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BRIEF REPORT
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# A novel protocol for de-isolating moderately and severely immunocompromised COVID-19 patients

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**Abstract:** Immunocompromised coronavirus disease 2019 patients are at a higher risk of prolonged viral shedding than immunocompetent patients. However, as of August 2023, there is no clear international standard for de-isolating vulnerable patients. A comprehensive assessment is advisable based on various information, such as the increase in immune escape of specific mutant strains as well as the patient's innate immunity and vaccination status; therefore, consultation with an infectious disease specialist is recommended. The patient population defined as moderately or severely immunocompromised by the Centers for Disease Control and Prevention and the European Centre for Disease Prevention and Control is significantly broad. A boundary between the two remains to be delineated, and the existing protocols allow the release of patients based on their symptoms alone. This may lead to an unnecessary extension or premature termination of isolation. In this study, we searched for studies, particularly those that used real-world data, discussed the results with experts in our hospital, and proposed new isolation criteria based on both testing and clinical symptoms. We classified patients into three groups namely severely, moderately, and mildly immunocompromised, defined by their background and the administration of immunosuppressive drugs. A separate flowchart for ending isolation is indicated for each group. This standard may be a useful support material, especially for non-specialists. Nevertheless, our criteria must be revised and added continuously; accumulating real-world data to support revision of and addition to the list is becoming increasingly important.

***Keywords*:** prolonged viral shedding, SARS-CoV-2, anti-CD20 therapy, hematological malignancy, solid tumor

## Introduction

Effective isolation of coronavirus disease 2019 (COVID-19) patients is essential to prevent outbreaks in hospitals (*1*). As of August 2023, no established criteria exist to de-isolate these immunosuppressed populations at risk of prolonged viral shedding in Japan. This situation may consequently result in suboptimal strategies such as insufficient or unnecessarily extended isolation.

Herein, we propose a novel strategy to de-isolate patients at risk of prolonged viral shedding in medical facilities.

## Materials and Methods

This protocol was developed based on current evidence and discussions with various experts last February 2023. Our authors include four certified infectious disease specialists (Iwamoto N, Ishikane M, Yamamoto K, and Ohmagari N), two certified nurses in infection prevention and control (Horii K, Kubota S), three experts in hematology (Hangaishi A, Shimazu H, Togano T), one expert (Yamashita H) in autoimmune disease, and one expert in solid tumor (Yamada Y).

Also, we performed a scoping review of searched the latest English-written articles on PubMed describing the real-world data. We searched using words including "COVID-19", "SARS-CoV-2", "immunocompromised", "seroconversion rate", "vaccination", and some specific immunosuppressive conditions like "B-cell depletion therapy", "chemotherapy", "hematologic malignancy", and "malignancy".

We initially decided to propose a flowchart and a detailed list of immunosuppressive drugs. We roughly divided the list into three categories based on the magnitude of immunosuppressive effect of the drug: mild, moderate, and severe. For the mild category,

we enlisted drugs with no evidence of prolongation or patients' seroconversion rates after the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) messenger ribonucleic acid (mRNA) vaccine was approximately > 90%. For the moderate category, we enlisted drugs with evidence of prolongation or patients' seroconversion rates after the SARS-CoV-2 mRNA vaccine was approximately 70–90%. For the severe category, drugs with profound immunosuppressive effects or clear evidence of extended viral shedding were included.

Our novel strategy has passed strict peer reviews by our authors and the cancer board in our hospital, which consists of 21 physicians with expertise in malignancy.

## Results and Discussion

We introduce a novel protocol to de-isolate COVID-19 patients with sustained contagiousness (Figure 1 and Table 1). Our flowchart shows the isolation of moderately or severely immunocompromised patients for at least 20 days. This strategy is based on the current guidelines of the Centers for Disease Control and Prevention (CDC) (*2*). However, for example, patients evaluated as severely immunocompromised will likely be long shedders, trespassing the 20-day border (*3*). Therefore, according to our criteria, a negative PCR test is required to de-isolate this special population. If the cycle threshold (Ct) value is measurable, it should be > 35, which is generally considered the cut-off for recovering SARS-CoV-2 in the culture of the upper airway sample (*4*). We rejected testing twice 24 hours apart as polymerase chain reaction (PCR) testing has excellent sensitivity and specificity, and we may be able to ignore the small risk of false negatives. In addition, although there is a risk of COVID-19 relapse in these populations, it will not occur within a day.

*Severely immunocompromised patients*

Multiple studies have attributed the prolongation of viral shedding to severely impaired B-cell function, which minimizes the humoral response. B-cell depletion is profound when patients receive B-cell depletion therapy (BCDT), such as the anti-cluster of differentiation (CD) 20 therapy drug (*5*). CD20 is an antigen widely expressed on the surface of B cells that plays a critical role in developing plasma cells from naïve B cells to the terminal phase. Thus, the blockade of CD20 hinders the development of B-cells from the beginning (*6*).

In addition, other BCDT, such as anti-CD19 therapy (*7*), and lymphopenic hematological malignancy receiving active chemotherapy, will likely create the same situation.

Bruton tyrosine kinase (BTK) is an enzyme that regulates B-cell proliferation and activation by stimulating B-cell receptor signaling (*8*). BTK inhibitors have a tremendous negative impact on B-cell function among individuals receiving these drugs whose seroconversion rate is substantially low (*9*).

Other potent factors that have profound adverse effects on immunogenicity include X-linked agammaglobulinemia (*10*), hematopoietic transplantation, chimeric antigen receptor-T cell therapy, lymphoma, B-cell related malignancy, solid tumor transplant, T-cell depletion therapy, and primary and acquired immunodeficiency (*11*).

The Ministry of Health, Labour and Welfare in Japan regulates the criteria for administering tixagevimab/cilgavimab (TIX/CIL) to severely immunocompromised patients (*12*). TIX/CIL is a monoclonal antibody combination consisting of two neutralizing antibodies against SARS-CoV-2 and is effective in preventing COVID-19. Owing to its limited distribution in

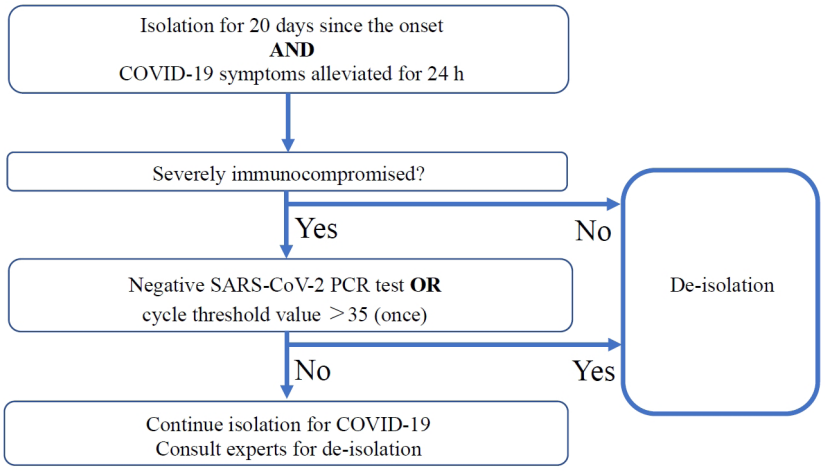


**Figure 1. A flowchart for de-isolating moderately or severely immunocompromised patients.** Patients categorized as "severely immunocompromised" are as follows: *i*) Primary immunodeficiency with antibody production failure or complex immunodeficiency, *ii*) Patients within 1 year of receiving B-cell depletion therapy, *iii*) Patients receiving Bruton's tyrosine kinase inhibitors, *iv*) Chimeric antigen receptor (CAR) recipients, *v*) Patients receiving immunosuppressive drugs for chronic graft-versus-host disease, *vi*) Recipients for hematopoietic cell transplantation, *vii*) Patients with hematologic malignancies undergoing aggressive therapy, *viii*) Lung transplant recipient, *ix*) Within 1 year of solid organ transplant, other than lung transplant, *x*) Solid organ transplant recipients recently treated with cell-depleting agents for acute rejection; *xi*) HIV patients with CD4 < 50/mm$^3$.

**Table 1. Criteria of the drugs classified by degree of immunosuppression**

| Degree | Large category | Category | Examples of the drugs |
|---|---|---|---|
| Mild | Steroids | Steroids | Equivalent to prednisolone < PSL 20 mg/d or < 2 weeks |
| | Immune checkpoint inhibitors | CTLA-4 inhibitors | Ipilimumab |
| | | PD-1 inhibitors | Nivolumab, pembrolizumab |
| | | PD-L1 inhibitors | Avelumab, atezolizumab, durvalumab |
| | Tyrosine kinase inhibitors | ALK inhibitors | Crizotinib, ceritinib, alectinib, brigatinib |
| | | BCR-Abl inhibitors | Imatinib, nilotinib, dasatinib, bosutinib |
| | | EGFR inhibitors | Cetuximab, panitumumab, vandetanib, lapatinib, gefitinib, erlotinib, lenvatinib, afatinib, osimertinib |
| | | HER2 inhibitors | Trastuzumab, pertuzumab |
| | | PDGFR α/β inhibitors | Gefitinib, imatinib, lenvatinib, nintedanib, pazopanib, regorafenib, sorafenib, sunitinib |
| | | VEGFR inhibitors | Ramucirumab, bevacizumab, lenvatinib, nintedanib, regorafenib, pazopanib, sorafenib, sunitinib |
| | Serine/threonine kinase inhibitors | BRAF inhibitors | Vemurafenib, dabrafenib |
| | | CDK 4/6 inhibitors | Palbociclib, sorafenib, ribociclib |
| | Hormonal therapies | Hormonal therapies | Tamoxifen |
| | Cytotoxic drugs | DNA synthesis inhibitors | Methotrexate(< 20 mg/week) |
| | | Folic acid synthesis inhibitors | Azathioprine(< 3 mg/kg/day), mercaptopurine(< 1.5 mg/kg/day), |
| | Interleukin inhibitors | IL-4/13 inhibitors | Dupilumab |
| | | IL-12/23 inhibitors | Ustekinumab |
| | | IL-17 inhibitors | Ixekizumab, secukinumab |
| | DMARDs | DMARDs | Hydroxychloroquine, salazosulfapyridine, igratimod, bucillamine, leflunomid |
| | Gut-specific integrins | Anti-α4β7integrin | Vedolizumab, natalizumab |
| | Others | Drugs associated with multiple sclerosis | Dimetyl fumarate, fingolimod, glateramer acetate, interferon-β 1a |
| Moderate | Steroids | Steroids | Equivalent to prednisolone ≥ PSL 20 mg/d and ≥ 2 weeks |
| | DMARDs | DNA synthesis inhibitors | Mercaptopurine(≥ 1.5 mg/kg/day), azathioprine(≥ 3 mg/kg/day), mycophenolate mofetil, mizoribine |
| | Cytotoxic drugs | Alkylating drugs | Temozolomide, ranimustine, melphalan, ifosphamide, cyclophosphamide |
| | | Antibiotics | Doxorubicin, epirubicin, idarubicin, aclarubicin, amrubicin, daunorubicin, bleomycin, mitomycin C, actinomycin D, |
| | | Antimetabolites | Fluorouracil/tegafur, gemcitabine, capecitabine, cytarabine |
| | | Calcineurin inhibitors | Tacrolimus, cyclosporin A |
| | | Folic acid synthesis inhibitors | Methotrexate(≥ 20 mg/week) |
| | | Microtubule inhibitors | Paclitaxel, docetaxel |
| | | Platinum-based drugs | Cisplatin, carboplatin, nedaplatin |
| | | Proteasome inhibitors | Bortezomib |
| | | Topoisomerase inhibitors | Irinotecan, nogitecan |
| | Immunomodulators | CTLA-4 | Abatacept |
| | | IL-2 inhibitors | Basiliximab |
| | | IL-6 inhibitors | Tocilizumab, sarilumab |
| | Tyrosine kinase inhibitors | JAK inhibitors | Baricitinib, peficitinib, tofacitinib, ruxolitinib |
| | Molecular-targeted drugs | mTOR inhibitors | Everolimus, sirolimus, rapalimus |
| | | TNF-α inhibitors | Etanercept, certolizumab, golimumab, adalimumab, infliximab |
| Severe | B-cell depleting therapies | Anti-CD19 inhibitors | Inebilizumab |
| | | Anti-CD20 inhibitors | Rituximab, obinutuzumab, ofatumumab |
| | | Anti-CD38 inhibitors | Daratumumab |
| | | Anti-CD52 inhibitors | Alemtuzumab |
| | Tyrosine kinase inhibitors | Bruton kinase inhibitors | Iburutinib, acalabrutinib, tirabrutinib |

Japan, TIX/CIL is approved only for the pre-exposure prevention of COVID-19. As the criteria cover our drug list sufficiently, we diverted the TIX/CIL criteria to de-isolation standards as severely immunocompromised patients.

*Moderately immunocompromised patients*

We defined moderately immunocompromised patients by extracting severely immunocompromised patients from the CDC and European Centre for Disease Prevention and Control (ECDC) criteria (*13,14*). Individuals with solid malignant tumors receiving active chemotherapy can have more sustained viral shedding than healthy patients but are mostly not more extended than patients with hematological malignancies (*15*). Cytotoxic agents such as alkylating agents, antimetabolites, microtubule inhibitors, topoisomerase inhibitors, rapamycin analogs and mechanistic targets of rapamycin (mTOR) (*16*); DNA synthesis inhibitors and folic acid synthesis agents (*17*) have a negative effect. We categorized mercaptopurine > 1.5 mg/kg/day, methotrexate > 20 mg/week, and corticosteroids equivalent to 20 mg/day for more than two weeks, referencing a guideline from the

Infectious Diseases Society of America (*18*).

Biologic agents for autoimmune diseases, Janus kinase inhibitors, DNA synthesis inhibitors, calcineurin blockers, B-cell activating factor inhibitors, methotrexate; corticosteroids (70–90%); and cytotoxic T-lymphocyte-associated protein 4 (< 70%) induce relatively low vaccination response rate, and thus put patients at risk for sustained viral shedding (*17*). Another data showed a reduced seroconversion rate in breast cancer patients receiving cyclin-dependent kinase 4/6 inhibitors (*19*). In a prospective cohort study, the seroconversion rate was reduced two months after receiving the last mechanistic target of rapamycin (mTOR), topoisomerase inhibitors. Additionally, antimetabolites, and alkylating drugs induce a low seroconversion rate (*16*).

Conversely, real-world data have shown an excellent (> 90%) vaccine response rate among patients with autoimmune diseases receiving interleukin (IL)-6 inhibitors tocilizumab and tumor necrosis factor (TNF)-alpha inhibitors (*17*). However, some autoimmune diseases such as rheumatic arthritis are risk factors for viral shedding prolongation, and immunosuppressive drugs are likely to be combined; patients with autoimmune disease are likely to have cumulative immunosuppression (*20*).

*Drugs with minimal effect on humoral response*

Not all cancer patients undergoing treatment should be categorized as moderate. Immune checkpoint inhibitors, such as programmed death-1 (PD-1) and programmed death ligand-1 inhibitors, have minimal impact on vaccine response based on real-world data (*21*).

A prospective cohort study showed that the seroconversion rate of tyrosine kinase inhibitors (TKIs) recipients two months after the second mRNA was not significantly different from the control group (*16*). However, real-world data for each kind of TKIs have been scarce. Another real-world data showed that hormonal therapy for breast cancer patients did not affect the seroconversion rate (*17*).

Immunomodulators, hydroxychloroquine, and salazosulfapyridine are described in this section. Methotrexate (< 20 mg/week), mercaptopurine (< 1.5 mg/kg), and azathioprine (3 mg/kg) should be put into this category (*15,16*).

The IL-4/13, IL-12/23 and IL-17a inhibitors have minimal effect on the seroconversion rate, and are thought to not interfere with T-cell and B-cell responses to vaccination (*15,22*).

Among the drugs used to treat patients with multiple sclerosis, leflunomide, teriflunomide, fingolimod, interferon-beta, glatiramer acetate, dimethyl fumarate, and natalizumab had minimal effect on immunodepleting phase (*17,23*).

*Discussion on the prolongation mechanism*

The prolongation mechanism is complex and is determined by multiple factors such as disease severity, duration, clinical stability, complications, host immunity, vaccination status, variant of the virus (the Omicron variant has spread nationwide since November 2021(*24*)), and immunosuppressive treatment (*20*). Immunologically, T and B cells play a prominent role in the immune response. The acquisition of immunity starts after immunization, previous history of infection, or the receipt of antibody treatment, as dendritic cells regulate the proliferation of $CD4^+$ T-cells into a variety of helper T cells, including Th1, Th2, Th17, T follicular helper cells ($T_{FH}$ cells), and T regulatory cells (*5,20*). The $T_{FH}$ cells help mature naïve B cells as well as in the development of antibodies and memory B cells during germinal center formation (*20*). In this mechanism, drugs can prolong viral shedding by affecting T cells, B-cells, or antibody responses.

The severity of immunosuppression can also be extrapolated from the vaccination effectiveness rate. In a landmark study by Barrière *et al*., antibody titers were measured in four groups after a series of SARS-CoV-2 mRNA vaccinations; all patients in the anti-CD20 therapy group had no immunological response, and most patients in the active hematological malignancy group had low or no response (*25*). Almost half of those receiving active treatment for solid tumors did not achieve an acceptable response rate, while only one had a good response in the healthy group.

*Major criteria issued regarding COVID-19 isolation*

As of August 2023, two major criteria have been issued regarding COVID-19 isolation. The CDC suggests lifting isolation after 20 days when the patient defervesces and is free from other symptoms, provided that the patient is negative from two consecutive SARS-CoV-2 antigen or polymerase chain reaction (PCR) tests, obtained 24 hours apart (*13*). Meanwhile, ECDC suggests a de-isolation when the patient defervesces and is free from other symptoms, provided that SARS-CoV-2 antigen or PCR tests obtained 24 hours apart are negative, or that it has been 20 days after the onset (*14*). CDC recommendations are categorized as fully test-based, whereas ECDC advocates a half-test and half-clinical-based strategy.

However, these criteria are insufficient for several reasons. First, no clear-cut border exists between moderately and severely immunocompromised patients, and each group should have their corresponding isolation policy. Second, the moderately and severely immunocompromised category corresponds to a large number of patients, which may lead to unnecessary isolation of immunocompetent patients. For example, the criteria refer to recipients of active treatment for solid tumors; however, some chemotherapies, such as immune checkpoint inhibitors, have minimal effect on immunosuppression, and

the extension of viral shedding may not occur (*21*). Third, severely immunocompromised patients who shed active SARS-CoV-2 for more than 20 days can discontinue isolation without testing following the ECDC criteria. This loophole may result in an outbreak in the hospital ward (*3*).

*Protocol for de-isolating immunosuppressed COVID-19 patients proposed by this study*

We proposed an original and straightforward protocol for de-isolating immunosuppressed COVID-19 patients. This protocol may help reduce the chance of in-ward outbreaks and the variation of infection control practices among the personnel in charge. To date, after implementing the novel protocol in our hospital in February 2023, there has never been any nosocomial outbreak whose index case is de-isolated immunocompromised patients. To cite another example to support the safety of this protocol, national cancer centers in Japan, where the de-isolating strategies are similar to ours, no outbreaks have occurred yet during the observation period (*26*).

However, several limitations are still yet to be solved. First, the isolation period cannot be determined by only the type of immunosuppressor used. Increased immune escape of specific variants, the patients' innate immunity, and vaccination have a significant role in their immune status. In general, the immunosuppressive effect of drugs is dose-dependent. Therefore, when drugs are combined, their immunosuppressive effects may accumulate. A combination of drugs in the mild category can cause extended viral shedding, which may then be categorized as moderate. Second, as the mechanism of viral shedding prolongation is complex, quantification of the immune status of the patient is unfeasible. Therefore, bias cannot be entirely removed when allocating those immunosuppressive drugs into each category. The list should be modified as real-world data for each drug is collected in the future; however, the process may take time. Third, it is unknown when the immune system recovers after using immunosuppressors. For example, anti-CD20 therapy profoundly reduces both B-cell and T-cell function; however, the recovery mechanism of the patients remains uncertain. Moreover, BCDT recipients may be prone to relapse. Even after de-isolation, these populations may need to be re-isolated if they become symptomatic again. The optimal strategy for these special populations, and the magnitude of impact of COVID-19 relapse remains unknown. Fourth, not all immunosuppressive drugs are included in our list as we could not find credible evidence for some drugs. Since we are exploiting a new frontier in an uncertain area, supporting evidence is scarce, which can be our major limitation.

When evaluating unfamiliar immunosuppressive drugs, it is vital to consider the lymphopenic effect of the drug or investigate whether it can affect the B-cell/T-cell cascade. A report from China described a significantly lower response rate after the second dose of SARS-CoV-2 vaccination among those with lymphocytopenia ($< 1{,}000/mm^3$). The included population received inactivated and not mRNA vaccines. Nevertheless, profound lymphocytopenia may be an indication of poor responders (*27*).

## Conclusion

Despite all the limitations, we firmly believe that our novel de-isolating strategy for the immunocompromised population is meaningful as it is simple enough to follow, particularly for non-experts. In addition, we hope that our work will be evaluated because we optimized de-isolation strategies for "moderate and severe immunocompromised patients. However, these criteria alone cannot decide when to lift isolation; therefore, expert consultation may still be needed. These criteria may need to be modified based on an analysis of real-world data using clinical and virological information.

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