ERS | monograph

Introduction

Aurelie Fabre [1], John R. Hurst [2] and Sheila Ramjug[3]

@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

[1]Dept of Histopathology, St Vincent's University Hospital and School of Medicine, University College Dublin, Dublin, Ireland. [2]Centre for Inflammation and Tissue Repair, University College London, London, UK. [3]Respiratory Medicine, Wythenshawe Hospital, Manchester University NHS Foundation Trust, Manchester, UK.

Correspondence: Sheila Ramjug (sheilaramjug@hotmail.com)

 Print ISBN: 978-1-84984-148-1. Online ISBN: 978-1-84984-149-8. Print ISSN: 2312-508X. Online ISSN: 2312-5098.

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

 https://doi.org/10.1183/2312508X.10017521

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 devasted 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.

References

1. Hui DS, Zumla A. Historical perspective: other human coronavirus infectious diseases, SARS and MERS. *In*: Fabre A, Hurst JR, Ramjug S, eds. COVID-19 (ERS Monograph). Sheffield, European Respiratory Society, 2021; pp. 28–38.
2. O'Reilly S, Angeliadis M, Murtagh R, *et al.* Drug repurposing and other strategies for rapid antiviral development: lessons from the early stage of the pandemic. *In*: Fabre A, Hurst JR, Ramjug S, eds. COVID-19 (ERS Monograph). Sheffield, European Respiratory Society, 2021; pp. 39–68.
3. Abdelhafeez S, Doherty D. Can the immune system be targeted to treat COVID-19? *In*: Fabre A, Hurst JR, Ramjug S, eds. COVID-19 (ERS Monograph). Sheffield, European Respiratory Society, 2021; pp. 69–85.
4. Copin M-C, Gibier J-B, Hofman V, *et al.* Lung pathology. *In*: Fabre A, Hurst JR, Ramjug S, eds. COVID-19 (ERS Monograph). Sheffield, European Respiratory Society, 2021; pp. 86–100.
5. Amati F, Vigni A, Misuraca S, *et al.* Respiratory failure: a patient's perspective and clinical cases. *In*: Fabre A, Hurst JR, Ramjug S, eds. COVID-19 (ERS Monograph). Sheffield, European Respiratory Society, 2021; pp. 1–13.
6. Perkins GD, Ji C, Connolly BA, *et al.* An adaptive randomized controlled trial of non-invasive respiratory strategies in acute respiratory failure patients with COVID-19. *medRxiv* 2021; preprint [https://doi.org/10.1101/2021.08.02.21261379].
7. RECOVERY Collaborative Group, Horby P, Lim WS, *et al.* Dexamethasone in hospitalized patients with Covid-19. *N Engl J Med* 2021; 384: 693–704.
8. Beigel JH, Tomashek KM, Dodd LE, *et al.* Remdesivir for the treatment of Covid-19 – final report. *N Engl J Med* 2020; 383: 1813–1826.
9. Wang Y, Zhang D, Du G, *et al.* Remdesivir in adults with severe COVID-19: a randomised, double-blind, placebo-controlled, multicentre trial. *Lancet* 2020; 395: 1569–1578.
10. RECOVERY Collaborative Group. Tocilizumab in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial. *Lancet* 2021; 397: 1637–1645.
11. REMAP-CAP Investigators, Gordon AC, Mouncey PR, *et al.* Interleukin-6 receptor antagonists in critically ill patients with Covid-19. *N Engl J Med* 2021; 384: 1491–1502.
12. Ananth S, Aujayeb A, Brosnahan SB, *et al.* Management in the ICU. *In*: Fabre A, Hurst JR, Ramjug S, eds. COVID-19 (ERS Monograph). Sheffield, European Respiratory Society, 2021; pp. 124–143.
13. Abo-Leyah H, Chalmers JD. Clinical trials during the pandemic: research design and lessons. *In*: Fabre A, Hurst JR, Ramjug S, eds. COVID-19 (ERS Monograph). Sheffield, European Respiratory Society, 2021; pp. 214–231.

14. Khan N, Lamb L, Moores R. Clinical features and acute management in adults. *In*: Fabre A, Hurst JR, Ramjug S, eds. COVID-19 (ERS Monograph). Sheffield, European Respiratory Society, 2021; pp. 101–123.
15. ATTACC Investigators, ACTIV-4a Investigators, REMAP-CAP Investigators, *et al.* Therapeutic anticoagulation with heparin in noncritically ill patients with Covid-19. *N Engl J Med* 2021; 385: 790–802.
16. Gramegna A, Mantero M, Amati F, *et al.* Post-COVID-19 sequelae. *In*: Fabre A, Hurst JR, Ramjug S, eds. COVID-19 (ERS Monograph). Sheffield, European Respiratory Society, 2021; pp. 180–196.
17. Lui LMW, Lee Y, McIntyre RS. Economic, physical and social determinants of health during lockdown: a call for renewed societal responses. *In*: Fabre A, Hurst JR, Ramjug S, eds. COVID-19 (ERS Monograph). Sheffield, European Respiratory Society, 2021; pp. 232–243.
18. Simonds AK, Boyton RJ. Vaccines: immunology, regulation and clinical management. *In*: Fabre A, Hurst JR, Ramjug S, eds. COVID-19 (ERS Monograph). Sheffield, European Respiratory Society, 2021; pp. 244–260.

Disclosures: A. Fabre has nothing to declare. J.R. Hurst reports receiving the following, outside the submitted work: support to attend meetings, and payment for educational and advisory work, both to him and his employer (University College London, London, UK), from pharmaceutical companies that make medicines to treat respiratory disease. S. Ramjug reports receiving the following, outside the submitted work: honoraria from Janssen and Bayer.

 https://doi.org/10.1183/2312508X.10017521