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.

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Inhaled corticosteroids and COVID-19-related mortality: confounding or clarifying?

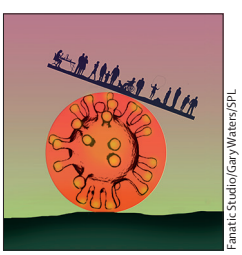
Inhaled corticosteroids (ICSs) are the mainstay of anti-inflammatory therapy for asthma and chronic obstructive pulmonary disease (COPD).[1,2] Studies have shown worse outcomes in patients with COVID-19 who have been admitted to hospital and have comorbidities including chronic lung diseases.[3–5] Whether ICSs protect against COVID-19 or contribute to worse outcomes from COVID-19 has been debated.[6,7] ICS use might reduce antiviral immunity and increase the frequency of pneumonia in patients with COPD.[8] However, ICS use reduces the frequency of exacerbations[1] and might even reduce replication of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2),[9] supporting the case for protection against COVID-19.

In *The Lancet Respiratory Medicine*, Anna Schultze and colleagues[10] use UK electronic primary care records to retrospectively interrogate associations between current ICS use (defined as a prescription within 4 months) and COVID-19-related deaths in patients with asthma and COPD. The COPD cohort (n=148 557) consisted of patients currently using ICSs and a long-acting β-agonists (LABA), with or without a long-acting muscarinic antagonist (LAMA), compared with patients using a LABA and LAMA. Although comorbidities were similar between groups, exacerbations in the previous year were more frequent in the ICS combination group, reflecting that ICSs are used in patients with exacerbations. In the asthma cohort (n=818 490), current ICS users were compared with those using short-acting β agonists (SABAs) only. The mean age, number of comorbidities, and number of exacerbations in the past year were lower in non-ICS users, indicating that between-group analyses might be confounded by baseline differences.

In the COPD cohort, ICS use was associated with an increased risk of COVID-19-related death after adjusting for relevant factors, including age and comorbidities (hazard ratio [HR] 1·39 [95% CI 1·10–1·76]). A sensitivity analysis showed that the risk of death in the COPD population was highest with ICS–LABA–LAMA (triple therapy; adjusted HR 1·43 [1·12–1·83]), and lower and non-significant with ICS–LABA (1·29 [0·96–1·74]), a difference that cannot be explained by ICS use. These sensitivity analyses suggest factors driving increased risk in the ICS combination group that are not attributable to ICS itself, including confounding by treatment indication (ie, patients prescribed triple therapy have an increased disease burden and worse prognosis). A negative control analysis supported this hypothesis, with increased risk of non-COVID-19-related death in ICS users.

In the asthma cohort, no increased risk of COVID-19-related death was found in low-to-medium dose ICS users compared with non-ICS users (adjusted HR 1·14 [95% CI 0·85–1·54]), suggesting ICS use had no bearing on COVID-19-related mortality. Schultze and colleagues found increased risk of COVID-19-related mortality in high-dose ICS users compared with non-ICS users (1·55 [1·10–2·18]), but no increase in non-COVID-19-related deaths. This result might relate to underlying disease characteristics beyond those captured in the health records, such as increased susceptibility to viral infections with more severe asthma.

Patients with asthma and COPD are understandably concerned about developing COVID-19. They are also concerned whether their medication affects their risk of becoming infected or their prognosis if they do develop COVID-19, and they look to their clinicians for answers to these questions. Does this analysis help answer their questions? We think it provides some insights, but not conclusive answers. The negative results for use of low-to-medium dose ICS in asthma and ICS–LABA in COPD argue against the hypothesis that ICS use



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See **Articles** page 1106

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increases the risk of COVID-19-related mortality. For the hypothesis that ICS use protects against COVID-19-related mortality, the results rule out a benefit large enough to overcome the effects of confounding factors, but do not completely exclude a smaller benefit.

Overall, the analysis is confounded and does not provide definitive answers that patients and clinicians need, although it hints that ICS use does not provide a strong protective effect. Similar to Schultze and colleagues, we believe that had the analysis taken into account clinical factors, such as disease severity and history of exacerbations, which might have influenced the choice of maintenance therapy, it might have reached different conclusions about possible harms. ICSs are used to reduce future risk of events including exacerbations and mortality;[1,2] therefore, ICS use inevitably identifies individuals with an increased disease burden associated with increased future risk. Analyses of associations between ICS use and COVID-19-related outcomes in real-life datasets cannot escape this issue, but the comprehensive analysis reported by Schultze and colleagues in a large sample of almost 1 million people is a valiant attempt to provide some clarity despite the confounding by treatment indication observed.

The analysis does not completely resolve whether regular ICS therapy for asthma or COPD either decreases or increases risk of death from COVID-19. This finding is in contrast with the very real harm patients requiring ICS therapy for their asthma or COPD might be at risk if they stop treatment because of unfounded concerns related to their effects in COVID-19. Until more information is available, patients with asthma and COPD who are stable while using ICS must continue on their treatment during the ongoing COVID-19 pandemic.

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ECMO for severe ARDS associated with COVID-19: now we know we can, but should we?

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See **Articles** page 1121

The initial months of the COVID-19 pandemic were dominated by studies reporting poor and varied outcomes in patients who developed severe acute respiratory distress syndrome (ARDS) associated with the disease. Variable mortality could have been related to heterogeneity in patient populations and pre-pandemic intensive care infrastructure, resource constraints imposed during the pandemic, and variability in duration of follow-up. As the pandemic has evolved, lower mortality attributable to the disease has been reported. For instance, in a cohort of 742 patients with COVID-19-associated ARDS from Spain, mortality for severe ARDS was 39%,[1] similar to findings of a large epidemiological study of patients with severe ARDS who did not have COVID-19.[2]