Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Impact of COVID-19 on Pediatric Immunocompromised Patients

James A. Connelly, MD[a], Hey Chong, MD, PhD[b], Adam J. Esbenshade, MD, MSCI[c], David Frame, PharmD[d], Christopher Failing, MD[e], Elizabeth Secord, MD[f], Kelly Walkovich, MD[g,*]

KEYWORDS

• Immunocompromised • Immunodeficiency • SARS-CoV-2 • COVID-19 • Pediatric • HIV • Cancer • Autoimmune

KEY POINTS

- Children and adolescents with primary or secondary immune deficiencies have not generally had increased incidence or severity of COVID-19 infection as was initially feared.
- Decreased access to care has led to delayed diagnosis and increased morbidity in some groups of immunocompromised patients, especially those with malignancies and rheumatologic disease.
- The current vaccines available for COVID-19 are not live vaccines and should be able to be safely used in immunocompromised children and adolescents, but the efficacy will have to be monitored carefully for each immune defect.
- The COVID-19 pandemic has normalized some infection-control procedures that are routine for immunocompromised children and adolescents and may bring more tolerance for their needs.

[a] Pediatric Hematology/Oncology, Monroe Carell Jr Children's Hospital, Vanderbilt University, 2220 Pierce Avenue, 389 PRB, Nashville, TN 37232, USA; [b] Pediatric Allergy & Immunology, UPMC Children's Hospital of Pittsburgh, One Children's Hospital Drive, 4401 Penn Avenue, Pittsburgh, PA 15224, USA; [c] Pediatric Hematology/Oncology, Monroe Carell Jr Children's Hospital, Vanderbilt University, 2220 Pierce Avenue, 388 PRB, Nashville, TN 37232, USA; [d] School of Pharmacy, University of Michigan, 1500 East Medical Center Drive, Ann Arbor, MI 48109, USA; [e] Pediatric Rheumatology, Essentia Health, 1702 South University Drive, Fargo, ND 58103, USA; [f] Pediatric Allergy & Immunology, Wayne State University, Wayne Pediatrics, 400 Mack Avenue, Detroit, MI 48201, USA; [g] Pediatric Hematology/Oncology, C.S. Mott Children's Hospital, University of Michigan, 1540 East Medical Center Drive, Ann Arbor, MI 48109, USA
* Corresponding author.
E-mail address: kwalkovi@med.umich.edu

Pediatr Clin N Am 68 (2021) 1029–1054
https://doi.org/10.1016/j.pcl.2021.05.007
pediatric.theclinics.com

INTRODUCTION

The severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) has caused critical coronavirus disease 2019 (COVID-19) most often in the elderly and individuals with comorbid medical conditions. Although growing evidence supports the importance of an intact innate immune response at the onset of viral infection, mortality caused by dysregulated immune responses, particularly in adults, has shown a spotlight on the delicate balance of a robust, but coordinated and controlled, immune activity against infection.[1] The pathologic role of the immune system has also been emphasized by the new multisystem inflammatory syndrome in children (MIS-C), which currently is believed to be a result of an aberrant adaptive immune response to SARS-CoV-2 infection.[2] The necessity of this immune equilibrium has manifested in the clinical care of severe COVID-19 and MIS-C with administration of immune suppressants to offset inappropriate immune activation.

This complex network of infection, immune response, and inflammation with SARS-CoV-2 has created concerns, questions, and challenges for immunocompromised children beyond fear of death from contracting SARS-CoV-2. This review examines how adaptations by health care systems to reduce SARS-CoV-2 transmission and treat the surge of COVID-19 patients impacted immunocompromised pediatric patients. While expansion of some services, such as telemedicine, provided a new safe venue to provide care for some patients, contraction of other services or parental anxiety to present to medical care units resulted in impaired access for other patients. We will also examine how the perceived danger of severe infection early in the pandemic triggered modifications of immune suppression, with negative ramifications in some patients, and the impact of prolonged quarantine-intensified psychosocial concerns in children and adolescents.

In addition, this publication will examine questions commonly faced among health care providers including how to test for SARS-CoV-2 with high sensitivity, how to treat active SARS-CoV-2 infection in immunocompromised youth, how to consider the safety and efficacy of COVID vaccine for the immunocompromised, and how to provide medical and psychosocial support while reducing infectious exposure in immunocompromised children. The outcomes of SARS-CoV-2 in immunocompromised patients to date are also reviewed. Lessons learned caring for immunocompromised children during the pandemic, including some unforeseen benefits of the lockdown, are presented as valuable education for providers caring for both healthy and sick children.

Testing for SARS-CoV-2 Infection in Immunocompromised Patients

Despite the potential for an altered immune response to SARS-CoV-2, asymptomatic presentations are common in pediatric immunocompromised patients (13%–62% in published cohorts; **Table 1**), emphasizing that the lack of signs and symptoms does not rule out infection. However, identifying SARS-CoV-2 infection is especially important in patients with immune deficits, where decisions on admission, treatment, and procedures may be dependent on ruling out acute infection. In addition, given that many immunocompromised children receive care in proximity to other immunocompromised patients in infusion centers or inpatient wards, using high-sensitivity testing is critical to curb exposures.

To that end, the Infectious Disease Society of America (IDSA), in recommendations from January 2021,[3] specifically recommends SARS-CoV-2 RNA testing in asymptomatic immunocompromised patients being admitted to the hospital and before hematopoietic stem cell (HSCT) or solid organ transplant (SOT) regardless of COVID-19

Table 1
Summary of published studies on pediatric immunocompromised patients and COVID-19

Country and Study Period	Study Design	Testing Strategy (%) and Detection (% Positive)	Patients Characteristics (%)	Clinical Course (%)	Treatment (%)	Outcomes (%)
Cancer and hematopoietic stem cell transplant						
Czech Republic[105] Up to 3/16/20	Care provider survey; 32 centers	>200 tested patients; 8 positive cases	8 patients: 7 ST, 1 ALL	All patients asymptomatic or had mild symptoms	2 HCQ, 2 AZI, 1 LPV/r	No deaths or ICU admissions
US (NY)[106] 3/10/20–4/6/20	Retrospective cohort; 2 centers	Asymptomatic (before admission, before procedure, before chemotherapy, contact, transfer), symptomatic (84); NP PCR; positive cases (11)	19 patients: Leukemia/lymphoma (32), ST (42), nonmalignant hematology (16), HSCT (11)	Asymptomatic (16), MV (2), ICU (26)	HCQ + AZI (16); Cancer-directed therapy delayed in oncology patients (64)	No deaths in oncology patients; 1 sickle cell patient died
Spain[107] Up to 4/15/20	Retrospective cohort in Madrid	NP PCR	15 patients: ALL (53), AML/MDS (13), lymphoma (7), NBL (7), ST (20)	Asymptomatic (13), mild/moderate (87)	HCQ (73); chemotherapy delayed (40)	No deaths or ICU admission at time of report
Italy[60] 2/20/20–4/15/20	Retrospective cohort in Lombardia; 6 centers	Asymptomatic (74): screening (65) or close contact (9); positive cases (7)	21 patients: leukemia (48), lymphoma (10), CNS (5), ST (38)	Severe (10)	Cancer treatment modified (48)	No deaths
France[108] Up to 4/16/20	Physician survey; 30 centers	NP PCR or CT; 33 cases identified and only reporting 5 severe cases	5 patients: 3 ALL, 1 allo-HSCT, 1 CNS	All 5 patients admitted to ICU	N/A	No deaths at time of reporting

(*continued on next page*)

Table 1
(*continued*)

Country and Study Period	Study Design	Testing Strategy (%) and Detection (% Positive)	Patients Characteristics (%)	Clinical Course (%)	Treatment (%)	Outcomes (%)
Italy[35] 2/23/20–4/24/20	Registry study; 13 centers	Asymptomatic (before chemotherapy or procedure) or symptomatic; NP PCR or bronchoalveolar lavage	29 patients: ALL (48), AML (7), lymphoma (10), CNS (3), ST (28), histiocytosis (3); 3 patients also had HSCT (10)	Asymptomatic (62), mild (24), moderate (14), severe/critical (0)	HCQ (31), AZI (31), LPV/r (10), GC (3); treatment suspended (55) or reduced/ delayed (7)	No deaths or ICU admissions; 1 lymphoma patient had progression after chemotherapy withdrawal due to COVID
United States (NY, NJ)[12] 1/15/20–4/27/20	Retrospective cohort; 13 centers	Asymptomatic (before procedure, treatment) and symptomatic; NP PCR; 578 tested, 98 positive cases (17)	98 patients: ALL (53), AML (9), lymphoma (3), CNS (9), NBL (5), ST (16), auto-HSCT (5), allo-HSCT (3); obese (22)	Asymptomatic (25), mild (45), moderate (11), severe (17), ICU (23), MV (8)	HCQ (15), AZI (15), TCZ (5), RDV (4), CVP (2), ANR + GC (1); interruptions to chemotherapy (67)	Died (4) – none solely due to COVID
France[52] Up to 5/28/20	Retrospective and prospective cohort; multicenter	NP PCR (92), serology (5), clinical + radiological diagnosis (3)	37 patients; ALL (27), AML (3), CML (3), NHL (3), CNS (19), ST (30), NBL (3); HSCT (11); 1 patient each for aplastic anemia, sickle cell, EBV-MAS, familial septic granulomatosis	Asymptomatic (24), ICU (15), MV (5)	HCQ (5), RDV (3), TCZ (5); treatment delayed in oncology patients (48) for a mean of 14 d	1 Patient with ALL died (3) from severe macrophage activation syndrome with COVID

Turkey[51] 3/11/20–5/31/20	Physician survey; 66 centers	Asymptomatic (contact history, before HSCT, before surgery) and symptomatic; NP PCR or symptomatic + chest CT findings/ contact history	51 patients: leukemia (51), lymphomas, and LCH/HLH (10), CNS (10), NBL (8), ST (22); 6 had undergone HSCT (12)	Asymptomatic/mild (49), moderate/severe (33), critical (18), ICU (18), MV (6)	No treatment (20), AZI (20), HCQ (8), HCQ + AZI (27), AZI + antivirals (2), HCQ + AZI + antivirals (6), CVP (2); interruption/delay in chemotherapy (63)	1 HSCT patient died (2) from COVID and also had concurrent recurrent leukemia and fungal infection
Egypt[47] mid-April to mid-June 2020	Prospective, non-intervention	NP PCR conducted on all admitted pediatric oncology patients	15 patients: ALL (67), AML (7), lymphoma (13), SOT (13)	Asymptomatic (33), mild (67)	HCQ, AZI, ceftriaxone, enoxaparin used per hospital guidelines; chemotherapy revised on individual basis	Died (13) – not related to COVID; 1 new oncology diagnosis patient died from treatment delay related to COVID
Mexico[11] 3/20/20–6/20/20	Retrospective cohort; 1 center	Only symptomatic tested; PCR; positive cases (58)	14 patients: leukemia (63), lymphoma (7), ST (21), CNS (7)	Oxygen required (80), no ICU or MV	Cancer treatment delayed until negative PCR	1 patient died with pulmonary metastases and pulmonary hemorrhage
Peru[109] 3/6/20–7/7/20	Retrospective cohort; 9 centers	PCR (49), serology (33), not reported (18)	69 patients: ALL (52), AML (4), lymphoma (7), CNS (5), ST (14), other (17)	Asymptomatic (54), ICU (4), but 2 patients who died did not have ICU beds available	AZI/IVM/GC (13); chemotherapy stopped (100)	Died due to COVID (4), died not related to COVID (6)
United Kingdom[110] 3/12/20–7/31/20	Retrospective + prospective registry study; 20 centers	Asymptomatic (before admission) and symptomatic; NP PCR	54 patients: ALL (44), AML (7), lymphoma (4), CNS (9), NBL (11), ST (19), other (6)	Asymptomatic (28), mild (63), moderate (2), severe (2), critical (6)	N/A	Died (2) – not related to COVID

(*continued on next page*)

Table 1
(continued)

Country and Study Period	Study Design	Testing Strategy (%) and Detection (% Positive)	Patients Characteristics (%)	Clinical Course (%)	Treatment (%)	Outcomes (%)
Mexico[111] 3/12/20–9/25/20	Retrospective cohort; 1 center	Asymptomatic (before procedure, before admission); NP PCR	38 patients: ALL (55), AML (8), histiocytosis (8), CNS (5), ST (21), NBL (3)	Asymptomatic (18), mild (71), ICU (5), MV (5)	Treatment delay (68)	Deaths (8) – not related to COVID
United States Pediatric Oncology COVID-19 Case Report[53] As of 1/21/21	Registry study; 93 centers	Asymptomatic and symptomatic	657 patients: HM (64), ST (36); in addition, a proportion of patients had an allo-HSCT (6) or auto-HSCT (3)	Asymptomatic: HM (33), ST (41); intubation: HM (4), ST (4); ICU: HM (13), ST (8); MIS-C: HM (2), ST (2)	Change in oncology therapy: HM (47), ST (37)	Died (2)
Global Global Registry of COVID-19 in Childhood Cancer[54] As of 2/10/21	Registry study; 48 countries	Asymptomatic and symptomatic; testing included NP (80.5), nasal (18.0), oropharyngeal swab (8.4), and blood serology (5.2)	1557 patients: ALL (49.1), ST (24.5), CNS (8.1), other HM (17.9), after HSCT for nonmalignant disorders (0.39); in addition, a proportion of cancer patients had an HSCT (5.16)	Asymptomatic (34.9), mild (36.1), moderate (9.3), severe (12.1), critical (17.6); ICU (9.1), MV (4.4)	No treatment (70.3), AZI (20.2), GC (14.7), RDV (4.8), IVIG (4.4), HCQ (4.0), LPV/r (2.0), CP (0.7), TZM (0.4), FPV (0.1); chemotherapy reduced (5.9) or withheld (37.6)	Died from COVID-19 (3.44), died from other causes (2.19)
Solid organ transplant						
United States (TX, CA, FL, CO)[50] 4/1/20–7/20/20	Retrospective cohort; 5 centers	NP PCR	26 SOT patients: liver (38), kidney (31), heart (23), lung (8); median time to COVID-19 from transplant 1246 d (range 12–6574 d)	Asymptomatic (23), hospitalized (20) for COVID-19 for median of 3 d, none required supplemental oxygen	No change in IST (92); 1 patient developed acute cellular rejection (kidney) 7 d after IST reduction for COVID	No deaths or ICU admissions

Europe[62]	Care provider survey; 18 centers	N/A	5 SOT patients: 2 kidney, 3 liver; 3 HSCT patients	All SOT had mild symptoms; HSCT: 1 mild, 2 moderate/ severe	No change in IST for all patients	No deaths or ICU admissions
Rheumatologic disorders						
Turkey[112] 3/11/20–4/15/20	Parent survey	23 patients with suspicion for COVID-19 tested with NP PCR (30% positive)	7 patients: 7 FMF (all on colchicine), 1 PFAPA	2 asymptomatic, 4 outpatient therapy, 1 hospitalized for 5 d	5 HCQ, 3 AZI, 4 OTV, 2 none	No deaths or ICU admissions
Spain[113] Up to 6/30/20	Registry study; 49 hospitals	N/A	8 patients: 3 JIA, 1 JDM, 1 cytoplasmic-ANCA vasculitis, 1 PFAPA, 1 polyarteritis nodosa, 1 phospholipid antibody syndrome	3 required oxygen, 1 with central line associated thrombosis, 1 with venous thrombosis and adrenal hemorrhage	5 HCQ, 1 RDV, 1 LPV/r, 1 TCZ, 1 enoxaparin; 1 reduction in IST	1 death in JDM from rapidly progressive interstitial lung disease before COVID
Chronic kidney disease on immunosuppressive therapy						
Spain[114] 3/1/20–4/15/20	Physician survey; 43 hospitals	PCR	16 patients: NS (31), renal dysplasia (31), uropathy (13), IgA nephropathy (6), vasculitis (6), scarring nephropathy (6), cortical necrosis (6); 9 patients (56) on IST and 3 patients had a kidney transplant (19)	Asymptomatic (19), no patients required oxygen	HCQ (38), LPLV/r (6); azathioprine stopped in vasculitis patient; MMF decreased in 2 of 3 and tacrolimus decreased in 1 of 3 transplant patients	No deaths or ICU admissions
Global[115] 3/15/20-End of April 2020	Retrospective survey; 16 centers	N/A	18 patients: kidney transplant (61), NS (17), ANCA-vasculitis (11), aHUS (6), ESKD with IBD (6)	Outpatient (39), oxygen support (17)	N/A	No deaths or ICU admissions

(*continued on next page*)

Table 1
(*continued*)

Country and Study Period	Study Design	Testing Strategy (%) and Detection (% Positive)	Patients Characteristics (%)	Clinical Course (%)	Treatment (%)	Outcomes (%)
Global[116] 3/15/20–7/5/20	Registry study; 30 countries	113 cases (104 by PCR or antibody testing, 9 clinically suspected)	113 patients: kidney transplant (47), NS (27), SLE (10), glomerulonephritis/ vasculitis (6), other (11); all on IST	Asymptomatic (21), admitted but no respiratory support (38), admitted with respiratory support (17), MV (4)	N/A	Died (4)
Inflammatory bowel disease						
Global[78] Before 3/26/20	Registry study; 102 sites	6 by NP PCR or 2 with symptoms + positive first degree relative	8 patients: 5 Crohn's disease, 2 Ulcerative colitis, 1 unclassified	All 8 with mild disease and no admissions	No suspension of IBD-related medications	No deaths or ICU admissions
Global[45] Before May 2020	Registry study; 33 countries	NP PCR	29 patients	Hospitalized (10)	N/A	No deaths or ICU admissions
Italy[65] 3/9/20–5/4/20	Retrospective cohort; 21 centers	6 COVID-19 cases identified out of 2291 patients (0.2%) by NP test	6 patients: 4 Crohn's disease, 2 ulcerative colitis	1 asymptomatic, 4 mild, 1 hospitalized for 7 d	No suspension of IBD-related medications	No deaths
Global[16] Before 10/1/20	Registry study; 23 countries	N/A	209 patients: Crohn's disease (66), ulcerative colitis (29), unclassified (5)	Hospitalized (7), MV (1); of the 2 patients on MV, 1 patient had MIS and 1 patient had secondary infection	N/A	No deaths

Inborn errors of immunity

Global[41] 3/16/20–6/30/20	Physician survey	Asymptomatic, symptomatic; PCR or serology	32 pediatric patients: CID (28), CVID or antibody deficiency (13), CGD (9), AGS (9), ALPS (9), WAS (6), XLA (3), CTLA4 deficiency (3), CMC with recurrent sepsis (3), MSMD (3), STAT1 GOF (3), GATA2 haploinsufficiency (3), XIAP deficiency (3), BMF (3); 2 had received HSCT, 1 gene therapy	Asymptomatic (25), ICU admission (28), MIS-C in patient with MSMD (*IFNGR2*)	Antibiotics (31), GC (16), immunoglobulin (16), RDV (9), LPV/r (3), CP (6), TCZ (3), chloroquine (3), aspirin (3), enoxaparin (3)	Deaths (6): 1 child with CGD and *Burkholderia* sepsis and HLH; 1 child following HSCT for XIAP deficiency, severe gut GVHD, septic shock, HLH
Israel[40] Mid-February to Mid-September 2020	Care provider survey; 10 centers	Contact tracing (27), symptomatic (73); NP PCR	11 pediatric patients: 3 Hyper-IgM, 2 X-linked agammaglobulinemia, 3 CID (*RELB* mutation), 2 CGD, 1 22q11.2 deletion syndrome	None hospitalized, asymptomatic (46), mild (54)	Additional dose of IVIG (9); no change in treatment for immune disorder	No deaths or ICU admissions
Iran[55]	Prospective study; 38 centers	Symptomatic only; PCR; incidence of 1 in 144 PID patients	16 pediatric patients: SCID (19), Omenn's syndrome (6), CID (13), CGD (13), IGF syndrome (13), WAS (6), AT (6), hyper-IgM (6), specific IgA deficiency (6), Griscelli syndrome type 2 (6), DIRA (6)	ICU (50)	AZI (69), IVIG (63), HCQ (50), other antibiotics (44), GC (6)	Death (50): 4 of 4 SCID/ Omenn's syndrome, STK4 deficiency, 1 of 2 IGF syndrome, Griscelli syndrome type 2, DIRA

(*continued on next page*)

Table 1 (*continued*)

Country and Study Period	Study Design	Testing Strategy (%) and Detection (% Positive)	Patients Characteristics (%)	Clinical Course (%)	Treatment (%)	Outcomes (%)
Other immunocompromised cohorts						
Spain[117] 3/1/20–3/31/20	Retrospective cohort; 1 center	NP PCR	8 patients: 5 HO (3 after HSCT), 2 SOT (1 liver, 1 kidney), 1 CKD	1 required oxygen, 1 HLH-like syndrome	5 Anti-viral treatment, 1 GC, 1 TCZ, 6 IST decreased or withdrawn	No deaths or ICU admissions
United Arab Emirates[118]	Retrospective cohort; 1 center	Contact tracing or symptomatic; NP PCR	5 patients: 1 CVID, 1 ST, 1 after splenectomy, 1 CKD, 1 SLE	3 asymptomatic, 2 mild	3 HCQ, 1 RDV, 1 FPV	No deaths or ICU admissions

Table includes only studies with at least 5 pediatric (age < 21 y) immunocompromised patients.

Abbreviations: AGS, Aicardi-Goutieres syndrome; aHUS, atypical hemolytic uremic syndrome; ALL, acute lymphoblastic leukemia; Allo-HSCT, allogeneic hematopoietic stem cell transplant; AML, acute myelogenous leukemia; ANCA, antineutrophil cytoplasmic antibody; ANR, anakinra; AT, ataxia telangiectasia; Auto-HSCT, autologous hematopoietic stem cell transplant; AZI, azithromycin; BMF, bone marrow failure; CID, combined immunodeficiency; CGD, chronic granulomatous disease; CKD, chronic kidney disease; CMC, chronic mucocutaneous candidiasis; CNS, central nervous tumor; CT, computed tomography; CVP, convalescent plasma; DIRA, deficiency of IL-1 receptor antagonist; EBV-MAS, EBV-induced macrophage activation syndrome; ESKD, End-stage kidney disease; FMF, familial mediterranean fever; FPV, favipiravir; GC, glucocorticosteroids; GOF, gain-of-function; HCQ, hydroxychloroquine; HM, hematology malignancy; HO, Hematologic-oncologic; HSCT, hematopoietic stem cell transplant; IBD, inflammatory bowel disease; ICU, intensive care unit; IGF, immunodeficiency; centromere instability, facial anomalies; IST, immunosuppressive therapy; IVIG, intravenous immunoglobulin; IVM, ivermectin; JDM, juvenile dermatomyositis; JIA, juvenile idiopathic arthritis; LPV/r, Lopinavir-ritonavir; MIS, multisystem inflammatory syndrome; MIS-C, multisystem inflammatory syndrome in children; MSMD, mendelian susceptibility to mycobacterial diseases; MV, mechanical ventilation; N/A, not available; NBL, neuroblastoma; NP, nasopharyngeal; NS, nephrotic syndrome; OTV, oseltamivir; PCR, polymerase chain reaction; PFAPA, periodic fever-aphthous stomatitis-pharyngitis-adenitis; RDV, remdesivir; SCID, severe combined immunodeficiency; SLE, systemic lupus erythematosus; SOT, solid organ transplant; ST, solid tumor; TCZ, tocilizumab; WAS, Wiskott-Aldrich syndrome; XLA, X-linked agammaglobulinemia; MDS, myelodysplastic syndrome; CML, chronic myeloid leukemia; NHL, non-Hodgkin lymphoma; LCH Langerhan cell histiocytosis; HLH, hemophagocytosis lymphohistiocytosis; TZM, temozolamide; CVID, common variable immunodeficiency; ALPS, autoimmune lymphoproliferative syndrome; CTLA4, cytotoxic T-lymphocyte-associated protein 4; STAT1, signal transducer and activator of transcription 1; XIAP, X-linked inhibitor of apoptosis protein; GVHD, graft versus host disease; PID, primary immunodeficiency.

exposure history or community SARS-CoV-2 infection rate.[4–6] This recommendation was based on the presumed risk of nosocomial transmission, although data are limited.[7] Of note, the IDSA guidelines specifically include cytotoxic chemotherapy, biologic or cellular therapy, high-dose steroids, and SOT or HSCT. There is no inclusion of patients with primary immunodeficiency, immune dysregulatory disorders, or HIV under the "immunocompromised patients," but biologically their immune deficits are similar. For asymptomatic outpatients receiving chemotherapy or other immunosuppressive medications for autoimmune disease, the IDSA recommends that the decision for testing before therapy be individualized as there remains a significant evidence gap to reliably guide practice.

It is important to note that numerous tests to detect the SARS-CoV-2 virus have emergency use authorization (EUA) and that their sensitivities and turn-around times are not uniform.[3,8] These assays detect parts of the virus via RNA or antigen testing, and molecular analysis can be completed via rapid reverse transcription polymerase chain reaction (sensitivity 98%, specificity 97%, 45–60 minutes for test completion), standard laboratory-based nucleic acid amplification testing (NAAT) (sensitivity 98%, specificity 97%), or rapid isothermal NAAT (sensitivity 81%, specificity 99%, 5–15 minutes for test completion) testing.[3] Thus, providers should appreciate the potential for false negative testing from rapid bedside testing, which may be less sensitive and miss asymptomatic patients as they are frequently completed via rapid isothermal NAAT. Beyond assay limitations, specimen inadequacy (eg, tentatively swabbing the nasopharynx of patients with thrombocytopenia) and timing of collection relative to the onset of symptoms can contribute to false negative tests.[8]

Serology testing is also available to detect past SARS-CoV-2 infection, but the utility of the test is unknown in patients with humoral immune defects who may fail to seroconvert as the assays rely on detection of anti-SARS-CoV-2 IgG, IgM, IgA, or total antibody. In addition, as immunoglobulin replacement products begin to include anti-SARS-CoV-2 IgG, the value of serologic detection will be unclear for patients on replacement therapy. Standard IDSA approaches for the use of serologic testing for SARS-CoV-2 infection should be followed for immunocompromised pediatric patients.[9]

Prevalence of SARS-CoV-2 Infection in Pediatric Immunocompromised Patients

Understanding the infectivity rate of SARS-CoV-2 has been a huge epidemiologic undertaking. In theory, immunocompromised children may be less likely to contract SARS-CoV-2 secondary to already ingrained infection prevention techniques, for example, hand washing and social isolation. However, interaction with the health care system may raise the risk of a positive contact as demonstrated in a Madrid study in which 4 of 15 cases (27%) of SARS-CoV-2 infections in pediatric oncology patients were traced to nosocomial exposure.[10] Comparison of infectivity rates with healthy children is difficult secondary to discrepancies in testing practices in immunocompromised patients who are more likely to undergo testing over concerns of developing severe COVID-19 or as a screen before hospital admissions, surgical procedures, or receiving chemotherapy. Therefore, immunocompromised children are more likely to be screened when asymptomatic, theoretically falsely raising the relative prevalence of SARS-CoV-2 in this population compared with immunocompetent children.

In review of the current 13 articles that detailed their testing strategy for pediatric oncology patients, just one cohort limited SARS-CoV-2 testing to symptomatic patients only.[11] Interestingly, this strategy was adopted in Mexico where resources for broad testing are limited, indicating that studies in poorly resourced countries may also underestimate the prevalence secondary to less aggressive screening. Among pediatric oncology hospitals in New York and New Jersey, the positivity rate at the

height of the pandemic was 16.95% with 32.7% of the cases being identified in asymptomatic patients.[12] Symptomatic patients were also more likely to be tested early in the pandemic as demonstrated in a single-center study at the UPMC Children's Hospital of Pittsburgh where immunocompromised pediatric patients with fever or respiratory symptoms were 3-times (58.0% vs 19.5%) as likely to be tested for SARS-CoV-2 in comparison to immunocompetent patients.[10] It is important to note that testing strategies continue to evolve as changes in disease prevalence and access to test supplies have fluctuated, and these early reports may not reflect current screening practices.

Another strategy to evaluate the burden of SARS-CoV-2 is to assess seroprevalence in pediatric cohorts. The UPMC Children's Hospital of Pittsburgh tested for the presence of SARS-CoV-2 IgG in convenience blood samples from immunocompromised and general pediatric patients.[10] In 485 immunocompromised patients, 1% were found to have IgG antibodies to SARS-CoV-2 spike protein, which was similar to the immunocompetent cohort (0.6%). Seroprevalence was highest in rheumatology (4.3%) and SOT (1.9%), with no detection of antibodies in HSCT, primary immunodeficiency, or inflammatory bowel disease (IBD) patients, although these data may underestimate the true prevalence given the possibility of poor humoral response to SARS-CoV-2 in some immunocompromised patients.

As of March 1, 2021, 2617 patients have met the case definition of MIS-C in the United States.[13] Estimating the prevalence of MIS-C in immunocompromised patients may prove more difficult as unlike SARS-CoV-2, MIS-C does not have specific testing but requires a constellation of symptoms and laboratory evidence of inflammation for diagnosis that may overlap with the underlying disorder, especially in rheumatology patients. MIS-C has been diagnosed in patients with underlying IBD, but presenting features including fever, gastrointestinal disease, mouth ulcers, and elevation of inflammatory markers are common manifestations of both conditions.[14–16] MIS-C, therefore, has the potential to be both underdiagnosed and overdiagnosed in immunocompromised patients and may require more specific findings such as Kawasaki-like features to confirm a MIS-C diagnosis.

Treatment of SARS-CoV-2 in Pediatric Immunocompromised Patients

Despite a large number of therapeutic studies related to COVID-19 being carried out over the past year, most participants are immunocompetent adults.[17,18] As such, treatment of immunocompromised patients mirrors that of immunocompetent patients. At the time of this publication, remdesivir, a nucleoside analog that when incorporated into RNA inhibits the replication of SARS-CoV-2 by causing delayed chain termination, is the only agent with Food and Drug Administration (FDA) approval for COVID-19 treatment. Remdesivir is approved for hospitalized patients (aged $\geq$12 years and weighing $\geq$40 kg) requiring supplemental oxygen[17,19,20] and through an EUA for hospitalized children weighing $\geq$3.5 kg. Currently there are insufficient data for use in nonhospitalized mild to moderate cases or for non–oxygen-requiring hospitalized patients, with the argument that remdesivir should be considered in these situations for immunocompromised patients. For hospitalized adult patients, dexamethasone afforded a survival benefit in patients receiving respiratory support and led to increased ventilator-free days in mechanically ventilated patients.[21,22] Dexamethasone in combination with remdesivir may be considered for immunocompromised patients with severe or critical COVID-19 requiring respiratory support but must be balanced with the risk for inadequate viral control and secondary infections.

Immunocompromised patients who have decreased ability or inability to make antibodies may be at risk for prolonged illness with decreased capacity to clear the

virus.[23] While no specific trials have been reported in this population, two therapies that could be considered are anti-SARS-CoV-2 monoclonal antibodies and convalescent plasma. Currently, the FDA has issued an EUA for the anti-SARS-CoV-2 monoclonal antibodies bamlanivimab,[24] bamlanivimab plus etesevimab,[25] and casirivimab plus imdevimab[26] for nonhospitalized adult and pediatric patients ($\geq$12 years and weighing $\geq$40 kg), who are at high risk for disease progression or hospitalization, including those with immunosuppressive disorders or those receiving immunosuppressive treatment. Convalescent plasma from recovered COVID-19 donors also received an EUA from the FDA for hospitalized patients early in the course of disease and those hospitalized with impaired humoral immunity.[27,28] This recommendation, however, is not fully supported by pediatric subspecialist groups who have advocated against routine administration of monoclonal antibodies for COVID-19 treatment because of the lack of evidence for safety and efficacy in children.[29]

As demonstrated in **Table 1**, although multiple additional therapies have been used in immunocompromised patients, there are no robust data to demonstrate the benefits or harm in this population. Until more data are available, immunocompromised pediatric patients should be followed up very closely, and therapeutic intervention considered on an individual basis.

Patients on immunosuppressive treatment for their underlying disorder present additional quandaries as there are limited studies that provide guidance regarding management of chronic immunosuppressant therapies in patients with COVID-19.[30] Concerns in pediatric immunocompromised patients with SARS-CoV-2 infection that must be balanced in the decision to maintain or modify chronic immune suppression include poor viral control, dysregulated immune responses, flare of underlying disorders, and acquisition of secondary infections. Universal guidelines are difficult if not impossible to develop given the diversity of disease and underlying risks of modifying immune suppression, as well as the knowledge that some immunosuppressant therapies (eg, cyclosporine A, thiopurine metabolites, mycophenolic acid)[31,32] have antiviral properties while others (eg, tocilizumab, dexamethasone)[21,33] have been attempted to control dysregulated immune responses in severe COVID-19. This dilemma has led physicians to perform an individualized risk-benefit evaluation to weigh the risk of reducing immunosuppression against the risk of disease flare or worsening disease activity which potentially could have both devastating short- and long-term consequences.[34] Thankfully, guidance in pediatric immunocompromised patient care is developing as our experience in COVID-19 expands. For example, the current recommendation for pediatric cancer patients with SARS-CoV-2 infections is to avoid major alterations in underlying therapy unless there is evidence of severe COVID-19 infection.[35]

Outcomes of SARS-CoV-2 in Pediatric Immunocompromised Patients

At the onset of the COVID-19 pandemic, it was assumed that poor antiviral immunity in immunocompromised patients would place them at high risk for complications as seen for other respiratory viruses including influenza, respiratory syncytial virus, and common strains of human coronavirus (OC43, NL63, HKU1, and 229E).[36–38] However, immunocompromised status and poor outcomes have not been reported during the SARS-CoV-1 and Middle East respiratory syndrome coronavirus (MERS-CoV) epidemics.[1] This somewhat paradoxic observation may stem from the unique immune pathology induced by SARS-CoV-2. The usual immune response to SARS-CoV-2 is an initial innate immune response through type I interferons followed by an adaptive humoral and cellular immune response.[39] Although adequate immune function is necessary to control SARS-CoV-2 infection, significant toxicity and death are often

a sequelae of inappropriate and dysregulated immune responses and not a direct consequence of viral invasion and replication.[40] This has raised the intriguing possibility that patients with primary or secondary immune defects may not be at increased risk of death from COVID-19 but also that certain subsets of patients may be protected from severe disease by their inability to mount a pathologic immune response to SARS-CoV-2.[41]

Initial studies in adults, however, have demonstrated that oncology and SOT patients are at higher risk for severe outcomes including intubation and death from COVID-19.[42–44] In contrast, IBD and rheumatology adult patients taking biologics and Janus kinase inhibitors displayed no increased incidence of severe disease.[45,46] The difference in outcomes may be related to the type and degree of immune suppression, but comorbidities such as hypertension, heart disease, diabetes, and chronic kidney disease were also highly prevalent in adult cancer and SOT patients with severe COVID-19.[42]

Clinical outcomes in immunocompetent children with COVID-19 are superior to adults, and several mechanisms including lower angiotensin-converting enzyme (ACE)-2 expression, enhanced immune tolerance, and fewer comorbidities have been proposed as reasons for the discrepant outcomes.[47] These protective features may be minimized in some immunocompromised populations as ACE-2 can be overexpressed in some patients with IBD and systemic lupus erythematous (SLE).[48,49] In addition, immune tolerance mechanisms may be disrupted by inborn errors of immunity such as pathogenic variants in *FOXP3* or *CTLA4*, and comorbidities exist because of the underlying genetic defect or toxicities related to treatment or prior infection.[49] Children may also be on relatively higher doses of immune suppression than adults for some conditions such as SOT, and therefore, COVID-19 outcome trends seen in immunosuppressed adults may not be translatable to pediatrics.[50]

A summary of currently published studies on pediatric immunocompromised cohorts is provided in **Table 1**, permitting some interesting early observations. First, in pediatric oncology patients, the risk of death is less than that in adults but appears to be higher than that of the general pediatric population and may be worse when compounded by certain high-risk demographics, for example, male, obese, and older age, or in patients with hematologic malignancies.[12,51–54] In contrast to oncology patients, published cohorts of pediatric rheumatology patients, SOT, chronic kidney disease on immune suppression, and IBD reported low rates of severe complications, but the literature is less extensive in these diseases.

COVID-19 severity in patients with inborn errors of immunity is dependent on the underlying defect. Although there is potential for reporter bias, complete absence of adaptive immunity appears lethal with mortality from COVID-19 in all reported severe combined immunodeficiency (SCID) patients not yet transplanted in an Iranian case series that included 3 patients with SCID and 1 patient with Omenn syndrome.[55] However, pediatric patients with nonsevere defects in adaptive immunity presented with asymptomatic or mild COVID-19 disease in a global (14 patients) and Israeli (9 patients) survey of medical providers.[40,41] Despite the concern for excessive immune activation in autoinflammatory disorders, severe disease has not been frequently reported and may be a misguided concern or the inflammation is well attenuated by preventive immunosuppression in these patients.[41] A similar concern is whether MIS-C will be more prevalent or severe in patients with autoinflammatory disorders, but it is too early to speculate as only a few anecdotal cases of MIS-C in patients with immune disorders are published to date.[14–16,41]

Overall, the clinical course in immunocompromised patients with SARS-CoV-2 is favorable, but some caution is warranted in caring for these patients. First, based on recent data demonstrating the importance of type I interferons in initial SARS-

CoV-2 control, patients who have severely deficient type I interferon signaling or immune disorders, for example, secondary to Toll-like receptor 3 or interferon regulatory factor 7 defects, or those that predispose to autoantibodies against type I interferons may be at risk for critical disease.[40,56,57] Second, some cases of death have been attributed to concurrent infections or an underlying primary disorder, highlighting the need for continued monitoring for additional infections, disease progression, and immune-related adverse events that may be independent or indirectly related to SARS-CoV-2 infection.[41] Third, changing therapy and supportive care measures against COVID-19 and evolution of new SARS-CoV-2 strains may alter outcomes in immunocompromised patients. Finally, atypical manifestations of SARS-CoV-2, such as hemophagocytic lymphohistiocytosis and cytopenias, have been infrequently reported, and providers need to remain vigilant for these and other new complications of COVID-19.

Impact to Access of Clinical Care for Immunocompromised Patients

The COVID-19 pandemic impacted access to care for non–SARS-CoV-2-infected patients as hospital systems scrambled to accommodate the surge of infected patients and limit transmission of infection among staff and patients. Unfortunately, the need to implement social distancing protocols, mobilization of SARS-CoV-2 testing, redeployment of providers and reduction in staff, use of critical care beds for severe COVID-19 patients, and parental and patient anxiety of traveling to medical centers all contributed to delayed access and untoward consequences for some immunocompromised patients. For example, surveyed pediatric rheumatologists indicated one-third of patients suffered a delayed diagnosis or joint injections due to lack of access for evaluation, and 21.9% had patients who experienced a flare due to delayed appointments.[58] A parental survey of children with rheumatic disease reported 14.3% had a treatment interruption with social restrictions and anxiety over new health center arrangements listed as the primary barrier to medical care access.[59]

In pediatric oncology, a significant drop in new diagnoses, including a decrease of 45% of expected new acute lymphoblastic leukemia diagnoses in Lombardia, Italy, and a gap of 35 days between new leukemia patients at the Children's Hospital of Philadelphia, where the historic mean gap between new diagnoses is 2.96 days, occurred early in the pandemic.[60,61] Although these reports have yet to describe a rebound of cancer diagnoses, extreme sickness in new cancer patients is documented, and these presentation delays to oncology centers have been attributed to parental reluctance to seek medical care, decreased referrals to major medical centers, limitations of telemedicine, and a diagnostic bias toward COVID-19 for presenting signs of a malignancy.[61] A survey of SOT and HSCT centers in Europe reported that two-third of centers reduced their transplant activity.[62] However, pediatric kidney transplants in the United States has largely returned to baseline after the initial surge of COVID-19.[63] In the United Kingdom, restrictions on endoscopy procedures resulted in most pediatric patients being diagnosed with "presumed IBD" without histologic confirmation.[64] IBD admissions for new diagnoses and endoscopic re-evaluation were also significantly reduced during the lock down in Italy.[65]

In attempts to maintain access to care while minimizing infectious exposure and conserving personal protective equipment, subspecialty providers pivoted toward telemedicine.[66] Expansion of telemedicine services was greatly aided by changes in reimbursement policies during the COVID-19 pandemic.[67] While not all clinical situations are amenable to virtual visits, subspecialists quickly adapted care for telemedicine including devising standardized virtual joint examinations and facilitating "care in place" with local laboratory evaluation and primary care collaboration for vital signs,

weight checks, and key examination findings as needed. The reduced risk of inadvertent infectious exposure as well as the historical advantages of increased flexibility of access and decreased financial burden (eg, travel, days of missed work, childcare) contributed to telemedicine appeal among immunocompromised patients. For example, 38 childhood cancer survivors or their proxies surveyed about their long-term follow-up virtual visits were highly satisfied with their visits (with 86% and 95%, "completely/very satisfied," respectively) with 82% preferring video visits to remain an option after the pandemic.[68] Further study of parental preferences is needed to optimize the telehealth care models.

In addition to medical care, continuation of psychosocial services to immunocompromised children and adolescents during this pandemic is vitally important. Patients with immunodeficiency, even before the pandemic, had lower health-related quality of life (HRQoL) than healthy peers and those with other chronic conditions.[69] With the onset of COVID-19, a nationwide pediatric healthy cohort of 1586 families from Germany reported lower HRQoL (measured by KIDSCREEN-10), more mental health problems (measured by SDQ), and increased anxiety (measured by SCARED) than before the pandemic.[70] While not yet formally assessed, it is anticipated that similar trends exist in immunocompromised patients.

Immunocompromised children and parents seeking trustworthy information and peer support have historically relied on philanthropic foundations, for example, Immune Deficiency Foundation, Race for Immunology, Alex's Lemonade Stand, and resources such as the Ryan White HIV/AIDS Program. Providers, similarly, have turned to prepandemic psychosocial service models such as those used for people with HIV that have historically used home visits, telemedicine and adherence programs inclusive of directly observed therapy, motivational interviewing sessions, and social work check-ins.[71–73] Home delivery of medication was already occurring for many high-risk patients, and continuation of this service has minimized treatment gaps for some patients. Unfortunately, the same services have not been available in many resource-poor areas of the United States and abroad, and services to those with HIV have suffered interruptions of heath care.[74–76] The same service interruptions may be inferred for other high-risk immune-deficient patients in poor-resource areas.

Changes to Management in Immunocompromised Patient in the COVID-19 Era

At the onset of the pandemic, uncertainty over the risk of severe COVID-19, drug shortages for medications used for both immunocompromised patients and SARS-CoV-2, and reallocation of resources to COVID-19 patient care and research led to numerous changes in management of immunocompromised children. Early in the pandemic, pediatric oncologists regularly delayed chemotherapy (48%–100% in published cohorts; see **Table 1**), and reports of patient deaths secondary to disease progression while delaying induction or pausing chemotherapy during SARS-CoV-2 infection have been reported. Pediatric oncology clinical trial enrollment decreased as resources were diverted to COVID-19 research, restrictions on research were made in an effort to curb SARS-CoV-2 transmission, and research staff furloughed to limit the negative institutional financial impact of COVID-19. As such, some pediatric oncology patients, particularly those with relapsed/refractory disease, had less options for therapy because of delays in opening new studies.[77]

In China and South Korea, 20% of pediatric IBD patients suffered disease exacerbation when infliximab infusions were delayed.[78] In the UK, standard treatment with a Tumor necrosis factor inhibitor was replaced with exclusive enteral nutrition for new IBD patients as diagnosis could not be confirmed secondary to reduction in endoscopy procedures.[64] Early guidance in pediatric rheumatology patients stressed

continuing current immune suppression to avoid disease flare.[79] However, concerns over SARS-CoV-2 also led to hesitancy to starting new immune suppression with worsening disease[58] despite that control of disease activity may also help reduce risk of severe infection in certain systemic disorders as demonstrated in adult patients with rheumatoid arthritis.[80,81]

In addition, drug shortages forced changes in management and mandated strategic planning to preserve doses for critical care.[82] In pediatric and adult rheumatology, many patients receiving IV tocilizumab were switched to the subcutaneous (SQ) form as the supply of IV tocilizumab was consumed for treatment of severe COVID-19. This switch to SQ tocilizumab resulted in patient/parent anxiety of the risk of disease flare or worsening disease activity even though switching to SQ route has been found to be an effective alternative for children with juvenile idiopathic arthritis.[83] Other drugs, for example, hydroxychloroquine, demonstrated a huge surge in prescriptions early in the pandemic presumably attributed to off-label use for COVID-19 treatment raising concern for decreased availability of the drug for SLE or other autoimmune indications.[84–86]

With concerns for nosocomial exposure, providers prioritized home-administered therapeutic options when possible, particularly for immunocompromised patients. The National Institute for Health and Care Excellence published COVID-19 rapid guidelines specifically recommending clinicians to consider switching IV medications to SQ form to minimize exposure of SARS-CoV-2. Anecdotally, children receiving IgG replacement were transitioned from IV IgG in-hospital infusion areas to either SQ or at-home IV IgG and when feasible, and outpatient chemotherapy regimens were favored, for example, SQ cytarabine versus IV vinblastine with prednisone for children with Langerhans cell histiocytosis given the success of cytarabine monotherapy in refractory disease.[87]

Considerations for COVID-19 Vaccination in Immunocompromised Patients

In December of 2020, Pfizer-BioNTech and Moderna both received EUAs for their COVID-19 vaccines from the FDA,[88,89] with the Janssen Biotech COVID-19 vaccine receiving an EUA in February 2021.[90] With the exception of HIV, patients with immune deficiency were largely excluded from the clinical trials.[91–93] Despite the current lack of safety and efficacy data in patients with compromised immune systems, there is general consensus among physicians that these nonlive vaccines should be administered to the vast majority of immunosuppressed patients.[94] The Centers for Disease Control and Prevention (CDC) also suggests that immunocompromised individuals receive the COVID-19 vaccine, with counseling on unknown safety profile and efficacy in this population.[95] Timing of vaccination in relation to immunosuppressive therapies is not completely understood, but adult patients with rheumatoid arthritis receiving the seasonal influenza vaccination demonstrated improved response if methotrexate was not given for at least 2 weeks after HCT.[96] It was also noted that flares were more common in patients with 4-week pauses of their methotrexate around the time of vaccination.[97] But the effects of immune suppression on COVID-19 vaccine response are not yet determined, and consideration to hold immunosuppressants after vaccination need to be considered on a case-by-case basis and ideally studied in clinical trials.[98] The CDC at the time of publication does not recommend revaccination of those who may have received the vaccine during chemotherapy or while on immunosuppressive medications and does not suggest antibody testing to assess for immunity after vaccination.[95]

Safety of vaccines in the immune compromised is different compared with that in immune-competent individuals. Live attenuated vaccines can cause disease in immunocompromised patients because of the inability to control the replication of the

pathogen even in its weakened state. The Pfizer-BioNTech and Moderna COVID-19 vaccines are not live, nor do they contain any actual virus to cause disease, and instead contain mRNA encoding the spike protein of SARS-CoV-2. The Janssen COVID-19 vaccine uses a recombinant, replication-incompetent adenovirus vector containing the full-length SARS-CoV-2 spike protein gene.[93] The vector shuttles the gene into the nucleus of the cell where it is transcribed and translated into the spike protein, but the genetic material does not integrate into host DNA, and because the vector does not replicate, it cannot cause human disease.[99] Therefore, as all 3 vaccines cannot result in infection, they are likely safe for patients with immunodeficiency. However, live attenuated COVID-19 vaccines are in development or clinical trials, so in the future, it will be important to know which vaccine is being offered with the live attenuated vaccines being avoided until workup and discussion with an immunologist.[100] Another theoretic concern is administration of vaccines in patients with autoimmune and autoinflammatory disorders with excessive production of inflammatory cytokines in response to viral products. However, given the risk of SARS-CoV-2 infection in these disorders, the immunology community has provided cautious support for vaccination in these patients and recommended it ideally should be administered during periods of low disease activity.[101]

In addition to safety concerns, efficacy of these vaccines is unclear and likely variable depending on the immune defect. Classically, antibody production is used as a measure of the protection offered from immunization, but vaccines may generate T-cell responses as well, which could be of benefit in those with humoral defects. Studies examining patients recovered from COVID-19 have found the presence of SARS-CoV-2-specific CD4+ and CD8+ T cells in circulation, and studies of the Pfizer-BioNTech vaccine found that two doses elicit T-cell responses against the SARS-CoV-2 spike protein.[102,103]

SUMMARY

While the COVID-19 pandemic triggered numerous clinical practice changes and resulted in severe consequences either directly or indirectly for select pediatric patients, important lessons were learned, and there are silver linings for immunocompromised children evident among the chaos. At a minimum, the pandemic raised global awareness of infection risk, viral transmissibility, and the immune system. Handwashing, comprehensive disinfection practices of shared surfaces, and mask wearing are more normalized. School shutdowns during the COVID-19 pandemic not only kept children from exposure to SARS-CoV-2 but also decreased the incidence of pneumonia, otitis media, streptococcal pharyngitis, urinary tract infections, croup, gastrointestinal infections, and asthma.[104] Strategies to mitigate SARS-CoV-2 infection including ventilation upgrades and cohorting methods are likely to help attenuate infectious exposures as students return to the classroom. In addition, the broad acceptance of virtual learning and incorporation of virtual learners in a hybrid classroom are practices expected to be of value to immunodeficient patients. Beyond schooling, the creative transition of other activities, for example, dance, karate, and enrichment opportunities, for example, art classes and streaming concerts, has allowed immunocompromised children to participate with their peers. As risk of SARS-CoV-2 transmission lessens, immunocompetent children will return to school and other in-person activities; the expanded services offered during the pandemic need to be continued for children with weakened immune systems.

From a health care perspective, the massive uptake of telemedicine provided an alternative strategy for patients with compromised immune systems to maintain access to care with increased convenience and decreased cost. Given that

immunocompromised patients are likely to benefit from continued telehealth options after the pandemic, it is imperative that action be taken to preserve the expansion of compensated telehealth options, while also appreciating that in-person visits are vital for some patients to diagnose new or progressive disease. In addition, strategies to mitigate barriers for telehealth uptake to improve equity of access as well as parental/patient preferences for care received in-person versus virtually must be explored.

Although global efforts have accelerated our understanding and care of SARS-CoV-2 patients, our knowledge of clinical outcomes and treatment in immunocompromised patients is limited, particularly in inborn errors of immunity and pediatric HIV. Challenges remaining for pediatricians include sustained, global collaboration to consolidate knowledge in these rare patient groups, continued adaptation of knowledge gained from immunocompetent patients to immunocompromised cohorts, and further study on the safety and efficacy of current and developing vaccines. Persistent advocacy for rare diseases is even more critical as the clinical, scientific, and philanthropic communities remain focused on COVID-19 care and research.

Finally, a comment that immunocompromised parents hear is, "I finally understand what it is like to live like you. I am afraid to get an infection. I cannot just go anywhere I want to go anymore". Although the COVID-19 pandemic has been difficult for everyone on a personal and professional level, the anxiety of infection and social isolation will persist for immunocompromised families even as the risk of SARS-CoV-2 transmission subsides. It is imperative that we leverage knowledge gained from this pandemic to improve the health and quality of life of immunocompromised children so that they may live without fear.

REFERENCES

1. D'Antiga L. Coronaviruses and Immunosuppressed Patients: The Facts During the Third Epidemic. Liver transplantation : official publication of the American Association for the Study of Liver Diseases and the. Int Liver Transplant Soc 2020;26(6):832–4.
2. Kabeerdoss J, Pilania RK, Karkhele R, et al. Severe COVID-19, multisystem inflammatory syndrome in children, and Kawasaki disease: immunological mechanisms, clinical manifestations and management. Rheumatol Int 2021;41(1):19–32.
3. Hanson KE, Caliendo AM, Arias CA, et al. The Infectious Diseases Society of America Guidelines on the Diagnosis of COVID-19: Molecular Diagnostic Testing. Clin Infect Dis 2021. https://doi.org/10.1093/cid/ciab048.
4. Waghmare A, Abidi MZ, Boeckh M, et al. Guidelines for COVID-19 Management in Hematopoietic Cell Transplantation and Cellular Therapy Recipients. Biol Blood Marrow Transplant 2020;26(11):1983–94.
5. Ljungman P, Mikulska M, de la Camara R, et al. The challenge of COVID-19 and hematopoietic cell transplantation; EBMT recommendations for management of hematopoietic cell transplant recipients, their donors, and patients undergoing CAR T-cell therapy. Bone Marrow Transplant 2020;55(11):2071–6.
6. Ritschl PV, Nevermann N, Wiering L, et al. Solid organ transplantation programs facing lack of empiric evidence in the COVID-19 pandemic: A By-proxy Society Recommendation Consensus approach. Am J Transplant 2020;20(7):1826–36.
7. Abbas S, Raybould JE, Sastry S, et al. Respiratory viruses in transplant recipients: more than just a cold. Clinical syndromes and infection prevention principles. Int J Infect Dis 2017;62:86–93.

8. Ravi N, Cortade DL, Ng E, et al. Diagnostics for SARS-CoV-2 detection: A comprehensive review of the FDA-EUA COVID-19 testing landscape. Biosens Bioelectron 2020;165:112454.
9. Hanson KE, Caliendo AM, Arias CA, et al. Infectious diseases Society of America guidelines on the diagnosis of COVID-19:serologic testing. Clin Infect Dis 2020. https://doi.org/10.1093/cid/ciaa1343.
10. Freeman MC, Rapsinski GJ, Zilla ML, et al. Immunocompromised Seroprevalence and Course of Illness of SARS-CoV-2 in One Pediatric Quaternary Care Center. J Pediatr Infect Dis Soc 2020. https://doi.org/10.1093/jpids/piaa123.
11. López-Aguilar E, Cárdenas-Navarrete R, Simental-Toba A, et al. Children with cancer during COVID-19 pandemic: Early experience in Mexico. Pediatr Blood Cancer 2021;68(2):e28660.
12. Madhusoodhan PP, Pierro J, Musante J, et al. Characterization of COVID-19 disease in pediatric oncology patients: The New York-New Jersey regional experience. Pediatr Blood Cancer 2021;68(3):e28843.
13. Center for Disease Control and Prevention. Health Department-reported Cases of Multisystem Inflammatory Syndrome in Children (MIS-C) in the United States. Available at: https://www.cdc.gov/mis-c/cases/index.html. Accessed March 1, 2021.
14. Meredith J, Khedim CA, Henderson P, et al. Paediatric Inflammatory Multisystem Syndrome temporally associated with SARS-CoV-2 (PIMS-TS) in a patient receiving Infliximab therapy for Inflammatory Bowel Disease. J Crohn's Colitis 2020. https://doi.org/10.1093/ecco-jcc/jjaa201.
15. Dolinger MT, Person H, Smith R, et al. Pediatric Crohn Disease and Multisystem Inflammatory Syndrome in Children (MIS-C) and COVID-19 Treated With Infliximab. J Pediatr Gastroenterol Nutr 2020;71(2):153–5.
16. Brenner EJ, Pigneur B, Focht G, et al. Benign Evolution of SARS-Cov2 Infections in Children With Inflammatory Bowel Disease: Results From Two International Databases. Clin Gastroenterol Hepatol 2021;19(2):394–6.e5.
17. Wang Y, Zhang D, Du G, et al. Remdesivir in adults with severe COVID-19: a randomised, double-blind, placebo-controlled, multicentre trial. Lancet (London, England) 2020;395(10236):1569–78.
18. Kalil AC, Patterson TF, Mehta AK, et al. Baricitinib plus Remdesivir for Hospitalized Adults with Covid-19. N Engl J Med 2021;384(9):795–807.
19. Beigel JH, Tomashek KM, Dodd LE, et al. Remdesivir for the Treatment of Covid-19 - Final Report. N Engl J Med 2020;383(19):1813–26.
20. Spinner CD, Gottlieb RL, Criner GJ, et al. Effect of Remdesivir vs Standard Care on Clinical Status at 11 Days in Patients With Moderate COVID-19: A Randomized Clinical Trial. JAMA 2020;324(11):1048–57.
21. Horby P, Lim WS, Emberson JR, et al. Dexamethasone in Hospitalized Patients with Covid-19. N Engl J Med 2021;384(8):693–704.
22. Tomazini BM, Maia IS, Cavalcanti AB, et al. Effect of Dexamethasone on Days Alive and Ventilator-Free in Patients With Moderate or Severe Acute Respiratory Distress Syndrome and COVID-19: The CoDEX Randomized Clinical Trial. JAMA 2020;324(13):1307–16.
23. Focosi D, Franchini M. COVID-19 neutralizing antibody-based therapies in humoral immune deficiencies: A narrative review. Transfus Apheresis Sci 2021;103071. https://doi.org/10.1016/j.transci.2021.103071.
24. Food and Drug Administration. Bamlanivimab EUA Letter of Authorization. Available at: https://www.fda.gov/media/143602/download. Accessed March 2, 2021.

25. Food and Drug Administration. Bamlanivimab and etesevimab EUA Letter of Authorization. Available at: https://www.fda.gov/media/145801/download. Accessed February 25, 2021.
26. Food and Drug Administration. Casirivimab plus imdevimab EUA Letter of Authorization. Available at: https://www.fda.gov/media/145610/download. Accessed February 25, 2021.
27. Joyner MJ, Bruno KA, Klassen SA, et al. Safety Update: COVID-19 Convalescent Plasma in 20,000 Hospitalized Patients. Mayo Clin Proc 2020;95(9):1888–97.
28. Food and Drug Administration. Convalescent plasma EUA Letter of Authorization. Available at: https://www.fda.gov/media/141477/download. Accessed February 23, 2021.
29. Wolf J, Abzug MJ, Wattier RL, et al. Initial Guidance on Use of Monoclonal Antibody Therapy for Treatment of COVID-19 in Children and Adolescents. J Pediatr Infect Dis Soc 2021. https://doi.org/10.1093/jpids/piaa175.
30. Ladani AP, Loganathan M, Danve A. Managing rheumatic diseases during COVID-19. Clin Rheumatol 2020;39(11):3245–54.
31. Cheng KW, Cheng SC, Chen WY, et al. Thiopurine analogs and mycophenolic acid synergistically inhibit the papain-like protease of Middle East respiratory syndrome coronavirus. Antiviral Res 2015;115:9–16.
32. Pfefferle S, Schöpf J, Kögl M, et al. The SARS-coronavirus-host interactome: identification of cyclophilins as target for pan-coronavirus inhibitors. PLoS Pathog 2011;7(10):e1002331.
33. Rosas IO, Bräu N, Waters M, et al. Tocilizumab in Hospitalized Patients with Severe Covid-19 Pneumonia. N Engl J Med 2021. https://doi.org/10.1056/NEJMoa2028700.
34. Warraich R, Amani L, Mediwake R, et al. Immunosuppression drug advice and COVID-19: are we doing more harm than good? Br J Hosp Med (London, Engl: 2005) 2020;81(6):1–3.
35. Bisogno G, Provenzi M, Zama D, et al. Clinical Characteristics and Outcome of Severe Acute Respiratory Syndrome Coronavirus 2 Infection in Italian Pediatric Oncology Patients: A Study From the Infectious Diseases Working Group of the Associazione Italiana di Oncologia e Ematologia Pediatrica. J Pediatr Infect Dis Soc 2020;9(5):530–4.
36. Memoli MJ, Athota R, Reed S, et al. The natural history of influenza infection in the severely immunocompromised vs nonimmunocompromised hosts. Clin Infect Dis 2014;58(2):214–24.
37. Asner S, Stephens D, Pedulla P, et al. Risk factors and outcomes for respiratory syncytial virus-related infections in immunocompromised children. Pediatr Infect Dis J 2013;32(10):1073–6.
38. Ogimi C, Englund JA, Bradford MC, et al. Characteristics and Outcomes of Coronavirus Infection in Children: The Role of Viral Factors and an Immunocompromised State. J Pediatr Infect Dis Soc 2019;8(1):21–8.
39. Batu ED, Özen S. Implications of COVID-19 in pediatric rheumatology. Rheumatol Int 2020;40(8):1193–213.
40. Marcus N, Frizinsky S, Hagin D, et al. Minor Clinical Impact of COVID-19 Pandemic on Patients With Primary Immunodeficiency in Israel. Front Immunol 2020;11:614086.
41. Meyts I, Bucciol G, Quinti I, et al. Coronavirus disease 2019 in patients with inborn errors of immunity: An international study. J Allergy Clin Immunol 2021;147(2):520–31.

42. Fung M, Babik JM. COVID-19 in Immunocompromised Hosts: What We Know So Far. Clin Infect Dis 2020. https://doi.org/10.1093/cid/ciaa863.
43. Kuderer NM, Choueiri TK, Shah DP, et al. Clinical impact of COVID-19 on patients with cancer (CCC19): a cohort study. Lancet (London, England) 2020; 395(10241):1907–18.
44. Akalin E, Azzi Y, Bartash R, et al. Covid-19 and Kidney Transplantation. N Engl J Med 2020;382(25):2475–7.
45. Brenner EJ, Ungaro RC, Gearry RB, et al. Corticosteroids, But Not TNF Antagonists, Are Associated With Adverse COVID-19 Outcomes in Patients With Inflammatory Bowel Diseases: Results From an International Registry. Gastroenterology 2020;159(2):481–91.e3.
46. Gianfrancesco M, Hyrich KL, Al-Adely S, et al. Characteristics associated with hospitalisation for COVID-19 in people with rheumatic disease: data from the COVID-19 Global Rheumatology Alliance physician-reported registry. Ann Rheum Dis 2020;79(7):859–66.
47. Ebeid FSE, Ragab IA, Elsherif NHK, et al. COVID-19 in Children With Cancer: A Single Low-Middle Income Center Experience. J Pediatr hematology/oncology 2020. https://doi.org/10.1097/mph.0000000000002025.
48. Garg M, Burrell LM, Velkoska E, et al. Upregulation of circulating components of the alternative renin-angiotensin system in inflammatory bowel disease: A pilot study. J Renin-Angiotensin-Aldosterone Syst 2015;16(3):559–69.
49. Sawalha AH, Zhao M, Coit P, et al. Epigenetic dysregulation of ACE2 and interferon-regulated genes might suggest increased COVID-19 susceptibility and severity in lupus patients. Clin Immunol (Orlando, FL) 2020;215:108410.
50. Goss MB, Galván NTN, Ruan W, et al. The pediatric solid organ transplant experience with COVID-19: An initial multi-center, multi-organ case series. Pediatr Transplant 2020;e13868. https://doi.org/10.1111/petr.13868.
51. Kebudi R, Kurucu N, Tuğcu D, et al. COVID-19 infection in children with cancer and stem cell transplant recipients in Turkey: A nationwide study. Pediatr Blood Cancer 2021;e28915. https://doi.org/10.1002/pbc.28915.
52. Rouger-Gaudichon J, Thébault E, Félix A, et al. Impact of the First Wave of COVID-19 on Pediatric Oncology and Hematology: A Report from the French Society of Pediatric Oncology. Cancers 2020;12(11). https://doi.org/10.3390/cancers12113398.
53. The Pediatric COVID-10 Cancer Case Report. POCC Rep as January 20, 2021. Available at: https://www.uab.edu/medicine/icos/icos-research/the-pocc-report/reports-updates. Accessed February 10, 2021.
54. COVID-19 and Childhood Cancer Registry. Available at: https://global.stjude.org/en-us/global-covid-19-observatory-and-resource-center-for-childhood-cancer/registry.html. Accessed February 10, 2021.
55. Delavari S, Abolhassani H, Abolnezhadian F, et al. Impact of SARS-CoV-2 Pandemic on Patients with Primary Immunodeficiency. J Clin Immunol 2021; 41(2):345–55.
56. Zhang Q, Bastard P, Liu Z, et al. Inborn errors of type I IFN immunity in patients with life-threatening COVID-19, 370. New York: Science; 2020. p. 6515.
57. Bastard P, Rosen LB, Zhang Q, et al. Autoantibodies against type I IFNs in patients with life-threatening COVID-19, 370. New York: Science; 2020. p. 6515.
58. Batu ED, Lamot L, Sag E, et al. How the COVID-19 pandemic has influenced pediatric rheumatology practice: Results of a global, cross-sectional, online survey. Semin Arthritis Rheum 2020;50(6):1262–8.

59. Koker O, Demirkan FG, Kayaalp G, et al. Does immunosuppressive treatment entail an additional risk for children with rheumatic diseases? A survey-based study in the era of COVID-19. Rheumatol Int 2020;40(10):1613–23.
60. Ferrari A, Zecca M, Rizzari C, et al. Children with cancer in the time of COVID-19: An 8-week report from the six pediatric onco-hematology centers in Lombardia, Italy. Pediatr Blood Cancer 2020;67(8):e28410.
61. Ding YY, Ramakrishna S, Long AH, et al. Delayed cancer diagnoses and high mortality in children during the COVID-19 pandemic. Pediatr Blood Cancer 2020;67(9):e28427.
62. Doná D, Torres Canizales J, Benetti E, et al. Pediatric transplantation in Europe during the COVID-19 pandemic: Early impact on activity and healthcare. Clin Transplant 2020;34(10):e14063.
63. Charnaya O, Chiang TP, Wang R, et al. Effects of COVID-19 pandemic on pediatric kidney transplant in the United States. Pediatr Nephrol (Berlin, Germany) 2021;36(1):143–51.
64. Ashton JJ, Kammermeier J, Spray C, et al. Impact of COVID-19 on diagnosis and management of paediatric inflammatory bowel disease during lockdown: a UK nationwide study. Arch Dis Child 2020;105(12):1186–91.
65. Arrigo S, Alvisi P, Banzato C, et al. Impact of COVID-19 pandemic on the management of paediatric inflammatory bowel disease: An Italian multicentre study on behalf of the SIGENP IBD Group. Dig Liver Dis : official J Ital Soc Gastroenterol Ital Assoc Study Liver 2021;53(3):283–8.
66. Hare N, Bansal P, Bajowala SS, et al. Work Group Report: COVID-19: Unmasking Telemedicine. J Allergy Clin Immunol In Pract 2020;8(8):2461–73.e3.
67. Kircher SM, Mulcahy M, Kalyan A, et al. Telemedicine in Oncology and Reimbursement Policy During COVID-19 and Beyond. J Natl Compr Cancer Netw 2020;1–7. https://doi.org/10.6004/jnccn.2020.7639.
68. Kenney LB, Vrooman LM, Lind ED, et al. Virtual visits as long-term follow-up care for childhood cancer survivors: Patient and provider satisfaction during the COVID-19 pandemic. Pediatr Blood Cancer 2021;e28927. https://doi.org/10.1002/pbc.28927.
69. Peshko D, Kulbachinskaya E, Korsunskiy I, et al. Health-Related Quality of Life in Children and Adults with Primary Immunodeficiencies: A Systematic Review and Meta-Analysis. J Allergy Clin Immunol In Pract 2019;7(6):1929–57.e5.
70. Ravens-Sieberer U, Kaman A, Erhart M, et al. Impact of the COVID-19 pandemic on quality of life and mental health in children and adolescents in Germany. Eur Child Adolesc Psychiatry 2021;1–11. https://doi.org/10.1007/s00787-021-01726-5.
71. Glikman D, Walsh L, Valkenburg J, et al. Hospital-based directly observed therapy for HIV-infected children and adolescents to assess adherence to antiretroviral medications. Pediatrics 2007;119(5):e1142–8.
72. Parsons GN, Siberry GK, Parsons JK, et al. Multidisciplinary, inpatient directly observed therapy for HIV-1-infected children and adolescents failing HAART: A retrospective study. AIDS Patient Care and STDs 2006;20(4):275–84.
73. Saberi P, Siedle-Khan R, Sheon N, et al. The Use of Mobile Health Applications Among Youth and Young Adults Living with HIV: Focus Group Findings. AIDS patient care and STDs 2016;30(6):254–60.
74. Ponticiello M, Mwanga-Amumpaire J, Tushemereirwe P, et al. Everything is a Mess": How COVID-19 is Impacting Engagement with HIV Testing Services in Rural Southwestern Uganda. AIDS Behav 2020;24(11):3006–9.

75. Lodge W 2nd, Kuchukhidze S. COVID-19, HIV, and Migrant Workers: The Double Burden of the Two Viruses. AIDS Patient Care and STDs 2020;34(6):249–50.
76. Shiau S, Krause KD, Valera P, et al. The Burden of COVID-19 in People Living with HIV: A Syndemic Perspective. AIDS Behav 2020;24(8):2244–9.
77. Auletta JJ, Adamson PC, Agin JE, et al. Pediatric cancer research: Surviving COVID-19. Pediatr Blood Cancer 2020;67(9):e28435.
78. Turner D, Huang Y, Martín-de-Carpi J, et al. Corona Virus Disease 2019 and Paediatric Inflammatory Bowel Diseases: Global Experience and Provisional Guidance (March 2020) from the Paediatric IBD Porto Group of European Society of Paediatric Gastroenterology, Hepatology, and Nutrition. J Pediatr Gastroenterol Nutr 2020;70(6):727–33.
79. Licciardi F, Giani T, Baldini L, et al. COVID-19 and what pediatric rheumatologists should know: a review from a highly affected country. Pediatr Rheumatol Online J 2020;18(1):35.
80. Accortt NA, Lesperance T, Liu M, et al. Impact of Sustained Remission on the Risk of Serious Infection in Patients With Rheumatoid Arthritis. Arthritis Care Res 2018;70(5):679–84.
81. Au K, Reed G, Curtis JR, et al. High disease activity is associated with an increased risk of infection in patients with rheumatoid arthritis. Ann Rheum Dis 2011;70(5):785–91.
82. Moss JD, Schwenk HT, Chen M, et al. Drug Shortage and Critical Medication Inventory Management at a Children's Hospital During the COVID-19 Pandemic. J Pediatr Pharmacol Ther 2021;26(1):21–5.
83. Ayaz NA, Karadağ Ş G, Koç R, et al. Patient satisfaction and clinical effectiveness of switching from intravenous tocilizumab to subcutaneous tocilizumab in patients with juvenile idiopathic arthritis: an observational study. Rheumatol Int 2020;40(7):1111–6.
84. Vaduganathan M, van Meijgaard J, Mehra MR, et al. Prescription Fill Patterns for Commonly Used Drugs During the COVID-19 Pandemic in the United States. JAMA 2020;323(24):2524–6.
85. Mendel A, Bernatsky S, Thorne JC, et al. Hydroxychloroquine shortages during the COVID-19 pandemic. Ann Rheum Dis 2020. https://doi.org/10.1136/annrheumdis-2020-217835.
86. Plüß M, Chehab G, Korsten P. Concerns and needs of patients with systemic lupus erythematosus regarding hydroxychloroquine supplies during the COVID-19 pandemic: results from a patient-centred survey. Ann Rheum Dis 2020. https://doi.org/10.1136/annrheumdis-2020-217967.
87. Simko SJ, McClain KL, Allen CE. Up-front therapy for LCH: is it time to test an alternative to vinblastine/prednisone? Br J Haematol 2015;169(2):299–301.
88. Food and Drug Administration. Pfizer COVID-19 Vaccine EUA Letter of Authorization. Available at: https://www.fda.gov/media/144412/download. Accessed February 25, 2021.
89. Food and Drug Administration. Moderna COVID-19 Vaccine EUA Letter of Authorization. Available at: https://www.fda.gov/media/144636/download. Accessed February 25, 2021.
90. Food and Drug Administration. Janssen Biotech COVID-19 Vaccine EUA Letter of Authorization. Available at: https://www.fda.gov/media/146303/download. Accessed February 27, 2021.
91. Polack FP, Thomas SJ, Kitchin N, et al. Safety and Efficacy of the BNT162b2 mRNA Covid-19 Vaccine. N Engl J Med 2020;383(27):2603–15.

92. Baden LR, El Sahly HM, Essink B, et al. Efficacy and Safety of the mRNA-1273 SARS-CoV-2 Vaccine. N Engl J Med 2021;384(5):403–16.
93. Sadoff J, Le Gars M, Shukarev G, et al. Interim Results of a Phase 1-2a Trial of Ad26.COV2.S Covid-19 Vaccine. N Engl J Med 2021. https://doi.org/10.1056/NEJMoa2034201.
94. D'Amico F, Rabaud C, Peyrin-Biroulet L, et al. SARS-CoV-2 vaccination in IBD: more pros than cons. Nat Rev Gastroenterol Hepatol 2021;1–3. https://doi.org/10.1038/s41575-021-00420-w.
95. Centers for Disease Control and Prevention. Interim Clinical Considerations for Use of COVID-19 Vaccines Currently Authorized in the United States. Available at: https://www.cdc.gov/vaccines/covid-19/info-by-product/clinical-considerations.html. Accessed March 3, 2021.
96. Park JK, Choi Y, Winthrop KL, et al. Optimal time between the last methotrexate administration and seasonal influenza vaccination in rheumatoid arthritis: post hoc analysis of a randomised clinical trial. Ann Rheum Dis 2019;78(9):1283–4.
97. Park JK, Lee MA, Lee EY, et al. Effect of methotrexate discontinuation on efficacy of seasonal influenza vaccination in patients with rheumatoid arthritis: a randomised clinical trial. Ann Rheum Dis 2017;76(9):1559–65.
98. Sonani B, Aslam F, Goyal A, et al. COVID-19 vaccination in immunocompromised patients. Clin Rheumatol 2021;40(2):797–8.
99. Livingston EH, Malani PN, Creech CB. The Johnson & Johnson Vaccine for COVID-19. JAMA 2021. https://doi.org/10.1001/jama.2021.2927.
100. Zhao J, Zhao S, Ou J, et al. COVID-19: Coronavirus Vaccine Development Updates. Front Immunol 2020;11:602256.
101. Velikova T, Georgiev T. SARS-CoV-2 vaccines and autoimmune diseases amidst the COVID-19 crisis. Rheumatol Int 2021;41(3):509–18.
102. Sahin U, Muik A, Derhovanessian E, et al. COVID-19 vaccine BNT162b1 elicits human antibody and T(H)1 T cell responses. Nature 2020;586(7830):594–9.
103. Anderson EJ, Rouphael NG, Widge AT, et al. Safety and Immunogenicity of SARS-CoV-2 mRNA-1273 Vaccine in Older Adults. N Engl J Med 2020;383(25):2427–38.
104. Hatoun J, Correa ET, Donahue SMA, et al. Social Distancing for COVID-19 and Diagnoses of Other Infectious Diseases in Children. Pediatrics 2020;146(4). https://doi.org/10.1542/peds.2020-006460.
105. Hrusak O, Kalina T, Wolf J, et al. Flash survey on severe acute respiratory syndrome coronavirus-2 infections in paediatric patients on anticancer treatment. Eur J Cancer 2020;132:11–6.
106. Gampel B, Troullioud Lucas AG, Broglie L, et al. COVID-19 disease in New York City pediatric hematology and oncology patients. Pediatr Blood Cancer 2020;67(9):e28420.
107. de Rojas T, Pérez-Martínez A, Cela E, et al. COVID-19 infection in children and adolescents with cancer in Madrid. Pediatr Blood Cancer 2020;67(7):e28397.
108. André N, Rouger-Gaudichon J, Brethon B, et al. COVID-19 in pediatric oncology from French pediatric oncology and hematology centers: High risk of severe forms? Pediatr Blood Cancer 2020;67(7):e28392.
109. Montoya J, Ugaz C, Alarcon S, et al. COVID-19 in pediatric cancer patients in a resource-limited setting: National data from Peru. Pediatr Blood Cancer 2021;68(2):e28610.
110. Millen GC, Arnold R, Cazier JB, et al. Severity of COVID-19 in children with cancer: Report from the United Kingdom Paediatric Coronavirus Cancer Monitoring Project. Br J Cancer 2021;124(4):754–9.

111. Palomo-Collí M, Fuentes-Lugo AD, Cobo-Ovando SR, et al. COVID-19 in Children and Adolescents With Cancer From a Single Center in Mexico City. J Pediatr Hematol Oncol 2020. https://doi.org/10.1097/MPH.0000000000002040.
112. Haslak F, Yildiz M, Adrovic A, et al. Management of childhood-onset autoinflammatory diseases during the COVID-19 pandemic. Rheumatol Int 2020;40(9):1423–31.
113. Calvo C, Udaondo C, Group tRDE-AW. COVID-19 in Children With Rheumatic Diseases in the Spanish National Cohort EPICO-AEP. J Rheumatol 2021. https://doi.org/10.3899/jrheum.201548.
114. Melgosa M, Madrid A, Alvárez O, et al. SARS-CoV-2 infection in Spanish children with chronic kidney pathologies. Pediatr Nephrol 2020;35(8):1521–4.
115. Marlais M, Wlodkowski T, Vivarelli M, et al. The severity of COVID-19 in children on immunosuppressive medication. Lancet Child Adolesc Health 2020;4(7):e17–8.
116. Marlais M, Wlodkowski T, Al-Akash S, et al. COVID-19 in children treated with immunosuppressive medication for kidney diseases. Arch Dis Child 2020. https://doi.org/10.1136/archdischild-2020-320616.
117. Pérez-Martinez A, Guerra-García P, Melgosa M, et al. Clinical outcome of SARS-CoV-2 infection in immunosuppressed children in Spain. Eur J Pediatr 2021;180(3):967–71.
118. El Dannan H, Al Hassani M, Ramsi M. Clinical course of COVID-19 among immunocompromised children: a clinical case series. BMJ Case Rep 2020;13(10). https://doi.org/10.1136/bcr-2020-237804.