

# Treating asthma in the COVID-19 pandemic

Ran Wang,<sup>1,2</sup> Andras Bikov ,<sup>1,2</sup> Stephen J Fowler <sup>1,2</sup>

The novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) originated from Wuhan, China, at the end of 2019 and has rapidly spread to cause a global pandemic associated with substantial morbidity and mortality.<sup>1</sup> By mid-April 2020, nearly two million confirmed cases of COVID-19 had been reported from 210 countries, resulting in over 100 000 deaths. Similar to previous novel coronavirus diseases (severe acute respiratory syndrome and Middle East respiratory syndrome), COVID-19 often leads to severe respiratory failure, and it might be assumed that patients with chronic respiratory diseases such as asthma would be at higher risk of developing severe illness. It is perhaps surprising then that, thus far, no clear association has been found<sup>2-5</sup>; asthma was reported in less than 1% of patients with COVID-19 from Wuhan,<sup>2,3</sup> and chronic airway diseases, including asthma, in 10%–13% of nearly 2400 patients hospitalised in New York City.<sup>4,5</sup> Although Williamson *et al* reported a modest increase in risk of COVID-19-related hospital deaths in asthma, this was mainly in patients recently receiving oral corticosteroids.<sup>6</sup> It seems unlikely that respiratory comorbidities would be under-reported, so what other explanations may be offered?

Shielding and self-isolation may be helping to reduce acquisition of SARS-CoV-2, but there is no reason to think this would differentially benefit those with asthma. Asthma control on a population scale may have improved, for example, due to reduced pollution, the use of face masks, better medication adherence and reduced smoking. However, it is also possible that the disease and/or its treatment may offer some protection. Whilst the expression of ACE2 in the airways is not different between asthmatic and healthy individuals, allergic sensitisation

in asthma has been associated with lower ACE2 expression in both upper and lower airways, suggesting a potential protective effect of the disease itself.<sup>7,8</sup>

Inhaled corticosteroids (ICS) are the mainstay of asthma treatment and are crucial in preventing acute exacerbations and hospitalisations and in minimising the risk of death, but whether ICS prevent viral infections per se is unclear. Most studies investigating the antiviral effects of glucocorticoids in experimental rhinovirus (RV)-induced exacerbations have found little evidence of protective effects.<sup>9</sup> In fact, preclinical data suggest that ICS may impair viral responses through the suppression of interferon-mediated innate and adaptive immunity, a possible explanation for the association of ICS with increased risk of pneumonia in chronic obstructive pulmonary disease and asthma.<sup>10,11</sup> However, a much higher risk of exacerbation is associated with ICS discontinuation. Some preclinical studies have shown antiviral effects of ICS against RV and coronavirus HCoV-229E,<sup>12,13</sup> and recent studies have suggested potential benefits specific to COVID-19 *in vitro*. For example, ciclesonide has been found to suppress the replication of SARS-CoV-2 through interaction with viral NSP15 during biogenesis, and fluticasone propionate has been identified as a potential therapeutic candidate in COVID-19.<sup>14,15</sup> The use of ICS in asthma has been associated with decreased expression of ACE2 and transmembrane protease serine 2 in sputum, suggesting ICS may reduce viral attachment and cell entry through these pathways.<sup>7</sup> Although preliminary, these data reinforce the view that the benefits of ICS treatment in asthma are likely to outweigh any potential risks. Urgent work is clearly needed to investigate any clinical effects of ICS against COVID-19.

There is little evidence for the direct effects of other asthma medications in COVID-19, and the use of systemic corticosteroids has been controversial.<sup>16</sup> Although the recent use of oral corticosteroids in asthma was associated with a higher risk of in-hospital COVID-19-related death than those who did not, this association may be reflective of poor disease control rather than the medication itself.<sup>6</sup> Therefore, optimising asthma

control, *via* optimising medication adherence, minimising the need for systemic steroids, avoidance of hospitalisation and hence (nosocomial) SARS-CoV-2 exposure, appears to be important in the protection against COVID-19.

Monoclonal antibodies are effective in optimising asthma control and reducing exacerbation rates, indirectly adding potential protective effects in severe asthma during the COVID-19 pandemic. Omalizumab (anti-IgE) has shown small but significant effects in reduction of RV infection duration, viral shedding and risks of RV illnesses in children,<sup>17</sup> but whether this is the case in COVID-19 is unknown. Little is known about the clinical effects of suppressing circulating eosinophils by anti-interleukin-5 biologics in COVID-19. Eosinophils have been implicated in antiviral immunity in preclinical studies, and eosinopaenia has been reported in over half of patients with COVID-19 and linked to poor prognosis.<sup>2,18</sup> In patients with mild asthma challenged with RV, mepolizumab did not affect clinical outcome, but a significant increase in viral shedding was observed.<sup>19</sup> The implications during the pandemic are unknown but whether accelerated efforts should be made in initiating appropriate biologics in the hope of reducing maintenance systemic glucocorticoids in severe asthmatics should be considered.

To date, there are no consistent data to suggest that well-controlled asthma is over-represented in COVID-19. Therefore, the objective of asthma management during the pandemic is centred on optimising asthma control and minimising risks of viral exposure. Along with following public health advice and social distancing, adequate asthma control *via* lifestyle changes and medication adherence must remain as the priority. Patients should be given adequate advice on risk prevention and a detailed asthma action plan with specific reference tailored to the current pandemic. The use of biological therapies can be effective in reducing the dosage of systemic corticosteroids, and it is likely that the benefit in continuing therapies outweighs any potential risks. Urgent research is needed to clarify the benefits and risks of asthma therapies during this new era.

**Twitter** Stephen J Fowler @StephenJ\_Fowler

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<sup>1</sup>Division of Infection, Immunity & Respiratory Medicine, Faculty of Biology, Medicine and Health, School of Biological Sciences, The University of Manchester, Manchester, UK

<sup>2</sup>Manchester Academic Health Science Centre and NIHR Manchester Biomedical Research Unit, Manchester University NHS Foundation Trust, Manchester, UK

**Correspondence to** Dr Stephen J Fowler, Infection, Immunity & Respiratory Medicine, The University of Manchester, Manchester, Manchester, UK; stephen.fowler@manchester.ac.uk

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#### ORCID iDs

Andras Bikov <http://orcid.org/0000-0002-8983-740X>

Stephen J Fowler <http://orcid.org/0000-0002-4524-1663>

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