Coronavirus disease 2019 in patients with inborn errors of immunity: lessons learned

Giorgia Bucciol[a,b], *Stuart G. Tangye*[c,d,*] *and Isabelle Meyts*[a,b,*]

Purpose of review
The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic has caused extreme concern for patients with inborn errors of immunity (IEIs). In the first 6 months of the pandemic, the case fatality rate among patients with IEIs resembled that of the general population (9%). This review aims at summarizing what we have learned about the course and outcome of coronavirus disease 2019 (COVID-19) in patients with different IEIs and what this can potentially teach us about the immune mechanisms that could confer protection or predisposition to severe disease.

Recent findings
A total of 649 patients with IEI and COVID-19 have been reported in the last year and a half, spanning all groups of the International Union of Immunological Societies classification of IEIs. For most patients, the underlying IEI does not represent an independent risk factor for severe COVID-19. In fact, some IEI may even be protective against the severe disease due to impaired inflammation resulting in less immune-mediated collateral tissue damage.

Summary
We review the characteristics of SARS-CoV-2 infection in a large number of patients with IEI. Overall, we found that combined immunodeficiencies, immune dysregulation disorders, and innate immune defects impairing type I interferon responses are associated with severe disease course.

Keywords
coronavirus disease 2019, inborn errors of immunity, primary immunodeficiency, severe acute respiratory syndrome coronavirus 2

INTRODUCTION

More than a year and a half into the coronavirus disease 2019 (COVID-19) pandemic, the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has infected more than 200 million individuals (confirmed cases) and caused more than 4 million deaths. Despite shielding and being prioritized in vaccination campaigns in many countries, many patients with previously known inborn errors of immunity (IEIs) became infected with SARS-CoV-2 and hundreds of these cases have now been reported in the scientific literature. Moreover, a number of reports validated the hypothesis that individuals who became severely ill with SARS-CoV-2 – a primary infection for both children and adults – could suffer from a hitherto unknown defined error of immunity [1▪▪,2▪▪,3,4,5▪,6▪▪,7▪,8▪▪]. Based on these studies, a picture of the impact of COVID-19 in IEI is emerging. Furthermore, we are quickly understanding the fundamental requirements for successful host defense against SARS-CoV-2, as well as immune mechanisms that contribute to disease severity.

OVERVIEW OF REPORTS OF CORONAVIRUS DISEASE 2019 IN PATIENTS WITH INBORN ERRORS OF IMMUNITY

We here analyze the published case series and single cases describing the outcome of COVID-19 in patients with IEIs. Removing duplicate patients, to the best of our knowledge, we count a total of 649 reported patients with IEI who were infected with

[a]Laboratory of Inborn Errors of Immunity, Department of Microbiology, Immunology and Transplantation, KU Leuven, [b]Childhood Immunology, Department of Pediatrics, UZ Leuven, Leuven, Belgium, [c]Garvan Institute of Medical Research, Darlinghurst and [d]St Vincent's Clinical School, UNSW Sydney, Randwick, New South Wales, Australia

Correspondence to Isabelle Meyts, Laboratory of Inborn Errors of Immunity, Department of Microbiology, Immunology and Transplantation, KU Leuven, Leuven, Belgium. Tel: +32 16343841;
e-mail: isabelle.meyts@uzleuven.be

*Stuart G. Tangye and Isabelle Meyts equally contributed.

Curr Opin Pediatr 2021, 33:648–656

DOI:10.1097/MOP.0000000000001062

KEY POINTS

- IEIs in general do not represent an independent risk factor for severe SARS-CoV-2 infection.
- Combined immunodeficiencies, immune dysregulation disorders and defects of innate immunity impairing type I interferon responses, show a higher rate of severe disease and higher mortality.
- Inborn errors of type I interferon responses and IEI in which patients harbor autoantibodies against these cytokines, confer a high risk for critical COVID-19, reflecting the crucial role of type I interferon in host defense against SARS-CoV-2.

SARS-CoV-2, spanning all subgroups of immune defects as defined by the International Union of Immunological Societies committee for IEI (Table 1) [1▪▪,3,4,5▪,9▪,10–65]. Patients were mostly included based on a positive molecular test, antigenic test, or serology, although some reports also include patients with symptoms and clinical imaging compatible with a diagnosis of COVID-19, with or without a history of exposure to infected individuals [10,12,14,15,18]. As a result, the case fatality rate (CFR) attributed to COVID-19 could be overestimated in some reports. For example, in a UK cohort of 67 patients with IEI Shields *et al.* [15] report 12 patients as having succumbed to COVID-19, although only 47 (62.7%) had a PCR-proven or serology-proven infection. Counting the remaining 20 patients as COVID-19 cases without proof could have led to an overestimation of COVID-19-related morbidity and mortality. Of note, since our knowledge on the multiple facets and complications COVID-19, such as multisystem inflammatory syndrome in children (MIS-C) and in adults (MIS-A), has grown gradually during the pandemic, some relevant features of the disease were not highlighted in early reports [5▪].

Antibody deficiencies

Reflecting the relative frequency of humoral immunodeficiencies among IEIs, the majority of patients who experienced COVID-19 are affected by antibody deficiency ($n = 330$, 51%) [5▪,9▪,10,12–17,19,24,26,28,30,33,34,36,37,42,44,45,48,52,53,55,57–62,64,66–69]. Among them, 200 have common variable immunodeficiency (CVID, 60% of all antibody deficiencies), 59 have X-linked agammaglobulinemia (XLA, 18%) and eight have autosomal recessive agammaglobulinemia (2%). The remaining 63 patients have other B-cell defects including TRNT1 deficiency ($n = 1$), activated PI3Kδ syndrome (APDS, $n = 4$), IgG subclass deficiency ($n = 2$), specific polysaccharide antibody deficiency (SPAD, $n = 13$), isolated IgA deficiency ($n = 15$), or unspecified antibody deficiency ($n = 28$). The rate of admission to ICU is 14% for the whole group of patients with Ab deficiencies and the subgroups of CVID and XLA patients. CFR is 8% for the whole group ($n = 26$), 9% for CVID, 8% for XLA, 8% for SPAD, and 13% for the unspecified antibody deficiencies, while the CFR of patients with IgA deficiency, other

Table 1. Patients with inborn errors of immunity affected by coronavirus disease 2019: type of immune defect and outcome

Type of IEI	No. of patients (%)	ICU admission rate[a]	Case fatality rate (no.)
Antibody deficiency	330 (51%)	14%	8% (26)
CVID	200 (31%)	14%	9% (17)
XLA	59 (9%)	14%	8% (5)
Combined immunodeficiency	94 (14%)	20%	13% (12)
SCID pre-HSCT	7 (1%)	57%	57% (4)
SCID post-HSCT or GT	10 (1.5%)	0%	0%
Disorder of immune dysregulation	62 (10%)	28%	15% (9)
APS-1	27 (4%)	41%	15% (4)
Autoinflammatory disease	54 (8%)	4%	6% (3)
Innate immune defect	39 (6%)	62%	10% (4)
Phagocyte defect	34 (5%)	8%	6% (2)
Complement defect	29 (4%)	0%	0%
Phenocopy (Good syndrome)	7 (1%)	75%	43% (3)
Total	649	16%	9% (59)

CVID, common variable immunodeficiency; GT, gene therapy; HSCT, hematopoietic stem cell transplantation; IEI, inborn error of immunity; SCID, severe combined immunodeficiency; XLA, X-linked agammaglobulinemia.
[a]Calculated on patients for whom the information was available.

B-cell defects or APDS is 0%. The cause of death was reported for 15 patients: 14/15 had one or multiple comorbidities and succumbed to respiratory failure with or without sepsis and multiorgan failure, and one child developed secondary hemophagocytic lymphohistiocytosis (HLH) and pulmonary hemorrhage [5▪,10,12,42,45,68].

Combined immunodeficiencies and posthematopoietic stem-cell transplantation/gene therapy

Ninety-four patients with a diagnosis of combined immunodeficiency (CID) were infected with SARS-CoV-2 (14%) [5▪,9▪,10,12–16,27,37,39,49,51,54,57,62,63,66]. The rate of ICU admission is 20% in this group, with a CFR of 13% ($n = 12$). This cohort included 17 patients with severe CID (SCID), 10 of whom had previously undergone hematopoietic stem-cell transplantation (HSCT) or gene therapy [5▪,10,12–14,39,49,51]. The CFR among children with SCID who had not been treated with HSCT is strikingly high ($n = 4/7$, all affected by preexisting unspecified lower respiratory tract infections, and one with Omenn syndrome also by BCGitis [13]), while none of the SCID patients after curative treatment required admission to the ICU or died, even in case of progressive graft failure ($n = 1$) [5▪,10,12,14,39,49,51]. The cause of death was respiratory failure in all four cases [13]. In addition, an adult with unspecified CID died of HLH, an adolescent with CD40L deficiency died of MIS-C with pneumonia, and a child with serine-threonine protein kinase 4 deficiency had hepatitis, bloody diarrhea, and died of cardiorespiratory failure [10,13,16]. Among syndromic forms of CID, SARS-CoV-2 infection has been reported in six patients (two adolescents and four adults) with autosomal dominant hyper-IgE syndrome due to heterozygous dominant negative signal transducer and activator of transcription 3 (*STAT3*) mutations [5▪,63]. One adult with severe comorbidities, including obesity and cardio-respiratory impairment, died of respiratory failure and shock, while the other patients survived and had mild disease.

A total of 15 other patients treated with HSCT or gene therapy were infected with SARS-CoV-2 [5▪,9▪,10,16,27,43]. Of three Wiskott–Aldrich syndrome (WAS) patients who underwent HSCT ($n = 2$) or gene therapy ($n = 1$), one succumbed to cytomegalovirus (CMV) encephalitis and bacterial pneumonia, while the other two survived [5▪,10]. Two patients who were transplanted to treat X-linked proliferative syndrome due to mutations in the gene encoding X-linked inhibitor of apoptosis protein (XIAP) died after being infected with SARS-CoV-2 post-HSCT: one was infected on day 6 post-HSCT and had a mild disease, but later succumbed to fungal infection in the context of poor engraftment, and the other died of sepsis and HLH in the context of severe graft-versus-host disease (GVHD) [5▪,10]. One patient each was transplanted for leukocyte adhesion deficiency III, nuclear factor-kappa B (NF-κB) essential modulator (NEMO) deficiency, cytotoxic T-lymphocyte associated protein 4 (CTLA4) haploinsufficiency, Chediak–Higashi syndrome, or chronic granulomatous disease (CGD), and all survived COVID-19 [5▪,10,16,27,43]. Finally, the Italian IEI network reports five additional patients (a sixth with WAS is already included in the report from Meyts *et al.*) with unspecified IEIs treated with HSCT, gene therapy or thymus transplantation, who all survived COVID-19 [9▪].

Immune dysregulation disorders

As for immune dysregulation disorders, COVID-19 has been reported in 62 patients (10%), the majority of whom were affected by autoimmune polyendocrine syndrome type 1 (APS-1, $n = 27$, 44%) [3,4,5▪,10,13,14,16,21,22,37,40,56,57,70]. The rate of ICU admission was 28% and CFR 15% ($n = 9$). The rate of admission to the ICU rises to 41% for APS-1 patients, while CFR remains at 15% ($n = 4$). All APS-1 patients who died succumbed to respiratory failure [21]. The high rate of severe disease and mortality among APS-1 patients is explained by their preexisting neutralizing antitype I interferon autoantibodies (anti-IFN-α and/or ω), which were shown to block the initial antiviral type I interferon response by Bastard *et al.* [7▪,21]. Eleven patients have CTLA4 haploinsufficiency or lipopolysaccharide-responsive and beige-like anchor protein (LRBA) deficiency (18%) and two succumbed (CFR 18%) [5▪,14–16,56]. Three patients had XIAP mutations, and 2/2 of these patients died post-HSCT [4,5▪,10].

Autoinflammatory disorders

Autoinflammatory disorders were present in 54 patients infected with SARS-CoV-2 (8%), 39 with familial Mediterranean fever (FMF, 72%) [5▪,12,13,20]. The rate of ICU admission was 4% and CFR 6% ($n = 3$) for the entire group, while both ICU admission rate and CFR were 3% ($n = 1$) for FMF patients. One child with unspecified autoinflammatory disease died of MIS-C and vasculitis, while a child with deficiency of IL-1 receptor antagonist syndrome died of respiratory failure [12,13]. Five children with Aicardi–Goutières syndrome (AGS, two reported to be on janus kinase (JAK) inhibitors) all survived [5▪,9▪,15].

Innate immune defects

Thirty-nine patients with innate immune defects and COVID-19 have been reported (6%) [1▪▪,5▪,10,16,23,35,38,47,71]. The rate of ICU admission of this group is the highest at 62%, potentially because a large number of patients was accounted for by studies focusing on innate immune defects in critical COVID-19 cases [1▪▪,23]. The CFR is 10% ($n = 4$). In one case, cause of death was septic shock and in another one neurological involvement with seizures, cerebral sinus thrombosis and venous infarction, and multiorgan failure [23,47].

Phagocyte defects

Thirty-four patients with phagocyte defects are reported (5%), among whom 18 have CGD (53%) [4,5▪,10,12–14,16,43,50,57,66]. ICU admission rate and CFR is 6% ($n = 2$). The cause of death in these two cases of children with CGD resulted from bacterial septic shock [5▪,12].

Complement deficiencies

Twenty-nine patients with complement deficiency, mostly hereditary angioedema, had mild or asymptomatic COVID-19 (4%) [10,15]. In some cases, infection was associated with an angioedema attack, however no infected patients required ICU admission, and all patients recovered.

Good syndrome

Finally, seven patients with Good syndrome (thymoma with hypogammaglobulinemia, 1%) have been reported to have been infected with SARS-CoV-2 [9▪,10,12,32,42]. They mostly displayed a severe phenotype, with 5/7 (75%) patients requiring admission to ICU admission, and three patients succumbing (CFR 43%). Cause of death in one case was respiratory failure, and septic shock, myocarditis, pneumonia and hyperinflammation in another [10,12].

SEVERITY OF CORONAVIRUS DISEASE 2019 IN PATIENTS WITH DIFFERENT TYPES OF INBORN ERRORS OF IMMUNITY

When the first reports on COVID-19 in patients with IEI emerged in 2020, we learned that overall mortality among these patients was comparable with global mortality at the time and that patients shared the same risk factors for severe and critical disease as the general population, though the median age of IEI patients with severe COVID-19 was lower and the rate of admission to ICU per age group higher [5▪,11]. A year later, we observe an ICU admission rate of 16% and a stable CFR in the IEI population (9%, 60/649 patients), which is higher than in the general population [global average 2.1% (range: 0.5–18%), <0.3% <40 years to 13–20% >80 years] [72–75]. Among the IEI patients reported with their age, CFR is 10% among children, 7% for 20–40 years, 10% for 40–60 years, 14% for 60–70 years, and 36% for >70 years. Among the 18 children with IEI who died, eight (47%) had a CID, three (17%) had an immune dysregulation disorder, two each (12%) an autoinflammatory disease, a phagocyte defect or XLA, and one an innate immunity disorder [5▪,10,12,13,47]. This includes four children with SCID pre-HSCT and five patients who either died from causes not directly related to COVID-19, or who were already in a severely compromised state at the time of infection. Mortality in the group aged 20–40 years was dominated by patients with APS-1 (4/9, 44%), followed by XLA and innate immunity disorders (two each, 22%), and CID (1/9, 11%). Above 40 years of age, 75% of deaths occurred among antibody deficient patients.

Differences between the CFRs in the IEI group and the general population can be explained by two factors: on the one hand, large scale screening for SARS-CoV-2 infection has significantly lowered the CFR in the general population. On the other hand, patients with IEIs tend to have more comorbidities at a younger age than the average otherwise-healthy person. Moreover, physicians tend to publish single cases when they are remarkable in their course or outcome, thus introducing a bias toward more severe cases being reported. Indeed, a large and elegant unbiased cohort study conducted by Milito *et al.* [9▪] on the whole Italian population of IEI patients with confirmed SARS-CoV-2 infection revealed a CFR of 3.8% in IEIs, which is very close to the overall CFR in Italy (~3%).

Combined immunodeficiencies

The CFR of COVID-19 in CIDs is slightly higher than the average for all IEIs reported to date (13%). Mortality from SARS-CoV-2 is extremely high in children with SCID pretransplantation, while SCID patients who underwent curative procedures show 100% survival rate, with no severe cases reported [10,12–14,39,49]. Together with fatal COVID-19 in three patients with acute and severe complications post-HSCT (GVHD, CMV infection, fungal infection, and graft failure), this could either indicate a role of cellular immunity in controlling SARS-CoV-2 infection, or an increased mortality in the context of an already compromised general state.

Immune dysregulatory disorders

A high rate of both ICU admission and mortality have been reported for patients with immune

dysregulatory disorders. Bastard *et al.* found preexisting neutralizing autoantibodies against IFN-α and ω, but rarely IFN-β, in at least 10% of patients with critical COVID-19 pneumonia (up to 20% in patients 80 years and older) [6▪▪,7▪]. These findings were confirmed by several groups [21,22,76–81]. For APS-1 patients, the presence of antitype I interferon antibodies was well known; however, no viral infection phenotype had been described until the pandemic [82]. Despite this, CFR among APS-1 patients is like the whole group of immune dysregulation disorders, indicating that immune dysregulation diseases arising from distinct genetic causes can predispose to severe COVID-19. On the other hand, patients affected by autoinflammatory disorders do not seem to have a specifically higher risk of severe COVID-19 and have mostly a mild course [5▪,10,20]. One prediction would be that elevated production or action of type I interferon, as one of the inflammatory mechanisms, provides effective innate host defense against SARS-CoV-2 infection, thereby minimizing disease severity.

Innate immune defects

Zhang *et al.* [1▪▪] performed a genetic screen of 13 loci associated with severe influenza infection or other severe viral infection. They found deleterious variants in *IFNAR1, IRF3*, *IRF7*, *TBK1,* and *TICAM1* in 3.4% of patients with critical COVID-19 [1▪▪]. van der Made *et al.* [23] performed whole exome sequencing in previously healthy pairs of previously healthy brothers with critical COVID-19 and identified two loss-of-function variants in *TLR7*. Asano *et al.* [8▪▪] have recently identified an additional 14 deleterious *TLR7* alleles in males with critical COVID-19. They showed an impaired type I interferon production by plasmacytoid dendritic cells. Significantly, several cases of very severe SARS-CoV-2 pneumonia in patients with MyD88 deficiency have also been reported [71]. This is arguably surprising since individuals with MyD88-deficiency have previously only been reported to suffer from severe invasive bacterial infections, rather than any viruses [83]. A previous study on SARS-CoV-1 demonstrated that MyD88 has an essential role in mice in controlling pulmonary viral replication [84]. Thus, it is possible that MyD88 plays a hitherto unknown role in early antiviral response against coronaviruses.

Multisystem inflammatory syndrome in patients with inborn errors of immunity

A new COVID-19-related clinical entity affecting children emerged in the first few months of the pandemic, namely MIS-C [85,86,87,88▪]. Unlike in acute COVID-19-related hyperinflammation, where multisystem inflammation and cytokine storm go together with severe respiratory symptoms and typically affect adults, MIS-C appears several weeks after SARS-CoV-2 exposure and is not correlated with the severity of the initial infection [85,86,87,88▪]. Similarly, MIS-A has been reported in adults [89]. Patients with MIS-C and MIS-A present with multiorgan involvement without severe respiratory illness, preceded by 4–6 weeks by an asymptomatic or paucisymptomatic SARS-CoV-2 infection. SARS-CoV-2 antibodies, positive PCR or a history of exposure are detected in almost all cases [85–87,89]. Although partly overlapping with Kawasaki disease, MIS-C generally affects older children (7.5–12 years), with a predilection for males and subjects of African or Hispanic ancestry. In more than 70% of cases patients have multiorgan dysfunction with mucocutaneous (70%), gastrointestinal (>80%), cardiovascular (80–100%), respiratory (50–70%), or neurologic involvement (40%) [85,86,87,88▪,90]. It has a more severe clinical course, often presenting with shock (50%), and a high prevalence of myocarditis (90%) [85,86,87,88▪]. Finally, it is associated with a pronounced hyperinflammatory state with higher levels of inflammatory markers and more severe cytopenia than in Kawasaki disease, often fulfilling the diagnostic criteria for HLH [85,86,87,88▪].

Among the 649 IEI patients with COVID-19, at least 23 had MIS-C or HLH. Ten patients (six children, four adults) met the criteria for HLH, although it is possible some of them would have been diagnosed with MIS-C if this entity had been known at the time of the earliest presentations [5▪]. Seven out of ten of these patients also had pneumonia or acute respiratory distress syndrome (ARDS), eight required ICU admission and three died (one adult, two children). Fourteen children (two females) were classified as suffering from MIS-C (median age 11 years, range 1–17) [3,4,5▪,12]. Seven out of 14 also had pneumonia or ARDS, six were admitted to the ICU and three died. There were no reports of MIS-A among patients with IEI, although hyperinflammation in the context of SARS-CoV-2 pneumonia was described [5▪,12]. Notably, there is an overrepresentation of disorders of immune dysregulation (5/62 patients, 8%, including two XIAP deficiency, one Chediak-Higashi syndrome and one SOCS1 deficiency) and phagocyte defects (4/34 patients, 11%, including three CGD), which are associated to increased or chronic inflammation.

DISCUSSION

The description of the clinical course and outcome of hundreds of patients with an IEI infected with

SARS-CoV-2 since the beginning of the pandemic gives us a better understanding of predisposing factors and immunological mechanisms underlying severe COVID-19. First, the crucial role of the type I interferon response is convincingly shown by the enrichment in pathogenic variant in genes responsible for interferon production and downstream signaling in several patients with critical COVID-19 [1▪▪,8▪▪,23]. Similarly, a high rate of severe disease occurred in patients with preexisting antitype I interferon autoantibodies, such as patients with APS-1 [21]. In fact, autosomal inborn errors of type I immunity and antitype I interferon autoantibodies underlie at least 10% of critical COVID-19 cases. A hypothesis that needs to be further explored is that the higher CFR and ICU admission rates seen in patients with different types of IEIs, and patients with disorders of immune dysregulation in particular, could be caused by the presence of these autoantibodies. Autoimmunity is indeed a feature of many IEIs and phenocopies of IEIs, like Good syndrome, in which antitype I interferon autoantibodies have already been described [91–94]. A collaborative effort to screen patients with IEI for anti-interferon auto-antibodies is ongoing (www.covidhge.com) [95–97].

The initial observation that patients with XLA had better outcomes than patients with CVID, possibly due to the absence of the proinflammatory Bruton tyrosin kinase (BTK)-dependent NF-κB activation, is not reflected in this larger cohort of patients, who show the same ICU admission rates and a similar CFR (9 vs. 8% in CVID and XLA patients, respectively) [5▪,11]. Since the median age of CVID patients is 40 years and that of patients with XLA or agammaglobulinemia is 23 years, patients with XLA seem to have a worse outcome at a younger age. This could potentially be explained by the fact that CVID patients often present later in life and so develop comorbidities at a later age, while patients with agammaglobulinemia often have chronic lung damage already in childhood. Alternatively CVID patients could have antitype I interferon autoantibodies as part of an autoimmune phenotype. Although patients with disorders of immune dysregulation are more at risk for both severe pulmonary COVID-19 and its inflammatory complications, such as MIS-C or HLH, patients with phagocyte defects are not susceptible to SARS-CoV-2 pneumonia but have an increased risk of hyperinflammation [4,5▪,12]. Significantly, patients with autoinflammatory disorders such as FMF and AGS also show no increased risk of severe disease compared with the general population [5▪,10,20].

Insight into immune mechanisms responsible for SARS-CoV-2 immunity and inflammation is driving therapeuticl trials with IL-6 inhibition with tocilizumab, BTK inhibition with ibrutinib and acalabrutinib, or JAK-STAT inhibition with ruxolitinib in patients with severe hyperinflammation in the context of COVID-19 [98,99,100▪]. Early therapy with type I interferon has also been attempted in several patients, although the timing of this treatment is challenging [100▪,101,102]. Caution should be used with regard to convalescent plasma, which has been successfully administered to several patients with IEIs and prolonged COVID-19, but has also been found to harbor antitype I interferon autoantibodies [27,33,39,42,45,48,49,76]. Therapeutic plasma exchange could be beneficial to remove deleterious autoantibodies and proinflammatory cytokines in critical patients, and it has been attempted with anecdotal positive results [100▪, 103–105]. Monoclonal antibodies that neutralize SARS-CoV-2, such as the combination of casirivimab and imdevimab (Regen-Cov) or sotrovimab, have also proven effective as primary or secondary prevention of COVID-19 [106,107]. Therefore, passive immunotherapy with these antibodies could potentially be used early in patients with IEIs at high risk for severe disease as a strategy to prevent the development of COVID-19-related complications or as aids in clearing the infection in patients with prolonged shedding of SARS-CoV-2 [108]. Finally, some patients with IEI are able to mount a humoral and/or cellular immunity against the virus in a natural infection setting or in a vaccination setting [67,109,110]. RNA-based vaccines against SARS-CoV-2 have proven safe and effective in patients with IEI, who should therefore be prioritized for early vaccination around the world, together with their family members as a mean of community-based protection in case of insufficient individual response to the vaccine [109,111].

CONCLUSION

We reviewed the characteristics and outcome of SARS-CoV-2 infection in patients with IEI and found that the underlying immune defect does not represent an independent risk factor for severe COVID-19, except for CID – though the number of patients is small–but especially immune dysregulation disorders (APS-1) and innate immune defects impairing type I interferon responses. Further studies are needed to assess the role of anti-type I interferon antibodies in larger cohorts of individuals with IEI and critical COVID-19, to better direct the therapeutic strategies most apt to prevent or treat severe complications in these patients.

Acknowledgements

We want to thank Yoni Maisel, whose Twitter updates on SARS-CoV-2 in patients with PID were extremely helpful for this work. We also want to thank the COVID19-Human Genetic Effort consortium and its leaders Prof Jean-Laurent Casanova and Prof Helen Su for the insightful discussions and collaborative scientific project since the onset of the pandemic.

Financial support and sponsorship

I.M. is a Senior Clinical Investigator at the Research Foundation – Flanders, and is supported by a KU Leuven C1 Grant (grant number C16/18/007); by a VIB GC PID Grant; by the Research Foundation – Flanders (FWO) (grant numbers G0C8517N, G0B5120N, and G0E8420N); by the CSL Behring Chair in Primary Immunodeficiency in Children; and by the Jeffrey Modell Foundation. S.G.T. is supported by Investigator and Program Grants awarded by the National Health and Medical Research Council of Australia and a UNSW Sydney COVID Rapid Response Initiative Grant. This work was supported by ERN-RITA.

Conflicts of interest

I.M. is supported by the CSL Behring Chair in Primary Immunodeficiency in Children, paid to Institution. There are no conflicts of interest for the remaining authors.

REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

- ■ of special interest
- ■■ of outstanding interest

1. Zhang Q, Bastard P, Liu Z, *et al.* Inborn errors of type I IFN immunity in ■■ patients with life-threatening COVID-19. Science 2020; 370:eabd4570.

The article demonstrates the presence of inborn errors of type I interferon immunity in a subgroup of patients with critical coronavirus disease 2019 (COVID-19).

2. Zhang Q, Bastard P, Bolze A, *et al.* Life-threatening COVID-19: defective ■■ interferons unleash excessive inflammation. Med (New York, NY) 2020; 1:14–20.

The article summarizes the findings of the COVID Human Genetic Effort consortium on the critical role of type I interferon in severe acute respiratory syndrome coronavirus 2 infection and the genetic or acquired errors of interferon responses that underlie severe disease in a large number of patients.

3. Lee PY, Platt CD, Weeks S, *et al.* Immune dysregulation and multisystem inflammatory syndrome in children (MIS-C) in individuals with haploinsufficiency of SOCS1. J Allergy Clin Immunol 2020; 146:1194–1200.e1.
4. Chou J, Platt CD, Habiballah S, *et al.* Mechanisms underlying genetic susceptibility to multisystem inflammatory syndrome in children (MIS-C). J Allergy Clin Immunol 2021; 148:732–738.e1.
5. Meyts I, Bucciol G, Quinti I, *et al.* Coronavirus disease 2019 in patients with ■ inborn errors of immunity: an international study. J Allergy Clin Immunol 2021; 147:520–531.

The article was the first and largest global survey of the presentation and outcome of COVID-19 in patients with inborn errors of immunity (IEIs).

6. Bastard P, Rosen LB, Zhang Q, *et al.* Autoantibodies against type I IFNs in ■■ patients with life-threatening COVID-19. Science 2020; 370:eabd4585.

The article describes the very high prevalence of antitype I interferon autoantibodies in patients (and especially men) with critical COVID-19.

7. Bastard P, Gervais A, Le Voyer T, *et al.* Autoantibodies neutralizing type I IFNs ■ are common in the elderly and account for about 20% of COVID-19 deaths. Sci Immunol 2021; 6:eabl4340.

The article expands on the findings of antitype I interferon autoantibodies in patients with life-threatening COVID-19.

8. Asano T, Boisson B, Onodi F, *et al.* X-linked recessive TLR7 deficiency in ■■ ~1% of men under 60 years old with life-threatening COVID-19. Sci Immunol 2021; 6:eabl4348.

The article expands the findings of inborn errors of interferon responses in young and healthy patients with critical COVID-19.

9. Milito C, Lougaris V, Giardino G, *et al.* Clinical outcome, incidence, and ■ SARS-CoV-2 infection-fatality rates in Italian patients with inborn errors of immunity. J Allergy Clin Immunol Pract 2021; 9:2904–2906.e2.

The article uses an elegant and unbiased approach to analyze the impact of COVID-19 in the Italian cohort of patients with IEIs, showing rates of severe disease and mortality similar to the general Italian population.

10. Goudouris ES, Pinto-Mariz F, Mendonça LO, *et al.* Outcome of SARS-CoV-2 infection in 121 patients with inborn errors of immunity: a cross-sectional study. J Clin Immunol 2021. doi: 10.1007/s10875-021-01066-8 [Epub ahead of print]
11. Quinti I, Lougaris V, Milito C, *et al.* A possible role for B cells in COVID-19? Lesson from patients with agammaglobulinemia. J Allergy Clin Immunol 2020; 146:211–213.e4.
12. Castano-Jaramillo LM, Yamazaki-Nakashimada MA, O'Farrill-Romanillos PM, *et al.* COVID-19 in the context of inborn errors of immunity: a case series of 31 patients from Mexico. J Clin Immunol 2021; 41:1463–1478.
13. Delavari S, Abolhassani H, Abolnezhadian F, *et al.* Impact of SARS-CoV-2 pandemic on patients with primary immunodeficiency. J Clin Immunol 2021; 41:345–355.
14. Marcus N, Frizinsky S, Hagin D, *et al.* Minor clinical impact of COVID-19 pandemic on patients with primary immunodeficiency in Israel. Front Immunol 2021; 11:614086.
15. Shields AM, Burns SO, Savic S, *et al.* COVID-19 in patients with primary and secondary immunodeficiency: the United Kingdom experience. J Allergy Clin Immunol 2021; 147:870–875.e1.
16. Esenboga S, Ocak M, Akarsu A, *et al.* COVID-19 in patients with primary immunodeficiency. J Clin Immunol 2021. doi: 10.1007/s10875-021-01065-9 [Epub ahead of print]
17. Guchelaar NAD, van Laar JAM, Hermans MAW, *et al.* Characteristics of COVID-19 infection and antibody formation in patients known at a tertiary immunology department. J Transl Autoimmun 2021; 4:100084.
18. Grumach AS, Goudouris E, Dortas Junior S, *et al.* COVID-19 affecting hereditary angioedema patients with and without C1 inhibitor deficiency. J Allergy Clin Immunol Pract 2021; 9:508–510.
19. Cohen B, Rubinstein R, Gans MD, *et al.* COVID-19 infection in 10 common variable immunodeficiency patients in New York City. J Allergy Clin Immunol Pract 2021; 9:504–507.e1.
20. Güven SC, Erden A, Karakaş Ö, *et al.* COVID-19 outcomes in patients with familial Mediterranean fever: a retrospective cohort study. Rheumatol Int 2021; 41:715–719.
21. Bastard P, Orlova E, Sozaeva L, *et al.* Preexisting autoantibodies to type I IFNs underlie critical COVID-19 pneumonia in patients with APS-1. J Exp Med 2021; 218:e20210554.
22. Meisel C, Akbil B, Meyer T, *et al.* Mild COVID-19 despite autoantibodies to type I IFNs in Autoimmune-Polyendocrine-Syndrome Type 1 (APS-1). J Clin Invest 2021; 131:e150867.
23. van der Made CI, Simons A, Schuurs-Hoeijmakers J, *et al.* Presence of genetic variants among young men with severe COVID-19. JAMA 2020; 324:663.
24. Ahanchian H, Moazzen N, Sezavar M, *et al.* COVID-19 in a child with primary antibody deficiency. Clin Case Rep 2021; 9:755–758.
25. Abraham RS, Marshall JM, Kuehn HS, *et al.* Severe SARS-CoV-2 disease in the context of a NF-κB2 loss-of-function pathogenic variant. J Allergy Clin Immunol 2021; 147:532–544.e1.
26. Aljaberi R, Wishah K. Positive outcome in a patient with coronavirus disease 2019 and common variable immunodeficiency after intravenous immunoglobulin. Ann Allergy Asthma Immunol 2020; 125:349–350.
27. Alkan G, Artac H, Oz SKT, Emiroglu M. Management of COVID-19 pneumonia in a child with NEMO deficiency. Immunol Res 2021; 69:391–393.
28. Almontasheri A, Al-Husayni F, Alsuraihi AK, *et al.* The clinical course of COVID-19 pneumonia in a 19-year-old man on intravenous immunoglobulin replacement therapy for X-linked agammaglobulinemia. Am J Case Rep 2021; 22:e929447–e929451.
29. Beccuti G, Ghizzoni L, Cambria V, *et al.* A COVID-19 pneumonia case report of autoimmune polyendocrine syndrome type 1 in Lombardy Italy: letter to the. J Endocrinol Invest 2020; 43:1175–1177.
30. Buckland MS, Galloway JB, Fhogartaigh CN, *et al.* Treatment of COVID-19 with remdesivir in the absence of humoral immunity: a case report. Nat Commun 2020; 11:6385.
31. Castano-Jaramillo LM, Yamazaki-Nakashimada MA, Mendoza SCS, *et al.* A male infant with COVID-19 in the context of ARPC1B deficiency. Pediatr Allergy Immunol 2021; 32:199–201.
32. Cos Esquius ML, López Montesinos I, Gimeno Martinez R, *et al.* Severe COVID-19 pneumonia in Good syndrome with a favorable outcome. Clin Immunol 2021. 108789. doi: 10.1016/j.clim.2021.108789 [Epub ahead of print]
33. Delgado-Fernández M, García-Gemar GM, Fuentes-López A, *et al.* Treatment of COVID-19 with convalescent plasma in patients with humoral immunodeficiency – Three consecutive cases and review of the literature. Enfermedades Infecc Microbiol Clin 2021; S0213-005X:00035-5.

34. Fill L, Hadney L, Graven K, *et al.* The clinical observation of a patient with common variable immunodeficiency diagnosed as having coronavirus disease. Ann Allergy Asthma Immunol 2020; 125:112–114.
35. Guisado Hernández P, Blanco Lobo P, Villaoslada I, *et al.* SARS-CoV-2 infection in a pediatrics STAT1 GOF patient under Ruxolitinib therapy-a matter of balance? J Clin Immunol 2021; 41:1502–1506.
36. Gupta S, Su H, Narsai T, Agrawal S. SARS-CoV-2-associated T-cell responses in the presence of humoral immunodeficiency. Int Arch Allergy Immunol 2021; 182:195–209.
37. Ho H, Mathew S, Peluso MJ, Cunningham-Rundles C. Clinical outcomes and features of COVID-19 in patients with primary immunodeficiencies in New York City. J Allergy Clin Immunol Pract 2021; 9:490–493.e2.
38. Jin H, Moss R, Reed JC, *et al.* IFN-γ receptor 2 deficiency initial mimicry of multisystem inflammatory syndrome in children (MIS-C). J Allergy Clin Immunol Pract 2021; 9:989–992.e1.
39. Keitel V, Bode JG, Feldt T, *et al.* Case report: convalescent plasma achieves SARS-CoV-2 viral clearance in a patient with persistently high viral replication over 8 weeks due to severe combined immunodeficiency (SCID) and graft failure. Front Immunol 2021; 12:645989.
40. Lange M, Linden T, Müller HL, *et al.* Primary haemophagocytic lymphohistiocytosis (Chédiak–Higashi syndrome) triggered by acute SARS-CoV-2 infection in a 6-week-old infant. Br J Haematol 2021. doi: 10.1111/bjh.17669. [Epub ahead of print]
41. Lemarquis A, Campbell T, Aranda-Guillén M, *et al.* Severe COVID-19 in an APS1 patient with interferon autoantibodies treated with plasmapheresis. J Allergy Clin Immunol 2021; 148:96–98.
42. London J, Boutboul D, Lacombe K, *et al.* Severe COVID-19 in patients with B cell alymphocytosis and response to convalescent plasma therapy. J Clin Immunol 2021; 41:356–361.
43. Mantravadi V, Nguyen ST, Morley SC, *et al.* Recovery from COVID-19 in a child with chronic granulomatous disease and T cell lymphopenia. J Clin Immunol 2021; 41:23–25.
44. Mira E, Yarce OA, Ortega C, *et al.* Rapid recovery of a SARS-CoV-2–infected X-linked agammaglobulinemia patient after infusion of COVID-19 convalescent plasma. J Allergy Clin Immunol Pract 2020; 8:2793–2795.
45. Mullur J, Wang A, Feldweg A. A fatal case of coronavirus disease 2019 in a patient with common variable immunodeficiency. Ann Allergy Asthma Immunol 2021; 126:90–92.
46. Pozzi MR, Baronio M, Janetti MB, *et al.* Fatal SARS-CoV-2 infection in a male patient with Good's syndrome. Clin Immunol 2021; 223:108644.
47. Schmidt A, Peters S, Knaus A, *et al.* TBK1 and TNFRSF13B mutations and an autoinflammatory disease in a child with lethal COVID-19. Npj Genomic Med 2021; 6:1–5.
48. Van Damme KFA, Tavernier S, Van Roy N, *et al.* Case report: convalescent plasma, a targeted therapy for patients with CVID and severe COVID-19. Front Immunol 2020; 11:596761.
49. van Oers NSC, Hanners NW, Sue PK, *et al.* SARS-CoV-2 infection associated with hepatitis in an infant with X-linked severe combined immunodeficiency. Clin Immunol 2021; 224:108662.
50. Vignesh P, Rawat A, Singh S. An update on the use of immunomodulators in primary immunodeficiencies. Clin Rev Allergy Immunol 2017; 52:287–303.
51. Zamperlini-Netto G, Fernandes JF, Garcia JL, *et al.* COVID-19 after hematopoietic stem cell transplantation: report of two children. Bone Marrow Transplant 2021; 56:713–715.
52. Zhou X, Zhou J, Zhao J. Recurrent pneumonia in a patient with new coronavirus infection after discharge from hospital for insufficient antibody production: a case report. BMC Infect Dis 2020; 20:500.
53. Ender E, Thimoty P. COVID-19 in a patient with CVID and contraindications to several potential treatments. Ann Allergy Asthma Immunol 2020; 125:S54–S117.
54. Gabryszewski SJ, England RN, Sun D, *et al.* Self-limited COVID-19 in a patient with artemis hypomorphic SCID. J Clin Immunol 2021. doi: 10.1007/s10875-021-01093-5 [Epub ahead of print]
55. Urschel D, Cardenas-Morales M, Hernandez-Trujillo V. Complications of coronavirus in a patient with CVID. Ann Allergy Asthma Immunol 2020; 125:S54–S117.
56. Ochoa S, Rosen L, Lionakis M, *et al.* COVID-19 in 3 patients with CLTA4 haploinsufficiency and absence of autoantibodies to type 1 interferons. J Clin Immunol 2021; 41(Suppl 1):S1–S135.
57. Sherkat R, Bolourinejad P, Salemi N, *et al.* The clinical coarse and outcome of SARS-COVID 19 in patients with inborn error of immunity, does it relate to the type of the immune defects. J Clin Immunol 2021; 41(Suppl 1):S1–S135.
58. Dhamija Y, Xie S, Zhang S, *et al.* Treatment of COVID-19 with convalescent plasma in a patient with X-linked agammaglobulinemia. J Clin Immunol 2021; 41(Suppl 1):S1–S135.
59. Mejia A, di Natale M, Balastegui H, *et al.* High dose intravenous immunoglobulin. The next step in therapy for severe COVID19 infection? J Clin Immunol 2021; 41(Suppl 1):S1–S135.
60. Westreich A, Persistently. Positive SARS-CoV-2 RT-PCR testing in a pediatric patient with X-linked agammaglobulinemia. J Clin Immunol 2021; 41(Suppl 1):S1–S135.
61. Iaboni A, Betschel S. A patient with X-linked agammaglobulinemia and COVID-19 infection treated with remdesivir and convalescent plasma. J Clin Immunol 2021; 41(Suppl 1):S1–S135.
62. Deyà-Martinez A, Garcia-Garcia A, Vlagea A, *et al.* Confirmed SARS-COV-2 infection in a cohort of children and young adults with moderate or severe primary immunodeficiencies. J Clin Immunol 2021; 41(Suppl. 1):S1–S135.
63. Khalid M, Urban A, Darnell D, Freeman AF. Clinical outcomes of SARS-CoV2 infection in STAT3 deficiency. J Clin Immunol 2021; 41:S1–S135.
64. Petricau C, Nedelea I, Deleanu D. Surprising protective mechanisms against severe forms of COVID-19 infection among common variable immunodeficiency patients-one center experience. Res Sq 2020.
65. Tangye SG, Al-Herz W, Bousfiha A, *et al.* Human inborn errors of immunity: 2019 update on the classification from the international union of immunological societies expert committee. J Clin Immunol 2020; 40:24–64.
66. Götzinger F, Santiago-Garcia B, Noguera-Julián A, *et al.* COVID-19 in children and adolescents in Europe: a multinational, multicentre cohort study. Lancet Child Adolesc Health 2020; 4:653–661.
67. Kinoshita H, Durkee-Shock J, Jensen-Wachspress M, *et al.* Robust antibody and T cell responses to SARS-CoV-2 in patients with antibody deficiency. J Clin Immunol 2021; 41:1146-1153.
68. Loh SY, Bassett J, Hoodless EJ, Walshaw M. Possible COVID-19 reinfection in a patient with X-linked agammaglobulinaemia. BMJ Case Rep CP 2021; 14:e240765.
69. Milošević I, Jovanović J, Stevanovic O. Atypical course of COVID-19 in patient with Bruton agammaglobulinemia. J Infect Dev Ctries 2020; 14:1248–1251.
70. Wahlster L, Weichert-Leahey N, Trissal M, *et al.* COVID-19 presenting with autoimmune hemolytic anemia in the setting of underlying immune dysregulation. Pediatr Blood Cancer 2020; 67:e28382.
71. Mahmood HZ, Madhavarapu S, Almuqamam M. Varying illness severity in patients with MyD88 deficiency infected with coronavirus SARS-CoV-2. Pediatrics 2021; 147:453–454.
72. Dong E, Du H, Gardner L. An interactive web-based dashboard to track COVID-19 in real time. Lancet Infect Dis 2020; 20:533–534.
73. CDCMMWR. Severe outcomes among patients with coronavirus disease 2019 (COVID-19) – United States. MMWR Morb Mortal Wkly Rep 2020; 2020:69.
74. WHO. WHO weekly epidemiological update on COVID-19 – Edition 51. Geneva: WHO; 2021. Available from: https://www.who.int/publications/m/item/weekly-epidemiological-update-on-covid-19–3-august-2021. [Accessed 24 August 2021]
75. European Centre for Disease Prevention and Control: COVID-19 situation update worldwide, as of week 31, updated 12 August 2021. Available from: https://www.ecdc.europa.eu/en/geographical-distribution-2019-ncov-cases.
76. Vazquez SE, Bastard P, Kelly K, *et al.* Neutralizing autoantibodies to type I interferons in COVID-19 convalescent donor plasma. J Clin Immunol 2021; 41:1169–1171.
77. Koning R, Bastard P, Casanova J-L, *et al.* Autoantibodies against type I interferons are associated with multiorgan failure in COVID-19 patients. Intensive Care Med 2021; 47:704–706.
78. Troya J, Bastard P, Planas-Serra L, *et al.* Neutralizing autoantibodies to type I IFNs in >10% of patients with severe COVID-19 pneumonia hospitalized in Madrid, Spain. J Clin Immunol 2021; 41:914–922.
79. Wijst MGP, van der. Vazquez SE, *et al.* Longitudinal single-cell epitope and RNA-sequencing reveals the immunological impact of type 1 interferon autoantibodies in critical COVID-19. bioRxiv 2021. Preprint.
80. Goncalves D, Mezidi M, Bastard P, *et al.* Antibodies against type-I Interferon: detection and association with severe clinical outcome in COVID-19 patients. medRxiv 2021P e1327; 10:.
81. Lopez J, Mommert M, Mouton W, *et al.* Early nasal type I IFN immunity against SARS-CoV-2 is compromised in patients with autoantibodies against type I IFNs. J Exp Med 2021; 218:e20211211.
82. Meager A, Visvalingam K, Peterson P, *et al.* Anti-interferon autoantibodies in autoimmune polyendocrinopathy syndrome type 1. PLoS Med 2006; 3:e289.
83. Picard C, von Bernuth H, Ghandil P, *et al.* Clinical features and outcome of patients with IRAK-4 and MyD88 deficiency. Medicine (Baltimore) 2010; 89:403.
84. Sheahan T, Morrison TE, Funkhouser W, *et al.* MyD88 is required for protection from lethal infection with a mouse-adapted SARS-CoV. PLOS Pathog 2008; 4:e1000240.
85. Verdoni L, Mazza A, Gervasoni A, *et al.* An outbreak of severe Kawasaki-like disease at the Italian epicentre of the SARS-CoV-2 epidemic: an observational cohort study. Lancet 2020; 395:1771–1778.
86. Gruber CN, Patel RS, Trachtman R, *et al.* Mapping systemic inflammation and antibody responses in multisystem inflammatory syndrome in children (MIS-C). Cell 2020; 183:982–995.e14.
87. Toubiana J, Cohen JF, Brice J, *et al.* Distinctive features of Kawasaki disease following SARS-CoV-2 infection: a controlled study in Paris, France. J Clin Immunol 2021; 41:526–535.

88. ■ Sancho-Shimizu V, Brodin P, Cobat A, *et al.* SARS-CoV-2–related MIS-C: a key to the viral and genetic causes of Kawasaki disease? J Exp Med 2021; 218:e20210446.

The article analyses the characteristics of multisystem inflammatory syndrome in children, which has emerged as a new entity distinct from Kawasaki disease in the COVID-19 pandemic.

89. Morris SB. Case series of multisystem inflammatory syndrome in adults associated with SARS-CoV-2 infection – United Kingdom and United States March–August. MMWR Morb Mortal Wkly Rep 2020; 69:1450–1456.
90. Feldstein LR, Rose EB, Horwitz SM, *et al.* Multisystem inflammatory syndrome in U.S. children and adolescents. N Engl J Med 2020; 383:334–346.
91. Martinez B, Browne SK. Good syndrome, bad problem. Front Oncol 2014; 4:307.
92. Meager A, Vincent A, Newsom-Davis J, Willcox N. Spontaneous neutralising antibodies to interferon-a and interleukin-12 in thymoma-associated autoimmune disease. Lancet 1997; 350:1596–1597.
93. Meager A, Wadhwa M, Dilger P, *et al.* Anticytokine autoantibodies in autoimmunity: preponderance of neutralizing autoantibodies against interferon-alpha, interferon-omega and interleukin-12 in patients with thymoma and/or myasthenia gravis. Clin Exp Immunol 2003; 132:128–136.
94. Burbelo PD, Browne SK, Sampaio EP, *et al.* Anticytokine autoantibodies are associated with opportunistic infection in patients with thymic neoplasia. Blood 2010; 116:4848–4858.
95. Walter JE, Rosen LB, Csomos K, *et al.* Broad-spectrum antibodies against self-antigens and cytokines in RAG deficiency. J Clin Invest 2015; 125:4135–4148.
96. Giardino G, Gallo V, Prencipe R, *et al.* Unbalanced immune system: immunodeficiencies and autoimmunity. Front Pediatr 2016; 4:107.
97. Malphettes M, Gérard L, Galicier L, *et al.* Good syndrome: an adult-onset immunodeficiency remarkable for its high incidence of invasive infections and autoimmune complications. Clin Infect Dis 2015; 61:e13–e19.
98. Roschewski M, Lionakis MS, Sharman JP, *et al.* Inhibition of Bruton tyrosine kinase in patients with severe COVID-19. Sci Immunol 2020; 5:eabd0110.
99. Chen C-Y, Chen W-C, Hsu C-K, *et al.* Clinical efficacy and safety of Janus kinase inhibitors for COVID-19: a systematic review and meta-analysis of randomized controlled trials. Int Immunopharmacol 2021; 99:108027.
100. ■ Vinh DC, Abel L, Bastard P, *et al.* Harnessing type I IFN immunity against SARS-CoV-2 with early administration of IFN-β. J Clin Immunol 2021; 41:1425–1442.

The article reviews the various therapies for COVID-19, focusing on those targeting the type I interferon responses and the proinflammatory pathways that are hyperactivated in severe disease.

101. Bastard P, Lévy R, Henriquez S, *et al.* Interferon-β therapy in a patient with incontinentia pigmenti and autoantibodies against type I IFNs infected with SARS-CoV-2. J Clin Immunol 2021; 41:931–933.
102. Lévy R, Bastard P, Lanternier F, *et al.* IFN-α2a therapy in two patients with inborn errors of TLR3 and IRF3 infected with SARS-CoV-2. J Clin Immunol 2021; 41:26–27.
103. Morath C, Weigand MA, Zeier M, *et al.* Plasma exchange in critically ill COVID-19 patients. Crit Care 2020; 24:481.
104. Ma J, Xia P, Zhou Y, *et al.* Potential effect of blood purification therapy in reducing cytokine storm as a late complication of critically ill COVID-19. Clin Immunol 2020; 214:108408.
105. de Prost N, Bastard P, Arrestier R, *et al.* Plasma exchange to rescue patients with autoantibodies against type I interferons and life-threatening COVID-19 pneumonia. J Clin Immunol 2021; 41:536–544.
106. O'Brien MP, Forleo-Neto E, Musser BJ, *et al.* Subcutaneous REGEN-COV antibody combination to prevent Covid-19. N Engl J Med 2021; 385:1184–1195.
107. Chen P, Nirula A, Heller B, *et al.* SARS-CoV-2 neutralizing antibody LY-CoV555 in outpatients with Covid-19. N Engl J Med 2021; 384:229–237.
108. Drouin AC, Theberge MW, Liu SY, *et al.* Successful clearance of 300 day SARS-CoV-2 infection in a subject with B-cell depletion associated prolonged (B-DEAP) COVID by REGEN-COV anti-spike monoclonal antibody cocktail. Viruses 2021; 13:1202.
109. Hagin D, Freund T, Navon M, *et al.* Immunogenicity of Pfizer-BioNTech COVID-19 vaccine in patients with inborn errors of immunity. J Allergy Clin Immunol 2021; 148:739–749.
110. Squire J, Joshi A. Seroconversion after coronavirus disease 2019 vaccination in patients with immune deficiency. Ann Allergy Asthma Immunol 2021; 127:383–384.
111. Fox TA, Kirkwood AA, Enfield L, *et al.* Low seropositivity and sub-optimal neutralisation rates in patients fully vaccinated against COVID-19 with B cell malignancies. medRxiv 2021. 2021.07.19.21260762.