Special Considerations in People Who Are Immunocompromised

Last Updated: February 29, 2024

Summary Recommendations
Prevention of COVID-19
• The COVID-19 Treatment Guidelines Panel (the Panel) recommends COVID-19 vaccination for everyone who is eligible, including those who are immunocompromised, according to the Centers for Disease Control and Prevention's Advisory Committee on Immunization Practices **(AI)**.
• Vaccine response rates may be lower in patients who are moderately or severely immunocompromised. Specific guidance on administering vaccines to these individuals is provided by the Centers for Disease Control and Prevention.
• Clinicians should strongly encourage all household members and close contacts of patients who are immunocompromised to be vaccinated against COVID-19 **(AI)**.
• Currently, antibody tests are not recommended for assessing SARS-CoV-2 immunity following COVID-19 vaccination or for assessing the need for vaccination in a person who is unvaccinated.
Management of Patients With COVID-19 Who Are Immunocompromised
• Clinicians should consult with the appropriate specialists when making decisions about stopping or adjusting the doses of immunosuppressive drugs in patients with COVID-19.
• When selecting treatments for COVID-19, clinicians should consider factors such as the underlying disease; the specific immunosuppressants being used; the severity of COVID-19; and the potential for drug-drug interactions, overlapping toxicities, and secondary infections.
• For nonhospitalized patients with mild to moderate COVID-19 who are immunocompromised, the Panel recommends prompt treatment with antiviral drugs at the doses and durations recommended for the general population **(AIII)**. For more information, see Therapeutic Management of Nonhospitalized Adults With COVID-19.
• For most hospitalized patients with severe or critical COVID-19 who are immunocompromised, the Panel recommends using antiviral drugs and immunomodulatory therapies at the doses and durations recommended for the general population **(AIII)**. For more information, see Therapeutic Management of Hospitalized Adults With COVID-19.
• For patients who are immunocompromised and have prolonged COVID-19 symptoms and evidence of ongoing viral replication, the optimal management is unknown. The data for these approaches are not definitive, but some Panel members would use 1 or more of the following treatment options:
– Longer and/or additional courses of ritonavir-boosted nirmatrelvir (Paxlovid)
– Longer and/or additional courses of remdesivir
– High-titer COVID-19 convalescent plasma from a vaccinated donor who recently recovered from COVID-19 likely caused by a SARS-CoV-2 variant similar to the variant causing the patient's illness
Each recommendation in the Guidelines receives a rating for the strength of the recommendation (A, B, or C) and a rating for the evidence that supports it (I, IIa, IIb, or III). See Guidelines Development for more information.

Introduction

Approximately 3% of people in the United States have immunocompromising conditions.[1] People who are immunocompromised are a heterogeneous population, and the severity of COVID-19 can vary significantly in this group. Some individuals who are immunocompromised may have a higher risk of hospitalization, complications, or death, and some may have outcomes that are comparable to those in the general population.

This section pertains to people who are moderately or severely immunocompromised, which includes those who:

- Are receiving active treatment for solid tumor and hematologic malignancies.
- Have hematologic malignancies (e.g., chronic lymphocytic lymphoma, non-Hodgkin lymphoma, multiple myeloma, acute leukemia) and are known to have poor responses to COVID-19 vaccines, regardless of the treatment status for the hematologic malignancy.
- Received a solid-organ or islet transplant and are receiving immunosuppressive therapy.
- Received chimeric antigen receptor T cell (CAR T-cell) therapy or a hematopoietic cell transplant (HCT) and are within 2 years of transplantation or are receiving immunosuppressive therapy.
- Have a moderate or severe primary immunodeficiency (e.g., severe combined immunodeficiency, DiGeorge syndrome, Wiskott-Aldrich syndrome, common variable immunodeficiency disease).
- Have advanced or untreated HIV infection (defined as people with HIV and CD4 T lymphocyte cell counts <200 cells/mm^3, a history of an AIDS-defining illness without immune reconstitution, or clinical manifestations of symptomatic HIV).
- Are receiving active treatment with high-dose corticosteroids (i.e., ≥20 mg prednisone or equivalent per day for ≥2 weeks), alkylating agents, antimetabolites, transplant-related immunosuppressive drugs, cancer chemotherapeutic agents classified as severely immunosuppressive, or immunosuppressive or immunomodulatory biologic agents (e.g., B cell–depleting agents).

Analyses have found a higher risk of hospitalization or death from COVID-19 in those with a variety of immunocompromising conditions, including rheumatic diseases, hematological malignancies, solid organ transplants, and HIV.[2-7] Factors that increase the risk of severe COVID-19 in the general population, such as older age, chronic kidney disease, cardiovascular disease, and other comorbidities, are significant drivers of risk in people who are immunocompromised. Moreover, some immunodeficiencies seem to increase the risk above and beyond traditional risk factors. For example, there is evidence that individuals who make autoantibodies to type I interferons (proteins that are critical to the protective immune response against viral infections) have a higher risk of severe COVID-19.[8] Similarly, certain classes of medications, such as T cell–depleting or T cell–suppressing agents (e.g., antithymocyte globulin, calcineurin inhibitors, mycophenolate mofetil, belatacept) and B cell–depleting agents (e.g., rituximab, ocrelizumab, obinutuzumab), have been associated with more severe disease and death.[7,9,10]

Prolonged shedding of SARS-CoV-2 has been reported in patients who are immunocompromised. A systematic review found that replication-competent virus could be detected for a median of 20 days in these patients, compared to 11 days in the general population.[11] Prolonged viral shedding may affect SARS-CoV-2 testing strategies and isolation durations for this group of patients. Moreover, case reports suggest that prolonged infections can create evolutionary pressure for the emergence of variants that resist therapies or evade vaccine-induced immunity.[12-14]

For any person who is eligible, clinicians should prescribe therapies for the treatment of COVID-19 as recommended in these Guidelines. However, if logistical constraints limit the availability of therapies, the COVID-19 Treatment Guidelines Panel (the Panel) suggests prioritizing the treatment of patients with COVID-19 who are at the highest risk of clinical progression (see Prioritization of Anti-SARS-CoV-2 Therapies for the Treatment of COVID-19 in Nonhospitalized Patients When There Are Logistical Constraints). Providers should use their clinical judgment when prioritizing patients for treatment and assess a patient's immunocompromised status, age, comorbidities, and vaccination status.

The sections below outline the Panel's rationale for the recommendations on preventing and managing COVID-19 in people who are immunocompromised. Some of the special considerations for patients who are immunocompromised include the timing of COVID-19 vaccination, the management of immunosuppressive medications, and the strategies for treating COVID-19.

Prevention of COVID-19

Vaccination

COVID-19 vaccination remains the most effective way to prevent serious outcomes and death from SARS-CoV-2 infection. The Panel recommends COVID-19 vaccination for everyone who is eligible, including those who are immunocompromised, according to the Centers for Disease Control and Prevention's (CDC) Advisory Committee on Immunization Practices **(AI)**.

Authorized or approved COVID-19 vaccines in the United States are not live-virus vaccines and can be safely administered to patients who are immunocompromised. However, in people who are immunocompromised, the immune response to vaccination may be blunted, and the timing of vaccination requires special consideration. Nevertheless, vaccination is still recommended, as it may confer partial protection, including the protection provided by vaccine-induced, cell-mediated immunity.[15]

The Panel recommends following the CDC's COVID-19 vaccination guidance for people who are moderately or severely immunocompromised. This guidance includes information on the use of the updated 2023–2024 mRNA vaccines, which target the SARS-CoV-2 Omicron variant lineage XBB.1.5. Current CDC guidance allows for the use of additional vaccine doses in people who are moderately or severely immunocompromised.[16] Data on the optimal timing for repeat vaccination in people who are immunocompromised are lacking; the CDC recommends an interval of at least 2 months after the last dose. Other considerations include the patient's current or expected level of immunosuppression, their age, comorbidities, and the time since their last vaccine dose. Clinicians should also account for the prevalence of SARS-CoV-2 infection in the community and whether the patient intends to travel.

A preprint of a large observational study from Israel suggests a potential benefit from administering COVID-19 boosters every 6 months in groups with the highest risk of COVID-19–related hospitalization or death.[17] The CDC-funded VISION Network evaluated the effectiveness of bivalent vaccines between September 13, 2022, and April 21, 2023, at 5 sites in 7 states.[18] Among adults who were immunocompromised, a lower vaccine effectiveness was observed for the bivalent booster, but vaccine effectiveness was sustained against critical COVID-19–associated outcomes, including intensive care unit admission and death. Vaccine effectiveness against hospitalization was 28% during the first 7 to 59 days after receipt of the bivalent dose and declined to 13% by 120 to 179 days; this indirectly supports using a 6-month interval for repeat vaccination.

The pivotal clinical trials that evaluated the safety and efficacy of the COVID-19 vaccines excluded people who were severely immunocompromised; therefore, the data for this population are less robust.[19,20] Observational data suggest that serological responses to vaccines may be blunted in patients who are immunocompromised.[21,22] However, the MELODY trial reported detectable immunoglobulin G spike protein antibodies in approximately 80% of a large cohort of individuals in the United Kingdom who were immunocompromised and had received at least 3 doses of COVID-19 vaccines.[23] Those who had received anti-CD20 therapies within the past year were less likely than other groups in the study to have detectable anti-spike protein antibodies. In another study conducted during the Omicron era, a fourth dose of an mRNA COVID-19 vaccine reduced the risk of SARS-CoV-2 infection and severe COVID-19 among patients receiving treatment for systemic autoimmune rheumatic diseases.[24]

Vaccination of Close Contacts

Clinicians should strongly encourage all household members and close contacts of patients who are immunocompromised to be vaccinated against COVID-19 **(AI)**. Before Omicron became the dominant circulating variant, a large cohort study of health care workers in Finland reported that COVID-19 vaccines were associated with a reduction in SARS-CoV-2 infections not only among vaccinated

individuals but also among unvaccinated adult household members.[25] A 2022 systematic review and meta-analysis of 96 studies reported that people who received a complete primary COVID-19 vaccine series had reduced susceptibility to SARS-CoV-2 infection and were less infectious if they become infected.[26]

Vaccination Timing and Immunosuppressive Therapies

If possible, COVID-19 vaccines should be administered at least 2 weeks before initiating or resuming immunosuppressive therapies. The timing of the vaccination should be determined based on the patient's current or planned immunosuppressive therapies, as well as the patient's medical condition and predicted response to the vaccine. Guidance about the timing of COVID-19 vaccination in solid organ transplant, HCT, and cellular immunotherapy candidates can be found in Special Considerations in Solid Organ Transplant, Hematopoietic Cell Transplant, and Cellular Immunotherapy Candidates, Donors, and Recipients. The CDC's guidance allows the use of additional vaccine doses in people who are immunocompromised. Each additional dose should be administered at least 2 months after the last dose.

The CDC recommends that HCT and CAR T-cell recipients who received doses of COVID-19 vaccines before or during treatment with HCT or CAR T-cell therapy should be revaccinated with the currently recommended primary vaccine series at least 3 months after the transplant or CAR T-cell therapy.[16] The American College of Rheumatology also provides guidance for temporarily stopping immunosuppressive regimens during vaccination.[27]

Polyethylene Glycol Allergies

The BNT162b2 (Pfizer-BioNTech) and mRNA-1273 (Moderna) mRNA vaccines contain polyethylene glycol (PEG), whereas the NVX-CoV2373 (Novavax) vaccine contains polysorbate 80. PEG and polysorbate are used in many products, including in agents used for cancer chemotherapy (e.g., PEG-asparaginase). PEG and polysorbate are structurally related, and cross-reactive hypersensitivity between these compounds might occur. The detection of PEG antibodies after vaccination was not associated with increased adverse reactions (such as delayed-onset reactions, including injection site rashes, or severe allergic reactions) to the mRNA COVID-19 vaccines.[28] Therefore, testing for anti-PEG antibodies should not be used as a screening tool to assess the risk of allergic reactions[29] and should not replace an assessment by a specialist in those rare individuals with a history of anaphylaxis.[30] The CDC has issued guidance on triaging people with a history of allergies or allergic reactions to the components of COVID-19 vaccines.

Pre-Exposure Prophylaxis

As of February 2024, no biomedical intervention other than vaccines prevents COVID-19 disease. Previously, the Food and Drug Administration (FDA) authorized the use of the anti-SARS-CoV-2 monoclonal antibodies tixagevimab plus cilgavimab (Evusheld) as pre-exposure prophylaxis (PrEP) of COVID-19 in certain people who were not expected to mount an adequate immune response to COVID-19 vaccination and in people with COVID-19 vaccine contraindications. Because the current Omicron subvariants are not susceptible to tixagevimab plus cilgavimab, this combination is not currently authorized by the FDA for use as PrEP of COVID-19.[31]

Serologic Testing to Guide Vaccination Strategies

Currently, antibody tests are not recommended for assessing SARS-CoV-2 immunity following COVID-19 vaccination or for assessing the need for vaccination in a person who is unvaccinated. More than 80 SARS-CoV-2 serologic tests, including quantitative, semiquantitative, neutralizing antibody, and point-of-care tests, have been issued Emergency Use Authorizations by the FDA to aid in detecting antibodies to SARS-CoV-2.[32] However, these tests are not currently authorized for routine use in making

individual medical decisions, and their ability to assess a person's level of immunity or protection from SARS-CoV-2 infection has not been evaluated.[33] Most of these tests have not been calibrated to a reference standard, limiting the ability to compare and reproduce results from different tests.

Management of Patients With COVID-19 Who Are Immunocompromised

Adjusting Chronic Immunosuppressive Therapies

Clinicians should consult with the appropriate specialists when making decisions about stopping or adjusting the doses of immunosuppressive drugs in patients with COVID-19. When selecting treatments for COVID-19, clinicians should consider factors such as the underlying disease; the specific immunosuppressants being used; the severity of COVID-19; and the potential for drug-drug interactions, overlapping toxicities, and secondary infections.

Early in the clinical course of COVID-19, the disease is primarily driven by the replication of SARS-CoV-2. Immunosuppressive medications can reduce the host immune responses that suppress viral replication, increasing the risk of prolonged viral shedding and infection.[34,35] Clinicians should consider adjusting the doses of immunosuppressive medications or substituting certain immunosuppressive medications, if possible, to improve the patient's immune response to infection. When making decisions about stopping or reducing the dose of immunosuppressive drugs, clinicians should balance the potential benefit of enhancing the patient's immune response to COVID-19 with the risk of exacerbating the underlying condition. They should also consider the role of immunomodulation in the treatment of COVID-19.

Clinicians should be aware that many immunosuppressive drugs, particularly biologic agents, have long half-lives or prolonged periods of biologic activity. Patients may remain immunosuppressed long after the drugs are stopped. Care should be taken to not stop glucocorticoids abruptly, since this may result in adrenal insufficiency. For medications other than glucocorticoids, decisions about dose adjustments should be made on a case-by-case basis. For example, for some autoimmune diseases, temporary cessation of immunosuppression is often possible, and restarting medications 7 to 14 days after symptom resolution may be appropriate.[27,36] Observational data suggest that patients receiving tumor necrosis factor–alpha (TNF-alpha) inhibitors may be at lower risk of progressing to severe COVID-19 than those receiving treatment with other immunomodulators.[37,38] Therefore, some patients with mild COVID-19 may safely continue receiving treatment with TNF-alpha inhibitors.

For solid organ transplant recipients, adjustments to immunosuppressive regimens should be individualized based on disease severity, the risk of graft rejection, the specific immunosuppressants being used, the type of transplant, the time since transplantation, the concentration of immunosuppressants, and the potential for drug-drug interactions.[39] See Special Considerations in Solid Organ Transplant, Hematopoietic Cell Transplant, and Cellular Immunotherapy Candidates, Donors, and Recipients for more information.

Therapeutic Management of Nonhospitalized Patients With COVID-19

For nonhospitalized patients with mild to moderate COVID-19 who are immunocompromised, the Panel recommends prompt treatment with antiviral drugs at the doses and durations recommended for the general population **(AIII)**. See Therapeutic Management of Nonhospitalized Adults With COVID-19 to review the Panel's recommendations. Some special considerations for using these therapies in people who are immunocompromised are outlined below.

Ritonavir-Boosted Nirmatrelvir (Paxlovid)

In the EPIC-HR trial, the use of ritonavir-boosted nirmatrelvir reduced the risk of hospitalization

or death when compared with placebo in nonhospitalized, unvaccinated adults who had laboratory-confirmed SARS-CoV-2 infection and a high risk of progressing to severe COVID-19.[40] Because the trial did not enroll many participants who were immunocompromised, the efficacy of ritonavir-boosted nirmatrelvir was not established for this population. In subsequent retrospective studies, some potential benefits of using ritonavir-boosted nirmatrelvir in people with various immunocompromising conditions have been observed.[41,42]

A retrospective study investigated the use of ritonavir-boosted nirmatrelvir for the treatment of COVID-19 in patients who were moderately or severely immunocompromised.[43] Among 3,188 patients, the use of ritonavir-boosted nirmatrelvir reduced the risk of death or hospitalization in extremely vulnerable patients, such as those with solid organ, bone marrow, or stem cell transplants; those with severe primary immunodeficiencies; and those receiving B cell–depletion therapy or treatment for hematologic malignancies.

Because ritonavir-boosted nirmatrelvir is the only highly effective oral antiviral therapy for COVID-19, it should be considered for patients who are immunocompromised if there are no potentially significant drug-drug interactions or if the interactions can be safely managed. Clinicians should be aware of drug-drug interactions that may be life- or organ-threatening (see Drug-Drug Interactions Between Ritonavir-Boosted Nirmatrelvir [Paxlovid] and Concomitant Medications).[44] Notably, calcineurin inhibitors (e.g., tacrolimus, cyclosporine A) and mammalian target of rapamycin drugs (e.g., sirolimus, everolimus) have important drug-drug interactions with ritonavir. For this reason, the American Society of Transplantation recommends preferentially using other therapies, such as remdesivir, over ritonavir-boosted nirmatrelvir in people who are taking calcineurin inhibitors or mammalian target of rapamycin inhibitors.[39] Ritonavir can inhibit the metabolism of many cancer-directed therapies and should only be given after consulting with specialty pharmacists and other appropriate specialists. Remdesivir and molnupiravir are other antiviral options for individuals who cannot receive ritonavir-boosted nirmatrelvir because of drug-drug interactions.

Observational studies and the EPIC-HR and MOVe-OUT trials have described SARS-CoV-2 viral rebound and the recurrence of COVID-19 symptoms in some patients who have completed treatment with ritonavir-boosted nirmatrelvir or molnupiravir.[45-49] However, viral rebound can also occur in patients who have not received treatment for COVID-19.[50] Some observational studies have reported that patients who were treated with ritonavir-boosted nirmatrelvir had a higher frequency of viral rebound and symptom recurrence than those who did not receive treatment.[51,52]

To date, virus detection and the recurrence of COVID-19 symptoms following the use of antiviral therapies have not been associated with progression to severe COVID-19.[53,54] Therefore, concerns about viral rebound or the recurrence of symptoms should not be a reason to avoid using antiviral therapies when their use is indicated.[49,55-57] A clinical trial that is evaluating the use of a second course of ritonavir-boosted nirmatrelvir to treat patients with viral rebound and symptom recurrence is underway (ClinicalTrials.gov Identifier NCT05567952). See Ritonavir-Boosted Nirmatrelvir (Paxlovid) for more information on rebound.

Remdesivir

Remdesivir was studied in nonhospitalized patients with mild to moderate COVID-19 who were at high risk of progressing to severe disease, and it was shown to be highly effective in reducing the risk of hospitalization and death.[58] However, this trial only included a small number of participants who were immunocompromised. Because remdesivir treatment for nonhospitalized patients requires an intravenous infusion for 3 consecutive days, there may be logistical constraints to administering this drug in many settings. It can be considered for patients who are immunocompromised if other options, such as ritonavir-boosted nirmatrelvir, are not appropriate or available.

Molnupiravir

In the MOVe-OUT trial, molnupiravir reduced the rate of hospitalization or death when compared with placebo in nonhospitalized patients with COVID-19.[59] However, this trial only enrolled a small number of participants who were immunocompromised. In a post hoc analysis of data from 55 patients who were immunocompromised, 2 of 24 patients (8%) who received molnupiravir were hospitalized or died through Day 29 compared with 7 of 31 patients (23%) who received placebo.[60] The PANORAMIC trial enrolled a larger population of people who were immunocompromised, but this population was heterogeneous and the results of the study were inconclusive.[61] Although the different treatment options have not been directly compared in clinical trials, the available evidence suggests that molnupiravir has a lower efficacy than ritonavir-boosted nirmatrelvir or remdesivir (see Molnupiravir). Other COVID-19 therapies should be prioritized over molnupiravir in patients who are immunocompromised.

COVID-19 Convalescent Plasma

There is insufficient evidence for the Panel to recommend either for or against the use of high-titer COVID-19 convalescent plasma (CCP) for the treatment of COVID-19 in nonhospitalized patients who are immunocompromised.

The FDA issued an Emergency Use Authorization that allows the use of high-titer CCP for the treatment of COVID-19 in nonhospitalized or hospitalized patients who have immunosuppressive disease or are receiving immunosuppressive treatment.[62] However, the evidence generated from well-designed clinical trials that evaluated the use of CCP for the treatment of nonhospitalized patients with COVID-19 is conflicting; these trials only enrolled a small number of patients who were immunocompromised.[63-66]

For a discussion on the potential use of high-titer CCP in patients who are immunocompromised and have prolonged viral replication, see the Therapeutic Management of Patients With COVID-19 Symptoms and Prolonged SARS-CoV-2 Replication section below.

Intravenous Immunoglobulin

The Panel **recommends against** the use of **intravenous immunoglobulin** (IVIG) for the prevention or treatment of acute COVID-19 in adults and children, except in a clinical trial **(AIII)**.

Some individuals who are immunocompromised and have hypogammaglobulinemia are candidates for receiving supplemental antibodies in the form of IVIG for the prevention of a variety of infections and in the setting of acute infections, including COVID-19. IVIG can be administered as outpatient or inpatient therapy. However, outside these specific circumstances, the Panel's recommendation should not preclude the use of IVIG when it is otherwise indicated for underlying conditions. See Intravenous Immunoglobulin for more information.

Therapeutic Management of Patients Who Are Hospitalized for COVID-19

For most hospitalized patients with severe or critical COVID-19 who are immunocompromised, the Panel recommends using antiviral drugs and immunomodulatory therapies at the doses and durations recommended for the general population **(AIII)**. See Therapeutic Management of Hospitalized Adults With COVID-19 for more information. The optimal management strategies and treatments for COVID-19 in hospitalized patients who are immunocompromised are unknown since these individuals were either excluded from or poorly represented in major clinical trials. Nevertheless, clinical experience and retrospective data suggest that many patients who are immunocompromised have the expected responses to standard therapies for COVID-19.

Remdesivir

Case reports suggest that remdesivir can suppress, but does not always eliminate, viral replication in this

population.[67,68] In a large retrospective study of hospitalized patients who were immunocompromised, including patients who did not require supplemental oxygen, patients who received remdesivir had a lower risk of mortality at 14 days and 28 days than patients who did not receive remdesivir.[69] The optimal duration of treatment with remdesivir in patients who are immunocompromised is unknown. Given the risk of prolonged viral replication in patients who are immunocompromised, some clinicians may choose to extend the course of antiviral therapy past 5 to 10 days. For patients receiving immunomodulatory therapy who have severe respiratory impairment due to COVID-19, clinicians may consider adding remdesivir treatment, although remdesivir has not been adequately studied in prospective clinical trials to determine whether there is a benefit in these patients.

Corticosteroids

The RECOVERY trial reported a survival benefit for dexamethasone in inpatients with COVID-19 who were receiving oxygen, high-flow nasal cannula oxygen, noninvasive ventilation, or mechanical ventilation; however, specific data regarding the subgroup of patients who were immunocompromised are not available.[70] Corticosteroids should not be used for the treatment of COVID-19 in patients who are not receiving oxygen. In the RECOVERY trial, no survival benefit was observed for dexamethasone among the subset of patients with COVID-19 who did not require supplemental oxygen at enrollment. In an observational cohort study of U.S. veterans, the use of dexamethasone was associated with higher mortality in hospitalized patients with COVID-19 who did not require supplemental oxygen.[70,71]

Patients who are immunocompromised may experience delayed development of favorable adaptive responses and a prolonged period of viral replication, as discussed above. For patients who are immunocompromised, are receiving minimal levels of conventional oxygen, and are earlier in the course of COVID-19 (e.g., those with <10 days of symptoms), the preferred approach may be emphasizing supportive care, using antiviral therapy, and avoiding corticosteroids. This strategy may reduce the duration of viral replication and the risk of secondary infections. Dexamethasone should be added if the patient has escalating oxygen requirements.

For patients who are immunocompromised and who were on chronic corticosteroids prior to hospitalization, the optimal dose of dexamethasone for the treatment of COVID-19 is unknown. The recommended dose of dexamethasone is 6 mg, which is equivalent to 40 mg of prednisone. This is the minimum dose of a steroid that should be used. Maintenance doses of corticosteroids should be discontinued while a patient is receiving dexamethasone, and the doses should be resumed as soon as possible after the patient recovers from COVID-19 or completes the course of dexamethasone.

Other Immunomodulators

Several randomized trials have shown that adding baricitinib or tocilizumab as a second immunomodulator to dexamethasone improves clinical outcomes in patients with severe or critical COVID-19.[72-74] Another randomized trial that examined the use of abatacept, cenicriviroc, or infliximab in combination with dexamethasone in hospitalized adults with COVID-19 reported no differences between the study arms in the primary endpoint of time to recovery.[75] However, patients who received infliximab or abatacept had a lower risk of mortality at 28 days. These trials generally excluded patients who were immunocompromised or only included small numbers of these patients. For patients who are immunocompromised, the use of these agents may provide a clinical benefit similar to the benefit seen in the general population. However, it is not clear whether augmenting immunomodulation in this population increases the risk of serious bacterial, invasive fungal, or parasitic infections.

The Panel currently recommends adding another immunomodulator to dexamethasone in hospitalized patients with COVID-19 who are hypoxemic and experiencing clinical progression (see Therapeutic Management of Hospitalized Adults With COVID-19). This approach can also be used for most patients

with COVID-19 who are immunocompromised. However, clinicians should consult with specialists to ensure that the risks of using additional immunosuppressive medications, including the risks of serious infections, do not outweigh the benefits. The patient should be closely monitored for secondary infections.

COVID-19 Convalescent Plasma

There is insufficient evidence for the Panel to recommend either for or against the use of high-titer CCP for the treatment of COVID-19 in hospitalized patients who are immunocompromised.

Three key randomized trials that evaluated the use of CCP for the treatment of COVID-19—RECOVERY, CONCOR-1, and REMAP-CAP—reported no evidence of a benefit of CCP in hospitalized patients with COVID-19. However, most of the patients enrolled in these trials were not immunocompromised.[76-78] Some of the subgroup analyses generated from clinical trials that enrolled patients who were immunocompromised suggested a potential benefit of CCP in this population,[78-80] but subgroup analyses need to be interpreted with caution (see Table 4c). Other clinical data from case series, retrospective case-control studies, and meta-analyses have been cited as support for the potential benefit of CCP in patients who are immunocompromised.[81-89] However, the patient populations differed across studies, and the studies had design limitations, making the findings difficult to interpret.

The RECOVER trial was a small, randomized trial that evaluated the use of plasma from donors who were vaccinated against COVID-19 or convalescent after SARS-CoV-2 infection as a treatment for COVID-19 in hospitalized people with cancer, people with immunosuppression, people with lymphopenia and D-dimer levels >1 µg/mL, and people aged >75 years.[79] Only the subgroup of patients with cancer who received plasma treatment experienced a shorter median time to improvement and lower mortality when compared with the control arm.

For a discussion on the potential use of high-titer CCP in patients who are immunocompromised and have prolonged viral replication, see Therapeutic Management of Patients With COVID-19 Symptoms and Prolonged SARS-CoV-2 Replication below.

Therapeutic Management of Patients Who Are Hospitalized for Reasons Other Than COVID-19

People who are immunocompromised and have COVID-19 but were hospitalized for conditions other than COVID-19 should receive the same treatments as nonhospitalized patients **(AIII)**. See Therapeutic Management of Nonhospitalized Adults With COVID-19 for more information.

Therapeutic Management of Patients With COVID-19 Symptoms and Prolonged SARS-CoV-2 Replication

For patients who are immunocompromised and have prolonged COVID-19 symptoms and evidence of ongoing viral replication (e.g., those with a low cycle threshold value, as measured by a reverse transcription polymerase chain reaction result or with a positive rapid antigen test result) despite receiving a course of antiviral therapy, the optimal management is unknown. Case reports and case series have described the treatment of these patients with additional antiviral treatments, prolonged courses of antiviral treatments, high-titer CCP, or combination therapy.[90-96] The data for these approaches are not definitive, but some Panel members would use 1 or more of the following treatment options:

- Longer and/or additional courses of ritonavir-boosted nirmatrelvir
- Longer and/or additional courses of remdesivir
- High-titer CCP from a vaccinated donor who recently recovered from COVID-19 likely caused by

a SARS-CoV-2 variant similar to the variant causing the patient's illness

Clinicians should be aware that the drug-drug interaction potential of ritonavir may change based on the duration of treatment. Although the primary concern with the use of a 5-day course of ritonavir is cytochrome P450 (CYP) 3A4 inhibition, the induction properties of ritonavir may become clinically relevant when it is used for ≥10 days.[97]

After longer courses of ritonavir-boosted nirmatrelvir are discontinued, drug-drug interactions caused by CYP3A4 inhibition are expected to resolve within 2 to 3 days.[98] Drug-drug interactions that are caused by induction (e.g., CYP2C9, CYP2C19, uridine diphosphate-glucuronyltransferase) resolve gradually and variably.

Clinicians should consult experts (e.g., pharmacists and physicians with HIV expertise) for guidance on drug-drug interactions when using extended courses of ritonavir-boosted nirmatrelvir. For more information, see Drug-Drug Interactions Between Ritonavir-Boosted Nirmatrelvir (Paxlovid) and Concomitant Medications. The Liverpool COVID-19 Drug Interactions website provides guidance on managing drug-drug interactions in patients who are receiving extended courses (i.e., ≥10 days) of ritonavir-boosted nirmatrelvir.

Considerations in Pregnant and Lactating People

Multiple studies have found that pregnant individuals have an increased risk of severe COVID-19 compared to age-matched controls, with increased rates of intensive care unit admission, mechanical ventilation, extracorporeal membrane oxygenation, and death.[99-101] Although hormonally mediated immunomodulation occurs during pregnancy, pregnancy is not a state of systemic immunosuppression. Changes in the immune response to certain infectious pathogens during pregnancy may increase the severity of respiratory illness in pregnant individuals. Physiologic changes, such as reduced pulmonary residual capacity, may also contribute to respiratory disease severity.[102-105] Pregnant people who have underlying immunocompromising conditions or are receiving immunosuppressive medications likely have an even higher risk of severe disease. This patient group should be prioritized for the prevention and treatment of COVID-19.

Prevention

The Panel recommends COVID-19 vaccination for everyone who is eligible, including pregnant and lactating individuals, according to the CDC's Advisory Committee on Immunization Practices **(AI)**. COVID-19 vaccination is strongly recommended for pregnant individuals due to their increased risk for severe disease.[106,107] Vaccination is especially important for pregnant people with concomitant risk factors such as underlying immunocompromising conditions (including those who are receiving immunosuppressive medications), as the risk for severe disease is likely additive.[100]

Treatment

Although pregnant patients have been excluded from the majority of the clinical trials that evaluated the use of COVID-19 therapeutics, pregnant patients with COVID-19 can be treated the same as nonpregnant patients, with a few exceptions. Pregnant patients who are immunocompromised or who have other risk factors likely have an even higher risk of severe COVID-19 and should be prioritized for treatment. Providers should refer to Pregnancy, Lactation, and COVID-19 Therapeutics for the Panel's guidance on treating COVID-19 in pregnant and lactating patients. Pregnant people who are immunocompromised are a heterogeneous group of patients, ranging from those who are mildly immunocompromised to those who are severely immunocompromised. Evaluating and managing pregnant patients require collaboration from a multidisciplinary team. This team should include a

transplant or specialty provider, an obstetrician or maternal-fetal medicine specialist, a pediatrician or neonatology specialist, and a pharmacist.

Considerations in Children

Although the overall risk of critical illness and death related to COVID-19 is lower in children than in adults, severe disease does occur, particularly in children with risk factors such as moderate or severe immunocompromising conditions. See Special Considerations in Children for a discussion of the risk factors for severe COVID-19 in children, and see Therapeutic Management of Nonhospitalized Children With COVID-19 for the Panel's framework for assessing a child's risk of progression to severe COVID-19 based on vaccination status, comorbidities, and age.

Prevention

The Panel recommends COVID-19 vaccination for everyone who is eligible, including children, according to the CDC's Advisory Committee on Immunization Practices **(AI)**.

Treatment

The majority of children with mild to moderate COVID-19 will not progress to more severe illness; therefore, the Panel recommends managing these patients with supportive care alone **(AIII)**. Few children, if any, have been enrolled in clinical trials of treatments for COVID-19. Among the children who were enrolled, very few were immunocompromised. Therefore, clinicians should be cautious when applying recommendations based on adult data to children. Clinicians need to consider the potential risks and benefits of therapy, the severity of the patient's disease, and underlying risk factors. See Therapeutic Management of Hospitalized Children With COVID-19 and Therapeutic Management of Nonhospitalized Children With COVID-19 for the Panel's treatment recommendations in these scenarios.

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