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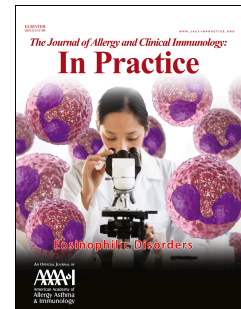
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COVID-19 Infections and Asthma

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39 Abstract (word count: 190)

40 The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and coronavirus disease  
41 (COVID-19) has infected over 200 million and led to the deaths of over 4.3 million people. While  
42 there are known risk factors for severe disease, asthma was initially hypothesized to be a risk  
43 factor for severe disease given the association between asthma exacerbations and respiratory  
44 viral illnesses in general. Fortunately, clinical outcomes for patients with asthma overall are  
45 similar to patients without asthma, without convincing evidence that asthma is a risk factor for  
46 severe disease. This may be explained in part by the decreasing gradient of angiotensin-  
47 converting enzyme-2 (ACE2) receptor from the upper to lower respiratory epithelium and that  
48 aeroallergen sensitized asthmatics can have up to 50% reduction in ACE2 receptor expression.  
49 Vaccination for patients with asthma is recommended for all without clear contraindications.  
50 COVID-19 specific treatment options are available depending on the severity of disease, we  
51 caution the use of systemic corticosteroids in asthmatic patients not requiring supplemental  
52 oxygen given an association with worse outcomes. Post-acute COVID-19 syndrome or long-  
53 haul COVID does not appear to be more prevalent in the asthma population, a multi-disciplinary  
54 approach to care is a reasonable option.

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and coronavirus disease (COVID-19) has infected over 200 million and led to the deaths of over 4.3 million people. (1) There are well established risk factors associated with severe disease and increased mortality such as older age, race, gender, obesity, hypertension, cardiovascular disease, and chronic obstructive pulmonary disease. (2-4) Given the propensity for respiratory viral illnesses to cause asthma exacerbations it was initially postulated that patients with asthma would be at higher risk for both infection and severe COVID-19 disease. (5) Despite this abundance of data for non-covid respiratory viruses, several groups have noted a reduction in overall asthma exacerbation rates during periods of social lock-down. (6-9) In this article we will discuss the clinical outcomes of patients with asthma who acquire infection, the influence of asthma and its comorbidities on SARS-CoV2-2 receptor expression and risk of COVID-19 infection, the safety and efficacy of the COVID-19 vaccinations and discuss how to differentiate between asthma related symptoms and residual covid-19 symptoms in patients with asthma who have recovered from COVID-19.

#### Clinical outcomes of patients with asthma who acquired SARS-CoV2 Infection

Respiratory viral illnesses are well known to be important causes of asthma exacerbations, in particular human rhinoviruses; these illnesses are a major contributor to asthma morbidity, need for acute care, and mortality.(5) Given this association there was reasonable concern regarding patients with asthma and their susceptibility for COVID-19 and their subsequent outcomes. The CDC initially declared asthma to be a risk factor for severe disease and currently still warns that patients with moderate to severe or uncontrolled asthma are more likely to be hospitalized from COVID-19 as of September 2021.(10) The prevalence of asthma in the initially described Wuhan cohort was relatively low, suggestive that asthma may not be a risk factor for severe disease, however, there was subsequent data suggesting a higher prevalence of asthmatics with covid-19 compared to the general population. (3, 11, 12) Subsequent data from the first few months of the

pandemic had conflicting results regarding asthma as a risk factor for severe disease with some reports supporting this theory and others supportive of asthma not being a risk factor for severe disease. (12-17) In the subsequent time since the beginning of the pandemic more robust data regarding both pediatric and adult outcomes have been published.

Asthma currently affects approximately 7 percent of the pediatric population in the United States, making it one of the most common pediatric chronic illnesses and it has been similarly represented in US pediatric cases of covid 19, though admittedly the data is limited worldwide. (18) Recent data supports that there is no increased risk in children with asthma infected with COVID-19 with regards to severity of disease. Ruano et al reported that there were no differences in lung function, need for oral corticosteroids, emergency care, or hospitalizations for pediatric asthmatics with and without COVID-19, though it was noted that in patients with probable COVID-19 there was increased use in controller and symptom reliever treatment.(19) This was independent of asthma severity or control in the last year., though the increased use of controller and symptom reliever therapy suggests possible COVID-19 induced exacerbations. (19) Beken et al reported that in children with asthma, with or without concurrent allergic diseases was not associated with an increased risk of hospitalization for COVID-19.(20) Additionally, there is the impact of COVID-19 on availability of medical services for asthmatic children with there being a clear reduction of in-person visits and new consultations. (21)Despite this there is clear evidence that during the pandemic there have been decreases in pediatric asthma related hospitalizations, emergency department visits, exacerbations, albuterol and oral corticosteroids use without increased adherence to controller therapy suggestive of improved asthma outcomes during this time period. (20, 21)There is a similar increase in telemedicine visits as well as decrease in influenza and particulate matter air population over this time period. (20)

There have been multiple studies demonstrating that there is no increased risk in general between adult patients with asthma and severe COVID-19 infection. (22-27) However, there may

exist a subset of patients in the asthma population, those with less-than-optimal control, who are at more risk for severe disease. Huang et al demonstrated that adult asthmatics who required clinical care in the previous 12 months prior to COVID-19 diagnosis were at increased risk of severe disease, conversely those who did not receive clinical care were not at increased risk for severe disease. (28) Additionally there is data to support that COVID-19 infection may not induce a severe exacerbation requiring oral corticosteroids or inhaled bronchodilators in asthmatic patients. (24) This is further supported as the prevalence of asthma in patients with COVID-19 is similar to the reported general population worldwide, and in some areas lower. The data suggests that asthma may in fact be a protective factor in COVID-19 infection for a variety of proposed mechanisms including: the differences in  $T_H2$  inflammation, decreased expression of angiotensin-converting enzyme, and use of inhaled corticosteroids in asthmatic patients. (22, 27, 29, 30) Adult asthma patients with COVID-19 infection have been shown to have a decreased mortality, rate of hospitalization, and intensive care unit admission. (26) Similarly, the presence of absolute eosinophilia patients with COVID-19, independent of the presence of comorbid asthma, may also be a protective factor as it is associated with decreased mortality. (26, 30) Adir et al showed the use of biologics in patients with severe asthma has no increased risk of COVID-19 infection nor increased risk for moderate to severe COVID-19 infection or all cause ninety-day mortality. (30) Interestingly recent systemic corticosteroid use, within one year, was associated with both moderate to severe COVID-19 infection and a composite endpoint of moderate to severe covid 19 infection and all-cause mortality.(30) This association had a positive correlation with the number of prescriptions in the previous year, with greater than 2 prescriptions having the highest hazard ratio. (30) (Figure 1). There may exist a subset of patients in the asthma population who are at more risk for severe disease, Huang et al demonstrated that adult asthmatics who required clinical care in the previous 12 months prior to COVID-19 diagnosis were at increased risk of severe disease, however those who did not receive clinical care were not at increased risk for severe disease. (28) From a mechanistic perspective, common cold viruses are well known

to induce postviral airway hyperresponsiveness lasting weeks to months. (31, 32) In this regard, the asthma exacerbations occurring in the year prior to covid exposure might lead to extended airway hyperresponsiveness that subsequently contributes to greater risk of covid hospitalization or death. It is also reasonable to hypothesize that a similar COVID-19 induced postviral airway hyperresponsiveness could lead to worse asthma control.

Impact of asthma and comorbid conditions on SARS-CoV2-2 receptor expression and risk of COVID-19 infection

Asthma is a well-recognized risk factor for more severe viral respiratory illnesses.(5) This has been consistently observed for both seasonal influenza and H1N1.(33) Further, type 2 inflammation has been shown to impair antiviral responses and increase susceptibility to respiratory infections, particularly rhinoviruses.(34, 35) Thus, there was significant concern at the onset of the COVID-19 pandemic that patients with asthma could be particularly at-risk for severe outcomes with SARS-CoV-2 infections. However, as noted above, asthma has not been consistently linked to enhanced COVID-19 risk. Mechanisms underlying this observation have been of interest since the beginning of the pandemic.

SARS-CoV-2 infects the respiratory epithelium through a process that involves binding the angiotensin-converting enzyme-2 (ACE2) receptor and cleavage of the viral spike protein by the transmembrane serine protease 2 (TMPRSS2).(36) Given the central role of the ACE2 receptor in SARS-CoV-2 infection, it has been hypothesized that it could relate to COVID-19 disease severity. There is a gradient of ACE2 expression from the upper to lower airway, with higher levels expressed in the upper airway epithelium, which corresponds to a greater susceptibility of upper airway cells to SARS-CoV-2 infection.(37)

Analyses of nasal epithelium in the Urban Environment and Childhood Asthma study identified significant impacts of asthma and respiratory allergy on epithelial *ACE2* expression.(38) Within the asthma population, there was an inverse association between the levels of aeroallergen sensitization and *ACE2* expression. In fact, those with the greatest levels of allergen sensitization had nearly a 50% lower *ACE2* expression compared to those with little or no allergen sensitization. Interestingly, allergen exposure is associated with further reductions in *ACE2* expression in both the upper and lower airways.(38) Multiple type 2 biomarkers associate with lower *ACE2* expression, and this appears to be driven by IL13 inflammatory pathways.(39, 40)

Increased *ACE2* expression has been associated with a number of risk factors for COVID-19 disease severity, notably increasing age(41). Peters et al examined factors that impact both *ACE2* and *TMPRSS2* expression in sputum cells in the Severe Asthma Research Program. While they did not identify significant differences in expression in asthma vs. control, other risk factors for COVID-19 morbidity and mortality associated significantly with receptor expression, including black race, male sex, and diabetes. hypertension, obesity, and cardiovascular disease. Further, Kasela et al identified active smoking, hypertension, and obesity to be associated with greater *ACE2* expression in bronchial epithelium.(42) Collectively, these associations highlight the potential relevance of *ACE2* expression to COVID-19 disease expression, and motivate further studies to directly evaluate the impact of *ACE2* expression on susceptibility to SARS-CoV-2 infection and disease severity.

Covid vaccine safety and effectiveness in patients with asthma

The CDC recommends vaccination against SARS-CoV2 for all patients over age 12, with the following two contraindications: 1) Severe allergic reaction after a previous dose or to a component of the COVID-19 vaccine and 2) Immediate allergic reaction of any severity to a previous dose of known (diagnosed) allergy to a component of the COVID-19 vaccine. (43) Anaphylaxis typically occurs at a rate of less than 1 per million doses for most vaccines, however the Pfizer-BioNTech COVID-19 vaccine showed initial data of 11.1 cases per million doses. (44, 45) While no specific vaccine component is known to be responsible, polyethylene glycol is one ingredient known to previously cause anaphylaxis. (45) Per the European Academy of Allergy and Clinical Immunology consensus statement there is no current data showing higher risk for AEFI in patients with allergic rhinitis or asthma. (46) There was no data in our literature review that patients with asthma in general will have less efficacy with the vaccine, though it would be reasonable to assume severe asthmatics on high levels of corticosteroids chronically may have a decrease response to the vaccine given their immunocompromised state. It is our general recommendation given the reduction in COVID-19 illness, need for hospitalization, and mortality in patients who have received vaccination that all patients with asthma, in the absence of contraindications, should receive vaccination against SARS-CoV2. (29, 47)

Summary of evidence-based treatment options for patients with acute SARS-CoV2 infection

What should I recommend if my patient with asthma has symptoms of covid-19? Regardless of vaccination status, the increased prevalence and contagiousness of the delta-variant warrants continued recommendation for covid-testing in all patients with acute symptoms. Asthma maintenance therapies including biologics should not be discontinued. The literature and misinformation regarding covid-specific treatment options has been overwhelming at times. To address this need for an evidence-based approach to care that is more timely than traditional

guideline statements, Cohen et al (ref) describe a Collaborative Writing Application involving ongoing review of articles by over 200 experts in 30 disciplines to provide an open-access clinical guideline that is available at [www.covidprotocols.org](http://www.covidprotocols.org). (48) In brief, for ambulatory patients with mild-to-moderate covid symptoms not requiring hospitalization, the treatment is largely supportive of symptoms unless the patient also has risk factors including age >60 years, cardiovascular disease, hypertension, diabetes, COPD, cancer, immunosuppressive medications, detectable HIV viral load or CD4 <200, TB, pregnancy, malnutrition. The presence of one or more of these risks of severe covid illness should prompt closer monitoring of ambulatory patients and consideration of monoclonal antibody treatments (e.g. Bamlanivimab-etesevimab, Casirivimab-imdevimab, or Sotrovimab) directed at the spike protein if available. Although the RECOVERY trial and several others have shown that dexamethasone use in hospitalized patients with covid-related respiratory failure reduces mortality, this benefit was not seen in admitted patients not requiring supplemental oxygen. This information, combined with the findings of Adir et al discussed above, provides a cautionary note discouraging the empiric use of systemic corticosteroids for ambulatory asthma patients with an acute covid illness. The PRINCIPLE trial and several others also show lack of efficacy for azithromycin in preventing hospitalization or other covid-related endpoints, leading to a recommendation against use by several guideline statements. All other covid-directed treatment options supported by clinical trials (remdesivir, therapeutic anticoagulation, tocilizumab, and baricitinib) are indicated only for subsets of hospitalized patients and independent of their comorbid asthma status.(49)

Evaluation of patients with asthma who have previously had covid

Perhaps more than any other respiratory virus, infection with SARS-CoV-2 has a high rate of prolonged symptoms beyond 4 weeks after the initial infection, in what has been termed post-acute COVID-19 syndrome or long-haul COVID . (50) Fatigue, cough, dyspnea and loss of taste

or smell are the most common findings in many studies, although the systemic inflammatory response to this infection can also lead to chronic symptoms including weakness, joint pain, sleep disruption, cognitive disturbances, chest pain, palpitation, thromboembolism, chronic kidney disease and hair loss (Figure 2). Most studies to date have follow up periods less than three months, with a few in the 6-12 month range. (51, 52) Severity of the acute illness is a risk for lingering symptoms in most studies. Although premorbid asthma has not been associated with an increased risk of post-acute COVID-19 syndrome, this patient subset is relatively small in most of the published literature suggesting a role for additional research using large pre-pandemic cohorts.

The British Thoracic Society has published guidance for managing patients during post-acute recovery period with the full document available online ([https:// britthoracic.org. uk/ about-us/ covid- 19- information- forthe-respiratory- community/](https://britthoracic.org.uk/about-us/covid-19-information-for-the-respiratory-community/)) and reviewed by George et al.(53, 54) Figure 3 shows the recommended follow-up algorithm for patients recovering from mild-to-moderate covid pneumonia not requiring acute ICU level care. Briefly, a plain chest radiograph with a clinical assessment 3 months after the acute infection is the first level of screening, with complete pulmonary function studies including lung volumes and diffusion capacity reserved for patients with abnormal radiographic findings. A 6 minute walk study, echocardiogram, and/or a chest CT scan is recommended for patients with abnormal chest X-rays and PFTs. This pragmatic approach is also parsimonious for patients with lingering respiratory symptoms, but should be expanded often with multi-disciplinary care for patients with extra-pulmonary long-covid symptoms. (50, 55)

Although new onset of incident asthma may be rare, Maestre-Muniz reported that approximately 20% of patients with asthma before their covid-related hospitalization required more intensive asthma treatment in the following year. (51) The work-up for patients with difficult to control asthma has been recently reviewed by Couillard et al. (56) Confirming the diagnosis

with pulmonary function studies, attending to adherence, and addressing comorbidities are cornerstones for all patients before considering advanced options such as biologic treatments. Additional research will be needed to evaluate whether resolution of infection from SARS-CoV-2 modifies the underlying inflammatory phenotype of patients with established asthma.

## Summary

The relationship between asthma and SARS-CoV-2 has fortunately not been one of worsened patient outcomes, but rather one demonstrating that overall patients with asthma have similar outcomes as their non-asthmatic counterparts. There does appear to be an inverse relationship between asthma control, either demonstrated by clinical control or corticosteroids use, and severity of COVID-19 disease, suggesting a subset of asthmatic patients may do worse than non-asthmatics. This finding may be driven by SARS-CoV-2 use of the ACE2 receptor for infection, the decreasing gradient of ACE2 expression from upper to lower airway epithelium, and the overall decrease in ACE2 expression in aeroallergen sensitized asthmatic patients.

We recommend vaccination for COVID-19 for all eligible patients without contraindications and COVID-19 specific therapies are discussed above. While post-acute COVID-19 syndrome or long-haul COVID does not appear to be more prevalent in the asthma population, careful evaluation including chest imaging, pulmonary function tests, 6 minute walk test, and echocardiogram: in addition to confirmation of a diagnosis of asthma may help guide care in patients with asthma who have post-acute COVID-19 syndrome or long-haul COVID. It is uncertain at this time if COVID-19 changes the underlying inflammatory phenotype in established asthma patients.

## Figure Legends

Figure 1. Association between systemic corticosteroid prescriptions and advanced COVID-19 illnesses in a population study with complete pharmacy records. Patients with asthma and a nasopharyngeal PCR diagnosis of COVID-19 (N = 8,242) were identified from health records with complete pharmacy data. Systemic corticosteroids had been used in the past year by 1358 patients, and biologics had been used by 50 in the last 120 days. Adjusted HRs and 95% confidence intervals are shown for the association between the number of filled corticosteroid prescriptions in previous year and composite of moderate to severe COVID-19 or all-cause mortality within 90 days following PCR date among adult asthmatic patients with positive PCR for SARS-CoV-2. For comparison, the association with biologic use was not significant (HR = 1.42 (0.70-2.88),  $p = 0.332$ ). This figure has been reproduced with permission (pending). (30)

Figure 2. Graphic summary of the usual course for acute and post-acute COVID-19 symptoms. The definition of post-acute COVID-19 relates to symptoms lasting longer than 4 weeks, a time point beyond which it is very unlikely to find live virus in clinical samples. This figure has been reproduced with permission. (50)

Figure 3. Follow up care and testing algorithm for patients with mild to moderate COVID-19 pneumonia not requiring acute care in the intensive care unit. The full guideline is available online (<https://britthoracic.org.uk/about-us/covid-19-information-for-the-respiratory-community/>). (53, 54)

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None (reference)

Journal Pre-proof

1 Prescription

2 Prescriptions

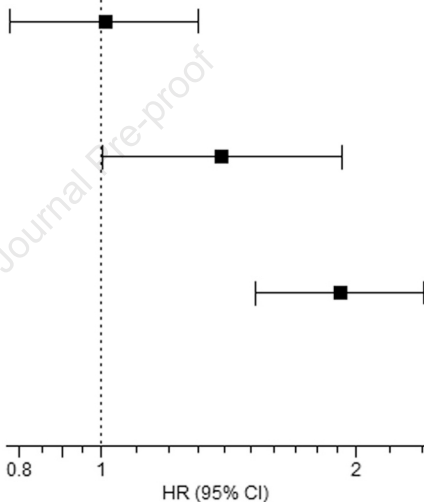
$\geq 3$  Prescriptions

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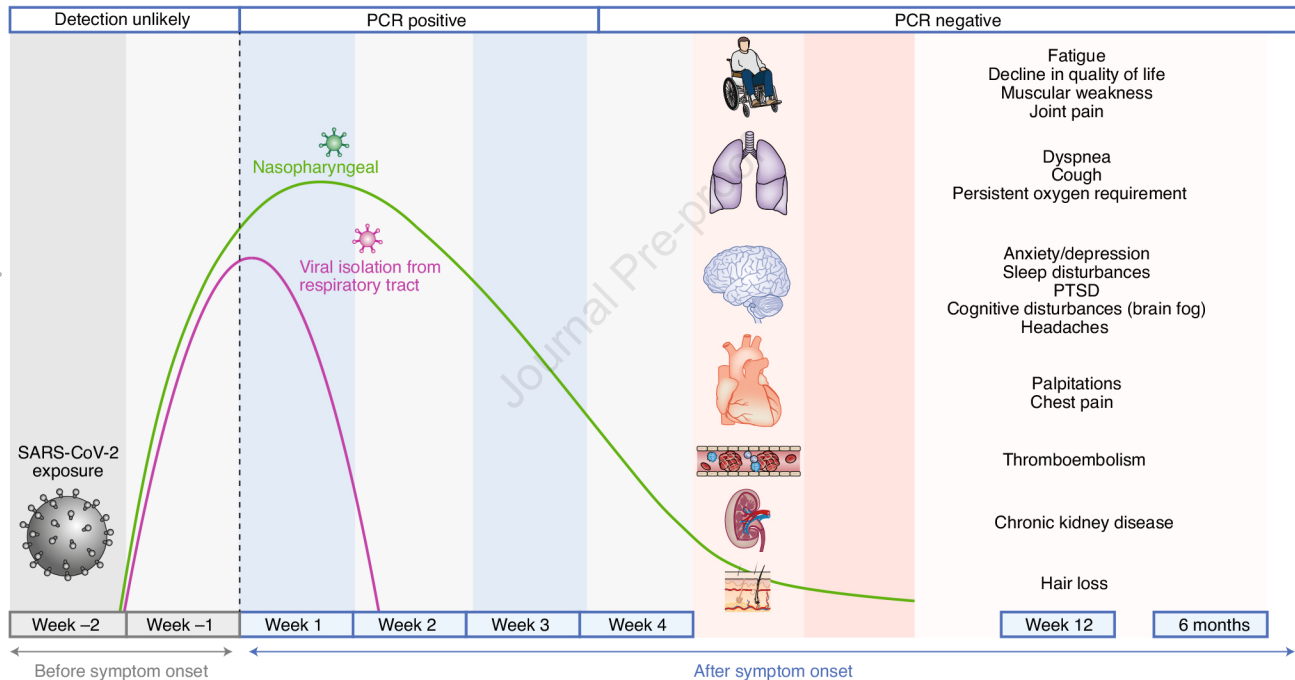
2

HR (95% CI)



Subacute/ongoing COVID-19

Chronic/post-COVID-19



**Mild to moderate pneumonia – typically cared for on ward or in community\***



**12 weeks after discharge - Step 1**

Pre-order Chest X-Ray - virtual clinic  
If diagnosed with PE<sup>3</sup>, combine follow up  
Chest X-Ray with post-PE<sup>3</sup> follow up\*

Normal

Normal

Discharge

**Discharge**  
Send template letter with  
advice to see GP for  
assessment if experiencing  
persistent, new or  
progressive respiratory  
symptoms

If abnormal CXR<sup>+</sup> pre-order full PFTs<sup>8</sup>

**Step 2**

Clinical assessment\* with PFT<sup>8</sup> review<sup>^</sup>  
If PE suspected proceed straight to CTPA<sup>5</sup>  
If PE not suspected, and patient clinically  
improving consider repeat Chest X-ray<sup>+</sup><sup>^</sup>

<sup>^</sup> Could be virtual

Normal

Discharge

Any abnormality<sup>+</sup>

High Resolution CT scan<sup>+</sup> and CTPA<sup>5</sup>  
Consider walk test  
Consider echocardiogram

Evidence of  
interstitial lung disease

Consider referral to  
specialist ILD<sup>7</sup> Service

Evidence of PVD<sup>4</sup>

Consider referral to  
specialist PH<sup>6</sup> service



**If no significant ILD<sup>7</sup> or PVD<sup>4</sup> to account for any disability consider other  
diagnoses, manage accordingly +/- discharge**

<sup>+</sup> If any suggestion of malignancy  
refer to cancer services

\* Consider Post-COVID-19 holistic  
assessment – see FAQ in document

- 3 Pulmonary embolism      6 Pulmonary Hypertension  
4 Pulmonary vascular disease      7 Interstitial lung disease  
5 CT Pulmonary angiogram      8 Pulmonary function test

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Oct 08, 2021

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