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Original Article

Effect of the coronavirus disease 2019 pandemic on morbidity among children hospitalized for an asthma exacerbation

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ABSTRACT

Background: Pediatric asthma exacerbations account for substantial morbidity, including emergency department (ED) visits and hospitalizations. Although the coronavirus disease 2019 (COVID-19) pandemic was associated with a decrease in pediatric asthma ED visits and hospitalizations, there is limited information on the clinical characteristics of children hospitalized with an asthma exacerbation during the pandemic.
Objective: To investigate the clinical characteristics of children hospitalized with an asthma exacerbation during the pandemic as compared with those hospitalized during the same months in the year prior.
Methods: A retrospective case-control study was conducted at the Children's National Hospital, Washington, DC, comparing demographic and clinical characteristics of all children, 2 to 18 years old, hospitalized for an asthma exacerbation between April to September 2020 (cases) and April to September 2019 (controls).
Results: We identified 50 cases and 243 controls. Cases were significantly older than controls (9.8 ± 4.3 years vs 6.7 ± 3.8 years; $P < .001$), had significantly less eczema (16% vs 32.1%; $P = .02$) and food allergies (6% vs 18.5%; $P = .03$), and were more noncompliant with controller medications (46% vs 24.7%; $P = .002$) than controls. Magnesium sulfate was more frequently administered in the ED to the cases than to the controls (84% vs 63%; $P = .004$). Its use was associated with older age, African American race, and Hispanic ethnicity, but was independent of comorbid conditions.
Conclusion: Patients hospitalized for asthma during the COVID-19 pandemic were older and have less atopy than those hospitalized prepandemic. A larger proportion received magnesium sulfate in the ED, suggesting patients had with more severe asthma presentation during the pandemic.

Introduction

Childhood asthma is one of the most common chronic pediatric diseases, and it is associated with severe morbidity and mortality. More than 5 million children in the United States live with asthma, and in 2018, approximately 75,000 children required hospitalization and more than 700,000 children visited the emergency department (ED).[1]

Respiratory viruses are the most well defined of the many known triggers for asthma exacerbations and poorly controlled asthma. Human rhinovirus, respiratory syncytial virus, and influenza virus have been consistently associated with childhood asthma ED visits and hospitalizations.[2,3] On the basis of these associations between poorly controlled asthma and viral illnesses, there was concern that children with asthma may be adversely affected by coronavirus disease 2019 (COVID-19) owing to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Instead, there was a decrease in ED visits and hospitalizations by more than 80% among children with asthma, including at our center.[4-7] Although SARS-CoV-2 can exacerbate asthma, children admitted to the hospital with asthma and COVID-19 infection did not seem to be at a higher risk of more severe COVID-19 or asthma symptoms than the healthy population.[8,9] The decrease in disease burden was also observed in the outpatient setting where children with asthma consistently required fewer controller medications and oral steroids compared with the prepandemic period.[4,10] Although our center reported fewer ED visits and hospitalization in 2020, the ratio of hospitalization, including to the intensive care unit, to ED visits was higher suggesting that children were more acutely ill at the time of presentation.[7] However, the details on the severity of asthma and its presentation among children who were hospitalized for an asthma exacerbation during the COVID-19 pandemic, as

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compared with those hospitalized in the pre–COVID-19 pandemic times, are not known.

To address this knowledge gap, we compared the characteristics of children hospitalized with an asthma exacerbation at a single urban pediatric medical center during April to September 2020 (pandemic) and April to September 2019 (prepandemic). We hypothesized that although fewer children would be hospitalized for asthma during the pandemic, those hospitalized would present with higher severity of disease and need higher levels of clinical disease management during their hospital stay.

Methods

Study Design and Study Population

This is a retrospective case-control study comparing consecutive cases series of patients admitted to the Children's National Hospital (CNH) in Washington, DC. Cases were defined as children aged 2 to 18 years hospitalized from the ED with an acute exacerbation of asthma between April 1 and September 30, 2020. Controls included children within the same age range that were hospitalized for an asthma exacerbation between April 1 and September 30, 2019. The 2 groups were matched by the month of hospitalization to address the seasonal variability of childhood asthma. Medical record numbers of children hospitalized for an asthma exacerbation were extracted from the electronic medical records system at CNH using International Classification of Diseases, Tenth Revision, discharge diagnoses codes where "asthma" was listed in the first or second position, excluding those with a diagnosis of cystic fibrosis, sickle cell disease, bronchiectasis, home ventilator use, or tracheostomy at any time in their lifetime. Subsequent chart review identified children with asthma who were hospitalized for reasons other than an acute asthma exacerbation and were further excluded. The study was approved by the Institutional Review Board committee at CNH.

Data Variables

Our primary outcome of interest was the receipt of administration of intravenous magnesium sulfate in the ED. Because magnesium sulfate is an ancillary medication reserved for severe exacerbations, its use is an objective measure of increased severity of asthma exacerbations at presentation. Our secondary outcomes included initial admission location (floor or intensive care unit [ICU]), length of stay, and medications administered in ED and throughout hospital admission (oxygen, continuous short-acting β-agonist for less than or more than one day, systemic steroids, ipratropium bromide, theophylline, or epinephrine and continuation of home inhaled corticosteroid therapy).

Covariates collected included demographic information, such as age of the patient, sex identified at birth (male/female), and race (African American, White, and other or unknown) and ethnicity (Hispanic or non-Hispanic). Baseline asthma characteristics included severity classification (intermittent, mild persistent, moderate persistent, or severe persistent) based on physician documentation, home asthma treatment (step 1 to step 6) as per the National Heart Lung and Blood Institute guidelines, history of previous ICU admissions, and most recent percent-predicted value of forced expiratory volume in 1 second, when available.[11] Comorbidities known to be associated with asthma morbidity included sleep-disordered breathing, gastroesophageal reflux disease, obesity, and chronic lung disease. Characteristics of the exacerbation leading to the hospitalization included duration of asthma symptoms before presenting to the ED, documented trigger for the asthma exacerbation (infection, allergenic, physical activity, environmental exposures, food, medication, noncompliance, or unknown), and associated allergies (eczema, allergic rhinitis or conjunctivitis, or food allergies). We also extracted information on COVID-19 testing results (positive, negative, or not tested) and occurrence of complications during admission (pneumothorax/pneumomediastinum, need for positive-pressure ventilation, intubation, and death).

To quantify a differential effect of COVID-19 on asthma hospitalizations relative to hospitalizations for other community-acquired lower respiratory tract illnesses in the same time period, we used International Classification of Diseases, Tenth Revision, codes to obtain number of hospitalizations for bacterial and viral pneumonia, acute bronchitis, and bronchiolitis and unspecified acute lower respiratory tract infection in the defined time periods in 2019 and 2020. We also quantified the proportion of children testing positive to common respiratory viruses based on testing of airway secretions using ePlex Respiratory Pathogen Panel (GenMark Diagnostics, Carlsbad, California) in the defined time periods.

Data Analysis

Univariate analysis of continuous variables was performed with the independent-sample *t* test and reported as means with SD. Categorical variables were analyzed using χ^2 or Fisher's exact test and reported as frequency distributions and percentages. Statistical significance was set a priori at *P* value of less than .05. On the basis of a prior study in a similar population,[12] our sample size allowed us to identify a 20% between-group difference in administration of intravenous magnesium sulfate. Given the findings from univariate analyses, a multivariable logistic regression analysis was conducted on need for administration of intravenous magnesium sulfate in the ED as the outcome of interest adjusted for covariates age, sex, race and ethnicity for their demographic significance, noncompliance for its clinical relevance, and obstructive sleep apnea, food allergies, and obesity given that these differed between the groups at *P* value less than .2.

Results

We identified 50 eligible cases and 243 eligible controls, which reflected a nearly 80% decline in hospitalizations during the pandemic (Fig 1). Cases were significantly older than controls (9.8 ± 4.3 years vs 6.7 ± 3.8 years; $P < .001$) (Table 1). The proportion of African Americans did not differ, but there was a trend toward fewer

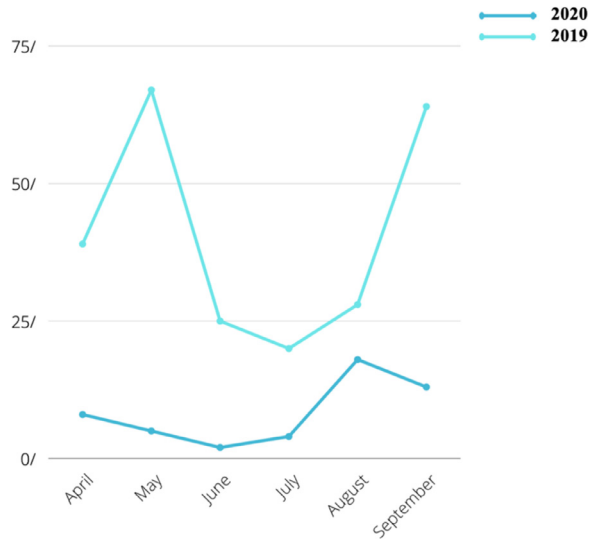

Figure 1. Trend of asthma hospitalizations before (light blue) and during (dark blue) the COVID-19 pandemic at Children's National Hospital. These curves depict the number of children hospitalized with an asthma exacerbations in each of the 6 months in 2019 and in 2020, that were included in this study.

Table 1
Comparison of Demographic and Clinical Characteristics Between Cases and Controls

Demographic and clinical variables	Controls n = 243	Cases n = 50	*P* value
Age (y) (mean ± SD)	6.7 ± 3.8	9.8 ± 4.3	**<.001**
Sex[a]			.50
Males	143 (58.8)	32 (64)	
Females	100 (41.2)	18 (36)	
Race[a]			.31
African American	185 (76.1)	43 (86)	
White	9 (3.7)	1 (2)	
Other or unknown	50 (20.6)	6 (12)	
Ethnicity[a]			.06
Hispanic	36 (14.8)	2 (4)	
Non-Hispanic	207 (85.2)	48 (96)	
Asthma classification[a]			.55
Intermittent	57 (23.5)	12 (24)	
Mild persistent	61 (25.1)	14 (28)	
Moderate persistent	60 (24.7)	12 (24)	
Severe persistent	15 (6.2)	6 (12)	
Unknown	50 (20.5)	6 (12)	
Home treatment step (per NHLBI guidelines)[a]			.43
Step 1	77 (31.7)	14 (28)	
Step 2	61 (25.1)	7 (14)	
Step 3	16 (6.6)	9 (18)	
Step 4	11 (4.5)	5 (10)	
Step 5	34 (14)	6 (12)	
None/unknown	41 (17.7)	9 (18)	
Asthma medications[a]			
Montelukast	38 (15.6)	10 (20)	.45
Low-dose ICS	62 (25.5)	10 (20)	.41
Medium-dose ICS	16 (6.6)	7 (14)	.08
High-dose ICS	32 (13.2)	5 (10)	.54
Low-medium–dose ICS-LABA	9 (3.7)	4 (8)	.25
High-dose ICS-LABA	5 (2.1)	2 (4)	.41
Comorbidities[a]			
OSA	10 (4.1)	5 (10)	.09
GERD	7 (2.9)	2 (4)	.68
Obesity (BMI > 95th percentile)	11 (4.5)	5 (10)	.12
Chronic lung disease of prematurity	10 (4.1)	1 (2)	.47
Others	61 (25.1)	10 (20)	.44
Atopic conditions[a]			
Eczema	78 (32.1)	8 (16)	**.02**
Allergic rhinitis/conjunctivitis	117 (48.1)	27 (54)	.45
Food	45 (18.5)	3 (6)	**.03**
Allergy medications[a]			
Topical	73 (30)	11 (22)	.25
Oral antihistamine	91 (37.4)	19 (38)	.94
Previous ICU stay[a]	82 (33.7)	19 (38)	.82

Abbreviations: BMI, body mass index; GERD, gastroesophageal reflux disease; ICS, inhaled corticosteroid; ICS-LABA, inhaled corticosteroid with long-acting β-agonist; ICU, intensive care unit; NHLBI, National Heart, Lung, and Blood Institute; OSA, obstructive sleep apnea.
The bolded *p* values are the ones that are statistically significant.
[a]Reported as number (percentage).

Hispanics among the cases compared with the controls (*P* = .06). A higher proportion of the controls reported the presence of eczema (32.1% vs 16%; *P* = .02) and food allergies (18.5% vs 6%; *P* = .03). There were no significant differences in the prevalence of other comorbidities, baseline asthma severity, National Heart, Lung, and Blood Institute guideline-based treatment level, or frequency of prior ICU hospitalizations.

In keeping with the fewer asthma hospitalizations during the pandemic, hospitalizations for other community-acquired lower respiratory tract illnesses, such as pneumonia, bronchitis, and bronchiolitis, were 86% lower between April and September 2020 (n = 138) as compared with 2019 (n = 979). This overlapped with a decrease in positivity rate on viral testing, with a 90% decrease in adenovirus, 98% decrease in influenza, 89% decrease in metapneumovirus, 97.5% decrease in parainfluenza, 95.5% decrease in respiratory syncytial virus, and 75.5% decrease in rhino-enterovirus positive tests (eTable 1).

The comparison of clinical details of interventions in the ED and during the hospital stay between cases and controls is summarized in Table 2. Intravenous magnesium sulfate was more frequently administered to the cases than to the controls (84% vs 63%; *P* = .001). Although there was no difference in the duration of symptoms before ED presentation, almost half of the acute exacerbations were attributed to infections in both groups. Although a higher proportion of cases reported noncompliance with controller medications (46% vs 24.7%; *P* = .002), a lower proportion of them were kept on inhaled corticosteroids during the hospital stay compared with the control group (30% vs 58.8%; *P* < .001).

Most of patients in each group were initially admitted to the general pediatric floor. Very few complications occurred during the hospitalization and were limited to the need for noninvasive ventilation, which did not differ between the controls (14.8%) and cases (8%).

Given the difference in administration of magnesium sulfate between the study groups and differences in comorbidities, a multivariable logistic regression model was developed, which demonstrated that increased magnesium sulfate use in cases was predicted by age, with every 1 year increase in age associated with a 16% higher likelihood of receiving magnesium. In addition, African American race and Hispanic ethnicity were associated with higher odds of magnesium sulfate administration in the ED. Its use was independent of sex, presence of comorbidities, including obstructive sleep apnea, eczema, food allergies, obesity, and baseline asthma management regimens, and reported compliance to preventative regimens (Table 3).

Discussion

Consistent with prior studies, we found a nearly 80% reduction in asthma hospitalizations to our urban academic pediatric medical center during the early months of the COVID-19 pandemic.[7] The reduction was similar to that for other community-acquired lower respiratory tract illnesses[13] and corresponded to fewer positivity rates for common respiratory viruses. However, a higher proportion of children hospitalized during the pandemic required magnesium sulfate in the ED, suggesting that these children presented with more severe exacerbations as compared with children hospitalized during the same calendar months in the prepandemic year. In addition, children hospitalized during the pandemic were older and had less atopy, with lower prevalence of coexistent eczema and food allergies, as compared with those hospitalized in the year prior.

Higher magnesium sulfate administration in the ED to children hospitalized during the first months of the pandemic is consistent with findings from a previous study from our institution that reported a higher ratio of hospitalization to ED visits, including pediatric intensive care admissions, during the fall of 2020, as compared with the prior 4 years, indicative of a more severe asthma illness at presentation during the pandemic times as compared with the years before.[7] These findings have high clinical relevance as the pandemic continues and is now affecting children to a higher extent.[14] The cases and controls did not differ with regard to several baseline asthma characteristics, such as severity classification, National Heart, Lung, and Blood Institute treatment level, prior intensive care unit hospitalization, or the time duration of symptoms before seeking medical attention. Although a higher proportion of cases reported being less compliant with controller medication use, suggesting a potential role of noncompliance in the higher severity of asthma exacerbation among children hospitalized during the pandemic as compared with those hospitalized in the same months in the year prior, noncompliance was not an independent predictor of need for magnesium in the ED, when adjusted for demographic variables and clinical comorbidities. Although the lower compliance may have contributed to the ED visit, the lack of its contribution to need for magnesium suggests that other clinical differences between cases from controls, such as lower prevalence of atopy, may underlie higher severity at presentation to the ED.

Table 2
Comparison of Hospital Course Between Cases and Controls

Variables	Controls n = 243	Cases n = 50	*P* value
Duration in days of asthma symptoms preceding ED visit (mean ± SD)	2.37 ± 1.81	2.38 ± 1.56	.97
Initial admission location[a]			.14
Floor	198 (81.5)	45 (90)	
PICU	45 (18.5)	5 (10)	
Need for transfer to PICU from floor[a]	15 (6.2)	3 (6)	.63
PICU duration of stay (mean ± SD)	0.84 ± 3.18	0.32 ± 0.77	.25
Total admission duration (mean ± SD)	2.71 ± 3.49	2.56 ± 0.91	.77
Trigger for asthma exacerbation[a]			
Infection	161 (66.3)	26 (52)	.05
Allergen	45 (18.5)	15 (30)	.07
Physical activity	8 (3.3)	0 (0)	
Environmental	24 (9.9)	6 (12)	.65
Noncompliance	60 (24.7)	23 (46)	**.002**
Unknown	20 (8.2)	2 (4)	.30
Medications used in ED/during admission[a]			
Oxygen	71 (29.2)	19 (38)	.22
Continuous SABA < 1 d	57 (23.5)	9 (18)	.40
Continuous SABA > 1 d	186 (76.5)	41 (82)	.40
Systemic steroids (oral or IV)	234 (96.3)	50 (100)	.17
ICS	143 (58.8)	15 (30)	**<.001**
Ipratropium bromide	212 (87.2)	45 (90)	.59
Magnesium sulfate	153 (63)	42 (84)	**.004**
Theophylline	1 (0.4)	0 (0)	
Epinephrine	63 (25.9)	14 (28)	.76
Positive COVID-19 PCR[a]	0 (0)	1 (2)	
Complication during admission[a]			.38
Invasive ventilation	4 (1.6)	0 (0)	
Noninvasive ventilation	36 (14.8)	4 (8)	
Pneumothorax or pneumomediastinum	2 (0.8)	0 (0)	

Abbreviations: COVID-19, coronavirus disease 2019; ED, emergency department; ICS, inhaled corticosteroid; PCR, polymerase chain reaction; PICU, pediatric intensive care unit; SABA, short-acting β-agonist.
The bolded *p* values are the ones that are statistically significant.
[a]Reported as number (percentage).

Additional factors unique to the pandemic that have been speculated to contribute to the observed differences include fear of presenting to health care facilities owing to concerns over COVID-19, which may have kept children with initial mild asthma symptoms at home during the pandemic. Financial difficulties in an economic downturn may have also resulted in delayed refilling of controller medications, missed routine asthma care visits, and difficulties with transportation,[7] all of which may have played a role in higher severity of asthma exacerbation at the time of presentation in the ED. The overall decline in hospitalizations for asthma and other lower respiratory tract illnesses[13] and decrease in viral positivity rates support that masking and social distancing,[15] including remote schooling, are effective in decreasing respiratory disease burden. Our observations of higher asthma severity at presentation in a subset of children in this setting identify a vulnerable group in whom these interventions were less protective and highlight the need to better understand the disease phenotype of children hospitalized for asthma during the pandemic.

Table 3
Multivariable Logistic Regression for Use of Magnesium Sulfate in ED

Variable	OR	*P* value
Cases[a]	2.27 (0.96-5.38)	.06
Age	1.16 (1.06-1.26)	**<.001**
Female	1.06 (0.61-1.84)	.84
African American race[b]	2.36 (1.01-5.49)	**.04**
Hispanic ethnicity[c]	3.27 (1.08-9.94)	**.04**
ICS	1.44 (0.80-2.60)	.22
ICS-LABA	0.98 (0.26-3.73)	.98
Compliance to controller medications	1.00 (0.50-1.98)	>.99
OSA	0.74 (0.21-2.64)	.64
Obesity	0.60 (0.15-2.46)	.48
Eczema	0.78 (0.44-1.39)	.40
Food allergies	1.40 (0.66-2.95)	.38

Abbreviations: ED, emergency department; ICS, inhaled corticosteroid; ICS-LABA, inhaled corticosteroid with long-acting β-agonist; OR, odds ratio; OSA, obstructive sleep apnea.
The bolded *p* values are the ones that are statistically significant.
[a]The control group served as the reference group.
[b]Whites and others served as the reference group.
[c]Non-Hispanics served as the reference group.

We found lower prevalence of atopic diseases, including eczema and food allergies, among the cases as compared with the controls suggesting that children with nonallergic asthma were over-represented in our cohort hospitalized during the pandemic. Furthermore, 50% of the cohort reported an infectious illness as the trigger for the presenting exacerbation. Taken together with lower prevalence of allergic asthma in the cohort, we speculate that viral illness-induced asthma exacerbations may present with a more severe presentation in children without allergy as compared with children with allergy.[16] In addition, hospitalization of fewer children with atopy in our study validates prior studies that reported a protective effect of atopy for patients with SARS-CoV-2 infection, who had fewer hospital admissions and shorter hospitalizations with a shorter intubation period than patients without atopy.[17,18] One mechanism hypothesized for this observation is the contribution of inhaled corticosteroid use to the down-regulation of angiotensin-converting enzyme 2 and transmembrane protease serine 2 receptors, which facilitate attachment and entry of the virus into the host cell, and have been linked with adverse outcomes among those infected with COVID-19 outcome.[9,19-21] The extent to which this mechanism contributed to our observation needs further investigation.

As compared with African Americans, Hispanic children constituted a smaller proportion of those hospitalized during the pandemic, an observation that approached statistical significance. A similar pattern was seen at the start of the pandemic where African American

children with asthma had higher outpatient, hospital, and telephone encounters with an almost unchanged rate of ED visits compared with the prepandemic times as compared with other races and ethnicities.[4,22] This observation validates the findings of a retrospective cohort study before the pandemic which reported that African Americans had more severe asthma on presentation to the ED and required more intravenous magnesium sulfate than Hispanics, even with similar urban housing and neighborhood environments.[12] The overlap between our findings and those of this prepandemic study from a hospital serving a similar urban minority pediatric population emphasizes the role that racial and ethnic disparities, in conjunction with environmental differences, continue to play in the multifactorial pathophysiology of asthma, even during the pandemic.[23,24]

There were high levels of reported noncompliance to controller therapy among our cohort hospitalized during the pandemic. It was intriguing that despite the high rates of noncompliance, fewer children were started or restarted on controller therapy during the pandemic than the year before. Studies reported fewer controller medication refills and cessation of controller therapy in the outpatient settings owing to the absence of symptoms among children with asthma.[10,25] Moreover, it is possible that the increasing demand for inhalers during the pandemic and the concerning risk of SARS-CoV-2 spread through the use of aerosolizing solutions contributed to more conservative prescription by medical providers.[25-27]

The study has several limitations, including the relatively small sample size from a single urban academic pediatric medical center and dependence on the Electronic Medical System documentation for data collection. Although there may have a potential risk of nonresponse or hidden bias because of incomplete documentation, it was unlikely to influence the cases and controls differently because documentation patterns and the electronic medical record did not change between the 2 time points. The study team was particularly careful with abstraction of information, focusing on the admission duration and the recorded medication in the medication administration system to avoid missed documentation. The findings may not be generalizable to all children because the study was conducted in a single tertiary center, with a predominance of urban minority population seeking asthma care at this hospital. However, the observations of high disease burden including greater need for magnesium sulfate, an objective measure of exacerbation severity, similar to a prepandemic study highlight that, racial disparities continue to exist for pediatric asthma during the pandemic. Moreover, the over-representation of children without atopic diseases among those hospitalized during the pandemic highlights the need for additional mechanistic studies to be conducted to facilitate development of therapeutics for pediatric nonallergic asthma.

In conclusion, our study corroborated a substantial drop in pediatric asthma hospital admissions during the COVID-19 pandemic. However, a higher proportion of children were treated with magnesium sulfate in the ED during the pandemic, suggesting higher asthma severity at presentation for children hospitalized for asthma during the pandemic as compared with the year before. This correlated with lower prevalence of eczema and food allergies among patients hospitalized for asthma during the pandemic, supporting a protective effect of atopy on COVID-19–related lung disease and suggestive of preponderance of nonallergic asthma among children hospitalized for an asthma exacerbation during the pandemic. Although COVID-19 pandemic is associated with fewer acute asthma visits for children, those that presented to the ED had higher severity of presentation and were enriched for children with nonallergic asthma.

Supplementary Data

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.anai.2022.03.033.

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Supplementary Data

eTable 1
Percent Positivity Rate of Viral Testing Among Children Hospitalized for a Respiratory Illness Between April to September 2019 and 2020

Virus	2019 (mean ± SD)	2020 (mean ± SD)
Adenovirus	7.72 ± 6.19	0.78 ± 2.06
Influenza	3.87 ± 5.85	0.08 ± 0.42
Metapneumovirus	4.96 ± 4.31	0.53 ± 1.55
Parainfluenza	7.71 ± 6.43	0.19 ± 1.01
RSV	3.72 ± 4.57	0.17 ± 0.62
Rhino-enterovirus	41.80 ± 13.74	10.23 ± 8.68

Abbreviation: RSV, respiratory syncytial virus.