



What can we learn from neonates with COVID-19?

Tian-Tian Xiao^{1,2} · Kai Yan^{1,2} · Lai-Shuan Wang^{1,2} · Wen-Hao Zhou^{1,2}

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The coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has become a global pandemic. Studies on epidemiological and clinical characteristics of patients with COVID-19 have indicated that children are susceptible to SARS-CoV-2 [1–3]. To date, the largest study in China reported that over 90% of 2143 children with COVID-19 were asymptomatic, or had mild or moderate illness, and that 5.8% presented critical illness [3]. Although the data of neonates are limited and only six neonates with COVID-19 have been reported thus far, several important points should be addressed from these neonatal cases.

What are the routes of transmission in the neonates?

The person-to-person transmission of SARS-CoV-2 has been confirmed by epidemiological studies of cases associated with COVID-19 [4]. Three late-onset neonatal COVID-19 cases were caused by familial aggregation infection, consistent with studies on children and adults with COVID-19 [4, 5]. However, COVID-19 still occurred in three neonates on day 2 after birth, even though strict infection control and preventive procedures were implemented [6]. A recent study described that the elevated IgM antibodies to SARS-CoV-2 were detected in a neonate born to its affected mother at 2 h after birth and the level of IgM was still elevated at 14 days later, indicating the possibility of vertical transmission [7]. However, a previous study showed that there were no clinical findings suggestive of COVID-19 in 19 neonates born to infected mothers, and all samples, including nasopharyngeal

and rectal swabs from neonates, amniotic fluid, cord blood, and breastmilk were detected negative for SARS-CoV-2 [8, 9]. Therefore, vertical transmission remains controversial. At present, no studies have demonstrated that there is live virus isolated from the stools of patients with COVID-19; therefore, fecal–oral transmission remains uncertain. Notably, one infected neonate presented vomiting and bloody stool with SARS-CoV-2 positive rectal swabs, indicating that the gastrointestinal system was involved in this neonate with COVID-19 [10].

What are the clinical characteristics of neonates with COVID-19?

Figure 1 shows the clinical history of six neonates with COVID-19. Four neonates presented mild illness. Two neonates with underlying conditions presented severe respiratory illness, consistent with the results obtained from children [3]. One neonate with atrial septal defect (ASD) presented critical severe pneumonia and cardiac dysfunction [11], whereas the other neonate born at a gestational age of 31 + 2 weeks was diagnosed with neonatal respiratory distress syndrome (NRDS) and sepsis with an *Enterobacter* agglomerates positive blood culture [6]. All the neonates had favorable outcomes (Fig. 1). The most common symptoms were fever, tachypnea and vomiting. However, different from children and adults, no neonates presented cough. Respiratory, gastrointestinal and cardiovascular systems can be all involved in neonates with COVID-19. Compared with adults, six neonates presented normal white blood cell counts and one had lymphocytopenia [6, 10–12]. Although the National Health Commission of the People's Republic of China has recommended serological diagnosis criteria for COVID-19, the features of immune response in neonates remain unclear. Two recent studies described the elevated IgM and IgG antibodies to SARS-CoV-2 in the neonates born to mothers with COVID-19; yet all the neonates were negative for SARS-CoV-2, and the follow-up time of the serological test was too short [7, 13]. Therefore,

✉ Wen-Hao Zhou
zhouwenhao@fudan.edu.cn

¹ National Clinical Research Center for Children's Hospital of Fudan University, Shanghai, China

² Department of Neonatology, Children's Hospital of Fudan University, 399 Wanyuan Road, Shanghai 201102, China

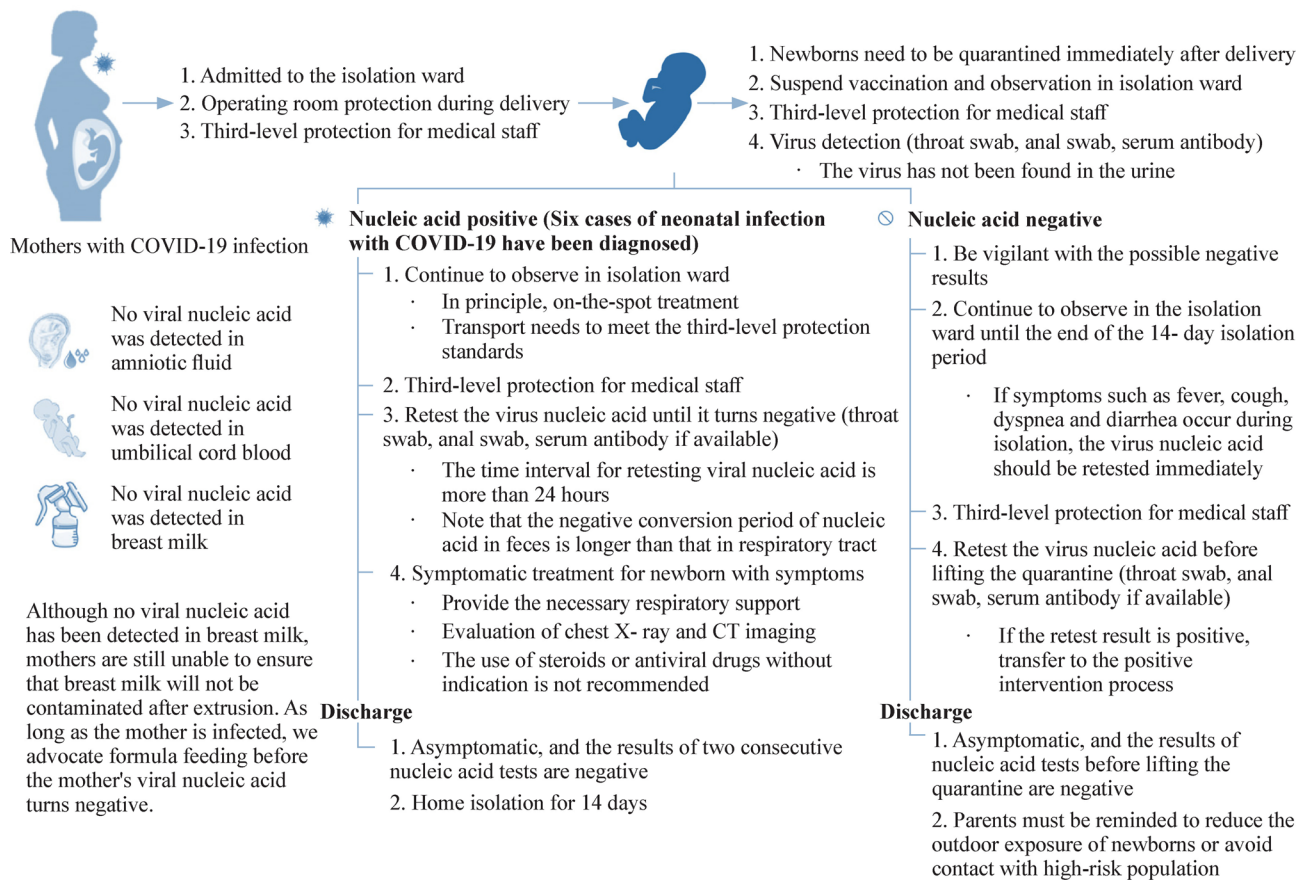


Fig. 1 The timeline and findings of six neonates infected with SARS-CoV-2

further studies should be initiated to investigate the dynamic immune response in neonates with COVID-19 or in neonates born to infected mothers. Also, typical imaging findings were observed in adults; yet radiological findings were non-specific in the six infected neonates [6, 10–12].

How to manage the neonates with COVID-19?

The flow diagram for managing neonates with COVID-19 is shown in COVID-19. Four affected neonates with mild symptoms were managed without intensive care. However, as stated above, one neonate with congenital heart disease (6.9 mm ASD) presented pneumonia and cardiac insufficiency; symptoms improved rapidly with inotropic therapy and fluid management in this neonate [11]. Another pre-term infant with pneumonia, neonatal respiratory distress syndrome (NRDS), and sepsis was recovered with non-invasive ventilation support, caffeine and antibiotics [6]. These two cases provided a clue that although the symptomatic neonates with COVID-19 with underlying pulmonary diseases or congenital heart diseases received no antiviral

therapy, they could improve rapidly after early and appropriate treatments. Moreover, the manifestations of neonatal COVID-19 are indistinguishable from NRDS, transient tachypnea, pneumonia, sepsis, etc. Therefore, it is important to investigate other etiologies if the clinical course of neonates with COVID-19 is not as expected and to protect those neonates with comorbidities including immunodeficiency disease, congenital heart disease, inherited metabolic disease, neuromuscular disorders, etc. Next, it is critical to decide discharge time from hospital. The current criterion is two consecutive results showing negative for SARS-CoV-2 using upper airway specimen (with at least a 24-h interval). However, the rectal swabs from two neonates remained positive for SARS-CoV-2 after nasopharyngeal swabs turned negative [10, 12], consistent with the results obtained from the study in pediatric patients [14]. Therefore, the criterion may need to be revised based on the available data. Currently, no evidences have shown that the SARS-CoV-2 can be transmitted from neonates to other neonates or to caregivers or healthcare workers. Importantly, as the possibility of fecal–oral transmission exists, the appropriate education should be offered to parents with respect to hand hygiene and disinfection of children’s excreta at home.

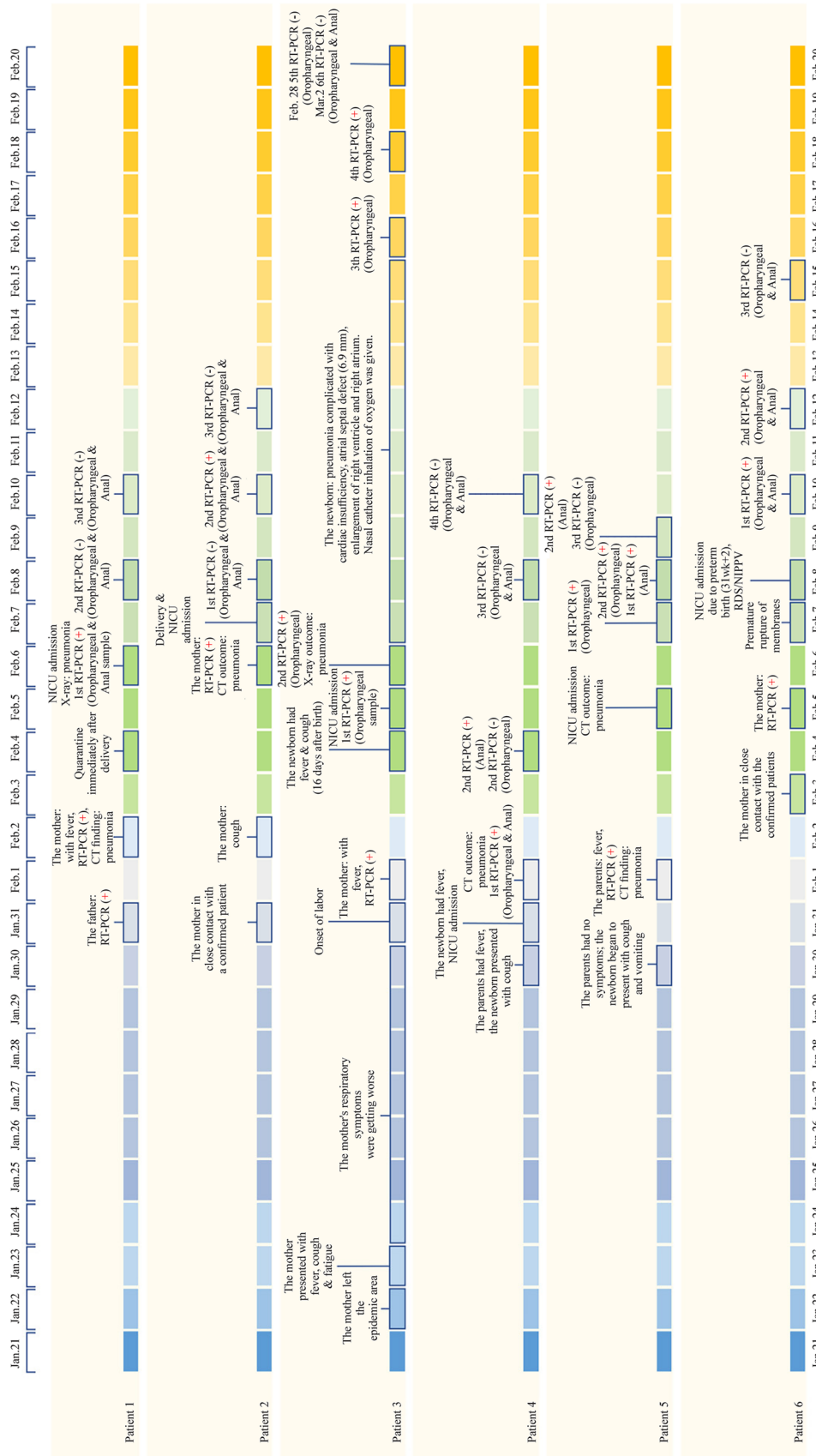


Fig. 2 The recommended management flow of neonates with COVID-19 or at high risk of infection

How to manage the neonates born to mothers with COVID-19?

Figure 2 shows the management flow for neonates born to mothers with COVID-19. As stated above, the familial cluster infection has been confirmed but vertical transmission remains uncertain. Thus, all neonates born to mothers with COVID-19 are at high risk of infection and should be separated from mothers, and fed by formula milk initially. The infected mothers with two consecutive negative tests for SARS-CoV-2 should be kept isolated for another 14 days, and then the infants can be breastfed by mothers. The isolated mothers should keep pumping to maintain breastmilk. Meanwhile, considering the virus may be excreted into the breastmilk of the infected mothers, donor milk and breastmilk can be considered for use after being screened for SARS-CoV-2. Family support should be offered in the case of maternal-neonatal separation and maternal depression. In the delivery room, to reduce the risk of the vertical transmission of SARS-CoV-2, delayed cord clamping (DCC) and mother-baby contact are also not recommended in China.

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Compliance with ethical standards

Ethical approval Not required for this viewpoint.

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