



**Joint statement on the current epidemics of new Coronavirus
SARS-CoV-2— COVID-19 for management of
Primary Immunodeficiency Disease (PID) Patients
From MSAI & MyPOPI**

(Original statement, as of 2020, 02nd April)

Coronavirus - what is it?

Coronaviruses (CoV) are a family of viruses that cause respiratory tract infections. They range from common colds to more serious illnesses like pneumonia.

Although coronaviruses commonly cause disease in animals, they can infect people too and spread between them. Recent examples include Severe Acute Respiratory Syndrome (SARS-CoV), and Middle-East Respiratory Syndrome (MERS-CoV).

In December 2019, a cluster of pneumonia cases was reported in Wuhan, Hubei Province, China, which linked to a new or novel coronavirus (2019-nCoV), a new strain of virus that has never been previously known or detected in humans. This virus was later known as SARS-CoV-2.

Coronavirus Disease 2019 (abbreviated “COVID-19”) is a disease caused by the SARS-CoV-2 virus. Initially, the disease was attributed to the spread of animals to humans. However, a growing number of new cases indicate that there is a human-to-human transmission.

Following the rapidly growing number of this coronavirus infections worldwide, the World Health Organization (WHO) has declared that COVID-19 as pandemic on March 10, 2020.

What is the current situation regarding COVID-19 in Malaysia?

The situation is changing all the time and we advise you to monitor for the latest advice applicable to your area.

As of 2020, 01st April, Malaysia recorded 142 new cases of COVID-19 and 45 total deaths with total cases of 2,908 have been reported nationwide¹. The major hotspots or area most infected are in Selangor and Kuala Lumpur.

A comprehensive response from the public health sector depending on the invasiveness of the virus and its spread highlights the fact that the recent COVID-19 outbreak should be taken seriously that in terms of number of patients and spread can pose a bigger threat to patients with a primary immunodeficiency (PID).

¹ Portal Rasmi Kementerian Kesihatan Malaysia: <http://www.moh.gov.my/index.php/pages/view/2019-ncov-wuhan>



How does it spread?

The transmission mode of COVID-19 is similar to the previous coronavirus outbreaks, spreading from person to person through:

- Respiratory droplets spreading when coughing or sneezing
- Close personal contact with an infected person (shaking hands or touching)
- Touching something with the virus on it and then touching your eyes, nose or mouth with unwashed hands.

The spread is similar to the spread of classic yearly influenza.

Clinical symptoms due to COVID-19 infection

Human coronaviruses commonly cause mild to moderate illness in the general population. So far, the main clinical signs and symptoms reported in this outbreak include *fever, dry cough, tiredness and shortness of breath*. Some patients may also experience *aches and pains, nasal congestion, sore throat, anosmia and/or diarrhoea*. These symptoms are usually mild and begin gradually. Some people become infected but don't develop any symptoms and do not feel unwell.

Approximately 80% of the affected people recover from the disease without needing special treatment.²

Should PID patients get systematically tested for COVID-19?

The situation is changing all the time and we advise you to monitor for the latest advice applicable to your local area.

The test is mainly via a nasal swab that would be sent to a dedicated microbiology laboratory for detection of this virus by polymerase chain reaction (PCR) method and the results are usually reported in 4 to 6 hours.

However, in light of shortage of manpower and availability of PCR, most national guidelines do not include or manage patients with chronic diseases including PID differently than other patients. However PID may have to be treated differently especially when admitted to hospital. PID patients may experience "unusual or atypical" COVID-19 symptoms. They may not have fever even after being infected with a serious virus. This has led to difficulties in diagnosing coronavirus among PID patients. Therefore, doctors should record in the patient's medical records as follows: "Due to this patient having primary immunodeficiency disease, the patient may not show symptoms of fever even when the disease or infection is severe".

Therefore it is deemed prudent to have all PID patients admitted to hospital tested for COVID-19 virus as a baseline and to monitor progress in hospital. The frequency

² The World Health Organization. Q&A on coronaviruses (COVID-19). 23 February 2020. Available at: <https://www.who.int/news-room/q-a-detail/q-a-coronaviruses> [Accessed 04-03-2020].



of repeating the tests would follow the latest KKM recommendations, but may need to be increased as necessary in PID patients. Other PID patients who are not admitted to hospital but who may need eventual testing for COVID-19 must be given due priority.

PID patients with humoral deficiencies will not produce antibodies towards COVID-19, thus rapid test kits detecting IgM and IgG towards COVID-19 should not be utilised in these subsets of patients.

Our recommendations for PID patients

There is currently no data pointing to whether PID patients are actually at higher risk of more severe disease from COVID-19 (as per the WHO, CDCs and PID expert healthcare professionals and NMO representatives along with patients themselves). However, it is known that PID patients are susceptible to infections with some leading to severe complications. Hence in this time span of COVID-19 pandemic, the PID patients face similar risk or even more.

What should PID patients do during the COVID-19 outbreak?

Patients with PID living in areas of high prevalence should follow every precaution and local, regional and national recommendations (e.g. staying at home, teleconsultation, work from home).

However, for PID patients, beyond the precautions mentioned above, we advise prompt phone contact with a doctor if an infection is suspected (should it be your PID expert, or your GP who should probably let your PID expert know about your condition in order to provide the best advice for each PID patient's specific condition). Patients should always keep the details of their PID diagnoses and medical charts, medications, PID expert doctor and next of kin at hand, in case urgent medical care is needed.

PID patients with lung and/or heart complications, solid organ transplants PID patients recipients, recent recipients of haematopoietic stem cell transplantation or gene therapy, PID patients undergoing treatment for a cancer (malignancy), as well as patients under immunosuppressive or immunomodulatory drugs (for autoimmune or inflammatory or autoinflammatory complicating the PID course) should remain on their specific therapy until recommended otherwise by their PID expert physician.

Immunosuppressive drugs (in particular corticosteroids), might limit signs of infections (fever and other clinical symptoms). It is recommended to contact your PID expert physician in case of unexplained change in clinical status including your well-being.

PID patients with significant respiratory issues (severe asthma, bronchiectasis or chronic respiratory failure) should receive special attention (as for any risk of respiratory infection).



Keep in mind that it is always essential to regularly continue to take the treatment for your PID.

Plasma Derived Medicinal Products (PDMPs), such as immunoglobulins (IVIG or SCIG) are safe and will protect you from many other infections. **Do not change or alter the IVIG/SCIG dose without consulting the clinical immunologist.**

If you are on immunosuppressive or immunomodulatory treatment, we strongly advise not to undertake any treatment changes except upon your medical caregiver's suggestion.

For everyone, including PID patients, we strongly recommend you to keep yourselves updated of the latest information on the COVID-19 outbreak in your region, for example provided by the Ministry of Health / Kementerian Kesihatan Malaysia (KKM), the Crisis Preparedness and Response Centre for Disease Prevention (CPRC) and The State CDC Officer of each respective state of Malaysia.

Plasma Derived Medicinal Products (PDMPs), including Immunoglobulins

According to a statement from Plasma Protein Therapeutics Association (PPTA) there is no risk of transmission of COVID-19 into **PDMPs**.³

For PID patients who are on immunoglobulin replacement therapy, there is no evidence to date that more frequent dosing of immunoglobulin will offer more protection. Whilst immunoglobulin replacement therapy provides protection against a range of infections, it does not guarantee immunity against coronavirus. PID patients on immunoglobulin replacement therapy who are showing poor clinical signs and are seriously ill should be quickly considered as candidates for convalescent plasma. It is possible that convalescent plasma from individuals that have recovered from COVID-19 infection will contain antibodies to SARS-CoV-2 and might be effective against the infection.

For PID patients whose condition does not require regular immunoglobulin replacement therapy (IRT), there is no need to start Immunoglobulin infusions since antibodies targeting COVID-19 is not expected to be contained in the existing preparations.

There is no recommendation to give immunoglobulins to the general population to protect or treat people against COVID-19.

National guidelines provided by Kementerian Kesihatan Malaysia & authorities should be followed.

We should stress the fact that only your PID expert – clinical immunologist would know best what to recommend to you.

³ The Plasma Protein Therapeutics Association. New Coronavirus (SARS-CoV-2) and Plasma Protein Therapies. Updated February 17, 2020. Available at: <https://www.pptaglobal.org/media-and-information/ppta-statements/1055-2019-novel-coronavirus-2019-ncov-and-plasma-protein-therapies> [Accessed 04-03-2020].



PRACTICAL GUIDELINES for PID PATIENTS ADMITTED TO HOSPITALS DURING COVID-19 PANDEMIC ENGAGEMENT

A. IN PATIENT

COVID-19 test is indicated. To treat as COVID-19 patients until result is obtained

Observe all existing Standard Operating Procedures as a COVID-19 patient.

Added emphasis include:

1. Strict isolation including barrier nursing especially infant and young children
2. One dedicated nurse is required who does not nurse other patients at the same time.
3. Observe strict hygiene.
4. Avoid touching as best as possible.
5. NO visitors except specific care givers / baby sitter, e.g. mother, nanny /nurse maid.
6. For SCID (severe combined immunodeficiency), mandatory COVID-19 and other viral studies testing of possibility of co-infections – e.g. RSV, influenza.
7. Microbiological studies for bacteria & fungus.
8. Lab Investigation:
FBC (look for absolute lymphocytopenia, thrombocytopenia), CRP, renal profiles, liver enzymes, ferritin, D-Dimer, LDH.
9. **Do not use antibody serology studies to diagnose infections in patients with PID as they do not mount proper antibody response, Use direct microbiological studies such as cultures and PCR.**

B. PID PATIENTS RECEIVING IMMUNOGLOBULIN REPLACEMENT THERAPY

PREFERABLY IN HOSPITAL WHERE CONSULTATION WITH A CLINICAL IMMUNOLOGIST IS READILY AVAILABLE

Observe COVID-19 care guidelines. Strict hygiene is mandatory.

A dedicated nurse is available.

Wherever possible a room is provided.

Duration of stay in Day care to be kept to a reasonable minimum at all times.

- i. Arrange for the required immunoglobulin product beforehand.
- ii. Patient enters day care when immunoglobulin products is available.
- iii. Patient is masked, hand sanitisation is observed.
- iv. Once immunoglobulin infusion completed, waiting time for administrative chores, e.g. appointment, letters kept to bare minimum.

Infusion in children should not be more than 4 hours. In doubt consult the clinical immunology team.



Ensure, the patient washes or sanitise their hands - on entry to Day care room and on leaving after completing of IRT.

Follow Protocol: Consensus recommendation for the use of Immunoglobulin Replacement Therapy in Immunodeficiency. APIIEG (Asia-Pacific Immunoglobulin for immunology Expert group. 2nd edition July 2009.

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About MSAI

The Malaysian Society of Allergy and Immunology, MSAI was founded by a small group of dedicated doctors on May 5, 1997 to provide better patient care and Quality of Life (QOL) for patients affected by allergy and primary immunodeficiency diseases (PID). MSAI is a member of the World Allergy Organization (WAO). Dedicated to its mission to create greater awareness on allergy and Primary Immunodeficiencies (PID) among doctors in Malaysia & in South-East Asia region, MSAI has hosted many symposiums, workshop and international congress. We have now embarked on our mission to establishing "Clinical Immunology" as a standalone subspecialty in Malaysia. Nonetheless, MSAI continues to contribute during these challenging times and is highlighting the plight of PID patients on the current background COVID-19 pandemic, to ensure the community and health care professionals on recommendations to manage PID patients with a potential risk of contracting the disease, thus guiding everyone on preventive measures and overall management.

About MyPOPI

Persatuan Pesakit Imunodefisiensi Primer Malaysia, MyPOPI (Malaysian Patient Organisation for Primary Immunodeficiencies) is a not for profit national patient organization and non-governmental association dedicated to improving awareness, access to early diagnosis and optimal treatments and care for primary immunodeficiency (PID) patients in Malaysia. Established in August 2014. MyPOPI is also a national member organization of International Patient Organisation for Primary Immunodeficiencies (IPOPI).

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Appendix

CONSENSUS RECOMMENDATIONS FOR THE USE OF IMMUNOGLOBULIN REPLACEMENT THERAPY IN IMMUNE DEFICIENCY

Practical aspects of IVIg replacement

On initiation of IVIg replacement therapy, a loading dose may be considered, with 1g/kg given either as a single dose or as several smaller doses over a few days. Doses should be rounded to the nearest amount contained within a vial rather than discarding IVIg. The half life of naturally occurring IgG in the normal host is approximately 21-28 days. There are various half lives quoted for different IVIg products (Table 1).

Maintenance doses are generally commenced at 0.4-0.6g/kg given each 3-4 weeks, and again doses should be rounded to finish each vial rather than discard IVIg. A higher maintenance dose of 0.6g/kg/4 weeks in adults and 0.8g/kg/4 weeks in children has been shown to reduce number (3.5 vs 2.5 per patient) and duration (33 vs 21 days) of infections amongst XLA and CVIDs patients.⁵ For some patients, particularly those on home IVIg therapy, more frequent infusions may be more convenient and are an acceptable alternative, with the same cumulative dose per month administered.

Use of topical analgesia prior to obtaining venous access should be considered, particularly in children. Options include local anaesthetic creams such as prilocaine and lignocaine (EMLA[®]; effective after 30-40 minutes), amethocaine (Ametop[®]; effective after 20-30 minutes), or the coolant spray ethyl chloride (effective immediately).

Each IVIg product has product information with suggested infusion rates, usually advising to commence each infusion slowly and increasing as tolerated. Most IVIg infusions will take 2-4 hours to complete. The Intragam[®]P data sheet suggests a starting rate of 1ml/minute, increasing each 15 minutes to 4ml/minute maximum, with no modification suggested for weight, however slower rates should be used in infants and young children. Other published recommendations include starting each infusion at 0.5-1mg/kg/min increasing to a maximum of 4mg/kg/minute,¹ with one study suggesting that rates of over 15mg/kg/min⁶ can be tolerated by selected patients.

Prior to starting each infusion, baseline recordings of heart rate, respiratory rate, blood pressure and temperature should be recorded, with repeat recordings if required. The batch numbers of IVIg product used during each infusion must be noted in the patient's records to enable retrospective verification in the event of transmitted infection.

IVIg infusions have been shown to be sufficiently safe to enable patients (adults and children) to receive infusions at home, with the help of a responsible adult. Home therapy is an option for patients established on IVIg who are not having infusion reactions. Therapy cannot be initiated at home because of the increased frequency of adverse reactions. In one large study of 290 patients

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| Intragam |
| Other Immunoglobulin product |

Table 2 Asia Pacific intramuscular and subcutaneous immunoglobulin products

| Product | Form | IgA | Excipient | Indicated for IgG replacement in PID | |
|--------------------------|-----------------|-------------------------------|-----------|--------------------------------------|--------|
| | | | | IM use | SC use |
| Gammanorm [®] | 16.5% solution | <0.082mg/ml | Glycine | Yes | Yes |
| Normal Immunoglobulin-VF | 16% solution | Not available | Glycine | Yes | No |
| Subgam [®] | 14-18% solution | Max 0.2% w/w of total protein | Glycine | Yes | Yes |