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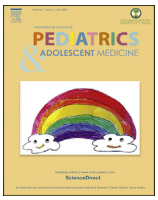

Editorial

Pediatric COVID-19: An update on the expanding pandemic

The coronavirus disease of 2019 (COVID-19)[1] is caused by a novel and highly contagious virus termed "Severe Acute Respiratory Syndrome Coronavirus Two," or "SARS-CoV-2" [2]. The virus was first recognized in the city of Wuhan, China in December 2019 [3] and has swept the globe at an unprecedented speed as a result of airline travel and sustained human-to-human transmission. The World Health Organization (WHO) declared COVID-19 a pandemic on March 11th, 2020 due to the rapid increase in the number of cases and the wide geographical spread outside of China [4]. At the time of the announcement, the WHO estimated a global mortality rate of 3.4% [5]. Most of the fatal cases have occurred in patients with advanced age or with preexisting medical comorbidities, including cardiovascular diseases, diabetes, hypertension, chronic respiratory disease and cancer [6]. Currently over five and a half million people have been infected, overwhelming global health systems and causing threats to health security [7].

Children of all ages are susceptible but have experienced a lower incidence of COVID-19 disease. Data from the Chinese Center for Disease Control and Prevention suggest that less than 1% of the 72,314 cases reported in China were in children under the age of 10 years, with a median age of approximately 7 years (range of 1–18 years) [6]. Data from around 150,000 laboratory-confirmed COVID-19 cases in the United States indicate that 2,572 (1.7%) cases were among children under the age of 18 years. The median age for all infected children was 11 years (with a range from 0 to 17 years of age) [8]. Males were more frequently infected than females in all pediatric age groups. Mortality was very unusual [6,8].

The SARS-CoV-2 virus is transmitted mainly via respiratory droplets [9]. Nearly 90% of children with COVID-19 were believed to have been infected via close contact with family members or community exposure [10]. Current data indicate that infected children are not themselves a major source of transmission. This is in contrast to influenza, where children have played an important role in the transmission to household contacts and are important drivers of epidemics in the community [11,12].

A very limited number of infections have been reported in infants and neonates. At the present time there is no evidence that SARS-CoV-2 is transmitted from mother to child during pregnancy [13–15]. Moreover, although the virus may be transmitted during birth or very shortly thereafter, this is unusual [16]. There is also currently no evidence that the virus is teratogenic, although, because of the small number of reported cases of infection during the first trimester (when embryogenesis occurs), a risk of congenital anomalies associated with COVID-19 cannot be completely excluded [16]. Data and prior experience with other respiratory viruses (e.g. influenza, SARS-CoV-1, MERS) suggest that antenatal transplacental transmission via maternal viremia is unlikely [13]. Analyses of amniotic fluid, serum, placenta, vaginal fluid and breastmilk from pregnant women confirmed to have COVID-19 infections have found no evidence of SARS-CoV-2 infections [13–16]. On the other hand, newborn infants may remain at high risk postnatally for infection through maternal respiratory secretions.

There have now been several series of COVID-19 in children. In a retrospective case series study of 2,143 children under the age of 18 years with 731 (34%) laboratory-confirmed cases and 1,412 (65.9%) suspected COVID-19 cases, the median age was 7 years (Interquartile range: 2-13). The clinical spectrum of illness ranged from asymptomatic to critical, with 94% being mild or moderate, 5.2% severe, and 0.6% critical [17]. Among the available US data on symptoms and signs for 291 of 2,572 (11%) pediatric cases and 10,944 of 113,985 (9.6%) cases among adults aged 18–64 years, fever, cough and shortness of breath were reported in 73% of children in comparison with 93% in adults. In pediatric patients the percentages of reported symptoms were 56% with fever, 54% with cough, and 13% with dyspnea, compared to 71%, 80%, and 43% in adults, respectively [8].

Lu et al. from Wuhan Children's Hospital reviewed the clinical features of 171 children who had confirmed COVID-19 infections. The median age was 6.7 years of age; 41.5% had a fever, 48.5% had coughing, and 46% pharyngeal erythema. Radiologically proven pneumonia was present in 111 (65%), but only 4 (2.3%) had hypoxemia with oxygen saturation <92%. Twelve children with radiologic pneumonia were asymptomatic [18]. Other less common reported symptoms in children include myalgia, sore throat, headache, and diarrhea. Coinfection with other pathogens was reported in 8 out of 20 (40%) children with confirmed COVID-19 and included influenza viruses A and B, *Mycoplasma pneumoniae*, respiratory syncytial virus, and cytomegalovirus [19].

Reverse transcription polymerase chain reaction (RT-PCR) is the recommended method for the confirmation of a COVID-19 infection, using upper respiratory specimens (nasopharyngeal and/or pharyngeal swabs) or, if they can be obtained, lower respiratory specimens [20,21]. High viral load from the nasopharynx was reported in an infant and remained positive for up to 16 days [22].

There is limited information on laboratory findings in children with COVID-19. In a review of 12 different studies that involved 66 children with confirmed COVID-19, 69% had normal white blood cell counts, 5% had neutrophilia, 6% had neutropenia, and 3% reported lymphocytopenia [23,24]. Lymphocytopenia was reported in more than 80% of critically ill adults with COVID-19 suggesting that the severity of Lymphocytopenia correlated with the severity of infection [25]. The low frequency of lymphopenia in children may be, at least in part, due to less severe COVID-19 encountered

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in children. C-reactive protein and procalcitonin were elevated in 13.6% and 10.6% of cases, respectively [23]. Elevation of liver enzymes, muscle enzymes and myoglobin, and an increased level of D-dimer have been reported in severe cases [26].

The radiological changes in the lungs of children with COVID-19 pneumonia have not been fully characterized. In a study of 171 children with PCR-confirmed COVID-19, 15.8% of patients' chest radiographs were read as normal [18]. Common computed tomography abnormalities in these children were bilateral ground glass opacities in 32.7%, local patchy shadowing in 18.7%, and interstitial abnormalities in 1.2% [18]. In a study describing the CT scan findings for 20 SARS-CoV-2-infected children aged 1 day to 14 years 7 months (with a median of 37.5 months), 16 (80%) had abnormal lung CT scans, including consolidation with halo signs, ground-glass opacities and fine mesh shadow [19]. Chest CT imaging abnormalities may be present even in asymptomatic patients [19].

The few clear risk factors identified in children include age and underlying medical conditions. Among available data for 745 hospitalized children less than 18 years old with confirmed COVID-19, 147 (range of 5.7%–20.0%) required intensive care unit admission of whom 95 were children aged less than 1 year [8]. In a report of 345 pediatric cases, 80 (23%) had at least one underlying condition. The most common were chronic lung disease (including asthma) in 40, cardiovascular disease in 25 and immunosuppression in 10 [8]. Furthermore, among 2143 pediatric patients with COVID-19 reported to China's CDC young children aged 1–5 years represented 7.3%, and this increased in infants less than 1 year of age to reach 10.6%.17.

The lower incidence of symptomatic and severely symptomatic COVID-19 in children compared to adults seems counterintuitive and is puzzling. There has been speculation that it could be due to children's younger immune systems and/or to a lower expression of ACE2 receptor cells [27]. Another possible explanation is that respiratory viral diseases are childhood diseases that often re-infect throughout life. Thus, essentially all adults already have immunity. Parenthetically, systemic viral diseases with a respiratory component, such as measles and varicella, are also often more severe in non-immune adults than in children. The three recent severe coronavirus epidemic diseases (SARS, MERS, and COVID-19) are new viruses to the human race, and they may derive at least some of their age-related severity from the fact that they are new.

At this point in time, there are no high-quality data available to support successful treatment strategies for COVID-19 in children. Most publications have commented on a variety of supportive treatments including antipyretics, oxygen therapy and antibiotics for secondary bacterial infections [26]. Clinical trials are also being conducted globally, with the intention of discovering effective and safe treatments. Over the last few weeks, two investigational drugs: Remdesivir and Hydroxychloroquine were granted an emergency use authorization (EUA) from the U.S. Food and Drug Administration (FDA)[28,29] for the treatment of suspected or laboratory-confirmed COVID-19 cases based on clinical trials showing that these investigational drugs can shorten the time to clinical recovery in some patients [30–33]. The FDA's authorization of Remdesivir has been extended to include hospitalized children with severe COVID-19 symptoms (patients requiring supplemental or mechanical ventilation) [29].

A panel of pediatric infectious disease physicians and pharmacists from North America has recommended Remdesivir as a preferred antiviral agent followed by Hydroxychloroquine for children with positive virologic COVID-19 testing [34]. This recommendation was subsequently endorsed by The Pediatric Infectious Diseases Society. Hydroxychloroquine may be considered (with careful consideration of its potential toxicities, particularly those related to QTc prolongation) as an alternative to Remdesivir in countries where the latter drug is not available or the patient is not a candidate for Remdesivir.

There is a growing need for well-designed controlled clinical trials to better define the safety and efficacy of potential treatments for COVID-19 in children. Hopefully these trials can be completed over the next several months to allow us to provide the best treatment for children in this global pandemic.

In summary

The majority of children with COVID-19 have a relatively mild and self-limited disease, and critical illness and mortality are rare. There have, however, been several recent reports of a Multi-Inflammatory Syndrome in Children (MIS-C) with features that in some subjects resemble Kawasaki Disease or Kawasaki Shock Syndrome [35,36]. The patients who present with this symptom complex do not have pneumonia but often have SARS-CoV-2 identified by PCR in upper respiratory samples or antibody evidence of past SARS-CoV-2 infection.

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