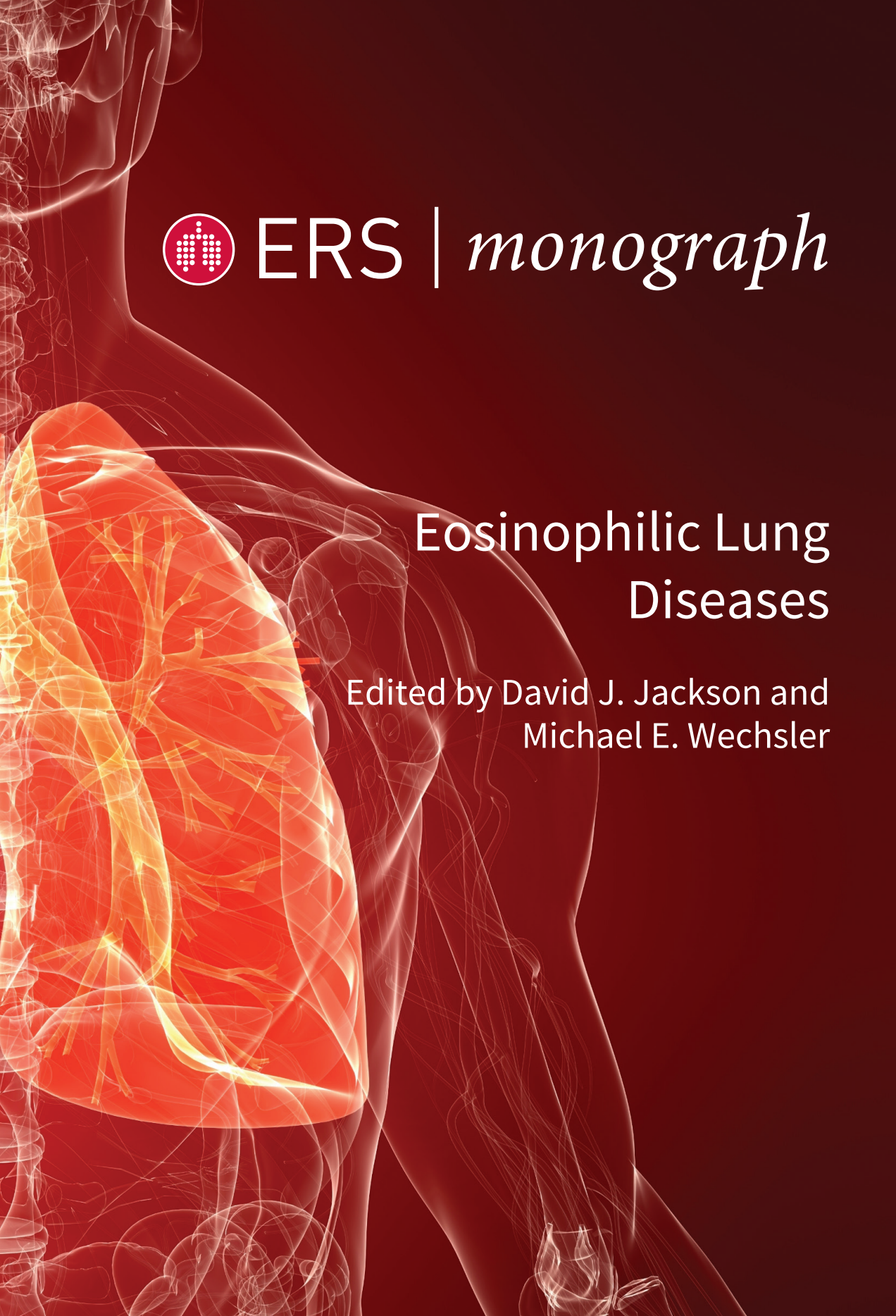




ERS | *monograph*

Eosinophilic Lung Diseases

Edited by David J. Jackson and
Michael E. Wechsler



Eosinophilic Lung Diseases

Edited by
David J. Jackson and Michael E. Wechsler

Editor in Chief
John R. Hurst

This book is one in a series of *ERS Monographs*. Each individual issue provides a comprehensive overview of one specific clinical area of respiratory health, communicating information about the most advanced techniques and systems required for its investigation. It provides factual and useful scientific detail, drawing on specific case studies and looking into the diagnosis and management of individual patients. Previously published titles in this series are listed at the back of this *Monograph*.

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Managing Editor: Rachel Gozzard
European Respiratory Society, 442 Glossop Road, Sheffield, S10 2PX, UK
Tel: 44 114 2672860 | E-mail: monograph@ersnet.org

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Preface

John R. Hurst 

It's an exciting time to be an eosinophil biologist, or a healthcare professional caring for people with eosinophilic diseases. Leveraging a deeper scientific understanding of these enigmatic cells, we now have specific biological treatments that are transforming the management of rare and common (lung) diseases alike.

As ever, this *Monograph* provides a state-of-the-art collection of reviews – here, covering the spectrum of eosinophilic lung diseases, including those with multisystem involvement. Given how quickly the field is moving, I congratulate the Guest Editors David J. Jackson and Michael E. Wechsler on delivering this excellent and timely collection. I would also like to extend my thanks to the chapter authors for their authoritative summaries.

The scope of this book is broad, basing approaches to the management of eosinophilic lung diseases on a fundamental understanding of eosinophil biology in health and disease. Important questions remain, not least around the safety of long-term eosinophil depletion, and there is still much to learn. The final chapter considers where future developments may lie.

So without further preamble, I invite you to read on and benefit from this excellent collection.

Disclosures: J.R. Hurst reports receiving grants, personal fees and non-financial support from pharmaceutical companies that make medicines to treat respiratory disease. This includes reimbursement for educational activities and advisory work, and support to attend meetings.





Guest Editors

David J. Jackson



David J. Jackson is an Associate Professor of Respiratory Medicine at King's College London (London, UK) and Clinical Director of Guy's Severe Asthma Centre, Guy's & St Thomas' NHS Trust (London, UK), a regional unit for severe asthma, eosinophilic granulomatosis with polyangiitis (EGPA) and other eosinophilic lung diseases, which receives approximately 1000 referrals per year from a network of hospitals across London and South-East England.

Following an MSc in allergy and a PhD investigating the mechanisms of virus-induced asthma exacerbations at Imperial College London (London, UK), David's more recent research has focused on the clinical aspects of severe asthma care, including investigating subphenotypes of asthma and EGPA made evident by their differential response to targeted biological therapies.

David is on the steering committee of the International Severe Asthma Registry (ISAR), is an assembly member of the Global Initiative for Asthma (GINA), and is on the asthma specialist advisory group of the British Thoracic Society (BTS). He holds senior editorial positions at several journals, including *Chest*, the *European Respiratory Review* and *Allergy*, and has published original research in *Nature Medicine*, *Science Translational Medicine*, *JAMA Internal Medicine* and *Lancet Respiratory Medicine*, as well as several other respiratory- and allergy-related journals.

Michael E. Wechsler



Michael E. Wechsler is Professor of Medicine in the Division of Pulmonary, Critical Care and Sleep Medicine at National Jewish Health (NJH) in Denver (CO, USA), Director of the NJH/Cohen Family Asthma Institute (Denver) and Associate Vice President for Innovation and Industry Relations at NJH.

Michael received AB and MMSc degrees from Harvard University (Boston, MA, USA) and an MD degree from McGill University (Montreal, QC, Canada). He completed medical training at Beth Israel Hospital (Boston), and as part of the Harvard Combined Pulmonary and Critical Care Fellowship Training Program.

In addition to clinical work in pulmonary and critical care medicine, Michael's research focuses on clinical and translational asthma, with emphasis on clinical trials in asthma, novel asthma therapies, bronchial thermoplasty, asthma pharmacogenomics and management of eosinophilic granulomatosis with polyangiitis (EGPA). He has led studies focusing on novel biological agents for asthma and related diseases, including benralizumab, dupilumab, mepolizumab, reslizumab, and tezepelumab.

Michael was a member of the Steering Committee and site Principal Investigator for the National Institutes of Health (NIH)-sponsored Asthma Clinical Research Network (ACRN; now called AsthmaNet), a multicentre asthma clinical trials consortium. He currently serves as the Principle Investigator of the Denver site of the Precision Intervention in Severe/Exacerbating Asthma (PRECISE) network.


A member of the American Society of Clinical Investigation, Michael has participated in many different task forces related to the study of eosinophilic lung diseases, sponsored by the NIH, the Food and Drug Administration (FDA), the European Respiratory Society (ERS) and the International Eosinophil Society (IES).

Michael is currently an Associate Editor of *Chest*. He has also served as Associate Editor of *Allergy* as well as on the editorial board of the *European Journal of Clinical Investigation*. Michael has published more than 250 peer-reviewed manuscripts relating to asthma, EGPA and eosinophilic lung diseases.



Introduction

David J. Jackson^{1,2}, and Michael E. Wechsler³

 @ERSpublications

This *Monograph* covers eosinophilic lung diseases, a long-standing challenge to clinicians. Recent research has increased understanding of eosinophil biology and has led to new therapeutic options, helping patients with these difficult-to-control diseases. <https://bit.ly/3mcgc21>

While eosinophils were discovered in the late 1800s, it has really only been over the last 20 years that those who treat lung disease have gained an appreciation of their importance in both health and disease. It has long been recognised that eosinophils play a role in homeostasis, defence against helminths and other infections, and are even involved in tumour immunity. However, it is their role in a variety of different diseases of the lung and other systemic disorders that has challenged clinicians for several decades. It has long been recognised that eosinophilic conditions like eosinophilic asthma, CEP, EGPA and other HESs are associated with significant morbidity and are difficult to treat. Corticosteroids have long been the mainstay of therapy and, along with other immunosuppressants, have been associated with significant morbidity in and of themselves. As we have gained a better understanding of eosinophil biology, we have also gained a better understanding of eosinophilic disorders, and over the last decade, we have finally developed effective therapies that target the eosinophil, and for the first time, are approved for treatment of these entities, revolutionising the care of our patients.

It is in this context that we set out to develop this *ERS Monograph*. So much knowledge has been gained in the last few years but unanswered questions concerning eosinophil biology still remain, including whether there are any long-term consequences of blocking eosinophil activity.

The overarching goal of this *Monograph* is to take the reader on a journey through the different eosinophilic lung diseases so that the practicing clinician is better equipped to recognise and treat patients with eosinophilia. First, however, we step back and review eosinophil biology so that the underpinnings of eosinophilic diseases and their targets can be better understood [1].

While primary eosinophilic disorders of the lung are a major focus of this *Monograph*, we recognise that there are several eosinophilic disorders that need to be excluded. From infections through malignancies to drug reactions, the chapter on the differential diagnosis

¹Guy's Severe Asthma Centre, Guy's and St Thomas' NHS Foundation Trust, London, UK. ²Faculty of Life Sciences and Medicine, King's College London, London, UK. ³National Jewish Health, Denver, CO, USA

Correspondence: David J. Jackson (david.jackson@gstt.nhs.uk)

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of pulmonary eosinophilia will ensure that the physician will not miss a key common eosinophil-related diagnosis [2].

Characterising eosinophilic patients is also critical to identifying what type of specific eosinophilic lung disease the patient has. The chapters on biomarkers [3] and imaging [4] help guide the physician through the challenges of establishing specific diagnoses.

Once these key aspects of eosinophil biology, differential diagnosis and establishing a diagnosis are better appreciated, the reader is then ready to delve into the specifics of each of the eosinophilic disorders. From eosinophilic asthma [5] to eosinophilic COPD [6], from allergic fungal airway disease [7] to eosinophilic pneumonias [8], and from HESs [9] to EGPA [10], each chapter educates the reader about these specific disorders with regard to presentation, epidemiology, disease course and finally, treatment.

The *Monograph* concludes with several important chapters that highlight the evolving complexity of eosinophils in the lungs [11–13]. What are the effects of eosinophils on the nerves? What role do eosinophils play in modulating immunity to respiratory viruses? What role do eosinophils play in driving autoimmune diseases? And what role do autoantibodies against eosinophils play in regulating tissue injury?

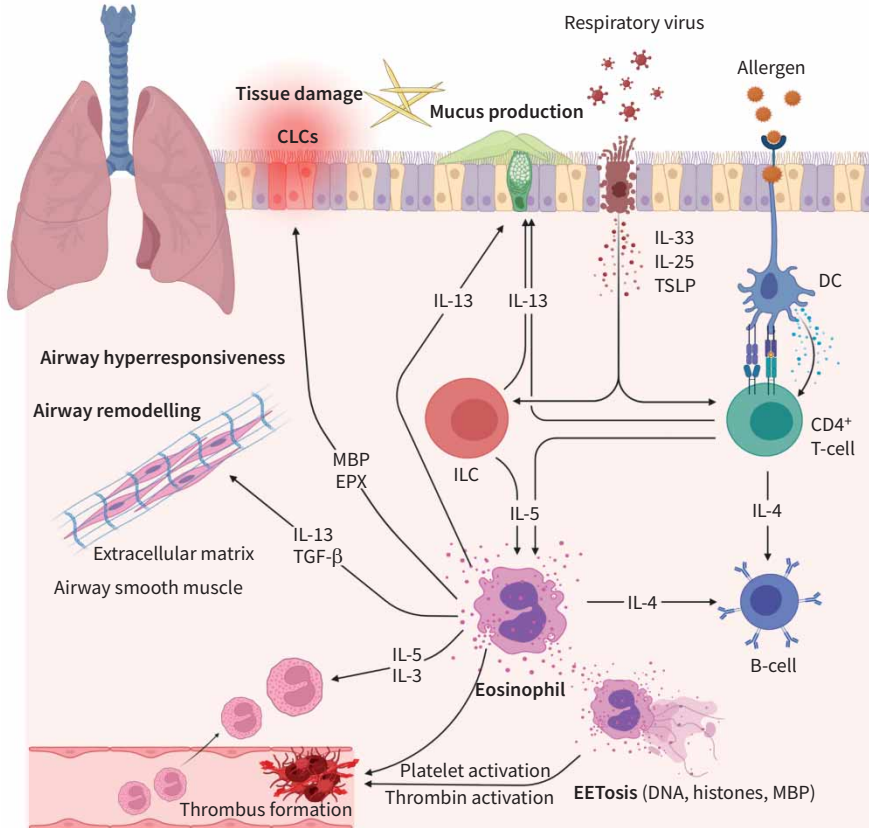


Figure 1. The multifaceted role of the eosinophil in eosinophilic lung diseases. DC: dendritic cell. Figure created using BioRender.com.

Lastly, given the increasing use of novel therapies that target IL-5 or its receptor, effectively reducing, or even eliminating blood eosinophils, we address the safety and impact of eosinophil depletion, particularly in the context of their purported important regulatory and homeostatic roles [14].

Our *Monograph* culminates with a final review of the future prospects of translational and clinical eosinophil research, including a review of eosinophil subsets and the impact of recent developments in spatial and single-cell transcriptomics [15].

Given the rapid advances in our understanding of eosinophil biology and the increased prevalence of eosinophilic lung diseases, as well as the appreciation of their morbidity, our goal is to provide an accessible one-stop compendium for those who want to engage in advanced learning about eosinophilic lung diseases. That being said, we recognise that our knowledge about eosinophils continues to evolve and that new therapies and treatment strategies will be developed. Our *Monograph* will provide the reader with the requisite background, knowledge and understanding to better appreciate the advances that will be coming in the near future, and how to apply them to all patients with eosinophilic lung diseases.

We extend our immense thanks to the authors of these chapters, who have done a stellar job. The authorship includes both world-leading authorities and up-and-coming stars in the field. We have convened a mixture of healthcare professionals and scientists, from around the world, and this has brought a diversity to the *Monograph* that is appropriate, given the global nature of the problems of eosinophilic lung diseases. We are grateful to the all the expert reviewers who gave up so much of their time to help us.

We are particularly grateful to our authors and reviewers as the *Monograph* was compiled during the COVID-19 pandemic – their efforts during such a challenging time are greatly appreciated. We would also like to thank the *ERS Monograph* team, and particularly John R. Hurst (Editor in Chief), Rachel Gozzard (ERS Monograph Managing Editor) and Caroline Ashford-Bentley (ERS Editorial and Library Services Coordinator). We have really enjoyed bringing this *Monograph* to together and we sincerely hope you will find the chapters as useful and interesting as we did.

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List of abbreviations

| | |
|-----------------|--|
| ABPA | allergic bronchopulmonary aspergillosis |
| AEP | acute eosinophilic pneumonia |
| ANCA | antineutrophil cytoplasmic antibody |
| BAL | bronchoalveolar lavage |
| CEP | chronic eosinophilic pneumonia |
| CLC | Charcot-Leyden crystal |
| COVID-19 | coronavirus disease 2019 |
| CRS | chronic rhinosinusitis |
| CRSwNP | CRS with nasal polyps |
| CT | computed tomography |
| ECP | eosinophil cationic protein |
| EDN | eosinophil-derived neurotoxin |
| EET | eosinophil extracellular trap |
| EGPA | eosinophilic granulomatosis with polyangiitis |
| EPX | eosinophil peroxidase |
| F_{ENO} | exhaled nitric oxide fraction |
| GM-CSF | granulocyte-macrophage colony-stimulating factor |
| HES | hypereosinophilic syndrome |
| ICAM | intracellular adhesion molecule |
| ICS | inhaled corticosteroid |
| IFN | interferon |
| Ig | immunoglobulin |
| IL | interleukin |
| ILC2 | type 2 innate lymphoid cell |
| MBP | major basic protein |
| MHC | major histocompatibility complex |
| OCS | oral corticosteroid |
| TGF | transforming growth factor |
| TNF | tumour necrosis factor |
| TSLP | thymic stromal lymphopoietin |
| VCAM | vascular cell adhesion molecule |