Special Considerations in People Who Are Immunocompromised

Last Updated: March 6, 2023

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<th>Summary Recommendations</th>
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<td><strong>Prevention of COVID-19</strong></td>
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<tr>
<td>• The COVID-19 Treatment Guidelines Panel (the Panel) recommends COVID-19 vaccination for all people who are moderately or severely immunocompromised (AIII).</td>
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<td><strong>General Management of Patients With COVID-19 Who Are Immunocompromised</strong></td>
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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.
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 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 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).

Data are evolving on the clinical outcomes of COVID-19 in people who are immunocompromised. 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 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) or B cell–depleting agents (e.g., rituximab, ocrelizumab, obinutuzumab), have been associated with more severe COVID-19 outcomes.

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. There is insufficient evidence to guide clinical recommendations on using combinations of antiviral agents for the treatment of COVID-19 or to support
extending the duration of COVID-19 therapies beyond the duration authorized or approved by the Food and Drug Administration (FDA).

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 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, and comorbidities.

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**

The Panel recommends COVID-19 vaccination for all people who are moderately or severely immunocompromised (AIII). Vaccination is the most effective way to prevent serious outcomes and death from SARS-CoV-2 infection. However, in people who are immunocompromised, the immune response to vaccination may be blunted, and the timing of vaccination requires special consideration. Authorized and approved COVID-19 vaccines in the United States are not live-virus vaccines, and they can be safely administered to patients who are immunocompromised.

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.\(^{15,16}\) Observational data suggest that serological responses to vaccines may be blunted in patients who are immunocompromised.\(^{17,18}\) 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.\(^4\) See the Centers for Disease Control and Prevention (CDC) webpage COVID-19 Vaccines for People Who Are Moderately or Severely Immunocompromised for the current COVID-19 vaccination schedule for this population.

**Vaccination of Close Contacts**

Clinicians should strongly encourage all close contacts to get vaccinated against COVID-19 as soon as possible (AI). Vaccinating household members, close contacts, and health care workers who provide care for patients who are immunocompromised is important to protect these patients from infection. There is evidence that vaccinated individuals who are infected with SARS-CoV-2 have lower viral loads than unvaccinated individuals, and COVID-19 vaccines are associated with a reduction in the number of SARS-CoV-2 infections not only among vaccinated individuals but also among their household contacts.\(^{19-24}\)

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

Vaccines can be administered at any time after anti-SARS-CoV-2 monoclonal antibody treatment.\(^{25}\)

**Vaccination Timing and Immunosuppressive Therapies**

If possible, the COVID-19 vaccination series should be completed at least 2 weeks before initiating or resuming immunosuppressive therapies. The timing of the vaccination series 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. 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. The American Society of Hematology and the National Comprehensive Cancer Network have specific guidance about the timing of COVID-19 vaccination around cancer chemotherapy, and the American College of Rheumatology also provides guidance for temporarily stopping immunosuppressive regimens during vaccination.

**Pre-Exposure Prophylaxis**

The prevalence of SARS-CoV-2 Omicron subvariants that are not susceptible to the anti-SARS-CoV-2 monoclonal antibody combination tixagevimab plus cilgavimab (Evusheld) is >90% in the United States. Therefore, tixagevimab plus cilgavimab is not currently authorized by the FDA for use as pre-exposure prophylaxis (PrEP) of COVID-19. The Panel recommends against the use of tixagevimab plus cilgavimab as PrEP of COVID-19 (AIII).

**Serologic Testing to Guide Vaccination Strategies**

There is currently 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 comparability and reproducibility of 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 reducing the doses of immunosuppressive drugs in patients with COVID-19 be made in consultation with the appropriate specialists; clinicians should consider factors such as the underlying disease, the specific immunosuppressants being used, the potential for drug-drug interactions, and the severity of COVID-19 (BIII).

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{28,33}

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{34} 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**

The Panel recommends prompt treatment with antiviral drugs for nonhospitalized patients with mild to moderate COVID-19 who are immunocompromised \textsuperscript{(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, ritonavir-boosted nirmatrelvir, when compared with placebo, reduced the risk of hospitalization or death in nonhospitalized, unvaccinated adults who had laboratory-confirmed SARS-CoV-2 infection and a high risk of progressing to severe COVID-19.\textsuperscript{35} However, as the trial enrolled very few participants who were immunocompromised, the efficacy of using this drug in this population is unknown.

Because ritonavir-boosted nirmatrelvir is the only highly effective oral antiviral drugs for the treatment of 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{36} 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{37}

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{38} There is currently no evidence to support routinely administering longer courses or a second course of ritonavir-boosted nirmatrelvir. 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{39} However, this trial included few participants who were immunocompromised
Because remdesivir requires an intravenous infusion for 3 consecutive days, there may be logistical constraints to administering this drug in many settings, but 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 in nonhospitalized patients with COVID-19, when compared with placebo. However, the MOVe-OUT trial enrolled very few participants who were immunocompromised. 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. 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 are immunocompromised or 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 enrolled few, if any, patients who were immunocompromised.

Some Panel members would use CCP to treat a patient who is immunocompromised and who has significant symptoms attributable to COVID-19, shows signs of active SARS-CoV-2 replication, and responds inadequately to available therapies. In these cases, clinicians should attempt to obtain 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.

Therapeutic Management of Patients Who Are Hospitalized for COVID-19
For most patients with COVID-19 who are immunocompromised, the Panel recommends using antiviral drugs and immunomodulatory therapies at the doses and durations that are 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 suggests that many patients who are immunocompromised have the expected responses to standard therapies for COVID-19.

Remdesivir
The optimal duration of treatment with remdesivir in patients who are immunocompromised is unknown. Case reports suggest that the drug can suppress, but does not always eliminate, viral replication in this population. 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. Similarly, although remdesivir has not been shown to confer a benefit in patients with more severe respiratory impairment due to COVID-19 (i.e., those who require high-flow nasal cannula [HFNC] oxygen, noninvasive ventilation [NIV], or mechanical ventilation), clinicians may consider using remdesivir along with immunomodulatory therapy in this population of patients who are immunocompromised.

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{49}

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, who are receiving minimal levels of conventional oxygen, and who are earlier in the course of COVID-19 (e.g., those with \textless{}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 steroid that should be used. Maintenance doses of corticosteroids should be discontinued while a patient is receiving dexamethasone, and they should be resumed as soon as possible after recovery from COVID-19 or after completion of the course of dexamethasone.

\textbf{Immunomodulators}

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{50-52} 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, which follows the Panel’s recommendations for the general population (see \textit{Therapeutic Management of Hospitalized Adults With COVID-19}). However, clinicians should consult with the appropriate specialists to ensure that the risks of additional immunosuppression, including the risks of serious infections, do not outweigh the benefits of additional immunosuppression and that the patient is closely monitored for infections.

\textbf{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 benefit from CCP in hospitalized patients with COVID-19. However, most of the patients enrolled in these trials were not immunocompromised.\textsuperscript{53-55} Some subgroup analyses generated from clinical trials that enrolled patients who were immunocompromised suggested a potential benefit from the use of CCP in this population,\textsuperscript{55, 57} but subgroup analyses need to be interpreted with caution. 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.\textsuperscript{58-66} However, the patient populations differed across studies, and the studies had design limitations, making the findings difficult to interpret.

Some Panel members would use CCP to treat a patient who is immunocompromised and who has significant symptoms attributable to COVID-19, shows signs of active SARS-CoV-2 replication, and responds inadequately to available therapies. In these cases, clinicians should attempt to obtain 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.

**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 Hospitalized Patients With Prolonged SARS-CoV-2 Replication**

For patients who are immunocompromised and hospitalized with symptomatic COVID-19 and have prolonged periods of significant viral replication despite receiving remdesivir and appropriate immunomodulatory drugs, the optimal management is unknown. In these cases, some Panel members would use 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.

**Special Considerations for Pregnant Individuals Who Are Immunocompromised**

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. 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, including pregnant individuals, who is eligible according to the CDC’s Advisory Committee on Immunization Practices (ACIP) (AII). 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 additive.

**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 for severe COVID-19 and should be prioritized for treatment. Providers should refer to the Panel’s recommendations in Therapeutic Management of Nonhospitalized Adults With COVID-19 and Therapeutic Management of Hospitalized Adults With COVID-19. Pregnant people who are immunocompromised comprise a heterogeneous group of patients, ranging from those who are mildly immunocompromised to those who are severely immunocompromised. The Panel recommends forming a collaborative, multidisciplinary team to make decisions regarding the evaluation and management of pregnant patients, including the involvement of a transplant or specialty provider, an obstetrician or maternal-fetal medicine specialist, a pediatrics or
neonatology specialist, and pharmacy services.

**Special Considerations for Children Who Are Immunocompromised**

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, including children, who is eligible according to the CDC’s ACIP (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, including children aged <18 years who are immunocompromised, have been enrolled in clinical trials of treatments for COVID-19. 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**


