

Schrempf, Claire Semaani, Silvia Stringhini, Stéphanie Testini, Deborah Urrutia Rivas, Charlotte Verolet, Jennifer Villers, Guillemette Violot, Nicolas Vuilleumier, Ania Wisniak, Sabine Yerly, María-Eugenio Zaballa.

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doi:10.1111/jpc.15977

Dear Editor,

RELAPSE OF IDIOPATHIC NEPHROTIC SYNDROME AFTER SARS-COV-2 VACCINATION: TWO CASE REPORTS

A 17-year-old girl being followed up for idiopathic nephrotic syndrome (INS) was admitted with complaints of lower extremity and pretibial oedema 19 days after the second dose of SARS-CoV-2 vaccine (each 0.3 mL dose contained 30 mcg modRNA administered intramuscularly in the deltoid muscle). The histopathological diagnosis of the patient, who was diagnosed at the age of 1.5 years, was minimal change disease; she had been treated with corticosteroids, levamisole, mycophenolate mofetil and enalapril. The patient, who was in remission for 4.5 years, discontinued treatment 3.5 years ago, and renal function and urinary protein excretion were within the normal range at follow-up. At admission, urea was 5 mmol/L, creatinine 44.2 umol/L, serum albumin 12 g/L, and spot urine protein/creatinine ratio 8.7 mg/mg. The other child, a 17.5-year-old girl, was being followed up for INS, presented with lower extremity oedema 12 days after the second dose of SARS-CoV-2 vaccine. Diagnosed with INS at the age of 2.5 years, the patient received corticosteroid treatment for 6 months and had not relapsed on follow-up. At admission, urea was 5 mmol/L, creatinine 42.4 umol/L, serum albumin 23 g/L, and spot urine protein/creatinine ratio was 4.1 mg/mg. Secondary causes of INS recurrences, such as allergic reactions, infections, and medications, were excluded in both cases. Clinical and laboratory findings of infections such as viral upper respiratory tract infection, urinary tract infection, diarrhoea, peritonitis and skin infections were not detected. Inflammatory markers were normal and cultures of urine and blood

were negative. INS recurrence was diagnosed and remission was achieved 2 weeks after commencing oral corticosteroids. Currently, in the steroid reduction phase and at the end of 6 months, the steroid treatment of the patients is planned to be discontinued.

To our knowledge, no relapses have been reported in children with INS following any types of SARS-CoV-2 vaccination. The immunogenic stimulus of vaccination may in theory trigger a relapse of nephrotic syndrome. Most reported new INS cases have been associated with mRNA vaccines, with the onset of glomerular disease occurring after the first or second dose. T-cell responses to foreign mRNA provoke swift production of cytokines that could trigger podocytopathies and augment B-cell production of disease-specific antibodies in the susceptible patient. Such cytokines or other soluble T-cell factors could amplify subclinical or quiescent glomerular diseases.^{1–3} But, glomerular disease risk from vaccination is likely lower than glomerular disease risk from COVID-19 infection. In addition to these two cases, we observed five patients who relapsed in association with SARS-CoV-2 infection in our clinic. A total of 16 children with INS and SARS-CoV-2 infection have been reported in our clinic, with the median age 9 years 9 months (range 4.7–17.5 years). In all patients the viral infection was mild; no child needed intensive care admission. Five of the nine INS patients without immunosuppressive therapy experienced a relapse during the SARS-CoV-2 infection; three patients were easily managed with oral corticosteroids and spontaneous remission was observed in two patients. No relapse was detected in seven patients who received immunosuppressive therapy and their treatment was not changed. In paediatric patients, the hypothetical risk of relapse following vaccination could be offset by the more concrete chance of relapse related to SARS-CoV-2 infection itself. Hence, the vaccination of patients with INS may be an effective option in reducing the spread of the virus and hindering potential severe health problems.^{1–4} We believe that SARS-CoV-2 vaccination should be performed in children with INS. However, we recommend close follow-up of patients with INS after SARS-CoV-2 vaccination and monitoring for possible signs of recurrence. Further studies are needed to investigate whether relapse of INS is specific for SARS-CoV-2 vaccination.

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Accepted for publication 4 April 2022.

Conflict of interest: None declared.

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doi:10.1111/jpc.15986

Dear Editor,

OTHER METRICS THAT COULD BE CONSIDERED AS
PREDICTORS OF PAEDIATRIC MORTALITY DUE TO SARS-COV-2
INFECTION

The research study by Sharma *et al.*,¹ to identify possible indicators for predicting mortality in children infected with SARS-CoV-2 is definitely a study that truly contributes to the current literature on child mortality due to SARS-CoV-2. Although the study methodology and results are well thought out, with an in-depth analysis of these predicting factors, there is definitely room for improvement.

Considering that hypoxia is one of the indicators that was given high importance by the investigators, it is slightly worrying that they used only pulse oximeter oxygen saturation (SpO_2) and not arterial blood gas (ABG) to check the severity of hypoxia. The researchers stated 'An SpO_2 reading <90% constituted severe hypoxia and was categorised as severe disease', but studies have showed that in patients with SpO_2 <90%, the exact estimation of SaO_2 and the evaluation of hypoxaemia by pulse oximeter are not as good as an ABG analyser.² By using an ABG analyser, the diagnostic value of the same would have been more accurate.

Another question that arises is in how many of the patients, several different disease manifestations occurred synchronously. The authors have delineated the different organ failures but they have not indicated disease manifestations and the frequency of the same. For example, in the case of presenting symptoms, a patient may have had myalgia and diarrhoea, and this could have been a contributing factor, but there is no evidence to suggest whether patients had any duality of symptoms. Since, multiple symptoms could have resulted in the deaths of the non-survivors.

Lastly, it was unclear if some of the children were admitted to the hospital due to re-infection with SARS-CoV-2, as re-infection increases severity of disease and chances of mortality.³ This could have potentially been the reason for severity of disease.

Though there is no way to confirm that these factors could have altered the reporting, but considering the above metrics, the authors could have strengthened their research findings in this study.

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Accepted for publication 6 April 2022.

Conflict of interest: None declared.

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