serum creatinine (4.7 mg/dL) were raised, with normal serum electrolytes. Prothrombin time was 16 sec with INR 1.6, and activated partial thromboplastin time (APTT) was 17 second. Liver function test was normal. His nasopharyngeal swab RT-PCR for SARS-CoV-2 was positive on day two of admission and he was shifted to the district Covid-hospital. Over the next few days, his respiratory status initially improved and oxygen flow was gradually reduced.

From the second week of illness, the patient developed repeated episodes of hemoptysis and occasional epistaxis and required blood transfusion for symptomatic anemia with hemoglobin dropping to 7.5 g/dL. His PT/INR and aPTT remained normal during this period, and anti-factor Xa was not done. Pulmonary thromboembolism was clinically suspected as the etiology of hemoptysis in the setting of the COVID-19 and DVT. Patient's repeat nasopharyngeal RT-PCR sample tested negative for SARS-CoV-2 on day 10 and rapid antigen test was also negative. Hence, he was shifted back to our center.

High-resolution computed tomography (HRCT) scan of chest could only be done on day 11 of the hospitalization and revealed multiple bilateral nodular paren-chymal opacities with areas of cavitation seen in bilateral lung fields (suggestive of septic emboli) with bilateral pleural effusion (left more than right). Repeat HRCT chest after four days reported bilateral nodular shadowing with multiple cystic bronchiectasis changes in both lung fields, more in upper lobes. Echocardiogram was reported normal. The patient's renal function recovered after the initial fluid resuscitation and did not required dialysis. Other investigations like blood culture, D-dimer, ferritin, IL-6, protein C and S, Factor V Leiden etc. could not be done due to non-availability at the facility. From day 20 of admission, his oxygen saturation remained greater than 90% at room air. Repeat USG thigh showed resolution of DVT. Both dexamethasone and LMWH were given for 10 days each. Oral warfarin was started after ceasing heparin but was stopped after onset of repeated hemoptysis. From the third week, he again developed high fever and the thigh swelling worsened. X-ray left femur demonstrated signs of acute osteomyelitis of the left femur. Antibiotics were upgraded and pus was drained from the thigh. Pus culture was sterile, as the patient was already on antibiotics. After two weeks of surgical drainage, he became afebrile and was discharged after 40 days of total hospitalization.

In addition to primary lung involvement due to COVID-19, this patient developed a hypercoagulable state with consequent DVT and suspected pulmonary thromboembolism, which greatly increased the comorbidity and duration of hospital stay. Although rarely reported in children [3,4], the hypercoagulable state can result in significant clinical sequelae. High altitude is also a predisposing factor for thromboembolic phenomenon [5].

ZAHID HUSSAIN,* RINCHEN WANGMO AND
SPALCHIN GONBO
Pediatric Unit, SNM Hospital,
Leh, Ladakh 194 101, India.
*drzahidpaed@gmail.com

REFERENCES

1. Ren B, Yan F, Deng Z, et al. Extremely high incidence of lower extremity deep venous thrombosis in 48 patients with severe COVID-19 in Wuhan. Circulation. 2020; 142:114-128.
2. Kolielat I, Galen B, Choinski K, et al. Clinical characteristics of acute lower extremity deep venous thrombosis diagnosed by duplex in patients hospitalized for coronavirus disease 2019. J Vasc Surg Venous Lymphat Disord. 2020 Jun 25 10.1016/j.jvsv.2020. 06.012.
3. Qiu H, Wu J, Hong L, Luo Y, Song Q, Chen D. Clinical and epidemiological features of 36 children with coronavirus disease 2019 (COVID-19) in Zhejiang, China: An observational cohort study. Lancet Infect Dis. 2020; 20:689-96.
4. Meena J, Yadav J, Saini L, Yadav A, Kumar J. Clinical features and outcome of SARS-CoV-2 infection in children: A systematic review and meta-analysis. Indian Pediatr. 2020; 57: 820-26.
5. Anand AC, Jha SK, Saha A, Sharma V, Adya CM. Thrombosis as a complication of extended stay at high altitude. Natl Med J India. 2001;14:197-201.
6. Xia W, Shao J, Guo Y, et al. Clinical and CT features in pediatric patients with COVID-19 infection: Different points from adults. Pediatr Pulmonol. 2020;55:1169.

Virus-Induced Wheezing With COVID-19

Pediatric coronavirus disease 2019 (COVID-19) has now been documented to be a milder illness worldwide except for the few presenting with pediatric multi-system hyperinflammatory syndrome (PIMS). Viral respiratory tract infections are the most common triggers of wheezing illnesses in children. With the ongoing pandemic, a rapid increase in wheezing-related illnesses may be theoretically anticipated. However, COVID-19 induced wheezing is currently thought to be rare. On a related note, a recently published online survey of members of the Pediatric Asthma in Real Life think tank and the World Allergy Organization Pediatric Asthma Committee [1] also suggested that COVID-19 is not associated with acute onset wheezing in children with underlying asthma. We report our experience with COVID-19 induced wheezing in three children (Table I), who presented to our emergency room with respi-ratory distress.

COVID-19 associated asthma exacerbation [2] is rare; although there is a theoretical risk of COVID-19 causing a virus triggered asthma exacerbation. Previous epidemics of the coronavirus also did not report significant numbers of asthma exacerbations [3].

Table I Associated Wheezing Characteristics of Children With COVID-19

	Case 1	Case 2	Case 3
Age, known wheezer	4 y, No	1y, Yes	10 y, No
Asthma predictive index	Negative	Positive	Negative
Clinical features	Fever, cough, breathing difficulty	Breathing difficulty	Fever, cough, breathing difficulty
Oxygen saturation	SpO_2 89%	SpO_2 94%	SpO_2 94%
Neutrophil-lymphocyte ratio	7.08	0.44	1.05
C-reactive protein	24	2.88	<2.8
Treatment	Salbutamol metered dose inhaler with spacer, IV $MgSO_4$,	Salbutamol metered dose inhaler with spacer	Salbutamol metered dose inhaler with spacer
Respiratory support	HFNO (@ 2 L/kg flow and 40% FiO_2)	Oxygen by nasal cannula @ 4 L/min	HFNO (@ 2 L/kg flow and 40% FiO_2)
Steroids	IV dexamethasone (@ 0.6 mg/kg/d)	Oral prednisolone (@ 1 mg/kg/d)	Oral prednisolone (@ 1mg/kg/d)
Hospital stay (d)	5	3	5

All children were RT-PCR positive, and had tachypnea, subcostal retractions, and bilateral expiratory wheeze; Chest X-ray showed bilateral lung hyper inflammation in all 3; None of the children had any comorbidity; and HFNO: High-flow nasal oxygen; FiO_2: Fraction of inspired oxygen.

Severe respiratory manifestations of COVID-19, though uncommon in children have been reported and may be presumed to involve clinical presentations related to small airways or alveolar involvement or both. If small airways are predominantly affected, treatment modalities will include bronchodilators, corticosteroids, oxygen supplementation and respiratory support as required. However, bronchodilators are potentially detrimental in a scenario of alveolar disease due to pro-inflammatory effects on alveoli, worsening of ventilation-perfusion mismatch and increased tachycardia [4]. There is no clear-cut separation of these phenotypes and overlap may be expected. Corticosteroids, typically in courses longer than that used in exacerbations of asthma, are currently in use for treating severe COVID-19 [4,5]. The role of antiviral treatment is not precisely known especially in the pediatric context [4].

In our cases, we utilized C-reactive protein (CRP) levels as an indicator of severity of inflammation. In one child CRP was elevated but other markers of inflammation including D-dimer, S. ferritin and serum fibrinogen were normal. More data is required to know if inflammation and hypercoagulable states more commonly occur with alveolar disease in contrast to small airways involvement as seen in these three cases. The limitation of our workup lies in not testing for viral co-infection which may have triggered the exacerbation as well.

Literature on pediatric asthma and COVID-19 is sparse and limited to case reports highlighting mild disease mostly not requiring hospitalizations and ICU care [1,6]. One of the mainstays of aerosol therapy in acute wheezing episodes is nebulizations. However, it also amplifies the risk of infection transmission by stimulating a cough reflex, as well as generating a high volume of respiratory aerosols that may be propelled over a longer distance thus infecting bystander hosts. An added disadvantage being an increased risk of deposition of virus in the lower lung [7], nebulizations in COVID-19 remains the least

suitable preference. Poor response to a metered dose inhaler/spacer, a child who is uncooperative or unable to follow the directions required for metered dose inhaler use and medication shortage remain the only possible indications of using nebulizers in these children. The Global initiative for asthma guidelines suggest that asthma exacerbations due to COVID-19 should be treated with corticosteroids as appropriate [8]. However, there is no research on the choice of corticosteroid. No adverse effects attributable to the use of steroids were noted in these children.

Though rare, COVID-19 infection in children may trigger a viral-induced wheeze that requires distinguishing from other viral and asthma triggers. Severe illness requiring substantial respiratory support may occur in these circumstances. Identifying similar presentations and reporting may help also to resolve the therapeutic dilemmas.

BHAKTI SARANGI, GURUPRASAD HASSAN SHANKAR* AND VENKAT SANDEEP REDDY
Department of Pediatrics, Bharati Hospital and Research Centre, Pune,Maharashtra, India.
*hsguru@gmail.com

REFERENCES

1. Papadopoulos NG, Custovic A, Deschildre A, *et al*. Impact of COVID-19 on Pediatric Asthma: Practice adjustments and disease burden. J Allergy Clin Immunol Pract. 2020;8:2592-2599.e3.
2. Abrams EM, Szefler SJ. Managing Asthma during Coronavirus Disease-2019: An example for other chronic conditions in children and adolescents. J Pediatr. 2020; 222:221-26.
3. Van Bever HP, Chng SY, Goh DY. Childhood severe acute respiratory syndrome, coronavirus infections and asthma. Pediatr Allergy Immunol. 2004;15:206-9.

4. Raghunathan V, Dhaliwal MS. Pharmacological management of COVID-19. J Pediatr Crit Care. 2020;7: S42-8.

5. Horby P, Lim WS, Emberson JR, *et al*. Dexamethasone in hospitalized patients with COVID-19 - Preliminary Report. N Engl J Med. 2020; NEJMoa2021436. [Epub ahead of print].

6. Barsoum Z. Pediatric asthma and coronavirus (COVID-19)-Clinical presentation in an asthmatic child-SN Compr Clin Med. 2020;1-3. [Epub ahead of print].

7. Amirav I, Newhouse MT. Transmission of coronavirus by nebulizer: A serious, underappreciated risk. CMAJ. 2020; 192:E346.

8. COVID-19: GINA Answers to Frequently Asked Questions on Asthma Management - Global Initiative for Asthma - GINA. Global Initiative for Asthma - GINA. 2020. Accessed September 16, 2020. Available from: *https://ginasthma.org/covid-19-gina-answers-to-frequently-askedquestions-on-asthma-management.*

Neurological Manifestations of COVID-19 in Children

Coronavirus disease 2019 (COVID-19) in children is mostly an asymptomatic or mildly symptomatic infection [1]. We seldom suspect COVID-19 in children with non-respiratory complaints, more so with isolated neurological manifestations. we present our experience of treating three children of COVID-19 who presented with only neurological symptoms.

A 2-year-old previously healthy boy who had one day fever, three watery stools and pain abdomen, presented with febrile status epilepticus, hypotensive shock and hypoxia. A diagnosis of acute febrile encephalopathy was entertained and he was started on fluid resuscitation. He was shifted to critical care unit where he was mechanically ventilated in view of poor respiratory efforts with encephalopathy and received ceftriaxone, vancomycin and acyclovir. Reverse transcription polymerase chain reaction (RT-PCR) for SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2) on a nasopharyngeal swab was positive and his antibody testing in serum was negative. His cerebrospinal fluid (CSF) analysis was in normal limits with negative RT-PCR for SARS-CoV-2. He fulfilled the criteria for multisystem inflammation syndrome MIS-C in children and was treated with intravenous immunoglobulin (IVIG) 2 grams/kg along with remdesivir. His fever and requirement for inotrope support persisted, and intravenous methylprednisolone (10 mg/kg/day) was given for 3 days. His general condition improved, he did not have any further seizures, and was extubated after 48 hours. He was switched over to oral prednisolone for 2 weeks and low dose aspirin for 6 weeks, and was doing well on follow-up six weeks later.

A 15-month-old previously healthy boy presented with simple febrile seizures. On day two, he developed a maculopapular rash over the extremities with bilateral non-purulent conjunctival congestion, periorbital puffiness and cheilitis. He had persistent high-grade fever of >103ºF even on the fifth day and was referred for further management. His father had confirmed SARS-CoV-2 infection one month back. He fulfilled the criteria for MIS-C with Kawasaki disease phenotype, and was treated with intravenous immunoglobulin (2 g/kg), aspirin and steroids, as in the previous child. He was well on follow-up four weeks later.

An 8-month-old boy was brought with complaints of high-grade fever of 103ºF for one day, followed by first episode of generalized tonic-clonic seizure lasting for more than 20 minutes on day one of illness. He was given intravenous midazolam followed by intravenous levetiracetam as the seizure episode was prolonged. There was a history of contact with confirmed SARS-CoV-2 in a close relative. His RT-PCR for SARS-CoV-2 in nasopharyngeal swab was positive**.** As the child did not have any encephalopathy or meningeal signs and no further episodes of seizures, CSF analysis and neuroimaging were deferred. He became afebrile from day three of illness. He was discharged on oral levetiracetam with a diagnosis of febrile status epilepticus, and is well on 2-weeks follow up.

With increasing numbers of SARS-CoV-2 infections, non-respiratory manifestations are being reported across all age groups. The reason hypothesized is the distribution of angiotensin-converting enzyme 2 receptors (ACE-2R) or unexplained immune mechanism. ACE-2R are also present on the endothelial cells in the cerebral vasculature. Neurological manifestations in COVID-19 can be due to virus breaching the blood-brain barrier and entering the brain either trans-neuronally via the olfactory mucosa that has a relatively high expression of the ACE2 receptors, which then through olfactory nerve, crosses the cribriform plate or via hematogenous route [1] or as sepsis-induced coagulopathy leading to cerebral infarction [2] or immune-mediated neurological syndrome or can travel retrogradely via axonal transport to the brain from the gut or lungs. Few autopsy studies have demonstrated the presence of the virus in capillary endothelial cells of the frontal lobe of the brain [3]. The virus can also reach the brain by trojan horse mechanism via infected leukocytes migration across the blood brain barrier [4].

Seizures, encephalopathy, agitation, diffuse upper motor neuron signs, encephalitis, acute necrotizing encephalopathy, stroke, anosmia, ageusia, and Guillain-Barré syndrome have all been reported in adults with COVID-19 [5]. Encephalopathy (diffuse brain dysfunction) and encephalitis (acute, diffuse, inflammatory condition of the brain) are a major devastating presentation. Intense inflammatory response against the virus, triggers cytokine storm causing subsequent hypoxic and metabolic insults resulting in multiple organ failure including diffuse brain dysfunction. Altered consciousness is the hallmark clinical feature of encephalopathy. Individuals with encephalopathy/encephalitis are either severely or critically ill