SARS-CoV-2 Infection in Children with Idiopathic Nephrotic Syndrome: A Multicentric Study

A multicenter retrospective study was conducted to assess the clinical spectrum of 30 severe acute respiratory syndrome coronavirus (SARS-CoV-2)-positive children with idiopathic nephrotic syndrome. Difficult to treat nephrotic syndrome was found to be a high-risk group with a high incidence of acute kidney injury and mortality.

Keywords: *Acute kidney injury, Difficult to treat nephrotic syndrome*.

During the global pandemic of severe acute respiratory syndrome coronavirus (SARS-CoV-2) infection, 'shielding' was advocated for children with underlying chronic disease and/or on long-term immunosuppression to prevent adverse outcomes. However, it did not prove to be useful. A study across 30 countries, of over 100 children with renal diseases, including those on immuno-suppression, reported mild SARS-CoV-2 infection with a low mortality restricted to low- and middle-income countries (LMICs) [1]. As data on children with renal diseases and coronavirus infection (COVID-19) in LMICs is lacking, we studied the epidemiological profile, clinical manifestations and complications in children with neph-rotic syndrome with SARS-CoV-2 infection.

We retrospectively reviewed 30 SARS-CoV-2 infected children (21 hospitalized) with idiopathic nephrotic syndrome across four tertiary care hospitals between 1 April, 2020 to 15 February, 2021 [2]. Patients were diagnosed by either nasal or oropharyngeal swabs using reverse transcriptase polymerase chain reaction (RT-PCR) and/or serum SARS-CoV-2 antibody levels and categorized based on national guidelines [3].

Treatment regimens were modified in hospitalized patients - *i*) Those currently on steroids or having received in last year were prescribed stress dose of steroids (0.3-0.5 mg/kg/day daily) till clinical and biochemical improvement; *ii*) Immunosuppression like mycofenolate mofetil (MMF), calcineurin inhibitors (CNIs) were withheld and restarted at same dose later; and *iii*) Biologicals like rituximab etc. were deferred. Out-patient management continued unmodified. Therapy for COVID-19 was largely supportive. Baseline serum creatinine was estimated using height independent method by Hoste (age) equation and estimated creatinine clearance (eGFR) of 120 mL/min/1.73 m^2 for children older than two years, while age-based normative eGFR was used for children ≤2 years of age. The rise from baseline to peak serum levels categorized the stage of AKI [4,5]. Complications including sepsis, shock, pneumonia, myocarditis and multisystem inflammatory syndrome in children (MIS-C) were treated. Steroid resistant NS (SRNS) and/or steroid dependent NS (SDNS) with failure of ≥2 immunosuppressive drugs or those with features of steroid toxicity were labelled as 'difficult to treat' NS (DTTNS) [2]

Of the 30 children reviewed, 21(70%) children with moderate to severe illness were hospitalized for a mean (SD) duration of 7.23 (6.43) days. With 23 (76.6%) children in relapse, the most common presenting complaint was fever (33.3%) followed by cough (30.0%) (**Web Table I**). Majority were SRNS (33.3%), and 12 (40%) were DTTNS. Respiratory support was required in 8 (26.6%) (3 mechanical ventilation) while 9 (30%) children developed AKI: 1 in stage 1, and 4 each in stage 2 and stage 3. A total of four children in the study progressed to stage 3 AKI, of which 3 succumbed (75%) as no patient could avail dialysis (**Web Table I**).

The most common immunosuppression was oral glucocorticoids (96.6%) followed by both MMF (23.3%) and CNI (23.3%) (**Web Table I**). Two patients received rituximab, one of whom had received a single dose one week prior to testing SARS CoV-2 positive and eventually died. The second patient had received two doses in last 2 years and was admitted for hypovolemia and edema control. In our study, 7 patients were diagnosed as first episode of nephrotic syndrome (FENS) of which four were RT-PCR positive, one diagnosed after 6 weeks of therapy and 2 retrospectively with positive SARS-CoV-2 antibodies. They all achieved complete remission after standard therapy.

Five (16.6%) children died and all of these had DTTNS. Three patients succumbed to respiratory failure with pneumonia; two patients had refractory shock while one had both as the immediate cause of death. Shock and use of nephrotoxic drugs was significantly higher in children with DTTNS than other categories of NS (**Table I**). Among children with DTTNS, 6 (50%) developed AKI with 33.3% progressing to stage 3 AKI (P<0.05).

While majority of children reported a mild-moderate type of illness, DTTNS was recognized as a high-risk group significantly associated with mortality. This may be due to the underlying etiology and higher use of immunosuppressive drugs. Onset of nephrotic syndrome after other viral illnesses like H1N1 is known, with occasional reports of cases after SARS CoV-2 infection [6,7]. In our

TABLE I Clinical and Management Characteristics of Children With Nephrotic Syndrome (*N*=30)

Characteristics	*DTTNS (n=12)*	*Other categories (n=18)*	*OR (95% CI)*	*P value*
Sepsis	8 (66.6)	9 (50.0)	2.0 (0.43-9.09)	0.367
Methylprednisolone	2 (16.7)	0	8.8 (0.38-201)	0.073
Nephrotoxic drugs	9 (75)	0	100 (4.68-2152)	-
Pneumonia	5 (41.7)	4 (22.2)	2.5 (0.50-12.2)	0.255
Ventilation	2 (16.7)	1 (5.6)	3.4 (0.27-42.4)	0.32
Mortality	5 (41.7)	0	27.13 (1.32-554)	0.003
Shock	3 (25.0)	0	13.6 (0.63-292)	0.025

DTTNS: difficult to treat nephrotic syndrome.

study, four among seven children with FENS were RTPCR-positive, while two were retrospectively diagnosed with positive COVID anti-body levels. Whether this is a temporal or a causal associa-tion with SARS-CoV-2 remains to be ascertained. Renal biopsy with definitive histological changes may clarify the pathogenesis.

Though, chronic illness, long-term immunosuppression and frequent hospital visits are known to increase risk of infections, including COVID-19; overall, a good outcome of non-renal pathologies on immunosuppression like hematological neoplasia/solid tumors and rheumatic diseases has been reported [8,9]. Associated sepsis and limited availability of hemodialysis could be responsible for a higher mortality in our study (17.2%) [10]. Lack of assessment of urine output, response to therapy and association of degree of proteinuria with AKI and mortality, limited our inference regarding these associations.

To conclude, children with DTTNS with SARS-CoV2 infection, comprise a high-risk group among children with NS, and require careful monitoring for complications like AKI. Availability of dialysis facilities in COVID wards may improve outcomes. Further research on larger number of children with NS may help understanding viral clearance time, time to achieve remission and long-term outcomes.

Ethics clearance: IEC, LHMC; No. LHMC/IEC/2021/03/64 dated July 7, 2021.
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