COVID-19 in children treated with immunosuppressive medication for kidney diseases

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ABSTRACT

Background  Children are recognised as at lower risk of severe COVID-19 compared with adults, but the impact of immunosuppression is yet to be determined. This study aims to describe the clinical course of COVID-19 in children with kidney disease taking immunosuppressive medication and to assess disease severity.

Methods  Cross-sectional study hosted by the European Rare Kidney Disease Reference Network and supported by the European, Asian and International paediatric nephrology societies. Anonymised data were submitted online for any child (age <20 years) with COVID-19 taking immunosuppressive medication for a kidney condition. Study recruited for 16 weeks from 15 March 2020 to 05 July 2020. The primary outcome was severity of COVID-19.

Results  113 children were reported in this study from 30 different countries. Median age: 13 years (49% male). Main underlying reasons for immunosuppressive therapy: kidney transplant (47%), nephrotic syndrome (27%), systemic lupus erythematosus (10%). Immunosuppressive medications used include: glucocorticoids (76%), mycophenolate mofetil (MMF) (54%), tacrolimus/ciclosporine A (58%), rituximab/glucocorticoids (76%), mycophenolate mofetil (MMF) (11%). 78% required no respiratory support during COVID-19 illness, 5% required bi-level positive airway pressure or ventilation. Four children died; all deaths reported were from low-income countries with associated comorbidities. There was no significant difference in severity of COVID-19 based on gender, dialysis status, underlying kidney condition, and type or number of immunosuppressive medications.

Conclusions  This global study shows most children with a kidney disease taking immunosuppressive medication have mild disease with SARS-CoV-2 infection. We therefore suggest that children on immunosuppressive therapy should not be more strictly isolated than children who are not on immunosuppressive therapy.

INTRODUCTION

The first reports of COVID-19 from the Wuhan province showed significant differences in the outcomes between children and adult patients.
disease reported to be infected with SARS-CoV-2. It was hosted by the European Rare Kidney Disease Reference Network and supported by the European, Asian and International paediatric nephrology societies. The members of these societies and the members of the PedNeph listserver were asked to include any child in their care fulfilling the inclusion criteria.

Inclusion criteria were all children (<20 years and under paediatric services) who have an underlying kidney disease and take immunosuppressive medication, with a diagnosis of COVID-19 (either laboratory confirmation with PCR or serology testing, or clinically highly suspected). The study was open for 16 weeks from 15 March 2020 to 05 July 2020 and included eight separate reminders sent electronically to the memberships of the above organisations.

Anonymised data were collected through an online platform including details of demographics, underlying kidney conditions, comorbidities and current immunosuppressive medication. Their symptoms at presentation were recorded, along with the method of COVID-19 diagnosis (laboratory or clinical). The severity and outcome of their COVID-19 was also reported.

Reporting authors followed their local guidance for ethical permission and information governance in reporting these data. Since all data were totally anonymised, formal ethical approval was not required in any of the centres; all reporting authors followed data governance procedures in their individual institutions.

Infection severity was graded using a 5-point scale according to clinical criteria (see Table 1). Data were analysed using summary statistics and are presented as mean or median with SD and IQR or numbers with percentages. Comparisons between two groups were performed with conventional statistical tests using SPSS V23.0.

**RESULTS**

Within 16 weeks from 15 March 2020 to 5 July 2020, 113 cases from 30 different countries were reported. One hundred and four cases were confirmed as COVID-19 by PCR or antibody testing, the remaining nine being clinically suspected. The demographics, underlying diagnoses and current immunosuppressive treatments are given in Table 2 below.

The median duration of immunosuppressive therapy before COVID-19 was 9.5 months (IQR 4–15.5 months). For 53% of included children, the authors provided an update on their clinical status to detect any long-term effects and paediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2 (PIMS-TS); the median time from illness to follow-up reporting was 43 days (IQR 29–62.5 days).

Table 1 Presenting symptoms, severity and clinical outcomes of 113 children with COVID-19 infection on immunosuppressive medication for a kidney disease

| Number of children presenting with each symptom of COVID-19 (%) | Maximal respiratory support required (%) | Outcome (%) | Infection severity grade within this study |
|---|---|---|---|
| 73 fever (65%) | 5 invasive ventilation (4%) | 4 death (4%) | 45 not admitted to hospital (grade 1) |
| 59 cough (52%) | 1 BiPAP (1%) | 2 patient on intensive care with recovery (2%) | 43 admitted to hospital with no respiratory support (grade 2) |
| 35 rhinitis (31%) | 5 high-flow nasal cannula oxygen (4%) | 68 admitted to hospital (60%) | 14 admitted to hospital and required supplemental oxygen (grade 3) |
| 17 diarrhoea (15%) | 14 supplemental face mask oxygen (12%) | 45 not admitted to hospital at any point (40%) | 5 admitted to hospital and required high-flow nasal cannula oxygen or BiPAP (grade 4) |
| 20 shortness of breath (18%) | 88 none (78%) | 6 admitted to intensive care or death (grade 5) | 6 admitted to intensive care or death (grade 5) |

BiPAP, bi-level positive airway pressure.

Table 2 Details of 113 children included in this study with kidney disease on immunosuppressive medication

| Median age (IQR) | Gender | Underlying kidney disease and reason for immunosuppression (%) | Coexistent pulmonary disease (%) |
|---|---|---|---|
| 13 years (7–16 years) | 51% female, 49% male | 53 kidney transplantation (47%) | 4 bacterial/fungal pneumonia (4%) |
| | | 30 nephrotic syndrome (27%) | 2 asthma/bronchospasm (2%) |
| | | 11 SLE (10%) | 9 haemodialysis (8%)—four kidney transplant, 1 nephrotic syndrome, 4 glomerulonephritis/ANCA |
| | | 7 other glomerulonephritis/vasculitis (6%) | 3 peritoneal dialysis (3%)—1 transplant, 1 nephrotic syndrome, 1 IgAN |
| | | 2 ANCA associated vasculitis (2%) | 2 IgA Nephropathy (2%) |
| | | 1 IgAVN-HSPN (2%) | 14 supplemental face mask oxygen (12%) |
| | | 2 atypical HUS (2%) | 35 rhinitis (31%) |
| | | 1 C3GN (1%) | 4 bacterial/fungal pneumonia (4%) |
| | | 1 tubulointerstitial nephritis (1%) | 5 invasive ventilation (4%) |
| | | 1 ESKD with IBD (1%) | 1 left ventricular dysfunction/hypertrophy (4%) |
| | | 1 tuberous sclerosis (1%) | 6 admitted to intensive care or death (grade 5) |
| | | 1 C3GN (1%) | 61 on mycophenolate mofetil (54%) |
| | | 41 asthma/bronchospasm (2%) | 58 on tacrolimus (51%) |
| | | 26 atypical HUS (2%) | 61 on mycophenolate mofetil (54%) |
| | | 25 haemodialysis (19%) | 11 having had rituximab (10%) |
| | | 41 haemodialysis (19%) | 9 on azathioprine (8%) |
| | | 18 haemodialysis (15%) | 8 on ciclosporine (7%) |
| | | 18 haemodialysis (15%) | 8 on ciclosporine (7%) |
| | | 18 haemodialysis (15%) | 5 on sirolimus (4%) |
| | | 18 haemodialysis (15%) | 3 having had basiliximab (3%) |
| | | 18 haemodialysis (15%) | 3 on everolimus (3%) |
| | | 18 haemodialysis (15%) | 2 having had ATG (2%) |
| | | 18 haemodialysis (15%) | 2 on eculizumab (2%) |
| | | 18 haemodialysis (15%) | 1 having had ofatutmumab (1%) |
| | | 18 haemodialysis (15%) | 1 having had alemtuzumab (1%) |
| | | 18 haemodialysis (15%) | 1 on adalimumab (1%) |
| | | 18 haemodialysis (15%) | 1 on levamisole (1%) |
| | | 18 haemodialysis (15%) | 11 having had rituximab (10%) |
| | | 18 haemodialysis (15%) | 61 on mycophenolate mofetil (54%) |
| | | 18 haemodialysis (15%) | 58 on tacrolimus (51%) |
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| | | 18 haemodialysis (15%) | 1 on levamisole (1%) |

ANCA, Anti-neutrophil cytoplasmic antibody; ATG, antithymocyte globulin; C3GN, C3 glomerulopathy; ESKD, end-stage kidney disease; HSPN, Henoch-Schönlein purpura nephritis; HUS, haemolytic uraemic syndrome; IBD, inflammatory bowel disease; IgAN, IgA Nephropathy; IgAVN, IgA vasculitis nephritis; SLE, systemic lupus erythematosus.
Table 3 Comparison of COVID-19-related symptoms and outcome in 582 children from 21 European countries (78% reported from tertiary and quaternary institutions) and 113 children on immunosuppression for kidney disease in our study.

| Symptom or Treatment | 582 paediatric cases | 113 paediatric cases on immunosuppressive therapy for kidney disease |
|----------------------|----------------------|---------------------------------------------------------------|
| Admitted to hospital | 62% 60%              |                                                               |
| Asymptomatic SARS-CoV-2 infection | 16% 19% |                                                              |
| Fever                | 65% 65%              |                                                               |
| URT symptoms         | 54% 52%              |                                                               |
| GI symptoms          | 22% 15%              |                                                               |
| Supplemental oxygen/High-flow nasal cannula oxygen | 13% 17% |                                               |
| CPAP/BiPAP           | 5% 1%                |                                                               |
| Mechanical ventilation | 4% 4%            |                                                               |
| Mortality            | 1% 4% (0% Europe and USA) |                                                               |

BiPAP, bi-level positive airway pressure; CPAP, continuous positive airway pressure; GI, gastrointestinal; URT, upper respiratory tract.

A similar distribution of disease severity was observed among kidney allograft recipients, patients with nephrotic syndrome and those with glomerulonephritis/vasculitis (p=0.33). Further analyses based on the severity of infection grade are detailed in online supplementary data.

Mean serum creatinine, reported in two-thirds of children, was 114±151 µmol/L at first presentation, increased in the course of COVID-19 to a peak of 149±199 µmol/L, and decreased to 98±130 µmol/L.

DISCUSSION

Our global survey of children receiving immunosuppressive treatment for kidney disease shows that the majority has a mild clinical course of COVID-19. Six children had a severe course needing ventilation and four of these children died. Notably, all fatal outcomes occurred in low-income countries.

There is now increasing evidence that children and adolescents are less susceptible to SARS-CoV-2 infection compared with adults. The incidence of clinically relevant SARS-CoV-2 infections is much lower in the paediatric than in the adult population and very few children die from the disease. In a UK study of 20 133 patients admitted to hospital with COVID-19, only 310 (1.5%) were below 18 years of age. Population-based studies have also shown that the severity of COVID-19 in children is lower than in adults. A Chinese study on 2135 children found that 112 (5.3%) developed severe and 13 (0.6%) critical disease.

A multicentre European study of 582 children from 21 different countries may provide the best comparator to our study. This study had 78% of its cases contributed from tertiary and quaternary institutions, therefore is likely to have been subject to similar biases as our study. Table 3 shows a comparison between that study and ours. Notably there were four deaths in the European study (case-fatality rate of 0.7%) compared with the four deaths in our study (case-fatality rate of 3.5%) but all deaths in our study were from low-income countries whereas none of the 74 cases from Europe and the USA took a fatal course.

In adult patients several risk factors have been described. Immunosuppressive treatment did not seem to be a risk factor to develop COVID-19 in 458 adult patients with an underlying rheumatological or autoimmune disease or in 159 children and young adults with nephrotic syndrome on immunosuppression.

The impact of immunosuppressive therapies on COVID-19 severity is also of importance. Numerous studies have explored the disease course of adult patients on immunosuppressive treatment, with several focusing on solid organ transplant recipients. These studies include relatively small numbers and report variable outcomes. The reported mortality ranges from none to 28%. A recent study from the European Renal Association–European Dialysis and Transplant Association registry found a mortality of 20% attributable to COVID-19 in adults with a kidney transplant. Data on children on immunosuppressive medication are scarce. Eight globally collected children with inflammatory bowel disease on immunosuppression all had a mild infection. The European multicentre study included 29 children on immunosuppressive therapy, and there was no significantly increased risk of intensive care unit admission in that cohort. Recent guidelines on return to school for paediatric transplant recipients highlight the lack of published data.

Our analyses do not show any significant difference in the severity of COVID-19, based on dialysis status, underlying kidney condition or number of immunosuppressant medications.

None of the children in our study were reported to have PIMS-TS, the very rare syndrome which has emerged and appears to be associated with SARS-CoV-2 in children.

Our study has important implications with regards to the prevention and management of COVID-19 in children taking immunosuppressive medication, the majority of whom have a mild clinical course with SARS-CoV-2 infection. At the same time, it is important to consider the indirect effects of COVID-19 on children and young people. There are numerous reports of delayed presentations to emergency departments and increased rates of child maltreatment. In addition the adverse impact of keeping children away from school should be taken into account.

Considering all these aspects, our data support the concept that the same social distancing measures should be applied in children on immunosuppressive therapy as recommended for healthy children at a given stage of the pandemic in a country or region. Children who are in the first few months immediately post-transplant may need some stricter social distancing measures (as were in place for many centres prior to COVID-19) as published data in this small subgroup are still limited.

One limitation of our study is the potential under-reporting of milder cases leading to over-representation of severe cases. To minimise this risk, we have sent out repeated reminders to the vast majority of paediatric nephrologists around the globe. Another limitation shared with many other COVID-19 studies is the unknown number of children on immunosuppression who have asymptomatic infection and never present to healthcare units, thereby precluding a valid estimation of the true population incidence. In addition, during the first wave of the COVID-19 pandemic many children on immunosuppressive medication would have been isolating at home and off school due to concerns about their susceptibility and national ‘lockdown’ measures, therefore it is difficult to know how many would have been exposed to SARS-CoV-2 infection.

In conclusion, our study finds that the majority of children on immunosuppression for kidney disease have a mild disease course with COVID-19. The advice to families should therefore be that children on immunosuppressive medication do not require additional strict social distancing precautions but should follow the recommendations given in their country at each given time, since there is no evidence for them to be at significantly increased risk of severe disease compared with the general population.
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