COVID-19 in immunocompromised children and adolescents

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Introduction

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, whilst the impact of immunocompromise on disease manifestations was unknown. As prevalence of the disease increased, studies have reported severe disease phenotypes, such as Multisystem Inflammatory Syndrome in Children (MIS-C) or Paediatric Inflammatory Multisystem Syndrome (PIMS-TS), respiratory failure and death, and have reported outcomes in immunocompromised cohorts.

Whilst 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 paediatric cases per 100,000 with rates of hospitalisation, ICU admission and death of 1.17%, 0.08% and 0.01% respectively.[1] 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 (e.g. obesity, diabetes, respiratory disease) and lower expression of angiotensin-converting enzyme 2, the receptor used by SARS-CoV-2 to enter cells.

Presentation of COVID-19 in immunocompromised children

In six 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%), rhinorrhoea (12-32%), anosmia (8-22%), gastrointestinal symptoms (8-25%) and dyspnoea (4-19%). This does not appear to differ from the symptomatology in non-immunocompromised children, although a meta-analysis demonstrated lower prevalence of fever, fatigue, myalgia, cough, dyspnoea and neurological symptoms in paediatric cancer patients compared to the general population and other immunocompromised cohorts.[2] 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 hyper-inflammatory complications such as haemophagocytic lymphohistiocytosis (HLH) and the newly emerged MIS-C, which is a poorly understood and under-recognised disease process that can lead to critical illness characterised by persistent fever, marked inflammation and evidence of single or multi-organ failure. Among the 393 immunocompromised children there were two cases of MIS-C (an incidence of 51 per 10,000 cases) and seven cases of HLH. In comparison, the incidence of MIS-C in non-immunocompromised children has been reported as 3.16 per 10,000 cases.[3] The difficulties in identifying COVID-associated complications arise from the non-specific presentation and delayed temporal association - usually 4-6 weeks - between the acute viral infection and the onset of the illness, resulting in a low sensitivity of PCR and a reliance on serological

assays, with variability in seroconversion and pre-existing 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 of bilateral, multifocal pulmonary infiltrates, however chest imaging is variably performed and radiological changes are variably reported. Chest imaging was performed in 31% of solid-organ transplant (SOT) patients, 41% of cancer patients and 34% of non-immunocompromised patients and was abnormal in 25%, 93% and 52% respectively.[4,5,6] This variability means that, like for non-immunocompromised children, chest imaging should not be relied on for diagnostic purposes.

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, hyperinflammatory phase of the disease was unknown. A prospective, cross-specialty cohort study that followed 1527 children on immunosuppressants reported only 38 infections, 4 hospitalisations and no severe cases, suggesting that immunocompromised children were not at increased risk of severe disease, although study outcomes were self-reported.[7] However, a meta-analysis demonstrated a significantly higher need for ICU (Intensive Care Unit) care (36% vs 23%) and higher mortality (23% vs 13%) in adult and paediatric SOT patients hospitalised with COVID-19 compared to the general population.[2] Outcomes for paediatric cancer patients were no different to the general population, although mortality was lower than in adult cancer patients (11% vs 28%).[2]

Table 1 shows the outcomes of COVID-19 infection in six varied cohorts of immunocompromised patients and a non-immunocompromised 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 hospitalisation rate (19% - 66%) in the immunocompromised cohorts, which likely reflects variation in clinical practices between centres/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 non-immunocompromised 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 hospitalisation, possibly due to the need to exclude or treat vaso-occlusive crises.[8,9,10,11] No studies reported differences in disease severity/outcomes based on sex, ethnicity, age, comorbidities, obesity or laboratory findings, although two studies reported a greater frequency of severe disease in older children that did not reach statistical significance, and all five patients with trisomy 21 required respiratory support or intensive care.[8,9,10]

Although overall, the presentation of COVID-19 infection in immunocompromised children is similar to that in immunocompetent children, the difference in 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 hospitalisation in immunocompromised children may reflect a tendency for physicians to have a lower threshold for admitting children with significant underlying co-morbidities.

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 treatment of hypoxaemic respiratory failure with respiratory support, usually with oxygen or invasive ventilation. The use of non-invasive ventilation and high-flow nasal oxygen was reported in three of the six studies. Refractory hypoxaemia can be managed with proning, inhaled nitric oxide and extracorporeal membrane oxygenation, which was used on only a single patient across the six cohorts.

Pharmacological therapy varies largely between centres 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 (NIH) treatment guidelines for children with COVID-19 infection recommend remdesivir (for hospitalised children older than 12), and remdesivir and dexamethasone (for hospitalised 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 treatment of immunocompromised children older than 12 and at risk for disease progression or hospitalisation on a case-by-case basis. It is recognised however that the efficacy of monoclonals depends of 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 hospitalised 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.[6,9,11] Long-term immunosuppression was reduced in 39% of renal patients and in 8% of SOL patients; the impact on the underlying disease and COVID-19 severity is unknown.[4,8] Reducing background immunosuppression during the initial stages of viral replication may improve viral clearance, while increasing it back to maintenance dose after seroconversion (12-14 days) may prevent a possible hyperinflammatory immune response to COVID-19 infection as well as minimise the risk of relapse from the underlying disease.

In the UK, the Joint Committee of Vaccination and Immunisation recommends vaccination to children over 12 years and to children 5-11 years who are immunocompromised. Very recently, reflecting a resurgence of COVID-19 infections world-wide, Moderna is seeking emergency-use authorization from regulators for its vaccine in babies, toddlers and pre-schoolers, 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 two doses of a COVID-19 vaccine of 89% in patients with solid-organ malignancy, 62% in haematological malignancy, 77% in immune-mediated inflammatory conditions and 35% in SOT, compared to 97% in immunocompetent recipients.[12] 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 myopericarditis, 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 aberrant T-cell response.

Research challenges

There are several challenges that make 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 paediatric 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 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 investigation of the role of specific therapy, such as convalescent plasma, in immunocompromised children. Longer term follow-up is needed of 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.

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Author	Type of study, subject age	Comorbidity	N	Symptoms n (%)	Asymptomatic n (%)	Hospitalised n (%)	ICU n (%)	Respiratory support n (%)	Death n (%)	Complication n (%)	COVID therapy n (%)
Marlais et al.	Multicentre worldwide prospective study on patients ≤19 years	Renal patients on immunosuppressant: steroids 86 (76%), TAC 58 (51%), MMF 66 (54%), RIX 11 (10%), AZA 9 (8%), CSA 8 (7%), CYC 8 (7%), SRL 5 (4%), BAS 3 (3%), everolimus 3 (3%), ATG 2 (2%), eculizumab 2 (2%), ofatumumab 1 (1%), alemtuzumab 1 (1%), adalimumab 1 (1%), levamisole 1 (1%) Diagnosis: kidney Tx 53 (47%), nephrotic syndrome 30 (27%), SLE 11 (10%), GN 7 (6%), other 12 (11%)	113	Fever 73 (65%), cough 59 (52%), rhinorrhoea 35 (31%), GI 17 (15%), dyspnoea 20 (18%)	21 (19%)	68 (60%)	6 (5%)	Total: 25 (22%) O2: 14 (12%) HFNO: 5 (4%) NIV: 1 (1%) IV: 5 (4%)	4 (4%)	Not reported	HCQ 10 (9%), oseltamivir 2 (2%), RDV 1 (1%), favipiravir 1 (1%), LPV/r 1 (1%)
Madhusoodan et al.	Multicentre US retrospective study on patients ≤21 years	CA on chemotherapy: mildly immunosuppressed 45 (46%), moderately immunosuppressed 21 (21%), severely immunosuppressed 32 (33%). Immumotherapy 10 (10%) (blinatumomab, RIX, BAS). Diagnosis: ALL 52 (53%), AML 9 (9.2%), lymphoma 3 (3%), CNS tumour 9 (9%), neuroblastoma 5 (5%), solid tumour 16 (16%), other 4 (4%)	98	Fever 60 (61%), cough 45 (46%), respiratory distress 19 (19%), fatigue 18 (18%), myalgia 11 (11%), GI 8 (8%), sore throat 5 (5%), anosmia 4 (4%), ageusia 3 (3%), other 17 (17%)	32 (33%)	28 (29%) *	17 (17%)	Total: 32 (33%) O2: 25 (26%) IV: 7 (7%)	4 (4%)	ARDS 12 (12%), bacterial superinfection 7 (7%), AKI 4 (4%), HLH 1 (1%) other 8 (8%)	HCQ 15 (15%), TOZ 5 (5%), RDV 4 (4%)
Meyts et al.	Multicentre worldwide retrospective study on patients ≤21 years	Inborn errors of immunity: CID 12 (38%), immune dysregulation 5 (16%), Aicardi-Goutières syndrome 3 (9%), CVID 2 (6%), phagocyte defect 3 (9%), hypogammaglobulianemia 2 (6%), x-linked agammaglobulinaemia 1 (3%), other 5 (16%)	32	Fever 23 (72%), cough 12 (38%), URTI 9 (28%), GI 8 (25%), myalgia 1 (3%), other 9 (28%)	9 (28%)	21 (66%)	6 (19%)	Total: 9 (28%) O2/NIV: 3 (9%) IV: 6 (19%)	2 (6%)	HLH 5 (16%), bacterial superinfection 4 (13%), sepsis 2 (6%), MIS-C 1 (3%)	Steroids 6 (19%), IVIG 5 (16%), RDV 3 (9%), LPV/r 2 (6%), convalescent plasma 2 (6%), aspirin 1 (3%), TOZ 1 (3%), chloroquine 1 (3%)
Goss et al.	Multicentre US prospective study on patients ≤18 years	Solid organ Tx on immunosuppression: TAC (+/- SRL, prednisolone, MMF, CSA, AZA) 25 (96%), SRL + prednisolone + CYC 1 (4%) Diagnosis: kidney Tx 8 (31%), liver Tx 10 (38%), heart Tx 6 (23%), lung Tx 2 (8%)	26	Cough 12 (46%), fever 9 (35%), sore throat 3 (12%), rhinorrhoea 3 (12%), anosmia 2 (8%), chest pain 2 (8%), GI 2 (8%), dyspnoea 1 (4%), headache 1 (4%)	6 (23%)	5 (19%) *	0 (0%)	Total: 0 (0%)	0 (0%)	None	HCQ 1 (4%)
Kamdar et al.	Single centre US retrospective study on patients <18 years	Mixed: SCD 30 (34%), CA on chemotherapy / immunotherapy 51 (59%), HSCT 6 (7%) Diagnosis: Leukaemia 22 (43%), solid tumour 19 (37%), brain tumour 5 (10%), lymphoma 3 (6%), histiocytic disorders 2 (4%)	87	Not reported	26 (30%)	21 (24%)	7 (8%)	Total: 10 (12%) O2: 3 (3%) IV: 7 (8%)	2 (2%)	MIS-C 1 (1%), thromboembolism 1 (1%)	RDV 6 (7%), convalescent plasma 2 (2%)
Rouger-Gaudichon et al.	Multicentre French retro- & prospective study on patients <25 years	Mixed: CA on chemotherapy 33 (89%), HSCT on immunosuppressant 4 (11%) Diagnosis: solid tumour 17 (46%), haematological CA 16 (43%), non-malignant 4 (11%)	37	Fever 20 (54%), cough 14 (38%), rhinorrhoea 12 (32%), fatigue 12 (32%), anosmia 8 (22%), GI 7 (19%), chest pain 6 (16%), myalgia 5 (14%), respiratory distress 5 (14%), tachycardia 4 (11%), headache 3 (8%), skin rash 2 (5%), neurological signs 2 (5%)	9 (32%)	20 (54%)	5 (14%)	Total: 6 (16%) O2: 1 (3%) NIV: 3 (8%) IV: 2 (5%)	1 (3%)	HLH 1 (3%), polyneuropathy 1 (3%)	HCQ 2 (5%), TOZ 2 (5%), RDV 1 (3%)
Götzinger et al.	Multicentre European prospective study on patients <18 years	No comorbidities 437 (75%). Comorbidities 145 (25%): chromosomal abnormalities 10 (2%), chronic pulmonary disease 29 (5%), congenital heart disease 25 (4%), CA 27 (5%), neurological disorder 26 (4%), CKD 9 (2%), immunodeficiency 3 (1%), on immunosuppressive therapy 29 (5%), chemotherapy in previous 6 months 25 (4%)	582	Fever 379 (65%), URTI 313 (54%), LRTI 143 (25%), GI 128 (22%), headache 28%	93 (16%)	363 (62%)	48 (8%)	Total: 75 (13%) O2: 19 (3%) NIV 31 (5%) IV: 25 (4%)	4 (0.7%)	Co-infection with another virus 29 (5%)	HCQ 40 (7%), RDV 17 (3%), LPV/r 6 (1%), oseltamivir 3 (1%), steroids 22

											(4%), IVIg 7 (1%), TOZ 4 (1%), anakinra 3 (1%), siltuximab 1 (<1%)

Legend: AKI: acute kidney injury, AML: acute myeloid leukaemia, ALL: acute lymphoblastic leukaemia, ARDS: acute respiratory distress syndrome, ATG: anti-thymocyte globulin, AZA: azathioprine, BAS: basilixumab, CA: cancer, CID: Combined Immunodeficiency, CKD: chronic kidney disease CSA: ciclosporin, CVID: common variable immunodeficiency CYC: cyclophosphamide, GI: gastrointestinal, GN: glomerulonephritis, HCQ: hydroxychloroquine, HFNO: high flow nasal oxygen, HLH: haemophagocytic lymphohistiocytosis, HSCT: haemopoietic stem cell transplant, ICU: intensive care unit, IV: invasive ventilation, IVIg: intravenous immunoglobulin, IQR: interquartile range, LPV/r: lopinavir/ritonavir, MMF: mycophenolate mofetil, MIS-C: multisystem inflammatory syndrome in children, NIV: non-invasive ventilation, O2: oxygen, RDV: remdesivir, RIX: rituximab, SCD: sickle-cell disease, SLE: systemic lupus erythematosus, SRL: sirolimus, TAC: tacrolimus, TOZ: tocilizumab, Tx: transplant, URTI: upper respiratory tract infection.
*Reported additional patients admitted but for reasons not related to COVID-19 infection

Table 1: Comparison of symptoms, outcomes and therapy in six large studies of immunocompromised children with COVID-19 infection, with a non-selective cohort (Götzinger et al.) for comparison