Review article

Impact of SARS-CoV-2 infection and COVID-19 on patients with inborn errors of immunity

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Since the arrival of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in December 2019, its characterization as a novel human pathogen, and the resulting coronavirus disease 2019 (COVID-19) pandemic, over 6.5 million people have died worldwide—a stark and sobering reminder of the fundamental and nonredundant roles of the innate and adaptive immune systems in host defense against emerging pathogens. Inborn errors of immunity (IEI) are caused by germline variants, typically in single genes. IEI are characterized by defects in development and/or function of cells involved in immunity and host defense, rendering individuals highly susceptible to severe, recurrent, and sometimes fatal infections, as well as immune dysregulatory conditions such as autoinflammation, autoimmunity, and allergy. The study of IEI has revealed key insights into the molecular and cellular requirements for immune-mediated protection against infectious diseases. Indeed, this has been exemplified by assessing the impact of SARS-CoV-2 infection in individuals with previously diagnosed IEI, as well as analyzing rare cases of severe COVID-19 in otherwise healthy individuals. This approach has defined fundamental aspects of mechanisms of disease pathogenesis, immunopathology in the context of infection with a novel pathogen, and therapeutic options to mitigate severe disease. This review summarizes these findings and illustrates how the study of these rare experiments of nature can inform key features of human immunology, which can then be leveraged to improve therapies for treating emerging and established infectious diseases. (J Allergy Clin Immunol 2023;151:818-31.)

Key words: *SARS-CoV-2, COVID-19, inborn errors of immunity, primary immune deficiencies, immune dysregulation, type I IFN signaling, cytokine storm*

Inborn errors of immunity (IEI) are diseases caused by germline pathogenic variants, typically in single genes.[1-4] IEI have an incidence of ~1 per 5,000 to 10,000 individuals.[1-5] Currently, pathogenic variants in more than 480 genes have been identified that cause IEI. These variants can lead to loss of expression, complete (null) or partial (hypomorphic) loss of function, gain of function (GOF; hypermorphic), haploinsufficiency, or dominant negative function of the encoded protein. IEI can present as autosomal dominant (AD; heterozygous variants), autosomal recessive (AR; homozygous/compound heterozygous variants), or X-linked (XL) recessive (hemizygous in male subjects; homozygous or heterozygous with skewed X inactivation in female subjects) conditions.[4,6] However, some IEI have incomplete penetrance, with a significant proportion of individuals carrying some pathogenic variants compromising protein function remaining unaffected.[7] The mechanism or mechanisms underlying incomplete penetrance remain unclear but may involve epistatic effects of modifier genes, epigenetics, and/or variants in additional genes.[7] It is also worth noting that a monogenic cause for the most common IEI—common variable immunodeficiency (CVID)—has only been determined for ~20-30% of affected individuals,[8] thus suggesting that most cases of CVID are likely to be oligo- or polygenic.

IEI are characterized by defects in immune cell development, and/or impaired innate and adaptive immune function of hematopoietic and nonhematopoietic cells. Consequently, affected individuals are highly susceptible to severe, recurrent, and sometimes fatal infections.[4,6] As a result of this immunodeficient state, vaccine efficacy can also be compromised in IEI, resulting in affected individuals having modest, if any, vaccine-induced immunity against infectious diseases. Thus, IEI patients continue to be susceptible to infection as well as being vulnerable to disease as a result of live-attenuated vaccines.[9]

Although historically considered to be immune deficiencies manifesting as infections, the clinical spectrum of IEI is

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Abbreviations used
APECED: Autoimmune polyendocrinopathy candidiasis ectodermal dystrophy
AR: Autosomal recessive
BTK: Bruton tyrosine kinase
CFR: Case fatality rate
COVID-19: Coronavirus disease 2019
CVID: Common variable immunodeficiency
GOF: Gain of function
ICU: Intensive care unit
IEI: Inborn errors of immunity
JAK: Janus kinase
mAb: Monoclonal antibody
SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2
XL: X linked
XLA: XL agammaglobulinemia

extremely broad, with autoimmunity, autoinflammatory diseases, allergy, bone marrow failure, and/or malignancy also being common maladies of patients.[1,3,4,6,10,11] Although most are individually rare, IEI are collectively common[5] and have enabled the delineation of fundamental roles of individual genes, proteins, signaling pathways, and cell types in immune cell development; immune homeostasis and regulation; antitumor immunity; and host defense against infectious diseases.[1-3] Thus, IEI provide insights into the molecular pathogenesis of more common diseases and have led to the development of targeted therapies for various immune dyscrasias.[1-3,12]

SARS-CoV-2 AND THE COVID-19 PANDEMIC

Coronaviruses have caused pandemics in the human population for decades.[13] Certainly we would have a short memory if we failed to recall the deadly toll of the original SARS coronavirus outbreak in 2002-3.[13] In December 2019, the novel coronavirus severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) emerged from Wuhan, China, and then spread rapidly to cause a catastrophic global pandemic.[14] At the time of writing, more than 650 million people have been infected and at least 6.6 million people have died from SARS-CoV-2 infection (www.covid19.who.int/, www.worldometers.info/coronavirus/). The clinical spectrum of coronavirus disease 2019 (COVID-19) due to SARS-CoV-2 infection ranges from asymptomatic to life-threatening disease. The global case fatality rate (CFR) due to SARS-CoV-2 infection is currently ~1.1%, but this varies widely across different countries, ranging from 0.1% to 5%, and even up to 10% to 15% for some regions (www.ourworldindata.org/grapher/deaths-covid-19-vs-case-fatality-rate). Importantly, early during the pandemic, when viral screening was restricted to symptomatic individuals and vaccines were still 12 to 18 months away, the average global CFR was 5% to 7%, and as high as 10% to 20% in the United Kingdom and some European countries[15,16] (www.ourworldindata.org/grapher/deaths-covid-19-vs-case-fatality-rate).

Several risk factors have been identified for developing severe disease, as defined by the World Health Organization. These include primarily age, with the frequency of severe cases/death escalating with each decade of increasing age. For example, the mortality rate for people aged <50 years was <1.0%; for individuals aged 60-80 or more years, the mortality rate was ~4% to 25%. Male sex as well as comorbidities such as cardiovascular/pulmonary disease, obesity, diabetes, and liver/kidney dysfunction also have an impact, albeit less than age.[16-19] Correlates of severe disease and mortality include lymphopenia, increased levels of inflammatory mediators, cytokines, chemokines,[18,20-26] and complement components,[27-29] which indicate the intense immune activation and inflammation that can lead to severe and potentially fatal SARS-CoV-2–induced cytokine storm and consequent tissue pathology.

In healthy individuals, SARS-CoV-2 infection induces functional $CD4^+$ and $CD8^+$ T cells and memory B cells specific for viral epitopes, as well as neutralizing antibodies.[30-39] These correlates of protective immunity are detectable 1 or 2 weeks after infection and persist at peak levels for 3 to 4 months. However, in most cases, levels of neutralizing IgG and of SARS-CoV-2–specific memory B cells and T cells dramatically wane 8 to 12 months after infection,[32-34,36-40] potentially compromising host defense against subsequent infections. Furthermore, several SARS-CoV-2 variants that have acquired mutations in the immunodominant spike domain, thus rendering these variants less susceptible to antibody-mediated neutralization, have emerged.[41] Waning of acquired immunity after natural infection, combined with immune-escape variants, are a significant challenge in controlling SARS-CoV-2 infection, resulting in COVID-19 continuing to represent a significant global health risk.

SARS-CoV-2 INFECTION, COVID-19, AND IEI

Since the beginning of the pandemic, it was recognized that people diagnosed with an IEI were potentially at risk of developing severe COVID-19. Over the past 2 years, outcomes of SARS-CoV-2 infection have been reported for ~1330 individuals with IEI. These studies range from reports of single cases or small numbers of patients[42-88] to cohort studies from Iran,[89-91] Turkey,[92-94] Brazil,[95,96] Israel,[97] Italy,[98-101] Spain,[102] the United Kingdom,[15,103,104] Mexico,[105] Denmark,[106,107] Poland,[108] the Czech Republic,[109] France,[110] and the United States,[111-114] as well as an international survey of 94 patients followed in 12 countries.[115] These studies have revealed key outcomes of SARS-CoV-2 infection in IEI and defined fundamental requirements for host defense against infection.

Patients with IEI infected with SARS-CoV-2

Affected patients have been found to represent most, if not all, categories of IEI as defined by the International Union of Immunological Societies Committee (Table I).[6] Of the ~1330 patients reported so far, approximately 60% have antibody deficiencies, consistent with antibody deficiency being the most common IEI.[6,8] This includes CVID, hypogammaglobulinemia, and specific antibody and immunoglobulin subclass deficiencies due to unknown genetic causes[8] (~600 cases), as well as XL (*BTK* pathogenic variants) and AR (eg, *TCF3* pathogenic variants) agammaglobulinemia (~110 cases) and a series of patients with pathogenic variants in single genes known to disrupt B-cell function and humoral immunity, such as *NFKB1, NFKB2, PIK3CD,* or *PIK3R1* (Table I). Outcomes of SARS-CoV-2 infections have also been reported for patients with the following:

- Severe combined (*JAK3, RAG, IL7RA, DCLRE1C*) or combined (*CD40LG, RASGRP1, RELB, STK4, WAS, ICOS, ATM, IKBKG, STAT3 DN, PGM3*) immunodeficiencies.

TABLE I. SARS-CoV-2 infection in defined IEI

Type of IEI	Gene defect/IEI	Approximate no. of patients	Study or studies
Severe combined immunodeficiency (n = 25)	*JAK3*	1	70
	RAG	3	92, 97, 115
	IL7RA	1	91, 94
	DCLRE1C	1	49
	IL2RG	4	77, 95, 115
	CD3D	1	105
	Not specified	15	95, 99, 108
Combined immunodeficiency (n = 91)	*STAT3 DN*	7	103, 109, 115, 176
	PGM3	1	102, 115
	ARPC1B	1	47, 105, 115
	WAS	8	47, 48, 95, 99, 100, 103, 105, 108, 109, 115
	ZAP70	1	115
	CD40L	9	94, 95, 97, 103, 109, 111, 116, 143
	RASGRP1	1	92
	CARD11	1	92, 103
	RELB	3	97, 116
	STK4	1	89
	DNMT3B/NBS1	4	89, 91, 94
	ICOS	1	15, 103
	IKBKG (NEMO)	3	72, 78, 94
	ATM	11	91, 92, 94, 99, 100, 102, 103, 108
	Di George syndrome	16	99, 100, 108
	Not specified	23	89, 92, 94, 95, 99, 103, 108
Predominantly antibody deficient (n = 714)	CVID*	589	51, 52, 58, 71, 75, 83, 92, 94, 95, 97-100, 102-109, 111-115, 143
	BTK	98	15, 46, 51, 53, 55, 60, 61, 66, 73, 85, 86, 91, 92, 94, 95, 97-100, 102-105, 108, 109, 111, 115, 116, 139, 140, 143
	AR agammaglobulinemia	9	99, 100, 115
	PIK3R1/PIK3CD GOF	7	64, 82, 91, 95, 99, 100, 115
	NFKB1	4	15, 91, 103, 111, 115
	NFKB2	3	43, 103, 115, 143
	IKZF1	1	91
Immune dysregulation (n = 64)	*AIRE* (APS1/APECED)	29	57, 84, 94, 118, 122, 149
	CTLA4	7	15, 97, 103, 115, 177
	LRBA	3	92, 97, 115
	SOCS1	1	76
	STAT3 GOF	1	111
	RAB27A	1	89
	CD70	1	89
	ALPS	5	95, 99, 102, 108
	XLP (*XIAP, SH2D1A*)	4	63, 95, 108, 109, 115
	PRKCD	1	115
	RLTPR/CARMIL2	2	94
	CD137	1	94
	STXBP2	2	88, 94
	Not specified/other	6	92, 99, 105, 108
Phagocytic defects, bone marrow failure (n = 36)	Chronic granulomatous disease (*CYBB; NCF2*)	28	15, 59, 89, 95, 97, 102, 103, 105, 108, 115
	GATA2	2	15, 103, 115
	DNAJC21	1	115
	Not specified/other	5	92, 99
Innate immune defects (n = 75)	*TLR3/UNC93B/TRIF/IRF3/IRF7/IRF9/TBK1*	23	65, 68, 69, 120, 123
	IFNAR1/2	7	42, 56, 87, 126
	STAT1/TYK2	2	126

(Continued)

TABLE I. *(Continued)*

Type of IEI	Gene defect/IEI	Approximate no. of patients	Study or studies
	TLR7	22	90, 124-126
	MYD88/IRAK4	8	45, 81, 95, 99, 102
	IFNGR1/IFNGR2/IL12RB1	5	54, 79, 95, 111, 115
	STAT1 GOF	6	50, 92, 95, 102, 109, 115
	CXCR4 GOF	2	94, 95
Autoinflammatory disorders (n = 96)	*MEFV*	68	93, 95, 110, 115
	IL1RN	1	89
	Aicardi-Goutières syndrome (*RNASEH2B, SAMHD1*)	5	15, 99, 100, 115
	TNFAIP3	1	15
	NLRP1, NLRP3, NLRP12	3	91, 95
	IL36RN	1	74
	ADA2	1	94
	Not specified/other	16	95, 108
Complement deficiencies (n = 55)	Hereditary angioedema (pathogenic *SERPING* variants), C3 deficiency, other	55	15, 91, 95, 96, 109
Phenocopies of IEI	Good syndrome	13	83, 100, 103, 105, 109
	Autoantibodies to type I IFNs	Many!	128-136

*Including hypogamma, immunoglobulin subclass deficiency, and specific antibody deficiency.

- Immune dysregulatory disorders (*STAT3* GOF, *AIRE, CTLA4, CD70, LRBA, RAB27A, SH2D1A, XIAP, RLTPR/CARML2, CD137, STXBP2, ALPS*).
- Phagocytic defects (chronic granulomatous disease, *GATA2*).
- Innate immune defects (*IFNGR1, IFNGR2, IFNAR1, IFNAR2, IL12RB1, IRAK4, MYD88, STAT1* GOF, *CXCR4, TBK1, TLR3, TLR7, IRF3, IRF7, IRF9*).
- Autoinflammatory disorders (*MEFV, TNFAIP3, IL36R, ADA2*).
- Complement deficiencies.
- Phenocopies of IEI.

A complete reference listing is provided in Table I.

Clinical features in IEI after SARS-CoV-2 infection

The clinical presentation of SARS-CoV-2 infection in patients with IEI resembled that of the general population[16,19] inasmuch that symptoms frequently include fever, cough, headache, upper respiratory symptoms, fatigue, and dyspnea.[15,89,91,92,94,95,97,99,102,103,105,106,108,109,115] Similarly, risk factors for hospital/intensive care unit (ICU) admission and developing severe and/or fatal disease were also consistent with those determined from studies of the general population. Thus, the most severe disease was observed in older patients with IEI as well as those with pre-existing comorbidities, such as previous infection; lung, kidney, heart, or gut disease, diabetes, and obesity; or after solid organ or hematopoietic stem cell transplantation.[43,58,89,91,92,94,95,98,103,105,106,108,111,112,115] Other predictors of severe disease in IEI patients included leukopenia (reduced numbers of B, $CD4^+$ T, and natural killer cells) and hypogammaglobulinemia/low IgG trough levels before infection, and increased levels of markers of systemic inflammation after infection.[43,46,58,66,103,109,111,114] Interestingly, and similar to the general population, ~10% to 20% of infected IEI patients were asymptomatic, and up to another ~30% to 50% developed only mild disease.[15,89,90,92-95,97-106,108-115]

Despite such similarities in disease presentation and risk factors for the general population and IEI patients, there were notable differences. First, the age of affected IEI patients was markedly younger than the general population (~28 years vs ~50-plus years).[16,44,79,81,84,89,91,93-95,100,102-104,108-110,115] There were also differences in age at infection for different IEI. Thus, SARS-CoV-2–infected patients with CVID, periodic fevers, or complement defects were generally older, and patients with defects in innate immune cell signaling due to pathogenic variants in *IRAK4, MYD88,* or *IFNAR1/IFNAR2* were generally younger, than the entire cohort of published IEI patients (Fig 1, *A*). Second, the proportion of IEI patients admitted to ICU—including younger individuals—was substantially higher than the general population (10-30% vs 2-5%).[15,16,44,81,91,92,94,102,105,109,111,115] Third, duration of disease—likely a result of prolonged viremia and virus shedding—was longer (1-6 months vs 1-2 weeks), and the likelihood of reinfection was greater, than observed for the general population.[46,55,59,77,83,84,92,99,100,104,106,107,116] Thus, COVID-19 generally manifests clinically at a younger age, runs a more protracted course, and has a more severe outcome requiring hospitalization and/or ICU admission in many individuals with IEI compared to the epidemiology of SARS-CoV-2 infection in the general population (Fig 2).[16,44] This is reminiscent of findings for SARS-CoV-2 infection in patients with cystic fibrosis. Here, it was found that many cystic fibrosis patients had mild disease and common risk factors such as diabetes and previous solid organ transplantation, but subgroups of patients exhibited increased hospitalization rates and younger age at presentation relative to the general population.[117]

Mortality due to SARS-CoV-2 infection in IEI

Depending on the country or region where different studies have been performed, as well as the size of the cohort being investigated, the CFR after SARS-CoV-2 infection in patients with IEI is highly variable, being 0,[97,102,106,113,114] 2% to 5%,[99,101,107-109] 5% to 10%,[92,95,103,104] 15% to 20%,[105,112] 20% to 30%,[94,111,118] and >30%.[15,89,91] From all available published studies, 113 of 1328 patients with IEI died after SARS-CoV-2

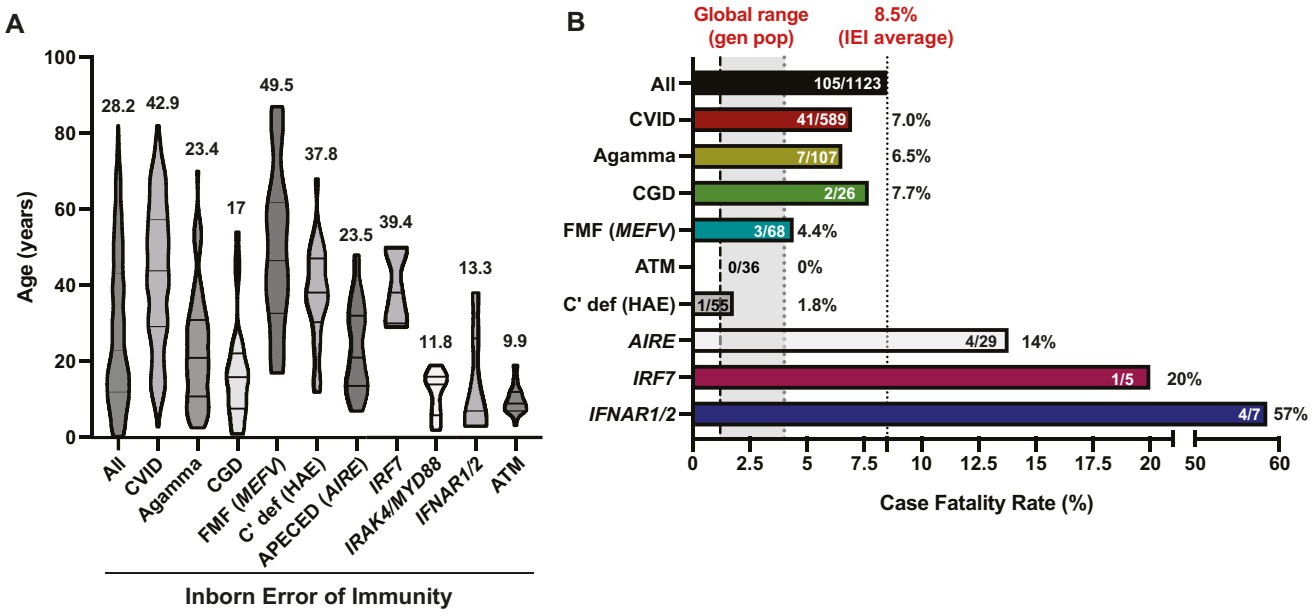

FIG 1. Features of cohorts of patients with IEI and SARS-CoV-2 infection. **(A)** Age of patients with the indicated IEI. Data are shown as median ages and quartiles for each patient group. Values above each data set represent the mean ages of patients with the indicated IEI. **(B)** CFR for all IEI patients, as well as range for the CFR in the general population (www.covid19.who.int/, www.worldometers.info/coronavirus/). Values in each patient group represent the number of deaths/total number of patients with the indicated IEI. *Agamma,* Agammaglobulinemia; *AIRE,* patients with APECED; *ATM,* ataxia telangiectasia; *C′ def,* complement deficiency; *CGD,* chronic granulomatous disease; *FMF,* familial Mediterranean fever; *IFNAR1/2,* patients with pathogenic variants in type I IFN receptors; *IRF7, MYD88/IRAK4,* patients with pathogenic variants in *IRF7* or *MYD88/IRAK4* that disrupt type I IFN signaling.

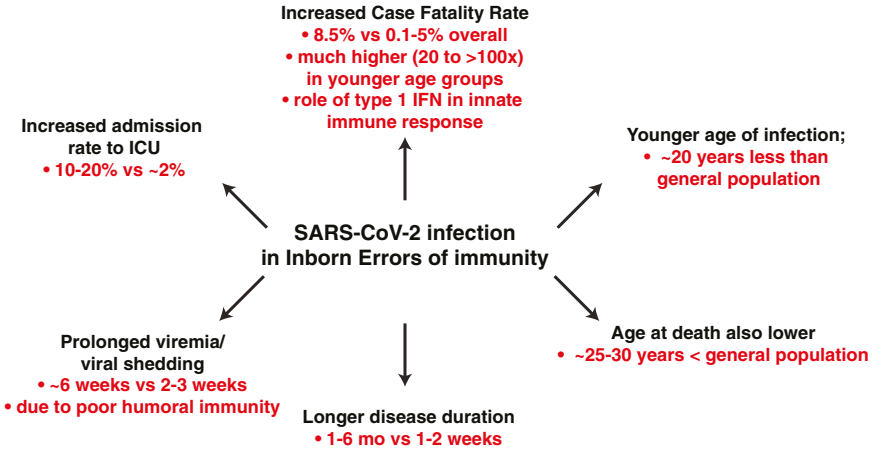

FIG 2. Consequences and outcomes of SARS-CoV-2 infection in patients with IEI.

infection, resulting in an overall CFR of 8.5% (Fig 1, *B*). Remarkably, this is highly similar to the CFR reported by Meyts et al[115] for an international survey of 94 patients with a broad range of IEI recruited from 12 countries (9.4%). The significant variability in CFR reported for many studies likely reflects the type of cohort being analyzed (eg, children vs adults; predominantly CVID due to unknown genetic defects vs severe combined immunodeficiency/combined immunodeficiency),[108] the predominant SARS-CoV-2 variant at the time of study,[41] the burden of SARS-CoV-2 infection in different countries and the relative impact this had on the respective health care systems, and the differences in screening for SARS-CoV-2 infection across the population. It is also important to note that the ~500 IEI described exhibit enormous diversity[6]—so much so that it is challenging to draw conclusions when assessing these patient cohorts with limited granularity. It is also likely that some IEI will result in greater predisposition to severe COVID-19, while others may even be protective,[119] thereby obscuring the overall severity of some IEI.

While it is difficult to make a direct comparison between CFR for IEI and the general population, this has been addressed for some countries. In Brazil,[95] Italy,[95,99-101] and the United Kingdom,[103] the CFR in IEI was ~2- to 4-fold greater than the

	Mediators of host defense	
Cell types:	Plasmacytoid DC type I IFN Respitatory epithelial cell	Naive sIgM sIgD Memory sIgM sIgG sIgA IgM IgG IgA Plasma cell
Function:	• rapid production of type I IFNs by immune (plasmacytoid DCs) and non-immune (epithelial) cells in response to SARS-CoV-2 exposure	• Ag-naïve B cells differentiate into memory B cells that rapidly respond following re-exposure /infection, and plasma cells producing neutralizing anti-SARS-CoV-2 specific IgG/IgA
Mechanisms of disease pathogenesis due to cellular defects:	• inborn errors that impair production of *(TLR3, TLR7, UNC93B1, TICAM1, TBK1, IRF3, IRF7)* or responses to *(IFNAR1/2, TYK2, STAT2, IRF7)* type I IFN • neutralizing autoAbs against type I IFNs (IFNα, ω)	• inborn errors affecting: - B cell development (eg *BTK*) - B cell function/differentiation • B-cell depletion therapy (rituximab)
Impact of impaired function on host defense	• severe, life-threatening, often fatal, SARS-CoV-2 infection • break through infection post-vaccination	• severe and/or prolonged disease • increased risk of re-infection
Treatments to manage cellular deficiencies/defects:	• IFNα (*TLR3, TLR7, UNC93B1, TICAM1, TBK1, IRF3, IRF7)* • IFNβ (not affected by autoAbs to type I IFNs) • plasma exchange to reduce levels of anti-IFN autoAbs	• convalescent plasma • anti-SARS-CoV-2 mAbs

FIG 3. Critical roles of innate and adaptive immune cells in host defense against SARS-CoV-2 infection and disease pathogenesis.

general population. More strikingly, though, were findings from Iran, Italy, the United Kingdom, and an international study that the CFR for IEI patients aged 20-60 years or 60-75 years was 20-50 times or 2.5-5 times greater, respectively, than the general population.[91,99,103,115] Furthermore, while the absolute number of patients analyzed is relatively small, the CFR for IEI patients aged 0-19 years is also much greater—possibly up to 100 times—than this age group in the general population.[91,99,103,115] Consequently, the overall average age at death due to SARS-CoV-2 infection in IEI patients is much younger than the general population (Fig 2; ~50 years vs ~80 years).[16,44,79,81,84,89,91,93-95,100,102-104,109,110,115] Thus, in addition to IEI patients' generally presenting with COVID-19 at a younger age and a greater proportion requiring admission to ICU than the general population, the mortality rate of SARS-CoV-2 infection is greater in IEI, especially at ages where SARS-CoV-2 has a very low—even negligible—CFR in the general population (Fig 2).[16,91,99,103,115]

INNATE IMMUNE DEFECTS PREDISPOSE TO SEVERE AND FATAL SARS-CoV-2 INFECTION

When comparing different IEI, there was often no correlation between the type of IEI and severity of disease/death after SARS-CoV-2 infection. For instance, the CFR for CVID, agammaglobulinemia, or chronic granulomatous disease were 7.2%, 6.2%, and 7.7%, respectively, compared to 8.5% for all IEI patients reported to date (Fig 1, *B*). However, there were several striking exceptions. First, although only few individuals have been identified, AR-pathogenic variants in *IFNAR1* or *IFNAR2,* encoding individual receptor subunits for type I IFNs, resulted in lethal COVID-19 in 4 (57%) of 7 patients (Fig 1, *B*) and an average age at death of 11.8 years.[42,56,87,120] Second, SARS-CoV-2 infection was severe in most patients with autoimmune polyendocrinopathy candidiasis ectodermal dystrophy (APECED) as a result of biallelic pathogenic *AIRE* variants. These individuals develop neutralizing autoantibodies against a range of cytokines, including type I IFN.[121] In the setting of SARS-CoV-2 infection of APECED patients, rates of hospitalization (72%, 21/29), ICU admission (59%, 17/29), and death (13.8%, 4/29)[57,84,115,118,122] were higher than all IEI patients as well as the general population (Fig 1, *B*).[16,19] Third, patients with biallelic pathogenic variants in *MYD88, IRAK,* or *IRF7*—which function downstream of virus-sensing Toll-like receptors to induce production of type I IFNs by dendritic cells—experience severe COVID-19, with 5 of 8 *MYD88/IRAK*-deficient and all 5 *IRF7*-deficient SARS-CoV-2–infected individuals developing COVID-19 pneumonia, requiring hospitalization and/or admission to ICU; 1 of 5 *IRF7*-deficient patient died

(Fig 1, *B*).[45,81,95,99,102,120,123] Thus, genetic lesions or autoantibodies that compromise innate immunity by disrupting production or function of type I IFNs underpin severe, life-threatening, and often fatal SARS-CoV-2 infection (Fig 3).

These findings have been validated by a forward genetics approach. Whole-exome and -genome sequencing of adults and children who developed severe and/or life-threatening SARS-CoV-2 infection/COVID-19 identified pathogenic variants in genes involved in type I IFN signaling. These include genes required for the production of (*TLR3, TLR7, UNC93B1, TICAM1, TBK1, IRF3, IRF7*) or responses to (*IFNAR1, IFNAR2, TYK2, STAT2, IRF7*) type I IFN produced by plasmacytoid dendritic cells or respiratory epithelial cells after viral infection.[65,90,120,123-126] Overall, genetic variants in the type I IFN signaling pathway were the cause of severe COVID-19 in ~3% of adults and ~10% of children (Fig 3).[120,126,127]

Parallel to these genetic studies was the discovery that neutralizing autoantibodies specific for type I IFNs cause severe COVID-19 in 10% to 20% of otherwise healthy individuals infected with SARS-CoV-2.[128-137] Interestingly, these autoantibodies were: (1) predominantly directed against IFN-α and IFN-ω but not IFN-β; (2) found in increasing proportions of affected patients with each decade of life; (3) associated with disease severity, prolonged virus clearance, and admission to ICU; (4) inversely related to serum levels of type I IFNs and interferon-stimulated gene signatures in myeloid cells;[78,128-137] and (5) enriched in affected male subjects compared to female subjects across different age intervals. This, together with XL *TLR7* deficiency, may contribute to the increased incidence of hospitalization and severe COVID-19 in male versus female subjects. These genetic and serologic studies unequivocally identified a fundamental nonredundant role for type I IFN–dependent immunity against SARS-CoV-2 infection, with 20% to 25% of cases of severe and life-threatening COVID-19 resulting from defective type I IFN production or function (Fig 3).

Additional anecdotal data have also linked impaired type I IFN–dependent immunity with susceptibility to SARS-CoV-2 infection. First, the CFR for autoinflammatory conditions such as Aicardi-Goutières syndrome or familial Mediterranean fever was lower than that for all reported cases of IEI (4.4% vs 8.5%; Fig 1, *B*).[15,93,95,99,110,115] Thus, increased basal type I IFN signaling in these conditions may enable prompt host defense against SARS-CoV-2. Second, a recent study of patients with systemic lupus erythematosus, which is characterized by overproduction of type I IFNs, found that a subset of these patients also produced autoantibodies against type I IFNs. Remarkably, while these autoantibody-positive patients were less likely to develop active lupus disease, members of this same group were at increased risk of severe viral infections and sequelae including COVID-19 pneumonia.[138]

B CELLS AND PROTECTIVE IgG IN HOST DEFENSE AGAINST SARS-CoV-2

The study of COVID-19 in IEI provides an elegant opportunity to define redundant and nonredundant requirements for host defense against SARS-CoV-2. Initial studies found that patients with congenital B-cell deficiency and agammaglobulinemia had relatively mild disease and prompt recovery after SARS-CoV-2 infection.[51,73,92,97,98] This led to a suggestion that B cells and neutralizing IgG may not be necessary for controlling SARS-CoV-2 infection and preventing severe COVID-19.[98] Consistent with this, the CFR for XL/AR agammaglobulinemia patients is lower than all IEI patients (6.2%, 6/97, vs 8.5%, Fig 1, *B*). However, COVID-19 and SARS-CoV-2 viremia/virus shedding are prolonged in many B-cell–deficient/agammaglobulinemia patients, resulting in pneumonia requiring extended or multiple hospital stays, as well as numerous treatments to control viral infection.[46,55,60,61,85,86,99,100,104,116,139] There have also been reports of chronic and/or repeated infections with worse outcomes than primary infection before vaccination, as well as breakthrough infections after vaccination in some XL agammaglobulinemia (XLA) patients.[100,104,109,116,140] Similar observations in terms of relapsing COVID-19, as well as reinfection and/or sustained infection with SARS-CoV-2, have been made for patients with primary antibody deficiencies,[82,104,116] further underscoring an important role for secreted immunoglobulin in controlling and clearing viral infection and attenuating disease. These findings from analysis of SARS-CoV-2 infection in individuals with congenital B-cell deficiency are also supported by studies of patients with rheumatic/musculoskeletal autoimmune diseases (rheumatoid arthritis, vasculitis, Sjögren syndrome, systemic lupus erythematosus) who are treated with B-cell–depleting therapies such as rituximab. In these cases, therapeutic B-cell depletion can result in high rates of hospital admissions, severe COVID-19 including protracted pneumonia and acute respiratory distress syndrome, and death after SARS-CoV-2 infection.[141,142] Thus, the inability to generate specific IgG responses to novel antigens as a result of a lack of naive B cells can have dire consequences in the setting of SARS-CoV-2 infection (Fig 3).

This apparent paradox of prolonged illness and viremia but often-milder disease and lower CFR in XLA patients who completely lack B cells may be explained by the nature of the genetic defect. On the one hand, agammaglobulinemia in these patients highlights a key role for specific immunoglobulins in controlling and clearing viral infection, even when responses of innate immune cells and $CD4^+$ and $CD8^+$ T cells are intact.[46,83] Indeed, administration of convalescent plasma isolated from previously infected healthy donors or anti–SARS-CoV-2–specific monoclonal antibodies (mAbs) led to rapid reductions in virus load and recovery in XLA—more so than observed with antiviral treatments alone (Fig 3).[46,53,55,61,85,86,104,139,143] Although convalescent plasma or anti–SARS-CoV-2 mAbs are a logical treatment for XLA patients, similar results have also been reported for other IEI patients who have near-normal B cells and serum immunoglobulin levels but defects in generating functional and protective IgG-dependent humoral immunity. For instance, passive IgG therapy led to dramatic improvements in the clinical course of SARS-CoV-2 infection in patients with pathogenic variants in *NFKB2*,[43] *IL2RG*,[77] *IKBKG* (NEMO),[72] and *PIK3CD* GOF,[82] as well as many cases of CVID.[83,103,104,109,143] In fact, anti–SARS-CoV-2 mAb or convalescent plasma greatly improved virus clearance and disease outcomes when combined with antivirals (eg, remdesivir).[43,104,143] Thus, while type I IFN–mediated innate immunity is indispensable for containing acute SARS-CoV-2 infection, antibodies are necessary to mitigate prolonged viral infection, minimize disease, and prevent reinfections (Fig 3).

On the other hand, Bruton tyrosine kinase (BTK) deficiency —the genetic cause of XLA—compromises production of

inflammatory cytokines by myeloid cells.[144] Thus, relatively mild pulmonary disease in XLA may result from a lessened cytokine storm after SARS-CoV-2–induced activation of BTK-deficient myeloid cells. This is consistent with findings that some SARS-CoV-2–infected XLA patients have lower serum IL-6 levels than infected individuals in the general population,[111] observations of mild COVID-19 in patients with B-cell malignancies who were treated with BTK inhibitors,[145] and rapid clinical improvement in COVID-19 patients treated with a BTK inhibitor as a therapeutic intervention.[146] These findings reveal dual roles for BTK in host defense and tissue pathology after SARS-CoV-2 infection. First, B cells and virus-specific antibodies are important for controlling prolonged infection. Second, BTK in myeloid cells may drive the SARS-CoV-2–induced cytokine storm characteristic of severe COVID-19. These findings provide a rationale for the use of passive immunoglobulin serotherapy (intravenous immunoglobulin, mAbs) to expedite virus clearance in IEI characterized by impaired humoral immunity, as well as of BTK inhibitors, Janus kinase (JAK) inhibitors, and tocilizumab (anti–IL-6R)[146-148] to quell SARS-CoV-2–induced production of inflammatory cytokines by myeloid cells. However, it needs to be emphasized that timing of the delivery of these treatments can also influence outcome and efficacy. For instance, if administered too early, JAK inhibits may attenuate the protective effect of type I IFNs, while delayed treatment with tocilizumab may be ineffectual. Similarly, these interventions may be better suited for some specific types of IEI, particularly as results from clinical trials of these inhibitors in the general population have been variable.

GENE-DIRECTED THERAPIES FOR COVID-19 IN SOME IEI

Delineation of the genetic and serologic causes of severe COVID-19 has led to the implementation of specific therapies in some IEI. For instance, the discovery that inborn errors in type I IFN signaling are a risk factor for severe COVID-19 inspired the use of IFN-α2a or IFN-β, anti–SARS-CoV-2 mAbs, or convalescent plasma to treat SARS-CoV-2 infection in individuals with pathogenic variants in *TLR3, IRF3, IRF7,* or *IRF9*,[68,69,123] which genetically disrupt type I IFN function, or patients with pathogenic *AIRE* variants or incontinentia pigmenti due to pathogenic *IKBKG* variants that result in production of neutralizing anti–type I IFN autoantibodies.[78,84,149] However, convalescent plasma has also been found to contain neutralizing anti–type I IFN autoantibodies,[137] which obviously could impact the efficacy of this treatment.

Similarly, plasma exchange was effective at reducing serum levels of neutralizing anti–type I IFN autoantibodies in an APECED patient.[57] While it is difficult to draw specific conclusions regarding possible therapies for SARS-CoV-2 infection in IEI from these anecdotal investigations, most treated patients exhibited mild disease, experienced rapid resolution of symptoms, and made a full recovery.[57,68,69,78,84,149] This contrasts with those IEI patients who did not receive specific treatments and experienced severe and even fatal COVID-19.[120,126,127] Thus, early provision of type I IFN or antibody against SARS-CoV-2 may represent an immunotherapeutic approach to prevent critical pneumonia in patients who are most vulnerable to severe SARS-CoV-2 infection due to disrupted type I IFN–mediated immunity. Furthermore, because anti–type I IFN autoantibodies are mostly directed against IFN-α and IFN-ω, IFN-β can still be used therapeutically for severe COVID-19 in individuals who develop these neutralizing autoantibodies.

VACCINES AGAINST SARS-CoV-2

The global rollout of several different SARS-CoV-2 vaccines (mRNA, adenoviral based, inactivated virus, viral proteins) has dramatically attenuated COVID-19–associated mortality.[150] These vaccines induce SARS-CoV-2–specific $CD4^+$ and $CD8^+$ T cells, memory B cells, and neutralizing serum IgG in >95% of healthy donors. Readouts of vaccine-induced immunity generally peaked 2 or 3 weeks after receipt of the second vaccine dose and then either significantly declined (specific IgG titers, $CD8^+$ T cells), plateaued ($CD4^+$ T cells), or even increased (memory B cells).[150-152] Regardless of these trajectories, SARS-CoV-2–specific adaptive cellular and humoral immunity remained detectable ~6 months after vaccination.[150-152] The magnitude of these vaccine-induced correlates of immunity in healthy individuals was generally comparable to or greater than those observed in convalescent individuals recovering from natural SARS-CoV-2 infection.[150-152]

While these findings are encouraging, several challenges remain in controlling SARS-CoV-2. First, vaccine efficacy declines from 85-95% at 2 to 4 weeks after full vaccination to 20-50% 6 months later, thus revealing an inability to completely resist future infection and highlighting the need for vaccine boosters.[150,153,154] Second, while successfully reducing disease severity, hospital admissions, and mortality, current vaccines do not effectively prevent SARS-CoV-2 transmission.[150,155] Third, the emergence of variants of concern—which can arise in immunocompromised individuals[156]—compromise vaccine efficacy, with vaccine-induced immunity being significantly reduced against several SARS-CoV-2 variants.[41,154,157] Thus, COVID-19 continues to represent a significant health risk despite the availability of several SARS-CoV-2 vaccines. Furthermore, findings from studies of IEI have established the importance of SARS-CoV-2–specific neutralizing IgG in preventing severe and prolonged disease as well as reinfection, so it is critical to continue encouraging vaccine and booster uptake in the general population.

EFFICACY OF SARS-CoV-2 VACCINES IN IEI PATIENTS

Many studies have initially assessed the immunogenicity and effectiveness of SARS-CoV-2 vaccines in IEI. The general findings from these studies were that (1) fewer patients mounted SARS-CoV-2–specific IgG (30-75%) and T-cell responses (~50-70%) compared to healthy donors (~95-100%), (2) titers of SARS-CoV-2–specific IgG, efficacy of virus neutralization, and magnitude of T-cell responses were reduced in patients compared to healthy donors, and (3) poor vaccine-induced immunity in patients correlated with reduced numbers of $CD4^+$ T cells or memory B cells, low serum IgG and IgA, and older age.[80,158-173] Importantly, IEI that disrupt type I IFN–mediated immunity or autoantibodies against type I IFN do not impair humoral immune responses to RNA vaccines.[174] Furthermore, despite normal levels of neutralizing IgG, some patients with anti–type I IFN autoantibodies develop breakthrough COVID-19 pneumonia.[175]

Overall, these studies established that SARS-CoV-2 vaccines are safe and well tolerated in people with IEI, and that they can induce specific adaptive immune responses, albeit at reduced levels compared to the general population. However, several significant unknowns remain. First, most studies assessed immune responses 2 to 8 weeks after the second vaccine dose. Thus, sustained durability of vaccine-induced immunity in IEI patients against SARS-CoV-2 has not been determined. Second, while almost all vaccine studies measured SARS-CoV-2–specific IgG, only a few determined virus neutralization. Thus, it is unknown whether vaccine-induced immunoglobulin in IEI patients can neutralize the original SARS-CoV-2 strain and emerging variants. Third, specific $CD4^+$ and $CD8^+$ T-cell responses in vaccinated IEI patients were not assessed in most studies. The paucity of data relating to responses of T-cell subsets impacts our ability to predict vulnerability of individuals with intrinsic T-cell defects to SARS-CoV-2 infection. Fourth, how waning immunity and SARS-CoV-2 variants impact host defense, as well as the capacity of vaccine booster doses to amplify immunity, in IEI patients is unexplored. Fifth, ~80% of all IEI patients assessed in these studies did not have a molecular diagnosis; most had CVID. Thus, it is difficult to (1) delineate cellular and molecular mechanisms underlying impaired immunity in IEI patients, (2) extrapolate these findings from predominantly CVID and antibody-deficient patients to IEI in general, (3) identify which pathways are necessary to elicit robust and long-lived immune responses, and (4) leverage these findings to develop methods to target specific key molecules/pathways to improve host defense against infectious diseases induced by next-generation vaccines. These are issues that need to be addressed in ongoing and future studies.

CONCLUSION

Analysis of individuals with single-gene defects that result in immune dysregulation have defined the fundamental requirements for immune homeostasis and host defense against a broad range of infectious agents. It was upon this foundation that the fields of genetics/genomics, basic and clinical immunology, and infectious diseases combined to make profound advances in unraveling the complexity of SARS-CoV-2 infection and severe COVID-19. Indeed, some of the key discoveries over the past 2 or 3 years have arisen from studying severe COVID-19 in otherwise healthy individuals, as well as in individuals with IEI. These studies established the framework to further define host factors necessary for early innate and sustained adaptive immune-mediated protection against SARS-CoV-2 infection and the establishment of immunologic memory, as well as mechanisms of severe disease and identifying opportunities for therapeutic intervention to manage COVID-19. Despite these breakthrough findings, there remains significant uncertainty regarding SARS-CoV-2 and IEI patients. These include the impact of standard treatments for IEI on immunity against SARS-CoV-2 infection and vaccination (eg, JAK inhibitors, TNF inhibitors, abatacept, rapamycin), long-term effects of SARS-CoV-2 infection/reinfection on IEI patients with autoimmunity and/or malignancy, whether long COVID and neurologic impacts are more prevalent in IEI compared to the general population, and the protective effect of neutralizing antibodies that are accumulating in donor blood products used for immunoglobulin replacement therapy. However, with the rapid pace of the advances already made since we first became aware of SARS-CoV-2, there is no doubt that answers to these questions —and more—will be delivered as we move into the third year (and, I hope, the last frontier) of this pandemic.

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