Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

scaffold for intravascular thrombus formation. It might also cause thrombotic microangiopathy in the microvasculature due to increased platelet–vessel wall interaction, as a consequence of the release of high-molecular-weight multimers of von Willebrand factor that are insufficiently cleaved by deficient ADAMTS13.

A marked relationship exists between broncho-alveolar coagulation and fibrinolysis, and the development of ARDS, in which intrapulmonary fibrin deposition as a result of deranged bronchoalveolar fibrin turnover is a crucial step. The clinical and laboratory picture of ARDS in ventilated patients with COVID-19 and important coagulation abnormalities suggests a potential role for bronchoalveolar fibrin turnover in the most severe disease.

As local and systemic immunothrombosis seem to have a central role in pulmonary and extrapulmonary vascular complications in COVID-19, therapeutic intervention in this process seems rational.[12] Besides general anti-inflammatory strategies (eg, dexamethasone), anti-IL-6 approaches have proved to be effective, as reviewed in this Series by Federico Angriman and colleagues.[8] Antithrombotic prophylaxis is another approach that might be beneficial. In a retrospective study of 449 patients who were admitted to hospital with severe COVID-19, mortality was lower in those who received prophylactic heparin than in patients who did not receive anticoagulant treatment;[13] among participants with more extensive coagulopathy, mortality was lower in heparin-treated patients. In fact, ample evidence exists to support the use of prophylactic low-molecular-weight heparin for the prevention of venous thromboembolism in all critically ill patients. Although the hypercoagulable state and the increased risk of thrombosis in patients with severe COVID-19 suggest that higher doses of heparin might be beneficial, this was not shown in a large randomised controlled trial,[14] and higher doses of heparin were associated with more haemorrhagic complications. Ongoing large, randomised studies—eg, REMAP-CAP (EudraCT 2015-002340-14) and RECOVERY (2020-001113-21)—are investigating the addition of antiplatelet agents to the antithrombotic regime.

We declare no competing interests.

Marcel Levi, Michiel Coppens
m.m.levi@amsterdamumc.nl

Department of Vascular Medicine, Amsterdam Cardiovascular Sciences, Amsterdam University Medical Centers, University of Amsterdam, Meibergdreef 9, 1105AZ Amsterdam, Netherlands (ML); University College London Hospitals NHS Foundation Trust, Department of Medicine, and Cardiometabolic Programme—National Institute for Health Research UCLH/UCL Biomedical Research Centre, London, UK (ML, MC)

1 McGonagle D, Bridgewood C, Meaney J. A tricompartmental model of lung oxygenation disruption to explain pulmonary and systemic pathology in severe COVID-19. *Lancet Respir Med* 2021; published online May 17. https://doi.org/S2213-2600(21)00213-7.
2 Osuchowski MF, Winkler MS, Skirecki T, et al. The COVID-19 puzzle: deciphering pathophysiology and phenotypes of a new disease entity. *Lancet Respir Med* 2021; published online May 6. https://doi.org/S2213-2600(21)00218-6.
3 Levi M, Thachil J, Iba T, Levy JH. Coagulation abnormalities and thrombosis in patients with COVID-19. *Lancet Haematol* 2020; **7:** e438–40.
4 Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *Lancet* 2020; **395:** 1054–62.
5 Lippi G, Plebani M, Henry BM. Thrombocytopenia is associated with severe coronavirus disease 2019 (COVID-19) infections: a meta-analysis. *Clin Chim Acta* 2020; **506:** 145–48.
6 Di Minno A, Ambrosino P, Calcaterra I, Di Minno MND. COVID-19 and venous thromboembolism: a meta-analysis of literature studies. *Semin Thromb Hemost* 2020; **46:** 763–71.
7 Damiani S, Fiorentino M, De Palma A, et al. Pathological post-mortem findings in lungs infected with SARS-CoV-2. *J Pathol* 2021; **253:** 31–40.
8 Angriman F, Ferreyro BL, Burry L, et al. Interleukin-6 blockade in patients with COVID-19: placing clinical trials into context. *Lancet Respir Med* 2021; published online April 27. https://doi.org/10.1016/S2213-2600(21)00139-9.
9 McElvaney O, Curley G, Rose-John S, McElvaney NG. Interleukin-6: obstacles to targeting a complex cytokine in critical illness. *Lancet Respir Med* 2021; published online April 16. https://doi.org/10.1016/S2213-2600(21)00103-X.
10 Varga Z, Flammer AJ, Steiger P, et al. Endothelial cell infection and endotheliitis in COVID-19. *Lancet* 2020; **395:** 1417–18.
11 Gralinski LE, Bankhead A, Jeng S, et al. Mechanisms of severe acute respiratory syndrome coronavirus-induced acute lung injury. *mBio* 2013; **4:** e00271-13.
12 Bonaventura A, Vecchié A, Dagna L, et al. Endothelial dysfunction and immunothrombosis as key pathogenic mechanisms in COVID-19. *Nat Rev Immunol* 2021: **21:** 319–29.
13 Tang N, Bai H, Chen X, Gong J, Li D, Sun Z. Anticoagulant treatment is associated with decreased mortality in severe coronavirus disease 2019 patients with coagulopathy. *J Thromb Haemost* 2020; **18:** 1094–99.
14 INSPIRATION Investigators. Effect of intermediate-dose vs standard-dose prophylactic anticoagulation on thrombotic events, extracorporeal membrane oxygenation treatment, or mortality among patients with COVID-19 admitted to the intensive care unit. *JAMA* 2021; **325:** 1620–30.

Non-invasive respiratory support strategies in COVID-19

Published **Online**
April 16, 2021
https://doi.org/10.1016/S2213-2600(21)00168-5

In hospitalised patients with COVID-19, an increase in oxygen requirements prompts the clinician to decide how and when to escalate treatment. A key treatment goal is to avoid, where possible, the need for invasive mechanical ventilation. However, up to 20% of hospitalised patients in the UK require admission to critical care units, and around 40% of those requiring invasive mechanical ventilation for

COVID-19 pneumonitis do not survive.[1] To date, the only treatments that have been shown to reduce the need for invasive mechanical ventilation are dexamethasone and interleukin-6 blockade.

Non-invasive respiratory support strategies, such as continuous positive airway pressure (CPAP) or high-flow nasal oxygen (HFNO), are attractive treatment options that might avoid the need for invasive mechanical ventilation and its inherent risks. In the context of COVID-19, concern has been raised that these strategies might cause harm to patients through delays to tracheal intubation or exacerbation of lung injury, to health-care workers through nosocomial infection, and to health-care systems through the high oxygen demand of devices.

This uncertain balance of harms and benefits has resulted in marked variation in international practice. A survey of 1132 participants across 85 countries used a case vignette of a previously healthy patient with severe hypoxaemia;[2] choice of initial oxygen strategy included HFNO (47%), CPAP or non-invasive ventilation (26%), and immediate tracheal intubation (7%), with remaining respondents opting to optimise conventional oxygen therapy.[2] Variability in practice was associated with country, hospital rurality, intensive care unit bed availability, and individual clinician characteristics.

There is a paucity of high-quality evidence for non-invasive respiratory support strategies in COVID-19. One multicentre, randomised controlled trial (RCT)[3] reported no difference in respiratory support-free days in 109 patients with COVID-19 and moderate to severe hypoxaemia who were treated with either helmet non-invasive ventilation or high-flow nasal oxygen, although a limitation of this study was the absence of a control group receiving standard oxygen therapy management. Other direct evidence remains limited to retrospective case series and cohort studies with inconsistent findings and the inherent risk of bias associated with observational study design.[4–6] For example, a retrospective study[6] reported failure rates of 66% in patients with COVID-19 receiving CPAP, and high mortality (55%) in those requiring invasive mechanical ventilation after CPAP failure. Evidence for HFNO, CPAP, and non-invasive ventilation as effective treatments for acute hypoxaemic respiratory failure is drawn from populations of patients without COVID-19. For example, a systematic review and network meta-analysis[7] concluded that non-invasive ventilation delivered by both helmet and mask interface reduced the risk of all-cause mortality and tracheal intubation, and that HFNO reduced the need for tracheal intubation. However, patient populations in included studies were those presenting with community-acquired pneumonia. COVID-19 is a novel disease and generalising data from other causes of acute hypoxaemic respiratory failure is inherently problematic.

In patients with viral influenzae and other coronaviruses, high failure rates of non-invasive ventilation in excess of 70% have been reported,[8] such that CPAP or HFNO might serve only to delay, rather than avoid, tracheal intubation. A concern regarding non-invasive ventilation use in patients with more compliant lungs is the potential for large tidal volume breathing to cause patient self-induced lung injury, which has a similar pathogenesis to ventilator-induced lung injury. However, the converse argument is that liberal use of tracheal intubation and mechanical ventilation in COVID-19 is likely to increase ventilator-associated complications and mortality.[9]

The risk of nosocomial COVID-19 transmission to health-care workers delivering non-invasive respiratory support strategies centres on potential aerosol generation. Early evidence from mechanistic evaluations of aerosol and droplet spread suggested that the risks of non-invasive strategies are comparable to standard oxygen therapy. Generation of aerosols might be influenced by the device, settings, and interface, but also by patient characteristics, such as viral load or coughing profile. However, the absence of substantive evidence does not indicate an absence of risk. Further research is needed to understand the risk to both health-care workers and other patients.

International guidelines on the management of acute hypoxaemic respiratory failure and the use of non-invasive respiratory strategies in the context of COVID-19 are prolific (appendix pp 1–3). In the UK, clinicians might be informed by recommendations from NHS England and the respiratory and intensive care–anaesthesia communities, as well as global organisations. Across guidelines, there is marked variability in transparency of development, process of synthesising evidence, and recommended approach. For example, in November, 2020, NHS England (appendix p 1) recommended CPAP as the preferred form of

See Online for appendix

non-invasive respiratory support in COVID-19 and advised against HFNO use on the basis of perceived absence of efficacy, oxygen use, and potential infection transmission to health-care workers, although this guidance is under review by NICE. By contrast, Surviving Sepsis Campaign guidelines (appendix p 1) support the use of HFNO, although they acknowledge that the strength of this recommendation is weak and based on low-certainty evidence.

WHO guidance (appendix p 1) adopts a balanced recommendation, including the use of all non-invasive respiratory support strategies, justified by the inadequate evidence base for any individual approach. Others, including the Australia and New Zealand Intensive Care Society, have moved away from a previous position of favouring one strategy over another, and now base their recommendations on living guidelines (appendix p 2) that suggest decisions regarding non-invasive respiratory support be based on risk assessment of the individual patient and health-care setting, with an emphasis on reducing the risk of infection transmission to health-care workers.

RCTs are urgently needed to evaluate the effectiveness of non-invasive respiratory support strategies in patients with COVID-19. At present, clinical practice is driven by personal preference and influence, prior experience, and the local availability of methods in the context of oxygen supplies. But against this backdrop of uncertain evidence on the safety, effectiveness, and optimal approach for management of acute hypoxaemic respiratory failure, it is essential for clinicians to demonstrate equipoise and randomise patients into available clinical trials in their health-care jurisdictions. For example, there have been a number of reports of pneumomediastinum and pneumothorax in patients with COVID-19 receiving either standard oxygen therapy or non-invasive respiratory support.[10] These reports are a cause for concern, although they are confounded by many unmeasured factors owing to their observational nature. Because non-invasive respiratory support is being used as part of usual care in many settings with no evidence of absence of harm, such reports further support the need for RCTs of non-invasive respiratory support in patients with COVID-19 compared with standard care. Clinical trials of non-invasive respiratory support should exclude patients with a contraindication to non-invasive support and ensure that data on harms, such as incidence of pneumomediastinum and pneumothorax, are reported.

By far the largest trial in this area is the UK RECOVERY-Respiratory Support trial,[11] funded and prioritised by the National Institute for Health Research as an urgent public health study. This adaptive, multicentre RCT evaluates the effectiveness of HFNO or CPAP against standard oxygen therapy across hospitalised patients with COVID-19 and acute hypoxaemic respiratory failure, with a primary outcome of tracheal intubation or mortality within 30 days of randomisation. As of April 12, 2021, more than 1200 patients had been randomly assigned, and enrolment to the trial features in two UK guidance pathways (appendix p 1).

During a pandemic, when the demand for critical care resources exceeds the available capacity,[12] use of non-invasive respiratory support in an individual patient in the absence of established evidence might be viewed as the only possible treatment, particularly if there is no option to participate in a clinical trial. However, where there are no critical care capacity issues and options to participate in a clinical trial exist, clinicians should be mindful that provision of this treatment outside the rigorous infrastructure of RCTs represents random empirical care. If one of these interventions is shown to be beneficial, this approach will have delayed answering the urgent clinical question at hand. If an intervention shows no favourable effect (or worse, harm), clinicians will need to justify their continued use of that unproven treatment as part of usual care rather than within a trial framework, as well as their decision to deny patients the opportunity to participate in nationally prioritised research. Understanding the most effective non-invasive respiratory support strategy in COVID-19 requires investigation of the relative benefits and harms to both the patient and the wider health-care system, which can only be addressed through randomisation to clinical trials.

All authors are responsible for the conduct and delivery of the RECOVERY-Respiratory Support trial, funded by the National Institute for Health Research (NIHR) and referenced in this Comment. BC reports educational fees from Fisher & Paykel, and her institution receives funds from NIHR for a trial in critically ill patients with acute respiratory failure; she is a Director of Research for the Intensive Care Society. GDP reports grants from the NIHR. DFM reports personal fees from consultancy for GlaxoSmithKline, Boehringer Ingelheim, Bayer, Novartis, and Eli Lilly, and from sitting on a data monitoring and ethics committee for a trial undertaken by Vir Biotechnology. DFM's institution has received grants from several funders for studies in patients with acute respiratory distress syndrome and COVID-19; in addition, he has a patent (US8962032) issued to his institution for a treatment for inflammatory disease. DFM is a Director of Research for the Intensive Care Society and

Programme Director of the NIHR Efficacy and Mechanism Evaluation programme.

*Ellen Gorman, Bronwen Connolly, Keith Couper, Gavin D Perkins, *Daniel F McAuley*
d.f.mcauley@qub.ac.uk

Wellcome–Wolfson Institute for Experimental Medicine, Queen's University Belfast, Belfast BT9 7BL, UK (EG, BC, DFM); Critical Care Unit, University Hospitals Birmingham NHS Foundation Trust, Birmingham, UK (KC, GDP); Warwick Clinical Trials Unit, Warwick Medical School, University of Warwick, Coventry, UK (KC, GDP); Regional Intensive Care Unit, Belfast Health and Social Care Trust, Belfast, UK (DFM)

1 Docherty AB, Harrison EM, Green CA, et al. Features of 20 133 UK patients in hospital with covid-19 using the ISARIC WHO Clinical Characterisation Protocol: prospective observational cohort study. *BMJ* 2020; **369:** m1985.
2 Azoulay E, de Waele J, Ferrer R, et al. International variation in the management of severe COVID-19 patients. *Crit Care* 2020; **24:** 486.
3 Grieco DL, Menga LS, Cesarano M, et al. Effect of helmet noninvasive ventilation vs high-flow nasal oxygen on days free of respiratory support in patients with COVID-19 and moderate to severe hypoxemic respiratory failure: the HENIVOT randomized clinical trial. *JAMA* 2021; published online March 25. https://doi.org/10.1001/jama.2021.4682.
4 Ashish A, Unsworth A, Martindale J, et al. CPAP management of COVID-19 respiratory failure: a first quantitative analysis from an inpatient service evaluation. *BMJ Open Respir Res* 2020; **7:** e000692.
5 Demoule A, Vieillard Baron A, Darmon M, et al. High-flow nasal cannula in critically ill patients with severe COVID-19. *Am J Respir Crit Care Med* 2020; **202:** 1039–42.
6 Arina P, Baso B, Moro V, et al. Discriminating between CPAP success and failure in COVID-19 patients with severe respiratory failure. *Intensive Care Med* 2021; **47:** 237–39.
7 Ferreyro BL, Angriman F, Munshi L, et al. Association of noninvasive oxygenation strategies with all-cause mortality in adults with acute hypoxemic respiratory failure: a systematic review and meta-analysis. *JAMA* 2020; **324:** 57–67.
8 Esquinas AM, Egbert Pravinkumar S, Scala R, et al. Noninvasive mechanical ventilation in high-risk pulmonary infections: a clinical review. *Eur Respir Rev* 2014; **23:** 427–38.
9 Tobin M. Basing respiratory management of COVID-19 on physiological principles. *Am J Respir Crit Care Med* 2020; **201:** 1319–20.
10 Elhakim TS, Abdul HS, Pelaez Romero C, Rodriguez-Fuentes Y. Spontaneous pneumomediastinum, pneumothorax and subcutaneous emphysema in COVID-19 pneumonia: a rare case and literature review. *BMJ Case Rep* 2020; **13:** e239489.
11 Perkins GD, Couper K, Connolly B, et al. RECOVERY-Respiratory Support: respiratory strategies for patients with suspected or proven COVID-19 respiratory failure; continuous positive airway pressure, high-flow nasal oxygen, and standard care: a structured summary of a study protocol for a randomised controlled trial. *Trials* 2020; **21:** 687.
12 Coppadoro A, Benini A, Fruscio R, et al. Helmet CPAP to treat hypoxic pneumonia outside the ICU: an observational study during the COVID-19

Challenges and opportunities to end tuberculosis in the COVID-19 era

Published **Online** March 24, 2021 https://doi.org/10.1016/S2213-2600(21)00161-2

On World Tuberculosis Day, 2020, we warned of the impending impact of COVID-19 on the tuberculosis pandemic. We also made a plea that the world must not forget tuberculosis while it focused on COVID-19.[1]

1 year later, on World Tuberculosis Day, 2021, we reflect on the compelling evidence of the challenges that COVID-19 has created for tuberculosis control and look forward to opportunities for integrated strategies to address the COVID-19 and tuberculosis pandemics.

We are not on course to eliminate tuberculosis. The Stop TB Partnership estimates that the past 12 months have pushed back global tuberculosis progress by 12 years.[2] Achieving the WHO's End TB Strategy goals will require an estimated US$15 billion additional funding annually. Less than half of the funding commitments made at the 2018 UN High Level Meeting on tuberculosis have been delivered. Cuts to the UK overseas Official Development Assistance will further contribute to this shortfall.

COVID-19 has challenged health systems and restricted essential health service delivery.[3] Health system infrastructure, from diagnostic tools to the workforce, has pivoted towards COVID-19 and away from competing illnesses, including tuberculosis.[4] Health-care access has been constrained due to transport disruptions, restricted movement, reduced opening hours, depleted staffing levels, fear, and stigma.[5]

In nine countries with a high tuberculosis burden, which contribute 60% of the world's tuberculosis cases, tuberculosis diagnosis and treatment decreased by 23%, equating to 1 million missed cases. Similar to the 2014–15 Ebola virus disease outbreaks, restricted access to health care has led to an increase in late, disseminated presentations of tuberculosis, associated with adverse treatment outcomes and death.[2] Indeed, the COVID-19 pandemic is predicted to increase tuberculosis deaths globally by 20% over the next 5 years.[6]

These challenges to tuberculosis diagnosis, notification, care, and cure, are especially concerning in the context of global antimicrobial resistance. Despite multidrug-resistant (MDR) tuberculosis being estimated to contribute up to one third of deaths from antimicrobial resistance globally, the minority of people with MDR tuberculosis have access to all-oral treatment regimens. Long, toxic regimens involving intravenous or intramuscular injections remain the mainstay in many