Special Populations

To date, the vast majority of the data generated about the epidemiology, clinical course, prevention, and treatment of COVID-19 have come from studies of nonpregnant adults. More information is urgently needed for other populations, such as pediatric patients, pregnant patients, transplant patients, and other immunocompromised patients with COVID-19.

Children with COVID-19 may have less severe disease overall when compared to adults, but the recently described multisystem inflammatory syndrome in children (MIS-C) requires further study. Data are also emerging on the clinical course of COVID-19 in pregnant patients, pregnancy outcomes in the setting of COVID-19, and vertical transmission of severe acute respiratory coronavirus 2, but further research is needed. There are special considerations for transplant recipients, cancer patients, and patients with other immunocompromising conditions (e.g., rheumatologic conditions, inflammatory bowel disease), as they may be at increased risk of serious complications and death as a result of COVID-19.

The following sections review and synthesize the available data for some of these populations and discuss the specific considerations that clinicians should take into account when caring for these patients.
Special Considerations in Pregnancy

**Epidemiology of COVID-19 in Pregnancy**

Initial reports of COVID-19 disease acquired in the third trimester were reassuring, although most early data were limited to case reports and case series.³⁴ Since that time, a large population-based cohort study in the United Kingdom evaluated outcomes in pregnant women hospitalized with confirmed severe acute respiratory syndrome coronavirus type 2 (SARS-CoV-2) infection. Among 427 pregnant women admitted to 197 obstetric units across the United Kingdom, the rates of critical care admission and severe SARS-CoV-2-associated maternal mortality were similar to those in the general population of women of reproductive age hospitalized with COVID-19 in the United Kingdom, although the pregnant women were not compared with age-matched, nonpregnant controls.⁸

In June 2020, the Centers for Disease Control and Prevention (CDC) released surveillance data evaluating SARS-CoV-2-related outcomes in reproductive aged women by pregnancy status. Among 326,335 women aged 15 to 44 years with positive test results for SARS-CoV-2, pregnant women were more likely to be hospitalized, be admitted to an intensive care unit (ICU), and receive mechanical ventilation. However, the overall absolute increase in rates of ICU admission and mechanical ventilation was low among the pregnant women and the nonpregnant women (1.5% vs. 0.9% for ICU admission, respectively, and 0.5% vs 0.3% for mechanical ventilation, respectively). COVID-19-related death rates were similar in the pregnant and nonpregnant populations. Pregnancy outcomes such as preterm birth or pregnancy loss were not evaluated.

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**Key Considerations**

<table>
<thead>
<tr>
<th>There is current guidance from the Centers for Disease Control and Prevention (CDC), the American College of Obstetricians and Gynecologists (ACOG), and the Society for Maternal-Fetal Medicine (SMFM) on the management of pregnant patients with COVID-19.¹⁴ This section of the COVID-19 Treatment Guidelines complements that guidance. Below are key considerations regarding the management of COVID-19 in pregnancy.</th>
</tr>
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<tbody>
<tr>
<td>• Pregnant women should be counseled about the potential for severe disease from SARS-CoV-2 infection and the recommended measures to take to protect themselves and their families from infection.</td>
</tr>
<tr>
<td>• If hospitalization for COVID-19 is indicated in a pregnant woman, care should be provided in a facility that can conduct maternal and fetal monitoring, when appropriate.</td>
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<tr>
<td>• Management of COVID-19 in the pregnant patient should include:</td>
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<tr>
<td>• Fetal and uterine contraction monitoring, when appropriate, based on gestational age</td>
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<tr>
<td>• Individualized delivery planning</td>
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<tr>
<td>• A multispecialty, team-based approach that may include consultation with obstetric, maternal-fetal medicine, infectious disease, pulmonary and critical care, and pediatric specialists, as appropriate</td>
</tr>
<tr>
<td>• The COVID-19 Treatment Guidelines Panel (the Panel) recommends that potentially effective treatment for COVID-19 should not be withheld from pregnant women because of theoretical concerns related to the safety of therapeutic agents in pregnancy (AIII).</td>
</tr>
<tr>
<td>• Decisions regarding the use of drugs approved for other indications or investigational drugs for the treatment of COVID-19 in pregnant patients must be made with shared decision-making between the patient and the clinical team, considering the safety of the medication for the pregnant woman and the fetus and the severity of maternal disease. For detailed guidance on the use of COVID-19 therapeutic agents in pregnancy, please refer to Considerations in Pregnancy in the Antiviral Therapy and Immune-Based Therapy sections of these Guidelines.</td>
</tr>
</tbody>
</table>

**Rating of Recommendations:** A = Strong; B = Moderate; C = Optional

**Rating of Evidence:** I = One or more randomized trials with clinical outcomes and/or validated laboratory endpoints; II = One or more well-designed, nonrandomized trials or observational cohort studies; III = Expert opinion
This analysis has a number of significant limitations, including:

- Pregnancy status was only available for 28% of the women of reproductive age with SARS-CoV-2 infection.
- It was not possible to determine whether the reasons for hospitalization, ICU admission, or mechanical ventilation were related to COVID-19, pregnancy, and/or delivery.

Pregnant women who are Hispanic or Black may be disproportionately affected by SARS-CoV-2 infection. Pregnant women should be counseled about the potential for severe disease from SARS-CoV-2 and measures to protect themselves and their families from infection, including physical distancing, face coverings, and hand hygiene. CDC, ACOG, and SMFM highlight the importance of accessing prenatal care. ACOG provides an FAQ on using telehealth to deliver antenatal care, when appropriate.

ACOG has developed an algorithm to evaluate and manage pregnant outpatients with suspected or confirmed SARS-CoV-2 infection. As in nonpregnant patients, SARS-CoV-2 infection in pregnant patients can present as asymptomatic/presymptomatic disease or with a wide range of clinical manifestations, from mild symptoms that can be managed with supportive care at home to severe disease and respiratory failure requiring ICU admission. As with other patients, in the pregnant patient with symptoms compatible with COVID-19, the illness severity, underlying comorbidities, and clinical status should all be assessed to determine whether in-person evaluation for potential hospitalization is needed.

If hospitalization is indicated, care should be provided in a facility that can conduct maternal and fetal monitoring, when appropriate. The management of COVID-19 in the pregnant patient may include:

- Fetal and uterine contraction monitoring, when appropriate, based on gestational age
- Individualized delivery planning
- A multispecialty, team-based approach that may include consultation with obstetric, maternal-fetal medicine, infectious disease, pulmonary and critical care, and pediatric specialists, as appropriate.

Other recommendations on the management of COVID-19, as outlined for the nonpregnant patient, also apply in pregnancy.

**Timing of Delivery**

- Detailed guidance relating to timing of delivery and risk of vertical transmission of SARS-CoV-2 is provided by ACOG.
- In most cases, the timing of delivery should be dictated by obstetric indications rather than maternal diagnosis of COVID-19. For women who had suspected or confirmed COVID-19 early in pregnancy who recover, no alteration to the usual timing of delivery is indicated.
- Vertical transmission of SARS-CoV-2 via the transplacental route appears to be rare but possible.

**Management of COVID-19 in the Setting of Pregnancy**

- Potentially effective treatment for COVID-19 should not be withheld from pregnant women because of theoretical concerns related to the safety of therapeutic agents in pregnancy.
- Decisions regarding the use of drugs approved for other indications or investigational agents for the treatment of COVID-19 in pregnant patients must be made with shared decision-making between the patient and the clinical team, considering the safety of the medication for the woman.
and the fetus and the severity of maternal disease. For detailed guidance on the use of COVID-19 therapeutic agents in pregnancy, please refer to Considerations in Pregnancy in the Antiviral Therapy and Immune-Based Therapy sections of these Guidelines.

- To date, most SARS-CoV-2-related clinical trials have excluded, or included only a very few, pregnant women and lactating women. This limitation makes it difficult to make evidence-based recommendations on the use of SARS-CoV-2 therapies in these vulnerable patients and potentially limits their COVID-19 treatment options. When possible, pregnant women and lactating women should not be excluded from clinical trials of therapeutic agents or vaccines for SARS-CoV-2 infection.

**Post-Delivery**

- Specific guidance for post-delivery management of infants born to mothers with known or suspected SARS-CoV-2 infection, including breastfeeding recommendations, is provided by the CDC and the American Academy of Pediatrics.¹⁶

**References**


Special Considerations in Children

Data on disease severity and pathogenesis of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection in children are limited. Overall, several large epidemiologic studies suggest that acute disease manifestations are substantially less severe in children than in adults, although there are reports of children with COVID-19 requiring intensive care unit (ICU)-level care.\(^1\)–\(^11\) Recently, SARS-CoV-2 has been associated with a potentially severe inflammatory syndrome in children (multisystem inflammatory syndrome in children [MIS-C], which is discussed below). Preliminary data from the Centers for Disease Control and Prevention (CDC) also show that hospitalization rates and ICU admission rates for children are lower than for adults. Severe cases of COVID-19 in children were associated with younger age and underlying conditions, although a significant number of the pediatric cases did not have complete data available at the time of the preliminary report. Without widespread testing, including for mild symptoms, the true incidence of severe disease in children is unclear. Data on perinatal vertical transmission to neonates are limited to small case series with conflicting results; some studies have demonstrated lack of transmission, whereas others have not been able to definitively rule out this possibility.\(^12\)–\(^14\) Specific guidance on the diagnosis and management of COVID-19 in neonates born to mothers with known or suspected SARS-CoV-2 infection is provided by the CDC.

Insufficient data are available to clearly establish risk factors for severe COVID-19 disease in children. Based on adult data and extrapolation from other pediatric respiratory viruses, severely immunocompromised children and those with underlying cardiopulmonary disease may be at higher risk for severe disease. Children with risk factors recognized in adults, including obesity, diabetes, and hypertension, may also be at risk, although there are no published data supporting this association and insufficient data to guide therapy. Guidance endorsed by the Pediatric Infectious Diseases Society has recently been published, which provides additional specific risk categorization when considering therapy.\(^15\) As data emerge on risk factors for severe disease, it may be possible to provide more directed guidance for specific populations at high risk for COVID-19 and to tailor treatment recommendations accordingly.

Currently, there are no Food and Drug Administration (FDA)-approved agents for the treatment of COVID-19. Based on preliminary clinical trial data, the investigational antiviral agent remdesivir is recommended for the treatment of COVID-19 in hospitalized patients with severe disease (see Remdesivir for detailed information). Of note, remdesivir has not been evaluated in clinical trials that include children with COVID-19. Remdesivir is available for children through an FDA Emergency Use Authorization or through a compassionate use program.

For other agents outlined in these guidelines, there are insufficient data to recommend for or against the use of specific antivirals or immunomodulatory agents for the treatment of COVID-19 in pediatric patients. General considerations such as underlying conditions, disease severity, and potential for drug toxicity or drug interactions may inform management decisions on a case-by-case basis. Enrollment of children in clinical trials should be prioritized when trials are available. A number of additional drugs are being investigated for the treatment of COVID-19 in adults; clinicians can refer to the Antiviral Therapy and Immune Based Therapy sections of these guidelines to review special considerations for use of these drugs in children and refer to Table 2 and Table 3b for dosing recommendations in children.

Multisystem Inflammatory Syndrome in Children

Emerging reports from Europe and the United States have suggested that COVID-19 may be associated with MIS-C (also referred to as pediatric multisystem inflammatory syndrome–temporally associated with SARS-CoV-2 [PMIS-TS]). The syndrome was first described in the United Kingdom, where
previously healthy children with severe inflammation and Kawasaki disease-like features were identified
to have current or recent infection with SARS-CoV-2. Additional cases of MIS-C have been reported
in other European countries, including Italy and France. Emerging data suggest that MIS-C may
be associated with pediatric patients who are slightly older than children typically seen with Kawasaki
disease, and some cases of MIS-C in young adults have been reported.

In the United States, from April 16 through May 4, 2020, the New York City Department of Health
and Mental Hygiene received reports of 15 hospitalized children with clinical presentation consistent
with MIS-C. Subsequently, the New York State Department of Health has been investigating several
hundred cases and a few deaths in children with similar presentations, many of whom tested positive for
SARS-CoV-2 infection by reverse transcriptase polymerase chain reaction (PCR) or serology. Several
other states are now reporting cases consistent with MIS-C.

The current case definition for MIS-C can be found on the CDC website. This case definition, which
may evolve as more data become available, includes:

- Fever, laboratory evidence of inflammation, and evidence of clinically severe illness requiring
  hospitalization, with multiorgan involvement, and
- No alternate diagnosis, and
- Recent or current SARS-CoV-2 infection or exposure to COVID-19.

From the available data, patients with MIS-C present with persistent fever, evidence of systemic
inflammation, and a variety of signs and symptoms of multiorgan system involvement, including
cardiac, gastrointestinal, renal, hematologic, dermatologic, and neurologic involvement.

Some patients who meet criteria for MIS-C also meet criteria for complete or incomplete Kawasaki
disease. An observational study compared data from Italian children with Kawasaki-like illness that was
diagnosed before and after the onset of the SARS-CoV-2 epidemic. The data suggest that the SARS-
CoV-2-associated cases occurred in children who were older than the children with Kawasaki-like illness
diagnosed prior to the COVID-19 epidemic. In addition, the rates of cardiac involvement, associated
shock, macrophage activation syndrome, and need for adjunctive steroid treatment were higher for the
SARS-CoV-2-associated cases. Many patients with MIS-C have abnormal markers of cardiac injury
or dysfunction, including troponin and brain natriuretic protein. Echocardiographic findings include
impaired left ventricular function, as well as coronary artery dilations, and rarely, coronary artery
aneurysms. At presentation, few patients are SARS-CoV-2 PCR positive (nasopharyngeal or nasal swab
or stool sample), but most have detectable antibodies to SARS-CoV-2. Emerging observations suggest
that there may be a wider range of severity of symptoms than initially recognized. Epidemiologic and
clinical data suggest that MIS-C may represent a post-infectious inflammatory phenomenon rather than a
direct viral process. The role of asymptomatic infection and the pattern of timing between SARS-CoV-2
infection and MIS-C are not well understood, and currently a causal relationship is not established.

Currently, there is limited information available about risk factors, pathogenesis, clinical course, and
treatment for MIS-C. Supportive care remains the mainstay of therapy. There are currently insufficient
data for the COVID-19 Treatment Guidelines Panel to recommend either for or against any therapeutic
strategy for the management of MIS-C. Although no definitive data are available, many centers consider
the use of intravenous immune globulin, steroids, and other immunomodulators (including interleukin-1
and interleukin-6 inhibitors) for therapy, and antiplatelet and anticoagulant therapy. The role of antiviral
medications that specifically target SARS-CoV-2 is not clear at this time. MIS-C management decisions
should involve a multidisciplinary team of pediatric specialists in intensive care, infectious diseases,
cardiology, hematology, and rheumatology.
References


People who are being treated for cancer may be at increased risk of severe COVID-19, and their outcomes are worse than individuals without cancer.\textsuperscript{1-4} A meta-analysis of 46,499 patients with COVID-19 showed that all-cause mortality (risk ratio 1.66; 95% CI, 1.33–2.07) was higher in patients with cancer, and that patients with cancer were more likely to be admitted to intensive care units (risk ratio 1.56; 95% CI, 1.31–1.87).\textsuperscript{5} The risk for immunosuppression and susceptibility to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection varies between cancer types, treatments administered, and stages of therapy (e.g., patients who are actively being treated compared to those in remission). In a study that used data from the COVID-19 and Cancer Consortium Registry, cancer patients who were in remission or who had no evidence of disease were at a lower risk of death from COVID-19 than those who were receiving active treatment.\textsuperscript{6} It is unclear whether cancer survivors are at increased risk for severe COVID-19 and its complications compared to people without a history of cancer.

Many organizations have outlined recommendations for treating patients with cancer during the COVID-19 pandemic, such as:

- National Comprehensive Cancer Network (NCCN)
- American Society of Hematology
- American Society of Clinical Oncology
- Society of Surgical Oncology
- American Society for Radiation Oncology
- International Lymphoma Radiation Oncology Group

This section of the COVID-19 Treatment Guidelines complements these sources and focuses on considerations regarding testing for SARS-CoV-2, management of COVID-19 in patients with cancer, and management of cancer-directed therapies during the COVID-19 pandemic. The optimal
management and therapeutic approach to COVID-19 in this population has not yet been defined.

Testing for COVID-19 in Patients With Cancer

The COVID-19 Treatment Guidelines Panel (the Panel) recommends molecular diagnostic testing for SARS-CoV-2 in patients with cancer who develop signs and symptoms of COVID-19 (AIII).

Patients with cancer who are receiving chemotherapy are at risk of developing neutropenia. The NCCN Guidelines for Hematopoietic Growth Factors categorizes cancer treatment regimens based on the risk of developing neutropenia. A retrospective study suggests that cancer patients with neutropenia have a higher mortality rate if they develop COVID-19. Due to the potential risk of poor clinical outcomes in the setting of neutropenia and/or during the perioperative period, the Panel recommends performing molecular diagnostic testing for SARS-CoV-2 prior to procedures that require anesthesia and before initiating cytotoxic chemotherapy and long-acting biologic therapy (BIII).

General Guidance on Medical Care for Cancer Patients During the COVID-19 Pandemic

Patients with cancer frequently engage with the health care system to receive treatment and supportive care for cancer and/or treatment-related complications. Telemedicine can minimize the need for in-person services and reduce the risk of SARS-CoV-2 exposure. The Centers for Disease Control and Prevention published a framework to help clinicians decide whether a patient should receive in-person or virtual care during the COVID-19 pandemic; this framework accounts for factors such as the potential harm of delayed care and the degree of SARS-CoV-2 transmission in a patient’s community. Telemedicine may improve access to providers for medically or socially vulnerable populations but could worsen disparities if these populations have limited access to technology. Nosocomial transmission of SARS-CoV-2 to patients and health care workers has been reported. Principles of physical distancing and prevention strategies, including masking patients and health care workers and practicing hand hygiene, apply to all in-person interactions.

Decisions about treatment regimens, surgery, and radiation therapy for the underlying malignancy should be made on an individual basis depending on the biology of the cancer, the need for hospitalization, the number of clinic visits required, and the anticipated degree of immunosuppression. Several key points should be considered:

- If possible, treatment delays should be avoided for curable cancers that have been shown to have worse outcomes when treatment is delayed (e.g., pediatric acute lymphoblastic leukemia).
- When deciding between equally effective treatment regimens, regimens that can be administered orally or those that require fewer infusions are preferred.
- The potential risks of drug-related lung toxicity (e.g., from using bleomycin or PD1 inhibitors) must be balanced with the clinical efficacy of alternative regimens or the risk of delaying care.
- Preventing neutropenia can decrease the risk of neutropenic fever and the need for emergency room evaluation and hospitalization during the COVID-19 pandemic. Granulocyte colony-stimulating factor (G-CSF) should be given with chemotherapy regimens that have intermediate (10% to 20%) or high (>20%) risks of febrile neutropenia.
- Cancer treatment regimens that do not affect outcomes of COVID-19 in cancer patients may not need to be altered. In a prospective observational study, receipt of immunotherapy, hormonal therapy, or radiotherapy in the month prior to SARS-CoV-2 infection was not associated with an increased risk of mortality among cancer patients with COVID-19. A retrospective study from Italy evaluated the incidence of SARS-CoV-2 infection in patients with prostate cancer and...
found that 114 of 37,161 patients (0.3%) who were treated with therapies other than androgen deprivation therapy became infected, compared to four of 5,273 patients (0.08%) who were treated with androgen deprivation therapy (OR 4.05; 95% CI, 1.55–10.59). The viral spike proteins required for cell entry of SARS-CoV-2 are primed by TMPRSS2, an androgen-regulated gene. Whether androgen deprivation therapy protects against SARS-CoV-2 infection requires further investigation in larger cohorts.20

- Radiation therapy guidelines suggest increasing the dose per fraction and reducing the number of daily treatments in order to minimize the number of hospital visits during the COVID-19 pandemic.15,16

Blood supply shortages will likely continue during the COVID-19 pandemic due to social distancing, cancellation of blood drives, and infection among donors. Revised donor criteria have been proposed by the Food and Drug Administration to increase the number of eligible donors.21 In patients with cancer, lowering the transfusion thresholds for blood products (e.g., red blood cells, platelets) in asymptomatic patients should be considered.22,23 At this time, there is no evidence that COVID-19 can be transmitted through blood products.24,25

Febrile Neutropenia

Cancer patients with febrile neutropenia should undergo molecular diagnostic testing for SARS-CoV-2 and evaluation for other infectious agents; they should also be given empiric antibiotics, as outlined in the NCCN Guidelines.26 Low-risk febrile neutropenia patients should be treated at home with oral antibiotics or intravenous infusions of antibiotics to limit nosocomial exposure to SARS-CoV-2. Patients with high-risk febrile neutropenia should be hospitalized per standard of care.26 Empiric antibiotics should be continued per standard of care in patients who test positive for SARS-CoV-2. Clinicians should also continuously evaluate neutropenic patients for emergent infections.

Treating COVID-19 and Managing Chemotherapy in Patients With Cancer and COVID-19

Retrospective studies suggest that patients with cancer who were admitted to the hospital with SARS-CoV-2 infection have a high case fatality rate, with higher rates observed in patients with hematologic malignancies than in those with solid tumors.27,28

Recommendations for treatment of COVID-19 are the same for cancer patients as for the general population (AIII) (see Potential Antiviral Drugs Under Evaluation for the Treatment of COVID-19 and Immune-Based Therapy Under Evaluation for Treatment of COVID-19). Dexamethasone treatment in patients with COVID-19 who require supplemental oxygen or mechanical ventilation has been associated with a lower mortality rate.29 In cancer patients, dexamethasone is commonly used to prevent chemotherapy-induced nausea, as a part of tumor-directed therapy, and to treat inflammation associated with brain metastasis. The side effects of using dexamethasone to treat SARS-CoV-2 are not anticipated to be different between patients with or without cancer. If possible, treatments that are not currently recommended for SARS-CoV-2 infection should be administered as part of a clinical trial, since the safety and efficacy of these agents have not been well defined in patients with cancer.

The NCCN recommends discontinuing G-CSF and granulocyte-macrophage colony-stimulating factor in patients with cancer and acute SARS-CoV-2 infection who do not have bacterial or fungal infections to avoid the hypothetical risk of increasing inflammatory cytokines and pulmonary inflammation.18,30 Secondary infections (e.g., invasive pulmonary aspergillosis) have been reported in critically ill patients with COVID-19.31,32
Decisions about administering cancer-directed therapy to patients with acute COVID-19 and those who are recovering from COVID-19 should be made on a case-by-case basis; clinicians should consider the indication for chemotherapy, the goals of care, and the patient’s history of tolerance to the treatment (BIII). The optimal duration of time between resolution of infection and initiating or restarting cancer-directed therapy is unclear. Withholding treatment until COVID-19 symptoms have resolved is recommended, if possible. Prolonged viral shedding (detection of SARS-CoV-2 by molecular testing) may occur in cancer patients, although it is unknown how this relates to infectious virus and how it impacts outcomes. Therefore, there is no role for repeat testing in those recovering from COVID-19, and the decision to restart cancer treatments in this setting should be made on a case-by-case basis. The Panel recommends that clinicians who are treating COVID-19 in patients with cancer consult with a hematologist or oncologist before adjusting cancer-directed medications (AIII).

Medication Interactions
The use of potential antiviral or immune-based therapies to treat COVID-19 can present additional challenges in cancer patients. Clinicians should pay careful attention to potential drug-drug interactions and overlapping toxicities between drugs that are used to treat COVID-19 and cancer-directed therapies, prophylactic antimicrobials, corticosteroids, and other medications (AIII).

Several anti-neoplastic medications have known interactions with therapies that are being investigated for COVID-19. Tocilizumab can interact with vincristine and doxorubicin. Any COVID-19 therapy that may cause QT prolongation must be used with caution in patients treated with venetoclax, gilteritinib, and tyrosine kinase inhibitor therapy (e.g., nilotinib). Dexamethasone is commonly used as an antiemetic for cancer patients and is recommended for treatment of certain patients with COVID-19 (see Corticosteroids for more information). Dexamethasone is a weak to moderate cytochrome P450 (CYP) 3A4 inducer; therefore, interactions with any CYP3A4 substrates need to be considered. Lopinavir/ritonavir is a CYP3A4 inhibitor, and it can increase methotrexate, vincristine, or ruxolitinib concentrations. Lopinavir/ritonavir is not recommended for the treatment of COVID-19; however, patients may receive it in a clinical trial. In general, concomitant use of lopinavir/ritonavir and CYP3A4 substrates should be avoided. If lopinavir/ritonavir is used in combination with a cytotoxic drug that is also a CYP34A substrate, clinicians should monitor for toxicities of the cytotoxic drug and adjust the dose if necessary.

Special Considerations in Children
Preliminary published reports suggest that pediatric patients with cancer may have milder manifestations of COVID-19 than adult patients with cancer, although larger studies are needed. Guidance on managing children with cancer during the COVID-19 pandemic is available from an international group with input from the International Society of Paediatric Oncology, the Children’s Oncology Group, St. Jude Global, and Childhood Cancer International. Two publications include guidance for managing specific malignancies, guidance for supportive care, and a summary of web links from expert groups that are relevant to the care of pediatric oncology patients during the COVID-19 pandemic. Special considerations for using antivirals in immunocompromised children, including those with malignancy, are available in a multicenter guidance statement.

References


18. National Comprehensive Cancer Network. NCCN hematopoietic growth factors: short-term recommendations...


Introduction

Treating COVID-19 in solid organ transplant (SOT), hematopoietic cell transplant (HCT), and cellular immunotherapy recipients can be challenging due to the presence of coexisting medical conditions, transplant-related cytopenias, and the need for chronic immunosuppressive therapy to prevent graft rejection and graft-versus-host disease. Transplant recipients may also potentially have increased exposure to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) given their frequent contact with the health care system. Since immunosuppressive agents modulate several aspects of the host’s immune response, the severity of COVID-19 could potentially be affected by the type and the intensity...
of the immunosuppressive effect of the agent, as well as by specific combinations of immunosuppressive agents. Some transplant recipients have medical comorbidities that have been associated with more severe cases of COVID-19 and a greater risk of mortality, which makes the attributable impact of transplantation on disease severity difficult to assess.

The American Association for the Study of Liver Diseases (AASLD), the International Society for Heart and Lung Transplantation, the American Society of Transplantation, the American Society for Transplantation and Cellular Therapy (ASTCT), the European Society for Blood and Marrow Transplantation (EBMT), and the Association of Organ Procurement Organizations provide guidance for clinicians who are caring for transplant recipients with COVID-19, as well as guidance for screening potential donors and transplant or cell therapy candidates. This section of the Guidelines complements these sources and focuses on considerations for managing COVID-19 in SOT, HCT, and cellular therapy recipients. The optimal management and therapeutic approach to COVID-19 in these populations is unknown. At this time, the procedures for evaluating and managing COVID-19 in transplant recipients are the same as for nontransplant patients (AIII). See Management of Persons with COVID-19, Potential Antiviral Drugs Under Evaluation for the Treatment of COVID-19, and Immune-Based Therapy Under Evaluation for Treatment of COVID-19 for more information. The medications that are used to treat COVID-19 may present different risks and benefits to transplant patients and nontransplant patients.

**Assessment of SARS-CoV-2 Infection in Transplant and Cellular Therapy Candidates and Donors**

The risk of transmission of SARS-CoV-2 from donors to candidates is unknown. The probability of donor or candidate infection with SARS-CoV-2 may be estimated by considering epidemiologic risk, obtaining clinical history, and testing with molecular techniques. No current testing strategy is sensitive enough or specific enough to totally exclude active infection. Living solid organ donors should be counseled on strategies to prevent infection and monitored for exposures and symptoms in the 14 days prior to scheduled transplant. HCT donors should practice good hygiene and avoid crowded places and large group gatherings during the 28 days prior to donation.

**Assessment of Transplant and Cellular Therapy Candidates**

Diagnostic molecular testing for SARS-CoV-2 is recommended for all potential SOT candidates with signs and symptoms that suggest acute COVID-19 infection (AIII). All potential SOT candidates should be assessed for exposure to COVID-19 and clinical symptoms that are compatible with COVID-19 before they are called in for transplantation and should undergo diagnostic molecular testing for SARS-CoV-2 shortly before SOT in accordance with guidance from medical professional organizations (AIII).

Clinicians should consider performing diagnostic testing for SARS-CoV-2 in all HCT and cellular therapy candidates who exhibit symptoms. All candidates should also undergo diagnostic molecular testing for SARS-CoV-2 shortly before HCT or cell therapy (AIII).

**Assessment of Donors**

The COVID-19 Treatment Guidelines Panel (the Panel) recommends following the guidance from medical professional organizations and assessing all potential HCT donors for exposure to COVID-19 and clinical symptoms that are compatible with COVID-19 before donation (AIII). Deceased donors should undergo screening for known symptoms and exposure to others with COVID-19 before transplantation, and decisions about using such organs should be made on a case-by-case basis (BIII). Recommendations for screening are outlined in the ASTCT and EBMT guidelines.
If SARS-CoV-2 Infection Is Detected or Strongly Suspected

If SARS-CoV-2 is detected or if infection is strongly suspected in a potential SOT donor or candidate, transplant should be deferred, if possible (BIII). The optimal disease-free interval before transplantation is not known. The risks of viral transmission should be balanced against the risks to the candidate, such as progression of the underlying disease and risk of mortality if the candidate does not receive the transplant. This decision should be continually reassessed as conditions evolve. For HCT and cellular therapy candidates, current guidelines recommend deferring transplants or immunotherapy procedures, including peripheral blood stem cell mobilization, bone marrow harvest, T cell collection, and conditioning/lymphodepletion in recipients who test positive for SARS-CoV-2 or who have clinical symptoms that are consistent with infection. Final decisions should be made on a case-by-case basis while weighing the risks of delaying or altering therapy for the underlying disease.

Transplant Recipients with COVID-19

SOT recipients who are receiving immunosuppressive therapy should be considered to be at increased risk for severe COVID-19. A national survey of 88 U.S. transplant centers conducted between March 24 and 31, 2020, reported that 148 SOT recipients received a diagnosis of COVID-19 infection (69.6% were kidney recipients, 15.5% were liver recipients, 8.8% were heart recipients, and 6.1% were lung recipients). COVID-19 was mild in 54% of recipients and moderate in 21% of recipients, and 25% of recipients were critically ill. Modification of immunosuppressive therapy during COVID-19 and the use of investigational therapies for treatment of COVID-19 varied widely among recipients. Initial reports of transplant recipients who were hospitalized with COVID-19 suggest mortality rates of up to 28%.

Risk of Graft Rejection

There have been no published reports of graft rejection in SOT recipients who received a diagnosis of COVID-19, although this may be due to a limited ability to perform biopsies. Acute cellular rejection should not be presumed in SOT recipients without biopsy confirmation in individuals with or without COVID-19. Similarly, immunosuppressive therapy should be initiated in recipients with or without COVID-19 who have rejection confirmed by a biopsy.

There is a lack of data on the incidence and clinical characteristics of SARS-CoV-2 infection in HCT and cellular therapy recipients. Experience with other respiratory viruses suggests that this population is at a high risk for severe disease, including increased rates of lower respiratory tract infection and mortality. Factors that may determine clinical severity include degree of cytopenia, time since transplant, intensity of the conditioning regimen, graft source, degree of mismatch, and the need for further immunosuppression to manage graft-versus-host disease. For other respiratory viruses, HCT recipients often exhibit prolonged viral shedding, which can have implications for infection prevention and for the timing of potential interventions.

Treatment of COVID-19 in Transplant Recipients

Currently, no drug has been approved by the Food and Drug Administration (FDA) for the treatment of COVID-19, although preliminary data suggest that the investigational antiviral drug remdesivir can be used in those with severe disease. Remdesivir is available for use in these patients under the FDA’s Emergency Use Authorization.

Preliminary data from a large randomized controlled trial have shown that a short course of dexamethasone (6 mg once daily for up to 10 days) can improve survival in patients with COVID-19 who are mechanically ventilated or who require supplemental oxygen. At this time, the risks and benefits of using dexamethasone in transplant recipients with COVID-19 who are receiving immunosuppressive therapy, which may include corticosteroids, are unknown.
The Panel’s recommendations for the use of remdesivir and dexamethasone in patients with COVID-19 can be found in the Remdesivir and Corticosteroids sections.

A number of other investigational agents and drugs that are approved by the FDA for other indications are being evaluated for the treatment of COVID-19 (e.g., antiviral therapies, COVID-19 convalescent plasma) and its associated complications (e.g., immunomodulators, antithrombotic agents). In general, the considerations when treating COVID-19 are the same for transplant recipients as for the general population. When possible, treatment should be given as part of a clinical trial. The safety and efficacy of investigational agents and drugs that have been approved by the FDA for other indications are not well defined in transplant recipients. Moreover, it is unknown whether concomitant use of immunosuppressive agents to prevent allograft rejection in the setting of COVID-19 affects treatment outcome.

The use of antiviral or immune-based therapies for the treatment of COVID-19 can present additional challenges in transplant patients. Clinicians should pay special attention to the potential for drug-drug interactions and overlapping toxicities with concomitant medications, such as immunosuppressants that are used to prevent allograft rejection (e.g., corticosteroids, mycophenolate, and calcineurin inhibitors such as tacrolimus and cyclosporine), antimicrobials that are used to prevent opportunistic infections, and other medications. Dose modifications may be necessary for drugs that are used to treat COVID-19 in transplant recipients with pre-existing organ dysfunction. Adjustments to the immunosuppressive regimen should be individualized based on disease severity, the specific immunosuppressants used, the type of transplant, the time since transplantation, the drug concentration, and the risk of graft rejection.7 Clinicians who are treating COVID-19 in transplant patients should consult with a transplant specialist before adjusting immunosuppressive medication (AIII).

Certain investigational or off-label therapeutics (e.g., remdesivir, tocilizumab) are associated with elevated levels of transaminases. For liver transplant recipients, the AASLD does not view abnormal liver biochemistries as a contraindication to using investigational or off-label therapeutics, although certain elevation thresholds may exclude patients from trials of some investigational agents.17 Close monitoring of liver biochemistries is warranted in patients with COVID-19, especially when they are receiving agents with a known risk of hepatotoxicity.

Calcineurin inhibitors, which are commonly used to prevent allograft rejection, have a narrow therapeutic index. Medications that inhibit or induce cytochrome P450 enzymes or P-glycoprotein may put patients who receive calcineurin inhibitors at risk of clinically significant drug-drug interactions, increasing the need for therapeutic drug monitoring and the need to assess for signs of toxicity or rejection.18 Similarly, transplant patients may be at a higher risk of adverse effects, particularly when their concomitant medications have overlapping toxicities. Specific concerns about the use of potential antiviral medications and immune-based therapy for COVID-19 in transplant patients are noted below. See Tables 2b and 3b for additional details.
Table 4. Special Concerns for Drugs That Are Being Evaluated for COVID-19 Treatment in Transplant Patients

<table>
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<tr>
<th>Drugs That Are Being Evaluated for COVID-19 Treatment</th>
<th>Concerns in Transplant Patients</th>
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| Azithromycin                                         | • Hepatotoxicity (cholestatic hepatitis, rare)  
  • Additive effect with other drugs that prolong the QTc interval. |
| Chloroquine and Hydroxychloroquine                    | • Moderate inhibition of CYP2D6.  
  • Inhibition of P-gp may increase levels of calcineurin inhibitors and mTOR inhibitors.  
  • Additive effect with other drugs that prolong the QTc interval. |
| Dexamethasone                                         | • Moderate CYP3A4 inducer  
  • Potential for additional immunosuppression and increased risk of OIs. |
| HIV Protease Inhibitors                               | • RTV and other PIs are strong inhibitors of CYP3A4. Coadministration will increase concentrations of tacrolimus, cyclosporine, everolimus, sirolimus, and prednisone.  
  • TDM and dose adjustment of immunosuppressant is necessary. Monitor for calcineurin inhibitor-associated toxicities. |
| Interleukin-6 Inhibitors                              | • Use of IL-6 inhibitors may lead to increased metabolism of drugs that are CYP substrates. Effects on CYP may persist for weeks after therapy.  
  • AEs include neutropenia and an increase in transaminases. See Table 3b. |
| Remdesivir                                           | • Strong P-gp inducers (e.g., rifampin) may reduce RDV exposure. Coadministration is not recommended.  
  • Increase in levels of serum transaminases.  
  • Accumulation of drug vehicle cyclodextrin in patients with kidney dysfunction. |
| Ribavirin                                            | • Significant toxicities, including anemia, Bradycardia, and an increase in serum transaminases levels. |

Key: AE = adverse effects; CYP = cytochrome P450; IL = interleukin; mTOR = mechanistic target of rapamycin; OI = opportunistic infection; P-gp = P-glycoprotein; PI = protease inhibitor; RDV = remdesivir; RTV = ritonavir; TDM = therapeutic drug monitoring

References


