

# Lessons unfolding from pediatric cases of COVID-19 disease caused by SARS-CoV-2 infection

The recent coronavirus outbreak, better known as COVID-19 in the United States or novel coronavirus pneumonia in China, has reached pandemic proportions. The illness is caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), also known as 2019-novel coronavirus (2019-nCoV). With the first adult cases reported in December 2019 in Wuhan, China, pediatric cases followed shortly thereafter with a strong tendency for familial clusters.<sup>1</sup> Interestingly, total numbers of symptomatic pediatric cases lag dramatically behind adult cases suggesting a protective effect of age.<sup>2</sup>

As pediatric pulmonologists, we are used to common respiratory viruses. Yet coronaviruses are unfamiliar. The first two human coronaviruses, HCoV-229E and HCoV-OC43 were identified in 1960s and are well-known causes of the common cold.<sup>3</sup> The 2002–2003 severe acute respiratory syndrome human coronavirus (SARS-HCoV) epidemic broadened the spectrum of human diseases caused by this group of viruses. The Coronaviridae family is further subclassified into four genera with the  $\alpha$ -coronaviruses (HCoV-229E and HCoV-NL63) and  $\beta$ -coronaviruses (HCoV-HKU1, HCoV-OC43, Middle East respiratory syndrome [MERS]-HCoV, and SARS-HCoV) affecting humans. Whereas  $\gamma$ - and  $\delta$ -coronaviruses mainly infect birds, with a few infecting mammals.

SARS-CoV-2 infection has unique features that offer clues to its underlying biology. The Chinese reports indicate that children are significantly less affected by COVID-19, and when children do develop symptoms, they include fever and dry cough that rarely advance to severe disease. The Chinese Center for Disease Control and Prevention identified 2143 children (aged 0–18 years) with laboratory-confirmed or suspected COVID-19; one death was reported in this group.<sup>4</sup> The most common symptoms are fever (65%) and cough (45%).<sup>5</sup> Up to one-third of reverse-transcription polymerase chain reaction confirmed-positive pediatric patients remain completely asymptomatic.<sup>6</sup> However, 6% of all pediatric patients with COVID-19 developed severe/critical illness, with upwards of 11% of infants under the age of 1 year developing severe/critical disease.<sup>4</sup>

Interestingly, the radiographic changes that are characteristic of SARS-CoV-2 infection can also be seen in pediatric patients, even without progress to severe disease. Case series of pediatric patients in various regions of China reported that nearly 50% to 80% of the children had abnormal computed tomography (CT) findings, often displaying ground-glass opacities and nodules, mostly located in the lower lobe of both lungs near the pleural area.<sup>6–8</sup>

Interestingly, one pediatric case series reported the chest CT findings of consolidation with a surrounding halo, suggesting parenchymal infection were seen in 50% of pediatric patients, a finding not previously

reported in adult patients with COVID-19. These authors suggested that this finding, coupled with a higher procalcitonin level in SARS-CoV-2-infected pediatric patients suggests a higher likelihood of coinfection in pediatric patients.<sup>9</sup> This highlights another key difference in clinical features of COVID-19 in pediatric patients as compared to adults and warns clinicians to monitor for signs of bacterial superinfection or coinfection with influenza or other viruses, and conversely to not rule out the possibility of SARS-CoV-2 in the setting of a positive flu swab.

Importantly, pediatric patients provide an opportunity to gain critical insight into disease pathogenesis and guide future vaccine or therapeutic development. Two main theories explaining the protective effect of age are currently being perused: (a) differences in pediatric immune responses as compared to adults, or (b) differences in airway epithelial cell make-up affecting the availability of viral binding sites.

Immunosenescence, the progressive decline in immune function with increasing age, is a possible explanation. Pediatric patients appear to maintain normal white blood cell counts and lymphocyte counts,<sup>7</sup> while adults often develop abnormalities in neutrophil counts and T-cell depletion.<sup>10</sup> However, the mechanism for this discrepancy is unclear.

Alternatively, lessons learned from prior coronavirus infections, namely SARS-CoV, the pathogen responsible for severe acute respiratory syndrome (SARS) outbreak in 2003, have shown that the virus binds to the angiotensin-converting enzyme type 2 (ACE2) receptor to allow viral entry into type II pneumocytes in the lung. As there is homology in the sequence of the receptor-binding domain for the two viruses, it is felt ACE2 receptor is also the site of entry for SARS-CoV-2.<sup>11</sup> As these ACE2 receptors are upregulated in individuals with COPD, hypertension, or smoking history, this may explain why these populations are at increased risk for more severe disease.<sup>8,12</sup>

As pediatric pulmonologists, we are on high alert for our most vulnerable patients with underlying lung disease. Although the overall pediatric numbers are low, rare lung disease in children may not fall into these categories. Cystic fibrosis (CF), for example, is rare in the Chinese population, so how both pediatric and adult CF patients fare with COVID-19 is yet to be seen. In the meantime, we should proceed with caution; optimizing treatments for underlying lung disease seems prudent. Furthermore, minimizing cough related to asthma could reduce the potential aerosolization of the virus in an otherwise asymptomatic carrier. In that same vein, choosing hydrofluoroalkane-inhaler administered medications over nebulizers will also help reduce the aerosolized virus.

Focusing on the pediatric population as a means of preventing disease spread is critical. Children are less likely to report symptoms

of COVID-19 and more likely to have mild or asymptomatic presentations. However, asymptomatic individuals can still actively shed the virus, transmitting disease.<sup>6</sup> Further, the incubation period of the illness, following exposure to the virus can range upward of 24 days,<sup>8</sup> leading to prolonged periods of viral shedding. These cases support the rationale for prolonged school closures and cancellation of public events and social gatherings in efforts to reduce the continued spread of the virus among asymptomatic or mild cases.

In summary, the pediatric experience with COVID-19 highlights a few key issues pertaining to our patients. First, because fewer pediatric patients are affected by COVID-19, disease patterns are less clear and warrant close monitoring rather than an assumption of a mild disease course in individual pediatric patients.<sup>13</sup> Second, differences in adults compared with children provide a key opportunity for the development of much-needed therapies and research into this area is urgently needed. Third, population measures directed toward social distancing, including school closures, appear to be important in slowing the spread of COVID-19.

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#### REFERENCES

1. Chan JFW, Yuan S, Kok KH, et al. A familial cluster of pneumonia associated with the 2019 novel coronavirus indicating person-to-person transmission: a study of a family cluster. *Lancet*. 2020; 395(10223):514-523.
2. Wu Z, McGoogan JM. Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China: summary of a report of 72314 cases from the Chinese center for disease control and prevention. *JAMA*. 2020. <https://doi.org/10.1001/jama.2020.2648> [published online ahead of print February 24, 2020].
3. Geller C, Varbanov M, Duval RE. Human coronaviruses: insights into environmental resistance and its influence on the development of new antiseptic strategies. *Viruses*. 2012;4(11):3044-3068.
4. Dong Y, Mo X, Hu Y, et al. Epidemiological characteristics of 2143 pediatric patients with 2019 coronavirus disease in China. *Pediatrics*. 2020;pii: e20200702. <https://doi.org/10.1542/peds.2020-0702> [published online ahead of print March 16, 2020].
5. Wang D, Ju XL, Xie F, et al. [Clinical analysis of 31 cases of 2019 novel coronavirus infection in children from six provinces (autonomous region) of northern China]. *Zhonghua Er Ke Za Zhi*. 2020; 58(4):E011.
6. Hu Z, Song C, Xu C, et al. Clinical characteristics of 24 asymptomatic infections with COVID-19 screened among close contacts in Nanjing, China. *Sci China Life Sci*. 2020. <https://doi.org/10.1007/s11427-020-1661-4>
7. Cao Q, Chen YC, Chen CL, Chiu CH. SARS-CoV-2 infection in children: transmission dynamics and clinical characteristics. *J Formos Med Assoc*. 2020;119(3):670-673.
8. Wang Y, Wang Y, Chen Y, Qin Q. Unique epidemiological and clinical features of the emerging 2019 novel coronavirus pneumonia (COVID-19) implicate special control measures. *J Med Virol*. 2020. <https://doi.org/10.1002/jmv.25748>
9. Xia W, Shao J, Guo Y, Peng X, Li Z, Hu D. Clinical and ct features in pediatric patients with COVID-19 infection: different points from adults. *Pediatr Pulmonol*. 2020. <https://doi.org/10.1002/ppul.24718>
10. Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet*. 2020;395(10223): 497-506.
11. Hoffmann M, Kleine-Weber H, Schroeder S, et al. ARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. *Cell*. 2020. <https://doi.org/10.1016/j.cell.2020.02.052>
12. Guan WJ, Ni ZY, Hu Y, et al. Clinical characteristics of coronavirus disease 2019 in China. *N Engl J Med*. 2020. <https://doi.org/10.1056/NEJMoa2002032>
13. Shen K, Yang Y, Wang T, et al. Diagnosis, treatment, and prevention of 2019 novel coronavirus infection in children: experts' consensus statement. *World J Pediatr*. 2020. <https://doi.org/10.1007/s12519-020-00343-7>