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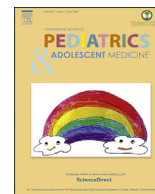
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Editorial

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%.

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.

References

- [1] World Health Organization WHO Director-general's remarks at the media briefing on 2019-nCoV on 11 February 2020. Available at: <https://www.who.int/dg/speeches/detail/who-director-general-s-remarks-at-the-media-briefing-on-2019-ncov-on-11-february-2020>. [Accessed 11 February 2020].
- [2] Gorbalenya AE, Baker SC, Baric RS, de Groot RJ, Drosten C, Gulyaeva AA, et al. Severe acute respiratory syndrome-related coronavirus: the species and its viruses—a statement of the Coronavirus Study Group. *bioRxiv* 2020. published online Feb 11. DOI: 2020;10(2020.02):07-937862.
- [3] WHO Novel coronavirus — China. <http://www.who.int/csr/don/12-january-2020-novel-coronavirus-china/en/>. [Accessed 19 January 2020].
- [4] WHO Director-General's opening remarks at the media briefing on COVID-19 - 11 March 2020. Available at: <https://www.who.int/dg/speeches/detail/who-director-general-s-opening-remarks-at-the-media-briefing-on-covid-19--11-march-2020>.
- [5] WHO director-general's opening remarks at the media briefing on COVID-19 - 3 March 2020 - world health organization, March 3, 2020. Available at: <https://www.who.int/dg/speeches/detail/who-director-general-s-opening-remarks-at-the-media-briefing-on-covid-19--3-march-2020>.
- [6] Wu Zunyou, McGoogan Jennifer M. Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China. Summary of a report of 72 314 cases from the Chinese. *Center for disease control and prevention. J Am Med Assoc* 2020;323(13):1239–42. <https://doi.org/10.1001/jama.2020.2648>.
- [7] Hopkins University John. COVID-19 resource center. <https://coronavirus.jhu.edu/map.html>.
- [8] CDC, COVID-19 Response Team. Coronavirus disease in children—United States February 12–April 2, 2020. *MMWR (Morb Mortal Wkly Rep)* April 6, 2020;69.
- [9] Cao Qing, Ching Chen Yi-, Chen b Chyi-Liang, Chiu Cheng-Hsun. SARS-CoV-2 infection in children: transmission dynamics and clinical characteristics. *J Formos Med Assoc* 2020;119:670e673.
- [10] 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 Mar 25.
- [11] Mimura S, Kamigaki T, Takahashi Y, Umenai T, Kudou M, Oshitani H. Role of preschool and primary school children in epidemics of influenza A in a local community in Japan during two consecutive seasons with A (H3N2) as a predominant subtype. *PLoS One* 2015;10(5).
- [12] Principi N, Esposito S, Gasparini R, Marchisio P, Crovari P. Burden of influenza in healthy children and their households. For the Flu-Flu Study Group *Arch Dis Child* 2004;89:1002–7. <https://doi.org/10.1136/adc.2003.04540>.
- [13] Schwartz D. An analysis of 38 pregnant women with COVID-19, their newborn infants, and maternal-fetal transmission of SARS-CoV-2: maternal coronavirus infections and pregnancy outcomes. *Arch Pathol Lab Med* Mar 2020. <https://doi.org/10.5858/arpa.2020-0901-SA> [Epub ahead of print].
- [14] Fan C, Lei D, Fang C, Li C, Wang M, Liu Y, et al. Perinatal transmission of COVID-19 associated SARS-CoV-2: should we worry? *Clin Infect Dis* 2020 Mar 17.
- [15] Chen H, Guo J, Wang C, Luo F, Yu X, Zhang W, et al. Clinical characteristics and intrauterine vertical transmission potential of COVID-19 infection in nine pregnant women: a retrospective review of medical records. *Lancet* 2020 Mar 7;395(10226):809–15.
- [16] Mimouni F, Lakshminrusimha S, Pearlman SA, Raju T, Gallagher PG, Mendlovic J. Perinatal aspects on the covid-19 pandemic: a practical resource for perinatal-neonatal specialists. *J Perinatol* 2020 Apr 10:1–7.
- [17] Dong Y, Mo X, Hu Y, Qi X, Jiang F, Jiang Z, et al. Epidemiological characteristics

- of 2143 pediatric patients with 2019 coronavirus disease in China. *Pediatrics* 2020 Mar 1.
- [18] Lu X, Zhang L, Du H, Zhang J, Li YY, Qu J, et al. SARS-CoV-2 infection in children. *N Engl J Med* 2020 Mar 18.
- [19] 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 May;55(5):1169–74.
- [20] World Health Organization. Laboratory testing for coronavirus disease (COVID-19) in suspected human cases. Interim Guid 2 March 2020. Available at: <https://apps.who.int/iris/bitstream/handle/10665/331501/WHO-COVID-19-laboratory-2020.5-eng.pdf?sequence=1&isAllowed=y>.
- [21] Sethuraman N, Stanleyraj S, Jeremiah MD, Ryo A. Interpreting diagnostic tests for SARS-CoV-2. *J Am Med Assoc* 2020 May 6. <https://doi.org/10.1001/jama.2020.8259> [Epub ahead of print].
- [22] Kam KQ, Yung CF, Cui L, Tzer Pin Lin R, Mak TM, Maiwald M, et al. A well infant with coronavirus disease 2019 with high viral load. *Clinical Infectious Diseases*; 2020.
- [23] Ludvigsson JF. Systemic review of COVID-19 in children shows milder cases and a better prognosis than adults. 2020. <https://doi.org/10.1111/APA.15270>.
- [24] Henry BM, Lippi G, Plebani M. Laboratory abnormalities in children with novel coronavirus disease 2019. *Clin Chem Lab Med* 2020 Mar 16:1 (ahead-of-print).
- [25] Yang X, Yu Y, Xu J, Shu H, Liu H, Wu Y, et al. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. *Lancet Respir Med* 2020 Feb 24.
- [26] Chen ZM, Fu JF, Shu Q, Chen YH, Hua CZ, Li FB, et al. Diagnosis and treatment recommendations for pediatric respiratory infection caused by the 2019 novel coronavirus. *World J Pediatr* 2020 Feb 5:1–7.
- [27] Lee PI, Hu YL, Chen PY, Huang YC, Hsueh PR. Are children less susceptible to COVID-19? *J Microbiol Immunol Infect* 2020 Feb 25.
- [28] Coronavirus (COVID-19) update: March 30, 2020. <https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-daily-roundup-march-30-2020>. Available at:.
- [29] Coronavirus (COVID-19) Update: FDA Issues Emergency Use Authorization for Potential COVID-19 Treatment. Available at: <https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-issues-emergency-use-authorization-potential-covid-19-treatment>; May, 1, 2020.
- [30] National Institute of Allergy and Infectious Diseases (NIAID). Adaptive COVID-19 treatment trial, shows Remdesivir accelerates recovery from advanced COVID-19. NIAIDNews@niaid.nih.gov.
- [31] Wang Y, Zhang D, Du G, Du R, Zhao J, Jin Y, et al. Remdesivir in adults with severe COVID-19: a randomised, double-blind, placebo-controlled, multicentre trial. *Lancet* 2020 Apr 29.
- [32] Geleris J, Sun Y, Platt J, Zucker J, Baldwin M, Hripcsak G, et al. Observational study of hydroxychloroquine in hospitalized patients with covid-19. *N Engl J Med* 2020 May 7.
- [33] Chen Z, Hu J, Zhang Z, Jiang S, Han S, Yan D, et al. Efficacy of hydroxychloroquine in patients with COVID-19: results of a randomized clinical trial. *MedRxiv* 2020 Jan 1.
- [34] Chiotos K, Hayes M, Kimberlin DW, Jones SB, James SH, Pinninti SG, et al. Multicenter initial guidance on use of antivirals for children with COVID-19/SARS-CoV-2. *J Pediatr Infect Dis Soc* 2020 Apr 22.
- [35] Verdoni L, Mazza A, Gervasoni A, Martelli L, et al. An outbreak of severe Kawasaki-like disease at the Italian epicentre of the SARS-CoV-2 epidemic: an observational cohort study. *Lancet* 2020. [https://doi.org/10.1016/S0140-6736\(20\)31103-X](https://doi.org/10.1016/S0140-6736(20)31103-X). published online May 13.
- [36] Dallan C, Romano F, Siebert J, Politi S, et al. Hyperinflammatory shock in children during COVID-19 pandemic. *Lancet* 2020. [https://doi.org/10.1016/S2352-4642\(20\)30164-4](https://doi.org/10.1016/S2352-4642(20)30164-4). Published Online May 19, 2020.

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