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Impact of COVID-19 on Pediatric Immunocompromised Patients

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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.
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 (% positive) and Detection (%) | Patients Characteristics (%) | Clinical Course (%) | Treatment (%) | Outcomes (%) |
|--------------------------|--------------|-----------------------------------------------|-----------------------------|---------------------|--------------|--------------|
| Czech Republic, 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), 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, 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, 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, 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 |

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| Country and Study Period | Study Design | Testing Strategy (% and Detection (% Positive)) | Patients Characteristics (%) | Clinical Course (%) | Treatment (%) | Outcomes (%) |
|--------------------------|-------------|-----------------------------------------------|------------------------------|--------------------|---------------|--------------|
| Italy                     | 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 | 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 | 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 |
| Country | Study Design | Cohort Characteristics | Number of Patients | Diagnosis | Symptoms | Treatment | Outcomes |
|---------|--------------|------------------------|--------------------|-----------|----------|-----------|----------|
| Turkey | Physician survey; 66 centers | Asymptomatic (contact history, before HSCT, before surgery) and symptomatic; NP PCR or symptomatic + chest CT findings/contact history | 51 | 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 | Prospective, non-intervention | NP PCR conducted on all admitted pediatric oncology patients | 15 | 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 | Retrospective cohort; 1 center | Only symptomatic tested; PCR; positive cases (58) | 14 | 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 | Retrospective cohort; 9 centers | PCR (49), serology (33), not reported (18) | 69 | 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 | Retrospective + prospective registry study; 20 centers | Asymptomatic (before admission) and symptomatic; NP PCR | 54 | 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 |

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| Country and Study Period | Study Design | Testing Strategy (% and Detection (%) Positive) | Patients Characteristics (%) | Clinical Course (%) | Treatment (%) | Outcomes (%) |
|--------------------------|--------------|-----------------------------------------------|-----------------------------|--------------------|--------------|--------------|
| Mexico 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 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 Registry of COVID-19 in Childhood Cancer 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 (0.7), CP (0.7), TPV (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 | 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 |

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**Table 1 (continued)**

| Country and Study Period | Study Design | Testing Strategy (% and Detection (%) Positive) | Patients Characteristics (%) | Clinical Course (%) | Treatment (%) | Outcomes (%) |
|--------------------------|--------------|-----------------------------------------------|-----------------------------|--------------------|--------------|--------------|
| Mexico 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 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 Registry of COVID-19 in Childhood Cancer 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 (0.7), CP (0.7), TPV (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 | 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

| Survey type          | Centers | Patients | Symptoms | IST | Death/ICU |
|----------------------|---------|----------|----------|-----|-----------|
| 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

| Country     | Survey type          | Centers | Patients | Symptoms | IST | Death/ICU |
|-------------|----------------------|---------|----------|----------|-----|-----------|
| Turkey      | Parent survey 3/11/20–4/15/20 | N/A     | 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

| Country     | Survey type          | Centers | Patients | Symptoms | IST | Death/ICU |
|-------------|----------------------|---------|----------|----------|-----|-----------|
| Spain      | 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

| Country     | Survey type          | Centers | Patients | Symptoms | IST | Reduced IST | Death/ICU |
|-------------|----------------------|---------|----------|----------|-----|-------------|-----------|
| Spain      | 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

| Country     | Survey type          | Centers | Patients | Symptoms | IST | Reduced IST | Death/ICU |
|-------------|----------------------|---------|----------|----------|-----|-------------|-----------|
| Global     | 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)
| 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**[^1]  
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**[^1]  
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**[^1]  
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 |

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[^1]: Impact of COVID-19 on Pediatric Immunocompromised
| Country and Study Period | Study Design | Testing Strategy (%) and Detection (%) Positive | Patients Characteristics (%) | Clinical Course (%) | Treatment (%) | Outcomes (%) |
|--------------------------|-------------|-----------------------------------------------|-----------------------------|---------------------|--------------|-------------|
| Other immunocompromised cohorts |
| Spain117 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 Emirates118 | 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; HCV, hepatitis C virus; HD, high-density lipoprotein; HEM, hemoglobin; HIV, human immunodeficiency virus; HLA, human leukocyte antigen; HO, hematologic-oncologic; HSCT, hematopoietic stem cell transplant; IBD, inflammatory bowel disease; IGF, immunodeficiency; IGVH, immunoglobulin heavy chain; IL-1RA, interleukin-1 receptor antagonist; IL-6, interleukin-6; IMM, immune function; INN, international nonproprietary name; IT, intrathecal; JDM, juvenile dermatomyositis; JIA, juvenile idiopathic arthritis; LC, leukemia; LCH, Langerhans cell histiocytosis; LCV, lymphocyte count; MDS, myelodysplastic syndrome; MFG, maternal, fetus, and gestational; MIS, multisystem inflammatory syndrome; MS, multiple sclerosis; 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-aphtous stomatitis-pharyngitis-adenitis; RDV, remdesivir; SCID, severe combined immunodeficiency; SLE, systemic lupus erythematosus; SOX, solid organ transplant; 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.\textsuperscript{4–6} This recommendation was based on the presumed risk of nosocomial transmission, although data are limited.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{9}

\textbf{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.\textsuperscript{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.\textsuperscript{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. 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. 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. 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. 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. 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. 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 ≥12 years and weighing ≥40 kg) requiring supplemental oxygen and through an EUA for hospitalized children weighing ≥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. 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. 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, bamlanivimab plus etesevimab, and casirivimab plus imdevimab for nonhospitalized adult and pediatric patients (≥12 years and weighing ≥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. 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.

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. 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) have antiviral properties while others (eg, tocilizumab, dexamethasone) 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. 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.

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). However, immunocompromised status and poor outcomes have not been reported during the SARS-CoV-1 and Middle East respiratory syndrome coronavirus (MERS-CoV) epidemics. This somewhat paradoxical 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. 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. 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.

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. In contrast, IBD and rheumatology adult patients taking biologics and Janus kinase inhibitors displayed no increased incidence of severe disease. 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.

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. These protective features may be minimized in some immunocompromised populations as ACE-2 can be overexpressed in some patients with IBD and systemic lupus erythematosus (SLE). 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. 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.

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. 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. However, pediatric patients with nonscere 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. 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. 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.

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. 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. 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. 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.

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. 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. A survey of SOT and HSCT centers in Europe reported that two-third of centers reduced their transplant activity. However, pediatric kidney transplants in the United States has largely returned to baseline after the initial surge of COVID-19. In the United Kingdom, restrictions on endoscopy procedures resulted in most pediatric patients being diagnosed with “presumed IBD” without histologic confirmation. IBD admissions for new diagnoses and endoscopic re-evaluation were also significantly reduced during the lockdown in Italy.

In attempts to maintain access to care while minimizing infectious exposure and conserving personal protective equipment, subspecialty providers pivoted toward telemedicine. Expansion of telemedicine services was greatly aided by changes in reimbursement policies during the COVID-19 pandemic. 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. 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. 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. 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. 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 health care. 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.

In China and South Korea, 20% of pediatric IBD patients suffered disease exacerbation when infliximab infusions were delayed. 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. Early guidance in pediatric rheumatology patients stressed...
continuing current immune suppression to avoid disease flare. However, concerns over SARS-CoV-2 also led to hesitancy to starting new immune suppression with worsening disease 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. In addition, drug shortages forced changes in management and mandated strategic planning to preserve doses for critical care. 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. 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.

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.

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 with the Janssen Biotech COVID-19 vaccine receiving an EUA in February 2021. With the exception of HIV, patients with immune deficiency were largely excluded from the clinical trials. 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. 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. 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. It was also noted that flares were more common in patients with 4-week pauses of their methotrexate around the time of vaccination. 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. 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.

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. 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. 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. 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.

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.

**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. 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.

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