

## Pediatric Patients and the Current COVID-19 Pandemic

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### Background

Similar to pediatric cases infected with severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS), children who acquired SARS-CoV-2 virus (Coronavirus Disease, COVID-19) were less likely to be infected, and showed milder symptoms than adults [1]. However, they are still vulnerable as the virus is very contagious. In addition, demographic data seem to be different from one country to the other as the virus continues to spread through the world.

In a study published in the New England Journal of Medicine by the Chinese CDC, the rate of COVID-19 infections in pediatrics below the age of 19 years was 2.1%, among over 72,000 cases [2]. Similarly, in the United States, pediatric patients with COVID-19 accounted for 1.7% among the 149,082 reported cases as of April 2, 2020 [3].

Another Chinese study reported a low mortality rate of 0.6% in children between the age of 1 day and 15 years (median 6.7 years). In this cohort, fever was reported in 41.5%, along with other common symptoms such as cough and pharyngeal edema. Nonetheless, 15.8% did not show any symptoms or radiologic signs of pneumonia [4]. In the same study, a total of 3 patients (1.7%) were ventilated and admitted to the ICU, all of which had predisposing conditions, including an infant with intussusception, who died after a month of admission with multi-organ failure [4]. Although an adolescent death was reported [2], infants were twice at a higher risk for severe illness, compared to older children [5].

### Pathogenesis and clinical presentation

Following the initial cases that suggest zoonotic transmission in Wuhan, subsequent cases were caused by human-human transmission, with an estimated reproduction number of three [2,6].

There is a known association between SARS-CoV-2 and angiotensin-converting enzyme 2 (ACE2) receptors, as they serve as co-receptors for the entry of the virus. ACE2 receptors are known to be expressed in multiple organs in the body, such as alveolar cells II in the lungs, gastrointestinal tract, testicles, heart and the kidney [7]. The broader expression of ACE2 receptors in adults' lungs may explain one of the possible reasons the disease is less common in pediatrics.

Severity of the disease is thought to be directly related to the increased levels of cytokines, which may increase the risk of tissue damage and pro-inflammatory process (cytokine storm) [8], subsequently leading to acute respiratory distress syndrome (ARDS).

Data representing clinical presentation of infected children are limited; however, fever and cough were among the most common features in pediatrics, with one third of the patients showing bilateral ground-glass opacity on chest x-ray. It is also not uncommon for pediatric patients to present with no symptoms or radiologic changes [4].

### Medical treatment

The current evidence until the time this paper is written (April 6<sup>th</sup> 2020), does not support the routine use of any specific therapeutic agents to treat COVID-19 in pediatric patients. Supportive care should commence as soon as those patients are identified, with special attention to treat the concomitant diseases, such as community acquired pneumonia, septic shock, and acute respiratory distress syndrome [9].

Although no data to support or oppose the use of steroids in critically ill COVID-19 patients, the adult surviving sepsis campaign suggest giving low dose steroids for refractory septic shock, and mechanically ventilated patients with acute respiratory distress syndrome [10]. They also prefer acetaminophen to ibuprofen as an antipyretic agent. As for antivirals, they recommend against using lopinavir/ritonavir and endorse no recommendations for the use of other specific therapies due to insufficient data [10].

As for hydroxychloroquine, the current evidence until the time of writing the paper is not sufficient to recommend its routine use. A small-randomized controlled trial was published (without peer-reviewing) evaluating hydroxychloroquine. The authors did not provide details on the characteristics of the patients in both treatment and control groups [11]. Patients in the control group were more likely to have cough and fever, and that was statistically significant, indicating no homogeneity between both groups, and making interpretations difficult. It is important to note that the study also did not appear to include patients with severe COVID-19 disease.

As for the combination with azithromycin, an open-label non-randomized trial that included a small number of patients, concluded that the combination has significantly reduced the viral load [12]. The study was published in the International Journal of Antimicrobial Agents in March 20<sup>th</sup> 2020, however later on in April 3<sup>rd</sup> 2020, the International Society of Antimicrobial Chemotherapy (ISAC), published an official statement stating that it “shares the concerns regarding the article published recently in the International Journal of Antimicrobial Agents. The ISAC Board believes the article does not meet the Society’s expected standard, especially relating to the lack of better explanations of the inclusion criteria and the triage of patients to ensure patient safety” [13]. Furthermore, monitoring for potential adverse events is paramount, especially when therapeutic combination agents are used.

There are plenty of ongoing clinical trials investigating the efficacy and safety of potential therapeutic options; they are registered on (<https://clinicaltrials.gov/>). No solid therapeutic recommendation could be made until data emerges from well-conducted randomized controlled studies.

### Conclusion

COVID-19 is an emerging infectious disease, with high transmission rate. The current data suggest children are less likely to be affected; however, infants and those with chronic comorbidities are at increased risk of disease complications. Treatment so far, up to the time of writing this short communication is supportive, and include management of co-infections, shock and acute respiratory distress syndrome. Many clinical trials are underway to test potential treatment options, which may be used in the treatment of patients with COVID-19 disease.

### Conflict of Interest

None declared.

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