EDITORIAL

Nasal ACE2 Levels and COVID-19 in Children

Ankit B. Patel, MD, PhD; Ashish Verma, MBBS

Coronavirus disease 2019 (COVID-19) has disproportionately affected certain vulnerable populations. Studies noted higher rates of certain comorbidities such as hypertension, diabetes mellitus, and chronic obstructive pulmonary disease in patients infected with COVID-19 with severe disease.[1] Additionally, areas with more racial/ethnic minorities and higher rates of poverty have been shown to have higher rates of COVID-19 hospitalization and death.[2] After adjustment for comorbidities, age has been independently associated with increased mortality due to COVID-19.[3] However, limited attention has been given to children, who appear to have lower risk of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection and mortality.

Related article

In this issue of *JAMA*, Bunyavanich et al[4] identify a possible factor that may be related to lower rates of SARS-CoV-2 infection in children. The authors evaluated gene expression in nasal epithelial samples collected as part of a study involving patients with asthma from 2015 to 2018. The nasal epithelium is one of the first sites of infection with SARS-CoV-2, and the investigators probed for the expression of the cell surface enzyme angiotensin-converting enzyme 2 (ACE2), which has been proven to bind to SARS-CoV-2 spike protein and promote internalization of the virus into human cells.[5] Among a cohort of 305 patients aged 4 to 60 years, older children (10-17 years old; n = 185), young adults (18-24 years old; n = 46), and adults (≥25 years old; n = 29) all had higher expression of *ACE2* in the nasal epithelium compared with younger children (4-9 years old; n = 45), and *ACE2* expression was higher with each subsequent age group after adjusting for sex and asthma.

Numerous studies have highlighted the low rates of SARS-CoV-2 infection in children compared with adults. Children have been shown to have fewer and less severe symptoms compared with adults.[6,7] This leads to the question of whether low rates of SARS-CoV-2 infection in children are due to low rates of testing in children, or if children are less susceptible to infection. An evaluation of 1286 close contacts of index cases in China found that infection rates in children were comparable with or slightly higher than in younger adults (aged 30-49 years) but were significantly lower than in older patients (aged ≥60 years).[8] This finding suggests that children seem to have similar rates of becoming infected compared with middle-aged adults following close contact with a person infected with SARS-CoV-2. In contrast, a targeted screening approach in Iceland found SARS-CoV-2 in 6.7% of children younger than 10 years old (n = 564) compared with in 13.7% of people aged 10 years or older (n = 8635). A population-wide screening approach not restricted to people at risk of disease in the same study found no positive cases of SARS-CoV-2 among children under 10 years old, whereas 0.8% of people older than 10 years were positive for SARS-CoV-2.[9] Although the true rate of acquiring SARS-CoV-2 infection among children of different age groups in the United States remains unclear, initial studies have suggested a lower incidence of SARS-CoV-2 infection in US children.[7]

While ACE2 binds to the receptor binding domain of SARS-CoV-2, a serine protease, TMPRSS2, is shown to cleave SARS-CoV-2 S protein, allowing for cell membrane fusion and endocytosis of the virus and subsequent viral replication. To better understand expression of these 2 key proteins, a number of single-cell RNA sequencing experiments have mapped them to various human cell types. One study using human and nonhuman primate tissue found *ACE2* expression in the secretory cells of the nasal epithelia (upper respiratory tract) and in the type II pneumocytes of the lower respiratory tract.[10] In fibrotic human lung tissue, only 1.4% of type II pneumocytes expressed *ACE2*, and 0.8% of type II pneumocytes expressed both *ACE2* and *TMPRSS2*. In human ethmoid sinus surgical specimens representing upper respiratory epithelia, 1.3% of all secretory cells expressed *ACE2* while 0.3% expressed both *ACE2* and *TMPRSS2* but were further enriched in secretory goblet cells.[11] The spatial resolution offered by single-cell RNA sequencing highlights the limited number of cells in the respiratory tract that express *ACE2*. Further evaluation of *ACE2* expression at the single-cell level in children could help explain whether a lower percentage of *ACE2*-expressing cells or a decrease in expression in *ACE2* expression per cell is related to lower *ACE2* expression in nasal epithelium, as noted in children identified by Bunyavanich et al.[4]

ACE2 has an important role in counterbalancing the effects of ACE. Angiotensin II, a product of ACE cleaving angiotensin I, can cause vasoconstriction, inflammation, and fibrosis by signaling through angiotensin II type 1 receptors. ACE2 can cleave angiotensin II to angiotensin 1-7, which can suppress inflammation and fibrosis and generate vasodilation by binding to the Mas receptor. Previous studies have found ACE2 to play a protective role in severe lung injury in ACE2 knockout mice.[12] If ACE2 can mitigate lung injury but serves as a receptor for viral entry, then is more *ACE2* or less *ACE2* expression protective for children? In the nasal epithelium of the upper airway, lower *ACE2* expression could be helpful in decreasing acquisition of SARS-CoV-2 infection. However, in the lower respiratory tract, it appears that decreased *ACE2* expression could portend a higher risk of developing severe acute respiratory distress and lung injury.

Bunyavanich et al[4] suggested that *ACE2* expression in the nasal epithelium in their cohort does not reflect *ACE2* expression in the pulmonary epithelium, and the expression of *ACE2* in the lower respiratory tract is under different regulation. This emphasizes the importance of understanding the distribution of ACE2 in cells in different parts of the respiratory epithelium but also between cell-bound and plasma fractions. ACE2 is cleaved from the cell membrane on binding with SARS-CoV-2, releasing ACE2 into the plasma. The role of soluble ACE2 in neutralizing SARS-CoV-2 virus has recently been shown in vitro,[13] but its activity in vivo is still to be determined. Ultimately, studying tissue expression of *ACE2* in the lower respiratory tract of children may be helpful in understanding differences in the severity of COVID-19 among children compared with adults.

A new study called Human Epidemiology and Response to SARS-CoV-2 (HEROS), funded by the National Institute of Allergy and Infectious Diseases, is designed to prospectively follow 6000 children to determine risk factors for development of COVID-19.[14] Data from this study could help identify whether the lower *ACE2* expression identified by Bunyavanich et al[4] correlates with lower rates of SARS-CoV-2 infection, and could serve to support the possibility that decreasing *ACE2* expression in the nasal epithelium may be a potential therapeutic approach to mitigate transmission of COVID-19.

ARTICLE INFORMATION

Author Affiliations: Renal Division, Brigham and Women's Hospital, Boston, Massachusetts.

Corresponding Author: Ankit B. Patel, MD, PhD, Brigham and Women's Hospital, 75 Francis St, Boston, MA 02132 (apatel38@bwh.harvard.edu).

Published Online: May 20, 2020. doi:10.1001/jama.2020.8946

Conflict of Interest Disclosures: Dr Patel reported receipt of grants from Relypsa and consulting fees from Third Rock Ventures. No other disclosures were reported.

REFERENCES

1. Richardson S, Hirsch JS, Narasimhan M, et al; Northwell COVID-19 Research Consortium. Presenting characteristics, comorbidities, and outcomes among 5700 patients hospitalized with COVID-19 in the New York City area. *JAMA*. Published online April 22, 2020. doi:10.1001/jama.2020.6775

2. Wadhera RK, Wadhera P, Gaba P, et al. Variation in COVID-19 hospitalizations and deaths across New York City boroughs. *JAMA*. Published online April 29, 2020. doi:10.1001/jama.2020.7197

3. Mehra MR, Desai SS, Kuy S, Henry TD, Patel AN. Cardiovascular disease, drug therapy, and mortality in COVID-19. *N Engl J Med*. Published online May 1, 2020. doi:10.1056/NEJMoa2007621

4. Bunyavanich S, Do A, Vicencio A. Nasal gene expression of angiotensin-converting enzyme 2 in children and adults. *JAMA*. Published online May 20, 2020. doi:10.1001/jama.2020.8707

5. Zhou P, Yang X-L, Wang X-G, et al. A pneumonia outbreak associated with a new coronavirus of probable bat origin. *Nature*. 2020;579(7798):270-273. doi:10.1038/s41586-020-2012-7

6. Castagnoli R, Votto M, Licari A, et al. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection in children and adolescents: a systematic review. *JAMA Pediatr*. 2020;174(9). doi:10.1001/jamapediatrics.2020.1467

7. Bialek S, Gierke R, et al; CDC COVID-19 Response Team. Coronavirus disease 2019 in children—United States, February 12–April 2, 2020. *MMWR Morb Mortal Wkly Rep*. 2020;69(14):422-426. doi:10.15585/mmwr.mm6914e4

8. Bi Q, Wu Y, Mei S, et al. Epidemiology and transmission of COVID-19 in 391 cases and 1286 of their close contacts in Shenzhen, China: a retrospective cohort study. *Lancet Infect Dis*. 2020;S1473-3099(20)30287-5. doi:10.1016/s1473-3099(20)30287-5

9. Gudbjartsson DF, Helgason A, Jonsson H, et al. Spread of SARS-CoV-2 in the Icelandic population. *N Engl J Med*. Published online April 14, 2020. doi:10.1056/NEJMoa2006100

10. Sungnak W, Huang N, Bécavin C, et al; HCA Lung Biological Network. SARS-CoV-2 entry factors are highly expressed in nasal epithelial cells together with innate immune genes. *Nat Med*. 2020;26(5):681-687. doi:10.1038/s41591-020-0868-6

11. Ziegler CGK, Allon SJ, Nyquist SK, et al. SARS-CoV-2 receptor ACE2 is an interferon-stimulated gene in human airway epithelial cells and is detected in specific cell subsets across tissues. *Cell*. Published online April 27, 2020. doi:10.1016/j.cell.2020.04.035

12. Imai Y, Kuba K, Rao S, et al. Angiotensin-converting enzyme 2 protects from severe acute lung failure. *Nature*. 2005;436(7047):112-116. doi:10.1038/nature03712

13. Monteil V, Kwon H, Prado P, et al. Inhibition of SARS-CoV-2 infections in engineered human tissues using clinical-grade soluble human ACE2. *Cell*. 2020;S0092-8674(20)30399-8. doi:10.1016/j.cell.2020.04.004

14. Study to determine incidence of novel coronavirus infection in US children begins. National Institutes of Health website. Published May 4, 2020. Accessed May 11, 2020. https://www.nih.gov/news-events/news-releases/study-determine-incidence-novel-coronavirus-infection-us-children-begins