A case series of children with Coronavirus Disease 2019: what have we learned?

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Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has emerged in Wuhan, China in December 2019 and rapidly disseminated globally to cause a pandemic of Coronavirus Disease 2019 (COVID-19) within less than 4 months [1]. SARS-CoV-2 can transmit efficiently among humans, with a case-fatality rate of 0.5% to 10% depending on locality [2]. As most of the large clinical cohorts of COVID-19 patients were focused on adult and elderly patients, the clinical characteristics of children with COVID-19 were not well described. Several articles recently published in *Clinical Infectious Diseases* have provided valuable information about the clinical course of COVID-19 among pediatric patients and their mothers.

Among the four neonates born to women with laboratory-confirmed COVID-19 in the third trimester, only one neonate had virological confirmation of COVID-19 with positive pharyngeal RT-PCR result [3-5]. This was similar to the findings in a systematic investigation on perinatal transmission among 5 pregnant SARS patients and their neonates, in which none of the neonates developed SARS [6]. Notably, all of the four neonates born to COVID-19 mothers were immediately separated from their mothers after birth to avoid transmission via close contact or droplets, suggesting that stringent infection control measures were useful to prevent perinatal mother-to-neonate transmission of SARS-CoV-2. In the single laboratory-confirmed case of neonatal COVID-19, it remains undetermined whether intrauterine transmission of SARS-CoV-2 occurred as serial maternal and fetal blood samples were not available for testing [3]. All four neonates and their mothers had good clinical outcome. Only one of the four neonates developed reduced fetal movement and fetal heart rate variability which required preterm delivery by emergency Cesarean section at 30 weeks of gestation, and remained well after birth [4]. Notably, pregnant SARS patients were significantly more likely to develop renal failure, disseminated intravascular coagulopathy, and death than non-pregnant SARS patients [7]. Increased risks of spontaneous miscarriage,

preterm delivery, intrauterine growth retardation, and severe gastrointestinal morbidity have also been reported in pregnant SARS patients [6, 8]. Thus, pregnant COVID-19 patients should be monitored closely for the development of any severe complications which would require urgent interventions and delivery of the fetus.

Cai et al. and Kam et al. reported a total of 11 children with laboratory-confirmed COVID-19 [9, 10]. All of the children were either asymptomatic or had mild to moderate disease. Consistent with a previous report, asymptomatic children could be shedding high viral loads in their respiratory tract specimens. Moreover, SARS-CoV-2 RNA could be detected in extrapulmonary specimens, including blood and feces. Viral RNA could be detected for up to 22 days in nasopharyngeal and throat swabs and more than 30 days in feces [9]. The CDC recommends the consideration of RT-PCR testing results for decisions on discontinuing transmission-based precautions for COVID-19 [11]. Prolonged viral shedding reported in children may pose a challenge for the saturated healthcare systems in areas where the number of COVID-19 cases is increasing rapidly. Further studies are required to determine the transmissibility of children with prolonged virus shedding.

One key question is whether mothers with COVID-19 can continue to provide breast feeding for their neonates. SARS-CoV-2 RNA was not detected in any of the breast milk samples in these reports. However, the optimal period for withholding breast feeding should be determined on a case-to-case basis. For example, the mother should probably refrain from breastfeeding while still shedding the virus from the respiratory tract as the majority of the world's population remains non-immune to SARS-CoV-2 and lack neutralizing maternal antibodies that could be transferred to the child.

From the experience of SARS in 2002-2003, the clinical course of neonates and children could be quite different from those of adults. Pediatric SARS patients had much better outcome than adult SARS patients [12]. This was also observed in COVID-19 patients.

A large series of 70,000 patients in China showed that only 1% of the patients were below 10 years old [13]. The biological basis of this apparent mild illness in children is not clear but may be related to different host immune response towards the viruses. One hypothesis for adults having more severe disease is the presence of cross-reactive disease-enhancing immunity induced by prior human coronavirus infection. Immunization of 2003 SARS-CoV was shown to worsen infection due to SARS-like coronaviruses in a mouse model [14]. Since coronavirus antibodies are less common in children than in adults, the relative lack of disease-enhancing antibodies may limit the disease severity [15]. For influenza virus, immune imprinting has been shown to be associated with vaccine effectiveness [16]. Whether immune imprinting due to prior exposure to other human coronaviruses affect immune response towards SARS-CoV-2 remains to be determined.

Notes

Author contributions. HC, JF-WC, and K-YY had roles in the study design, data collection, data analysis, data interpretation, and writing of the manuscript. All authors reviewed and approved the final version of the manuscript.

Potential conflicts of interest. We declare no competing interests.

Acknowledgements. None.

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