



ERS | *monograph*

Rare Diseases of the Respiratory System

Edited by Thomas O.F. Wagner,
Marc Humbert, Marlies Wijzenbeek,
Michael Kreuter and Helge Hebestreit

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Editor in Chief
Peter M.A. Calverley

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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Preface

Peter M.A. Calverley 

Welcome to this, the 100th issue of the *ERS Monograph*. The *Monograph* is one of the European Respiratory Society's longest running publications and from its inception it has been a reliable and accessible source of authoritative, up-to-date information about all aspects of respiratory disease. Over the years, we have covered an enormous number of topics, some on several occasions. This revisiting of topics reflects the changes in understanding and progress in therapy that have occurred in our field. In this anniversary issue, we look again at the diagnostic and therapeutic problems raised by pulmonary conditions that are relatively rare but nonetheless very impactful for those who suffer from them.



Although they are individually infrequent, taken together, one or more of the wide range of disorders described in this issue is likely to crop up in clinical practice on a regular basis. Thanks to the hard work of our expert Guest Editors, led by Professor Thomas O.F. Wagner, we now have access to an excellent source of information and guidance when caring for these illnesses.

This volume is timely, not just because it marks an important milestone in the history of the *ERS Monograph* but because it allows us to celebrate the success of the European Reference Network for Rare Diseases of the Respiratory System (ERN-LUNG; <https://ern-lung.eu/>), which is itself a lesson in the value of collaboration between experts in many different countries. This is an approach very much in line with the mission of the European Respiratory Society. The contributors writing here are largely drawn from that network and the chapters they have written will engage and inform all who read them.

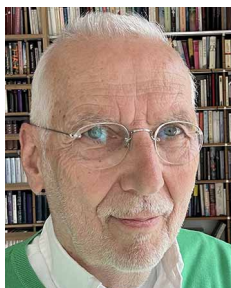
So, we have completed our first 100 issues – now on to the next 100, but not before you have sampled the many interesting topics covered herein.

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Guest Editors

Thomas O.F. Wagner



Thomas O.F. Wagner is a professor of internal medicine, and from 1997 to 2016, was Head of the Department of Pneumology and Allergology, as well as Head of the Christiane Herzog CF Center for Children and Adults, at University Hospital Frankfurt (Frankfurt, Germany). Since 2010, he has been Head of the Frankfurt University Hospital Reference Centre for Rare Diseases (Frankfurt).

Thomas received his medical and research training at Bonn University (Bonn, Germany) and Freiburg University (Freiburg, Germany), and his post-doc training at Colorado State University (Fort Collins, CO, USA) and at Medizinische Hochschule Hannover (Hannover, Germany). He is an MD, holds a PhD equivalent (Prof. Dr med. habil.) and has board qualifications in pneumology, allergology, endocrinology and intensive care medicine.

Thomas' main research activities include lung transplantation, cystic fibrosis, ventilator therapy, rare diseases, and public health issues, including the economics of healthcare. He has numerous publications and has supervised more than 25 medical dissertations.

Thomas is the Coordinator of the European Reference Network for Rare Diseases of the Respiratory System (ERN-LUNG; <https://ern-lung.eu/>). He has been a member of the European Commission (EC) Rare Diseases Task Force (EUCERD), is an active partner in the RD Joint Action and coordinates a number of European and national projects (ERN-LUNG, the RD Registry Data Warehouse, eSupport, etc.).

Since his active role in a European pilot project in RD networking (ECORN-CF), a European online expert advisory board for patients and care team members, Thomas has been heavily involved in European networking projects, bringing together patients, patient organisations and all care team members. ECORN-CF is a good example of his networking skills: after initial funding from the EC, the project is now sustainably supported by patient organisations, more than 12 years after its starting date.

Marc Humbert

Marc Humbert is Dean and Professor of Respiratory Medicine at the Université Paris-Saclay Faculty of Medicine in Le Kremlin-Bicêtre, France. He is the Director of the Respiratory and Intensive Care Medicine Department, French PH Reference Centre, Assistance Publique Hôpitaux de Paris (Le Kremlin-Bicêtre).

Marc is Past President of the European Respiratory Society (ERS). He was also Chief Editor of the *European Respiratory Journal* from 2013 to 2017 and is now the Section Editor in charge of Pulmonary Vascular Medicine.

Marc has received several distinctions, including the 2006 ERS Cournand Lecture Award, the 2009 Descartes-Huygens Award from the Royal Netherlands Academy of Arts and Sciences, the 2016 Rare Disease Award of the Fondation de France, the 2018 ERS Award for Lifetime Achievement in Pulmonary Arterial Hypertension, the Excellence 2019 Award from the Fondation du Souffle, and the 2020 American Heart Association's 3CPR (Council on Cardiopulmonary, Critical Care, Perioperative and Resuscitation) Distinguished Achievement Award.

Since 2017, Marc has been the Vice-Coordinator of the European Reference Network for Rare Diseases of the Respiratory System (ERN-LUNG; <https://ern-lung.eu>).

In 2018, Clarivate Analytics listed Marc as one of the world's most highly cited researchers in the field of clinical medicine.

Marlies Wijsenbeek

Marlies Wijsenbeek is a pulmonary physician and Professor of Interstitial Lung Diseases at the Erasmus University Medical Centre in Rotterdam, a national expert centre for interstitial lung diseases in the Netherlands and member of ERN-LUNG (the European Reference Network for Rare Lung Diseases European Reference Network for Rare Diseases of the Respiratory System; <https://ern-lung.eu>). She is Chair of the multidisciplinary ILD centre.

Marlies' research interests include e-health, patient-centred outcome measures in ILD, cough in ILD, and new therapies in ILD and sarcoidosis.

Marlies is Chair of the Idiopathic Interstitial Pneumonia Group of the European Respiratory Society (ERS), Lead of the Functional Committee for Training and Continued Medical Education of ERN-LUNG, a member of the scientific advisory board of the European Idiopathic Pulmonary Fibrosis and Related Disorders



Federation (EU-IPFF), an Associate Editor of the *European Respiratory Journal* and a member of the International Advisory Board of *Lancet Respiratory Medicine*. In 2021 she was awarded the ERS mid-career gold medal in ILD.

Michael Kreuter



Michael Kreuter is Director of the Lung Center Mainz (Mainz, Germany) and Professor of Pneumology at the University of Mainz. In this role, he is Head of the Department of Pneumology at the University Clinic Mainz, and of Pneumology and Critical Care Medicine at the Marienhaus Klinikum Mainz. He is also principal investigator of the German Centre for Lung research (Germany).

Michael is board certified in internal medicine, pulmonology and haematology-oncology. Following a clinical fellowship in Münster (Germany) and a research fellowship at Harvard Medical School (Boston, MA, USA), Michael moved to the Thoraxklinik (Heidelberg, Germany), where he has been since 2005. In 2023 he took over the academic and clinical position in Mainz.

Michael's clinical and scientific interest focuses on interstitial and rare lung diseases. He is conducting various research projects on comorbidities, epidemiology, biomarkers, and diagnosis and therapy of interstitial lung diseases. He is also committed to educational programmes and is one of the organisers of the annual European Respiratory Society (ERS) virtual school on ILD.

Helge Hebestreit






Helge Hebestreit is Professor and Vice Director of Paediatrics, Director of the Centre for Rare Diseases, and Head of Paediatric Pulmonology and of the Cystic Fibrosis Centre at the University Hospital in Würzburg (Germany). He also coordinates the Commission on Rare Diseases of the German Society of Paediatrics and is Chair of the German Working Group of the Centres for Rare Diseases.

Helge's main research interests include: health service research in rare diseases in general; and exercise as a diagnostic and therapeutic tool in people with chronic lung conditions, especially cystic fibrosis.

Helge is Lead of the Core Network for Other Rare Lung Diseases at the European Reference Network for Rare Diseases of the Respiratory System (ERN-LUNG; <https://ern-lung.eu/>).

Introduction

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Rare respiratory diseases pose a significant burden and can be challenging to diagnose and treat. This *Monograph* provides an up-to-date, comprehensive resource to the clinician, both for educational purposes and for clinical care. <https://bit.ly/ERSM100intro>

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Respiratory system disorders play a crucial role in the burden of disease and account for a huge portion of morbidity and mortality. People with rare diseases – according to the European definition, affecting not more than five in 10 000 – share symptoms and functional impairments with many more common diseases. Diagnosing these diseases can be challenging due to their rarity, and treating these conditions is complex because of often quite specific needs and treatment options.

To address this, the European Respiratory Society (ERS) has published Rare Diseases of the Respiratory System – the 100th issue of the *ERS Monograph*. The previous *Monograph* in this thematic area, entitled Orphan Lung Diseases and edited by Jean-Francois Cordier [1], was published in 2011 and needed an update.

To reflect the close collaboration of ERS with the European Reference Network for Rare Diseases of the respiratory system (ERN-LUNG; <https://ern-lung.eu/>), Thomas O.F. Wagner, was honoured to guest edit this new *Monograph* within a team of esteemed co-guest editors, since dealing with rare diseases nowadays requires networking and teamworking. This collaboration of networks has allowed for most of the recent progress made. A good example of the impact of networking on the improvement of care and research for people with rare lung diseases are the clinical trials networks. These collaborative infrastructures have fostered the development and market authorisation of many new drugs for rare diseases.

Another evolutionary change of this book compared with its predecessor is that the reviews it contains now offer a more comprehensive overview of the whole spectrum of rare diseases of

the respiratory system, providing readers with essential information about these diseases, their diagnosis and their treatment.

The book is structured into thematic sections, with significant overlap between some of the sections. The first two chapters provide an overview of how to identify rare diseases of the respiratory system and their differential diagnosis [2, 3]. The sections that follow cover rare diseases of the lung interstitium [4–7], rare diseases of the airways or alveoli [8–13], and rare pulmonary vascular diseases [14–17]. The authors of each chapter are experts in their respective fields, and they provide valuable insight into the diagnosis and treatment of rare respiratory diseases. For instance, chapter 3 discusses ILDs and covers differential diagnosis, definitions, clinical phenotype, radiological classifications and histological characterisation [4]. Section 4 covers rare diseases of the airways or alveoli, such as bronchiolitis [8] and alveolar proteinosis [9], as well as primary ciliary dyskinesia [10], cystic fibrosis [11], bronchiectasis [12] and α_1 -antitrypsin deficiency [13]. Section 5 provides a comprehensive overview of pulmonary vascular diseases, including pulmonary arterial hypertension [14], chronic thromboembolic PH [15], and PH complicating the course of other rare lung diseases [16]. The authors in this section provide clinical guidance, diagnostic and therapeutic approaches, and refer the reader to the right sources for detailed up-to-date information.

Overall, this book should constitute an excellent resource for healthcare professionals, researchers and students interested in rare diseases of the respiratory system. The authors provide comprehensive coverage of the whole spectrum of rare respiratory diseases, highlighting both the progress made in recent years and the areas where more work is needed. They also promote the idea of exchange, encouraging healthcare professionals to work together and share knowledge to improve diagnostic and therapeutic options for patients with rare respiratory diseases. Authors and editors belong to and/or support the vision and mission of ERN-LUNG. This network, funded by the European Commission in 2017, is the European information and collaboration hub offering expert support to patients and professionals and will be able to connect readers who want more detailed or specific information on any topic within the field of rare diseases of the respiratory system with the respective experts.

We are confident that Rare Diseases of the Respiratory System will prove a valuable resource for anyone interested in respiratory medicine. It provides a comprehensive overview of rare respiratory diseases, their diagnosis, and treatment, and promotes the exchange of knowledge among healthcare professionals.

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List of abbreviations

ANCA	antineutrophil cytoplasmic autoantibodies
BAL	bronchoalveolar lavage
CT	computed tomography
D_{LCO}	diffusing capacity of the lung for carbon monoxide
FVC	forced vital capacity
GM-CSF	granulocyte–macrophage colony stimulating factor
HRCT	high-resolution CT
ILD	interstitial lung disease
MRI	magnetic resonance imaging
PAS	periodic acid–Schiff
PFT	pulmonary function test/ing
PH	pulmonary hypertension