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.

acute inhalation lung injury, along with the presence of vacuolisation of macrophages and pneumocytes, and most importantly the detection of vitamin E acetate in BAL fluid, provide important diagnostic clues for this condition.

We declare no competing interests.

Mikhail Kazachkov, Melodi Pirzada
Mikhail.kazachkov@nyulangone.org

Department of Pediatrics, NYU Langone Health, New York, NY 10016, USA (MK); and Department of Pediatrics, NYU Winthrop Hospital, Mineola, NY, USA (MP)

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Dexamethasone in hospitalised patients with COVID-19: addressing uncertainties


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The impressive results of the RECOVERY trial established that a moderate dose of dexamethasone (6 mg daily for 10 days) reduced mortality in hospitalised patients with COVID-19 and respiratory failure who required therapy with supplemental oxygen or mechanical ventilation.[1] The data also indicated that dexamethasone might increase mortality in hospitalised patients who were not receiving oxygen. This landmark trial and the subsequent practice guidelines from several academic and health organisations recommending dexamethasone use in patients with severe COVID-19 have changed clinical practice for hospitalised patients on supplemental oxygen or mechanical ventilation.[2] These favourable findings are supported by three other trials[3–5] of glucocorticoids for COVID-19, which stopped enrolment in early June, 2020, when the RECOVERY trial results were released. Each of these trials showed some evidence of benefit, although none had completed enrolment. A prospective meta-analysis of these and other trials, totalling 1703 participants (1007 [59%] from the RECOVERY trial), confirmed a reduction in 28-day mortality (summary odds ratio [OR] 0·66, 95% CI 0·53–0·82; p<0·001), with minimal heterogeneity across studies.[6] While confirming beneficial effects of corticosteroids for critically ill hospitalised patients with COVID-19, some unanswered questions and issues remain that deserve discussion and should be addressed in future research.

Because the design of the largest trial, RECOVERY, was pragmatic, data were scarce in some domains. For example, physicians were able to exclude patients from the trial whom they determined should not be a candidate for treatment with dexamethasone, but reasons for exclusion were not recorded. Thus, we do not know why 1707 patients were unsuitable for randomisation. Patients might have been excluded because of perceived contra-indications, including uncontrolled diabetes, acute delirium, underlying malignancy, immunosuppression, or other conditions in which corticosteroids might have harmful effects. Therefore, the benefit–risk profile of corticosteroids across the full spectrum of patients with critical COVID-19 and a range of comorbidities remains uncertain.

A second limitation of the RECOVERY trial is that no data are available on the level of oxygen support. In retrospect, this was an important omission from the database. Such data might have revealed differential benefit or harm with dexamethasone treatment according to level of oxygen supplementation.

Moreover, the need for higher levels of oxygen might have been a good indicator that severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection had caused some degree of lung injury and that these patients were likely to benefit from dexamethasone therapy.

A third limitation is that the vast majority of patients in these trials were not receiving remdesivir. Although monotherapy with remdesivir does not reduce mortality,[7,8] it is conceivable that the beneficial effects of dexamethasone in patients on supplemental oxygen or mechanical ventilation might be attenuated by the administration of an effective antiviral agent. There might also be an additive benefit of both remdesivir and dexamethasone if remdesivir enhances viral clearance and dexamethasone further decreases the injurious effects of the inflammatory responses to COVID-19.

A fourth limitation is the lack of any data on viral clearance, which is likely to be an important factor in determining harm versus benefit of dexamethasone.[9] The normal response to viral infection requires transcriptional upregulation of interferons and recruitment of host inflammatory cells, but corticosteroids in the earlier phase of viral infection can suppress host antiviral responses, potentially leading to more severe lung injury. However, if corticosteroids are administered when viral control has been achieved, they can have a beneficial effect by reducing inflammation and the severity of acute lung injury. Since most of the RECOVERY trial patients treated with oxygen support or mechanical ventilation received dexamethasone more than 7 days since sympton onset, it is possible that viral replication had declined in most patients, particularly since some evidence suggests that SARS-CoV-2 infection, unlike influenza, might be largely cleared in most patients within 7 days.[10] Nevertheless, this is an important and unmeasured variable in the RECOVERY trial.

What steps need to be taken to learn more about the effects of dexamethasone in hospitalised patients with COVID-19? More studies on viral clearance and endogenous immune responses,[11] both before and after dexamethasone administration, could provide insights into potential beneficial and harmful effects. COVID-19 mortality has been found to be related to impaired interferon responses and dysregulated endogenous proinflammatory responses,[12] variables that could be measured in circulating blood samples both before and after dexamethasone treatment. More detailed studies of dexamethasone in hospitalised patients receiving different levels of oxygen support (from low-flow oxygen to high-flow nasal oxygen), along with detailed respiratory and microbiological data, could help to determine whether the benefit of dexamethasone is dependent on the level of oxygen support and other respiratory variables. This information is needed because it is not entirely clear what level of illness should prompt treatment with dexamethasone in non-mechanically ventilated patients with COVID-19. All of these future studies are likely to include remdesivir, which could be an important cofactor that was not part of the RECOVERY trial. Finally, beneficial new therapeutics for COVID-19 are being tested, including monoclonal antibodies, anticoagulation strategies, and additional treatments to block specific arms of the inflammatory cascade, as well as additional antiviral agents. Thus, an ongoing assessment of the interaction of dexamethasone with other therapeutics will be needed as new findings emerge.

There is one more issue to be considered. Should the favourable results of the RECOVERY trial prompt a reconsideration of dexamethasone treatment for acute respiratory distress syndrome (ARDS) due to other causes? This is a key question, as recent work suggests that both classical ARDS and its major risk factor, sepsis, have identifiable subtypes with differential responses to therapy. For example, in one sepsis subtype, randomisation to corticosteroids was associated with increased mortality (OR 7·9, 95% CI 1·6–39·9; $p_{interaction}$=0·02).[13] A Spanish open-label, randomised, multicentre trial in 277 patients with moderate-to-severe non-COVID-19-related ARDS found a 15% absolute reduction in 60-day mortality (36% to 21%; p=0·0047) in dexamethasone-treated patients.[14] This study had important limitations, including the open-label design and the modest overall number of participants (the trial was stopped for low enrolment after 5 years, 2013–18). Nevertheless, we believe that it is reasonable to consider a prospective double-blind, randomised trial design for classical ARDS that will include a sufficient number of patients to be adequately powered for 90-day mortality. Because COVID-19 and classical ARDS have considerable heterogeneity, future trials should incorporate plans for both understanding heterogeneity and prospectively identifying treatment-responsive subgroups of patients.[15]

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*Michael A Matthay, B Taylor Thompson
michael.matthay@ucsf.edu

Cardiovascular Research Institute, Departments of Medicine and Anesthesia, University of California, San Francisco, CA 94143, USA (MAM); and Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA (BTT)

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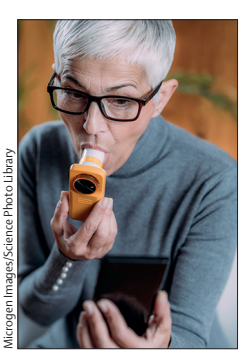
Home monitoring for patients with ILD during the COVID-19 pandemic and beyond



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The current COVID-19 pandemic has challenged the continuity of health care and research. Health-care providers around the world are required to deal with social distancing and quarantine measures, while simultaneously ensuring quality of care for their patients. Consequently, eHealth applications, such as home monitoring, have gained increasing interest during the past months. For the vulnerable population of patients with interstitial lung diseases, home monitoring could be particularly relevant. We describe experiences with home monitoring in interstitial lung diseases, the effect of COVID-19 on its use, and opportunities for more hybrid forms of monitoring.

Interstitial lung diseases are a heterogeneous group of often progressive and deadly diseases. Treatment generally consists of immunosuppression or antifibrotic treatment, and supportive measures. Regular hospital visits are required for comprehensive patient support, including monitoring disease course and response to treatment. Lung function (ie, forced vital capacity) is the most used outcome measure to guide treatment decisions, and the accepted primary outcome for clinical trials in interstitial lung disease. Hospital visits can be challenging for patients because of dyspnoea, supplemental oxygen needs, and dependency on caregivers. Furthermore, travel distances can be considerable because in many countries, care for interstitial lung disease is centralised in specialist centres. Hence, monitoring physiological parameters and symptoms at home could have advantages for both clinical practice and research.[1]

During the past 5 years, the feasibility and reliability of home monitoring and home spirometry in interstitial lung disease have been increasingly studied. Studies in idiopathic pulmonary fibrosis showed that home spirometry yielded reliable results, predicted disease progression better than did hospital spirometry, and could possibly decrease sample sizes for future trials.[2,3] A 24-week randomised controlled trial suggested that a home monitoring program tended to improve