COVID-19 in Immunocompromised Children and Adolescents

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At the onset of the coronavirus disease 2019 (COVID-19) pandemic, children were thought to be at low risk for infection, severe disease and death, while the impact of immunocompromise on disease manifestations was unknown. As the prevalence of the disease increased, studies have reported severe disease phenotypes, such as Multisystem Inflammatory Syndrome in Children (MIS-C) or Pediatric Inflammatory Multisystem Syndrome, respiratory failure and death, and have reported outcomes in immunocompromised cohorts.

While it is impossible to know the true rates of infection, due to asymptomatic carriage and variable testing policies, European surveillance data from August 2020 to October 2021 reported 2692 pediatric cases per 100,000 with rates of hospitalization, intensive care unit (ICU) admission and death of 1.17%, 0.08% and 0.01%, respectively. The very low rates of severe outcomes in children compared to adults are thought to be partly due to higher levels of cross-reactive humoral immunity to other coronaviruses, lower rates of comorbidities (eg, obesity, diabetes and respiratory disease) and lower expression of angiotensin-converting enzyme 2, the receptor used by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) to enter cells.

PRESENTATION OF COVID-19 IN IMMUNOCOMPROMISED CHILDREN

In 6 large studies, including a total of 393 immunocompromised children with COVID-19, 19%–32% of patients were asymptomatic and were detected through screening (Table 1). The most common presenting symptoms in immunocompromised children are fever (35%–65%), cough (38%–52%), rhinorrhea (12%–32%), anosmia (8%–22%), gastrointestinal symptoms (8%–25%) and dyspnea (4%–19%). This does not appear to differ from the symptomatology in immunocompromised adults, although a meta-analysis demonstrated a lower prevalence of fever, fatigue, myalgia, cough, dyspnea and neurological symptoms in pediatric cancer patients compared to the general population and other immunocompromised cohorts.

Complications of COVID-19 infection were reported in immunocompromised children, including acute respiratory distress syndrome (0%–12%), bacterial superadded infection (0%–13%) and venous thromboembolism. Of particular concern in children are the hyperinflammatory complications such as haemophagocytic lymphohistiocytosis (HLH) and the newly emerged MIS-C, which is a poorly understood and under-recognized disease process that can lead to critical illness characterized by persistent fever, marked inflammation and evidence of single or multi-organ failure. Among the 393 immunocompromised children, there were 2 cases of MIS-C (an incidence of 51 per 10,000 cases) and 7 cases of HLH. In comparison, the incidence of MIS-C in nonimmunocompromised children has been reported as 3.16 per 10,000 cases. The difficulties in identifying COVID-associated complications arise from the nonspecific presentation and delayed temporal association—usually 4–6 weeks—between the acute viral infection and the onset of the illness, resulting in low sensitivity of PCR and reliance on serological assays, with variability in seroconversion and preexisting seropositivity. In addition, some COVID-associated complications may overlap with the clinical and laboratory manifestations seen in the underlying immunosuppressive condition.

Similar to immunocompetent children with COVID-19, laboratory findings in immunocompromised children are nonspecific and variable; lymphopenia, elevated C-reactive protein and elevated transaminases are the most commonly reported abnormalities (23%–42%, 17%–63% and 0%–53%, respectively). COVID-19 causes characteristic radiological changes in bilateral, multifocal pulmonary infiltrates; however, chest
<table>
<thead>
<tr>
<th>Author</th>
<th>Type of study, subject age</th>
<th>Comorbidity</th>
<th>N</th>
<th>Symptoms n (%)</th>
<th>Asymptomatic n (%)</th>
<th>Hospitalized n (%)</th>
<th>ICU n (%)</th>
<th>Respiratory support n (%)</th>
<th>Death n (%)</th>
<th>Complication n (%)</th>
<th>COVID therapy n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Marlais et al</td>
<td>Multicentre, worldwide prospective study on patients ≤19 years</td>
<td>Renal patients on immunosuppressant: steroids 86 (78%), MMF 66 (54%), RTX 54 (48%), Aza 9 (8%), CSA 8 (7%), CYP 8 (7%), SRL 5 (4%), RA 3 (3%), AVM 3 (3%), corticosteroids 2 (2%), azathioprine 1 (1%), basilixumab 1 (1%), leumanblixmab 1 (1%)</td>
<td>113</td>
<td>Fever 73 (65%), cough 59 (52%), rhinorhoea 35 (31%), GI 17 (15%), dyspnea 20 (18%)</td>
<td>21 (19%)</td>
<td>68 (60%)</td>
<td>6 (5%)</td>
<td>Total: 25</td>
<td>4 (4%)</td>
<td>Not reported</td>
<td>HQC 10 (9%), oseltamivir 2 (2%), RDV 1 (1%), favipiravir 1 (1%), LPV/r 1 (1%)</td>
</tr>
<tr>
<td>Madhusoodan et al</td>
<td>Multicentre, US retrospective study on patients ≤21 years</td>
<td>CA on chemotherapy, mildly immunosuppressed 45 (46%), moderately immunosuppressed 21 (21%), severely immunosuppressed 32 (33%), immunomotherapy 10 (10%) (biltnustumab, RIX, BAS)</td>
<td>98</td>
<td>Fever 60 (61%), cough 45 (46%), rhinorhoea 32 (33%)</td>
<td>32 (33%)</td>
<td>28 (29%)</td>
<td>17 (17%)</td>
<td>Total: 32</td>
<td>4 (4%)</td>
<td>ARDS 12 (12%), HCQ 15 (15%), TOZ 5 (5%), RDV 4 (4%)</td>
<td></td>
</tr>
<tr>
<td>Meyts et al</td>
<td>Multicentre, worldwide retrospective study on patients &lt;21 years</td>
<td>Inborn errors of immunity: CID 12 (36%), immune dysregulation 5 (16%), Aicardi-Goutières syndrome 3 (9%), CVID 2 (6%), phagocytophicyc 4 (9%), hypogammaglobulinemia 2 (6%), x-hanked agammaglobulinemia 1 (3%), other 5 (16%)</td>
<td>32</td>
<td>Fever 23 (72%), cough 12 (38%), rhinorhoea 9 (28%)</td>
<td>9 (28%)</td>
<td>21 (66%)</td>
<td>6 (19%)</td>
<td>Total: 9</td>
<td>2 (6%)</td>
<td>HLH 5 (16%), bacterial superinfection 7 (22%), AKI 4 (4%), HLH 1 (1%) other 8 (8%)</td>
<td></td>
</tr>
<tr>
<td>Goss et al</td>
<td>Multicentre US prospective study on patients ≤18 years</td>
<td>Solid organ Tx on immunosuppression: TAC ± SRL, prednisolone, MMF, CSA, AZA 25 (96%), SRL+ prednisolone + CYC 4 (4%)</td>
<td>26</td>
<td>Cough 12 (46%), fever 9 (35%), rhinorhoea 3 (12%), anosmia 2 (8%), chest pain 2 (8%), GI 2 (8%), dyspnea 1 (4%), headache 4 (14%)</td>
<td>6 (23%)</td>
<td>5 (19%)</td>
<td>0 (0%)</td>
<td>Total: 0</td>
<td>0 (0%)</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>Kandrar et al</td>
<td>Single center, US retrospective study on patients &lt;18 years</td>
<td>Mixed: SCD 30 (34%), CA on chemotherapy/immunotherapy 51 (59%), HSCT 7 (7%)</td>
<td>87</td>
<td>Not reported</td>
<td>26 (30%)</td>
<td>21 (24%)</td>
<td>7 (8%)</td>
<td>Total: 10</td>
<td>2 (2%)</td>
<td>MIS-C 1 (1%), thromboembolism 1 (1%)</td>
<td>RDV 6 (7%), convalescent plasma 2 (2%)</td>
</tr>
<tr>
<td>Rouger-Gaudichon et al</td>
<td>Multicentre, French retrospective &amp; prospective study on patients &lt;25 years</td>
<td>Mixed: CA on chemotherapy 33 (88%), HSCT on immunosuppres-sion 4 (11%)</td>
<td>37</td>
<td>Fever 20 (54%), cough 14 (38%), rhinorhoea 12 (32%), fatigue 12 (32%), anosmia 8 (22%), GI 7 (19%), chest pain 5 (16%), myalgia 5 (14%), respiratory distress 7 (14%), tachycardia 3 (8%), headache 3 (8%), skin rash 2 (5%), neurological signs 2 (5%)</td>
<td>9 (32%)</td>
<td>20 (54%)</td>
<td>5 (14%)</td>
<td>Total: 16</td>
<td>1 (3%)</td>
<td>MIS-C 1 (3%), polyneuropathy 1 (3%)</td>
<td>HCQ 2 (5%), TDZ 2 (5%), RDV 1 (3%)</td>
</tr>
<tr>
<td>Götzinger et al</td>
<td>Multicentre, European prospective study on patients ≤18 years</td>
<td>No comorbidities 437 (75%), chromosomal abnormalities 10 (2%), chronic pulmonary disease 29 (5%), congenital heart disease 25 (4%), CA 27 (5%), neurological disorder 26 (4%), CRD 9 (2%), immunodeficiency 3 (1%), on immunosuppressive therapy 29 (5%)</td>
<td>582</td>
<td>Fever 379 (65%), URTI 313 (54%), LRTI 143 (25%), GI 128 (22%), headache 28 (8%)</td>
<td>98 (16%)</td>
<td>363 (62%)</td>
<td>48 (8%)</td>
<td>Total: 75</td>
<td>4 (6%)</td>
<td>Co-infection with another virus 29 (5%)</td>
<td>HCQ 40 (7%), RDV 17 (3%), LPV/r 6 (1%), oseltamivir 3 (1%), favipiravir 3 (1%), lopinavir/ritonavir 3 (1%), BDM-C 2 (1%), noninvasive ventilation 3 (1%), invasive ventilation 3 (1%), convalescent plasma 2 (1%), aspirin 1 (1%)</td>
</tr>
</tbody>
</table>

*Reported additional patients admitted but for reasons not related to COVID-19 infection.

AKI, acute kidney injury; ALL, acute lymphoblastic leukaemia; AML, acute myeloid leukaemia; ARDS, acute respiratory distress syndrome; ATG, anti-thymocyte globulin; AZA, azathioprine; BAS, basilixumab; CA, cancer; CID, combined immunodeficiency; CRD, chronic kidney disease; CSA, ciclosporin; CVID, common variable immunodeficiency; CYC, cyclophosphamide; GI, gastrointestinal; GN, glomerulonephritis; HQC, hydroxychloroquine; HFN0, high flow nasal oxygen; HLH, haemophagocytic lymphohistiocytosis; HSCT, hematopoietic stem cell transplant; ICU, intensive care unit; IQ, interleukin-12 response; IV, invasive ventilation; IVIG, intravenous immunoglobulin; LPV/r, lopinavir/ritonavir; MIS-C, multisystem inflammatory syndrome in children; MMF, mycophenolate mofetil; NIV, noninvasive ventilation; O2, oxygen; RDV, remdesivir; RX, rituximab; SCD, sickle-cell disease; SLE, systemic lupus erythematosus; SRL, sirolimus; TAC, tacrolimus; TOZ, tocilizumab; Tx, transplant; URTI, upper respiratory tract infection.
SEVERITY OF COVID-19 IN IMMUNOCOMPROMISED CHILDREN

Early in the pandemic, it was presumed that immunocompromise would increase the risk of severe COVID-19 infection, due to uncontrolled viral replication and poor viral clearance, and the impact of immunocompromise on the later, severe and hyperinflammatory phase of the disease was unknown. A prospective, cross-specialty cohort study that followed 1527 children on immunosuppressants reported only 38 infections, 4 hospitalizations and no severe cases, suggesting that immunocompromised children were not at increased risk of severe disease, although study outcomes were self-reported. However, a meta-analysis demonstrated a significantly higher need for ICU care (36% vs. 23%) and higher mortality (23% vs. 13%) in adult and pediatric SOT patients hospitalized with COVID-19 compared to the general population. Outcomes for pediatric cancer patients were no different from the general population, although mortality was lower than in adult cancer patients (11% vs. 28%).

Table 1 shows the outcomes of COVID-19 infection in 6 varied cohorts of immunocompromised patients and a nonimmunocompromised cohort for comparison, which was selected for its similarity in study design and recruitment of patients from tertiary and quaternary institutions. There was a large range in hospitalization rate (19%–66%) in the immunocompromised cohorts, which likely reflects variation in clinical practices between centers/countries. The best outcomes were observed in a cohort of SOT recipients; no patients required respiratory support (including supplemental oxygen or ventilation) or died. In the other studies, the rate of respiratory support was 12%–22%, ICU admission was 5%–19%, invasive ventilation was 4%–19% and death was 2%–6%, compared to 13%, 8%, 4% and 1%, respectively in the nonimmunocompromised cohort. There was no correlation between disease severity and underlying diagnosis, form of drug immunosuppression and degree of chemotherapy-induced immunosuppression, with the exception of patients with sickle-cell disease who were more likely to require hospitalization, possibly due to the need to exclude or treat vaso-occlusive crises. No studies reported differences in disease severity/outcomes based on sex, ethnicity, age, comorbidities, obesity or laboratory findings, although 2 studies reported a greater frequency of severe disease in older children that did not reach statistical significance, and all 5 patients with trisomy 21 required respiratory support or intensive care.

Although overall, the presentation of COVID-19 infection in immunocompromised children is similar to that in immunocompetent children, the difference in the prevalence of various complications is difficult to attribute to immunosuppression alone. There is a great variability in practices related to COVID-19 testing strategies in immunocompromised children, potentially leading to underreporting of asymptomatic/minimally symptomatic COVID-19 infection. Different thresholds for hospitalization in immunocompromised children may reflect a tendency for physicians to have a lower threshold for admitting children with significant underlying comorbidities.

The most likely causative factors leading to poorer outcomes of COVID-19 infection in immunosuppressed children are related to impaired viral control and viral clearance, dysregulated immune response reflecting both COVID-infection and underlying disease that can predispose to hyperinflammation, as well as potential flares of underlying conditions and increased risk of secondary, often healthcare-related, infections.

THERAPEUTICS AND VACCINATION IN IMMUNOCOMPROMISED CHILDREN

The most important intervention in severe COVID-19 infection is the treatment of hypoxic respiratory failure with respiratory support, usually with oxygen or invasive ventilation. The use of noninvasive ventilation and high-flow nasal oxygen was reported in 3 of the 6 studies. Refractory hypoxemia can be managed with proning, inhaled nitric oxide and extracorporeal membrane oxygenation, which was used on only a single patient across the 6 cohorts.

Pharmacological therapy varies largely between centers and countries (Table 1). Decreased ability to mount antibody responses post-COVID-19 infection could be associated with risk for prolonged illness or complications in immunosuppressed children. The current National Institute of Health treatment guidelines for children with COVID-19 infection recommend remdesivir (for hospitalized children older than 12 years), and remdesivir and dexamethasone (for hospitalized children of all ages if they require high flow oxygen or ventilation), as well as anti-SARS-CoV-2 monoclonal antibodies (bamlanivimab, bamlanivimab plus etesevimab and casirivimab plus imdevimab), specifically for the treatment of immunocompromised children older than 12 years and at risk for disease progression or hospitalization on a case-by-case basis. It is recognized, however, that the efficacy of monoclonals depends on the type of COVID-19 virus strain and that new therapeutic agents are likely to emerge as the pandemic evolves. Other therapeutic options, such as baricitinib, tocilizumab and other IL-6 targeted therapies can be considered on a case-by-case basis as well, especially in hospitalized children with hyperinflammatory syndromes. Convalescent plasma is currently investigated in clinical trials in children.

Chemotherapy was delayed in 13%–67% of patients infected with SARS-CoV-2 in an attempt to reduce immunosuppression, although no trials on the impact of this on COVID-19 severity and cancer prognosis are available. Long-term immunosuppression was reduced in 39% of renal patients and 8% of SOL patients; the impact on the underlying disease and COVID-19 severity is unknown. Reducing background immunosuppression during the initial stages of viral replication may improve viral clearance, while increasing it back to a maintenance dose after seroconversion (12–14 days) may prevent a possible hyperinflammatory immune response to COVID-19 infection as well as minimize the risk of relapse from the underlying disease.

In the UK, the Joint Committee of Vaccination and Immunisation recommends vaccination for children over 12 years and for children 5–11 years who are immunocompromised. Very recently, reflecting a resurgence of COVID-19 infections worldwide, Moderna is seeking emergency-use authorization from regulators for its vaccine in babies, toddlers and preschoolers, based on encouraging clinical trial data. Immunocompromised patients, however, have reduced seroconversion rates after vaccination, which could translate in reduced protection from both infection and severe disease. A meta-analysis demonstrated seroconversion rates after 2 doses of a COVID-19 vaccine of 89% in patients with solid-organ malignancy, 62% in hematological malignancy, 77% in immune-mediated inflammatory conditions and 35% in SOT, compared to 97% in immunocompetent recipients. For maximal protection, vaccination should occur before immunosuppression is commenced and additional doses may be offered, while other preventative measures, such as household vaccination and infection control measures may also be required.
To date, immunocompromise has not been demonstrated to predispose to post-vaccination myocarditis, which is reported with higher rates in adolescent males after mRNA vaccines, although further research is needed to address the role of different classes of immunomodulating drugs on this complication potentially resulting from the aberrant T-cell response.

RESEARCH CHALLENGES

There are several challenges that make the interpretation of studies on COVID-19 in immunocompromised children difficult for researchers and clinicians. There are low numbers of patients in studies due to low rates of pediatric immunocompromise and low case rates within these cohorts, likely as a result of the practice of shielding. Furthermore, the low rates of severe illness and mortality may not lead to statistically significant results. Retrospective study design, inclusion only of patients presenting to or being admitted to hospital and underreporting of asymptomatic/minimally symptomatic infection may contribute to apparent higher rates of severe infection. In immunocompromised children, attributing causality of complications or severe disease to COVID-19 can be challenging due to co-existent pathology, such as neutropenic sepsis in chemotherapy recipients.

Comparing studies throughout the pandemic is challenging because of evolving recommendations regarding testing, public health strategies and available therapeutics. Additionally, changes in SARS-CoV-2 strain predominance and variation in immunity due to the previous infection, and more recently vaccination, are several confounding variables that impact outcomes.

Finally, studies on immunocompromised children have included highly heterogeneous cohorts with large variations in length, intensity and modality of immunocompromise and it is becoming increasingly clear that ‘not all immunocompromise is equal’.

DIRECTIONS OF FUTURE RESEARCH

Future work must establish the role of different types of immunocompromise on disease severity and vaccination efficacy. The serological threshold required to prevent infection is unknown and a more accurate biomarker of immunity to monitor vaccination response that also acknowledges T-cell immunity is needed. There is a need for the investigation of the role of specific therapy, such as convalescent plasma, in immunocompromised children. Longer-term follow-up is needed for immunocompromised COVID-19 patients to establish rates and severity of reinfection, the impact of the infection and immunocompromising therapy discontinuation on the underlying disease, as well as to monitor the efficacy of vaccines in the context of ongoing SARS-CoV-2 mutations. Vaccination is likely to become available for children <5 years of age soon and the efficacy and side effect profile of this should be carefully monitored in both immunocompromised and immunocompetent children.

REFERENCES