

# Considerations for asthma management and viral transmission in the era of COVID-19

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## ABSTRACT

**Background:** As the global COVID-19 pandemic has unfolded, there has been much debate surrounding the optimal management of patients with asthma who are at risk of or contract COVID-19, whether asthma and steroids are risk factors for severe COVID-19, and how transmissible the virus is among children.

**Objective:** The objective of this study is to provide allergists and other clinicians with pearls pertaining to the management of patients with asthma in the setting of the COVID-19 pandemic and to provide some information regarding the risk of transmission among the pediatric population.

**Methods:** Utilizing the case of one of our own patients with asthma who developed COVID-19 as context, we review the recent literature discussing the risk of COVID-19 in patients with asthma, the management of asthma medications in the time of the pandemic, and the risk of viral transmission.

**Results:** Despite initial reports that asthma was a risk factor for developing severe COVID-19, subsequent investigation has shown that this is likely not true. Additionally, the use of systemic or inhaled glucocorticoids does not appear to increase the risk of severe COVID-19, but there is no evidence guiding the use of biologic therapy. There is conflicting evidence regarding the ability of children to transmit the virus.

**Conclusion:** We provide pearls that asthma does not appear to be associated with an increased risk of COVID-19 and continued use of inhaled corticosteroids appears to be safe. While there is no evidence guiding the use of biologic therapies, a recent position paper suggests that they should be continued unless a patient contracts COVID-19, at which point they should be held until clinical recovery occurs.

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## QUESTION

A 9-year-old boy with mild persistent asthma and allergic rhinitis develops a dry cough and headache. He has no fever or dyspnea. His medications include fluticasone 44  $\mu$ g/actuation: two puffs twice daily, montelukast 5 mg daily, and cetirizine 5 mg daily. Spirometry one month prior showed a FEV1/FVC of 90.4 (102% predicted, lower limit of normal 77.4) and a FEV1 of 1.35 L (94% predicted, lower limit of normal 1.16 L) with no bronchodilator response. The result of his nasopharyngeal polymerase chain reaction (PCR) test is positive for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). His

symptoms are mild, and he does not require the use of his rescue inhaler. How should his medications be managed?

- A. Discontinue fluticasone, continue all other medications
- B. Start a burst of oral corticosteroids
- C. Continue current medications with no changes
- D. Add a long-acting  $\beta$ -agonist
- E. Increase the inhaled corticosteroid to a moderate dose

## INTRODUCTION

There has been significant debate and investigation into whether asthma is a risk factor for coronavirus disease 2019 (COVID-19) and into how asthma medications should be managed in light of the current pandemic. In addition, there is much debate about the transmissibility of SARS-CoV-2 among children. We recently evaluated the patient discussed in the aforementioned question. His older sister and mother had both previously tested positive, ~1 week earlier, for COVID-19, with his mother being the index case in the

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family. All three recovered uneventfully at home with periodic monitoring via nurse phone calls for symptom assessment. They never developed hypoxia or required an in-person health care visit. They did not require remdesivir, systemic corticosteroids, or any other COVID-19 directed medical therapy. Approximately 2 months later, the patient was scheduled to be seen in the allergy clinic for follow-up of his asthma.

As part of our institutional protocol, he underwent repeated SARS-CoV-2 nasopharyngeal PCR testing and serum SARS-CoV-2 immunoglobulin G testing, both results were positive. He had no cough, fever, headache, diarrhea, or any other symptoms of COVID-19. The clinical significance of the positive test was unclear at the time; however, due to the presumed risk of asymptomatic viral shedding, his appointments were canceled. In light of the uncertainty surrounding this case, we aimed to review the recent literature that discusses the risk of COVID-19 in patients with asthma, the medical management of asthma during the COVID-19 pandemic, and the risk of SARS-CoV-2 transmissibility among children.

## CLINICAL CHARACTERISTICS AND PATHOPHYSIOLOGY

Although it is accepted that the clinical course of COVID-19 tends to be milder in children, there previously was significant concern that children with asthma were at higher risk of COVID-19 when a preliminary report showed that asthma was the most common comorbid condition in children with COVID-19.<sup>1</sup> However, a recent study demonstrated that asthma was not a risk factor for hospitalization in patients with COVID-19.<sup>2</sup> A recent investigation showed decreased expression of angiotensin-converting enzyme 2 (ACE2), the cellular receptor for SARS-CoV-2, in patients with allergic rhinitis and asthma with allergen sensitization but not in nonallergic asthma.<sup>3</sup> ACE2 has been shown to be upregulated in patients who are smokers, who have diabetes, or who have hypertension, all of which are associated with severe COVID-19.<sup>4</sup>

Thus, the down-regulation of ACE2 in allergic conditions may provide a mechanistic explanation for the observational data suggesting that co-morbid allergic asthma may not be a significant risk factor for severe COVID-19 infection in children.

While there are case reports of children transmitting the virus, many familial studies have suggested that this is uncommon.<sup>5,6</sup> A recent Chinese cohort study showed that familial cluster transmission was responsible for approximately 88% of pediatric infections in their cohort but noted that the main reason children were not spreading infection in their study was that they had little contact with the outside world during a period of quarantine.<sup>6</sup> In

addition, results of the recent study suggest that children are at low risk of transmitting the virus, a determination that was made largely through contact tracing that demonstrated that the children were rarely the index case when multiple family members were infected.<sup>7</sup>

However, all of these studies<sup>5-7</sup> may be reflective of the fact that adults are more likely to have been working in areas where outbreaks were occurring while children were staying home from school, as was the situation in our case. In addition, these studies<sup>5-7</sup> do not rule out the possibility that a child could spread the virus to other family members despite not being the family index case. In our case, it is difficult to know if the patient contracted the virus from his mother (the index case) or his older sister. Interestingly, a German study recently demonstrated that viral loads from nasopharyngeal swabs are as high in children as they are in adults, so it is reasonable to conjecture that the child's ability to transmit the virus is as high as the adult's ability.<sup>8</sup> More investigation is needed to truly determine the risk of viral spread among children, particularly as schools attempt to re-open.

## DIAGNOSIS

A diagnosis of COVID-19 is not different in patients with asthma compared with those without asthma. However, one interesting component of the aforementioned case is the patient's positive PCR test result 2 months after recovery from clinical disease. It was unclear at the time if this represented an infectious state, a carrier status from his previous infection, a false positive, or asymptomatic re-infection. Differentiating between these possibilities could potentially help inform the risk of transmissibility. Analysis of recent data suggests that patients can carry SARS-CoV-2 in upper respiratory secretions for up to 90 days after the initial diagnosis but that risk of transmissibility after the recommended 2-week quarantine period is extremely low.<sup>9</sup> With that in mind, our patient's positive repeated test result could have represented asymptomatic carriage, with a low risk of transmissibility. It is now not recommended to repeat SARS-CoV-2 testing in individuals who are asymptomatic and who have recovered from clinical disease within 90 days of the initial diagnosis (which was often done to "clear" patients of infectious risk before spirometry, follow-up appointments, *etc.*) due to the risk of a positive result of unclear clinical significance that creates diagnostic confusion. Additionally, false positive PCR tests can occur given that the test measures viral particles as opposed to intact, infectious virus. Re-infection has been reported and could have been the source of our

patient's repeat positive PCR, but this is unlikely given his lack of symptoms and quarantine at home in the two months between tests.<sup>9,10</sup> Serum SARS-CoV-2 IgM could have helped delineate this possibility further, but as previously mentioned was not assessed in this case.

## MANAGEMENT

The management of COVID-19 includes supportive care and use of a variety of medical therapies depending on comorbidities and disease severity. There has been concern over how to manage patients with asthma who may be at risk of or contract COVID-19, with particular concern over the use of steroids. Initial guidance from the WHO was to avoid corticosteroid use in suspected COVID-19 due to concern that inhibition of antiviral interferons would lead to increased viral replication, but subsequent clinical trials have shown lower 28 day mortality in patients with COVID-19 requiring intubation or supplemental oxygen who were treated with dexamethasone.<sup>11,12</sup> Patients with asthma are known to have increased baseline Th2 inflammation that is increased further by viral infection, which decreases production of anti-viral interferons.<sup>11</sup> Treatment with corticosteroids decreases Th2 inflammation which could secondarily help restore production of anti-viral interferons in patients with asthma.<sup>11</sup> This mechanism provides justification for continued use of steroids in asthmatics during the COVID-19 pandemic, as does a recent study that showed that the use of systemic or inhaled corticosteroids in patients with asthma was not associated with COVID-19 associated hospitalization.<sup>2</sup> Current treatment guidelines recommend continuing inhaled corticosteroids in asthmatics who contract COVID-19.<sup>13,14</sup> The alternative of discontinuing could lead to the development of uncontrolled asthma, which could increase risk of adverse outcomes in COVID-19. The aforementioned link between corticosteroids, Th2 inflammation, and anti-viral interferons may also suggest a potential benefit to systemic corticosteroid use in asthmatics who develop COVID-19, although no trial has specifically addressed this to date. It should be noted that our patient never developed hypoxia, and thus would not qualify for systemic corticosteroids based on prior clinical trials and treatment guidelines.

There has been no study assessing the risk of contracting COVID-19 or developing severe disease in patients with asthma treated with FDA approved biologics including omalizumab (anti-IgE), mepolizumab (anti-IL-5), reslizumab (anti-IL-5), benralizumab (anti-IL-5 receptor), and dupilumab (anti-IL4 receptor alpha). To help guide clinicians given the lack of evidence based information, the European

Academy of Allergy and Clinical Immunology recently released a position statement suggesting that these medications should be continued in patients unless they contract COVID-19, at which point they should consider being paused until clinical recovery occurs.<sup>15</sup>

## Correct Answer

C. Continue current medications with no changes

## Pearls

- Allergic asthma does not seem to be associated with an increased risk of severe COVID-19
- Inhaled corticosteroids should be continued in patients with asthma who contract COVID-19 because their use has not been associated with COVID-19-related hospitalization

## Pitfalls

- Repeating SARS-CoV-2 testing within 90 days of recovery from previous COVID-19 is not recommended even in patients who may be undergoing routine spirometry because positive tests in that time frame may represent noninfectious carriage
- There is no current evidence to guide the use of biologic therapy in patients with asthma during the COVID-19 pandemic

## REFERENCES

1. CDC COVID-19 Response Team. Coronavirus disease 2019 in children-United States, February 12-April 2, 2020. *MMWR Morb Mortal Wkly Rep.* 2020; 69:422-426.
2. Chhiba KD, Patel GB, Vu THT, et al. Prevalence and characterization of asthma in hospitalized and non-hospitalized patients with COVID-19. *J Allergy Clin Immunol.* 2020; 146:307-314.e4.
3. Jackson DJ, Busse WW, Bacharier LB, et al. Association of respiratory allergy, asthma and expression of the SARS-CoV-2 receptor ACE2. *J Allergy Clin Immunol.* 2020; 146:203-206.e3.
4. Brake SJ, Barnsley K, Lu W, et al. Smoking upregulates angiotensin-converting enzyme-2 receptor: a potential adhesion site for novel coronavirus SARS-CoV-2 (Covid-19). *J Clin Med.* 2020; 9:841.
5. Chan JF-W, Yuan S, Kok K-H, et al. A familial cluster of pneumonia associated with the 2019 novel coronavirus indicating person-to-person transmission: a study of a family cluster. *Lancet.* 2020; 395:514-523.
6. Zhen-Dong Y, Gao-Jun Z, Run-Ming J, et al. Clinical and transmission dynamics characteristics of 406 children with coronavirus disease 2019 in China: a review. *J Infect.* 2020; 81:e11-e15.
7. Lee B, Raszka WV Jr. COVID-19 transmission and children: the child is not to blame. *Pediatrics.* 2020; 146:e2020004879
8. Jones TC, Muhlemann B, Veith T, et al. An analysis of SARS-CoV-2 viral load by patient age. *Research Network Zoonotic*

- infectious diseases. 2020. Available online at [https://zoosen.charite.de/fileadmin/user\\_upload/microsites/m\\_cc05/virologie-ccm/dateien\\_upload/Weitere\\_Dateien/analysis-of-SARS-CoV-2-viral-load-by-patient-age.pdf](https://zoosen.charite.de/fileadmin/user_upload/microsites/m_cc05/virologie-ccm/dateien_upload/Weitere_Dateien/analysis-of-SARS-CoV-2-viral-load-by-patient-age.pdf); accessed August 20, 2020.
9. Park YJ, Choe YJ, Park O, et al. Contact tracing during coronavirus disease outbreak, South Korea, 2020. *Emerg Infect Dis.* 2020; 26:2465–2468. <https://dx.doi.org/10.3201/eid2610.201315>.
  10. To KK, Hung IF, Ip JD, et al. COVID-19 re-infection by a phylogenetically distinct SARS-coronavirus-2 strain confirmed by whole genome sequencing. *Clin Infect Dis.* 2020. Available at <https://doi.org/10.1093/cid/ciaa1275>.
  11. Tillet R, Sevinsky J, Hartley P, et al. Genomic evidence for a case of reinfection with SARS-CoV-2. *SSRN.* 2020. Available at SSRN: <https://ssrn.com/abstract=3680955>.
  12. Kumar K, Hinks TSC, Singanayagam A. Treatment of COVID-19 exacerbated asthma: should systemic corticosteroids be used? *Am J Physiol Lung Cell Mol Physiol.* 2020; 318(6):L1244–L1247.
  13. Horby P, Lim WS, Emberson JR, et al. Dexamethasone in hospitalized patients with Covid-19-Preliminary report. *N Engl J Med.* 2020. Available at: <https://www.nejm.org/doi/10.056/NEJMoa2021436>.
  14. Bellanti JA. The role of the allergist/immunologist in the COVID-19 pandemic: A Janus-faced presentation. *Allergy Asthma Proc.* 2020. Doi: 10.2500/aap.2020.41.200072.
  15. Vultaggio A, Agache I, Akdis CA, et al. Considerations on biologicals for patients with allergic disease in times of the COVID-19 pandemic: an EAACI statement. *Allergy.* 2020; 75: 2764-2774. □