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.

Although the STOIC study showed that inhaled budesonide treatment reduced the relative risk of clinical deterioration by 91%, this finding was not replicated in the PRINCIPLE trial.[6,10] In that prospective study, inhaled corticosteroids in older patients (aged ≥65 years or ≥50 years with comorbidities) shortened the time to self-reported recovery by 2·94 days, but did not reach significance in terms of preventing hospitalisation or death.[10] The cohort studied by Baker and colleagues are, by comparison, younger (mean age 45 years), but the reasons for the different conclusion are unclear. Of note, both studies included few participants with asthma (15% in the STOIC study[6] and 13% in the PRINCIPLE trial[10]), the typical users of inhaled corticosteroids.

An important question remains. How might delivery of budesonide to the lower respiratory tract affect the nasal mucosa and the outcome of COVID-19? Although Baker and colleagues[5] show that type 2 inflammatory mediators are reduced after budesonide treatment, the differences in individual mediators were not large nor were they present in both the plasma and nasal samples. Notably, Baker and colleagues[5] did not assess the lower respiratory tract where we might expect to see greatest changes. It is possible that the changes found by Baker and colleagues[5] in the nasal mucosa and plasma might represent only a small fraction of more distinct changes occurring in the lower respiratory tract, and that these changes in the lower respiratory tract affect the outcome of COVID-19. Assessment of the lower airway is not always possible in clinical studies of this type but would be useful to bring clarity to these findings.

The findings of Baker and colleagues[5] represent an important step towards improving our understanding of how local immune responses drive disease outcome in COVID-19, highlighting the need to consider treatments that target mucosal and systemic responses. Although the study provides evidence that inhaled budesonide might be beneficial in some cases of early COVID-19, further research is needed to understand exactly how this effect is mediated and which patients might benefit most.

PJMO reports grants from the EU Innovative Medicines Initiative (IMI) 2 Joint Undertaking during the submitted work; grants from UK Medical Research Council, EU-IMI, UK National Institute for Health Research, and UK Research and Innovation-Department for Business, Energy and Industrial Strategy; and personal fees from Pfizer, Nestle, Janssen, and Sequris, outside the submitted work. FL declares no competing interests.

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The pandemic and the great awakening in the management of acute hypoxaemic respiratory failure

Published **Online** March 16, 2022 https://doi.org/10.1016/S2213-2600(22)00051-0

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The ability to provide invasive mechanical ventilation (IMV) and high-quality, supportive intensive care was substantially limited during the peak of the pandemic because of the unprecedented demand for intensive care unit (ICU) resources. As a result, clinicians turned towards less invasive and innovative approaches to manage patients with acute hypoxaemic respiratory failure. Techniques such as awake prone positioning of non-intubated patients, a seemingly simple approach that was largely only tested in observational studies before

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the pandemic, were used.[1] The positive physiological benefits of prone positioning seen in patients on IMV, such as improved oxygenation, homogenisation of transpulmonary pressure, decreased lung compression, and improved ventilation–perfusion matching,[2] prompted adjunctive use of awake prone positioning as a strategy to avoid IMV and ICU admission in patients with COVID-19-related acute hypoxaemic respiratory failure.

In *The Lancet Respiratory Medicine*, Li and colleagues[3] report the findings of a systematic review and meta-analysis investigating the effects of awake prone positioning in non-intubated patients with COVID-19-related acute hypoxaemic respiratory failure. Awake prone positioning significantly reduced the need for intubation with a trial-sequential analysis projecting a relative risk reduction of 16%. However, awake prone positioning did not reduce mortality and ICU admission rates. Furthermore, awake prone positioning only reduced the need for intubation among patients requiring advanced respiratory support (high-flow nasal cannula or non-invasive ventilation) and in those who underwent awake prone positioning in an ICU setting. The authors hypothesise that these results might be due to a higher incidence of intubation in this homogeneous group of patients contributing greater statistical power and precision, and better health-care worker to patient ratios in the ICU, leading to better patient adherence with awake prone positioning. Given that some studies were terminated early, the aggregation of the current data through meta-analysis and trial-sequential analysis will help inform clinicians about the potential benefits and harms of awake prone positioning.

However, there are some questions that arise from these findings: should all patients with COVID-19-related acute hypoxaemic respiratory failure receive awake prone positioning, and should it only be performed in an ICU setting? Given that these patients have significant hypoxaemia and limited physiological reserve, awake prone positioning in patients requiring advanced respiratory support should ideally be performed in an ICU to minimise the risks to the patient. However, this should be balanced with resource-allocation issues such as ICU bed availability and staffing. This calls for an integrated, multidisciplinary team approach and the development of clear management pathways for patients with acute hypoxaemic respiratory failure, in which early, adjunctive awake prone positioning is part of the continuum of care along with other respiratory supports and agreed criteria for ICU admission and IMV. Two factors might partly account for the absence of mortality benefit in the RCT analysis: first, a low statistical power given the low event rate; second, confounding by the timing of intubation. Defining the timepoint when the risks of combining less-invasive respiratory supports and awake prone positioning to delay endotracheal intubation and IMV outweigh the benefits of avoiding IMV in an individual patient is challenging.[4]

How should we design meaningful clinical trials to inform the management of patients with acute hypoxaemic respiratory failure in non-intubated, heterogeneous groups of patients with or without COVID-19? The absence of a research grade definition for acute hypoxaemic respiratory failure, the complexity of developing universally agreed triggers for IMV, and developing core outcome measures that look beyond the need for intubation and mortality are all substantial limitations to designing clinical trials. Although it is challenging, we should consider devising a syndromic definition based on a constellation of validated clinical criteria to risk stratify acute hypoxaemic respiratory failure resulting from a variety of causes. This all encompassing approach might facilitate clinical trials, but it might also reduce the ability of clinicians to personalise supportive care. We should consider the following approaches in regard to clinical trials that investigate the adjunctive use of awake prone positioning in patients with acute hypoxaemic respiratory failure. There appears to be a dose–response association between awake prone positioning and treatment success;[5] selecting patients with better adherence to treatment protocols and creating an environment that promotes such adherence might increase the treatment effect. Equally, selecting patients with a higher risk of the outcome of interest—eg, those requiring advanced respiratory support—and excluding those in whom there is poor early improvement in oxygenation following awake prone positioning might enable further enrichment of trials.[6,7]

The intention of avoiding endotracheal intubation and IMV with the use of less-invasive respiratory supports and awake prone positioning should not be driven by resource constraints alone. These supports might be a viable option, especially in patients who are unlikely to benefit from IMV. Even in non-pandemic times, IMV

adds substantial costs to health care,[8] and the risk–benefit ratio of IMV varies considerably with age, comorbidities, and baseline functional status. It is time that we looked beyond short-term survival and define which populations of patients with acute hypoxaemic respiratory failure are most likely to meaningfully benefit from IMV. In addition to drawing from the evidence base, engagement with patients is central to making this decision.

The pandemic has certainly allowed us to reimagine the future management of acute hypoxaemic respiratory failure. There are many approaches clinicians can take to delay IMV or avoid IMV altogether. The risk–benefit ratio and the costs of this approach requires investigation in clinical trials. The majority of patients with acute hypoxaemic respiratory failure who receive IMV do so because of worsening hypoxaemia and respiratory muscle fatigue from an increased work of breathing.[9] In addition to awake prone positioning, pharmacological adjuncts such as nitric oxide gas, which were introduced in attempt to improve oxygenation in non-intubated patients during the pandemic, need further testing in clinical trials. Environmental modifications, staff education, patient compliance, and the pharmacological management of anxiety and agitation are all critical components to the success of awake strategies that aim to avoid IMV. Minimising the reliance on the diseased native lungs for gas exchange with the use of extracorporeal techniques merits consideration too. For example, extracorporeal carbon dioxide removal might allow better control of respiratory effort and in select patients might help prevent IMV. Awake extracorporeal membrane oxygenation[10] without IMV might be a viable option in select patients. Moving forward, although IMV is inevitable in some patients, there might be room for better integration and greater personalisation of respiratory supports that allow patients to be awake, ambulatory, and rehabilitate while maintaining their autonomy.

A concerted, collaborative undertaking of research across disciplines is needed to tackle acute hypoxaemic respiratory failure globally. Inequities in health-system access is morally confronting. Future acute hypoxaemic respiratory failure research should also focus on low-cost, high-value respiratory supports, such as awake prone positioning, which are tailored for resource poor settings. Hopefully, in the post-pandemic world, we will be one step closer to offering more personalised, equitable, value-driven, and evidence-based respiratory supports for patients with acute hypoxaemic respiratory failure.

We declare no competing interests. KS acknowledges research support from Metro North Hospital and Health Service.

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Ending the tuberculosis syndemic: is COVID-19 the (in)convenient scapegoat for poor progress?

Tuberculosis is a syndemic. Elimination requires a syndemic approach that addresses the individual and societal vulnerabilities that determine whether we become infected, get sick, die, or get better with disability and an impact on livelihoods.[1] The WHO End TB Strategy, a global initiative launched in 2015,

Published **Online** March 23, 2022 https://doi.org/10.1016/S2213-2600(22)00123-0