Special Considerations in People Who Are Immunocompromised

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Summary Recommendations

Prevention of COVID-19

- COVID-19 vaccination remains the most effective way to prevent serious outcomes and deaths from SARS-CoV-2 infection and should be considered the first line of prevention. The COVID-19 Treatment Guidelines Panel (the Panel) recommends COVID-19 vaccination for everyone who is eligible (AI), including those who are moderately or severely immunocompromised.
- 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.
- All close contacts of people who are immunocompromised are strongly encouraged to stay up to date with COVID-19 vaccination and boosters (AI).
- There is insufficient evidence for the Panel to recommend either for or against the use of SARS-CoV-2 serologic testing to assess for immunity or to guide clinical decisions about using COVID-19 vaccines.

Management of Patients With COVID-19 Who Are Immunocompromised

- The Panel recommends consulting with the appropriate specialists when making decisions about stopping or adjusting the doses of immunosuppressive drugs in patients with COVID-19 (BIII).
- When selecting treatments for COVID-19, clinicians should consider factors such as the underlying disease; the specific immunosuppressants being used; the potential for drug-drug interactions, overlapping toxicities, and secondary infections; and the severity of 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). 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.
- Some people who are immunocompromised have prolonged, symptomatic COVID-19 with evidence of ongoing SARS-CoV-2 replication. Without definitive data, 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
  - The ritonavir-boosted nirmatrelvir that was packaged in accordance with the Emergency Use Authorization (EUA) is the only ritonavir-boosted nirmatrelvir available at this time. For information on how to request expanded access use of ritonavir-boosted nirmatrelvir (e.g., for a course of treatment longer than 5 days), see “May health care providers prescribe Paxlovid for uses not authorized under EUA?” in this Frequently Asked Questions document from the Food and Drug Administration.

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. 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
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 or an increased risk of severe COVID-19, 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 [CD4] 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 when administered 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. 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. 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.

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. 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.

For any person who is eligible, clinicians should prescribe therapies for the treatment of COVID-19 as recommended in these Guidelines. However, at times during the pandemic, logistical constraints have limited the availability of therapies. In those cases, 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 according to the guidance from the Centers for Disease Control and Prevention (CDC). This recommendation applies to:

- People who are moderately or severely immunocompromised
- People with active cancer and those receiving treatment for cancer
- Transplant and cellular immunotherapy candidates and recipients
- People with HIV
- All potential organ and hematopoietic cell donors
- Household members, close contacts, and health care workers who provide care for immunocompromised patients

Authorized and 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 with a primary series and booster doses is still recommended, as it may confer partial protection, including protection from vaccine-induced, cell-mediated immunity.

The Panel recommends following the current [COVID-19 vaccination guidance](https://www.cdc.gov/coronavirus/2019-ncov/vaccines/doses.html) from the CDC for people who are moderately or severely immunocompromised. This guidance only includes the use of the bivalent vaccines (which target the original SARS-CoV-2 virus strain plus the Omicron subvariants BA.4 and BA.5) and allows for additional doses in high-risk groups, including people aged >65 years and people with immunocompromising conditions. There is a lack of data on the optimal timing for repeat vaccination in people who are immunocompromised, and the CDC recommends an interval of at least 2 months after the last dose. Other considerations may include the patient’s current or expected level of immunosuppression, their age, comorbidities, and the time since their last vaccine dose. Clinicians should also take into account 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 of administering COVID-19 boosters every 6 months in groups with the highest risk of COVID-19–related hospitalization or death. 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. Among adults who were immunocompromised, a lower vaccine effectiveness (VE) was observed for the bivalent booster, but VE was sustained against critical COVID-19–associated outcomes, including intensive care unit (ICU) admission and death. VE 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.\textsuperscript{20,21} Observational data suggest that serological responses to vaccines may be blunted in patients who are immunocompromised.\textsuperscript{22,23} However, a preprint of the MELODY trial reported detectable immunoglobulin G spike protein antibodies in approximately 80% of people in a large cohort of individuals in the United Kingdom who were immunocompromised and had received at least 3 doses of COVID-19 vaccines.\textsuperscript{24} Those who received anti-CD20 therapies within the past year had the lowest prevalence of detectable anti-spike protein antibodies.

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 as soon as possible\textsuperscript{25}. Before Omicron became the dominant circulating variant, COVID-19 vaccines were shown to be associated with a reduction in SARS-CoV-2 infections not only among vaccinated individuals but also among unvaccinated adult household members in a large cohort study of health care workers in Finland.\textsuperscript{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 and infectiousness. However, the vaccines were more effective against the Alpha variant than the Delta and Omicron variants.\textsuperscript{26}

Vaccination Timing and Anti-SARS-CoV-2 Monoclonal Antibodies

Vaccines can be administered at any time after receiving anti-SARS-CoV-2 monoclonal antibodies (mAbs).\textsuperscript{27}

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 \textit{Special Considerations in Solid Organ Transplant, Hematopoietic Cell Transplant, and Cellular Immunotherapy Candidates, Donors, and Recipients}. The CDC guidance allows the use of additional bivalent vaccine doses in people who are immunocompromised. Each additional dose should be administered at least 2 months after the last dose.

HCT and CAR T-cell recipients who received doses of COVID-19 vaccines prior to or during treatment with an HCT or CAR T-cell therapy should be revaccinated with a primary vaccine series at least 3 months after the transplant or CAR T-cell therapy.\textsuperscript{28} The American Society of Hematology has specific guidance about the timing of COVID-19 vaccination around cancer chemotherapy,\textsuperscript{28} and the American College of Rheumatology also provides guidance for temporarily stopping immunosuppressive regimens during vaccination.\textsuperscript{29}

Polyethylene Glycol Allergies

The BNT162b2 (Pfizer-BioNTech) and mRNA-1273 (Moderna) mRNA bivalent 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 has not been shown to correlate with adverse reactions.\textsuperscript{30} Therefore, testing for anti-PEG antibodies should not be used as a screening
tool to assess the risk of allergic reactions and should not replace an assessment by a specialist in those rare individuals with a history of anaphylaxis. 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**

Tixagevimab plus cilgavimab (Evusheld) is the only anti-SARS-CoV-2 mAb regimen that was shown to be effective for pre-exposure prophylaxis (PrEP) of COVID-19, and it was the only mAb regimen that was authorized by the Food and Drug Administration (FDA) for this use. However, nearly all currently circulating Omicron subvariants in the United States are not susceptible to this combination. Therefore, tixagevimab plus cilgavimab is not currently authorized by the FDA for use as PrEP of COVID-19, and there are currently no other options for PrEP. The Panel recommends against the use of anti-SARS-CoV-2 mAbs such as tixagevimab plus cilgavimab (Evusheld) for PrEP of COVID-19 (AIII).

**Serologic Testing to Guide Vaccination Strategies**

There is insufficient evidence for the Panel to recommend either for or against the use of SARS-CoV-2 serologic testing to assess for immunity or to guide clinical decisions about using COVID-19 vaccines. More than 80 SARS-CoV-2 serologic tests, including quantitative, semiquantitative, neutralizing antibody, and point-of-care tests, have been issued Emergency Use Authorizations (EUAs) by the FDA to aid in detecting antibodies to SARS-CoV-2. 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. 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**

The Panel recommends that decisions regarding stopping or adjusting the doses of immunosuppressive drugs in patients with COVID-19 be made in consultation with the appropriate specialists (BIII). When selecting treatments for COVID-19, clinicians should consider factors such as the underlying disease; the specific immunosuppressants being used; the potential for drug-drug interactions, overlapping toxicities, and secondary infections; and the severity of COVID-19.

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. 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.\textsuperscript{29,37}

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.\textsuperscript{38} 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.\textsuperscript{39} 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.\textsuperscript{40,41}

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 potential drug-drug interactions or if the potential 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).\textsuperscript{42} Notably, calcineurin inhibitors (e.g., tacrolimus, cyclosporine A) and mammalian target of rapamycin (mTOR) 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 mTOR inhibitors.\textsuperscript{38} Ritonavir can inhibit the metabolism of many cancer-directed therapies and should only be given after consulting with specialty pharmacists and other appropriate specialists.

Case reports have described reoccurring COVID-19 symptoms and positive SARS-CoV-2 test results in some patients who have completed treatment with ritonavir-boosted nirmatrelvir.\textsuperscript{43} A randomized trial is currently evaluating the effectiveness of longer courses or a second course of ritonavir-boosted nirmatrelvir (ClinicalTrials.gov Identifier NCT05438602). People with COVID-19 who are immunocompromised should not delay or avoid taking ritonavir-boosted nirmatrelvir due to concerns about the rebound of symptoms after treatment completion (see Ritonavir-Boosted Nirmatrelvir [Paxlovid]).

**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.\textsuperscript{44} 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. However, this trial only enrolled a small number of participants who were immunocompromised. 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. Although the different treatment options have not been directly compared in clinical trials, the available evidence suggests that molnupiravir has a lower efficacy than the other options (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 EUA 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. However, the evidence generated from well-designed clinical trials that evaluated the use of CCP for the treatment of nonhospitalized patients is conflicting; these trials only enrolled a small number of patients who were immunocompromised.

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**

Some individuals who are immunocompromised and have hypogammaglobulinemia are candidates for receiving supplemental antibodies in the form of intravenous immunoglobulin (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 **recommends against** the use of IVIG for the prevention or treatment of acute COVID-19 in adults and children, except in a clinical trial (AIII). This 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. In a large retrospective study of patients who were immunocompromised, patients who
received remdesivir had a lower risk of mortality than patients who did not receive remdesivir.\textsuperscript{54} The optimal duration of treatment with remdesivir in patients who are immunocompromised is unknown. Some clinicians may choose to extend the course of antiviral therapy past 5 to 10 days in patients who are immunocompromised, given the risk of prolonged viral replication. Given the increased likelihood of prolonged viral replication in patients receiving immunomodulatory therapy, clinicians may consider adding remdesivir to patients who are immunocompromised and have severe respiratory impairment due to COVID-19 (i.e., those who require high-flow nasal cannula [HFNC] oxygen, noninvasive ventilation [NIV], or mechanical ventilation), even though remdesivir has not been shown to confer a benefit in these patients in clinical trials.

**Corticosteroids**

The RECOVERY trial reported a survival benefit for dexamethasone in inpatients with COVID-19 who were receiving oxygen, HFNC oxygen, NIV, or mechanical ventilation; however, specific data regarding the subgroup of patients who were immunocompromised are not available.\textsuperscript{55} Unless otherwise indicated, 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.\textsuperscript{55,56}

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.

**Interleukin-6 Inhibitors and Janus Kinase Inhibitors**

Randomized trials have shown that adding interleukin (IL)-6 inhibitors and Janus kinase (JAK) inhibitors to dexamethasone improves clinical outcomes in patients with severe or critical COVID-19. These trials generally excluded patients who were immunocompromised or only included small numbers of these patients.\textsuperscript{57-59} 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.

For most patients who are immunocompromised, adding IL-6 or JAK inhibitors to dexamethasone is reasonable for those who are hypoxemic and experiencing clinical progression. This follows the Panel’s treatment recommendations for the general population (see [Therapeutic Management of Hospitalized Adults With COVID-19](https://www.covid19treatmentguidelines.nih.gov/)). 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 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.\(^{60-62}\) Some of the subgroup analyses generated from clinical trials that enrolled patients who were immunocompromised suggested a potential benefit of CCP in this population,\(^{62-64}\) 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.\(^{65-73}\) 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 convalescent and/or vaccinated against COVID-19 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. 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.\(^{63}\)

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.

**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 documented the treatment of these patients with additional antiviral treatments, prolonged courses of antiviral treatments, high-titer CCP, or combination therapy.\(^{74-78}\) 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. Even though cytochrome P450 (CYP) 3A4 inhibition by ritonavir is the primary concern when a 5-day course of ritonavir is used, clinicians should take into account that induction properties may become clinically relevant when ritonavir is used for 10 days or longer.\(^{79}\)
After discontinuing longer courses of ritonavir-boosted nirmatrelvir, drug-drug interactions due to CYP3A4 inhibition largely resolve within 2 to 3 days. 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 for 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 ICU admission, mechanical ventilation, extracorporeal membrane oxygenation, and death. 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. 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 as soon as possible for everyone who is eligible according to the CDC’s Advisory Committee on Immunization Practices (ACIP), including pregnant individuals (AI). COVID-19 vaccination is strongly recommended for pregnant individuals due to their increased risk for severe disease. 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 addictive.

**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 comprise 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 pediatrics 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 adults, severe disease does occur, particularly in children with risk factors such as moderate to 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 as soon as possible for everyone who is eligible according to the CDC’s ACIP, including children (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.

**References**


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