Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

The Impact of Coronavirus Disease 2019 on Pediatric Asthma in the United States

Aishwarya Navalpakam, MD[a], Elizabeth Secord, MD[b], Milind Pansare, MD[c,*]

KEYWORDS

• COVID-19 • Pediatric asthma • United States

KEY POINTS

- The COVID-19 pandemic caused morbidities and mortalities of historic proportion and disrupted health-care delivery in the United States.
- The elderly and patients with chronic illnesses including asthma are at increased risks of poor outcomes.
- Limited data in the United States indicate children with asthma have done well despite multiple challenges to health-care delivery.
- It is important to adhere to asthma treatment guidelines to maintain asthma control in children during the pandemic.

INTRODUCTION

Coronaviruses are a common cause of upper respiratory infections in children.[1] A novel human coronavirus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), mutated in bats in Wuhan, China, and has been attributed to be the cause of a global pandemic leading to illness and death in 2020.[2] Initially, asthma was thought to be a risk factor for poor clinical outcomes in adult patients with coronavirus disease 2019 (COVID-19). However, limited data currently available have not shown significant COVID-19 illness or increase in asthma exacerbations in children during the pandemic. In this article, we aim to outline impact of COVID-19 on pediatric asthma in the United States and current recommendations for asthma care.

[a] Division of Allergy and Immunology, Department of Pediatrics, Pediatric Specialty Center, Children's Hospital of Michigan, 4th Floor, 3950 Beaubien Boulevard, Detroit, MI 48236, USA; [b] Department of Pediatrics, Wayne State University, Detroit, MI, USA; [c] Department of Pediatrics, Division of Allergy and Immunology, Pediatric Specialty Center, Children's Hospital of Michigan, Central Michigan University, Suite # 4018, 4th Floor, 3950 Beaubien Boulevard, Detroit, MI 48236, USA
* Corresponding author.
E-mail address: mpansare@dmc.org

Pediatr Clin N Am 68 (2021) 1119–1131
https://doi.org/10.1016/j.pcl.2021.05.012
pediatric.theclinics.com

IMPACT OF COVID-19 IN THE UNITED STATES

The United States has become an epicenter during the pandemic, reporting the highest number of cases and deaths due to COVID-19. In the United States alone by December 31, 2020, a total aggregate count of COVID-19 cases of 19,663,976 and total deaths of 341,199 were reported by states and territorial jurisdictions to the Centers for Disease Control and Prevention (CDC). These numbers continue to increase. In the age-group of 0 to 17 years, the total number of reported COVID-19 cases was 1,500,972 (10.5% estimated from the age reported in 14,226,540 cases) and the death count was 211 (<0.2% estimated from the age reported in 237,889 deaths) during the same period.[3] The CDC had listed asthma as a risk factor for COVID-19 outcomes, particularly morbidity and mortality.[4] Asthma is the most common chronic respiratory disease in children, affecting about 6 million children in the United States in ages 0 to 17 years. Every year, one in 6 children with asthma visits the ED and about 1 in 20 children with asthma is hospitalized for the same condition (https://cdc.gov.asthma). Practitioners and parents alike anticipated and rapidly prepared for the significant impact of SARS-CoV-2 infections in children with asthma. The reality was not what was anticipated.

RESPIRATORY VIRUSES AND ASTHMA

Asthma in children is often triggered by respiratory viruses. It is theorized that the type I interferon production, which is important for defense against viruses, is decreased in asthmatic individuals and is inhibited by Th2 inflammation seen in allergic asthma.[5] Studies also suggest that in atopic individuals, certain respiratory viruses such as respiratory syncytial virus (RSV) or human rhinovirus (RV), owing to the formation of specific IgE, may cause exacerbations.[5] RSV and RV have actually been implicated in the development of asthma. Other viruses such as influenza, coronavirus, adenovirus, parainfluenza virus, and metapneumovirus are considered risk factors for asthma exacerbations. At the advent of the COVID-19 pandemic, there was a concern that SARS-CoV-2 infection may also result in increased asthma exacerbations in children, which surprisingly did not occur.

PATHOPHYSIOLOGY OF SEVERE ACUTE RESPIRATORY SYNDROME CORONAVIRUS-2

COVID-19 is caused by the novel coronavirus SARS-CoV-2. It is a single-stranded RNA virus (ssRNA) that contains a spike protein (S protein) that binds to angiotensin-converting enzyme 2 (ACE2) receptors found on human cells. The ssRNA is inserted into the airway epithelial cells, where it replicates causing local inflammation, tissue damage, and cytokine release. The majority of these ACE2 receptors are located on type II alveolar epithelial cells. There are other associated receptors such as type II cellular transmembrane serine protease (TMPRSS2) that activate S protein and allow for the fusion of the viral membrane into the host cell.[6]

POTENTIAL ASTHMA-PROTECTIVE FACTORS AGAINST COVID-19

The pathophysiologic hallmark of asthma is chronic airway inflammation. Generally, two types of inflammatory asthma are described: type 2-high (T2) asthma and type 2-low (T1) asthma, based on the expression of T helper cell type 2 (TH2) cytokines. Type 2-high asthma is characterized by eosinophilic airway inflammation, elevated levels of cytokines such as interleukin (IL) 4, IL-5, and IL-13, and elevated levels of IgE. This is also known as allergic asthma that appears earlier in life, is responsive to corticosteroids, and is a common phenotype in children. The type 2 low asthma

phenotype is more common in adults, has later disease onset, has less allergic comorbidities, and is less responsive to corticosteroids.

ACE2 receptor expression appears to vary with asthma phenotype. A study of two large adult asthma cohorts identified increased expression of the ACE2 gene in the bronchial epithelium of patients with type 2-low or T1-high asthma.[7] Interestingly, these patients also tended to have higher known risk factors for COVID-19 including hypertension, lymphopenia, and male gender.[7,8] This suggests that the T2-low phenotype is likely associated with higher risk of COVID-19. Another study of cohort of children with asthma, the Urban Environment and Childhood Asthma (URECA) cohort, revealed that allergic sensitization in children (positive IgE tests for allergens, either skin or serum testing) with asthma was associated with decreased ACE2 expression in children.[9] The type 2-high asthma phenotype characterized by the elevated serum IgE level, fractional exhaled nitric oxide (FeNO), and IL-13 expression was associated with decreased ACE2 receptor expression in this URECA cohort.[9] It suggests that T2 high-asthma and allergic sensitization is associated with decreased ACE2 receptor expression and may be a cause of decreased SARS-CoV-2 infection in these patients. This may be important to pediatric patients with asthma who tend to have the T2-high asthma phenotype. Children, when compared to adults, have lower ACE2 receptors in their nasal epithelium. This may account for the decreased incidence of COVID-19 in children.[10]

The use of inhaled corticosteroids (ICSs) may also provide a protective role for asthma from COVID-19. Cultures of human nasal and tracheal epithelial cells reveal that the combination of glycopyrronium, a long-acting muscarinic antagonist, formoterol, a long-acting beta-2 agonist, and budesonide, an ICS, inhibits replication of HCoV-229E, a virus that causes common cold by preventing receptor expression and decreases virus-induced airway inflammation.[11] When gene expression of ACE2 and TMPRSS2 was analyzed in sputum cells from patients with severe asthma, it was found that the use of ICSs was associated with lower expression of these receptors.[12] These studies suggests patients with asthma who are adherent to their ICSs thus may have decreased risk of COVID-19.

COVID-19 AND ASTHMA PREVALENCE

The number of adult patients with asthma hospitalized owing to COVID-19 across the world is low, with incidence reported from 1% to 2.7%.[13] An online questionnaire sent to 91 pediatric practitioners in 27 countries attempted to estimate the incidence of clinically relevant COVID-19 in pediatric patients with asthma. They noted that incidence is 12.8 times less frequent in children than in adults.[14] A retrospective study of a large cohort in Israel also showed that patients with asthma have a lower susceptibility for COVID-19 in pediatric and adult patients. The study did not find any difference in the rate of hospitalization in patients with COVID-19 with or without asthma.[15] A nationwide study in Japan examining asthma during the COVID-19 outbreak found decreased asthma admissions in 2020 compared with previous years for children and adults.[16] A study of 212 children with allergic asthma in Spain found no significant difference in asthma control or severity between patients with and without COVID-19.[17]

In the United States, adult data suggest that there is no significant increased risk of mortality associated with a history of asthma. A matched cohort study of adult patients with asthma admitted to Massachusetts General Hospital with COVID-19 found that patients with asthma were less likely to require intensive care and mechanical ventilation and did not have increased risk of mortality.[18] A large COVID-19 registry with 11,405 patients from the Mount Sinai Health System in NYC revealed that of the

54.8% of patients who were COVID-19 positive, only 4.4% had asthma, suggesting there was no significant association between asthma history and disease.[19]

The early data from Wuhan regarding hospitalized pediatric patients and those with severe COVID-19 do not list asthma as a risk factor.[20,21] As per the CDC, in the United States, as of January 2021, 10.8% of 16,212,877 COVID-19 cases are found in children. However, these data are changing and not necessarily accurate of the true incidence in children owing to lack of prioritization of testing in this population. Hospitalization is reported to be low among children when compared with adults (CDC). Owing to a paucity of data, there has been an urgent call for further studies in childhood asthma in the current pandemic.[22]

Asthma exacerbations have a seasonal pattern, generally have increased prevalence in the late fall and spring, and are seen across North America and known as the September peak or asthma epidemic.[23,24] This is attributed to viral upper respiratory infections (URI), air pollutants, weather changes, and increase in aeroallergens.[25] Viral infections particularly account for asthma exacerbations in children during the start of school in early fall. Although respiratory viruses are a risk factor for asthma exacerbations, this did not seem to pertain to the current SARS-CoV-2 infection outbreak. Previously, SARS-CoV infection, which caused the first SARS outbreak in 2002, did not appear to be associated with an increase in asthma exacerbations in children.[26] However, there are very few studies published evaluating incidence, trends, hospitalization, and mortality related to pediatric asthma with COVID-19 in the United States. Some of the published studies in the US population are summarized in **Table 1**.[27–31]

IMPACT ON PEDIATRIC ASTHMA: MORBIDITY AND MORTALITY

Various studies from around the world, including China, Brazil, Italy, Switzerland, and the United States, reveal that asthma is not associated with increased risk of mortality in adult patients with COVID-19.[13] The Morbidity and Mortality Weekly Report from October 2020 that evaluated COVID-19 trends among school-age children (N = 277, 285) noted that 1.2% were hospitalized, 0.1% had intensive care unit (ICU) admissions, and less than 0.1% died. Of those patients (hospitalized, ICU admissions, died owing to COVID-19), each had at least one underlying medical condition, and 55% of the underlying conditions were accounted for by chronic lung disease including asthma, emphysema, and chronic obstructive pulmonary disease (COPD).[32] The final determination of COVID-19 impact toward pediatric asthma morbidity and mortality remains to be seen owing to lack of sufficiently powered studies providing significant data.

IMPACT ON PEDIATRIC ASTHMA: CLINICAL CARE

As the pandemic surged worldwide, international and governmental agencies of countries across all the continents responded by implementing control measures to contain the spread of virus. In the United States, federal, state, and local governments passed many unprecedented regulations including stay-at-home orders; the closing of local businesses, universities, and schools; social distancing; and face mask mandates. In the initial surge of disease, health resources were targeted toward the care of seriously ill patients with COVID-19, and nonurgent care was deferred to the alternate delivery model. The federal government declared a public health emergency and also allocated resources to provide medical care. The Health Insurance Portability and Accountability Act was relaxed, which allowed physicians to use their personal electronic devices to communicate with their patients during the pandemic.[33] The Centers

Table 1
Summary of pediatric asthma and COVID-19 studies

Study	Timeline	Asthma Findings
Kenyon et al,[27] 2020 Initial ED impact of COVID-19 in pediatric asthma • Retrospective chart review • Compared daily ED visits for asthma for the January–April period in 2020 to years 2016–2019	January to April from years 2016 to 2020	• ED utilization for asthma decreased by 3 standard deviations below the mean in year 2020 as compared with years 2016–2019. • Decreased ED visits by 76% in March–April 2020 (COVID) as compared with January–March 2020 (pre–COVID-19)
Taquechel et al,[28] 2020 Asthma health-care utilization during COVID-19 • Retrospective chart review • Compared outpatient, inpatient, and ED visits for asthma for the January to May period from years 2015–2020	January to May from years 2015 to 2020	Until March 17, 2020, similar visits (when compared with 2015–2019) After March 17, 2020: • Outpatient in-person asthma encounters decreased by 87%. • Hospital encounters decreased by 84%. • Telephone encounters increased by 19%. • TM visits increased by 61%. Other findings: • Decreased asthma-related steroid prescriptions. • Decreased frequency of rhinovirus infections.
Bandi et al,[29] 2020 Risks of COVID-19 in asthma in children aged <18 y evaluated by the TM clinic • Tested for SARS-CoV-2 (PCR) • Documented asthma status	March 12, 2020, to April 20, 2020	474 patients tested→ 5.2% tested positive for SARS-CoV-2 • Rate of asthma in SARS-CoV-2–positive cases: 12% • Rate of asthma in SARS-CoV-2–negative cases:10% ○ No significant difference ○ Asthma not a risk factor for infection
Bailey et al,[30] 2020 SARS-CoV-2 testing in US children • Retrospective cohort study	January 1, 2020, to September 8, 2020	135794 patients tested for SARS-COV-2→ 4% positive • 7% had severe illness (ICU care, increased length of stay, ventilation). • 0.2% died. • Asthma had a negative association with SARS-CoV-2 positive test results (SR, 0.86 [95% CI, 0.80–0.91]).

(*continued on next page*)

Table 1
(*continued*)

Study	Timeline	Asthma Findings
Secord et al,[31] 2021 ED visits for pediatric asthma • Retrospective chart review	March 15 to May 31 in 2019 and in 2020	Asthma ED visits significantly decreased during school closure from March 15 to May 31, 2020, when compared with the same period in 2019. • Average daily ED visits for asthma of 17 in 2019 vs 3.5 in 2020 • Total ED visits for asthma of 1304 in 2019 vs 260 in 2020 (P = .001)

Abbreviations: ED, emergency department; PCR, polymerase chain reaction; SR, standardized ratio.

for Medicare & Medicaid Services also promoted telemedicine (TM) by waiving previous restrictions of patient qualification for TM visits, by permitting office-based and home-based video encounters on personal devices with patients, and by improving reimbursements.[34]

In the United States, practitioners actively responded by establishing virtual clinics and using telehealth tools in all medical specialties to curb the pandemic.[35] An ad hoc expert panel of allergy/immunology specialists from the United States and Canada developed a consensus document to guide specialists in lieu of reduced services due to the pandemic.[36] The guidelines on COVID-19 and allergy contingency planning noted "If the allergy/immunology office does not have personal protective equipment available, it would be recommended that no patients with co-potential for asthma exacerbation and COVID-19 be seen at the office; the patient should instead be seen at a facility capable of isolation and equipped for asthma care." These recommendations are expected to be adjusted based on disease prevalence. Most ambulatory allergy services in the country restricted new patient appointments and procedures. The established patients were evaluated in virtual platforms. Sick patients were referred to facilities equipped with personnel protection, laboratory testing for SARS-CoV-2, and high acuity care treatments. Diagnostic testing and therapeutic interventions for allergic disease and asthma were restricted owing to concerns of the spread of the virus. This included testing for allergic sensitization, lung functions, FeNO, and nebulized treatments and allergy injections.[36,37] Clinicians considered health-care delivery during the pandemic to be suboptimal and are eager to resume face-to-face encounters as soon as possible. Parents were also unwilling to bring their children to hospitals and clinics for fear of contracting the virus during the pandemic. Many raised concerns about inhaled or oral steroids and risks of COVID-19 infections. Despite the multiple challenges of wildly spreading disease and misinformation, the patient outcomes with asthma were not worse and have been better than expected, generally. This is likely due to initial fear of susceptibility to severe COVID-19 with asthma, which prompted families to adopt health safety measures and improve adherence to asthma medications. A study at a health system in Wisconsin using electronic medication monitors noted a 14.5% relative increase in asthma controller adherence across all age-groups from January to March 2020.[38] The increased adherence is due to parental concern about asthma control during the outbreak.[39] School closures in particular also reduced exposures to allergens and viruses among children, which are important triggers of asthma, thus enabling improved asthma control.

COVID-19 AND ASTHMA TREATMENT GUIDELINES

There were some initial concerns about continuing ICSs and oral corticosteroids for asthma owing to fear of contracting the virus because steroids can impair immune responses. A meta-analysis of 39 trials revealed that ICS use was not associated with higher risk of pneumonia or respiratory infection due to COVID-19.[40] A study of RNA expression in bronchial brushes of a cohort of adult patients with asthma in the United Kindgom found that there was no significant difference in expression of ACE2 receptor and TMPRSS between healthy controls and patients with moderate and severe asthma undergoing varying corticosteroid treatment.[41] There was no greater risk for asthmatics than the general population for risk of COVID-19, regardless of the severity of asthma and various corticosteroid treatment intensities. This supports the use of inhaled steroids in the management of asthma.

In response to the pandemic, the Global Initiative for Asthma (GINA) updated guidelines on asthma care during the pandemic.[42] The guideline emphasized the

importance of optimal asthma management and medication adherence in reducing the risk of asthma exacerbations. The guidelines also recommend continuing prescribed medications including daily ICSs and biologic therapy.[42] The American Academy of Allergy, Asthma, and Immunology also reiterated that patients with asthma should continue to use their medications and aim for good control.[43] Both recommended the controller medication dose not be reduced or discontinued during the pandemic unless there is clear-cut benefit after careful consideration of risk/benefit for the child.[36,42,43] Systemic or oral steroids are recommended for use in moderate to severe asthma exacerbations that are unimproved with bronchodilators.[42,43] There is no evidence to suggest impairment of immune response to COVID-19 in patients treated with biologics for asthma. It is reasonable to continue administration of these agents during the pandemic.[42–44] Allergen immunotherapy used as an adjunct is also recommended to be continued with adjustment in doses and duration.[43]

COVID-19: USE OF NEBULIZERS AND SPIROMETRY

Many national and international societies including the GINA, National Asthma Council Australia, and American College of Allergy, Asthma and Immunology recommend against using nebulizers to reduce the risk of spreading the virus, with a preference for pressurized metered dose inhalers (MDIs).[42,43] SARS-CoV-2 is transmitted via droplets and aerosols. Owing to aerosol treatments, SARS-CoV-2 may persist in the air for up to 2 hours and may be recirculated and remain on dependent surfaces, promoting virus spread.[45] There is also concern that the particles that are generated with nebulization may stimulate cough in patients, which can spread the pathogen.[46] Use of the albuterol MDI (90 mcg/puff), 4 to 8 puffs every 20 minutes for 3 doses and then inhalation using the valved holding chamber every 1 to 4 hours, has shown to be as effective as nebulized therapy for mild to moderate asthma exacerbation in children.[47] MDIs with spacers have comparable efficacy with nebulizers, take shorter time for delivery, are more portable, and are less likely to spread the virus during the pandemic. Nebulizer treatments may still be necessary in very young or sick children and are

Box 1
Guidelines for minimizing risk of SARS-CoV-2 transmission[42]

Follow CDC guidelines[a]

Follow state and local directives on public health measures to control disease.

CDC guidelines for schools and childcare program.

Social and physical distancing measures
- Avoid close contact from other people—remain six feet away from others at all times.
- Practice self-isolation if you are in a high-risk group or if you are sick.
- Stay home and avoid large crowds and indoor spaces.

Face mask and personal protection measures:
- Wash hands using a sanitizing handwash containing at least 60% alcohol.
- Refrain from touching your face.
- Cover your mouth/nose when coughing with your elbow or a tissue.
  - Dispose of your tissue immediately afterward.
- Wear a face mask or face covering in public settings (now recommended by the CDC).
- Clean and disinfect surfaces regularly.

[a]https://www.cdc.gov/coronavirus/2019-ncov/prevent-getting-sick/prevention.html.

preferred in settings equipped with infection control measures. Most hospitals and clinics have rapidly adapted to the change of using MDIs to help control the pandemic without compromising asthma outcomes.

Spirometry is an important tool of asthma management but poses a considerable risk for the spread of infection to individuals and the surrounding surfaces within and around the test areas. The American Thoracic Society recommends prioritizing patients' clinical status by screening for urgent cases, ensuring protection of the health-care worker, and using in-line filters for spirometry.[48] The full operation of lung function services can resume when virus prevalence is low.[48] General guidelines for infection control and daily asthma management adapted from GINA guidelines are highlighted in **Box 1** and **Table 2**. The Food and Drug Administration under the Emergency Use Authorization approved two mRNA vaccines for ages more than 18 years in December 2020 for control of the pandemic.[47] Many other vaccines are in the research pipeline and under investigation for use in children.

Table 2
General guidance for care of patients with asthma during the COVID-19 pandemic[36]

Asthma Medications	• Continue daily controller (inhaled corticosteroids) as prescribed • Step down in treatment only in cases risk/benefit is carefully evaluated • For severe asthma: continue biologic therapy or oral corticosteroids if prescribed. • Close monitoring—use control tests such as the ACT, peak flow meter, and periodic virtual or clinic visits • Provide all patients with a written asthma action plan ○ Recommend that patients do not share inhalers and spacer devices

Acute Exacerbations	• Use a short course of OCS when appropriate for severe asthma exacerbations
	• Avoid nebulizers where possible to reduce the risk of spreading virus.
	  ○ Nebulizers may be required for:
	  ■ Severe or life-threatening exacerbation
	  ■ Young children (<4 y)
	  ■ Patients who are unable to use MDIs even with a valved holding chamber.
	  ○ Strict infection control procedures if aerosol-generating procedures are needed
	• A pressurized metered dose inhaler (MDI) via a spacer is preferred for mild to moderate asthma exacerbation.

Spirometry	• Avoid in patients with confirmed or suspected COVID-19 or if COVID-19 cases are high in community ○ Practice appropriate aerosol, droplet, and contact precautions if spirometry is needed. • Consider home peak flow monitoring • Follow local public health measures to control spread of infection—including personal hygiene and use of PPE.
Vaccination	• Recommend the annual influenza vaccine. • Follow CDC guidelines for COVID-19 vaccination. • After obtaining COVID-19 vaccines, continue to wear a mask and avoid close contact with others.

Abbreviations: ACT, asthma control test; OCS, oral corticosteroid; PPE, personal protection equipment.

SUMMARY

The COVID-19 pandemic has had a severe economic and health impact all over the world, including the United States, in particular. The available data, albeit limited, suggest that the initial concerns of the serious impact of COVID-19 illness in children with asthma are not evident to date. The reduction in asthma morbidities is likely due to a combination of improved adherence and decreased exposure to both allergens and viral infections in children. International guidelines are updated to guide physicians in the midst of the pandemic. In the face of unprecedented time, it is important to be vigilant, adhere to treatment guidelines, and implement preventive measures to eradicate the virus and improve outcomes for children with asthma.

CLINICS CARE POINTS

- The COVID-19 pandemic has caused catastrophic impact on health and well-being of humans globally.
- Unlike children, adults with chronic illnesses and other health risk factors had poorer outcomes.
- Current evidence suggests most children with chronic asthma were able to maintain asthma control during the pandemic.
- It is important to adhere to recommendations of international and national asthma guidelines for treatment of both acute exacerbation and chronic asthma.
- A multipronged measure including stepped pharmacotherapy based on asthma severity is necessary to maintain asthma control in children during the pandemic.
- Current evidence suggests favorable outcomes with inhaled corticosteroids and biologics used in treatment of asthma.
- It is important to implement CDC guidelines on SARS-CoV-2 infection control and vaccinations when available.

DISCLOSURE

The authors have nothing to disclose.

REFERENCES

1. Kahn JS, Mcintosh K. History and recent advances in coronavirus discovery. Pediatr Infect Dis J 2005;24(Suppl):S223–6.
2. Platto S, Xue T, Carafoli E. COVID-19: an announced pandemic. Cell Death Dis 2020;11:799–812.
3. COVID-19 Stats. COVID-19 Incidence, by Age Group -United States, March 1–November 14, 2020. MMWR Morb Mortal Wkly Rep 2021;69:1664.
4. Centers for Disease Control and Prevention. Coronavirus disease 2019 (COVID-19): people who are at high risk 2020. Available at: https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/asthma.html.
5. Novak N, Cabanillas B. Viruses and asthma: the role of common respiratory viruses in asthma and its potential meaning for SARS-CoV-2. Immunology 2020;161(2):83–93.
6. Singh SP, Pritam M, Pandey B, et al. Microstructure, pathophysiology, and potential therapeutics of COVID-19: A comprehensive review. J Med Virol 2020.

7. Camiolo M, Gauthier M, Kaminski N, et al. Expression of SARS-CoV-2 receptor ACE2 and coincident host response signature varies by asthma inflammatory phenotype. J Allergy Clin Immunol 2020;146(2):315–24.e7.
8. Wakabayashi M, Pawankar R, Narazaki H, et al. Coronavirus disease 2019 and asthma, allergic rhinitis: molecular mechanisms and host-environmental interactions. Curr Opin Allergy Clin Immunol 2021;21(1):1–7.
9. 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(1):203–6.e3.
10. Bunyavanich S, Do A, Vicencio A. Nasal gene expression of angiotensin-converting enzyme 2 in children and adults. JAMA 2020;323(23):2427–9.
11. Yamaya M, Nishimura H, Deng X, et al. Inhibitory effects of glycopyrronium, formoterol, and budesonide on coronavirus HCoV-229E replication and cytokine production by primary cultures of human nasal and tracheal epithelial cells. Respir Investig 2020;58(3):155–68.
12. Peters MC, Sajuthi S, Deford P, et al. Covid-19-related genes in sputum cells in asthma. Relationship to demographic features and corticosteroids. Am J Respir Crit Care Med 2020;202(1):83–90.
13. Skevaki C, Karsonova A, Karaulov A, et al. Asthma-associated risk for COVID-19 development. J Allergy Clin Immunol 2020;146(6):1295–301.
14. Papadopoulus NG, Custovic A, Deschildre A, et al. Pediatric Asthma in Real Life collaborators. Impact of COVID-19 on pediatric burden of asthma: Practice adjustments and disease burden. J Allergy Clin Immunol Pract 2020;8:2594–9.
15. Green I, Merzon E, Vinker S, et al. Covid-19 susceptibility in bronchial asthma. J Allergy Clin Immunol Pract 2021;9(2):684–92.e1.
16. Abe K, Miyawaki A, Nakamura M, et al. Trends in hospitalizations for asthma during the COVID-19 outbreak in Japan. J Allergy Clin Immunol Pract 2021;9(1):494–6.e1.
17. Ruano FJ, Somoza Álvarez ML, Haroun-Díaz E, et al. Impact of the COVID-19 pandemic in children with allergic asthma. J Allergy Clin Immunol Pract 2020;8(9):3172–4.e1.
18. Robinson LB, Fu X, Bassett IV, et al. COVID-19 severity in hospitalized patients with asthma: A matched cohort study. J Allergy Clin Immunol Pract 2021;9(1):497–500.
19. Lieberman-Cribbin W, Rapp J, Alpert N, et al. The impact of asthma on mortality in patients with covid-19. Chest 2020;158(6):2290–1.
20. Zheng F, Liao C, Fan Q-H, et al. Clinical characteristics of children with coronavirus disease 2019 in hubei, china. Curr Med Sci 2020;40(2):275–80.
21. Sun D, Li H, Lu X-X, et al. Clinical features of severe pediatric patients with coronavirus disease 2019 in Wuhan: a single center's observational study. World J Pediatr 2020;16(3):251–9.
22. Castro-Rodriguez JA, Forno E. Asthma and COVID-19 in children: A systematic review and call for data. Pediatr Pulmonol 2020;55(9):2412–8.
23. Wisniewski JA, McLaughlin AP, Stenger PJ, et al. A comparison of seasonal trends in asthma exacerbations among children from geographic regions with different climates. Allergy Asthma Proc 2016;37(6):475–81.
24. Larsen K, Zhu J, Feldman LY, et al. The annual september peak in asthma exacerbation rates. Still a reality? Ann Am Thorac Soc 2016;13(2):231–9.
25. Castro CR, Tarabichi Y, Gunzler DD, et al. Seasonal trends in asthma exacerbations: Are they the same in asthma subgroups? Ann Allergy Asthma Immunol 2019;123(2):220–2.

26. Van Bever HP, Chng SY, Goh DY. Childhood severe acute respiratory syndrome, coronavirus infections and asthma. Pediatr Allergy Immunol 2004;15(3):206–9.
27. Kenyon CC, Hill DA, Henrickson SE, et al. Initial effects of the COVID-19 pandemic on pediatric asthma emergency department utilization. J Allergy Clin Immunol Pract 2020;8(8):2774–6.e1.
28. Taquechel K, Diwadkar AR, Sayed S, et al. Pediatric asthma health care utilization, viral testing, and air pollution changes during the covid-19 pandemic. J Allergy Clin Immunol Pract 2020;8(10):3378–87.e11.
29. Bandi S, Nevid MZ, Mahdavinia M. African American children are at higher risk of COVID-19 infection. Pediatr Allergy Immunol 2020;31(7):861–4.
30. Bailey LC, Razzaghi H, Burrows EK, et al. Assessment of 135 794 pediatric patients tested for severe acute respiratory syndrome coronavirus 2 across the united states. JAMA Pediatr 2021;175(2):176–84.
31. Secord E, Poowuttikul P, Pansare M, et al. Pediatric emergency visits for asthma drop significantly with covid 19 school closure. J Allergy Clin Immunol 2021; 147(2):AB150.
32. Leeb RT, Price S, Sliwa S, et al. Covid-19 trends among school-aged children - united states, march 1-september 19, 2020. MMWR Morb Mortal Wkly Rep 2020;69(39):1410–5.
33. American Telemedicine Association. ATA commends. Congress for giving HHS authority to waive restrictions on telehealth for Medicare beneficiaries in response to the COVID-19 outbreak. Arlington (VA): American Telemedicine Association; 2020. Available at: www.americantelemed.org/press-releases/ata-commends-congress-for-waiving-restrictionson-telehealth-for-medicare-beneficiaries-in-response-to-the-covid-19-outbreak/. Accessed March 16, 2020.
34. Centers for Medicare & Medicaid Services. Coverage and payment related to COVID-19 Medicare. 2020. Available at: https://www.cms.gov/files/document/03052020-medicare-covid-19-fact-sheet.pdf. Accessed: March 15, 2020.
35. Hollander JE, Carr BG. Virtually perfect? Telemedicine for Covid-19. N Engl J Med 2020;382:1679–81.
36. Shaker MS, Oppenheimer J, Grayson M, et al. COVID-19: pandemic contingency planning for the allergy and immunology clinic. J Allergy Clin Immunol Pract 2020;8:1477–88.e5.
37. Cardinale F, Ciprandi G, Barberi S, et al. Consensus statement of the Italian society of pediatric allergy and immunology for the pragmatic management of children and adolescents with allergic or immunological diseases during the COVID19 pandemic. Ital J Pediatr 2020;46:84.
38. Kaye L, Theye BA, Smeenk I, et al. Changes in medication adherence among patients with asthma and COPD during the COVID-19 pandemic. J Allergy Clin Immunol Pract 2020;8:2384–5.
39. Oreskovic NM, Kinane TB, Aryee E, et al. The unexpected risks of covid-19 on asthma control in children. J Allergy Clin Immunol Pract 2020;8(8):2489–91.
40. Cazeiro C, Silva C, Mayer S, et al. Inhaled corticosteroids and respiratory infections in children with asthma: a meta-analysis. Pediatrics 2017;139(3).
41. Bradding P, Richardson M, Hinks TSC, et al. ACE2, TMPRSS2, and furin gene expression in the airways of people with asthma-implications for COVID-19. J Allergy Clin Immunol 2020;146(1):208–11.
42. GINA interim guidance on COVID-19 and asthma. Available at: https://ginasthma.org/wp-content/uploads/2020/12. Accessed: January12, 2020.
43. AAAAI. Asthma and COVID-19 2020. Available at: https://www.aaaai.org/ask-the-expert/covid. Accessed: December 20, 2020.

44. Morais-Almeida M, Aguiar R, Martin B, et al. COVID-19, asthma, and biological therapies: What we need to know. World Allergy Organ J 2020;13:100–26.
45. Cazzola M, Ora J, Bianco A, et al. Guidance on nebulization during the current COVID-19 pandemic. Respir Med 2020;176:106236.
46. Mei-Zahav M, Amirav I. Aerosol treatments for childhood asthma in the era of COVID-19. Pediatr Pulmonol 2020;55(8):1871–2.
47. Camargo CA Jr, Rachelefsky G, Schatz M. Managing asthma exacerbations in the emergency department: Summary of the National Asthma Education and Prevention Program Expert Panel Report 3 guidelines for the management of asthma exacerbations. J Allergy Clin Immunol 2009;124(2):S5–14.
48. Crimi C, Impellizzeri P, Campisi R, et al. Practical considerations for spirometry during the COVID-19 outbreak: Literature review and insights. Pulmonology 2020.