Persistent SARS-CoV-2 Infection:

An Auckland Regional approach to assessment and management

Background

Persistent SARS-CoV-2 infection (PSI) is an emerging complication of COVID-19 that affects profoundly immunocompromised patients. While rare, it is an important condition as PSI can cause progressive, sometimes fatal pulmonary disease and could plausibly generate SARS-CoV-2 variants of concern. PSI has been described by case reports and case series. Due to its rarity, the strength of evidence derived from these publications is weak, however there are common features that inform the approach discussed in this document.

The purpose of this document is to outline a regionally-agreed approach to patients with suspected or confirmed PSI and highlight the benefits of early identification of those at risk.

Acute COVID-19 in immunocompromised people (defined here as the first 14 days of illness) should be managed the same as the general population as described in the New Zealand guideline for Clinical Management of COVID-19 in hospitalised adults, with some additional considerations. The primary clinician(s)/specialty coordinating the usual care of an immunocompromised person should be involved in the decision-making, where possible, as many effective therapies for COVID-19 involve immune modulation and efficacy data are limited in the immunocompromised. Some additional considerations for profoundly immunocompromised people are described at the end of this document.

People at Risk of Persistent SARS-CoV-2 Infection

A wide variety of pre-disposing immunocompromised states have been described in association with PSI. [1-15] [16-18] However the most commonly reported is profound B-cell depletion, either due to an underlying immunodeficiency or as a result of targeted treatment, especially anti-CD20 agents (e.g. rituximab). [1]

While not an exhaustive list, the following are considered to increased risk of PSI:

- Receipt of anti-CD20 monoclonal antibody therapy (e.g. rituximab) within the past 6 months
- Treated B-cell haematologic malignancy (e.g. multiple myeloma, chronic lymphocytic leukaemia, lymphoma) within the past 6 months
- Primary or acquired hypogammaglobulinaemia (IgG <3), even if now on replacement immunoglobulin
- Primary immunodeficiency associated with severe B-cell or combined cellular defects
- Solid organ transplant, haematopoietic stem cell transplant or CAR-T cell therapy within the past 6 months
- Graft-versus-host disease currently treated with multi-modal immunosuppressive therapy
- Advanced HIV with CD4 <200
- Other conditions (on case by case basis) felt to have profound immunocompromise on the basis of combined immunosuppression, functionally equivalent to the above groups.

A person meeting any of these criteria requires discussion with an Infectious Diseases Consultant prior to considering removal from isolation precautions (and ideally as early as possible following diagnosis of COVID-19) as traditional 'duration of illness' strategies may not apply.

Mildly or moderately immunocompromised people (e.g. atopic dermatitis treated with ciclosporin, or systemic lupus erythematosus treated with hydroxychloroquine alone) do not appear to be at risk of PSI, and are likely to experience an illness similar to age and comorbidity-matched immunocompetent controls.

Identification and Assessment of Persistent SARS-CoV-2 Infection

In people meeting the criteria outlined above, PSI should be actively considered by a multi-disciplinary team of clinicians, including (at least) infectious diseases, public health and a clinician responsible for managing the patient's underlying condition (e.g. haematologist, immunologist, rheumatologist).

The most common clinical syndrome appears to be persistent or relapsing typical COVID-19 symptoms, particularly fever, cough and dyspnoea. [1,10] However, asymptomatic PSI has been described[13]

Serial radiography of people with PSI has demonstrated progressive pulmonary interstitial changes with fluctuating ground-glass infiltrates, occasionally thought to mimic organising pneumonia. [5,6,11,12,16,17] However, treatment with further immunosuppression (e.g. corticosteroids) in such cases has been associated with increased viral replication and deterioration of respiratory symptoms.

SARS-CoV-2 viral load in upper respiratory tract samples (as measured by both PCR cycle threshold (Ct) and viral culture) can fluctuate over time, however in the majority of reports remains persistently positive. In addition, persistent SARS-CoV-2 viraemia has been frequently described. [1] As a result, it is likely that people with PSI can remain infectious to others as long as their infection persists.

Additionally, in some patients upper respiratory tract PCR tests can become negative (usually transiently) despite persistent SARS-CoV-2 infection in other body compartments. [7]

Despite such complexities, we generally diagnose persistent SARS-CoV-2 infection when:

1) ≥ 20 days since infection[$] AND
2) Persistent and / or relapsing symptoms of COVID-19 AND
3) Persistent positive SARS-CoV-2 PCR tests (*OR* rapid antigen, if PCR unavailable) * [&] AND
4) No evidence of serologic response[#] to infection

[$]It may be reasonable on a case-by-case basis to treat as 'possible' PSI if meeting other criteria between day 14 and 20 of illness

*While not validated in most laboratories, a positive blood PCR test is strongly suggestive of persistent infection, regardless of symptoms and serologic response.

[&] Culture-positive SARS-CoV-2 from upper respiratory tract samples after day 20 of illness would also support the diagnosis of persistent infection. A low PCR cycle threshold (Ct) (e.g. less than 25) is associated with increased likelihood of positive viral culture and may be considered equivalent for the purposes of this definition.

[#]Serologic response is defined as a incrementing anti-spike IgG result on locally available SARS-CoV-2 antibody assay. It is important to acknowledge that 'serologic respose' in itself might not represent an effective immune response (particularly if low-titres) and will be influenced by administration of passive anti-SARS-CoV-2 antibody therapy including IVIG, convalescent plasma and monoclonal antibody treatment.

If a person is suspected of having PSI in an outpatient setting, assessment in hospital is warranted, with appropriate COVID-19 infection prevention measures in place. This assessment should include aspects described in the New Zealand guideline for Clinical Management of COVID-19 in hospitalised adults, as well as a SARS-CoV-2 PCR test (with Ct value) and SARS-CoV-2 serology.

Patients with PSI need to remain in isolation, until clearance is advised by a multidisciplinary team including a Public Health physician.

Treatment of Persistent Infection

In addition to prolonged illness, PSI is associated with accelerated viral evolution [3,8,13,15-17,19] This has been shown to increase the rate of mutations in the S-gene, which may plausibly select for variants able to escape the patient's ineffective immune response. PSI has recently been suggested as a path to the evolution and emergence of the Omicron variant of concern. [20,21] As such, it is hoped that early identification and treatment of PSI will reduce potential for viral mutagenesis, reduce the emergence of new variants, and reduce the risk of spread to the wider population.

Treatment of PSI with the goal of 'clearance' of viral infection is informed by case series, which support the combination of an effective antiviral with an effective anti-SARS-CoV-2 antibody therapy as the most effective approach. [1,2 7,9,11,17]Antiviral monotherapy appears to be associated with transient reduction in viraemia and systemic inflammatory response, but not with cure. [1,5,6,12,17] Antibody monotherapy is not always associated with cure, and has been shown to be associated with viral escape variants. [8,11,14,17,19,22-24]

Based on current availability of therapeutics in New Zealand, regardless of PSI illness severity, we currently recommend:

a) Admission to hospital

b) Repeat baseline investigations:
    a. as per New Zealand guideline for Clinical Management of COVID-19 in hospitalised adults,
    b. SARS-CoV-2 serology
    c. Swab for SARS-CoV-2 PCR with Ct value and send to ESR for viral culture and whole genome sequencing

c) Consider and evaluate for alternative cause of symptoms, including other opportunistic infections.

d) Reduction in 'usual' immunosuppressive medication should be considered (if possible) in discussion with the patient's primary clinician. The introduction of additional immunosuppression (e.g. corticosteroids) should be avoided unless required for treatment of acute (or relapsed) hypoxic COVID-19 pneumonitis.

e) Antiviral therapy:
    a. 5 day course of remdesivir (200mg IV on Day 1, then 100mg IV daily on Day 2 to 5)
    b. Oral antiviral medication (e.g. nirmatrelvir/ritonavir) may be considered if available, although there is no evidence yet of these agents' efficacy in PSI

f) Anti-SARS-CoV-2 antibody therapy, at any time during antiviral treatment. Either:
    a. Monoclonal antibody therapy with predicted efficacy against the likely or confirmed infecting SARS-CoV-2 variant (preferred option)
    b. Two 'units' of high-titre convalescent plasma from recovered and vaccinated donors (discuss with transfusion medicine specialist at the New Zealand Blood Service).

Follow-up and Removal From Isolation

After a person is considered to have PSI, clinical and virological follow-up is necessary until there is objective evidence supporting clearance of infection. There are limited data to guide this decision, and so we suggest that follow-up involves decision-making from a multidisciplinary team of clinicians involved in that person's care, including an Infectious Diseases and Public Health physician.

It is important to carefully explain to the patient the rationale for extending the duration of isolation, that symptoms may relapse, and that improving clinical course does not necessarily indicate clearance of SARS-CoV-2 infection.

While follow-up plans should be individualised, the following may be appropriate for most people:

- Extend duration of isolation until planned re-assessment, which would commonly occur two or three weeks later. A person may need to remain in isolation with regular re-assessments of their status (e.g. every two weeks).
- Enrol in local 'covid Hospital in the Home' programme, or similar hospital-based outpatient monitoring service for symptom monitoring (unless staying in managed isolation and quarantine facility).
- Regular nasopharyngeal SARS-CoV-2 PCR with Ct value (on the same PCR platform to allow comparison).
- Repeat serology after 13-20 days (i.e. prior to planned review of need to extend isolation) if not treated with anti-SARS-CoV-2 antibody therapy (NB anti-spike monoclonal antibody therapy can be detected as anti-S antibody in SARS-CoV-2 serology assays).
- Formal clinical evaluation should be considered if deterioration in symptoms or inability to sufficiently perform remote assessment

Many patients with confirmed COVID-19 will have this 'flagged' on their electronic health record. It is important to ensure that those at risk of PSI, or with confirmed PSI, remain flagged as a patient with confirmed COVID-19 until they have formally been considered recovered and removed from isolation.

The decision of when to remove a person with PSI from isolation should be made after a multidisciplinary discussion, including Infectious Diseases, Medical Officer of Health and the person's primary caring clinician (e.g. Haematology). As part of this discussion, the group should consider the individual's social circumstances and their individual risk to the general population (e.g. anticipated contact with other vulnerable people through occupation or hospital-based care).

The following criteria might be considered reasonable grounds to remove a patient from isolation:

1. Improving or resolved COVID-19 symptoms AND
2. Development of anti-Spike antibodies OR treatment with anti-SARS-CoV-2 antibody therapy AND

3. Two upper respiratory PCR tests (or RAT tests if PCR unavailable) > 48 hours apart that are either negative OR with Ct value nearing upper limit of detection (e.g. >35 cycles)

After de-isolation, all people with PSI need to be informed that they should be re-tested for SARS-CoV-2 if they develop COVID-19 symptoms, as they may be at risk of both PSI relapse and acquisition of a new SARS-CoV-2 infection.

Acute COVID-19 in People at Risk of PSI : Additional Considerations

As described earlier, the management of acute COVID-19 is the same for both immunocompromised people and the general adult population. However, in addition, immunocompromised outpatients (regardless of vaccination status) with acute COVID-19 may benefit from treatment with anti-SARS-CoV-2 monoclonal antibodies (e.g. casivirimab/imdevimab or sotrovimab) to reduce risk of progression to severe COVID-19.

Also, there are limited data that suggest benefit from treatment of select hospitalised patients with anti-SARS-CoV-2 antibody therapy. The RECOVERY trial demonstrated reduction in mortality for patients treated with casivirimab/imdevimab who were seronegative (as measured by anti-Spike antibody). [25] In contrast, a more recent study did not show any benefit from treatment with sotrovimab for hospitalised patients. [26] Additionally, while there are currently no studies that suggest benefit from convalescent plasma (CPL) in acute COVID-19, a post-hoc subgroup analysis of the convalescent plasma domain of REMAP-CAP suggested benefit among immunocompromised patients, and is re-opening recruitment for immunocompromised patients in 2022. [27]

Therefore, if available, hospitalised immunocompromised patients should be considered for treatment with a monoclonal anti-SARS-CoV-2 antibody therapy with anticipated efficacy against their likely infecting SARS-CoV-2 variant. If such an agent is not available, and if clinical equipoise regarding the role of high-titre convalescent plasma in profoundly immuncompromised patients remains, CPL could be considered as it is plausible that select people with acute COVID-19 who are at risk of PSI might benefit from CPL by i) reduction in risk of progression to severe / critical COVID-19 and ii) reduced risk of developing PSI.

Below is a summary of how to approach acute COVID-19 in people at risk of PSI:

1) Manage all patients as described by New Zealand guideline for Clinical Management of COVID-19 in hospitalised adults including early antiviral therapy and anti-SARS-CoV-2 antibody therapy. There is a lack of evidence regarding the utility of immunomodulation therapy in the immunocompromised population. However, corticosteroids will usually be appropriate for those with moderate or severe/critical disease and further immunomodulatory therapy with tocilizumab/baricitinib may be indicated (e.g. in those who are deteriorating with a hyperinflammatory phenotype, where it is felt a clinical benefit is likely and outweighs any risk); these decisions could be discussed with the individual's primary physician and the local Infectious Diseases consultant.
2) Additionally, request 'COVID-19 serology' as part of baseline testing at point of hospital admission
3) If the patient requires hospital-level care for moderate to critical illness, should be reviewed (remotely or in-person) by an Infectious Diseases consultant
4) Patients at risk of PSI may be considered for use of CPL if all of the following criteria are met:
    a. Not eligible for anti-SARS-CoV-2 monoclonal antibody therapy

   b. Not eligible for recruitment into a clinical trial of anti-SARS-CoV-2 antibody therapy (monoclonal antibody OR convalescent plasma)
   c. No evidence of serologic response to prior SARS-CoV-2 vaccination or infection
   d. No clinical improvement within first 48 hours of hospital admission OR severe/critical illness
   e. Convalescent plasma is anticipated to have neutralising efficacy against the circulating SARS-CoV-2 variant
   f. The individual's possible benefit is felt to outweigh possible harm after discussion by a multidisciplinary group of clinicians involved in the person's care (including at minimum the primary treating team and an Infectious Diseases physician)
5) If >7 days of illness and prescribing CPL, consider concurrent antiviral therapy
6) All patients at risk of PSI should receive follow-up to observe for possible persistent infection.

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