



ERS | *monograph*

COVID-19

Edited by Aurelie Fabre,
John R. Hurst and
Sheila Ramjug

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Sheila Ramjug

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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Preface

Anh Tuan Dinh-Xuan 

Even though SARS-CoV-2 can theoretically infect a variety of organs after binding to the ubiquitous ACE2 cell membrane receptor, the respiratory system is still the most frequently impacted due to the airborne nature of the infective agent. The clinical picture is very heterogeneous, but the potential for severe life-threatening conditions in adults comes from lung injury, as inflammatory processes causing airways, alveolar and vascular dysfunction and damage can lead to rapidly progressive acute hypoxaemic respiratory failure. Since its appearance in December 2019, it has become rapidly apparent that this new disease behaves very differently from previously known viral pneumonias in terms of risk factors and clinical, radiological and biological presentations. It has challenged, and continues to challenge, our knowledge whilst also urging in-depth basic research and rapidly evolving clinical guidance, both of which are mandatory to improve patient care and support public health decisions.



Adaptive mutations of the SARS-CoV-2 genome alter its pathogenic potential, which in turn increases the already significant obstacles to drug and vaccine development. As with other RNA viruses, the rate of nucleotide substitution in the SARS-CoV-2 genome is fast, and this rapid evolution is mainly shaped by natural selection. Despite the extraordinary speed of vaccine development against COVID-19 and >8 billion vaccine doses administered to date, the very recent emergence of omicron, yet another variant of concern which threatens to supersede the already dreadful delta variant, highlights the ongoing difficulties of achieving global control of the pandemic.

Nevertheless, at the time of writing in December 2021, 2 years after the pandemic outbreak, we can state that much has been learned about the pathogenesis, epidemiology and clinical management of COVID-19. No other medical condition has ever had such a “high speed” dynamic in the emergence of medical knowledge, as reflected by the unprecedented exponential rise in scientific publications over the past 2 years.

In my position as European Respiratory Society (ERS) Publications Committee Chair, I am pleased to introduce this latest issue of the *ERS Monograph*. With 15 chapters entirely dedicated to COVID-19, written by 50 leading experts in the field, it reflects the relentless efforts of the ERS and its members to add another stone to fortify the scientific compendium against past, current and future pandemic waves.

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Guest Editors

Aurelie Fabre

Aurelie Fabre is a Consultant Histopathologist and Full Clinical Professor at St Vincent's University Hospital (Dublin, Ireland) and the School of Medicine at University College Dublin (UCD) (Dublin), with a special interest in thoracic pathology (lung and cardiac). She provides national expertise on interstitial and cystic lung diseases, participating in various multidisciplinary meetings. She is an active member of the UCD lung research group, supervises research projects and collaborates with national and international groups on lung fibrosis and COVID-19 research.



Aurelie was Chair of the European Respiratory Society (ERS) Group for Molecular Pathology and Functional Genomics (2018–2021). She is a member of various ERS task forces: genetics in pulmonary fibrosis; the ERS/European Society for Thoracic Surgeons (ESTS)/European Society for Radiotherapy and Oncology (ESTRO)/European Society of Radiology (ESR)/European Society of Thoracic Imaging (ESTI) statement on management of incidental findings from low-dose CT screening for lung cancer; the ERS/European Alliance of Associations for Rheumatology (EULAR) guidelines on connective tissue disease-associated interstitial lung disease (ILD); and the ERS task force on optimising experimental research in respiratory diseases. She is also a member of the Irish Thoracic Society (ITS) lung fibrosis ILD/idiopathic pulmonary fibrosis subgroup.

John R. Hurst

John R. Hurst is Professor of Respiratory Medicine at University College London (London, UK), where he has worked since 2007. He has a particular research and clinical interest in COPD but, like most respiratory healthcare professionals, he found himself facing the clinical challenge of acute and later post-COVID-19 as waves of the pandemic unfolded from the first quarter of 2020. He is Chief Editor of the *ERS Monograph*.



Sheila Ramjug





Sheila Ramjug is a Consultant Pulmonologist with a specialist interest in pulmonary vascular and interstitial lung disease, working in Wythenshawe Hospital, Manchester University NHS Foundation Trust (Manchester, UK).

She obtained her first consultant position at the start of the COVID-19 pandemic and due to her previous cardiothoracic intensive care experience, she initially worked in the COVID-19 intensive care unit, after which she transitioned to care for patients on the acute COVID-19 wards. During this time, Sheila had the opportunity to develop local venous thromboembolism guidance in COVID-19 in relation to national and international standards, as well as reviewing discharged COVID-19 patients with evidence of venous thromboembolism.

Sheila is part of the *ERS Monograph* editorial board as the previous early career member representative for the Pulmonary Vascular Disease Assembly of the European Respiratory Society.



Introduction

Aurelie Fabre ¹, John R. Hurst ² and Sheila Ramjug³



@ERSpublications

The COVID-19 *ERS Monograph* details the immense achievement of the respiratory community in this evolving area. It offers a comprehensive understanding of the virus, its pathological consequences, potential long-term sequelae, and current best practice. <https://bit.ly/3Efam73>

In March 2020, Sheila distinctly remembers sitting in a hospital lecture theatre in Lausanne, Switzerland, for a European Respiratory Society (ERS) masterclass on pulmonary vascular disease, where the course facilitator announced, “it is unfortunate that the Chinese delegates are unable to attend”. This was the last face-to-face conference Sheila attended. At the time of writing, 265 million people had been affected worldwide by the COVID-19 virus and 5.2 million people had died.

At the start of the pandemic, there was an overwhelming amount of information, especially on social media, about: the different methods countries were employing to help reduce transmission of the virus; asymptomatic carriers; which countries had the lowest rates of morbidity and mortality; and the best strategies to help manage patients with COVID-19. For clinicians, in the initial stages of the pandemic, it seemed very unnatural to be relying solely on supportive measures, without evidence-based, disease-modifying interventions. There was an eagerness for knowledge and to be informed of other health professionals’ experiences with this unknown entity.

This *Monograph* is a reflection of the immense work the respiratory and wider medical community has achieved in this ever-evolving area. It aims to give the reader a comprehensive understanding of the virus itself, its pathological consequences, current best clinical practice, and the potential long-term consequences not only for the patient but for society as a whole, concluding with strategies to combat the virus.

The first section of the *Monograph* explores the history of coronavirus [1], the virus itself [2], its effects upon the immune system [3] and the pathological consequences of infection [4]. Coronaviruses are a common cause of upper respiratory tract infections, particularly in children. Historically though, it was not until 2002 (with SARS-CoV-1) and again in 2012 (with MERS) that the virus developed severe and potentially lethal capabilities. The COVID-19 virus is a positive-sense, single-stranded RNA virus. Both the innate and adaptive immune system are affected by the virus, but it is an impaired host immune response that is

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associated with more severe forms of the disease. By exploring the immunological responses, the reader will understand the deleterious effects of a maladaptive immune response to COVID-19 and how various pathways can be targeted for therapies such as immune modulation (for example, IL-6 inhibitors), as well as vaccine development (for example, spike protein).

With COVID-19 infection, a variable pathological process occurs in the lung. In those who are critically ill, it is now well-established from *post mortem* examinations that the lungs have evidence of diffuse alveolar damage with lymphoid infiltration of the interstitium and capillary or arteriolar microthromboses. In those with less respiratory compromise, this is reflected in the lung tissue by lymphocytic-type pneumonia with atypical hyperplasia of type II pneumocytes.

Describing the variety of patterns of lung injury helps respiratory teams appreciate the likely severity of the disease, the benefits of suggested therapeutics and the potential long-term consequences, such as lung fibrosis in those who have been ventilated for longer periods.

Another fundamental chapter of this *Monograph* is the patient perspective, which presents the powerful narrative of a COVID-19 survivor [5]. They detail their hospital experience in the general ward as well as in the ICU. At the start of the pandemic, many advocated early intubation and some clinicians were reticent to consider high-flow oxygenation or noninvasive measures for respiratory support, partly due to the fear of aerosolisation of the COVID-19 virus. More recent observational studies have demonstrated the utility of high-flow oxygenation and perhaps even noninvasive therapy to help reduce the need for invasive ventilation [6]. Proning has been a central part of our supportive therapy for awake and ventilated patients, and thanks to trial data [7–11], we are now equipped with therapeutics [12].

The rapid response to the virus in terms of the design and swift implementation of large international clinical trials to ascertain the effects of differing therapeutics was a major accomplishment and success [13]. Barriers that prevented collaborative work disappeared, and respiratory scientists and clinicians around the world worked as one. Currently, we are able to offer: dexamethasone, which RCTs have shown to have mortality benefits; remdesivir, an anti-viral drug that inhibits viral RNA transcription; and tocilizumab and sarilumab, which are monoclonal antibodies that block the IL-6 receptor, thus instigating a reduction in pro-inflammatory cytokines [7–11, 14].

With the advent of large, adaptive platform trials, recommendations have been made pertaining to the role of therapeutic *versus* prophylactic anticoagulation in COVID-19 patients [15]. The suggestion is that therapeutic anticoagulation should be strongly considered in moderately unwell general ward patients with a low risk of bleeding. Patients receiving high-flow oxygenation, NIV or invasive ventilation should, conversely, be offered prophylactic anticoagulation.

For those who survive COVID-19, there is emerging evidence of the persistence of diverse symptoms after the acute phase of the disease. These enduring symptoms may be respiratory in nature but many patients also suffer from extra-respiratory post-COVID sequelae. This chapter of the *Monograph* offers a comprehensive guide to post-COVID sequelae, together with the rationale and benefits of rehabilitation in this typically younger cohort of patients, in order to support their return to being productive members of society [16].

Predictably, the COVID-19 pandemic has had a detrimental effect on society, not only on the physical health of some of those significantly affected but also upon mental and economic

health. Health inequalities in society in terms of viral transmission, access to healthcare as well as the ability to access digital health have also never been as apparent [17].

The final chapter is written by Professor Anita K. Simonds, the ERS President during part of the pandemic. The chapter covers the development of COVID-19 vaccines. It details how it was possible for vaccines to be developed rapidly using prior knowledge of coronaviruses and existing vaccines, alongside immense collaborative work [18].

We would like to thank all invited authors and reviewers for their willingness to make time in their busy clinical and research schedule to write and review each chapter published in this *Monograph*, and for the high quality of their content thanks to their knowledge of the field.

The COVID-19 pandemic has devastated our way of life and some have sorrowfully experienced their loved ones and colleagues losing their lives or livelihood to the virus. We believe COVID-19 survivors are a testament to the phenomenal work of the global medical and scientific communities who, in these unprecedented times, have come together to openly share findings and discuss potential therapies to combat the virus. This edition of the *Monograph* is dedicated to the entire respiratory community, and serves as a testament to their endeavours and sacrifices that have allowed us to acquire so much knowledge about a new disease in such a short space of time.

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List of abbreviations

ACE	angiotensin-converting enzyme
AGP	aerosol-generating procedure
ARDS	acute respiratory distress syndrome
CPAP	continuous positive airway pressure
CRP	C-reactive protein
CT	computed tomography
DVT	deep vein thrombosis
F_{iO_2}	fractional inspired oxygen
FVC	forced vital capacity
HCoVs	human coronaviruses
HFNC	high-flow nasal cannula
ICU	intensive care unit
IFN	interferon
IL	interleukin
LDH	lactate dehydrogenase
LMWH	low-molecular-weight heparin
MERS	Middle East respiratory syndrome
MERS-CoV	MERS coronavirus
NIV	noninvasive ventilation
PPE	personal protective equipment
PTSD	post-traumatic stress disorder
RCT	randomised controlled trial
SARS	severe acute respiratory syndrome
SARS-CoV-1	SARS coronavirus
SARS-CoV-2	SARS coronavirus 2
S_{pO_2}	oxygen saturation
TNF	tumour necrosis factor
WHO	World Health Organization