ESID COVID-19 Statement

Since the start of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic, there has been rapid progress with understanding disease, clinical phenotypes and biology, improving treatment and implementing vaccination trials. Data is accumulating about the impact of COVID-19 for patients with Inborn Errors of Immunity (IEI). The purpose of this statement is to summarise our state of knowledge and set out ESID's current guidance for professionals in the IEI community in Europe. We will update this statement as evidence emerges.

What do we know about COVID-19 in IEI?

There have been relatively few IEI patients reported with severe COVID-19 either in the literature or in the multiple studies carried out to date (Meyts et al JACI2021 Feb;147(2):520-53; Shields et al., J Allergy Clin Immunol. 2021 Mar;147(3):870-875.e; Milito et al J Allergy Clin Immunol Pract. 2021 Jul; 9(7): 2904–2906.e2; Deya-Martinez et al., Clin Immunol. 2021 Sep;230:108821; Simoes Goudouris et al., J Clin Immunol. 2021 Oct;41(7):1479-1489; Castano-Jaramillo et al., J Clin Immunol. 2021 Oct;41(7):1463-1478; reviewed in Bucciol et al., Curr Opin Pediatr. 2021 Dec 1;33(6):648-656; Milota T et al., Front. Immunol., 28 February 2022). This may relate to the rarity of IEI and the fact that patients with IEI were advised to reduce exposure by taking additional precautions in the first waves of the pandemic. It is therefore not known whether this means that IEI patients are less at risk than initially presumed.

What we can say so far is that, in general

- Asymptomatic and mild COVID-19 disease is seen in patients with IEI, even in disorders where T-cell function is impaired (for example combined immunodeficiency).
- Severe COVID-19 in IEI is more frequently seen in patients who are older or have comorbidities, similar to the general population.
- Specific IEI may predispose affected patients to more severe COVID-19 disease (see below).
- A different course of COVID-19 is seen in some patients, particularly with antibody deficiency. This is characterised by prolonged viral infection usually without the classical inflammatory complications of COVID-19.

COVID-19 in specific IEI conditions

The information presented below highlights groups of IEI patients where the underlying disease has been reported to give rise to a different risk of severe COVID-19. It is important to note that COVID-19 outcomes in IEI have mainly been derived from data collected prior to the availability of antibody and antiviral treatments and prior to the B.1.1.529 Omicron variant, that appears to give rise to less severe disease.

Impaired type I interferon (IFN) signalling has emerged as an important susceptibility factor for SARS-CoV-2. Both the presence of autoantibodies that neutralise type I IFNs and rare genetic deleterious variations in genes of the type I IFN pathway have been demonstrated to be associated with life-threatening COVID-19 pneumonia (Bastard et al Science. 2020 Oct 23;370; Zhang et al Science. 2020 Oct 23;370); Manry J et al., Research Square 2022 Jan 14 doi: 10.21203/rs.3.rs-1225906/v1. ; Bastard P et al Sci Immunol. 2021 Aug 19;6(62):eabl4340; Asano T., Sci Immunol. 2021 Aug 19;6(62):eabl4348).

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Thus, patients with forms of IEI that result in reduced type I immunity, due to impaired production of type I IFN (e.g. inborn errors of the TLR3-, TLR-7, MDA5- or IRF7-dependent pathways), or impaired activity of type I IFNs (e.g. APS-I/APECED), or impaired cellular responses to type I IFNs (e.g. inborn errors causing loss of function in IFNAR1-, IFNAR2, STAT1-, STAT2- and IRF9-dependent pathways), should be considered to be at high risk of life-threatening COVID-19.

In particular, a number of patients with APS1/APECED have already been reported to have had life-threatening COVID-19 (Meisel et al., J Clin Invest. 2021 Jul 15;131(14):e150867 and Bastard et al., J Exp Med. 2021 Jul 5;218(7):e20210554) **and therefore specific care with preventive measures (such as more rigorous social distancing, mask wearing and vaccination) should be considered to prevent SARS-CoV-2 infection in these patients.**

Severe Combined immunodeficiency: It is unclear why some patients with untreated SCID have severe COVID-19 while others are asymptomatically infected. Specific risk occurs in the peri-transplant period (see below).

Common variable immunodeficiency is associated with variable outcomes, likely reflecting the clinical heterogeneity of this group of patients. Co-morbidities known to be associated with worse COVID outcome in the general population, such as pre-existing lung and liver disease have higher prevalence in CVID and are also associated with worse outcome in this group (Shields et al, J Allergy Clin Immunol. 2021 Mar;147(3):870-875.e).

X-linked Agammaglobulinemia and other IEI with very low/absent B-cells appear to be specifically associated with inability to clear SARS-CoV-2 virus leading to prolonged infection (Brown et al., J Allergy Clin Immunol. 2022 Feb;149(2):557-561.e1; reviewed in Ponsford et al., Curr Opin Allergy Clin Immunol. 2021 Dec 1;21(6):525-534.)

Phagocyte disorders, autoinflammatory diseases and hereditary angioedema (HAE) do not appear to be associated with severe COVID-19. The risk for patients with HAE is considered to be equivalent to the general population.

Patients after HSCT who are still considered to be immunosuppressed (i.e. who are on immunosuppressive medication or who are already practising usual post-HSCT social distancing and special hygiene measures) should take particular precautions to limit their risk of exposure to SARS-CoV-2 and should be prepared to do so for a longer period than anticipated. Specific consideration needs to be given to vaccination (see below).

Can we recommend any additional management for IEI patients with COVID-19?
Several treatments now exist for COVID-19. Broadly, these can be divided into:

(a) neutralising monoclonal antibodies (mAbs) which target the spike protein of the virus and prevent it from invading human cells. When considering a specific mAb the product chosen needs to be effective against the dominant strain of SARS-CoV2 at the time of infection (or ideally against the specific strain, if known).
(b) convalescent plasma which contains polyclonal antibodies against SARS-CoV2: these products are less standardised than mAbs with respect to safety, dosing and efficacy but have been suggested as an alternative in situations where no mAb is available (Lang-Meli et al., J Clin Immunol. 2022 Feb;42(2):253-265; Brown et al, J Allergy Clin Immunol 2022; 149:557-561).

(c) other directly acting antiviral drugs which block viral replication: both oral (eg nirmatrelvir/ritonavir or molnupiravir) and intravenous (eg remdesivir) medications are available, although licensing of individual products varies by country.
(d) medications which reduce the inflammation associated with severe COVID-19 (eg corticosteroids, tocilizumab, JAK inhibitors)

It is of utmost importance that IEI physicians are involved in the care of IEI patients with SARS-CoV-2 infection and liaise with other clinical teams managing the patient, such as infectious disease colleagues and intensivists.

Treatment early in the course of infection

Neutralising mAbs and antiviral drugs have been demonstrated to be effective in unvaccinated, immunocompetent people if given early in the course of infection (eg Gupta et al, New Engl J Med, 385(21):1941-1950; Weinreich et al, New Engl J Med 384(3):238-251; Fischer et al, medRxiv 2021.06.17.21258639). Increasing evidence supports benefit for IEI patients (Pulvirenti et al J Infect Dis. 2021 Nov 8;jiab554) and we would recommend early treatment with mAb (especially in those with antibody deficiency who are likely to have responded poorly to vaccination) and/or directly acting antivirals. Among the antivirals, nirmatrelvir/ritonavir and remdesivir appear to be more effective than molnupiravir and are the preferred therapies. However, if these treatments cannot be administered due to contraindications or logistical concerns, molnupiravir can be considered.

Most mAbs, nirmatrelvir/ritonavir and remdesivir have been approved for children ≥12 years of age and ≥40kg. For younger children, only limited safety and efficacy data exist and specialist paediatric advice should be sought. Molnupiravir is approved for adult patients above 18 years of age. Contraindications and specific adverse effects need to be taken into account when advising for therapy.

Treatment later in the disease course

Treatment with mAbs in hospitalised patients, including many patients later in the disease course, has been demonstrated in the RECOVERY trial (UK) to be effective in patients who are anti-SARS-CoV-2 antibody negative at the time of admission (Horby et al, medRxiv 2021.06.15.21258542). This is likely to apply to many IEI patients, especially those with antibody deficiencies, and we would support treatment with mAbs in seronegative hospitalised IEI patients. Convalescent plasma may be an alternative (Lang-Meli et al., J Clin Immunol. 2022 Feb;42(2):253-265) if mAbs are not available but does not have the same level of evidence. There are no data regarding the use of sequential infusions of mAb or convalescent plasma if infection is not cleared following an initial dose.

Consideration should also be given to the use of directly acting antivirals (eg remdesivir or nirmatrelvir/ritonavir) in addition to mAbs in hospitalised patients. If mAbs are not available, antiviral medications should be given as monotherapy but this approach is less preferred.

Patients with IEI can suffer chronic or relapsing infection. Successful treatment has been observed for chronic infection using a combination of antibody-based therapeutics (mAb or convalescent plasma) and antiviral drugs or antibody-based therapeutics alone, but case numbers to date are small (eg Brown et al, J Allergy Clin Immunol 2022; 149:557-561; Lang-Meli et al., J Clin Immunol. 2022 Feb;42(2):253-265).

Medications to reduce inflammation (such as dexamethasone) should be given in IEI when indicated, but clinicians should remain vigilant for secondary infection.

With regard to follow up, patients with IEI may remain PCR positive for SARS-CoV-2, with or without symptoms, for longer periods than immunocompetent individuals. Serial PCR measurements may be helpful to support clinical suspicion of ongoing SARS-CoV-2 infection in persistently symptomatic patients. The role of serial measurements in asymptomatic patients for infection control purposes is undefined at present but can be helpful to demonstrate persistent infectivity vs. viral clearance. This may be of particular importance if treatment was administered, to identify persistent infection post-treatment with convalescent plasma, monoclonal antibodies or antivirals as this may signify the emergence of a resistant viral escape variant.

Prevention of COVID-19 in patients with IEI?

In addition to vaccination (see below), handwashing, mask-wearing and social distancing advice remain the key recommendations to prevent SARS-CoV-2 infection. Patients with IEI are recommended to follow local and national guidance and remain updated about local and travel advice. Advice about work and school attendance should be based on local and national guidance.

Immunoglobulin products collected earlier in the pandemic and prior to widespread vaccination of the donor pool contain only limited concentrations of antibodies to SARS-CoV-2. More recently, antibodies to SARS-CoV-2 have been reported in immunoglobulin products although the level of protection they confer is unclear (Volk et al., BioDrugs. 2022 Jan;36(1):41-53). mAb have been demonstrated to be useful in post-exposure prophylaxis in (immunocompetent) household members exposed to infection (O'Brien et al, New Engl J Med 385:1184-1195), and this strategy could be considered for IEI patients (especially those with antibody deficiency) where mAb are licensed for this indication. mAb are also postulated to be effective as pre-exposure prophylaxis in IEI patients who fail to respond to vaccination. However, this remains unproven and clinical trials are ongoing.

For professional guidance, risk stratification for groups of IEI have been published by some national immunology networks eg UKPIN (http://www.ukpin.org.uk/news-item/2020/03/24/covid-19-uk-pin-update), API (http://www.kinderimmunologie.de/neuartiges-Coronavirus), the Belgian IEI Group (https://covid-19.sciensano.be/sites/default/files/Covid19/Risicogroepen%20pediatrie%20NL%20FINAL.pdf) and CEREDIH (https://www.ceredih.fr/rubric_news/mise-jour-des-recommandations-covid-19-l-intention-des-m-decins-et-des-patients-enfants-et-adultes-atteints-de-dip).

Recommendation about COVID-19 vaccinations in IEI

Multiple SARS-CoV-2 vaccinations are now in routine use including mRNA, protein or replication-deficient vector vaccines. We recommend that patients with IEI receive any of the available COVID-19 vaccinations provided that they are not live vaccines.

Over multiple studies, a significant proportion of patients with IEI have been reported to generate T-cell responses to COVID-19 vaccination and detectable antibodies against the SARS-CoV-2 spike protein (Hagin et al., J Allergy Clin Immunol. 2021 Sep;148(3):739-749; Amodio et al., Front Immunol. 2021 Oct 4;12:727850; Delmonte et al., J Allergy Clin Immunol. 2021 Nov;148(5):1192-1197; Bergman et al., EBioMedicine. 2021 Dec;74:103705; Fernandez Salinas et al., J Allergy Clin Immunol. 2022 Jan;149(1):76-77; Pham et al., J Allergy Clin Immunol. 2022 Mar;149(3):907-911.e3; Shields et al., Research Square, doi:10.21203/rs.3.rs-1180392/v1). In many IEI groups, however, the antibody response to COVID-19

vaccination is lower than that seen in healthy control groups and data is currently lacking for the efficacy of T-cell and antibody responses to prevent or ameliorate COVID in patients with IEI.

Our current advice is that IEI patients should be vaccinated according to their national vaccination schedule to include primary courses and booster doses of vaccination.

Post HSCT COVID-19 vaccination is strongly recommended for all patients above the age of 5 years, also in those already vaccinated before HSCT. Since the vaccine response is expected to be weaker in patients early after HSCT, vaccination is recommended from 6 months post HSCT (or as early as 3 months in high prevalence areas) in the absence of uncontrolled, severe GVHD, and a third "booster" dose may be considered before 6 months to increase efficacy. Further practice guidelines considering HSCT are available and regularly updated at https://www.ebmt.org/covid-19-and-bmt

Global Research efforts on COVID19 and IEI

COIEI19 is the follow-up international survey of COVID-19 in IEI patients which follows on from an initial survey launched during Spring 2020 (published in Meyts et al JACI 2020 Sept 24: S0091-6749(20)31320-8). It is a fully GGDPR compliant survey, open to any healthcare professional in the world and aims to promote increased knowledge in the field. The link can be found at: https://dsp.institutimagine.org/coIEI/connexion.php

The ESID registry is also collecting COVID-19 data related to IEI. Individual patients can be marked has having experienced SARS-CoV2 infection (y/n) and/or have a diagnosis of COVID-19 related hyperinflammation syndrome. **We would encourage ESID members to login to the registry and update information for their patients** as this will create an important resource for our IEI community, to enable further research and better information to guide professionals and patients.

In depth study of the genetics of severe COVID19 is ongoing via: www.covidhge.com

An international survey of patients with APS1/APECED and COVID is in progress and physicians with affected patients can contact Anne Puel (anne.puel@institutimagine.org) or Paul Bastard (paul.bastard@institutimagine.org).

ESID is additionally collaborating with PReS, ISSAID, ERN-RITA and PRINTO networks for an international survey of COVID-19 related Hyperinflammation in children and young adults, "HyperPED-COVID". For further information contact printo@gaslini.org

Information for the global IEI community

• The IPOPI COVID-19 statement, jointly prepared with the collaboration of regional and international IEI expert societies and

• the Joint IPOPI-ESID statement on the use of Monoclonal antibodies for IEI patients in context of COVID-19 pandemic,

are found at: https://ipopi.org/latest-news-on-covid-19-and-IEI/

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