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Review
Immunizing the imperfect immune system
Coronavirus disease 2019 vaccination in patients with inborn errors of immunity
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ABSTRACT
Objective: To update clinicians on current evidence regarding the immunogenicity and safety of coronavirus disease 2019 (COVID-19) vaccines in patients with inborn errors of immunity (IEI).

Data Sources: Peer-reviewed, published studies in PubMed, clinical trials listed on ClinicalTrials.gov, and professional organization and governmental guidelines.

Study Selections: Literature searches on PubMed and ClinicalTrials.gov were performed using a combination of the following keywords: primary immunodeficiency, COVID-19, SARS-CoV-2, and vaccination.

Results: A total of 26 studies met the criteria and were included in this review. Overall, antibody responses to COVID-19 vaccination were found in 72% of study subjects, with stronger responses observed after messenger RNA vaccination. Neutralizing antibodies were detected in patients with IEI, though consistently at lower levels than healthy controls. Risk factors for poor antibody responses included diagnosis of common variable immunodeficiency, IEI with presence of autoimmune complications, agammaglobulinemia, and other causes of B cell aplasia, including recent treatment with rituximab. T cell responses were detectable in most patients with IEI, with poorer responses often found in patients with common variable immunodeficiency.

Safety of COVID-19 vaccines in patients with IEI was acceptable with high rates of reactogenicity but very few serious adverse events, including in patients with immune dysregulation.

Conclusion: COVID-19 vaccines are safe in patients with IEI and seem to be immunogenic in most individuals, with stronger responses found after messenger RNA vaccinations.

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Introduction
Since its emergence, coronavirus disease 2019 (COVID-19) has been a considerable threat to immunocompromised patients. From the earliest days of the ongoing COVID-19 pandemic, patients with underlying comorbidities or those with immunosuppression seemed to be at increased risk of severe disease.1,2 The subsequent development

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of effective vaccines targeting severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has been a critical tool in combating the pandemic. However, vaccine immunogenicity and safety in patients with inborn errors of immunity (IEI), in whom vaccine responses are often abnormal, have been an important topic of research. With the introduction of effective monoclonal antibodies and antiviral medications targeting SARS-CoV-2, including descriptions of increasing antibody titers against SARS-CoV-2 in immunoglobulin preparations, the question of appropriate prophylactic management of this population is an area of ongoing interest.

Here, we review the impact of the COVID-19 epidemic on patients with IEI and the current data regarding the use of COVID-19 vaccines in this patient population. Immunogenicity, efficacy, and safety in patients on immunosuppressive medications will also be briefly summarized given the frequent use of immunomodulatory therapy in patients with IEI, including passive immunity for patients unlikely to respond to vaccination. Finally, current recommendations for vaccinations in patient populations with IEI will be discussed.

**Coronavirus Disease 2019 in Patients With Inborn Errors of Immunity**

Multiple case series have addressed the elevated morbidity and mortality of COVID-19 in patients with IEI. Meyts et al. published an international case series of 94 patients with IEI representing a broad spectrum of immune defects. From this cohort, the clinical presentation and risk factors for severe COVID-19, including chronic lung disease and increased age, were similar to the general population. Intensive care unit admissions and mortality were elevated compared with the general population and trended toward increased severity at a younger age. On the basis of 100 patients, Shields et al. revealed that patients with IEI and secondary immunodeficiency were at increased risk of morbidity and mortality from COVID-19, including at younger ages, with risk factors for hospitalization including prophylactic antibiotics, chronic liver disease, and chronic lung disease. Many additional small case series have been published with similar observations, including a meta-analysis which revealed a 1.3-fold increased mortality in IEI. Certain IEIs have also been associated with particularly severe COVID-19, including patients who produce type I interferon autoantibodies or those with primary interferon pathway defects. Unfortunately, the pandemic has had a substantial impact on psychosocial functioning and mental health in patients with IEI and caregivers.

The immunologic response to natural SARS-CoV-2 infection has been investigated in patients with IEI. Kinoshita et al. published the first report of detectable serologic and cellular immunity to COVID-19 in patients with IEI. Hanitsch et al. reported 5 patients with IEI and severe or fatal COVID-19 who had prolonged viral shedding for up to 4 months and viremia in 3 of the 5 cases. All patients had observable CD4+ T cell responses, but no humoral response to SARS-CoV-2. Furthermore, persistent viral shedding and increased viral replication have been found in multiple immunocompromised populations, leading to concern about immunocompromised persons serving as a viral reservoir, with intrahost viral evolution leading to novel variants.

**Coronavirus Disease 2019 Vaccination in Healthy Individuals**

To date, 3 vaccines (Modern mRNA-1273, Pfizer BNT162B2, and Johnson and Johnson Ad26.COV2.S) are available in the United States after phase III clinical trials revealed robust prevention of COVID-19 disease. Although reactogenicity was common, all 3 vaccines were immunogenic and effective. There were 2 vaccines that used a 2-primary dose messenger RNA (mRNA) platform for healthy individuals (mRNA-1273 and BNT162B2), whereas the Ad26.COV2.S involves a single dose of a replication-incompetent human adenovirus type 26 vector. Thus far, in the setting of an excellent safety profile, BNT162B2 and mRNA-1273 have received full approval from the US Food and Drug Administration (FDA). Owing to ongoing concerns regarding increased risk of thrombosis with thrombocytopenia syndrome, emergency authorization of Ad26.COV2.S is now limited to individuals for whom other COVID-19 vaccines are not accessible or clinically appropriate, or in individuals who would not otherwise receive COVID-19 vaccination. In addition to serologic response, both CD4+ and CD8+ T cell responses have been detected in healthy individuals after vaccinations with each vaccine although CD4+ T cell responses are more robust than CD8+ T cell response (Fig 1).

Although safe and effective, immunogenicity of vaccines in the United States wanes in several months. T cell responses, however, seem to be more durable in healthy individuals than serologic response. Thus, booster vaccinations are now recommended for all COVID-19 vaccines per the US Centers for Disease Control as of March 2022. Emerging variants to SARS-CoV-2, most prominently Delta and Omicron, have also challenged vaccine efficacy. Recipients of BNT162B2 had detectable neutralizing antibodies to the Omicron variant, but with reduced titers compared with the ancestral virus, Beta or Delta variants. Similarly, Hoffman et al. found that mRNA vaccinations resulted in neutralization of Omicron variant, but with neutralizing titers 4 to 5 times lower than wild type virus, and Liu et al. revealed that cellular responses to the Delta and Omicron variants were more durable than antibody responses after vaccination with AdV26.COV2.S or BNT162B2.

**Response to Other Vaccinations in Inborn Errors of Immunity**

Increased risk of poor adaptive immune responses in patients with IEI leads to concern for decreased benefit from vaccination (Fig 1). Thus, immunogenicity of vaccines, including influenza, has been investigated in a spectrum of immunodeficiencies. Friedmann et al. found that only 1 of 17 patients with common variable immunodeficiency (CVID) had a humoral response to influenza vaccination. However, most patients with CVID produced ICOS+ T follicular helper cells and influenza virus-specific T cells, although at a lower magnitude than healthy controls (HC). Similar studies have also revealed detectable T cell responses after influenza vaccination in patients with CVID, primary antibody deficiency (PAD), and patients with X-linked agammaglobulinemia (XLA), including in patients with severely decreased to absent antibody responses. Some groups have hypothesized that T cell immunity, even in the setting of suboptimal serologic response, provides some protection against severe influenza disease in patients with IEI, and thus advocate for inactivated influenza vaccination.

**Response to Coronavirus Disease 2019 Vaccination in Inborn Errors of Immunity**

As of April 2022, 23 studies have been published evaluating immunogenicity of COVID-19 vaccination in IEI (Table 1). Delmonte et al. published one of the first cohorts comparing HC with 81 diverse patients with IEI and 2 patients with thymoma after completion of their primary vaccination series (2 doses of mRNA vaccination [n = 80] or 1 dose of AdV26.COV2.S [n = 3]). Of the patients with IEI, 85% developed detectable anti-S-antibodies after completing their primary vaccination series. Certain genetic diagnoses (including autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy [APECED]), previous use of rituximab, CD3+ T cell count less than 1000, and CD19+ B cell count less than 100 were associated with lower anti-spike immunoglobulin (IgG) titers. Similarly, Bergman et al. assessed antibody responses to the receptor binding domain of spike (RBD) in 90 patients with IEI within a larger case series of 449 immunocompromised patients after their primary vaccination series with BNT162B2. Of the patients with IEI, 73% seroconverted after...
vaccination, including 68% of patients with CVID and 78% of patients with monogenic disease. Two patients with hypomorphic severe combined immunodeficiency owing to ARTEMIS deficiency and a patient with CARD11 deficiency did not seroconvert, though overall patients with IEI had higher seroconversion than patients with solid organ transplants or chronic lymphocytic leukemia. In a follow-up study addressing salivary spike-specific immunoglobulin G (IgG) after vaccination, patients with IEI had weaker salivary responses, although overall salivary titers did correlate with serum neutralizing capacity.37 Lower seroconversion rates (33% for patients with CVID) were observed by Fernandez et al.38 In the largest case series to date, van Leeuwen et al assessed 505 patients with IEI after vaccination with mRNA-1273. Overall, mild antibody deficiencies and phagocytic defects had similar seroconversion to HCs, whereas more severe IEI, including CVID and combined immunodeficiency (CID), had lower seroconversion rates.39

In a longitudinal study in the United Kingdom, Ponsford et al described 304 patients with IEI, 49 of whom had molecularly confirmed SARS-CoV-2 infection.39 Of these individuals, 2 patients, both with CID, died of COVID-19 after vaccination, as compared with 9 patients who were unvaccinated. Furthermore, 67% had detectable anti-spike IgG, with humoral responses absent in 3 patients with XLA and 8 with CID, including the 2 deceased patients. Combined IgA and IgM deficiency or decreased B cell count (<50E6 cells/L) were associated with lower humoral vaccine response. Pfizer mRNA vaccination produced 50% higher postvaccination titers as compared with ChAdOx1-S NCoV-19, a replication deficiency adenoviral vector vaccine authorized internationally. Age and previous SARS-CoV-2 infection were not associated with significant differences in postvaccine titer (P < .05).39 Similarly, higher antibody titers were observed by Barmettler et al and Shields et al with mRNA vaccination.44,61 Immuno-

genicity of COVID-19 booster doses in IEI, for a total of 3 doses in patients receiving mRNA vaccines or 2 doses of Ad26.COV2.S, is also under investigation. Barmettler et al assessed 31 patients with PAD, 3 of whom received primary vaccination with Ad26.COV2.S after a heterologous mRNA vaccine boost. All patients increased mean anti-spike antibody levels to that of HC after primary series vaccination.44 This finding is similar to reports of improved immunogenicity after booster doses in patients with other mechanisms of immunosuppression.62

Several studies have used immunophenotyping to understand the impact of B cell dysfunction on serologic response to COVID-19 vacci-
nation in primary antibody deficiencies. In 17 patients with CVID assessed after BNT162B2 vaccination, Abo Helo et al found that patients with normal numbers of peripheral B cells and switched memory B cells mounted a serologic response. In contrast, only 5 of 7 patients with decreased switched memory B cells despite normal total B cells mounted a response, and responses were absent in patients without peripheral B cells.40 Similar results were found by Schultz et al, with number of naive B cells serving as a predictor for response to mRNA vaccination.41 Pulvirenti et al compared humoral responses in 34 previously SARS-CoV-2–infected patients with CVID before vaccination, 38 SARS-CoV-2–naive patients with CVID after 2 vaccinations with BNT162B2, and 20 SARS-CoV-2–convalescent patients with CVID after vaccination with BNT162B2.42 Detection of spike-specific IgG was more common post SARS-CoV-2 natural infec-
tion as compared with post-vaccination. Furthermore, antibody response was boosted by vaccination in previously SARS-CoV-2 –infected patients. The investigators postulated that SARS-CoV-2 infection primed a more efficient classical memory B cell response, whereas BNT162B2 vaccination alone induced noncanonical B cell responses in CVID characterized by CD19+CD27+CD24-CD38– atypical memory B cells with low binding capacity of IgG to spike protein.63 Similarly, Salinas et al investigated 41 patients with CVID and 6 with XLA after vaccination with BNT162B2. Anti-spike IgG was found to be higher in patients with previous infection, and vaccination boosted response in most patients for whom data were available. Patients with CVID generated atypical spike-specific B cells and unde-
tectable RBD-specific B cells, whereas HCs generated spike-specific typical memory B cells and RBD-specific B cells.58

Although early studies focused mainly on seroconversion, several studies have in addition evaluated functional activity of anti-spike antibodies. A hierarchy of functional tests have included the following: (1) anti-spike RBD antibody; (2) trimeric anti-spike antibody; (3)
| Author                  | Total number of patients with IEI | Vaccine                        | IEI diagnosis                      | Humoral immunity findings                        | Cellular immunity findings |
|-------------------------|----------------------------------|--------------------------------|------------------------------------|--------------------------------------------------|-----------------------------|
| Abo Helo et al          | 17                               | BNT162B2                       | CVID                               | 65%<sup>a</sup>                                  | NR                          |
| Amodio et al            | 21                               | BNT162B2                       | XLA, CVID, antibody deficiency     | 95% anti-spike RBD antibody, 86% anti-trimeric spike Ab | 76%<sup>a</sup>              |
| Antoli et al            | 28                               | BNT162B2, mRNA-1273, ChAdOx1   | CVID                               | 71.4%                                           | 71%                         |
| Arroyo-Sanchez et al    | 18                               | BNT162B2, mRNA-1273, ChAdOx1   | CVID                               | 83% any, 50% neutralizing                        | 83%                         |
| Barretttler et al       | 62                               | BNT162B2, mRNA-1273, Ad26.COV2.S | CVID                               | 59.7% after initial series; 14x higher after booster serologic response | NR                          |
| Barrios et al           | 17                               | BNT162B2                       | CVID                               | 70.5%                                           | 82%                         |
| Bradley et al           | 78                               | BNT162B2                       | CVID, XLA, CID, “monogenic”        | 73%                                              | 100%                        |
| Delmonte et al          | 81                               | BNT162B2, mRNA-1273, Ad26.COV2.S | SCID, APECED, CD40L, CID, CVID, FOXN1, hypogammaglobulinemia, MagT1, immune dysregulation, RAG, RALD, SASH3, STAT3 | 85%                                              | NR                          |
| Fernandez-Salinas et al| 33                               | BNT162B2                       | CVID                               | 33%                                              | NR                          |
| Goda et al              | 30                               | ChAdOx1                        | CVID                               | 83% Any after booster                            | 53% after ChAdOx1           |
| Gupta et al             | 10                               | BNT162B2                       | CVID                               | 80% Neutralizing after mRNA booster NR           |                             |
| Hagin et al             | 26                               | BNT162B2                       | XLA, hypogammaglobulinemia, STAT1 GOF, CVID, STAT3 LOF, FRAXI, Complement deficiency, IgG2 deficiency, CVID | 69%                                              | 73%                         |
| Jalil, Abraham et al    | 1                                | BNT162B2                       | CVID                               | 100%                                             | NR                          |
| Jalil, Rowane et al     | 1                                | BNT162B2                       | MagT1                              | 100%                                             | NR                          |
| Oshiro et al            | 1                                | Coronovac                      | XLA                                | 0%                                               | 100%                        |
| Pham et al              | 33                               | BNT162B2, mRNA-1273            | Hypogammaglobulinemia, XLA, CVID, SAD, Good syndrome, CD40L, CTLA4 haploinsufficiency, PIK3R1 deficiency, ataxia telangiectasia, ATGAP1 deficiency | 48% anti RBD-specific Ab; 6% with ACE2 receptor blocking activity > 50% | NR                          |
| Ponsford et al          | 156                              | BNT162B2, mRNA-1273, ChAdOx1   | CVID, hypogammaglobulinemia, CID, SAD, DiGeorge, XLA, STAT1 GOF, APECED, CD40L, CGD, CTLA4, complement 2 deficiency, ADA2, IFNGR1, CHI1, STAT3 LOF, idiopathic CD4+ T cell lymphopenia, WAS | 67%                                              | NR                          |
| Pulvirenti et al        | 58                               | BNT162B2                       | CVID                               | 34% post-vaccination; 100% post-infection and vaccination serologic response | 1/9 after immunization, 0/3 convalescent and immunized |
| Romano et al            | 5                                | BNT162B2, mRNA-1273            | CVID                               | 80%                                              | NR                          |
| Salinas et al           | 47                               | BNT162B2                       | CVID, XLA                         | 20%                                              | 70% CVID, 83% XLA           |
| Sauerwein et al         | 73                               | BNT162B2                       | CVID, PAD                          | 48% of CVID, 77% of PAD                           |                             |
| Schulz-Cherry et al     | 25                               | mRNA-1273, BNT162B2            | SAD, subclass deficiency, CVID, “other” | 73%                                              | NR                          |
neutralizing activity of antibodies against spike protein by pseudo-
neutralizing antibody/angiotensin-converting enzyme 2 receptor
blocking activity; and (4) in vitro viral neutralizing antibody assays.
Amodio et al investigated 21 patients with XLA, CID, and unclassified
antibody deficiency who received BNT162B2.41 Both HC and patients
with IEI had an increase in anti-spike antibody levels; however, levels
were lower in patients with IEI, and antitrimeric antibodies, which
correlate with neutralization, were present in HC but absent in
patients with IEI.66 The presence of less effective antibody by neu-
tralization or pseudoneutralization in patients with IEI was also
found in large case series recently published by Shields et al and
van Leeuwen et al.66,61 Similarly, in a study by Pham et al, 33
patients with humoral defects were evaluated post-BNT162B2 or
mRNA-1273 vaccine. Although 16 of 33 subjects had detectable
RBD-specific IgG responses, only 2 of 16 had an angiotensin-con-
verting enzyme 2 receptor block activity more than 50%, suggesting
that many patients with IEI have suboptimal neutralization activity
against SARS-CoV-2.64

Many studies have sought to evaluate spike-specific T cell
responses after vaccination, especially in patients who are expected
to have poor or absent antibody responses. Amodio et al revealed
that all HC had T cell responses, but only 16 of 21 patients with IEI
had detectable cellular immune responses. Of note, in the patients
with IEI who have a T cell response, the magnitude of their T cell
response seemed to be greater than HC which may be a compensa-
tory mechanism for poorer antibody responses.61 Similarly, Arroyo-
Sanchez et al evaluated 18 patients with CVID, including 1 patient
who received ChAdOx1-S.63,67 Although 83% of patients with CVID
also have an anti-spike T cell response, the magnitude of both anti-
bodies and cellular responses in CVID was lower than HC. Hagin
et al. published a series of 26 patients, including CID, immune dysregu-
lation, and XLA. They found that 73% of patients exhibited a cellular
response.60 With specific regard to cytotoxic CD8+ T cells, Gupta et al
revealed that SARS-CoV-2-specific tetramer+ CD8+ T cells and func-
tional CD8+ 107a− granzyme B− perforin+ T cells were significantly
lower in 5 patients with CVID after BNT162B2 compared with HC (P
<0.0003).60 Van Leeuwen et al also noted spike-specific T cell
responses that were comparable to HC by Ifn-γ release assay, with
exception of patients with CVID (67% responders vs 88% in HC).
Finally, in 168 patients with IEI evaluated by Shields et al, 46% of
individuals had detectable T cell responses. Importantly, the presence
of T cell response was associated with improved antibody responses.61

Though general vaccine response rates have been reassuring, the
durability of immunity in patients with IEI has been a critical ques-
tion. To this end, several recent studies have evaluated longitudinal
efficacy of COVID-19 vaccination in patients with IEI. Ponsford et al
noted that increased time since vaccination was associated with fall-
ing titers, similar to trends in HC. Shields et al also found a gradual
decline in titers in the 6 months after vaccination, although higher
titers were observed in patients who received BNT162b2 vs ChA-
dox1-S. Di Fusco et al evaluated the rate and severity of break-
through infections in immunocompromised patients who received
BNT162b2 vaccination during late 2020 to mid-2021. In their cohort,
7 of 3190 (0.22%) of patients with IEI had breakthrough infections in
the 8-month study period. This rate was comparable with patients
with rheumatologic conditions and patients receiving antimetabolite
therapy but lower than solid organ transplant recipients.68 There
were 11 breakthrough cases observed by Shields et al in a case series
of more than 500 patients with IEI, 10 of them occurred in recipients
of ChAdOx1-S.61

In addition to prevention, Bradley et al published a notable case
report of a male adult with Wiskott-Aldrich syndrome who had per-
sistent COVID-19 with undetectable humoral and equivocal T cell
response to SARS-CoV-2 on day 140 of illness who was subsequently
treated for COVID-19 with 2 doses of BNT162B2. Vaccines were well
tolerated. Two weeks after completion of his series, he had detectable

| Table 1 (continued) |
|---------------------|
| **Author**          | **Total number of patients with IEI** | **Vaccine** | **mRNA-1273** | **ChAdOx1-S** | **BCG** |
| Shields et al66     | 168                                    | 11          | 505          |              |        |
| Spigarelli et al66  | 100                                    | 20          | 40           |              |        |
| van Leeuwen et al66 | 168                                    | 11          |              |              |        |

**Abbreviations:** AE, adverse event; AGP, anti-gamma globulinemia; ARDS, acute respiratory distress syndrome; BNT162b2, messenger RNA-1273 vaccine; CID, common variable immunodeficiency; CVID, common variable immunodeficiency; CPC, COVID-19 convalescent plasma; HI, hemagglutination inhibition; IFN, interferon; IEI, inborn errors of immunity; IFN-γ, interferon γ; Ig, immunoglobulin; mRNA, messenger RNA; NR, not reported; P, percentage; RBD, receptor binding domain; RPOC, respiratory syncytial virus; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SCID, severe combined immunodeficiency; SMI, secondary malignant histiocytosis; T1D, type 1 diabetes mellitus; XLA, X-linked agammaglobulinemia.
anti-spike cellular and humoral responses with declining SARS-CoV-2 viral load on respiratory polymerase chain reaction. He was finally SARS-CoV-2 virus clear at 72 days after his first vaccine dose and 218 days after his initial positive test result.47

Safety of Coronavirus Disease 2019 Vaccinations in Inborn Errors of Immunity

To date, COVID-19 vaccines have had an excellent safety profile in patients with IEI (Table 2). Reactogenicity to mRNA vaccines is common in patients with IEI and seems to occur more frequently than in the general population (Table 2). Common symptoms include fever, myalgias, and fatigue, but severity does not seem to be increased in patients with IEI. Given the high rates of reactogenicity and the rare inflammatory events after COVID-19 vaccines, safety of the vaccines in patients with IEI with autoimmune or autoinflammatory complications has been a particular concern for clinicians. Importantly, several publications have noted limited to no marked flaring of autoinflammatory disorders after COVID-19 vaccination. Peet et al evaluated 130 patients with a variety of autoinflammatory disorders who received one or more doses of COVID-19 vaccines (ChAdOx1-S or BNT162B2), and no serious adverse reactions or hospitalizations were reported after vaccination.69 Of note, most of these patients did not interrupt immunomodulatory therapy during vaccination. Furthermore, substantial inflammatory disease flares have not been found after receipt of mRNA vaccines. In the limited number of patients with IEI complicated by autoimmunity or primary immunodysregulatory disorders, vaccinations have been similarly well tolerated without worsening of autoimmune conditions. In addition, studies of patients with autoinflammatory conditions including systemic lupus erythematosus, rheumatoid arthritis, and inflammatory bowel disease have described excellent tolerance of COVID-19 vaccines without notable induction of disease flares.70–72

Serious adverse events after COVID-19 vaccination have included anaphylaxis, myocarditis, idiopathic thrombocytopenic purpura, and vaccine-associated immune thrombotic thrombocytopenia.74–76 These events have been extremely rare, and to date, there has been no evidence that patients with IEI are at higher risk for adverse events after COVID-19 vaccinations. As immune thrombocytopenia (ITP) and vaccine-associated immune thrombotic thrombocytopenia seem to be antibody mediated, it is possible that use of immunoglobulin replacement therapy may provide some risk reduction against these adverse effects. However, given the small number of patients with IEI who have been vaccinated, the true risk of these adverse effects remains unclear. ITP and vaccine-induced thrombotic thrombocytopenia (VITT) seem to be more highly associated with adenoviral vaccines, and accordingly, in patients with thrombotic risks or history of ITP, avoidance of adenoviral vaccines would be prudent.

Immunosuppression and Coronavirus Disease 2019 Vaccine Responses

Many patients with IEI require immunosuppressive therapy for management of autoimmune or autoinflammatory disease, and many such therapies could affect the efficacy and safety of vaccines. B cell-targeting therapies have well described impacts on antibody production, and T cell-targeting therapy may decrease induction of cytotoxic responses and T follicular helper cells. Delmonte et al noted that overall use of immunomodulators in patients with IEI did not significantly affect the chances of antibody responses after COVID-19 vaccination, though patients treated with rituximab in the previous 5 years uniformly failed to generate SARS-CoV-2 antibodies after 2 vaccinations (P > .05).36 Notably, 4 patients receiving Janus kinase inhibitors had intact antibody responses. Studies of COVID-19 vaccine responses in non-IEI immunosuppressed populations have revealed
similar outcomes. However, data from van Leeuwen et al revealed that COVID-19 vaccine nonresponders with IEI had statistically significantly increased autoimmune cytopenias, granulomatous lymphocytic interstitial lung disease, and use of immunosuppressive medications, including in a multivariable logistic regression model, as compared with responders (P < .0001). A meta-analysis by Ramirez et al of more than 11,000 patients with autoimmune conditions revealed humoral and cellular responses in 85% of patients overall, but neutralizing antibody responses were less robust than in NC. Anti-B cell therapy was also associated with poorer antibody responses (37% overall from 9 studies) consistent with data from patients with IEI. 

Immunoglobulin Replacement Therapy and Coronavirus Disease 2019 Vaccination

Patients with IEI frequently receive immunoglobulin replacement therapy (IGRT) providing protection against many circulating and vaccine-preventable illnesses. The delay from plasma donation to product (typically approximately 9 to 10 months) may affect coverage of emerging viral variants. In addition, IGRT adversely affects active vaccination against pathogens that are targeted by donor antibodies. Studies evaluating SARS-CoV-2 antibody titers in commercial immunoglobulin products have revealed an increasing trend in titers over time, but with lot-to-lot variability. A more recent study by Miller et al revealed that the upward trend in neutralizing antibodies has continued in commercially available products in 2021. Thankfully, Delmonte et al did not note any difference in response to COVID-19 vaccination in patients with IEI who were receiving IGRT vs those who were not. Many other case series similarly revealed preserved antibody and cellular responses after vaccination in patients receiving IGRT. Given the safety of the vaccines in patients with IEI and the potential benefit of cellular responses, it is felt that vaccination of those receiving IGRT is advisable. Longitudinal studies of SARS-CoV-2 titers in commercially available immunoglobulin preparations will be useful to understand the potential impact of IGRT on diagnostics and risk of COVID-19 in patients receiving this therapy.

Passive Immune Therapies Against Coronavirus Disease 2019

Passive immunotherapies, including monoclonal antibodies targeting the spike RBD of SARS-CoV-2, have been developed and are indicated for acute treatment, post-exposure prophylaxis, and longer-term preventative therapy of COVID-19. Preventative therapy, currently authorized as tixagevimab co-packaged with cilgavimab, is specifically intended for those who are not expected to mount adequate responses to active vaccination, and therefore would be appropriate for patients with IEI. During the delta variant surge, use of monoclonal antibody therapy for breakthrough infections in high-risk patients reduced hospitalization by 77%, and the number needed to treat to prevent hospitalization of 1 immunocompromised patient was 12. Furthermore, in patients with high risk of severe COVID-19 owing to APECED, monoclonal antibody therapy has been used successfully to prevent disease progression. Unfortunately, evasion of monoclonal antibody therapy with emerging variants develops rapidly. High-risk patients were found to have 74% reduction in progression to severe COVID-19 after receiving sotrovimab; however, the FDA has recently reversed emergency use authorization because of lack of efficacy against emerging Omicron subvariants. In contrast, bebtelovimab has recently received FDA emergency use authorization and maintains activity against the novel Omicron BA.2 subvariant. The full impact of monoclonal therapies on vaccine efficacy remains unclear, though case reports of successful seroconversion with vaccination post-monoclonal antibody therapy support active immunization in this setting. Presently, vaccine doses are recommended at least 2 weeks before giving a preventative monoclonal antibody therapy to minimize the chance of interference (Fig 2), though large studies of vaccine efficacy with or without monoclonal antibody therapy have not been performed.

Limitations and Future Needs

Much progress has been made to understand COVID-19 vaccine responses in patients with IEI, but many questions remain unanswered. Ideal vaccine regimens, timing of boosters, and the duration of protection after vaccination in IEI remain unclear. To date, most of the studies have been conducted in the United States and Europe, and therefore little data are available regarding the numerous additional platforms and vaccines used around the world. At this time, only 1 study in 1 patient addresses Coronovac, which uses a whole inactivated virus. The preponderance of data are from mRNA vaccines which pose an international vaccination challenge given the need for cold chain and freezer storage. With the prevalence of IEI globally, and the observed increased immunogenicity of mRNA vaccinations in this patient population, distribution and availability to patients with immunodeficiency are critical. Fortunately, preliminary data on uptake of COVID-19 vaccination in patients with IEI are encouraging. Ponsford et al reported that 93% of 302 patients with IEI in the United Kingdom had received their second dose by September 2021, whereas only 14 patients declined. Efficacy and immunogenicity may be mildly compromised in patients with IEI, but COVID-19 vaccines with available data seem to have a favorable safety profile, even in the setting of autoimmune and autoinflammatory diseases. Thus, although benefit may be limited in

Figure 2. Proposed workflow for active and passive COVID-19 immunization in patients with IEI. COVID-19, coronavirus disease 2019; IEI, inborn errors of immunity; mRNA, messenger RNA; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.
In a Nutshell

- The vast majority of patients with IEI will have at least some response to COVID-19 vaccines which supports the use of vaccination broadly in this population.
- Patients with CID, CVID, or other PAD, especially those with abnormal B cell phenotyping, are likely to have decreased cellular and/or humoral vaccine responses.
- Prior use of rituximab is associated with decreased vaccine response, but vaccine responses are generally preserved with other immunosuppressive or immunomodulatory medications.
- Thus far, COVID-19 vaccines have an excellent safety profile in patients with IEI.
- In addition to active vaccination, passive immunization may be provided with monoclonal antibodies or Ig replacement therapy although protection may vary.
- mRNA vaccines demonstrate increased immunogenicity and durability as compared to other platforms.
- Vaccine boosters appear to improve immunogenicity in patients with IEI.

Some patients, risk is also minimal for non-live vaccination platforms. Vaccination, especially if an mRNA vaccine is available, should be strongly recommended to most, if not all, patients with IEI. Given the stronger immunogenicity observed in mRNA vaccines (mRNA-1273 and BNT162B2) compared with adenovirus-based vaccines, including in patients with IEI, and the association between adenoviral vaccines and very rare but serious complications owing to VITT, mRNA vaccines should be preferred in the IEI population when available.

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## Table 1
Online Resources for COVID-19 Vaccination in IEI

| Organization | Web resource |
|--------------|--------------|
| American Academy of Allergy Asthma & Immunology | [https://www.aaaai.org/Tools-for-the-Public/Conditions-Library/Related-Conditions/COVID-resources](https://www.aaaai.org/Tools-for-the-Public/Conditions-Library/Related-Conditions/COVID-resources) |
| American Cancer Society | [https://www.cancer.org/treatment/treatments-and-side-effects/physical-side-effects/low-blood-counts/infections/covid-19-vaccines-in-people-with-cancer.html](https://www.cancer.org/treatment/treatments-and-side-effects/physical-side-effects/low-blood-counts/infections/covid-19-vaccines-in-people-with-cancer.html) |
| American College of Allergy, Asthma, & Immunology | [https://acaai.org/news/allergy/](https://acaai.org/news/allergy/) |
| American College of Rheumatology | [https://www.rheumatology.org/Portals/0/Files/COVID-19-Vaccine-Clinical-Guidance-Rheumatic-Diseases-Summary.pdf](https://www.rheumatology.org/Portals/0/Files/COVID-19-Vaccine-Clinical-Guidance-Rheumatic-Diseases-Summary.pdf) |
| European Society for Immunodeficiency | [https://primaryimmune.org/news/covid-19-update-vaccines-monoclonal-antibodies-antivirals](https://primaryimmune.org/news/covid-19-update-vaccines-monoclonal-antibodies-antivirals) |
| International Organization for the Study of Inflammatory Bowel Disease | [https://ihdbd.org/covid-19-information](https://ihdbd.org/covid-19-information) |
| International Society of Heart and Lung Transplantation | [https://ishlt.org/wp-content/uploads/2021/01/gutjnl-2020-324000.full_pdf](https://ishlt.org/wp-content/uploads/2021/01/gutjnl-2020-324000.full_pdf) |
| National Comprehensive Cancer Network | [https://www.nccn.org/covid-19](https://www.nccn.org/covid-19) |
| US Centers for Disease Control and Prevention | [https://www.cdc.gov/coronavirus/2019-ncov/vaccines/recommendations/immuno.html](https://www.cdc.gov/coronavirus/2019-ncov/vaccines/recommendations/immuno.html) |
| World Health Organization | [https://www.who.int/publications/i/item/WHO-2019-nCoV-vaccines-SAGE_recommendation-immunocompromised-persons](https://www.who.int/publications/i/item/WHO-2019-nCoV-vaccines-SAGE_recommendation-immunocompromised-persons) |

Abbreviations: COVID-19, coronavirus disease 2019; IEI, inborn errors of immunity.