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. While there remains relatively little published information about the impacts of COVID-19 for patients with Primary Immunodeficiency (PID), data are gradually emerging. The purpose of this statement is to summarise what we know so far and set out ESID's current guidance for professionals in the PID community in Europe. We will update this statement as evidence emerges.

What do we know about COVID-19 in PID?

Patients with PID are assumed to be more susceptible to SARS-CoV-2 infection and severe COVID-19 based on the fact that immune function is impaired. Despite this, there have been relatively few PID patients reported with severe COVID-19 either in the literature or in the two retrospective survey studies carried out to date (Meyts et al JACI 2020 Sept 24: S0091-6749(20)31320-8; Shields et al JACI accepted). This may relate to the rarity of PID and the fact that patients with PID were advised to reduce exposure by taking additional precautions in the first wave of the pandemic. In any case, it is still too early to know whether this means that PID 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 PID, even in disorders where T-cell function is impaired (for example combined immunodeficiency).
- Severe COVID-19 in PID is more frequently seen in patients who are older or have comorbidities, similar to the general population.
- Specific PID 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 PID conditions

Impaired type I interferon (IFN) signalling is emerging as an important susceptibility factor for SARS-CoV-2, from large studies of infected patients. 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).

Thus, patients with forms of PID that result in reduced type I immunity, due to impaired production of type I IFN (e.g. inborn errors of the TLR3-, 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. Anti-type I IFN autoantibodies may be seen in other PID and in patients with thymoma. The significance of these is currently under investigation and it is too early to make specific clinical recommendations.

In particular, a number of patients with APS1/APECED have already been reported to have had life-threatening COVID-19 and therefore specific care with preventive measures (such as more rigorous

social distancing, mask wearing) should be considered to prevent SARS-CoV-2 infection in these patients.

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 (ie 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. Further practice guidelines considering HSCT are available and regularly updated at https://www.ebmt.org/covid-19-and-bmt

Can we recommend any additional management for PID patients with COVID-19?

To date there are insufficient data to recommend specific therapies for PID patients with SARS-CoV-2 infection. Many different agents have been used in small numbers of patients and large studies are required. Based on management of other viral infections in PID and the presence of prolonged SARS-CoV-2 infection in some PID patients, therapies such as antiviral agents and monoclonal antibodies, although of only modest benefit in hospitalised non-immunodeficient patients, warrant specific study in patients with PID. However, all reports of potential benefit in PID are so far anecdotal. Consideration and prompt management of secondary bacterial infections is recommended. Individualised treatment should be directed by the patient's PID physician based on knowledge of the underlying PID. **Therefore, it is of utmost importance that PID physicians are involved in the care of PID patients with SARS-CoV-2 infection and liaise with other clinical teams managing the patient, such as infectious disease colleagues and intensivists.**

There are emerging data that patients with PID may remain PCR positive for SARS-CoV-2, with or without symptoms, for longer periods than immunocompetent individuals. Studies testing for persistence of infectious virus are needed to determine the significance of this, especially in asymptomatic PID patients. 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.

Prevention of COVID-19 in patients with PID?

Handwashing, mask-wearing and social distancing advice remain the key recommendations to prevent SARS-CoV-2 infection. Patients with PID 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 prior to the pandemic do not demonstrate neutralising antibodies to SARS-CoV-2 and should not be considered to confer any protection (Schwaiger J Infect Dis2020 Nov 13; 222(12):1960-1964).

For professional guidance, risk stratification for groups of PID 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 PID 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 emerging COVID-19 vaccinations in PID

Multiple SARS-CoV-2 vaccinations are in clinical trials and many more are in development. National COVID-19 vaccination programs are planned for roll-out in the coming months. We recommend that patients with PID receive COVID-19 vaccinations provided that they are not live vaccines. The rationale is as for the influenza vaccination, that T-cell responses may be generated even in the absence of an antibody response. The vaccines currently in clinical trials are either mRNA, protein or replication-deficient vector vaccines. Live vaccines, should they become available in the future, should not be administered to those patients with PID who have a contraindication for live vaccines. There are currently no data for efficacy and safety of COVID-19 vaccinations in PID patients to inform specific guidance and therefore our current advice is that PID patients should be vaccinated according to their national vaccination schedule. We will update this advice if more information becomes available for PID in general or for specific pathway defects.

Global Research efforts on COVID19 and PID

COPID19 is the follow-up international survey of COVID-19 in PID 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/copid/connexion.php

The ESID registry is also collecting COVID-19 data related to PID. 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 PID 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 patients

IPOPI and multiple national patient groups have regularly updated information for patients on their websites.

The IPOPI statement, jointly prepared with the collaboration of regional and international PID expert societies, is found at: https://ipopi.org/latest-news-on-covid-19-and-pid/

The statement was reviewed by the CWP on 12th January 2021 and the following update agreed:

"Current COVID vaccinations are not licensed for children. We would, however, recommend that adult household members also receive COVID vaccination (with any of the currently available mRNA, protein or replication-deficient vector vaccines) to provide additional protection for PID patients at risk for severe COVID''

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