

Severe respiratory viral infections in children with history of asymptomatic or mild COVID-19

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Abstract

Importance: The spectrum of complications of COVID-19 in children, including the effect of COVID-19 on later viral infection, is not known.

Objective: To examine the features of children hospitalized for respiratory illness with history of prior COVID-19.

Design: Retrospective observational case series at a single pediatric quaternary medical center in New York City. Data were obtained from review of medical records.

Participants: Children with prior mild or asymptomatic COVID-19 and no known risk factors for severe respiratory disease, who were hospitalized at our center for acute respiratory illness from October 2020 to May 2021, were reviewed.

Main Outcomes and Measures: Co-morbidities, history of prior COVID-19 symptoms, respiratory viral panel findings, acuity of illness, degree of respiratory decompensation based on support and interventions required, duration of hospitalization, and overall clinical course were assessed from the medical record.

Results: This study included 5 patients (median age, 4 years; age range: 0.8–9 years; 4 [80%] male). All had positive COVID-19 serology, 1 (20%) had mild symptoms, while the others had no symptoms of prior Sars-CoV-2 infection, 3 (60%) had asthma, and the remaining had no co-morbidities. All were admitted between April and May 2021. Two were re-admitted for respiratory symptoms in the subsequent 3 months.

Conclusions and Relevance: This case series describes a possible association between severe lower respiratory tract infection and prior mild COVID-19 in children. Larger cohort studies describing the respiratory effects of prior COVID-19 in children are needed.

KEYWORDS

asymptomatic, COVID-19, lower respiratory tract infection, pediatric

1 | INTRODUCTION

The COVID-19 pandemic is responsible for tremendous morbidity and mortality worldwide. Although COVID-19 vaccination implementation has begun, the Sars-CoV-2 virus continues to spread rampantly in different parts of the globe. To date, age has been considered a major factor in determining risk and prognosis with COVID-19 disease. While the rate of severe complications and death is significantly lower in children compared to adults, children are just as likely to be infected as adults¹⁻⁵ and the complete spectrum of short and long term complications is not well documented. In early 2020, multisystem inflammatory syndrome associated with COVID-19 (MIS-C) was described as a novel and severe complication in children and adolescents recovering from infection with Sars-CoV-2.⁶ Many cases have been reported globally, but the underlying immune mechanisms are not understood.

New York City was the initial epicenter of the COVID-19 pandemic in the United States. During the peak months of the pandemic, we had very few pediatric admissions to our children's hospital, which is a quaternary medical center in a large metropolitan region. In early 2021, as the numbers of new infections started to ebb, we observed children with no underlying chronic lung disease presenting with acute respiratory failure in the setting of infections with common and typically mild respiratory pathogens. The majority had asymptomatic or mild prior COVID-19 infection. It is not known if prior COVID-19 infection is associated with altered response to other respiratory viral infections that could explain these severe presentations. We present five cases of children with severe lower respiratory tract infections leading to hospital admission for acute respiratory failure. All of these children had prior mild or asymptomatic COVID-19 infection.

2 | METHODS

For this retrospective case series, the study period was October 2020 to May 2021. Children less than 18 years of age admitted for respiratory distress in the setting of a non-Sars-CoV-2 viral infection were considered for this study. Children were included in the case series if they had a previous asymptomatic or mild infection with Sars-CoV-2 based on history and either nasal PCR or positive COVID-19 serology, and no other known factors for severe respiratory disease. Infections were considered asymptomatic when the parent reported absence of symptoms. Well controlled mild to moderate persistent asthma was not considered a significant risk factor for severe respiratory disease. COVID-19 serology was determined using the Elecsys[®] Anti-SARS-CoV-2 immunoassay, which detects antibodies to the nucleocapsid antigen of SARS-CoV-2 with 100% (88.3%, 100%) sensitivity and 99.8% (99.7%, 99.9%) specificity. Clinical course, laboratory values, and imaging were obtained from the electronic medical record. The study was approved by the institutional review board of Columbia University Irving Medical Center under expedited review with a waiver of consent.

2.1 | Case presentations

2.1.1 | Case 1

A 10-month-old boy with no notable past medical history was referred to the emergency department (ED) by his pediatrician for fever, cough, difficulty breathing, hypoxia, and lethargy (Table 1). His SpO₂ was 73% in RA, and improved with supplemental oxygen via non-rebreather mask. On examination, he was cyanotic and in moderate respiratory distress, with coarse breath sounds and rhonchi bilaterally. His chest X-ray demonstrated hyperinflation, prominent interstitial markings, and patchy perihilar opacities. Respiratory viral panel was positive for respiratory syncytial virus (RSV) and adenovirus. White blood cell (WBC) and differential were normal. Procalcitonin and CRP were elevated, 0.73 ng/ml and 89.06 mg/L (8.9×10^4 µg/L), respectively. COVID-19 serology was positive with no history of symptomatic illness in the past. He was treated with ceftriaxone, bilevel positive airway pressure (BiPAP) and supplemental oxygen. Respiratory support was weaned completely and he was discharged home in 2 days.

2.1.2 | Case 2

A 28-month-old boy with autism and moderate persistent asthma, well controlled on inhaled corticosteroids, presented with fever for 3 days, vomiting, cough and nasal congestion for 2 days, and worsening respiratory distress for 1 day (Table 1). He was hospitalized once in the previous year for acute respiratory failure secondary to bronchospasm in the setting of Rhino/enteroviral (REV) infection. He had COVID-19 about 2 months before the current illness, in which he had fever, vomiting, and nasal congestion, but did not require hospitalization. In the ED, he was tachypneic, tachycardic, and his SpO₂ was 75% in room air. He was in moderate respiratory distress and had bilateral wheezing. Respiratory viral panel was positive for REV, and negative for Sars-CoV-2. Chest X-ray showed mild prominence of lung markings and no focal consolidation. WBC and differential were normal. Procalcitonin and CRP were elevated, 0.32 ng/ml and 74.41 mg/L (7.4×10^4 µg/L), respectively. COVID-19 serology was positive. He was treated with intermittent albuterol, ceftriaxone, BiPAP and supplemental oxygen, initially requiring FiO₂ 1.0. Respiratory support, oxygen, and albuterol were gradually weaned and he was discharged home after 2 days with instructions to complete 5 days of prednisolone and continue low dose inhaled corticosteroids.

He presented again 2 months later with fever, nasal congestion, decreased oral intake, and difficulty breathing and was admitted for status asthmaticus in the setting of REV infection. Chest X-ray demonstrated prominent lung markings and bilateral bronchial wall thickening. He was treated with continuous albuterol, IV methylprednisolone, and continuous positive airway pressure (CPAP) with supplemental oxygen. He was discharged home after 3 days.

TABLE 1 Clinical characteristics of patients

Patient ID	Age	Sex	Co-morbidities	Presentation of prior Sars-CoV-2 infection	RVP results	Chest imaging	Discharge diagnosis	Duration of hospitalization (days)
1	10 months	M	None	Asymptomatic	Respiratory syncytial virus, adenovirus	hyperinflated lungs, prominent interstitial markings, patchy right perihilar opacities	Acute respiratory failure in the setting of viral illness	2
2	2.3 years	M	Moderate persistent asthma	Fever, vomiting, nasal congestion	Rhino/enterovirus	mild prominence of lung markings	Status asthmaticus	2
3	3 years	M	None	Asymptomatic	Rhino/enterovirus	Bilateral patchy opacities	Pediatric ARDS	40
4	5 years	F	Moderate persistent asthma	Asymptomatic	Rhino/enterovirus, respiratory syncytial virus	Patchy bibasilar opacities	Anoxic brain injury	23
5	9 years	M	Mild persistent asthma	Asymptomatic	Rhino/enterovirus	N/A	Exacerbation of asthma	4

2.1.3 | Case 3

A 3-year-old boy with no notable past medical history presented to the ED after 1 day of cough, nasal congestion, fever, and increased work of breathing (Table 1). On initial examination, he had severe respiratory distress, oxygen saturation (SpO₂) of 85% in room air, diminished aeration, wheezing, and prolonged exhalation. Respiratory viral panel was positive for REV, and negative for Sars-CoV-2. COVID-19 antibodies were present, with no history of a prior symptomatic illnesses. Chest X-ray demonstrated multifocal opacities. Total WBC was normal, and differential demonstrated 90% neutrophils and 6% lymphocytes. Procalcitonin and CRP were elevated, 0.58 ng/ml and 80.6 mg/L (8.1 × 10⁴ μg/L), respectively. He was treated with continuous albuterol 10 mg/h, intravenous (IV) methylprednisolone, ceftriaxone, and noninvasive positive pressure ventilation with supplemental oxygen. He initially showed mild improvement in the first 2 days, but then worsened and developed increasing hypoxemia. Albuterol was discontinued in view of lack of wheeze and two short episodes of supraventricular tachycardia, and ceftriaxone was changed to piperacillin-tazobactam. Repeat imaging demonstrated worsening bilateral atelectasis and he was intubated on day 4 of admission for management of pediatric ARDS. Bronchoscopy and bronchoalveolar lavage was performed on day 6 and revealed cell differential of 86% neutrophils, 1% lymphocytes, and 13% monocytes/macrophages. Respiratory viral panel from BAL fluid was again positive for REV. Bacterial and fungal cultures, Pneumocystis jiroveci PCR, and galactomannan were negative. Computed tomography (CT) chest with contrast on day 12 of admission showed bilateral lower lobe consolidation. Contrast echocardiography did not suggest intracardiac or pulmonary shunt. Investigations for primary immunodeficiency to explain the severity of his illness including vaccine titers, quantitative immunoglobulins, granulocyte dihydrorhodamine fluorescence, and cytokine panel, were unrevealing. His respiratory support was gradually weaned and he was extubated on day 24 of admission, and eventually discharged home without supplemental oxygen on day 40. He was seen for pulmonary follow up 3 weeks later and was progressing with feeding and physical therapy. He presented again 2 months later with fever, cough, difficulty breathing and hypoxemia in the setting of REV infection. Chest X-ray showed new bilateral patchy opacities. He was treated with CPAP, supplemental oxygen, IV methylprednisolone, and intermittent albuterol. He was weaned to room air and discharged after 6 days.

2.1.4 | Case 4

A 5-year-old girl with allergies and well controlled asthma with no prior hospitalizations was transferred to our intensive care unit after cardiac arrest and resuscitation (Table 1). She had cough and respiratory distress for 2 days, and then reportedly had a coughing fit in which she requested asthma medicines. She collapsed and EMS was called home. She received cardiopulmonary resuscitation for 8 min,

epinephrine and sodium bicarbonate. She was intubated in a local ED and started on asthma therapies. She developed seizures and received levetiracetam and midazolam infusion. Initial arterial blood gas showed metabolic and respiratory acidosis, with pH 6.89, PCO₂ 77 mmHg (10.3 kPa), PO₂ 470 mmHg (62.7 kPa), bicarbonate 19.1 mmol/L. WBC and differential were normal. Respiratory viral panel was positive for REV and RSV. COVID-19 serology was positive with no history of recent illness consistent with COVID-19. Chest X-ray showed patchy bibasilar opacities. She was transferred to our intensive care unit for management of respiratory failure and seizures. CT scan of the head with contrast on day 2 of hospitalization demonstrated findings of acute hypoxic ischemic brain injury. Tracheostomy and gastrostomy tube were placed on day 13 of hospitalization. She was transferred to a pediatric chronic care and rehabilitation facility on hospital day 23.

2.1.5 | Case 5

A 9-year-old boy with history of well controlled mild persistent asthma and eczema was admitted with status asthmaticus in the setting of REV infection (Table 1). He used low dose inhaled corticosteroids on a daily basis with good adherence, and had not required systemic corticosteroids for 3 years. He had no prior hospitalizations for respiratory issues. During this presentation, he developed symptoms of difficulty breathing and cough, and symptoms progressed in severity despite treatment with albuterol at home. On arrival to the ED, he had moderate respiratory distress, decreased aeration bilaterally with wheezing. He initially received nebulized albuterol and ipratropium, IV magnesium sulfate, continuous albuterol 15 mg/h and IV methylprednisolone. Sars-CoV-2 PCR was negative. COVID-19 antibodies were detected, with no recollection of a symptomatic illness in the recent past. He remained hospitalized for 4 days. He was discharged home to continue on low dose inhaled corticosteroids. He returned for pulmonary follow up 2 months later and reported well controlled symptoms. His spirometry and lung volumes were normal.

3 | RESULTS

In this case series, we describe five children who were hospitalized for severe respiratory symptoms secondary to a viral lower respiratory tract infection. Four out of five were male. Four children had prior asymptomatic Sars-CoV-2 infection, and one had mild symptoms. The time elapsed since Sars-CoV-2 infection was 2 months for the child with symptomatic illness. For the four children with asymptomatic illness, the time since the initial infection is unknown. Two children had no known medical conditions, and three had asthma. All were admitted between mid-April 2021 and mid-May 2021. Two were re-admitted with respiratory symptoms in the following 3 months.

While all required hospitalization to an acute care unit, the severity of illnesses varied amongst the five children. Three children

stayed in the hospital for less than a week, while two had prolonged admissions. One, sadly, developed anoxic brain injury after cardiac arrest that occurred while the child had difficulty breathing and coughing at home.

4 | DISCUSSION

This small case series highlights a possible association between the development of severe presentations of viral lower respiratory tract infections and prior asymptomatic or mild COVID-19 infection in young children with well controlled asthma or no history of respiratory disease. Post-COVID condition, a term which includes postacute COVID-19 syndrome (PACS), postacute sequelae of Sars-CoV-2 infection, and "Long COVID," is described in adults with widely varying frequency.⁷⁻¹² It is a protracted constellation of symptoms that persist after initial COVID-19 illness, including those who did not require hospitalization.¹³⁻¹⁵ Common symptoms include fatigue, shortness of breath, chest pain, and cough.^{9,11,16} There is some evidence to suggest that female sex is a risk factor for PACS,¹⁷ but this has not been noted consistently amongst all cohorts.^{9,11,18} Several studies have described postacute COVID-19 symptoms in children and young adults, indicating that long COVID symptoms are not limited to the adult population.¹⁹⁻²³ In these cohorts, the predominant respiratory symptoms were exercise intolerance, dyspnea, and cough. Zhang et al described chest CT findings of fibrosis and patchy opacities in 7 children who were evaluated 30 days after hospitalization for COVID-19.²⁴

Distinct from our patient sample, individuals with PACS reported in the current literature generally had symptomatic illness initially with lingering symptoms or persistent radiological findings. All but one of the children described here were reportedly asymptomatic during their Sars-CoV-2 infection, and presented later with an acute respiratory illness. Interestingly, the majority of our patients are male. Male sex is associated with more severe COVID-19 illness, although the mechanism by which sex influences morbidity is not known.²⁵ While there are emerging data on the long term sequelae of COVID-19 in children, our observation of severe lower respiratory tract infections, especially in relatively healthy children with asymptomatic COVID-19 illness, is not described in the literature. As our patient population resides in New York City, the original epicenter of COVID-19 in the United States, it is conceivable that other parts of the country will have similar observations in the upcoming months. Of note, the Food and Drug Administration granted emergency use authorization to one COVID-19 vaccine for 12-15-year-old children in May 2021, at the conclusion of our study. Thus, our findings are based on a sample of unimmunized pediatric patients.

Our study is limited by its small sample size and retrospective nature of data collection. For this report, we only considered children who were known to have prior SARS-CoV-2 infection based on history, prior positive PCR, or positive COVID-19 serology. We did not include or assess for inclusion of children who were known to have never been infected with Sars-CoV-2. Therefore, controlled

epidemiologic studies are required to determine whether an association between prior SARS-CoV-2 infection and greater susceptibility to non-SARS-CoV-2 respiratory viral infections truly exists. Additionally, COVID-19 serology is not assessed in all children, and in our institution is more likely to be measured in children with severe illness. False positive COVID-19 antibody testing can occur by detecting antibodies to other coronaviruses. However, given the high sensitivity of the test and high prevalence of COVID-19 antibodies amongst adults in New York City,²⁶ we feel that it is likely that the children in our case series had true prior infection. Future prospective cohort studies and case-control studies can better assess the degree and variety of respiratory complications in the pediatric Sars-CoV-2 infected population. This information will be particularly relevant as COVID-19 precautions are being relaxed in the some parts of the United States and world. Just as a resurgence of RSV with the subsiding of mask wearing and social distancing has been described, it is logical to expect a resurgence of other respiratory viral infections as well.^{27,28} Additionally, further information on complications of COVID-19 in children, a group generally thought to be low risk, may help inform future preventive measures in the youngest members of our society.

5 | CONCLUSIONS

In conclusion, this small, observational case series describes severe acute lower respiratory tract infections in children with prior asymptomatic or mild COVID-19. It is possible that altered response to respiratory viral infections is a feature of PACS. Larger prospective cohort studies in children would provide more information about risk factors for this presentation.

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How to cite this article: Rai N, Cornett JA, Zachariah P, Quittell L, Lovinsky-Desir S. Severe respiratory viral infections in children with history of asymptomatic or mild COVID-19. *Pediatric Pulmonology.* 2022;57:361-366. doi:10.1002/ppul.25752