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Managing Asthma during Coronavirus Disease-2019: An Example for Other Chronic Conditions in Children and Adolescents

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The novel coronavirus disease-2019 (COVID-19), caused by the pathogen severe acute respiratory syndrome corona virus (SARS-CoV-2), has now spread around the globe with more than 1.8 million individuals affected and more than 110 000 deaths internationally.¹⁻⁴ As of April 12, 2020, there are 530 830 cases in the US with more than 20 000 deaths.^{2,3} The Institute for Health Metrics and Evaluation has predicted that this pandemic could exceed current healthcare capacity in the US with a total of 81 114 deaths (95% CI, 38 242-162 106) through August 2020.⁵

Asthma is one of the most common chronic diseases of childhood in the US. Data from the US Department of Health and Human Services notes that asthma prevalence increased between 2001 and 2010 and is now at its highest prevalence ever (overall 8.4% in 2010).⁶ In the US, approximately 7 million children have asthma.⁶ The morbidity of asthma in the US is high, and is higher in children than adults. Children missed 10.5 million school days owing to asthma in 2008; there were 6.7 million primary care visits related to asthma and 600 000 asthma-related emergency department visits for children in 2007.⁷

Multiple guidelines have emerged from international societies on the management of medical care during the COVID-19 pandemic, which include a section on pediatric asthma, including a North American guideline on contingency planning for allergy and immunology clinics during a pandemic and a Canadian Pediatric Society statement on asthma management during the COVID-19 pandemic.^{8,9} Owing to the high prevalence of asthma in the US, which is at the current epicenter of a global pandemic, the goal of this commentary is to provide an overview of what is known, and what is yet to be learned, about COVID-19 and pediatric asthma.

Differentiating Asthma from COVID-19

Symptoms of COVID-19 can be similar to those of worsening asthma, or an asthma exacerbation. Dry cough and shortness of breath, commonly seen in asthma, are among the most common presenting symptoms of COVID-19 in case series of children admitted to the hospital in China, as well as in available data from the Centers for Disease Control and Prevention (CDC) in the US.¹⁰⁻¹²

CDC	Centers for Disease Control and Prevention
COVID-19	Novel coronavirus disease-2019
OCS	Oral corticosteroids
SARS-CoV-2	Severe acute respiratory syndrome corona virus

Fever, a common presenting symptom of COVID-19, may help to differentiate COVID-19 from an asthma exacerbation, although fever can be present in other virus-triggered asthma exacerbations as well.^{3,10-12} Other less common symptoms of COVID-19, better described in the adult population, may help to differentiate COVID-19 from asthma and include myalgia, confusion headache, pharyngitis, rhinorrhea, loss of sense of smell and taste, diarrhea, nausea, and vomiting.¹² A travel history, close contact with someone infected with COVID-19, and absence of a prior atopic history in a child also help to differentiate the two.

Because there is substantial overlap between the clinical presentation of worsening asthma and COVID-19 and increasing community spread decreases likelihood of known contact with a case, screening for COVID-19 is required if available in any child with asthma who comes to medical attention with worsening cough or shortness of breath.^{8,13}

The Role of Asthma in COVID-19 Morbidity and Mortality

There is a theoretical risk that infection with COVID-19 in a child with asthma may increase the risk of pneumonia or acute respiratory disease.¹⁴ As a result, the CDC lists moderate to severe asthma as a risk factor for COVID-19 morbidity and mortality.¹⁴ However, to date the literature is ambiguous on whether preexisting asthma increases the risk of either COVID-19 infection, or morbidity/mortality owing to COVID-19, in children.

The evidence on COVID-19 risk factors derives largely from the adult population. Four case series, all from Wuhan, China, of adults admitted to hospital with COVID-19 did not list asthma as an underlying preexisting condition in any of those patients.^{12,15-17} In a large case series of 1099 adult patients from 552 hospitals in 30 provinces in China, asthma was not listed as a preexisting condition in any of the patients

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described.¹⁸ In contrast, recent data released from the CDC of US hospitalizations in March 2020 notes that 27.3% of adults 18-49 years of age who were hospitalized with COVID-19 had a history of asthma.³ In adults aged 50-64 years of age hospitalized for COVID-19 asthma was present in 13.2% and in those 65 years or older asthma was present in 12.9%.^{3,19} As a result, the American Academy of Allergy, Asthma & Immunology notes that “those with asthma in the 18-49 year old age range may be at increased risk of hospitalization owing to COVID-19.”¹⁹

Although there is a paucity of literature on pediatric risk factors, the case series to date from Wuhan on hospitalized pediatric cases do not list asthma as a preexisting risk factor for morbidity or mortality.^{10,11} It is further reassuring that children seem to be at a lesser risk of COVID-19 morbidity and mortality than the adult population in general, although severe infection still can occur.^{13,20} The CDC morbidity and mortality report notes that among the 149 082 reported US cases of COVID-19 for which age is known, only 2572 (1.7%) occurred in children 18 years of age and younger.³ Although among the patients with information on underlying conditions, 23% had at least 1 underlying condition such as asthma, only 5.7% of children infected with COVID-19 required hospitalization (compared with 10% of adults aged 18-64 years) and only 3 deaths were reported in children (<1% of pediatric cases). In a case series from China of 72 000 cases, approximately 1% were children aged 0-18 years of age with only 1 death reported in the adolescent population (and none in children under 10 years of age).^{13,21}

Another risk in children with asthma is that infection with COVID-19 could trigger a viral-induced asthma exacerbation. There is minimal literature on this risk from COVID-19, but there are data on the risk of asthma exacerbations triggered from other coronavirus infections, with mixed findings. SARS, owing to human coronaviruses HCoV-229E and HCoV-OC43, did not cause an increase in asthma exacerbations in children during the 2002 epidemic, or induce bronchial hyperreactivity or eosinophilic inflammation.²² In fact, paradoxically, asthma exacerbations actually decreased during that time, which was attributed to improvements in hygiene measures related to the epidemic.²² However, in contrast, nonepidemic coronaviruses are found commonly in the respiratory tracts of children with an asthma exacerbation and have contributed to bronchial hyper-reactivity and eosinophilic inflammation.²³⁻²⁶

In summary, based on available information to date, it is unclear whether there is a significantly increased risk of COVID-19 morbidity among children with asthma.^{8,9} It is also unknown whether asthma medications such as high-dose inhaled corticosteroids or asthma biological therapies pose a risk in managing COVID-19 infections. Before any definitive conclusions can be drawn, larger scale data are required from pediatric populations, and from heterogeneous locations that have been impacted by COVID-19. It also remains unclear if COVID-19 increases the risk of asthma exacerbations. As a result, good asthma control is essential as a precautionary measure during this time.^{8,9,13,20}

Treatment of Asthma During the COVID-19 Pandemic

In addition to the current burden of COVID-19, the spring season is often a time for asthma exacerbations owing to emergence of seasonal aeroallergens, and other respiratory viruses.²⁷ The best way to prevent an exacerbation is consistent proper use of medicines to control asthma, such as inhaled corticosteroids and/or montelukast. As a result, children should remain on their current asthma medications during the COVID-19 outbreak.^{8,9} This recommendation is supported by multiple international organizations, including the CDC, the Global Initiative for Asthma, and the North American consensus guideline on allergy care during the COVID outbreak.^{8,9,28,29} It is recommended that children not step down any controller medication during this time unless “this is clearly favorable from an individual standpoint, with careful consideration of the balance between benefit and harm/burden.”⁸ Other recommendations to maintain asthma control include avoiding known asthma triggers such as aeroallergens, frequent handwashing, physical distancing, and regular review of inhaler technique.^{9,29} An exacerbation, if it occurred, “could require [children] to enter the healthcare system, which would put them at increased risk of being exposed to SARS-CoV-2 during the current pandemic.”⁸

Some biologic agents, such as omalizumab (anti-IgE) and mepolizumab (anti-IL5), are approved for use in moderate to severe asthma in adolescents.³⁰ The current recommendation for adolescents who are using these medications is to continue their use.⁸ There is no current evidence that use of these medications increases the risk of COVID-19 infection or morbidity.

If a child is using a nebulized asthma relief medication, this should be switched to a metered dose inhaler or dry powder inhaler (turbuhaler or diskus) under most circumstances.^{8,9} Nebulization increases the risk of viral lower lung deposition.^{8,9,31} It also increases the risk of infection transmission owing to both stimulating a cough reflex, as well as generating “a high volume of respiratory aerosols that may be propelled over a longer distance than is involved in a natural dispersion pattern.”³¹ It was poignantly noted in a recent editorial that “there is a possibility that nebulizer therapy in patients with COVID-19 infection can transmit potentially viable coronavirus to susceptible bystander hosts.”³¹ The only possible reasons for a child to use a nebulizer at home during the COVID-19 pandemic are a poor response to a metered dose inhaler/spacer, a child who is either uncooperative or unable to follow the directions required for metered dose inhaler use, or medication shortages (which are discussed in greater detail elsewhere in this article).^{8,9,31}

Treatment of Asthma Exacerbations during COVID-19

The CDC and the World Health Organization have recommended against oral corticosteroid (OCS) use as a treatment

for COVID-19.^{32,33} This recommendation is based on experience with influenza, SARS-CoV, and Middle East respiratory syndrome coronavirus, where OCS use prolonged viral replication and was associated with prolonged viral clearance, increased complication rates, increased risk of mechanical ventilation, and higher mortality rates.³⁴⁻³⁷ It has been noted that OCS therapy increases the risk of nosocomial infection and secondary infection.³⁸ However, there is a distinction between OCS use as a therapy for COVID-19, and OCS use as a treatment of asthma exacerbations.⁸ There is broad consensus that asthma exacerbations should be treated aggressively and in keeping with current guideline recommendations.⁹ Multiple national and international organizations such as the Global Initiative for Asthma recommend OCS use as required, and in keeping with the child's asthma action plan, during COVID-19.^{8,9,28}

The use of nebulized medications are especially discouraged in a healthcare setting, where infection transmission to other vulnerable patients is a risk.^{9,31} If used, proper personal protective equipment is required. It must also be considered that nebulized viral droplets can persist in the air for hours.³⁹

For any child with asthma who is having progressive or worsening symptoms, COVID-19 screening protocols must be used to help determine their level of risk as well as the need for COVID-19 testing at an appropriate facility.⁸

For children hospitalized with an asthma exacerbation either documented or suspected to be associated with COVID-19 that is progressing, it might be decided to use one of the agents currently being considered in adults, for example, hydroxychloroquine,^{40,41} or to seek compassionate release of remdesivir. There are no current data on the safety and efficacy of these agents in children and thus should be discussed in the setting of the hospital policy.^{42,43} Although the dosage of these medications in adolescents may be similar to adults, the appropriate adjustment for children under 12 years of age remains to be defined.

Ongoing Challenges during COVID-19

Medication Shortages

There is a growing medication shortage across North America, including asthma medications such as albuterol.³⁹ In many cases, such as with albuterol, these medications increasingly are being used in confirmed or suspected patients with COVID-19 to help with respiratory issues. To help combat the shortage of albuterol specifically, the US Food and Drug Administration approved the first generic albuterol inhaler on April 8, 2020.⁴⁴ If faced with an albuterol shortage, other available options include substituting other short-acting beta-agonists, using an expired albuterol inhaler, and ensuring good asthma control, which decreases the need for reliever medications in general.^{9,39} Many of the substitute short-acting beta-agonists are dry powder inhalers (diskus or turbuhaler) and as such children often need to be at least 6 years of age to produce enough inspiratory force to use these devices properly.^{9,45} For adolescents

12 years and older, another option is inhaled corticosteroid-formoterol for both maintenance and relief therapy as supported by the Global Initiative for Asthma 2019 update.^{46,47} Nebulized albuterol should only be considered as a last resort, and proper infection prevention protocols need to be followed.^{8,9,31} If no other medications are available, epinephrine inhalers might be considered as well, if used prudently.

Virtual Visits

With the need for significant healthcare resource reallocation, as well as shortages of personal protective equipment, much of the allergy/immunology specialty has converted to largely virtual visits, or visit deferral, during the COVID-19 outbreak.⁸ Owing to the need for almost exclusively virtual visits at this time, having a peak flow meter in homes may be helpful to diagnose an acute exacerbation at home, by comparing baseline measurements with those during highly symptomatic times. There are several advantages to virtual visits, including access to specialists, removing the transportation barrier required for an in-person visit, allowing those too sick to travel to connect with a healthcare provider, and, most important in the current context, prevention of infection transmission with in-person visits.⁴⁸

Virtual visits should be prioritized for children who have poorly controlled asthma, have worsening asthma symptoms, or who have required dose escalations of their asthma medications in the past several months' time.⁸ It is recommended that follow-up visits for children with mild to moderate or well-controlled asthma be postponed during COVID-19, or converted to virtual visits if time permits.⁸ It also is recommended that children of any asthma severity who have been well controlled for the past 6-12 months (no emergency room visits, ≤ 1 OCS dose, ≤ 2 exacerbations in the past 6-12 months) have visits deferred or converted to virtual visits (time permitting).⁸ For children with moderate to severe asthma exacerbations, an in-person visit likely is necessary but, as noted in the joint North American guideline on COVID-19 and allergy contingency planning, "If the allergy/immunology office does not have [personal protective equipment] available, it would be recommended that no patients with a co-potential for an asthma exacerbation and COVID-19 be seen at that office; the patient should instead be seen at another facility capable of COVID-19 isolation which is staffed and equipped to assess and manage asthma."⁸ Recommendations may be adjusted over time, based on the duration of COVID-19 and the time required for physical distancing.

Asthma Clinical Trials

It is currently recommended that entry into any asthma clinical trial be suspended during the COVID-19 pandemic.⁸ For children with asthma already participating in clinical trials, consideration could be given to virtual visits if possible.⁸ Procedures that require forced expiratory maneuvers such as spirometry, methacholine challenge, or induced sputum samples should be postponed to minimize staff risk and potential room contamination. Medication withdrawal as part

of research protocols also should be deferred to a later time. Consideration should be given to telephone or telemedicine visits to limit exposure to a medical setting.

Impact of Social Determinants of Health on Asthma and COVID-19

There are many social determinants of health that have an impact on pediatric asthma morbidity, including caregiver income; physical environment, including exposure to second-hand smoke; access to health services; and race/ethnicity.⁴⁹⁻⁵¹ There is likely an interplay between some of these social determinants of health and the impact of COVID-19 on children with asthma. It has been suggested that exposure to second-hand smoke increases COVID-19 morbidity.^{52,53} Of those hospitalized in the US for COVID-19, data from the CDC indicate that 33.1% were non-Hispanic black, although they only make up 18% of the catchment area population.³ A recent editorial notes that low-income families are at higher risk of COVID-19 because low-income jobs mostly cannot be performed remotely, often do not pay sick days, and are often not associated with insurance benefits; as a result, it may not be possible for these families to afford the steps necessary for physical distancing.⁵⁴

Although the relationships between these variables needs to be further elucidated, it is possible that measures that impact social determinants of health, such as reducing exposure to second-hand smoke or improving healthcare access in low-income neighborhoods, may improve prognosis in children with asthma who contract COVID-19. In addition, these families could benefit from counseling on having the appropriate amount of medications available for home during this period of restricted travel. In addition, they should check medications to be sure that none is expired.

Impact of COVID Restrictions

It is possible that children may not be severely affected by SARS-CoV-2 for some undefined reason to date, but they can still be carriers and could transmit virus to vulnerable people, including elderly relatives. Therefore, social distancing has included children, which has necessitated discontinuing school. It remains to be determined what impact this step will have on children, including those children with asthma. Often, parents discontinue medications in children during the summer months because they are doing well and they are out of school.⁵⁵ However, this year is different, because school was discontinued during the spring season, a time of seasonal allergen exacerbation and viral infection. School adds a certain structure to the day and there is some level of administration of asthma medication administration around the school day. Clinicians and parents should observe for potential breakdowns in adherence to controlling medications, especially in families in chaotic circumstances. The impact on education of home schooling, especially in families that lack an organizational structure, remains to be seen. Finally, it has been suggested that school closures will increase the risk of childhood obesity, a known risk factor

for worsening asthma.⁵⁶ Whether this occurs, and how this influences asthma control, also is yet unknown.

Conclusions

In the face of uncharted territory and unprecedented times, there remains much to be learned about the impact of pediatric asthma on the course of SARS-CoV-2 virus infection. Although adult data suggest that asthma is a risk factor for COVID-19 morbidity and mortality, such a risk in children is unclear. Differentiating COVID-19 from worsening asthma, or an asthma exacerbation, is challenging. As a result, pediatricians and families have an essential role in ensuring that children with asthma maintain good asthma control during this time. Children and adolescents with asthma should remain on their current asthma medications and practice physical distancing, regular handwashing, and aeroallergen avoidance. Treatment of asthma exacerbations should include OCS if required. Nebulized medications are not recommended at this time owing to the increased risk of viral transmission. Healthcare providers should remain alert for changing policies and recommendations knowledge advances. ■

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