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Horizontal transmission of severe acute respiratory syndrome coronavirus 2 to a premature infant: multiple organ injury and association with markers of inflammation

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A male infant, born at 27 weeks' gestation, presented to our emergency department at 8 weeks of age (35 weeks corrected gestational age) following a 2-day history of poor feeding, sneezing, and dyspnoea. The infant had required 3 days of ventilation after birth because of neonatal respiratory distress syndrome, and had been fed with maternal expressed breast milk from day 3 of life. He had been discharged from the neonatal unit 10 days before presentation, in good health, with no ongoing respiratory support. There had been no cases of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection on the neonatal unit before or following discharge, members of the infant's household (parents and a 4-year-old sibling) were asymptomatic, and there were no other reported contacts.

On initial assessment, the infant was in respiratory failure and presumed septic shock. Blood pressure was unrecordable, and severe lactic acidosis was identified (venous blood pH 6·8, lactate 22 mmol/L). Resuscitation was commenced and respiratory support was instituted. The infant was ventilated with an initial fraction of inspired oxygen (FiO_2) of 1·00 (figure 1). Empirical antimicrobial treatment (cefotaxime [50 mg/kg every 8 h], clarithromycin [15 mg/kg every 12 h], amoxicillin [30 mg/kg every 8 h], and gentamicin [5 mg/kg once a day]) and antiviral treatment (aciclovir [20 mg/kg every 8 h]) were initiated intravenously. A complete septic screen was done. A chest X-ray showed bilateral airspace opacification (figure 2), and quantitative RT-PCR showed that the patient's nasopharyngeal swab sample was positive for SARS-CoV-2. A blood culture, taken on admission, was positive for *Staphylococcus epidermidis*, at which point intravenous vancomycin (10 mg/kg three times a day) was initiated as a targeted treatment. Subsequent blood cultures on hospital days 3 and 5 and all vascular catheter tip cultures were negative. Bacterial cultures of cerebrospinal fluid, urine, and respiratory secretions were negative, and quantitative RT-PCR analysis of respiratory secretions identified no other common respiratory viruses.

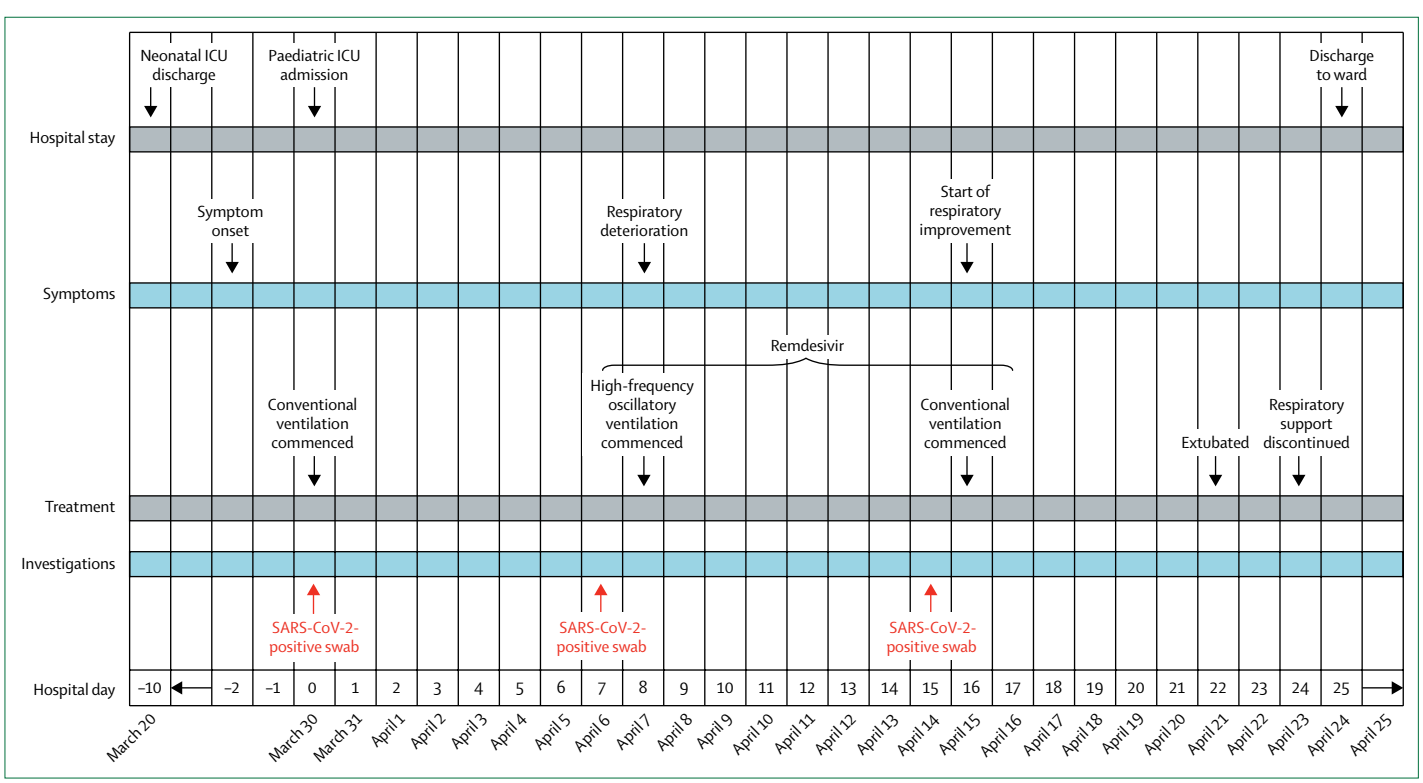

Figure 1: **Timeline of hospital stay, symptoms, treatment, and investigations**
ICU=intensive care unit. SARS-CoV-2=severe acute respiratory syndrome coronavirus 2.

Over the first week following admission, biochemical evidence of renal and liver dysfunction resolved (figure 3). Normal cardiac function was shown on echocardiogram, and cardiac rhythm remained sinus. However, the infant became increasingly difficult to ventilate and repeat chest X-rays on hospital day 8 showed worsening bilateral airspace opacification consistent with acute respiratory distress syndrome (figure 2). On hospital day 8, conventional ventilation at high pressures (27/10 cm H_2O) was considered to be failing, with a partial pressure of carbon dioxide of 12 kPa and FiO2 of 1·00. High-frequency oscillatory ventilation was commenced in conjunction with continuous inhaled nitric oxide and prone positioning. Antimicrobial treatment was optimised for a respiratory focus of infection, with the cessation of cefotaxime and initiation of intravenous meropenem (20 mg/kg every 12 h). The antiviral remdesivir was prescribed on compassionate grounds and administered intravenously (2·5 mg/kg loading dose, followed by 1·25 mg/kg daily for 10 days; figure 1).

Over the following days, there was a gradual improvement in respiratory function. The inspired concentrations of oxygen and nitric oxide were weaned, and the infant was switched back to conventional ventilation on day 16 of admission (figure 1). The infant was extubated on hospital day 22 onto high-flow oxygen with an FiO2 of 0·25, and was weaned from all respiratory support on day 24. At the time of publication, the infant remains an inpatient on the general paediatric ward while sedation is weaned, and is expected to be discharged within days. He is bottle feeding normally and there are no neurological sequalae evident at present.

The results of longitudinal measurement of blood inflammatory markers, including interleukin 6 (IL6), interleukin 10, ferritin, lactate dehydrogenase, and C-reactive protein are presented in figure 3, along with SARS-CoV-2 viral load from respiratory tract samples, blood leucocyte counts, renal function, liver function, and oxygen requirement.

We present here the first detailed description, to our knowledge, of a premature infant with severe SARS-CoV-2 infection in whom longitudinal assessment of multiple organ injury, blood inflammatory markers, and viral load is described.

The symptoms of SARS-Cov-2 infection are highly variable and have been reported to be mild in the paediatric population as compared with adults.[1] However, paediatric severe disease is recognised.[2,3] On April 25, 2020, Public Health England issued a national alert identifying an increase in children presenting with a multisystem inflammatory state, thought to be related to SARS-CoV-2 infection, requiring intensive care treatment.

Within the paediatric population, there is a disparity in the severity of illness reported in relation to age. Infants infected with SARS-CoV-2 are more severely affected than are older children. Compared with older age groups, higher proportions of children under 1 year of age are hospitalised (62%) and admitted to intensive care (5%).[4] There is currently a paucity of detailed data on neonates and premature infants infected with SARS-CoV-2. Reports of infection in neonates born to mothers with active infection have generally shown a mild clinical course.[5,6]

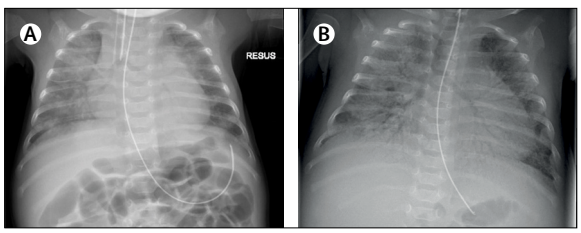

Figure 2: **Chest X-rays**
(A) Bilateral airspace opacification was visible on admission. (B) Repeat X-ray (hospital day 8) showed worsening bilateral airspace opacification consistent with acute respiratory distress syndrome.

The infant described in this report was severely unwell at presentation. Evidence of renal, liver, and bone marrow dysfunction during the early stages of admission (and rapid recovery) were probably a reflection of the shocked state in which the infant presented, rather than the effect of the virus itself or thromboembolic disease. Notably, despite recovery of marrow function, lymphopenia persisted—a frequently reported observation in adult COVID-19. We cannot rule out the possibility of a bacterial co-infection contributing to disease severity. However, within the context of the disease progression and the results of thorough microbiological investigation, *S epidermidis* (cultured from a blood sample taken at admission) was considered to be unlikely to be a disease-causing pathogen. The deterioration in respiratory function over the first week and progressive X-ray changes consistent with acute respiratory distress syndrome are similar to the findings in severely affected adults. The institution of high-frequency oscillatory ventilation and inhaled nitric oxide on day 8 of admission probably improved the ventilation–perfusion mismatch, somewhat relieving the hypoxaemia. Similar adult treatment strategies have involved continuous inhaled epoprostenol to achieve vasodilation in ventilated areas of the lung. It is unclear to what extent ventilating in the prone position was of benefit, as there was temporal overlap of this manoeuvre with the modifications in ventilation described above. We cannot rule out the possibility of pulmonary thrombi (commonly identified in adult disease) contributing to the deterioration, because no CT scan was done.

Because of the deterioration in respiratory function on day 8 of admission, we considered the possibility of a hyperinflammatory response. Raised inflammatory markers have been associated with more severe disease in adults with COVID-19;[7] specifically, raised blood IL6 concentration has been shown to be predictive of respiratory failure.[8] Furthermore, an anti-IL6 monoclonal antibody (tocilizumab) has been used to treat severe

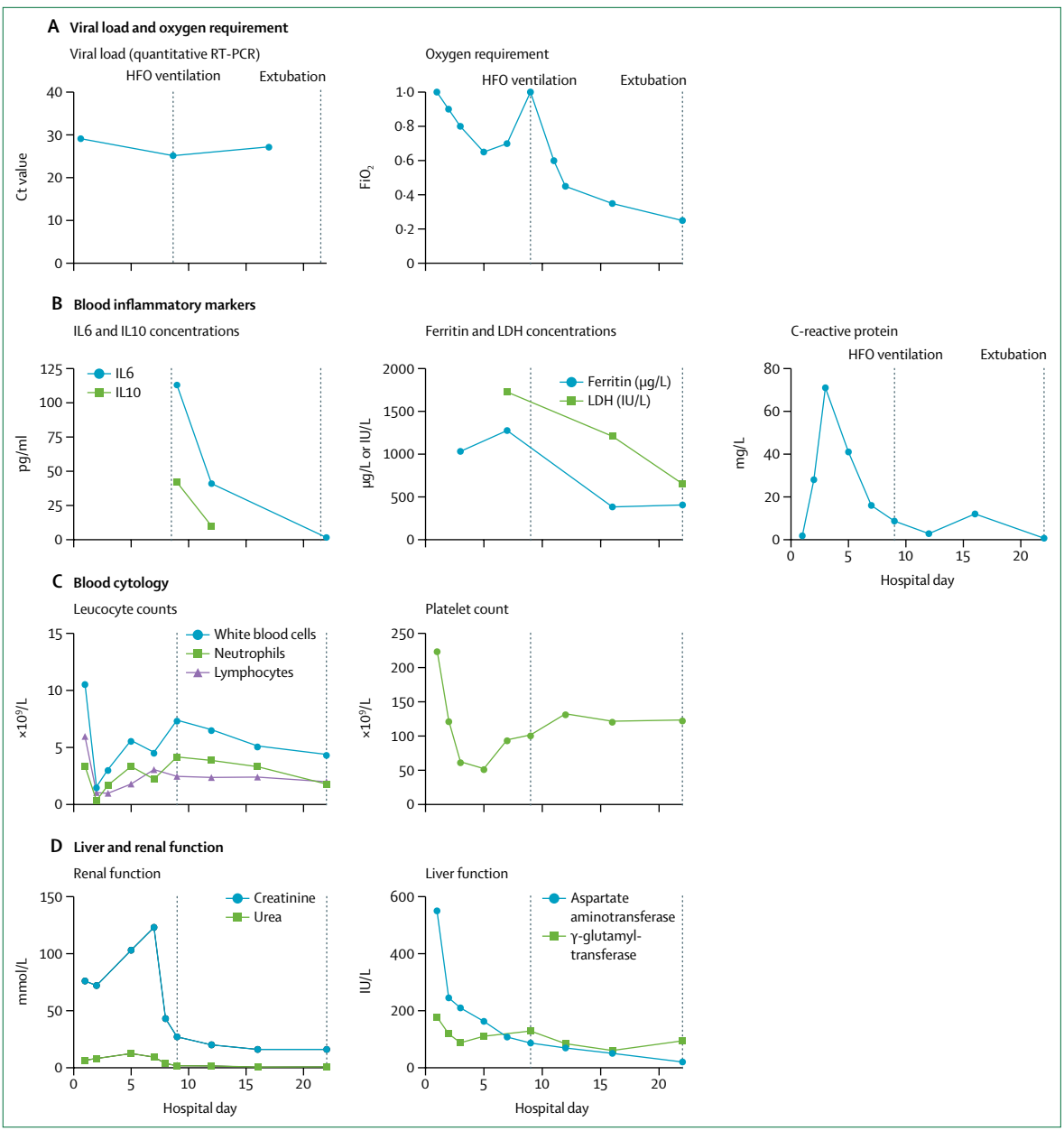

Figure 3: **Longitudinal measurements of viral load, oxygen requirement, and laboratory findings**
Normal ranges: IL6 <6·3 pg/mL, IL10 <3 pg/mL, ferritin <400 µg/L, LDH <240 IU/L, C-reactive protein <5 mg/L, creatinine 13–39 µmol/L, urea 0·8–5·5 mmol/L, γ-glutamyl-transferase 9–40 IU/L, aspartate aminotransferase 8–60 IU/L. HFO=high-frequency oscillation. Ct=threshold cycle. IL6=interleukin 6. IL10=interleukin 10. LDH=lactate dehydrogenase.

COVID-19, with anecdotal success, and randomised controlled trials of this therapy are underway (NCT04335071). At the point of respiratory deterioration, our patient's blood IL6 concentration was high (113 pg/mL [normal range <6·3 pg/mL]). In an adult cohort in Germany, the risk of respiratory failure was 22 times greater in adults with an IL6 concentration of >80 pg/mL compared with those with lower IL6 concentrations.[8] Respiratory improvement in this infant appeared to be associated with a decrease in IL6 concentration, ferritin, and lactate dehydrogenase, rather than a decrease in viral load, suggesting that the host pulmonary inflammatory response might have been important with regard to respiratory failure.

At the point of respiratory deterioration, remdesivir was also prescribed. Remdesivir is a prodrug of a nucleotide analogue that inhibits viral RNA polymerases, and in-vitro testing has shown activity against SARS-CoV-2.[9] Outcomes of an adult cohort with severe COVID-19 treated with remdesivir have recently been published, although viral

load in these patients was not reported.[10] The stable viral load in our patient does not suggest that remdesivir was important in the clinical improvement of this infant. No side-effects from remdesivir were apparent at the time of writing.

SARS-CoV-2 can cause severe disease in infants, resulting in multiple organ injury. The severity of respiratory disease might be related to the host inflammatory response, as seen in adults with COVID-19. Detailed monitoring of the inflammation is recommended in paediatric severe disease, modulation of which might represent a potential avenue of treatment.

Contributors

Data collection and interpretation: JC, BD, PD, KH, and AG collected and interpreted the data. JC prepared the original draft of the manuscript. AG, KH, BZ, AV, and PD reviewed and edited the manuscript. All authors reviewed and approved the final version of the manuscript.

Declaration of interests

We declare no competing interests.

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