



ERS | *monograph*

# Severe Asthma

Edited by Kian Fan Chung,  
Elliot Israel and Peter G. Gibson

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Kian Fan Chung, Elliot Israel  
and Peter G. Gibson

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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# Contents

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Severe Asthma	Number 84
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Preface	v
Guest Editors	vi
Introduction	ix
List of abbreviations	xii
1. Definition and impact <i>William W. Busse</i>	1
2. Understanding the experience of people living with severe asthma <i>Vanessa M. McDonald, Erika Kennington and Michael E. Hyland</i>	16
3. The contribution of comorbidities, psychosocial factors and adherence to the presentation of severe asthma <i>Mark Hew and Liam G. Heaney</i>	30
4. Clinical phenotypes: adults <i>Tae-Bum Kim, Elisabeth H. Bel and Wendy Moore</i>	48
5. Clinical phenotypes: children <i>W. Gerald Teague and Graham Roberts</i>	64
6. Mechanisms underlying fixed airflow obstruction and exacerbations <i>Nizar N. Jarjour and Satoshi Konno</i>	82
7. Clinical biomarkers and noninvasive assessment <i>Sarah Svenningsen, Stephen J. Fowler and Parameswaran Nair</i>	93
8. Imaging <i>Salman Siddiqui, Mario Castro and Christopher E. Brightling</i>	113
9. Pathophysiology <i>Ian M. Adcock and Sharon Mumby</i>	132
10. The lessons from U-BIOPRED <i>Scott S. Wagers and Ian M. Adcock</i>	152
11. SARP: dissecting subphenotypes and endotypes <i>Deborah A. Meyers, Sally E. Wenzel and Eugene R. Bleecker</i>	167

12. Molecular phenotypes <i>Kian Fan Chung, Stelios Pavlidis and Ian M. Adcock</i>	184
13. Metabolic dysfunction <i>Anne E. Dixon and Fernando Holguin</i>	195
14. Corticosteroid responsiveness and resistance <i>Pankaj Bhavsar, Georgina Harmer, Ian M. Adcock and Kian Fan Chung</i>	211
15. Mechanisms in children <i>Joerg Mattes and Stanley Szefler</i>	231
16. Evaluation and management in children <i>Mehtap Haktanir Abul, Ahmad Salahaddine Naja, Anne Fitzpatrick, Wanda Phipatanakul and Louise Fleming</i>	246
17. Evaluation of difficult-to-treat and severe asthma in adults <i>Elliot Israel and Helen Reddel</i>	265
18. Biologics targeting type 2 inflammation <i>Ian D. Pavord, Rahul Shrimanker and Nicola A. Hanania</i>	285
19. Nonpharmacological interventions: behavioural and interventional approaches <i>Vamsi P. Guntur and Michael E. Wechsler</i>	304
20. Management in adults <i>Peter G. Gibson, Kian Fan Chung and Elliot Israel</i>	315
21. The next decade of continuing progress <i>Kian Fan Chung, Elliot Israel and Peter G. Gibson</i>	327
Case 1 <i>Anne E. Vertigan and Christopher L. Grainge</i>	334
Case 2 <i>Claire N. McBrien and Andrew Menzies-Gow</i>	338
Case 3 <i>Christopher H. Fanta</i>	342
Case 4 <i>Katarzyna Duszyk, Peter G. Gibson and Vanessa M. McDonald</i>	345



# Preface

John Hurst

Asthma is the most common chronic respiratory disease and of wide relevance to the majority of respiratory clinicians. Despite considerable research activity and clinical experience, the challenge of severe asthma remains – defined broadly as asthma that responds poorly to currently available medications. It is now 8 years since the *ERS Monograph* on Difficult-to-Treat Asthma and it has rightly proved one of our most popular editions. With the rapid pace of change in the field, it was clear that the edition needed updating and thus it is a pleasure to introduce this completely new *Monograph* on Severe Asthma. The Guest Editors, Professors Fan Chung, Elliot Israel and Peter G. Gibson have produced an excellent book that provides a state-of-the-art summary of the field, bringing the latest research findings through to clinical practice and including the patient voice. I thank them for their considerable work.



Addressing topics from definitions, mechanisms and pathophysiology, through to clinical phenotypes and management, there is truly something here to interest everyone. The authors consider both paediatric and adult disease, with example case histories. I have no doubt that this issue will be popular and well-read, and I unreservedly recommend it to all those with a clinical and/or research interest in severe asthma as a new “go to” reference work on the topic.

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**Disclosures:** John 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

Kian Fan Chung



Kian Fan Chung is Professor of Respiratory Medicine and Head of Experimental Studies at the National Heart and Lung Institute, Imperial College London (London, UK). He is also an Honorary Consultant Respiratory Physician at the Royal Brompton and Harefield NHS Trust (London, UK), and a Senior Investigator of the UK National Health Service National Institute for Health Research.

Kian Fan Chung trained in internal and respiratory medicine in London and Oxford (UK), before undertaking post-doctoral training as a Medical Research Council UK Visiting Scientist at the Cardiovascular Research Institute at the University of California San Francisco (San Francisco, CA, USA). He was awarded MD and DSc degrees in 1983 and 2001, respectively, from the University of London (London, UK).

Kian Fan Chung has a major interest in developing precision medicine for chronic obstructive airways disease. His team studies epithelial–macrophage interactions at the airway interface, the effects of mitochondrial oxidant stress, the mechanisms of corticosteroid resistance and the pulmonary impact of environmental pollution and nanoparticles.

He has received research grants from the UK Medical Research Council, the UK National Environmental Research Council, the UK Engineering and Physical Sciences Research Council, the Wellcome Trust, the European Union (EU) Innovative Medicines Initiative, EU Horizon 2020, the US National Institute of Health, the US National Institute for Environmental Health Sciences and the US Health Effects Institute.

Kian Fan Chung serves on the editorial boards of several respiratory and pharmacological journals. He has authored and co-authored more than 800 scientific articles, reviews and book chapters.

## Elliot Israel

Elliot Israel is the Gloria and Anthony Simboli Distinguished Professor in Asthma Research and Professor of Medicine at Harvard Medical School (Boston, MA, USA), and the Director of Clinical Research in the Pulmonary and Critical Care Division at the Brigham and Women's Hospital (Boston, MA, USA). He directs the Brigham and Women's Hospital Severe Asthma Program.



Elliot Israel received his medical degree from the Johns Hopkins University School of Medicine (Baltimore, MD, USA). He completed training in internal medicine at the Johns Hopkins Hospital and Weill Cornell Medical Center at the New York-Presbyterian Hospital (formerly New York Hospital; New York, NY, USA). He undertook fellowships in pulmonary and critical care medicine and allergy and immunology at Harvard Medical School. He is board-certified in allergy and immunology, pulmonary medicine, critical care medicine and internal medicine.

Elliot Israel's research interests include severe asthma, using precision medicine to optimise therapeutic interventions, pharmacogenetic influences on treatment responses, and the role of fatty acid metabolites in asthma pathobiology. He leads a US federally funded study to test novel interventions to narrow disparities in asthma outcomes. At Brigham and Women's Hospital, he is principal investigator of a USA National Institutes of Health-funded initiative to advance precision medicine using adaptive design techniques to identify novel treatments for severe asthma. He leads the protocol design committee of that initiative.

Elliot Israel has authored over 200 peer-reviewed publications and is member of the USA National Asthma Education and Prevention Program (NAEPP) Committee examining asthma guidelines. He is the recipient of the Harvard Medical School Daniel D. Federman Outstanding Clinical Educator Award.

## Peter G. Gibson

Peter G. Gibson works as a doctor who cares for people with respiratory diseases and as a clinical scientist investigating the mechanisms and treatment of asthma, COPD, cough and other airway disorders.

He is a concept leader who has developed innovative approaches around: inflammatory subtypes of asthma and cough; airway biomarkers; neurogenic mechanisms, laryngeal dysfunction and related treatments for refractory cough; multidimensional



assessment and management of complex airway disorders such as severe asthma, airways diseases in the elderly; and asthma in pregnant women.

Peter Gibson's research metrics records an *H* index of 82 (Scopus), 593 published articles and effective mentorship of clinical researchers. He has had continuous research grant funding from the National Health and Medical Research Council (NHMRC), Asthma NSW, MSRP, the Cooperative Research Centre for Asthma and Airways and a successful NHMRC Centres of Research Excellent (CRE) programme.

His peers have awarded him several research medals, including the 2018 European Respiratory Society (ERS) Gold Medal in Asthma, and elected him as the President of the Thoracic Society of Australia and New Zealand (TSANZ; 2015–2016).

His research, clinical practice and participation in guidelines panels serve to bring research developments into focus as effective healthcare interventions that improve the health of people suffering from breathing disorders.

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# Introduction

Kian Fan Chung<sup>1</sup>, Elliot Israel<sup>2</sup> and Peter G. Gibson  <sup>3,4,5</sup>

 @ERSpublications

The comprehensive *ERS Monograph* on Severe Asthma provides an update on the latest advances and future plans for severe asthma <http://bit.ly/2ZKA4N1>

Severe asthma has now been recognised as a distinct form of asthma that responds poorly to currently available medications; it is the asthma group with the greatest unmet need. Although the definition of severe asthma remains a pragmatic one, under this umbrella definition, there exist different phenotypes that can be distinguished on clinical presentation and natural history, and on certain biomarker features. In the last 10 years, substantial progress has been made in terms of understanding some of the mechanisms that drive severe asthma and with it, there has been the introduction of novel targeted therapies (particularly in the form of monoclonal antibodies that target components of the type 2 pathway) which are bringing therapeutic relief to a high number of patients with severe asthma.

In the introduction to the *ERS Monograph* on Difficult-to-Treat Severe Asthma published 8 years ago, the editors pondered the most pertinent information that had emerged in the 10 years prior to the book's publication, reflecting that: "the disease is heterogeneous, and the challenge for the next 10 years would be to understand the different types of severe asthma" [1]. In 2019, we can say that there have been significant advances in our understanding of the heterogeneous nature of severe asthma, such that new targeted treatments have been introduced for a particular phenotype of severe asthma: eosinophilic severe asthma. These advances have been made possible following the consensus agreement in 2014 on a definition of severe asthma that offers a pragmatic, bedside characterisation [2]. This basic stepping stone subsequently led to the description of clustering approaches that defined several clinical phenotypes from asthma cohorts around the world. More recently, a greater understanding of the mechanistic heterogeneity has been achieved through a precision medicine approach, with findings that have yet to be applied to the clinical problem.

This *Monograph* is comprehensive in its coverage of all aspects of severe asthma, including its definition, evaluation, epidemiology, diagnosis, pathology, treatable traits, clinical and molecular phenotypes, mechanisms, treatment and management. It captures the progress

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that has been made in the past decade with particular focus on our recent understanding of the mechanistic heterogeneity, using analysis of various ‘omics platforms and analytical methods applied to well-defined asthma cohorts. How these advances have led to improved management targets is emphasised. The final chapter of the *Monograph* looks to the future, providing a summary of what we might be expecting to occur in the next decade of severe asthma. We are of the opinion that the advances made in the next decade will result in better targeted treatments for selected groups and may pinpoint the actual causes of severity of asthma. Finally, several clinical cases of severe asthma are presented to obtain an appreciation of the clinical spectrum of the problem.

This book brings together the clinical and scientific expertise of those currently working to solve the problem of severe asthma, with chapters written by experts from around the world to ensure a truly international spirit of collaboration. It should appeal to those involved in the management of severe asthma patients, as well as to those seeking to improve quality of life and to those aiming find ways of controlling this chronic disease.

We would like to thank all of the authors of this *Monograph* for dedicating part of their busy schedule to writing these chapters. Severe asthma can have such a tremendous impact on the lives of patients. We would therefore like to dedicate this book to our patients, who have helped us focus on their greatest unmet need: to find new ways to control asthma. We hope that this *Monograph* will provide some hope for the future.

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# List of abbreviations

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<b>ABPA</b>	allergic bronchopulmonary aspergillosis
<b>ACQ</b>	Asthma Control Questionnaire
<b>BAL</b>	bronchoalveolar lavage
<b>BMI</b>	body mass index
<b>COPD</b>	chronic obstructive pulmonary disease
<b>CRTH2</b>	chemoattractant receptor homologous molecule expressed on Th2 lymphocytes
<b>CT</b>	computed tomography
<b>FeNO</b>	exhaled nitric oxide fraction
<b>FEV1</b>	forced expiratory volume in 1 s
<b>FRC</b>	functional residual capacity
<b>FVC</b>	forced vital capacity
<b>GINA</b>	Global Initiative for Asthma
<b>GM-CSF</b>	granulocyte-macrophage colony-stimulating factor
<b>ICS</b>	inhaled corticosteroid
<b>ICU</b>	intensive care unit
<b>IFN</b>	interferon
<b>Ig</b>	immunoglobulin
<b>IL</b>	interleukin
<b>ILC</b>	innate lymphoid cell
<b>LABA</b>	long-acting $\beta$ -agonist
<b>LAMA</b>	long-acting muscarinic antagonist
<b>MMP</b>	matrix metalloproteinase
<b>MRI</b>	magnetic resonance imaging
<b>NSAID</b>	non-steroidal anti-inflammatory drug
<b>OCS</b>	oral corticosteroid
<b>SARP</b>	Severe Asthma Research Program
<b>TGF</b>	transforming growth factor
<b>TNF</b>	tumour necrosis factor
<b>TSLP</b>	thymic stromal lymphopoietin
<b>U-BIOPRED</b>	Unbiased Biomarkers in the Prediction of Respiratory Disease
<b>VCD</b>	vocal cord dysfunction
<b>VOC</b>	volatile organic compound