REVIEW ARTICLE

COVID-19 IN PATIENTS WITH ASTHMA: REVIEW AND IMPLICATIONS FOR CARE OF ADULT PATIENTS WITH AN OSTEOPATHIC COMPONENT

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KEYWORDS

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ABSTRACT

Patients with asthma who have COVID-19 typically present with rhinitis, rhinosinusitis, cough, and shortness of breath and rarely with wheezing. Family physicians should consider a patient's asthma subtype, pertinent medical history, and medications. Maintenance medications, including inhaled corticosteroids (ICS), should be continued for most patients. Whether to start ICS in patients with asthma who have COVID-19 should be considered, as the risks and benefits are unclear, and systemic corticosteroids should be avoided in patients with asthma who have COVID-19 if alternatives exist. Pregnant patients with both asthma and COVID-19 should be comanaged by an obstetrician, with consideration for early induction of labor. Behavioral health topics and osteopathic principles and manipulative techniques should be considered in patients with COVID-19 and asthma. Generalities are challenging to make, but patients with asthma do not seem to have worse outcomes with COVID-19 than patients without asthma.

INTRODUCTION

Discovered in 2019, the SARS-CoV-2 virus is an enveloped positive-sense, single-stranded RNA virus. Within the virus family *Coronaviridae*, it is the seventh subtype of the human coronavirus (CoV), similar in structure to past SARS-CoV and MERS-CoV viruses. COVID-19, the syndrome that the SARS-CoV-2 virus causes, may include such mild symptoms as cough, rhinitis, rhinosinusitis, anosmia, dysgeusia, myalgia, fatigue, and fever. Severe illness may be characterized by atypical pneumonia, pulmonary edema, acute respiratory distress syndrome, multisystem organ failure, and septic shock.[1]

Patients with asthma with heterogeneous origins of varied symptoms and treatment challenges are a unique cohort of patients. The objective of this article is to review the pathophysiology of the SARS-CoV-2 virus, the sequelae of COVID-19 syndrome, the basics of asthma physiology, and the implications of care for patients with both asthma and COVID-19 in an effort to educate and empower readers toward evidence-based management recommendations.

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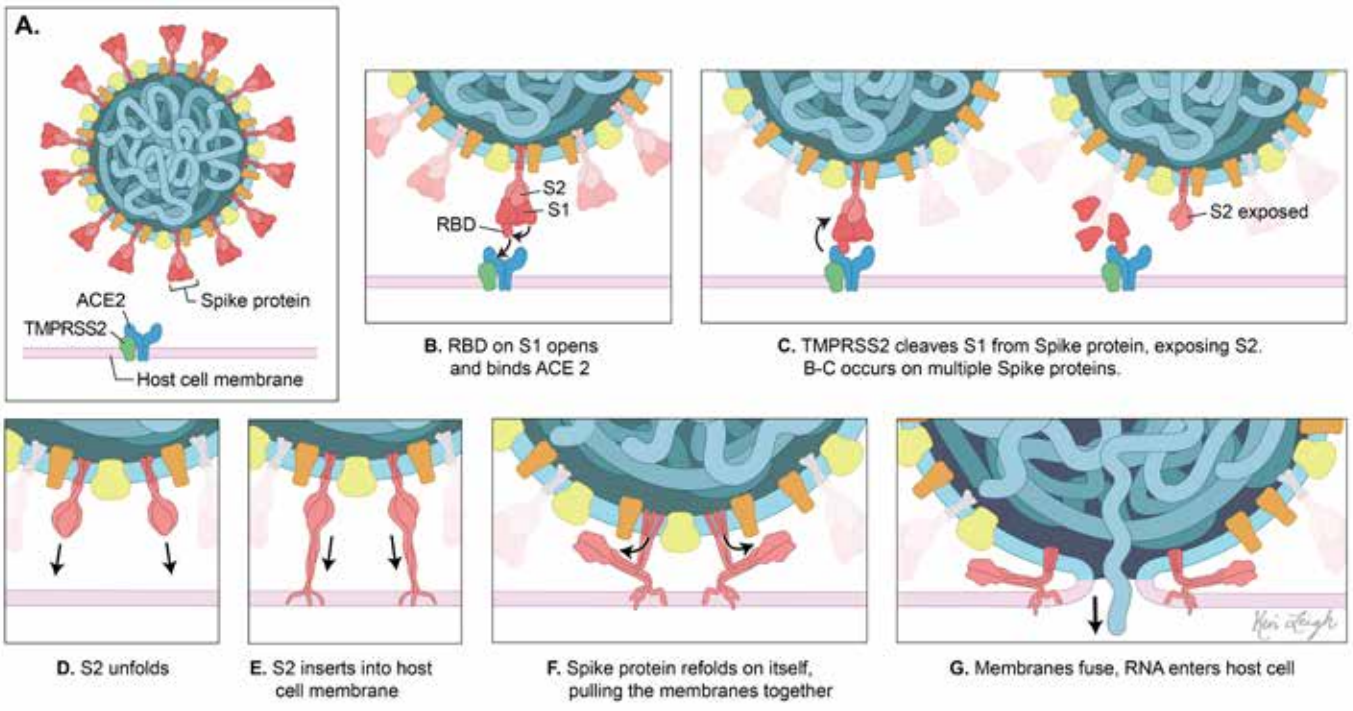
SARS-COV-2 VIRUS PATHOPHYSIOLOGY

Exposure to SARS-CoV-2 typically comes from aerosolized droplets (commonly 1–5 µm in diameter) several meters from an infected person[1] or by long-range transmission from environmental pollen bioaerosol complexes linked with the virus.[2] After a person is exposed, the spike glycoprotein (S protein) of the virus binds to the angiotensin-converting enzyme 2 (ACE2) receptors of both type I and type II pneumocytes of the host (Figure 1). Following attachment, the transmembrane serum protease 2 present on the extracellular membrane of the epithelial cells will cleave the S protein into subunits, which facilitate the transmission of the uncoated RNA genome of the virus across the membrane and into the cell.[3]

Each RNA genome creates replicase transcriptase polypeptides, which create more viral RNA. This, in conjunction with the upregulation of the expression of the ACE2 receptors in the presence of the S protein, causes an exponential increase in viral load. This S protein of the SARS-CoV-2 virus has a 10–20-fold increase in binding capacity compared with its distant relatives, the SARS-CoV and MERS-CoV viruses, suggesting a key point in the virulence of this virus.[4]

FIGURE 1:

SARS-CoV2 entering a host cell



ASTHMA PATHOPHYSIOLOGY

Asthma encompasses obstructive lung disease with airway inflammation, bronchial smooth muscle contraction, increased mucus production, and bronchial hyperresponsiveness. Common symptoms include cough, shortness of breath, chest tightness, and wheezing.[5] The two most common asthma subtypes reported are "atopic" and "nonatopic." Atopic asthma is more common, associated with baseline increased histamine, total IgE, attenuated interferon (IFN) response, a Th2-skewed immunity, and increased eosinophils.[2,3] Nonatopic asthma is typically associated with obesity, metabolic syndrome, and smoking, though without a clear origin or etiology. It often includes a Th1- or Th17-mediated immune response and may be associated with an increased IFN response, including interleukin 6 (IL-6), which is common and difficult to control.[4,6]

EXACERBATIONS REVIEW

Asthma exacerbations describe worsening of baseline symptoms, with respiratory infections as common triggers secondary to increased, attenuated IFN response.[7] The CoV viral subclass is a common trigger.[1,8] Estimates of 80% of respiratory triggers secondary to CoV are documented, although one study countered with no strong link between CoV and asthma exacerbations.[9]

ISOLATION CONSIDERATIONS

A Dutch study showed that patients with asthma exhibited higher rates of fear of becoming infected with SARS-CoV-2 compared with controls.[10] Patients with asthma seem more motivated to reduce the risk of respiratory viral infections by using behavioral interventions such as social distancing and mask-wearing, compared with patients who do not have asthma.[11,12] Furthermore, patients with asthma were more likely to avoid clinics and hospitals for non-COVID issues secondary to concerns about COVID-19 and hospital-acquired infections.[10,13] A Greek retrospective cohort study theorized that primary care effectively managed patients with asthma and that such patients had decreased environmental exposures with limited aggravating factors, were avoiding health care secondary to fear of COVID-19, and showed a 68% reduction in admissions since the onset of the pandemic.[14]

COVID-19 AND ASTHMA PREVALENCE

An accurate prevalence of asymptomatic and mild COVID-19 patients with asthma remains unclear secondary to lack of testing in asymptomatic patients and those with mild symptoms, varying diagnostic criteria, and decreased hospital presentations of patients with asthma.[14] Patients with both asthma and COVID-19 were most likely to present with rhinitis and rhinosinusitis

symptoms. Diagnosing asthma remains challenging secondary to the closure of pulmonary function testing laboratories, secondary to the aerosolization of the procedure.[13,15] Hospitalized patients often demonstrate cough and shortness of breath, with wheezing as a rare feature.[1] Patients with asthma who have COVID-19 generally have other comorbidities such as obesity, sleep apnea, and GERD.[16]

A review of the literature postulates that early studies from China and Italy significantly underrepresented asthma in COVID-19 patients.[7] A retrospective cohort study from Illinois showed that the prevalence of COVID-19 patients with asthma was 14.4%,[16] though a Spanish study showed a prevalence of 4.45%.[9] An Israeli retrospective cohort study conducted a chart review of all patients with documented asthma, showing 10.2% were positive for COVID-19 by PCR testing, not statistically significant compared with patients who did not have asthma. Further analysis showed that the use of systemic corticosteroids (SCS) or biologic therapy did not increase the risk of COVID-19 in patients with asthma.[17,18] Data reported here can be compared with the national asthma prevalence in the United States of 8.0% based on the US Centers for Disease Control and Prevention's (CDC) National Reported Prevalence of 2019.[19] The heterogeneity of the studies and varied data mean that generalities about association or correlation with COVID-19 and asthma are difficult to make.

COVID-19 SEVERITY AND COMPLICATIONS

The CDC reports that asthma is a risk factor for severe COVID-19.[4,19] The severity of COVID-19 correlates directly with the magnitude of innate immune response and cytokine storm within the lower respiratory tract.[4] The nonatopic subtype of asthma tends to be proinflammatory with increased baseline levels of IL-6, showing a significant association with severe infection.[4,20] Alternatively, atopic asthma shows a Th2-skewed immunity with a decreased cytokine and overall antiviral response to SARS-CoV-2.[2-4,11,12] The decreased IFN response of many patients with asthma decreases expression of ACE2 on the cell membrane, decreasing available binding sites for the S protein and decreasing viral replication within the pneumocytes.[3,21] In conclusion, severity, need for ICU-level care, and mortality are not significantly different for patients with asthma compared to those with no underlying chronic respiratory disease.[9]

A retrospective cohort study showed that hospitalization rates were not different between COVID-19 patients with or without asthma.[16] Compared to patients with chronic obstructive pulmonary disease (COPD), obstructive sleep apnea (OSA), and other chronic respiratory diseases, asthma patients have been found to have a lower risk of mortality with COVID-19.[1] Hosoki et al. proposes the varying presentations and pathophysiology between atopic and nonatopic asthma, and the inability to separate them upon review helps explain the diversity of data in the literature.[1] Palmon et al. postulated that a portion of patients with asthma may have had unresolved postviral hyperreactivity of the airway from prior non–SARS-Co-2 infections, leading to increased risk of complications.[21] Strauss et al, a review of the Cleveland Clinic COVID-19 Research Registry, demonstrated patients using intranasal steroids for rhinitis had a lower risk of hospitalization, ICU admission, and in-hospital mortality.[22]

Inflammatory markers, including C-reactive protein (CRP), lactated dehydrogenase (LDH), and ferritin were lower in patients with asthma compared with patients without asthma.[16] Eosinophilia is common in patients with atopic asthma, a feature of the innate immune response implicated in increased disease severity, frequent exacerbations, and tissue remodeling.[9] Conversely, eosinopenia, which is common with severe COVID-19, has been demonstrated to have a dose-dependent relationship to risk of ICU-level admission. Thus, the eosinophilia of patients with asthma is theorized to be protective.[9,17]

Low-quality evidence shows that ICS use blocks RNA replication and minimizes the cytokine response.[8,23] ICS use in patients with asthma did not increase the risk of COVID-19-related hospitalizations in the United States, and a Japanese case series suggests that ICS may assist with COVID-19 recovery.[24] Systemic corticosteroid use was a notable risk factor for moderate-to-severe COVID-19 with increased mortality compared to nonuse, with outcomes showing a statistically significant dose-responsive increase in severity. Biologic therapy use showed no increased risk of COVID-19 severity or mortality compared to nonuse.[17]

PREGNANCY CONSIDERATIONS

A Washington state study following 46 pregnant patients with asthma and COVID-19 showed that pregnant patients with asthma have a higher risk of contracting severe COVID-19 and experiencing delivery complications. This suggests comanagement with obstetrics and consideration of preterm induction and delivery may decrease risks of complications, including improved neonatal lung function.[25]

BEHAVIORAL HEALTH CONSIDERATIONS

Patients with asthma often have an association with depression or anxiety secondary to physical limitations, fear of respiratory distress, and increased cholinergic activity.[7,26] A Dutch study showed patients with asthma had a higher rate of fear of becoming infected with SARS-CoV-2 compared with controls, with many people with asthma avoiding clinics and hospitals in an effort to reduce the risk of COVID-19 exposure and hospital-acquired infections.[7]

OSTEOPATHIC CONSIDERATIONS

Osteopathic examination should focus on breathing mechanics; lymph circulation and mobilization of immune cells by targeting somatic dysfunctions of the thoracic spine, ribs, and diaphragm; and viscerosomatic reflexes.[27-29] Haney et al. (2021) succinctly describes various osteopathic manipulation treatment options to consider based on patient presentation.[30] A 1999 randomized controlled trial showed a statistically significant improvement in peak expiratory flow in pediatric patients compared to those receiving sham therapy.[28]

CONCLUSION

Family physicians should consider a patient's asthma subtype, pertinent medical history, medications, and symptoms at onset as part of an effort to individualize treatment. Most patients who have both asthma and COVID-19 will complain of rhinitis, rhinosinusitis, cough, shortness of breath, and, rarely, wheezing. Maintenance medications such as ICS should be continued for most patients. Starting an ICS should be considered individually, and SCS should be avoided if alternatives exist. Pregnant patients are at high risk for complications and should be comanaged with obstetrics, with consideration for preterm induction of labor. Behavioral health and osteopathic considerations should be made individually. The CDC states that asthma is a risk factor for severe COVID-19, but varied studies reviewed do not demonstrate this correlation. However, generalities are difficult, and family physicians should be empowered to make individualized recommendations.

LITERATURE SEARCH

The authors searched PubMed, Google Scholar, the Elsevier COVID-19 collection, and DeGruyter.com resources, beginning April 10, 2021, after invitation to write the review, through the submission date of August 24, 2021. A repeat literature search was conducted on April 6, 2022, to find up-to-date articles for the second revision. Key words are COVID-19, SARS-CoV-2, asthma, inhaled glucocorticoids, atopic, osteopathic, anxiety, and depression. Each article was reviewed, summarized by the authors independently, and included if the article added value to the objective of describing the relationship between asthma and COVID-19.

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