



Coronavirus disease 2019 and pediatric asthma: friend or foe?

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Purpose of review

The interplay of asthma and coronavirus disease 2019 (COVID-19) in children is yet unknown. The purpose of this review is to determine the interplay of asthma and asthma therapeutics and COVID-19.

Recent findings

There is no evidence to date that asthma is a risk factor for more severe COVID-19 outcomes, especially in children. There is actually some basis to suggest that children with atopic asthma may be at reduced risk of asthma exacerbations during COVID-19. The impact of asthma therapeutics on COVID-19 outcomes is unclear, but guidance is relatively uniform in recommending that those with asthma remain on current asthma medications. A focus on social determinants of health may be increasingly important during the pandemic and beyond.

Summary

Asthma in children appears to be more friend, than foe, during COVID-19.

Keywords

asthma therapeutics, coronavirus disease 2019, pediatric asthma

INTRODUCTION

The coronavirus disease 2019 (COVID-19) pandemic has gripped the entire world for close to the past 2 years, with over 245 million cases and close to 5 million deaths internationally as of 28 October 2021 [1]. In the United States to date, there have been more than 44 million cases and more than 715 000 deaths. While the impact of the global pandemic has been mitigated with international vaccination efforts, the impact of the pandemic, in particular among those with underlying conditions, remains an international concern. Asthma is one of the most common chronic diseases of childhood [2]. The pandemic, and its impact on the respiratory system, has placed children and their families on 'high alert' [3]. However, the influence of pediatric asthma on COVID-19 remains an evolving, and yet to be completely elucidated, story. The goal of this article is to review the interplay of asthma, and asthma therapeutics, with COVID-19.

ASTHMA AS A RISK FACTOR (OR LACK THEREOF) FOR CORONAVIRUS DISEASE 2019 OUTCOMES

Overall, children are less symptomatic with COVID-19 than adults and the risk of severe COVID-19

outcomes is very low. Based on data from the Centers for Disease Control and Prevention (CDC), children comprise less than 0.1% of all COVID-19 mortality [4]. Among the reported cases of COVID-19 for which age is known in the United States, only 2572 (1.7%) occurred in children 18 years and younger [5]. While among the patients with information on underlying conditions, 23% had at least one 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) [5]. A summary of 72 314 cases from the Chinese CDC found only 1% of case patients were 9 years or younger, and no deaths occurred in this age group [6].

Intrinsically, one would assume that asthma would serve as a risk factor for more severe

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Curr Opin Allergy Clin Immunol 2022, 22:95–100

DOI:10.1097/ACI.0000000000000809

KEY POINTS

- There is no evidence to date that asthma is a risk factor for more severe COVID-19 outcomes.
- The impact of asthma therapeutics on COVID-19 outcomes is unclear.
- A focus on social determinants of health may be increasingly important during the pandemic and beyond.

COVID-19 outcomes. Childhood asthma involves an ‘umbrella of high risk factors’ including airway inflammation, epithelial damage, mucous hypersecretion, and reduced innate immune response, all of which would seem to increase the risk associated with a respiratory virus [7]. This theoretical risk and pathophysiologic reasoning has led multiple international organizations including the CDC to list asthma as a risk factor for COVID-19 morbidity and mortality based on the theoretical risk that infection may increase the risk of an acute respiratory process [8].

However, to date there is no evidence that asthma is a risk factor for more severe COVID-19 outcomes, especially in children. A national prospective Canadian study of 264 children admitted to hospital with COVID-19 infection found that while 39.3% of those children admitted had at least one comorbidity including chronic lung disease, asthma was an exception [9^{***}]. A systematic review (though not limited to the pediatric population) did not find any increased risk of COVID-19 among those with asthma [10]. In fact, it was stated in the European Academy of Allergy and Clinical Immunology (EAACI) pediatric section statement that a classification of asthma as a risk factor is ‘based more on common sense rather than mounting evidence’ [11^{***}]. A systematic review on whether asthma constitutes a risk factor for COVID-19 severity in children, conducted in three stages noted in the first stage that, of 67 studies, none included data on pediatric asthma as a comorbidity for COVID-19 [12^{***}]. In the second search (34 studies), none included data on children and in the third search, none included data on children [12^{***}]. The conclusion of the systematic review, in the words of the authors was that ‘there is scarcely any data on whether childhood asthma...constitute risk factors for severe acute respiratory syndrome (SARS)-CoV-2 infection or COVID-19 severity’.

It is possible that the hyperinflammation causing severity and complications with COVID-19 may be downregulated with asthma (due to inefficient

IFN- α production and the anti-inflammatory influence of the Th2 pathway) [13,14]. A prevailing theory is also related to the host angiotensin converting enzyme 2 (ACE2) receptor, which facilitates SARS-CoV-2 attachment to host cell membranes in the nasal epithelium and lung [7]. ACE2 expression has been shown to be lower in children overall, and further reduced in those with both allergic sensitization and asthma [15]. The Th2 pathway has a role in ACE2 regulation [15]. In a retrospective examination of nasal epithelium from 305 individuals aged 4–60 years in New York, it was found that compared with younger children, ACE2 gene expression was significantly higher in older children ($P=0.01$), young adults ($P<0.001$), and adults ($P=0.001$) [16].

THE ROLE OF CORONAVIRUS DISEASE 2019 (OR LACK THEREOF) IN ASTHMA EXACERBATIONS

Historically, seasonal coronavirus infection is associated with asthma exacerbations in children [17]. However, previous coronavirus epidemics have not been associated with a risk of asthma exacerbations. For example, with SARS, also a novel coronavirus epidemic, the incidence in children was low and symptoms were predominantly mild with low morbidity and mortality [18]. SARS did not induce bronchial hyper-reactivity nor cause eosinophilic inflammation and was not associated with an increase in asthma exacerbations [18].

In keeping with previous coronavirus epidemics, there is actually some basis to suggest that children with atopic asthma may be at reduced risk of asthma exacerbations during COVID-19. A retrospective review of 212 children with confirmed atopic asthma in Spain found that, compared with those children with asthma who did not develop COVID-19, those who did had no significant difference in asthma treatment, lung function, asthma severity or asthma control [19]. In fact, families did not report any worsening of symptoms compared with a similar time period in the previous year among the atopic children with asthma who developed COVID-19 [19]. During the first 5 weeks of the lockdown in Slovenia, there was a 71–78% decrease in pediatric asthma admissions compared with the same time periods in the last 3 years [20]. At a large US tertiary care center during the spring of 2020, a 76% reduction in asthma emergency department (ED) visits was noted, with similar trends for children of all levels of acuity [21^{*}]. The percentage of children with asthma subsequently admitted to the hospital also decreased (from 31 to 22%). Electronic health records from Children’s Hospital of Philadelphia found that, compared with the 5 previous

years, in-person asthma encounters decreased by 87% (outpatient) and 84% (emergency and inpatient), and asthma-related systemic steroid prescriptions decreased [22]. A study of pediatric patients with asthma treated in the Children's Hospital of Orange County found 78, 90, 68% reductions in hospitalization, ED visits and asthma exacerbations, respectively, compared with pre-COVID-19 2020, and significant reductions in albuterol and inhaled corticosteroid use ($P < 0.05$) [23]. A retrospective chart review of children utilizing the pediatric ED in the Bronx from March to June 2020 found a significant reduction in asthma-related ED visits ($P < 0.0001$) [24]. While not specific to children, a cohort from a US database of healthcare claims for over 200 million privately insured patients found a significant decline in asthma exacerbations after the COVID-19 pandemic onset ($P < 0.001$) [25].

It is possible that public health measures resulting in masking, reduced viral transmission, reduced outdoor aeroallergen exposure, reduced traffic/industrial pollution, and improved air quality overall are contributing to the reduction in asthma exacerbations [26]. During the first spring of the pandemic in Slovenia, when a dramatic reduction in asthma exacerbations was noted, there was also a 51–58% decrease in admissions for acute respiratory tract infections and a 48–58% reduction in the air nitrogen dioxide level [although concentrations of particulate matter with a diameter of less than 10 micrometers (PM₁₀) did not change substantially] [20]. The Children's Hospital of Orange County study found a significant reduction in PM_{2.5} and influenza rates during the pandemic, as well as increased use of telehealth resources which may serve previously under-accessed populations (with greater use in the publicly insured group compared with the commercially insured group) [23]. Other possibilities include that patients and their families are avoiding seeking care during the pandemic, and/or that the pandemic has led to improved compliance with asthma medications [25].

ASTHMA MEDICATIONS AND CORONAVIRUS DISEASE 2019 RISK

Inhaled corticosteroids

The impact of inhaled corticosteroids (ICS) therapy on COVID-19 outcomes is unclear. A meta-analysis of 39 trials ($N = 11\,615$ children with asthma) on ICS use does not support an increased risk of respiratory infection in general [27]. A statement from the EAACI notes that 'since asthma itself may be a risk factor for the severity of COVID-19 disease and since the use of ICS does not pose an increased risk for

pulmonary or systemic infections in children with asthma, their regular use is unlikely to increase the risk of acquiring the infection or increasing the severity of the present infection' [11¹¹].

There is a pathophysiologic basis to the possibility that ICS use may reduce risk of severe COVID-19 outcomes. ICS use has a beneficial impact on pulmonary physiology and reduces the risk of acute respiratory distress syndrome [28]. Studies (although not specific to the pediatric population) have found ICS therapy to reduce ACE2 pulmonary expression, which has the potential to reduce susceptibility to SARS-CoV-2 infection and severe COVID-19 infection [29], although to what extent this impacts real-world clinical outcomes remains unclear [30]. In addition, Inhaled ciclesonide has been shown in vitro to suppress SARS-CoV-2 replication in cultured cells potentially due to antiviral in addition to anti-inflammatory activity, although to date no clinical trials have examined the use of ICS in COVID-19 [31]. A systematic review of whether use of ICS is a risk factor for adverse outcomes due to COVID-19 (not specific to the pediatric population) found that, among 59 publications, there was no evidence on whether ICS use is a factor for adverse or beneficial outcomes in acute respiratory infections due to coronavirus infection [32]. Studies are ongoing but it has been noted that while it is unknown whether ICS protects against COVID-19, 'to dismiss this hypothesis... is premature' [28].

The Global Initiative for Asthma (GINA) strategy, as well as the American Academy of Allergy, Asthma and Immunology (AAAAI) recommend remaining on ICS therapy during the pandemic [33,34]. Nebulization should be avoided if possible as it is aerosol generating [35,36¹¹]. Remaining on ICS therapy is essential for asthma control, and any reduction or taper in dosing carries the risk of asthma exacerbations, ED visits, and/or a need for oral corticosteroid (OCS) use [26]. In fact, it has been suggested that even in a child for whom asthma is very well controlled, and in whom ICS dose reduction would be considered, greater caution should be exercised and could be based on atopic status and baseline risk [26]. As noted by the AAAAI, the 'optimal control of asthma symptoms is the first defense against COVID-19' [33].

Oral corticosteroids

As with ICS, the impact of OCS therapy on COVID-19 outcomes remains unknown. There is little to no evidence in the pediatric population and evidence is evolving in the adult asthma population. A large study based on primary care records in the United Kingdom found that, among adults, the risk of

COVID-19 death was increased among those who had recently needed OCS therapy for asthma [37]. In a study of 8242 adults with asthma, OCS therapy was associated with a significantly increased risk of moderate-to-severe COVID-19, as well as all-cause mortality within 90 days (although not associated with increased risk of SARS-CoV-2 infection) [38]. In addition, with previous coronavirus epidemics such as SARS and Middle Eastern Respiratory Syndrome, OCS use was associated with reduced viral clearance [39]. The CDC notes that due to the immunosuppressive effects of OCS therapy, using OCS does place individuals at higher risk of severe COVID-19 outcomes [40]. However, overall, a systematic review and meta-analysis (total 1703 adult patients) noted administration of systemic corticosteroids compared with usual care reduced 28-day all-cause mortality among those critically ill with COVID-19 (although used as a COVID-19 treatment and not specific to asthma) [41]. The GINA strategy recommends that while minimizing the use of OCS therapy is important, OCS therapy should be considered in those with severe asthma and could be used for a short course for a severe asthma exacerbation during the pandemic [34].

Biologic medications

Current recommendations are to remain on asthma biologic medications during COVID-19, other than the possible exception of suspension of biologic medications during an acute phase of a COVID-19 infection [11¹¹,42]. The AAAAI has stated that there is no evidence that the immune response to COVID-19 will be impaired in patients with asthma on biologic therapies and that it would be ‘reasonable’ to continue administration of biologics in patients with asthma [33,43]. This recommendation is supported by several international allergy/pulmonology organizations including the British Thoracic Society [44,45]. The GINA strategy similarly supports remaining on biologic medications [34].

There are no studies specific to COVID-19 outcomes in children and adolescents on biologic therapy during COVID-19. There is some limited evidence in the adult asthma population that use of biologics is not associated with a higher risk of COVID-19 infection or severe outcomes. For example, a prospective study of 676 adults with severe asthma on biologic therapy found a low incidence of COVID-19 infection (2.1%) among patients with severe asthma, and only 5% presented COVID-19-related symptoms [46]. In a cohort study of 8242 patients with asthma who tested positive for SARS-CoV-2 infection, biologics were not an increased risk of SARS-CoV-2 infection, nor with a significantly

increased risk of moderate-to-severe COVID-19 infection, nor with the composite end point of moderate-to-severe COVID-19 or all-cause mortality within 90 days [38].

Home-based administration of biologics has emerged as an option during COVID-19. A study of 23 children with asthma on biologic therapy noted that home administration of omalizumab and mepolizumab, virtually supported by video calls and home spirometry, was safe and accurate without any significant adverse events [47]. In addition, it was positively perceived by children and their caregivers. At-home administration of omalizumab or mepolizumab has been demonstrated to be a cost-effective strategy [48]. Multiple international organizations support home-based administration of biologics when possible during the pandemic [43,48,49].

UNINTENDED CONSEQUENCES AND THE ROLE OF SOCIAL DETERMINANTS OF HEALTH

Clear evidence exists for the negative impact that adverse determinants of health can have on COVID-19 outcomes among children and their families [50,51]. Children and their families experiencing homelessness are at higher risk of COVID-19, and lack access to care [52]. Poverty, which has increased exponentially in the United States and elsewhere during the pandemic, has been strongly associated with COVID-19 outcomes, with a US study noting a close to four-fold higher death rate among counties with more, versus less, poverty [53]. There are racial and ethnic discrepancies in COVID-19 infection, with a two-fold higher rate of cases among Hispanic persons, a three-fold higher rate of hospitalization and a two-fold higher rate of death [54]. For Black or African American non-Hispanic persons, there is a three-fold higher risk of hospitalization and a two-fold higher risk of death [54]. While necessary, sequelae of public health policies such as school closures disproportionately impact those facing adverse determinants [55]. It has been stated that ‘no credible scientist, learning expert, teacher or parent believes that children aged 5 to 10 years can meaningfully engage in online learning without considerable parental involvement, which many families with low incomes are unable to provide because parents must work outside the home’ [56]. On the contrary, the impact of adverse social determinants and COVID-19 outcomes are compounded in children with asthma [50], as food insecurity, poverty, race/ethnicity and many other determinants can have persistent effects on childhood asthma outcomes as well [50,57].

CONCLUSION

The interplay of asthma and COVID-19 remains an evolving story and while it is yet to be fully elucidated, asthma appears to be more friend than foe. There is no evidence to date that asthma is a risk factor for more severe COVID-19 outcomes, especially in children. There is actually some basis to suggest that children with atopic asthma may be at reduced risk of asthma exacerbations during COVID-19. The impact of asthma therapeutics on COVID-19 outcomes is unclear, but guidance is relatively uniform in recommending that those with asthma remain on current asthma medications. A focus on social determinants of health may be increasingly important during the pandemic and beyond.

Acknowledgements

None.

Financial support and sponsorship

None.

Conflicts of interest

E.M.A. is an employee of Public Health Agency of Canada (PHAC). The views expressed are her own and not those of PHAC.

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- of special interest
- of outstanding interest

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