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COVID-19 in Pediatrics: A Laboratory Perspective

TO THE EDITOR:

Since the initial outbreak of the Corona Virus Disease 2019 (COVID-19) in Wuhan, China, December, 2019, the pathogenic virus, Severe Acute Respiratory Syndrome Corona-

virus 2 (SARS-CoV-2) has rapidly spread worldwide. On March 11th, 2020, the World Health Organization declared a pandemic of SARS-CoV-2 with nearly 118 000 cases and 4300 deaths confirmed in 114 countries. The United States has thus far reported nearly 1, 118 000 cases of confirmed infections and over 64 000 deaths, as of May 1st, 2020.

People of all ages, including infants and children, are susceptible to SARS-CoV-2 infection. The first infected pediatric case was reported in the city of Shenzhen, 1000 km away from the outbreak center, Wuhan. The very first review that includes pediatric patients reported by January 30, 2020, 9692 confirmed cases of SARS-CoV-2 in 31 provinces and cities in China. Among them, there were 28 cases aged from 1 month to 17 years *(1)*. A later article reported 416 children under 10 years old (0.9%) out of 44 672 confirmed cases in China by February 11th, 2020, with the expansion of diagnostic criteria to include imaging findings *(2)*. Another publication included 2143 pediatric patients with COVID-19 reported to the Chinese Center for Disease Control and Prevention from January 16 to February 8, 2020 *(3)*. There were 731 (34.1%) laboratory-confirmed cases and 1412 (65.9%) suspected cases. The median age of all patients was 7 years (interquartile range 2–13), and 1213 cases (56.6%) were male.

In the report from China by February 11th, 2020 *(2)*, with 416 children younger than 10 years, 134 cases had clinical records documented. Most of the infections in children were diagnosed from familial clusters. The main clinical manifestations in children were fever (76.1%); cough; followed by vomiting, diarrhea, and other digestive system symptoms; and viral pneumonia-like changes in chest imaging (70.4%). Two critical cases that progressed rapidly to respiratory failure after onset have been reported in China, one with congenital heart disease and the other with bilateral hydronephrosis and calculus of the left kidney *(1, 4)*. Compared to infected adults, children tend to have milder clinical symptoms, faster recovery, and better prognosis. On the other hand, the asymptomatic infected children may act as "carriers" and potentially shed virus, and this poses a serious challenge to people in close contact, especially pediatric medical workers. Notably, although a positive viral nucleic acid test is the "gold standard," some cases need 2 or even 3 tests to be confirmed, so clinical "false negative" children with negative nucleic acid testing results may still be a potential source of infection. It is suggested that in clinical suspected cases, continuous and repeated sample collections are needed to improve the accuracy *(4)*.

Dong et al. *(3)* reported epidemiological findings in both laboratory-confirmed cases ($N = 731$) and suspected cases ($N = 1412$) of children. Suspected cases were identified based on 2 of the 3 following conditions after excluding influenza and other common respiratory infections: (*a*) fever or respiratory symptoms or digestive symptoms or fatigue; (*b*) normal or decreased white blood cell count with decreased lymphocyte count or increased C-reactive protein levels; (*c*) abnormal chest X-ray imaging (pneumonia-like changes) and ground glass opacities on chest computed tomography. Suspected cases meeting either one of the following criteria were defined as confirmed cases: (*a*) Nasal and pharyngeal swab specimens or blood samples tested positive for SARS-CoV-2 nucleic acid using a realtime reverse-transcriptase polymerase-chain-reaction (RT–PCR) assay; (*b*) Genetic sequencing of respiratory tract or blood samples is highly homologous with SARS-CoV-2. Among the 2143 suspected and confirmed cases reported by Dong et al., 94.1% of all patients were asymptomatic, mild, or moderate (4.4,

50.9, and 38.8%, respectively) cases. The proportion of severe or critical cases was 10.6, 7.3, 4.2, 4.1, and 3.0% for the age groups of <1, 1–5, 6–10, 11–15, and ≥16 years, respectively. One fatality of a 14-year-old boy in Hubei province was reported. In contrast, Lu X et al. *(5)* reviewed the symptoms commonly found in 1391 children who had been confirmed to have SARS-CoV-2 infection from a single center designated to treat infected children under 16 years of age in Wuhan. They found that 15.8% of the cases were asymptomatic, and the most common symptoms were cough, red/sore throat, and fever. Taken the limited data available to date, the percentage for asymptomatic pediatric patients may range from 4.4 to 15.8%.

Regarding laboratory tests, based on the several articles on pediatric patients cited above *(1, 2, 4)* and an all-age study with 1099 patients that included 9 patients aged 0–14 years *(6)*, no differences have been reported in clinical findings between children and adults. Lippi and Plebani *(7)* have summarized laboratory findings from published literature, and we hereby show in Table 1 the characteristic laboratory findings in children. In the early stage of the onset, the total number of white blood cells in the peripheral blood was normal or decreased, the lymphocyte count decreased, and some patients had decreased albumin and increased liver enzymes, muscle enzymes, including increased CK and myoglobin, and increased lactate dehydrogenase (LDH). Most patients had normal or slightly elevated C-reactive protein, increased erythrocyte sedimentation rate, and normal procalcitonin. In severe cases, D-dimer as well as procalcitonin increased, ferritin levels increased, and the number of peripheral blood lymphocytes decreased progressively (Table 1). In contrast, the 2003 SARS-CoV infection resulted in high fever in most pediatric patients. Some patients had temporary abnormality of myocardial enzymes and liver function *(8)*.

There were a number of neonatal infections reported, posing the question of possible mother-to-child vertical transmission. Chen et al. *(9)* reported in 21 pregnant women with confirmed infection in late pregnancy, the amniotic fluid, placenta samples of mothers, and pharyngeal swabs of newborns (collected twice in 24 hours) showed negative results for nucleic acid test. The pharyngeal swab nucleic acid tests of 14 neonates were also

Table 1. Biochemical patterns in pediatric COVID-19 patients

Albumin	Normal or decreased
Alanine and aspartate aminotransferases	Increased
Creatine kinase, myoglobin, lactate dehydrogenase	Increased
Creatinine, blood urea nitrogen	Increased
D-dimer, CRP, procalcitonin	Normal or increased, progressive increases in patients associated with worse outcomes
Bilirubin	Normal or increased
ESR	Normal or increased
Cardiac troponin	Increased in patients that progress to cardiac symptoms

negative on days 5 and 10 of their hospitalization *(9)*. Nevertheless, Zeng et al. *(10)* reported 3 neonates with symptomatic COVID-19 (9%) out of 33 neonates born to mothers with COVID-19. The authors suggested that since strict infection control and prevention procedures were implemented during the delivery, the route of vertical maternal–fetal transmission remains a possibility, despite that other studies found all samples from affected mothers, including amniotic fluid, cord blood, and breast milk, were negative for SARS-CoV-2 *(9, 11)*.

In summary, people of all ages are generally susceptible to SARS-CoV-2 infections, with the propensity increasing with age and comorbidities. Within the pediatric population, infants had higher rates of serious illness than older children . Most of the infections in children are familial clusters that are asymptomatic (up to 16%) or have mild symptoms (up to 51%). These children could be potential sources of infection. The asymptomatic pneumonia found in pediatric patients indicates follow up for these patients should include pulmonary function assessment. To date, critical cases in children identified all had underlying conditions and progressed rapidly, so children with underlying diseases should be aggressively protected by early isolation. Although no laboratory evidence for mother-to-child vertical transmission has been found, the fact that up to 10% neonates born to infected mothers developed symptomatic COVID-19 still suggests that vertical transmission cannot be ruled out and newborns from infected mothers should be isolated immediately after delivery to avoid postnatal exposure. Biochemical features in pediatric patients will be further defined with increased numbers of confirmed patients in the pediatric ages, who have not thus far been tested because of mild clinical symptoms. It is important to note that biochemical findings in the pediatric population in the United States may be different and need to be further studied. Biochemical findings in children, along with levels of cytokines and T cell responses in this population, as well as assessment of antibody titers, may give us mechanistic insights into SARS-CoV-2 infection, morbidity, and mortality.

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