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COVID-19 Infections and Asthma



Philip A. Palmon, MD^a, Daniel J. Jackson, MD^{a,b}, and Loren C. Denlinger, MD, PhD^a *Madison, Wis*

The severe acute respiratory syndrome coronavirus 2, which causes coronavirus disease 2019 (COVID-19), has infected more than 200 million and led to the deaths of more than 4.3 million people. Although there are known risk factors for severe disease, asthma was initially hypothesized to be a risk factor for severe disease given the association between asthma exacerbations and respiratory viral illnesses in general. Fortunately, clinical outcomes for patients with asthma overall are similar to those for patients without asthma, without convincing evidence that asthma is a risk factor for severe disease. This may be explained in part by the decreasing gradient of angiotensin-converting enzyme-2 receptor from the upper to lower respiratory epithelium and that aeroallergen-sensitized patients with asthma can have up to 50% reduction in angiotensin-converting enzyme-2 receptor expression. Vaccination for patients with asthma is recommended for all without clear contraindications. COVID-19-specific treatment options are available depending on the severity of disease. We caution the use of systemic corticosteroids in patients with asthma not requiring supplemental oxygen given an association with worse outcomes. Postacute COVID-19 syndrome or long-haul COVID does not appear to be more prevalent in the population with asthma, and a multidisciplinary approach to care is a reasonable

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INTRODUCTION

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which causes coronavirus disease 2019 (COVID-19), has infected more than 200 million and led to the deaths of more than 4.3 million people.¹ There are well-established risk factors associated with severe disease and increased mortality such as older age, race, sex, 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 a higher risk for both infection and severe COVID-19.⁵ 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 lockdown.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-CoV-2 receptor expression and risk of COVID-19 infection, the safety and efficacy of the COVID-19 vaccinations, and 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-COV-2 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 Centers for Disease Control and Prevention 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 patients with asthma with COVID-19 compared with 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

^aDivision of Allergy, Pulmonary & Critical Care Medicine, Department of Medicine, University of Wisconsin School of Medicine & Public Health, Madison, Wis

^bDivision of Allergy, Immunology & Rheumatology, Department of Pediatrics, University of Wisconsin School of Medicine & Public Health, Madison, Wis

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Conflicts of interest: P. A. Palmon has no relevant conflicts of interest. D. J. Jackson reports receiving grant funding from the National Institute of Allergy and Infectious Diseases, the National Heart, Lung, and Blood Institute (NHLBI), and GlaxoSmithKline, and personal fees from Sanofi, Regeneron, Novartis, AstraZeneca, Vifor Pharma, and Pfizer. L. C. Denlinger has consulted with AstraZeneca and Sanofi-Regeneron, and has grant funding from NHLBI outside the submitted work, including participation in the Severe Asthma Research Program (SARP) and PrecISE Trial networks. Within the last 3 years, the following companies provided financial support for study activities at the coordinating and clinical centers beyond the third year of patient follow-up for the SARP network: AstraZeneca, Boehringer-Ingelheim, Genentech, GlaxoSmithKline, Sanofi-Genzyme-Regeneron, and TEVA. These companies had no role in study design or data analysis, and the only restriction on the funds was that they be used to support the SARP initiative. Within the last 3 years, the following companies have provided study drugs for the PrecISE Trial Network: GlaxoSmithKline, Laurel, Sun Pharma, Vifor, Viatris/CSL Behring, and Viatro.

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Corresponding author: Loren C. Denlinger, MD, PhD, Department of Medicine, University of Wisconsin School of Medicine & Public Health, 600 Highland Ave, Clinical Sciences Center, Box 9988, Madison, WI 53792. E-mail: lcd@medicine.wisc.edu

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Abbreviations used

ACE2- angiotensin-converting enzyme-2
COVID-19- coronavirus disease 2019
SARS-CoV-2- severe acute respiratory syndrome coronavirus 2

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% 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 are limited worldwide.¹⁸ Recent data support that there is no increased risk in children with asthma infected with COVID-19 with regard to severity of disease. Ruano et al¹⁹ reported that there were no differences in lung function, need for oral corticosteroids, emergency care, or hospitalizations for pediatric patients with asthma with and without COVID-19, though it was noted that in patients with probable COVID-19 there was increased use of controller and symptom reliever treatment. 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 al²⁰ reported that in children with asthma, with or without concurrent allergic diseases, there was no association with an increased risk of hospitalization for COVID-19. In addition, there is the impact of COVID-19 on availability of medical services for asthmatic children, with there being a clear reduction in 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, and albuterol and oral corticosteroid 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 pollution 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 population with asthma, those with less-than-optimal control, who are at more risk for severe disease. Huang et al²⁸ demonstrated that adult patients with asthma who required clinical care in the previous 12 months before 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. In addition, there are data to support that COVID-19 infection may not induce a severe exacerbation requiring oral corticosteroids or inhaled bronchodilators in patients with asthma.²⁴ This is further supported because the prevalence of asthma in patients with COVID-19 is similar to that reported in the general population worldwide, and in some areas lower. The data suggest that asthma may in fact be a protective factor in COVID-19 infection for various proposed mechanisms including the differences in T_H2 inflammation, decreased expression of angiotensin-converting enzyme, and use of inhaled corticosteroids in patients with asthma.^{22,27,29,30} Adult asthma patients with COVID-19 infection have been shown to have a decreased mortality, rate of hospitalization, and

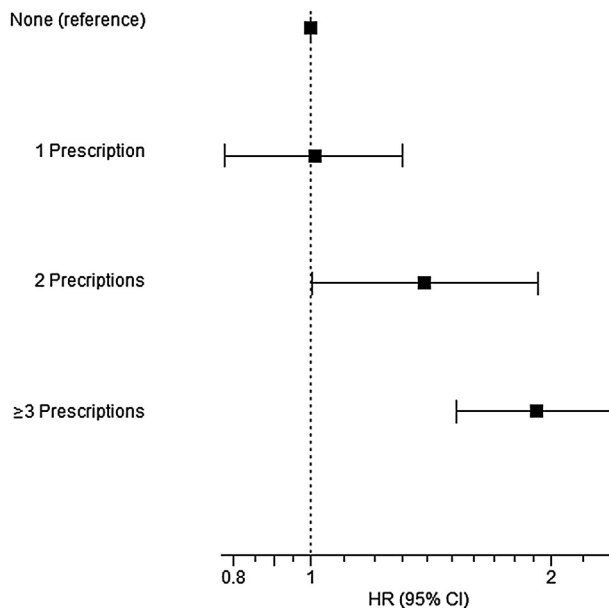


FIGURE 1. Association between systemic corticosteroid prescriptions and advanced COVID-19 illnesses in a population study with complete pharmacy records. Patients with asthma and a nasopharyngeal PCR diagnosis of COVID-19 (N = 8242) were identified from health records with complete pharmacy data. Systemic 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% CI 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 result for SARS-CoV-2. For comparison, the association with biologic use was not significant (HR = 1.42; 95% CI, 0.70-2.88; *P* = .332). *HR*, Hazard ratio. This figure has been reproduced with permission.³⁰

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 because it is associated with decreased mortality.^{26,30} Adir et al³⁰ showed that 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 90-day mortality. Interestingly, recent systemic corticosteroid use, within 1 year, was associated with both moderate to severe COVID-19 infection and a composite end point 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 ratio³⁰ (Figure 1). There may exist a subset of patients in the population with asthma who are at more risk for severe disease. Huang et al²⁸ demonstrated that adult patients with asthma who required clinical care in the previous 12 months before 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. 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 before COVID exposure might lead to extended airway hyperresponsiveness that subsequently contributes to a 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-COV-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 Furthermore, 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 2.³⁶ Given the central role of the ACE2 receptor in SARS-CoV-2 infection, it has been hypothesized that it could relate to COVID-19 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 with 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 IL-13 inflammatory pathways.^{39,40}

Increased ACE2 expression has been associated with a number of risk factors for COVID-19 severity, notably increasing age.⁴¹ Peters et al⁴² examined factors that impact both ACE2 and transmembrane serine protease 2 expression in sputum cells in the Severe Asthma Research Program. Although they did not identify significant differences in expression in asthma versus control, other risk factors for COVID-19 morbidity and mortality associated significantly with receptor expression, including Black race, male sex, diabetes, hypertension, obesity, and cardiovascular disease. Furthermore, Kasela et al⁴³ identified active smoking, hypertension, and obesity to be associated with greater *ACE2* expression in bronchial epithelium. Collectively, these associations highlight the potential relevance of ACE2 expression to COVID-19 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 Centers for Disease Control and Prevention recommends vaccination against SARS-CoV-2 for all patients older than 12 years, with the following 2 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.⁴⁴ 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.^{45,46} Although no specific vaccine component is known to be responsible, polyethylene glycol is one ingredient known to previously cause anaphylaxis.⁴⁶ Per the European Academy of Allergy and Clinical Immunology consensus statement, there are no current data showing higher risk for severe allergic reactions to the COVID-19 vaccines in patients with allergic rhinitis or asthma.⁴⁷ There were 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 that those with severe asthma on high levels of corticosteroids chronically may have a decreased 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-CoV-2.^{29,48}

SUMMARY OF EVIDENCE-BASED TREATMENT OPTIONS FOR PATIENTS WITH ACUTE SARS-COV-2 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 have 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 al⁴⁹ describe a Collaborative Writing Application involving ongoing review of articles by more than 200 experts in 30 disciplines to provide an open-access clinical guideline that is available online.⁵⁰ 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 more than 60 years, cardiovascular disease, hypertension, diabetes, chronic obstructive pulmonary disease, cancer, immunosuppressive medications, detectable HIV viral load or CD4 less than 200, tuberculosis, pregnancy, and malnutrition. The presence of 1 or more of these risks of severe COVID illness should prompt closer monitoring of ambulatory patients and consideration of mAb treatments (eg, bamlanivimab-etesevimab, casirivimab-imdevimab, or sotrovimab) directed at the spike protein if available. Although the

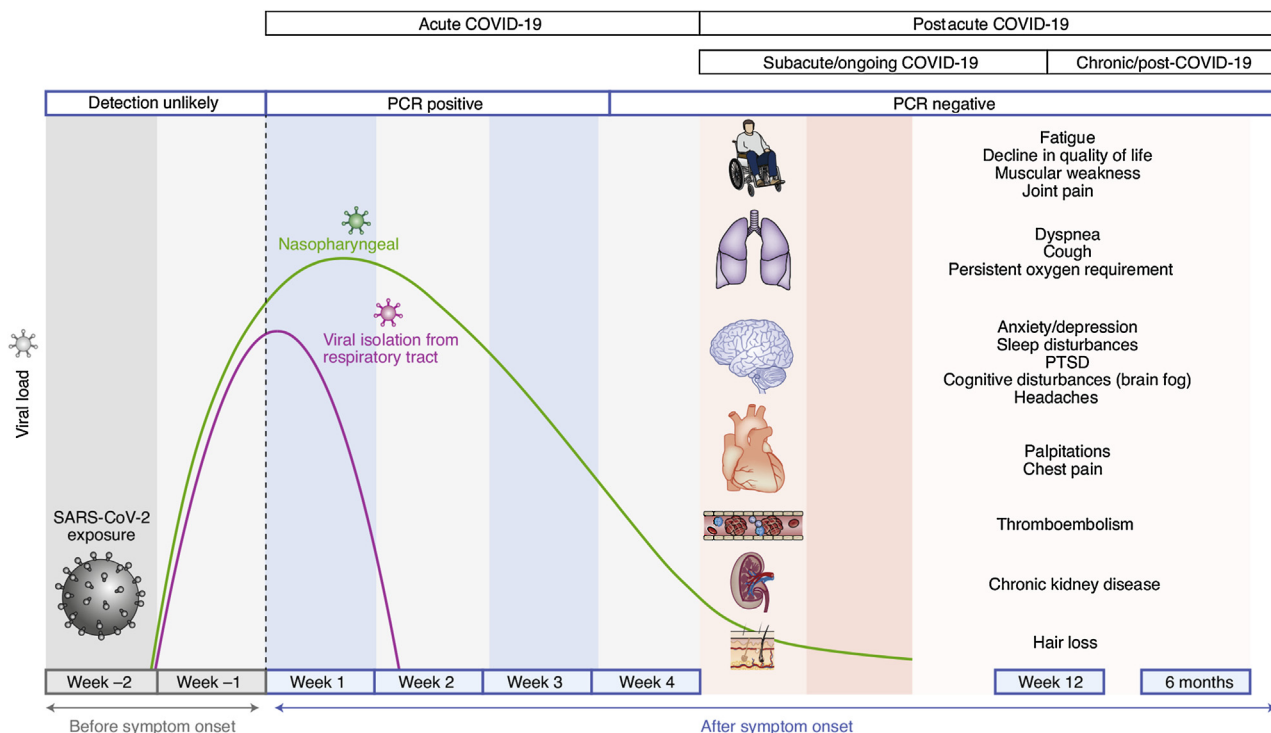


FIGURE 2. Graphic summary of the usual course for acute and postacute COVID-19 symptoms. The definition of postacute COVID-19 relates to symptoms lasting longer than 4 weeks, a time point beyond which it is very unlikely to find live virus in clinical samples.⁵² PTSD, Posttraumatic stress disorder. This figure has been reproduced with permission.⁵²

Randomized Evaluation of Covid-19 Therapy (RECOVERY)⁵⁹ 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 al³⁰ discussed above, provides a cautionary note discouraging the empiric use of systemic corticosteroids for ambulatory asthma patients with an acute COVID illness. The Platform Randomized trial of Interventions against COVID-19 In older peoPLE (PRINCIPLE)⁶⁰ trial and several others also show lack of efficacy for azithromycin in preventing hospitalization or other COVID-related end points, 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.⁵¹

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 postacute COVID-19 syndrome or long-haul COVID.⁵² 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 3 months, with a few in the 6- to 12-month range.^{53,54} 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 postacute COVID-19 syndrome, this patient subset is relatively small in most of the published literature, suggesting a role for additional research using large prepanemic cohorts.

The British Thoracic Society has published guidance for managing patients during postacute recovery period with the full document available online and reviewed by George et al.^{55,56} Figure 3 shows the recommended follow-up algorithm for patients recovering from mild to moderate COVID pneumonia not requiring acute intensive care unit 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 computed tomography scan is recommended for patients with abnormal chest X-rays and pulmonary function tests. This pragmatic approach is also parsimonious for patients with lingering respiratory symptoms, but should be expanded often with multidisciplinary care for patients with extrapulmonary long-COVID symptoms.^{52,57}

Although new onset of incident asthma may be rare, Maestre-Muñiz et al⁵³ reported that approximately 20% of patients with asthma before their COVID-related hospitalization required more intensive asthma treatment in the following year. The workup for patients with difficult to control asthma has been

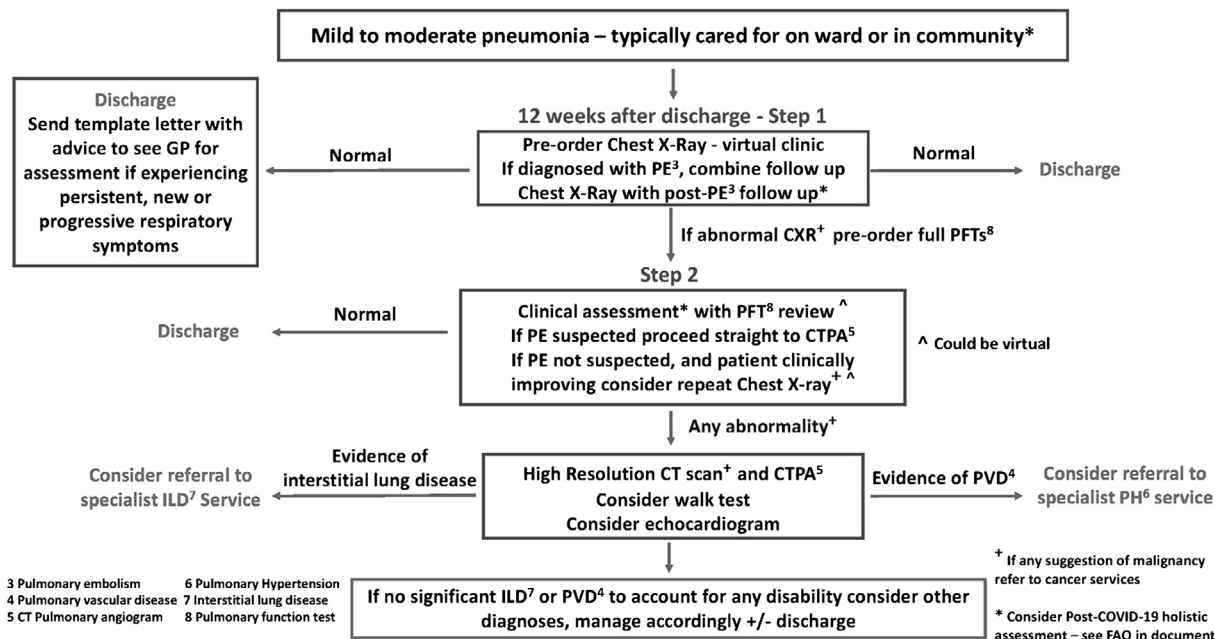


FIGURE 3. Follow-up care and testing algorithm for patients with mild to moderate COVID-19 pneumonia not requiring acute care in the intensive care unit. The full guideline is available online.^{55,56}

recently reviewed by Couillard et al.⁵⁸ 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 nonasthmatic counterparts. There does appear to be an inverse relationship between asthma control, demonstrated either by clinical contact or by corticosteroids use, and severity of COVID-19 disease, suggesting a subset of patients with asthma may do worse than those without asthma. 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 patients with asthma.

We recommend vaccination for COVID-19 for all eligible patients without contraindications, and COVID-19– specific therapies are discussed above. Although postacute COVID-19 syndrome or long-haul COVID does not appear to be more prevalent in the population with asthma, 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 postacute COVID-19 syndrome or long-haul COVID. It is uncertain at this time whether COVID-19 changes the underlying inflammatory phenotype in patients with established asthma.

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