




Impact of COVID-19 Pandemic in Children with CKD or Immunosuppression

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Infections are a major concern in children on KRT and with CKD. Risk factors include immunosuppression, multiple contacts in dialysis units, and hospital visits (1).

Italy was one of the countries most affected by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) outbreak (2). Although adults with CKD and kidney transplant recipients are known to be at greater risk for disease severity due to immunosuppression and comorbidities (3), little is known about the equivalent pediatric population.

We report data from a nationwide observational study performed by the Italian Society of Pediatric Nephrology during the lockdown period in order to better understand the clinical effect of coronavirus disease 2019 (COVID-19) in children with immunosuppression or CKD. Data were collected by means of a phone-based structured questionnaire between April 13 and 24, 2020, and data referred to the whole period from the detection of first cases to the pandemic peak in Italy (February 20 to April 15, 2020). The primary objective was to identify patients with severe COVID-19 as defined by any of the following: death, admission to Pediatric Intensive Care Unit, mechanical ventilation, and the need to change ongoing immunosuppressive treatment due to a documented SARS-CoV-2 infection. The presence of fever, respiratory, gastrointestinal, or flu-like symptoms and adherence to lockdown measures were also assessed. Inclusion criteria were age <18 years and one of the following diagnoses: primary or secondary GN and idiopathic nephrotic syndrome requiring long-term immunosuppressive therapy, CKD stages 3–5, dialysis, or kidney transplant. National rates of participation were calculated estimating the number of prevalent cases. Data regarding COVID-19 swab testing in the enrolled population were compared with those of the general Italian population for the same age range and time period. The study was approved by the local ethics committees of each participating center.

A total of 1572 patients (median age, 11.1 years; interquartile range, 7.2–14.7) were included. Patient characteristics are summarized in Table 1. According to the estimated number of children with CKD and chronic GN and the prevalence of patients with transplants and

patients on dialysis from all Italian pediatric kidney transplant centers and the Italian Registry of the Pediatric Chronic Dialysis, respectively, the enrolled patients represented 67% of the entire Italian pediatric population with the aforementioned kidney diseases. The majority (71%) are considered at risk for viral infections because of immunosuppression, with 14% receiving three or more agents. On the other hand, 29% of patients had CKD stages 3–5, with 93 on dialysis. Hypertension was present in 20% of children, and 20% of the total cohort was on renin-angiotensin-aldosterone system blockers. Nonspecific infectious symptoms were identified in 12%. Patients were quarantined at home in 83% of cases, yet 35% underwent at least one hospital visit during the observation, and 51% had parents working outside, including health care workers (Table 1).

No patients fulfilled the criteria for the presence of severe COVID-19.

Nevertheless, swab tests were performed in 84 patients, mostly symptomatic children (46 of 84) or those with a confirmed familial SARS-CoV-2 case (four of 84). A significantly higher percentage of patients underwent swab testing compared with the healthy Italian pediatric population (5% versus 1%; $P=0.005$); however, the percentage of positive tests was not significantly different (4% versus 2%; $P=0.43$). Only three patients (0.19%) tested positive for SARS-CoV-2, all living in the worst-affected Italian region (Lombardy). One was on immunosuppressive therapy for Henoch–Schönlein purpura, and the other two had CKD secondary to congenital abnormalities of kidneys and urinary tract. Two had symptoms (fever and skin rash); the other was asymptomatic and was tested because of family exposure. None had leukopenia or required x-ray. Baseline therapies were not modified, and each child had a mild clinical course, in line with previous patient series in a similar population (4,5).

Severity of COVID-19 in the adult population seems to be associated with the presence of comorbidities, including immunosuppression, hypertension, and CKD. Even with similar characteristics, no patient in our fragile population had severe COVID-19. The absolute risk of SARS-CoV-2 infection was not significant, and the ratio of positive to

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Table 1. Characteristics of enrolled patients

Demographics	Total, n=1572
Median age (range), yr	11 (1–18)
Boys	988 (63%)
Diagnosis	
On immunosuppressive treatment	1116 (71%)
<i>Nephrotic syndrome</i>	652 (41%)
<i>Chronic GN</i>	176 (11%)
<i>Kidney transplant</i>	288 (18%)
CKD	456 (29%)
<i>Stage 3–5</i>	363 (23%)
<i>Hemodialysis</i>	49 (3%)
<i>Peritoneal dialysis</i>	44 (3%)
CKD on immunosuppressive treatment	8 (0.005%)
Arterial hypertension	318 (20%)
Immunosuppressive treatment	1116 (71%)
Steroids	644 (41%)
Calcineurin inhibitors	392 (25%)
Mycophenolate mofetil	485 (31%)
Rituximab (within 6 mo)	34 (2%)
Hydroxychloroquine	15 (1%)
Cyclophosphamide	3 (0%, 2%)
mTOR inhibitors	21 (1%)
Azathioprine	21 (1%)
No. of immunosuppressive drugs per patient	
<i>Not specified</i>	174 (11%)
1	520 (33%, 1%)
2	195 (12%)
3 or more	227 (14%)
Angiotensin antagonist treatment	308 (20%)
Angiotensin-converting enzyme inhibitors	268 (17%)
Angiotensin receptor blockers	23 (1%)
Both	17 (1%)
Patients with symptoms during the previous 2 mo	197 (12%)
Fever	90 (6%)
Upper respiratory tract involvement	124 (8%)
Peripheral oxygen saturation <95%	1 (0%, 1%)
Flu-like symptoms	22 (1%)
Gastrointestinal symptoms	24 (1%)
Others	32 (2%)
Patients who received at least one swab test	84 (5%)
Risk factors	
Patients with at least one family member with COVID-19	8 (0%, 5%)
Adherence to containment measures to reduce the risk of contagion adopted by parents of nephropathic children	1572 (100%)
<i>Stay at home</i>	1303 (83%)
<i>Play outside</i>	209 (13%)
<i>Go for a walk</i>	55 (3%)
<i>Free to go out</i>	5 (0.3%)
<i>Other measures</i>	
Handwashing/sanitizing	1488 (95%)
Play with friends	230 (15%)
Hospital visits	550 (35%)
Parents working outside the home	1218 (77%)
<i>Only the mother</i>	99 (8%)
<i>Only the father</i>	405 (33%)
<i>Both</i>	124 (10%)
<i>None</i>	590 (48%)

The percentages of each item refer to the total number of patients (1572). mTOR, mammalian target of rapamycin; COVID-19, coronavirus disease 2019.

performed tests is comparable with the general pediatric population.

Our study has some limitations, including potential recall bias from the survey and the overall small number of swab tests performed. We did not aim to assess the prevalence of SARS-CoV-2 infection because of the very strict swab testing policy in place in Italy during the worst phase of the pandemic, limiting the screening to only symptomatic

children. Instead, we planned a pragmatic study in order to clarify the real effect of the disease and elucidate clinical recommendations in those times of uncertainty.

Although the reason is unclear, the incidence of COVID-19 is known to be low in the pediatric population, with a generally benign clinical trend. Considering the exposure to hospital environment in over a third of patients, our data show that even children in the advanced stages of CKD or on

immunosuppressive therapy are at low risk of clinically relevant COVID-19.

Disclosures

E. Benetti reports employment with Pediatric Nephrology Dialysis and Transplant Unit, Azienda Ospedale Università Padova. R. Chimenz reports employment with Università degli Studi di Messina. C. Corrado reports employment with Ospedale Civico Palermo. M. Giordano reports employment with Pediatric Hospital Giovanni XXIII. I. Guzzo reports employment with Bambino Gesù Children's Hospital. L. Massella reports employment with Bambino Gesù Children's Hospital and Research Institute and serving on the editorial board of *Nephron*, section "Case Studies in Genetics." A. Mastrangelo reports employment with Fondazione Istituto di Ricerca e Cura a Carattere Scientifico Ca' Granda Ospedale Maggiore Policlinico Milano. G. Montini reports consultancy agreements with Alnylam and Bayern. W. Morello reports receiving honoraria from Sanofi-Genzyme. A. Pasini reports employment with Azienda Ospedaliero Universitaria, Policlinico Sant'Orsola-Malpighi. L. Peruzzi reports employment with Regina Margherita Children's Hospital, Città della Salute e della Scienza di Torino and receiving honoraria from Alnylam, Chiesi, and Dicerna. L. Annicchiarico Petruzzelli reports employment with Santobono Pausilipon. G. Puccio reports receiving honoraria from Associazione per il Bambino Nefropatico Onlus and serving as a scientific advisor or member of *EuroMediterranean Biomedical Journal*. E. Vidal reports employment with University of Udine, Udine, Italy; receiving honoraria from Bellco-Medtronic; and serving as vice-chair of the European Society for Pediatric Nephrology/European Renal Association-European Dialysis and Transplant Association Registry. All remaining authors have nothing to disclose.

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A. Mastrangelo, G. Montini, W. Morello, L. Peruzzi, and E. Vidal conceptualized the study; A. Mastrangelo, G. Montini, W. Morello, and L. Peruzzi designed the study; A. Mastrangelo and W. Morello designed the data collection instrument; G. Montini and L. Peruzzi coordinated data collection; E. Benetti, R. Chimenz, C. Corrado, M. Giordano, I. Guzzo, L. Massella, M. Materassi, A. Pasini, C. Pecoraro, L.A. Petruzzelli, and E. Vidal collected data; A. Mastrangelo,

G. Montini, W. Morello, and L. Peruzzi supervised data collection; G. Puccio carried out the initial analyses; G. Puccio and E. Vidal performed statistical analysis; A. Mastrangelo and W. Morello drafted the initial manuscript; E. Benetti, R. Chimenz, C. Corrado, M. Giordano, I. Guzzo, L. Massella, A. Mastrangelo, M. Materassi, W. Morello, A. Pasini, C. Pecoraro, L.A. Petruzzelli, G. Puccio, and E. Vidal reviewed and revised the manuscript; G. Montini and L. Peruzzi critically reviewed the manuscript for important intellectual content; and all authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

References

1. Scaggis Huang FA, Danziger-Isakov L: Infectious disease risks in pediatric renal transplantation. *Pediatr Nephrol* 34: 1155–1166, 2019
2. Fagioli S, Lorini FL, Remuzzi G: Covid-19 Bergamo Hospital Crisis Unit: Adaptations and lessons in the province of Bergamo. *N Engl J Med* 382: e71, 2020
3. Akalin E, Azzi Y, Bartash R, Seethamraju H, Parides M, Hemmige V, Ross M, Forest S, Goldstein YD, Ajaimy M, Liriano-Ward L, Pynadath C, Loarte-Campos P, Nandigam PB, Graham J, Le M, Rocca J, Kinkhabwala M: COVID-19 and kidney transplantation. *N Engl J Med* 382: 2475–2477, 2020 10.1056/NEJMc2011117
4. Marlais M, Wlodkowski T, Vivarelli M, Pape L, Tönshoff B, Schaefer F, Tullus K: The severity of COVID-19 in children on immunosuppressive medication. *Lancet Child Adolesc Health* 4: e17–e18, 2020 10.1016/S2352-4642(20)30145-0
5. Melgosa M, Madrid A, Álvarez O, Lumbrales J, Nieto F, Parada E, Perez-Beltrán V; Spanish Pediatric Nephrology Association: SARS-CoV-2 infection in Spanish children with chronic kidney pathologies. *Pediatr Nephrol* 35: 1521–1524, 2020

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