Inhaled corticosteroids and COVID-19: a systematic review and clinical perspective

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There is no evidence on benefits or harms of inhaled steroids in COVID-19. It is essential that epidemiological studies of COVID-19 include detailed information on comorbidities and prior medication to help answer this question. https://bit.ly/2XVwIsa

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The current coronavirus 2019 (COVID-19) pandemic, caused by severe acute respiratory syndrome-coronavirus 2 (SARS-CoV-2) infection, raises important questions as to whether pre-morbid use or continued administration of inhaled corticosteroids (ICS) affects the outcomes of acute respiratory infections due to coronavirus. Many physicians are concerned about whether individuals positive for SARS-CoV-2 and taking ICS should continue them or stop them, given that ICS are often regarded as immunosuppressive. A number of key questions arise. Are people with asthma or COPD at increased risk of developing COVID-19? Do ICS modify this risk, either increasing or decreasing it? Do ICS influence the clinical course of COVID-19? (figure 1). Whether ICS modify the risk of developing COVID-19 or the clinical course of COVID-19 in people who do not have lung disease should also be considered (figure 1).

COVID-19 has an initial period characterised by cough and fever, followed by the development of dyspnoea after around 8 days in ∼20% of patients, with pulmonary infiltrates in about 10% [1, 2]. Approximately 25% of patients admitted to hospital developed acute respiratory distress syndrome (ARDS) a median 10.5 days after symptom onset [2].

In vitro models suggest that there is impaired interferon production and other antiviral innate immune responses to experimental rhinovirus and influenza infection in both asthma and COPD, and this could potentially increase susceptibility to viral infections including COVID-19. However, not all studies have replicated these findings [3]. For instance, a study of the response of asthmatic children to natural colds, including some due to coronavirus, showed an appropriate innate response [4]. These contrasting results may reflect the heterogeneity in innate immune responses between individuals and/or variability in the response to different viruses [5].

Surprisingly, the prevalence of chronic respiratory disease among patients with SARS and COVID-19 appears to be lower than among the general population [6]. This is not the case for other chronic diseases and leads us to hypothesise that lung disease, patients' behaviour or, more likely, their treatment may have some protective effect. Sadly, patients with underlying lung disease who develop COVID-19 and are hospitalised have worse outcomes, with a case fatality rate of 6.3% compared to 2.3% overall in China [7].
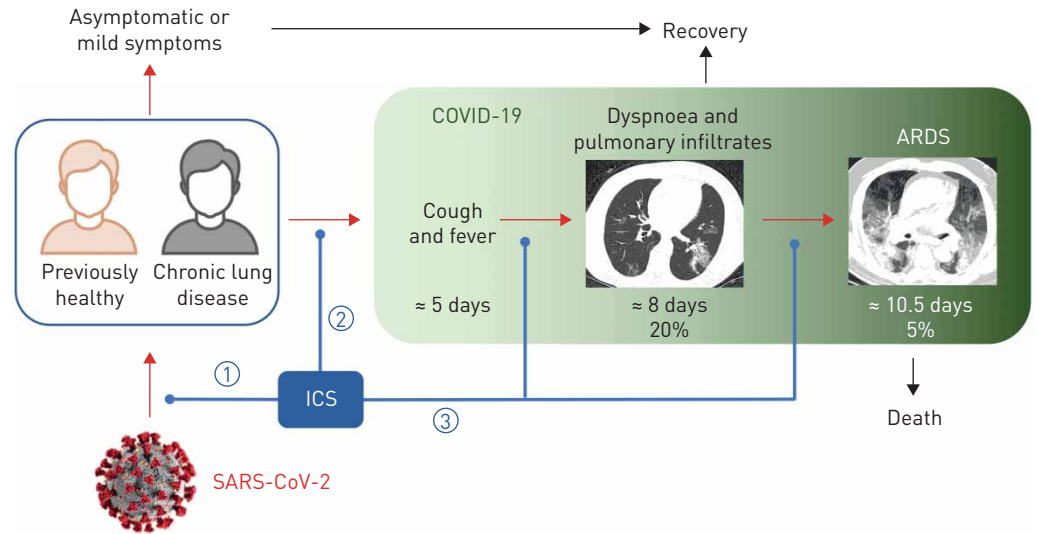
FIGURE 1 Potential steps in the development and evolution of severe acute respiratory syndrome-coronavirus 2 (SARS-CoV-2) infection that may be affected beneficially or adversely by inhaled corticosteroids (ICS). 1) Infection with SARS-CoV-2; 2) development of coronavirus 2019 (COVID-19) disease; 3) progression of COVID-19. ARDS: acute respiratory distress syndrome.

These individuals may have less reserve to cope with the pulmonary effects of severe infection or their immunopathological abnormalities may make them more susceptible to developing pulmonary inflammation and ARDS.

ICS, alone or in combination with bronchodilators, are used extensively in the treatment of asthma [8], and combined with bronchodilators have a role in the management of some patients with COPD [9]. There are a number of paradoxes about their effects on viral infections and exacerbation rates which are relevant when considering ICS use during the COVID-19 pandemic. ICS use in asthma and COPD is associated with an increased risk of upper respiratory tract infections [10, 11]. In people with COPD, ICS use is associated with a higher prevalence of pneumonia [12] and a change in the lung microbiome, although not a change in respiratory virus detection [13]. The evidence in asthma is less clear cut, but at least one observational study has shown an increased risk of pneumonia or lower respiratory infection [14]. In vitro studies have suggested that corticosteroids may impair antiviral innate immune responses [15, 16] and that ICS use leads to delayed virus clearance [17]. Other studies, however, have shown normal responses in patients on ICS [18]. It is important to note that most studies have been carried out with rhinovirus and there may be differences in the response to other viruses.

Conversely, there is evidence to suggest that taking ICS may be beneficial in dealing with virus infections, specifically those due to coronavirus. Pre-treatment of human respiratory epithelial cells in vitro with budesonide, in combination with glycopyrronium and formoterol, has inhibitory actions on coronavirus HCoV-229E replication and cytokine production [19]. Furthermore, early, not yet peer-reviewed data, suggest ciclesonide blocks SARS-CoV-2 RNA replication in vitro [20] and inhibits SARS-CoV-2 cytopathic activity [21], which may be of great relevance to reducing the risk of developing of COVID-19 in response to SARS-CoV-2 infection or reducing the severity of the disease.

ICS use undoubtedly reduces the rate of exacerbations in both asthma and COPD. If people with stable asthma stop or reduce their ICS inappropriately in response to concerns about immunosuppression and worries about developing COVID-19, they may be at significant risk of having an exacerbation. Approximately 40–60% of COPD and up to 80% of asthma exacerbations are due to viral infections, including common coronaviruses [22]. Therefore, the use of ICS must either reduce the risk of becoming infected or modify the subsequent inflammatory response and lung damage. In vitro, corticosteroids inhibit rhinovirus and respiratory syncytial virus-induced cytokine release [3] but the timing of exposure to ICS appears important with pre-treatment less effective than administration at the time of infection [23].

Self-management plans advise asthma patients to increase the dose of ICS at the onset of an exacerbation to reduce the risk of progression to a severe event and reduce the need for oral corticosteroids. In people with COVID-19, corticosteroids may theoretically modulate the inflammatory response and reduce the risk of developing ARDS. Systemic corticosteroids were widely used during previous coronavirus outbreaks

(SARS and Middle East respiratory syndrome (MERS)); however, a systematic review of published literature on their use in SARS was not able to conclude that treatment was beneficial and there was some evidence of possible harm [24]. Current interim guidance from World Health Organization on clinical management of COVID-19 advises against the use of systemic corticosteroids outside of clinical trials [25]. There is currently very low-quality evidence from a case series report from Japan of improvement in three patients with COVID-19 requiring oxygen, but not ventilatory support, after being given inhaled ciclesonide [26]. There was no control group and it is not known whether the patients would have improved spontaneously.

We undertook a rapid systematic review to evaluate whether pre-morbid use or continued administration of inhaled steroids is a risk factor for adverse outcomes in acute respiratory infections due to COVID-19, SARS or MERS. The review was conducted using the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) checklist in March 2020 [27]. We searched PubMed, EMBASE, Scopus and Google Scholar for relevant studies on (COVID-19 or SARS or MERS or coronavirus) and "corticosteroids". As it was not anticipated that there would be any randomised controlled clinical trials available for analysis, case–control, cohort studies and case series were eligible for inclusion provided data from a comparison group was available.

In total 771 publications were identified by the search strategies. The abstracts of these publications were screened by two reviewers (D.M.G. Halpin and D. Singh) and 59 publications were identified for full text review. Following examination of the full texts including translations of those in Chinese, no publications were identified as having data on prior ICS use in patients with SARS, MERS or COVID-19 infection. No data were available for either a qualitative or narrative answer to the review question.

A few studies did report the prevalence of comorbidities, including chronic respiratory disease and occasionally specifically asthma or COPD, but in general studies provided little or no information about patients' pre-morbid health or medication. Even if data on the prevalence of ICS use had been available, their interpretation would have been impossible without also having data on the severity of the underlying respiratory disease to allow adjustment for this as a confounding factor.

At present, there is no evidence as to whether pre-morbid use or continued administration of ICS is a factor for adverse or beneficial outcomes in acute respiratory infections due to coronavirus. Further data and studies are urgently needed. As a start, it is essential that epidemiological studies of COVID-19 include detailed information on patients' comorbidities and prior medication in order to allow analyses of possible benefits or harms of ICS or other therapy. Randomised controlled intervention studies are also needed to assess the benefits of ICS in treating COVID-19 in both patients with and without chronic respiratory disease. These have begun [28, 29].

At the present time in this COVID-19 pandemic, clinicians should be aware that there is no evidence to support the withdrawal of ICS in patients treated with these drugs, and to do so is likely to be harmful. Patients with asthma and COPD who are stable while using ICS should continue on their treatment. If there is uncertainty about the diagnosis, physicians should be more careful about initiating ICS or ICS/long-acting β-agonist in patients without clear objective evidence of asthma. Similarly, there is no evidence to suggest a change in the advice for asthma patients to increase the dose of ICS at the onset of an exacerbation.

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