COVID-19 and Special Populations

Last Updated: October 9, 2020

Key Considerations

| 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-19.¹⁻⁴ This section of the COVID-19 Treatment Guidelines complements that guidance. Below are key considerations regarding the management of COVID-19 in pregnancy.
| • 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.
| • 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.
| • Management of COVID-19 in the pregnant patient should 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
| • 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).
| • 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 the pregnancy considerations subsection of each individual section of the Guidelines.

Rating of Recommendations: A = Strong; B = Moderate; C = Optional
Rating of Evidence: I = One or more randomized trials without major limitations; IIa = Other randomized trials or subgroup analyses of randomized trials; IIb = Nonrandomized trials or observational cohort studies; III = Expert opinion

To date, most 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 regarding COVID-19 in other patient populations, such as in children, pregnant individuals, and other populations as outlined in the following sections of the Guidelines.

Although children with COVID-19 may have less severe disease overall than adults with COVID-19, 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 syndrome coronavirus 2 (SARS-CoV-2). There are special considerations for transplant recipients, patients with cancer, persons with HIV, and patients with other immunocompromising conditions, as some of these patients may be at increased risk of serious complications as a result of COVID-19.

The following sections review the available data on COVID-19 in some of these populations and discuss the specific considerations that clinicians should take into account for the prevention and treatment of SARS-CoV-2 infections in these populations.
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.\(^5\sim7\) 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.

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.\(^9\) 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.\textsuperscript{10}
• 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.\textsuperscript{11-13}

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 (AIII).
• 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 the pregnancy considerations subsection of each individual section of the 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\textsuperscript{14,15} and the American Academy of Pediatrics.\textsuperscript{16}

References


Special Considerations in Children

Last Updated: April 21, 2021

**Summary Recommendations**

- SARS-CoV-2 infection is generally milder in children than in adults, and a substantial proportion of children with the disease have asymptomatic infection.
- Most children with SARS-CoV-2 infection will not require any specific therapy.
- Children who have a history of medical complexity (e.g., due to neurologic impairment, developmental delays, or genetic syndromes including trisomy 21), obesity, chronic cardiopulmonary disease, or who are immunocompromised, as well as nonwhite children and older teenagers may be at increased risk for severe disease.
- There are limited data on the pathogenesis and clinical spectrum of COVID-19 disease in children. There are no pediatric data from placebo-controlled randomized clinical trials and limited data from observational studies to inform the development of pediatric-specific recommendations for the treatment of COVID-19.

**Specific Therapy for Children**

- In the absence of adequate data on the treatment of children with acute COVID-19, recommendations are based on outcome and safety data for adult patients and the child's risk of disease progression.
- Most children with mild or moderate disease can be managed with supportive care alone (AIII).
- **Remdesivir** is recommended for:
  - Hospitalized children aged ≥12 years with COVID-19 who have risk factors for severe disease and have an emergent or increasing need for supplemental oxygen (BIII).
  - Hospitalized children aged ≥16 years with COVID-19 who have an emergent or increasing need for supplemental oxygen regardless of whether they have risk factors for severe disease (BIII).
- In consultation with a pediatric infectious disease specialist, **remdesivir** can be considered for hospitalized children of all ages with COVID-19 who have an emergent or increasing need for supplemental oxygen (CIII).
- The COVID-19 Treatment Guidelines Panel (the Panel) recommends using **dexamethasone** for hospitalized children with COVID-19 who require high-flow oxygen, noninvasive ventilation, invasive mechanical ventilation, or extracorporeal membrane oxygenation (BIII).
- There are insufficient pediatric data for the Panel to recommend either for or against the use of anti-SARS-CoV-2 monoclonal antibody products for children with COVID-19 who are not hospitalized but who have risk factors for severe disease. Based on adult studies, bamlanivimab plus etesevimab or casirivimab plus imdevimab may be considered on a case-by-case basis for nonhospitalized children who meet Emergency Use Authorization (EUA) criteria for high-risk of severe disease, especially those who meet more than one criterion or are aged ≥16 years. The Panel recommends consulting a pediatric infectious disease specialist in such cases.
- The Panel **recommends against** the use of **convalescent plasma** for hospitalized children with COVID-19 who do not require mechanical ventilation, except in a clinical trial (AIII). The Panel **recommends against** the use of **convalescent plasma** for pediatric patients with COVID-19 who are mechanically ventilated (AIII). In consultation with a pediatric infectious disease specialist, high-titer convalescent plasma may be considered on a case-by-case basis for hospitalized children who meet the EUA criteria for its use.
- There are insufficient data for the Panel to recommend either for or against the use of baricitinib in combination with remdesivir for the treatment of COVID-19 in hospitalized children in whom corticosteroids cannot be used.
- There are insufficient data for the Panel to recommend either for or against the use of tocilizumab in hospitalized children with COVID-19 or multisystem inflammatory syndrome in children (MIS-C). The Panel **recommends against** the use of **sarilumab** for hospitalized children with COVID-19 or MIS-C, except in a clinical trial (AIII).
- MIS-C is a serious delayed complication of SARS-CoV-2 infection that may develop in a minority of children and young adults.
- Consultation with a multidisciplinary team is recommended when considering and managing immunomodulating therapy for children with MIS-C (AIII). Intravenous immunoglobulin and/or corticosteroids are generally used as first-line therapy, although interleukin-1 antagonists have been used for refractory cases. The optimal choice and combination of immunomodulating therapies have not been definitively established.
Epidemiology

Data from the Centers for Disease Control and Prevention (CDC) demonstrate a lower incidence of SARS-CoV-2 infection and severe disease in children than in adults. However, without more systematic testing for children, including for children with mild symptoms as part of contact tracing, or seroprevalence studies, the true burden of pediatric SARS-CoV-2 infection remains unclear. Data on the pathogenesis and disease severity of SARS-CoV-2 infection in children are increasing but are still limited compared to the data in adults. Several large epidemiologic studies suggest that severe manifestations of acute disease are substantially less common in children than in adults. Although only a small percentage of children with COVID-19 will require medical attention, intensive care unit (ICU)-admission rates for hospitalized children are comparable to those for hospitalized adults with COVID-19.

Clinical Manifestations

The signs and symptoms of SARS-CoV-2 infection in children may be similar to those in adults, but most children may be asymptomatic or only have a few symptoms. The most common signs and symptoms of COVID-19 in hospitalized children are fever, nausea/vomiting, cough, shortness of breath, and upper respiratory symptoms. Of note, signs and symptoms of COVID-19 may overlap significantly with those of other viral infections, including influenza and other respiratory and enteric viral infections. Although the true incidence of asymptomatic SARS-CoV-2 infection is unknown, asymptomatic infection was reported in up to 45% of children who underwent surveillance testing at the time of hospitalization for a non-COVID-19 indication.

SARS-CoV-2 has been associated with a potentially severe inflammatory syndrome in children and young adults (multisystem inflammatory syndrome in children [MIS-C]), which is discussed below.

Risk Factors

Data to clearly establish risk factors for severe COVID-19 in children are limited. Data reported to CDC show lower hospitalization rates and ICU admission rates for children with COVID-19 than for adults with the disease. COVID-19-related hospitalization rates for children were highest in children aged <2 years and higher in Hispanic and Black children than in White children. The majority of hospitalized children with acute COVID-19 had underlying conditions, with obesity, chronic lung disease, and prematurity (data collected only for children aged <2 years) being the most prevalent. Risk factors such as obesity may be more applicable to older teenagers.

In a large study of hospitalized children from the United Kingdom, age <1 month, age 10 to 14 years, and Black race were associated with admission to critical care unit on multivariate analysis. Another large multicenter study from Europe identified male sex, pre-existing medical conditions, and the presence of lower respiratory tract disease at presentation as additional risk factors for ICU admission in multivariable models.

Deaths associated with COVID-19 among those aged <21 years are higher among children aged 10 to 20 years, especially young adults aged 18 to 20 years, as well as among Hispanic, Black, and American Indian/Alaska Native persons. A high proportion of the fatal cases of pediatric COVID-19 are in children with underlying medical conditions, most commonly chronic lung disease, obesity, and neurologic and developmental disorders.
Based on data for adults with COVID-19 and extrapolations from data for non-COVID-19 pediatric respiratory viral infections, severely immunocompromised children and those with underlying cardiopulmonary disease may be at higher risk for severe COVID-19. Initial reports of SARS-CoV-2 infection among pediatric patients with cancer and pediatric solid organ transplant recipients have demonstrated a low frequency of infection and associated morbidity; however, similar reports for other immunocompromised pediatric populations are limited. A few reports have demonstrated a higher prevalence of asthma in pediatric COVID-19 cases, although the association of asthma with severe disease is not clearly defined. Congenital heart disease may be associated with increased risk of severe COVID-19, but the condition has not been consistently identified as a risk factor. Guidance on the treatment of COVID-19 in children endorsed by the Pediatric Infectious Diseases Society specifies additional risk factors to consider when making decisions about antiviral and monoclonal antibody therapy for pediatric patients.

Persistent symptoms after acute COVID-19 have been described in adults, although the incidence of this sequelae in children remains unknown and is an active area of research (see Clinical Spectrum of SARS-CoV-2 Infection). Cardiac imaging studies have described myocardial injury in young athletes who had only mild disease; additional studies are needed to determine long-term cardiac sequelae.

**Vertical Transmission and Infants Born to Mothers with SARS-CoV-2 Infection**

Vertical transmission of SARS-CoV-2 is thought to be rare, but suspected or probable vertical transmission has been described. Initial data on perinatal transmission of SARS-CoV-2 were limited to small case series with conflicting results; some studies demonstrated lack of transmission, whereas others were not able to definitively rule out this possibility. Among 100 women with SARS-CoV-2 infection who delivered 101 infants, only two infants had equivocal reverse transcription polymerase chain reaction (RT-PCR) results that may have reflected SARS-CoV-2 infection even though most of the infants remained with their mothers, in rooms with infection prevention measures in place, and were breast fed.

Infants born to individuals with SARS-CoV-2 infection may have higher risk of poor clinical outcomes than those born to individuals without SARS-CoV-2 infection, although data are conflicting. In a systematic review of case series in pregnant women with confirmed SARS-CoV-2 infection (predominantly from China), the preterm birth rate was 20.1% (57 of 284 births were preterm; 95% CI, 15.8–25.1), the cesarean delivery rate was 84.7% (33 of 392 births were by cesarean delivery; 95% CI, 80.8–87.9), there was no vertical transmission, and the neonatal death rate was 0.3% (1 of 313 neonates died; 95% CI, 0.1–1.8). In a prospective cohort study of 263 infants born in the United States, the rates for preterm births, neonatal ICU admissions, and respiratory disease did not differ between infants born to mothers with and without SARS-CoV-2 infection. A cohort study from Sweden demonstrated that 5-minute Apgar scores and birth weight for gestational age did not differ between infants born to mothers with and without SARS-CoV-2 infection.

Coronavirus Disease 2019 (COVID-19)-Associated Hospitalization Surveillance Network (COVID-NET) data from CDC that captured 598 hospitalized, pregnant women with SARS-CoV-2 infection showed a pregnancy loss rate of 2% among 458 pregnancies completed during COVID-19-related hospitalizations and a preterm birth rate of 12.9% compared to 10% for the general U.S. population. A systematic review and meta-analysis of studies that included 2,567 pregnancies concluded that SARS-CoV-2-positive mothers were at increased risk of iatrogenic preterm birth. This risk was predominantly due to caesarean sections (21.8% of births) performed due to maternal illness and fear of maternal decompensation. In contrast, there was no increase in the rate of spontaneous preterm birth relative to the expected rate in pregnant individuals without SARS-CoV-2 infection. Finally, a prospective cohort study from the United Kingdom of 66 neonates with SARS-CoV-2 infection found that 3% may have had vertically acquired infection and 12% had suspected nosocomially acquired infection. 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 CDC.

**Treatment Considerations**

There are no results available from clinical trials evaluating treatment for COVID-19 in children, and observational data on the safety or efficacy of drug therapy in children with COVID-19 are extremely limited. More high-quality studies, including randomized trials, are urgently needed. Guidance for the treatment of COVID-19 in children has been published and is mostly extrapolated from recommendations for adults with COVID-19.\(^{41,42}\) The older the child and the more severe the disease, the more reasonable it is to follow recommendations for adult patients with COVID-19 (see Therapeutic Management of Adults With COVID-19). To address the uncertain safety and efficacy of these treatment options, children should be enrolled in clinical trials and multicenter pragmatic trials whenever possible.

The majority of children with mild or moderate COVID-19 will not progress to more severe illness and thus should be managed with supportive care alone (AII). The risks and benefits of therapy should be assessed based on illness severity, age, and the presence of risk factors outlined above.

**Remdesivir**

Remdesivir is the only drug approved by the Food and Drug Administration (FDA) for the treatment of COVID-19 (see Remdesivir for detailed information). It is approved for the treatment of COVID-19 in hospitalized adult and pediatric patients (aged ≥12 years and weighing ≥40 kg). It is also available through an FDA Emergency Use Authorization (EUA) for the treatment of COVID-19 in hospitalized pediatric patients weighing 3.5 kg to <40 kg or aged <12 years and weighing ≥3.5 kg.\(^{43}\) Remdesivir has not been evaluated in clinical trials that include children, and there have been no results from systematic evaluations of pharmacokinetics, efficacy, or toxicity in younger children, although studies are ongoing (see ClinicalTrials.gov). However, based on adult data, the potential benefits of remdesivir are likely to be greater for hospitalized children with COVID-19 who are at higher risk of progression due to older age (i.e., aged ≥16 years) or medical condition than for those without these risk factors. Remdesivir is recommended for hospitalized children aged ≥12 years with COVID-19 who have risk factors for severe disease and have an emergent or increasing need for supplemental oxygen (BIII). Remdesivir is also recommended for hospitalized children aged ≥16 years with COVID-19 who have an emergent or increasing need for supplemental oxygen even in the absence of risk factors (BIII). Remdesivir can be considered for other hospitalized children of all ages with COVID-19 who have an emergent or increasing need for supplemental oxygen in consultation with a pediatric infectious disease specialist (CIII).

**Dexamethasone**

Dexamethasone is recommended for the treatment of hospitalized adults with COVID-19 who require mechanical ventilation or supplemental oxygen through a high-flow device (see Corticosteroids and Therapeutic Management of Adults With COVID-19 for detailed information). The safety and effectiveness of dexamethasone or other corticosteroids for COVID-19 treatment have not been sufficiently evaluated in pediatric patients and thus caution is warranted when extrapolating recommendations for adults to patients aged <18 years. The COVID-19 Treatment Guidelines Panel (the Panel) recommends using dexamethasone for children with COVID-19 who require high-flow oxygen, noninvasive ventilation, invasive mechanical ventilation, or extracorporeal membrane oxygenation (ECMO) (BIII). It is not routinely recommended for pediatric patients who require only low levels of oxygen support (i.e., via a nasal cannula only). Use of dexamethasone for the treatment of severe COVID-19 in children who are profoundly immunocompromised has not been evaluated, may be harmful, and therefore should be considered only on a case-by-case basis. If dexamethasone is not available, alternative glucocorticoids such as prednisone, methylprednisolone, or hydrocortisone can be
considered. The dexamethasone dosing regimen for pediatric patients is dexamethasone 0.15 mg/kg/dose (maximum dose 6 mg) once daily for up to 10 days.

Anti-SARS-CoV-2 Monoclonal Antibodies

Although EUAs have been issued for bamlanivimab plus etesevimab and casirivimab plus imdevimab for the treatment of nonhospitalized, high-risk patients aged ≥12 years and weighing ≥40 kg with mild to moderate COVID-19, there are currently no data available to determine which high-risk pediatric patients defined in the EUAs will likely benefit from these therapies. Consequently, there are insufficient data for the Panel to recommend either for or against the use of these monoclonal antibodies in children with COVID-19 who are not hospitalized but are at high risk of severe disease and/or hospitalization. In consultation with a pediatric infectious disease specialist, bamlanivimab plus etesevimab or casirivimab plus imdevimab can be considered on a case-by-case basis for children who meet the EUA criteria, but should not be considered routine care. This recommendation is primarily based on the absence of data assessing efficacy or safety in children or adolescents, limited data with which to identify children at the highest risk of severe COVID-19, as well as the low overall risk of progression to serious disease in children, and the potential risk associated with infusion reactions.

Additional guidance is provided in a recent publication endorsed by the Pediatric Infectious Diseases Society. There are currently no data to support the use of anti-SARS-CoV-2 monoclonal antibodies in hospitalized children for COVID-19. Emerging data regarding the prevalence and clinical significance of SARS-CoV-2 variants, and the efficacy of monoclonal antibodies against variants, may inform the choice of specific anti-SARS-CoV-2 monoclonal antibody therapy in the future.

Convalescent Plasma

FDA has also issued an EUA for the use of high-titer convalescent plasma for the treatment of hospitalized patients with COVID-19 (see Convalescent Plasma for detailed information). The safety and efficacy of convalescent plasma have not been evaluated in pediatric patients with COVID-19. There are insufficient data for the Panel to recommend either for or against the use of convalescent plasma for the treatment of COVID-19 in either pediatric outpatients or in hospitalized children who do not require mechanical ventilation. The Panel recommends against the use of convalescent plasma for pediatric patients with COVID-19 who are mechanically ventilated (AIII). In consultation with a pediatric infectious disease specialist, convalescent plasma may be considered on a case-by-case basis for children who meet the EUA criteria for its use.

Baricitinib

FDA has also issued an EUA for the use of baricitinib in combination with remdesivir in hospitalized adults and children aged ≥2 years with COVID-19 who require supplemental oxygen, invasive mechanical ventilation, or ECMO. The safety and efficacy of baricitinib have not been evaluated in pediatric patients with COVID-19, and pediatric data regarding its use for other conditions are extremely limited. Thus, there are insufficient data for the Panel to recommend either for or against the use of baricitinib in combination with remdesivir for the treatment of COVID-19 in hospitalized children in whom corticosteroids cannot be used (see Kinase Inhibitors for detailed information).

Tocilizumab

Data on tocilizumab use for the treatment of non-COVID-19 conditions in children are limited to very specific clinical scenarios (e.g., chimeric antigen receptor T cell-related cytokine release syndrome). The use of tocilizumab for severe cases of acute COVID-19 has been described in pediatric case series. Data on tocilizumab efficacy from trials in adults with COVID-19 are conflicting, and
benefit has only been demonstrated in a subset of hospitalized patients (see Interleukin-6 Inhibitors). There are insufficient data for the Panel to recommend either for or against the use of tocilizumab for hospitalized children with COVID-19 or MIS-C. If used, tocilizumab should be used in combination with dexamethasone. The Panel recommends against the use of sarilumab for hospitalized children with COVID-19 or MIS-C, except in a clinical trial (AIII).

As for other agents outlined in these Guidelines, there are insufficient data for the Panel to recommend either for or against the use of specific antivirals or immunomodulatory agents for the treatment of COVID-19 in pediatric patients. Considerations, such as underlying conditions, disease severity, and potential for drug toxicity or drug interactions, may inform decisions on the use of these agents in pediatric patients with COVID-19 on a case-by-case basis. Children should be enrolled in clinical trials evaluating COVID-19 therapies whenever possible. A number of additional drugs are being investigated for the treatment of COVID-19 in adults; refer to the Antiviral Therapy and Immunomodulators sections to review special considerations for use of these drugs in children and refer to Table 2d and Table 4b for recommendations on pediatric dosing regimens.

Multisystem Inflammatory Syndrome in Children

A small subset of children and young adults with SARS-CoV-2 infection develop MIS-C. This immune manifestation is also referred to as pediatric multisystem inflammatory syndrome–temporally associated with SARS-CoV-2 (PMIS-TS), although the case definitions for the syndromes differ slightly. This syndrome was first described in Europe, where previously healthy children with severe inflammation and Kawasaki disease-like features were identified to have current or recent infection with SARS-CoV-2. The clinical spectrum of MIS-C has been described in the United States and is similar to that described for PIMS-TS. MIS-C is consistent with a post-infectious inflammatory syndrome related to SARS-CoV-2.48,49 Most MIS-C patients have serologic evidence of previous SARS-CoV-2 infection, but only a minority are RT-PCR positive for SARS-CoV-2 at presentation.50,51 The peak incidence of MIS-C lags about 4 weeks behind the peak of acute pediatric COVID-19 hospitalizations. Emerging data suggests that adults may also develop a similar syndrome, multisystem inflammatory syndrome in adults (MIS-A), although it is not clear if this is a postinfectious complication similar to MIS-C.50-52 Although risk factors for MIS-C have not been established, in an analysis of MIS-C cases in the United States, most of the children were nonwhite, and obesity was the most common comorbidity.53 Unlike in children with acute COVID-19, the majority of children who present with MIS-C do not seem to have underlying comorbid conditions other than obesity.

Clinical Manifestations

The current CDC case definition for MIS-C includes:

- An individual aged <21 years presenting with fever, laboratory evidence of inflammation, and evidence of clinically severe illness requiring hospitalization with multisystem (i.e., more than two) organ involvement (cardiac, renal, respiratory, hematologic, gastrointestinal, dermatologic, or neurologic); and
- No alternative plausible diagnoses; and
- Positive for current or recent SARS-CoV-2 infection by RT-PCR, antigen test, or serology; or COVID-19 exposure within the 4 weeks prior to the onset of symptoms.54

Fever >38.0°C for ≥24 hours or report of subjective fever lasting ≥24 hours
Including, but not limited to one or more of the following: an elevated C-reactive protein, erythrocyte sedimentation rate, fibrinogen, procalcitonin, d-dimer, ferritin, lactic acid dehydrogenase, interleukin (IL)-6, or neutrophils, or reduced lymphocytes or albumin levels
Distinguishing MIS-C from other febrile illnesses in the community setting remains challenging, but presence of persistent fever, multisystem manifestations, and laboratory abnormalities could help early recognition. The clinical spectrum of hospitalized cases has included younger children with mucocutaneous manifestations that overlap those with Kawasaki disease, older children with more multiorgan involvement and shock, and patients with respiratory manifestations that overlap with acute COVID-19. Patients with MIS-C are often critically ill and up to 80% of children require ICU admission. Most patients with MIS-C have markers of cardiac injury or dysfunction, including elevated levels of troponin and brain natriuretic protein. Echocardiographic findings in these cases include impaired left ventricular function, as well as coronary artery dilations, and rarely, coronary artery aneurysms. Reported mortality rate in the United States for hospitalized children with MIS-C is 1% to 2%. Longitudinal studies are currently ongoing to examine the long-term sequelaes of MIS-C.

The pathogenesis of MIS-C is still being elucidated. Differences have been demonstrated between MIS-C and typical Kawasaki disease in terms of epidemiology, cytopenias, cytokine expression, and elevation of inflammatory markers. Immunologic profiling has also shown differences in cytokine expression (tumor necrosis factor alpha and IL-10) between MIS-C and acute COVID-19 in children.

Management

Currently, there are only observational data available to guide treatment for MIS-C. Supportive care remains the mainstay of therapy. There are currently insufficient data for the Panel to recommend either for or against any specific therapeutic strategy for the management of MIS-C. MIS-C management decisions should involve a multidisciplinary team of pediatric specialists including experts in intensive care, infectious diseases, cardiology, hematology, and rheumatology. Although no clinical trial data are available, many centers have described the use of immunomodulatory therapy (e.g., intravenous immune globulin [IVIG], corticosteroids, IL-1 and IL-6 inhibitors). The American College of Rheumatology has outlined initial diagnostic and treatment considerations for MIS-C, recommending IVIG and/or corticosteroids as first-tier therapies and other biologic agents as second-line options. An observational study from Europe used propensity matching to compare short-term outcomes in children with MIS-C who were treated initially with IVIG alone or IVIG and methylprednisolone. They observed a lower risk of treatment failure (defined as persistence of fever), more rapid improvement in hemodynamic support, less severe left ventricular dysfunction, and shorter ICU stays among children initially treated with the combination therapy. These findings must be confirmed with additional prospective studies. The role of antiviral therapy in MIS-C is not clear, therefore the use of remdesivir should be reserved for patients who have features of acute COVID-19.

References


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Special Considerations in Adults and Children With Cancer

Last Updated: April 21, 2020

Summary Recommendations

- Given the effectiveness of the SARS-CoV-2 vaccines in the general population and the increased risk of severe COVID-19 and mortality in patients with cancer, the COVID-19 Treatment Guidelines Panel (the Panel) recommends SARS-CoV-2 vaccination for patients with active cancer or patients who are receiving treatment for cancer (AIII). See the text below for information on the appropriate timing for SARS-CoV-2 vaccination in these patients.
- The Panel recommends performing molecular diagnostic testing for SARS-CoV-2 in patients with cancer who develop signs and symptoms that suggest COVID-19 (AIII) and in asymptomatic patients prior to procedures that require anesthesia and before initiating cytotoxic chemotherapy and long-acting biologic therapy (BIII).
- The recommendations for treating COVID-19 in patients with cancer are the same as those for the general population (AIII). See Antiviral Drugs That Are Approved or Under Evaluation for the Treatment of COVID-19 and Immunomodulators Under Evaluation for the Treatment of COVID-19 for more information.
- 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).
- Clinicians who are treating COVID-19 in patients with cancer should consult a hematologist or oncologist before adjusting cancer-directed medications (AIII).
- Decisions about administering cancer-directed therapy during SARS-CoV-2 infection 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).

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Rating of Evidence: I = One or more randomized trials without major limitations; IIa = Other randomized trials or subgroup analyses of randomized trials; IIb = Nonrandomized trials or observational cohort studies; III = Expert opinion

People who are being treated for cancer may be at increased risk of severe COVID-19, and clinical outcomes of COVID-19 are generally worse in people with cancer than in people without cancer. 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). The risk for immunosuppression and susceptibility to 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. 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, managing COVID-19 in patients with cancer, and managing 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.

Vaccination for SARS-CoV-2 in Patients With Cancer

The clinical trials that evaluated the SARS-CoV-2 vaccines that have received Emergency Use Authorizations from the Food and Drug Administration excluded severely immunocompromised patients. The Advisory Committee on Immunization Practices notes that the authorized SARS-CoV-2 vaccines are not live vaccines; therefore, they can be safely administered to immunocompromised people.\(^7\) Given the effectiveness of the SARS-CoV-2 vaccines in the general population and the increased risk of severe COVID-19 and mortality in patients with cancer, the COVID-19 Treatment Guidelines Panel (the Panel) recommends SARS-CoV-2 vaccination for patients with active cancer or patients who are receiving treatment for cancer \((\text{AI}III)\).

The mRNA vaccines contain polyethylene glycol (PEG), and the Johnson & Johnson (J&J)/Janssen vaccine contains polysorbate. In patients who experience a severe anaphylactic reaction to PEG-asparaginase, consider performing allergy testing for PEG prior to vaccination with either of the mRNA vaccines or consider using the J&J/Janssen vaccine with precautions.\(^8\)\(^-\)\(^10\)

When determining the timing of SARS-CoV-2 vaccination in patients with cancer, clinicians should consider the following factors:

- If possible, patients who are planning to receive chemotherapy should complete vaccination for SARS-CoV-2 at least 2 weeks before starting chemotherapy.\(^11\)\(^,\)\(^12\)
- In patients with hematologic malignancy who are undergoing intensive chemotherapy (e.g., induction chemotherapy for acute myelogenous leukemia), vaccination should be delayed until neutrophil recovery.\(^13\)
- Hematopoietic stem cell and chimeric antigen receptor T cell recipients can be offered SARS-CoV-2 vaccination starting at least 3 months after therapy.\(^12\)

It is unknown whether the immune response to SARS-CoV-2 vaccination can increase the risk of graft-versus-host disease or other immune-related complications. Studies of responses to influenza vaccination have shown that the immune response in cancer patients varies based on the type of cancer, whether the patient has received chemotherapy recently, and the type of chemotherapy.\(^14\)\(^,\)\(^15\) Additional research is needed to understand the vaccine response in patients with cancer. Outside of a clinical study, antibody testing is not recommended to assess immunity to SARS-CoV-2 following vaccination in patients with cancer. For people who received COVID-19 vaccines during chemotherapy or treatment with other immunosuppressive drugs, revaccination after they regain immune competence is currently not recommended.\(^7\)

Vaccination of household members, close contacts, and health care providers who provide care for immunocompromised patients is imperative to protect immunocompromised patients from infection. All close contacts are strongly encouraged to get vaccinated as soon as possible.

Testing for COVID-19 in Patients With Cancer

The Panel recommends molecular diagnostic testing for SARS-CoV-2 in patients with cancer who develop signs and symptoms of COVID-19 \((\text{AI}III)\).

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.\textsuperscript{16} 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).\textsuperscript{17,18}

**General Guidance on Medical Care for Patients With Cancer 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.\textsuperscript{19} 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.\textsuperscript{20-22} Principles of physical distancing and prevention strategies, including masking patients and health care workers and practicing hand hygiene, apply to all in-person interactions.\textsuperscript{23}

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.\textsuperscript{24,25}
- The potential risks of drug-related lung toxicity (e.g., from using bleomycin or PD-1 inhibitors) must be balanced with the clinical efficacy of alternative regimens or the risk of delaying care.\textsuperscript{26}
- Preventing neutropenia can decrease the risk of neutropenic fever and the need for emergency department 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%) risk of febrile neutropenia.\textsuperscript{27}
- 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.\textsuperscript{28} 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 4 of 5,273 patients (0.08%) who were treated with androgen deprivation therapy (OR 4.05; 95% CI, 1.55–10.59).\textsuperscript{29} A small cohort study of patients with prostate cancer from Finland did not find an association between androgen deprivation and incidence of SARS-CoV-2 infection.\textsuperscript{30} The viral spike proteins that SARS-CoV-2 uses to enter cells are primed by TMPRSS2, an androgen-regulated gene. Whether androgen deprivation therapy protects against SARS-CoV-2 infection requires further investigation in larger cohorts or clinical trials.\textsuperscript{29}
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.\textsuperscript{24,25}

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.\textsuperscript{31} In patients with cancer, lowering the transfusion thresholds for blood products (e.g., red blood cells, platelets) in asymptomatic patients should be considered.\textsuperscript{32,33} At this time, there is no evidence that COVID-19 can be transmitted through blood products.\textsuperscript{34,35}

**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.\textsuperscript{36} 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.\textsuperscript{36} Empiric antibiotics should be continued per standard of care in patients who test positive for SARS-CoV-2. Clinicians should also continually 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.\textsuperscript{37,38}

Recommendations for the treatment of COVID-19 are the same for cancer patients as for the general population (AIII). See Antiviral Drugs That Are Approved or Under Evaluation for the Treatment of COVID-19 and Immunomodulators Under Evaluation for the Treatment of COVID-19 for more information. Dexamethasone treatment has been associated with a lower mortality rate in patients with COVID-19 who require supplemental oxygen or invasive mechanical ventilation.\textsuperscript{39} 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 dexamethasone are expected to be the same in patients with cancer as in those 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 cytokine levels and pulmonary inflammation.\textsuperscript{27,40} Secondary infections (e.g., invasive pulmonary aspergillosis) have been reported in critically ill patients with COVID-19.\textsuperscript{41,42}

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,\textsuperscript{2} 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 a hematologist or oncologist before adjusting cancer-directed medications (AIII).

Medication Interactions
The use of 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 antineoplastic medications have known interactions with therapies that are being investigated for COVID-19. For example, tocilizumab can interact with vincristine and doxorubicin. Any COVID-19 therapy that may cause QT prolongation must be used with caution in patients who are being treated with venetoclax, gilteritinib, or tyrosine kinase inhibitor therapy (e.g., nilotinib). Dexamethasone is commonly used as an antiemetic for cancer patients and is recommended for the treatment of certain patients with COVID-19 (see Therapeutic Management of Adults With COVID-19). 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 CYP3A4 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


Special Considerations in Solid Organ Transplant, Hematopoietic Stem Cell Transplant, and Cellular Therapy Candidates, Donors, and Recipients

Last Updated: April 21, 2021

Summary Recommendations

Vaccination for SARS-CoV-2

- Given the effectiveness of SARS-CoV-2 vaccines in the general population and the increased risk of worse clinical outcomes of COVID-19 in transplant and cellular therapy recipients, the COVID-19 Treatment Guidelines Panel (the Panel) recommends SARS-CoV-2 vaccination for potential transplant and cellular therapy candidates, potential donors, and recipients (AIII). See the text below for information on the appropriate timing for SARS-CoV-2 vaccination in these patients.

Potential Transplant and Cellular Therapy Candidates

- The Panel recommends diagnostic molecular testing for SARS-CoV-2 for all potential solid organ transplant (SOT), hematopoietic cell transplant (HCT), and cell therapy candidates with signs and symptoms that suggest acute COVID-19 infection (AIII).
- The Panel recommends following the guidance from medical professional organizations that specialize in providing care for SOT, HCT, or cell therapy recipients when performing diagnostic molecular testing for SARS-CoV-2 in these patients (AIII).
- If SARS-CoV-2 is detected or if infection is strongly suspected, transplantation should be deferred, if possible (BIII).

Potential Transplant Donors

- The Panel recommends assessing all potential SOT and HCT donors for signs and symptoms that are associated with COVID-19 according to guidance from medical professional organizations (AIII).
- The Panel recommends performing diagnostic molecular testing for SARS-CoV-2 if symptoms are present (AIII).
- If SARS-CoV-2 is detected or if infection is strongly suspected, donation should be deferred (BIII).

Transplant and Cellular Therapy Recipients With COVID-19

- Clinicians should follow the guidelines for evaluating and managing COVID-19 in nontransplant patients when treating transplant and cellular therapy recipients (AIII). See Therapeutic Management of Adults With COVID-19 for more information.
- The Panel recommends that clinicians who are treating COVID-19 in transplant and cellular therapy patients consult with a transplant specialist before adjusting immunosuppressive medications (AIII).
- When treating COVID-19, clinicians should pay careful attention to potential drug-drug interactions and overlapping toxicities with immunosuppressants, prophylactic antimicrobials, and other medications (AIII).

Rating of Recommendations: A = Strong; B = Moderate; C = Optional
Rating of Evidence: I = One or more randomized trials without major limitations; IIa = Other randomized trials or subgroup analyses of randomized trials; IIb = Nonrandomized trials or observational cohort studies; III = Expert opinion

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 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),¹ 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 COVID-19 Treatment 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 those for nontransplant patients (AIII). See Therapeutic Management of Adults With 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.

**Vaccination for SARS-CoV-2 in Solid Organ Transplant, Hematopoietic Stem Cell Transplant, and Cellular Therapy Candidates, Donors, and Recipients**

The clinical trials that have evaluated the SARS-CoV-2 vaccines that have received Emergency Use Authorizations from the Food and Drug Administration have excluded severely immunocompromised patients.²⁻⁴ The Advisory Committee on Immunization Practices notes that the currently authorized COVID-19 vaccines are not live vaccines; therefore, they can be safely administered to immunocompromised people.⁵ The efficacy rates for the available vaccines may be lower in immunocompromised patients than in the general population, and the relative efficacy of the different vaccines for transplant candidates or recipients is currently unknown. Given the effectiveness of SARS-CoV-2 vaccines in the general population and the increased risk of worse clinical outcomes of COVID-19 in transplant and cellular therapy recipients, the COVID-19 Treatment Guidelines Panel (the Panel) recommends SARS-CoV-2 vaccination for potential transplant and cellular therapy candidates, potential donors, and recipients (AIII).

When determining the timing of SARS-CoV-2 vaccination in SOT, HCT, and cell therapy recipients, clinicians should consider the following factors:

- Ideally, SOT candidates should receive SARS-CoV-2 vaccines while they are awaiting transplant.
- In general, vaccination should be completed at least 2 weeks prior to SOT or started 1 month after SOT.
- In certain situations, it may be appropriate to delay vaccination until 3 months after SOT, such as when T cell or B cell ablative therapy (with antithymocyte globulin or rituximab) is used at the time of transplant.⁶
- At this time, reducing the dose of immunosuppressants and holding immunosuppressants prior to SARS-CoV-2 vaccination are not recommended.
- SARS-CoV-2 vaccines can be offered as early as 3 months after a patient receives HCT or chimeric antigen receptor T cell (CAR-T) therapy, although the efficacy of the vaccines may be reduced compared to the efficacy observed in the general population.⁷⁻⁸ Patients who are scheduled to receive cytotoxic or B cell–depleting therapies should complete their SARS-CoV-2 vaccination prior to initiation or between cycles of cytotoxic or B cell–depleting therapies if possible.
• After completing SARS-CoV-2 vaccination, immunocompromised persons should be advised to continue to exercise precautions to reduce their risk of SARS-CoV-2 exposure and infection (e.g., they should continue wearing a mask, maintain a distance of 6 feet from others, and avoid crowds and poorly ventilated spaces). It is unknown whether the immune responses to SARS-CoV-2 vaccination can increase the risk of graft-versus-host disease or other immune-related complications. Outside of a clinical study, antibody testing is not recommended to assess immunity to SARS-CoV-2 following COVID-19 vaccination in transplant patients. For people who received COVID-19 vaccines during treatment with immunosuppressive drugs, revaccination after they regain immune competence is currently not recommended.

Vaccination of household members, close contacts, and health care providers who provide care for immunocompromised patients is imperative to protect immunocompromised patients from infection. All close contacts are strongly encouraged to get vaccinated as soon as possible.

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 that a donor or candidate may have SARS-CoV-2 infection can be estimated by considering the epidemiologic risk, obtaining a 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 a 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. 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.

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.

Assessment of Donors

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. 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. Recommendations for screening are outlined in the ASTCT and EBMT guidelines.

If SARS-CoV-2 Infection Is Detected or Is 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. 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, regardless of whether the individual has COVID-19. Similarly, immunosuppressive therapy should be initiated in recipients with or without COVID-19 who have rejection confirmed by a biopsy.

There are limited data on the incidence and clinical characteristics of SARS-CoV-2 infection in HCT and cellular therapy recipients. Recent data from the Center for International Blood and Marrow Transplant Research demonstrated a mortality rate of approximately 30% within a month of COVID-19 diagnosis among a cohort of 318 HCT recipients. This mortality rate was observed in both allogeneic and autologous recipients. Older age (≥50 years), male sex, and receipt of a COVID-19 diagnosis within 12 months of transplantation were associated with a higher risk of mortality among allogeneic recipients. In autologous recipients, patients with lymphoma had a higher risk of mortality than patients who had plasma cell disorder or myeloma.

A smaller study demonstrated a slightly lower mortality rate among HCT and cellular therapy recipients than earlier reports. This study found that the number of comorbidities, the presence of infiltrates on initial chest imaging, and neutropenia were predictors for increased disease severity. Additional factors that have been used to determine the clinical severity of other respiratory viral infections include the degree of cytopenia, the intensity of the conditioning regimen, the graft source, the degree of mismatch, and the need for further immunosuppression to manage graft-versus-host disease. Prolonged viral shedding has been described in SOT and HCT recipients; this can have implications for infection prevention and for the timing of potential therapeutic interventions.

**Treatment of COVID-19 in Transplant Recipients**

Currently, the antiviral agent remdesivir is the only drug that is approved by the Food and Drug Administration (FDA) for the treatment of COVID-19. Outpatient transplant recipients who are immunosuppressed or who have certain underlying comorbidities are candidates for the anti-SARS-CoV-2 monoclonal antibodies that are available through Emergency Use Authorizations (see Anti-SARS-CoV-2 Monoclonal Antibodies). Transplant recipients who are hospitalized with mild to
moderate COVID-19 may be considered for anti-SARS-CoV-2 monoclonal antibodies that are available through expanded access programs.

Data from a large randomized controlled trial found that a short course of dexamethasone (6 mg once daily for up to 10 days) improved survival in hospitalized patients with COVID-19 who were mechanically ventilated or who required supplemental oxygen. Tocilizumab used in combination with dexamethasone is recommended for some patients with severe or critical COVID-19 who exhibit rapid respiratory decompensation (see Interleukin-6 Inhibitors). The risks and benefits of using both dexamethasone and tocilizumab in transplant recipients with COVID-19 who are receiving immunosuppressive therapy are unknown. Because both dexamethasone and tocilizumab are immunosuppressive agents, patients who receive this combination should be closely monitored for secondary infections.

The Panel’s recommendations for the use of remdesivir, dexamethasone, and tocilizumab in patients with COVID-19 can be found in Therapeutic Management of Adults With COVID-19.

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 for 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.

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. Clinicians who are treating COVID-19 in transplant patients should consult a transplant specialist before adjusting immunosuppressive medication (AIII).

Certain therapeutics (e.g., remdesivir, tocilizumab) are associated with elevated levels of transaminases. For liver transplant recipients, the AASLD does not consider abnormal liver biochemistries a contraindication to using remdesivir. 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 (CYP) 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. Among the drugs that are commonly used to treat COVID-19, dexamethasone is a moderate inducer of CYP3A4, and interleukin-6 inhibitors may lead to increased metabolism of CYP substrates. Close monitoring of serum concentration of calcineurin inhibitors should be considered when these drugs are used.

Additional details about the adverse effects and drug interactions of antiviral medications and immune-based therapy for COVID-19 are noted in Tables 2d, 3c, and 4c.
References


Special Considerations in People With HIV

Last Updated: April 21, 2021

<table>
<thead>
<tr>
<th>Summary Recommendations</th>
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<tbody>
<tr>
<td><strong>Prevention of COVID-19</strong></td>
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<tr>
<td>• The COVID-19 Treatment Guidelines Panel (the Panel) recommends that people with HIV receive SARS-CoV-2 vaccines regardless of their CD4 T lymphocyte cell count or HIV viral load, because the potential benefits outweigh the potential risks (AIII).</td>
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<tr>
<td><strong>Diagnosis of COVID-19</strong></td>
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<tr>
<td>• The Panel recommends using the same approach for diagnosing SARS-CoV-2 infection in people with HIV as in people without HIV (AIII).</td>
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<tr>
<td><strong>Management of COVID-19</strong></td>
</tr>
<tr>
<td>• Recommendations for the triage, management, and treatment of COVID-19 in people with HIV are the same as those for the general population (AIII).</td>
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<tr>
<td>• In people with advanced HIV and suspected or documented COVID-19, HIV-associated opportunistic infections (OIs) should also be considered in the differential diagnosis of febrile illness (AIII).</td>
</tr>
<tr>
<td>• When starting treatment for COVID-19 in patients with HIV, clinicians should pay careful attention to potential drug-drug interactions and overlapping toxicities among COVID-19 treatments, antiretroviral (ARV) medications, antimicrobial therapies, and other medications (AIII).</td>
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<tr>
<td>• People with HIV should be offered the opportunity to participate in clinical trials of vaccines and potential treatments for SARS-CoV-2 infection.</td>
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**Introduction**

Approximately 1.2 million persons in the United States are living with HIV. Most of these individuals are in care, and many are on antiretroviral therapy (ART) and have well-controlled disease. Similar to COVID-19, HIV disproportionately affects racial and ethnic minorities and persons of lower socioeconomic status in the United States; these demographic groups also appear to have a higher risk for severe outcomes with COVID-19. Information on SARS-CoV-2/HIV coinfection is evolving rapidly. The sections below outline the current state of knowledge regarding the prevention and diagnosis of SARS-CoV-2 infection in people with HIV, treatment and clinical outcomes in people with HIV who develop COVID-19, and management of HIV during the COVID-19 pandemic. In addition to these Guidelines, the Department of Health and Human Services (HHS) Panel on Antiretroviral Guidelines for Adults and Adolescents has developed the Interim Guidance for COVID-19 and Persons with HIV.
Clinical Outcomes of COVID-19 in People With HIV

Data are emerging on the clinical outcomes of COVID-19 in people with HIV. In a case series of people with COVID-19 in Europe and the United States, no significant differences were observed in the clinical outcomes for COVID-19 between people with HIV and people who did not have HIV. For example, the Veterans Aging Cohort Study compared the clinical outcomes for 253 veterans with HIV and COVID-19 and the outcomes for a matched comparator arm of 504 veterans without HIV who developed COVID-19. More than 95% of the participants in this study were male. In this comparison, no differences were found between the outcomes for patients with HIV and those who did not have HIV.

In contrast, worse outcomes for patients with HIV and COVID-19, including increased COVID-19 mortality rates, have been reported by subsequent cohort studies in the United States, the United Kingdom, and South Africa. In a multicenter cohort study of 286 patients with HIV and COVID-19 in the United States, lower CD4 T lymphocyte (CD4) cell counts (i.e., <200 cells/mm³) were associated with a higher risk for the composite endpoint of intensive care unit admission, mechanical ventilation, or death. This increased risk was observed even in patients who had achieved virologic suppression of HIV. In another study of 175 patients with HIV and COVID-19, a low CD4 count or a low CD4 nadir was associated with poor outcomes. In a cohort study conducted in New York, people with HIV and COVID-19 had higher rates of hospitalization and mortality than people with COVID-19 who did not have HIV.

Prevention of COVID-19 in People With HIV

The COVID-19 Treatment Guidelines Panel (the Panel) recommends using the same approach for advising persons with HIV on the strategies to prevent acquisition of SARS-CoV-2 infection that is used for people without HIV. There is currently no clear evidence that any antiretroviral (ARV) medications can prevent the acquisition of SARS-CoV-2 infection.

People with HIV should receive SARS-CoV-2 vaccines, regardless of their CD4 count or HIV viral load, because the potential benefits outweigh the potential risks. People with HIV were included in the clinical trials of the two mRNA vaccines and the adenovirus vector vaccine that are currently available through Emergency Use Authorizations (EUA) from the Food and Drug Administration; however, the safety and efficacy of these vaccines in people with HIV have not been reported. Typically, people with HIV who are on antiretroviral therapy (ART) and who have achieved virologic suppression respond well to licensed vaccines. Guidance for using these vaccines, including guidance for people with HIV, is available through the Advisory Committee on Immunization Practices (ACIP). A patient’s HIV status should be kept confidential when administering a vaccine.

Diagnostic and Laboratory Testing for COVID-19 in People With HIV

Diagnosis of COVID-19 in People With HIV

The Panel recommends using the same approach for diagnosing SARS-CoV-2 infection in people with HIV as in those without HIV. There is currently no evidence that the performance characteristics of nucleic acid amplification testing differ in people with and without HIV when diagnosing acute SARS-CoV-2 infection. The Panel recommends against the use of serologic testing as the sole basis for diagnosis of acute SARS-CoV-2 infection. However, if diagnostic serologic testing is performed in a patient with HIV, the results should be interpreted with caution because cross-reactivity between antibodies to SARS-CoV-2 and HIV has been reported.

Correlation of CD4 Count in People With HIV and COVID-19

The normal range for CD4 counts in healthy adults is about 500 to 1,600 cells/mm³. Persons with HIV who have a CD4 count of ≥500 cells/mm³ have similar cellular immune function to persons...
without HIV. In people with HIV, a CD4 count <200 cells/mm³ meets the definition for AIDS. For patients on ART, the hallmark of treatment success is plasma HIV RNA below the level of detection by a polymerase chain reaction assay. Lymphopenia is a common laboratory finding in patients with COVID-19; in patients with HIV, clinicians should note that CD4 counts obtained during acute COVID-19 may not accurately reflect the patient’s HIV disease stage.

There have been some reports of persons with advanced HIV who have presented with COVID-19 and another coinfection, including *Pneumocystis jirovecii* pneumonia. In patients with advanced HIV who have suspected or laboratory-confirmed SARS-CoV-2 infection, clinicians should consider a broader differential diagnosis for clinical symptoms and consider consulting an HIV specialist (AIII).

**Clinical Presentation of COVID-19 in People With HIV**

It is currently unknown whether people with HIV have a higher incidence of SARS-CoV-2 infection or a higher rate of progression to symptomatic disease than the general population. Approximately 50% of persons with HIV in the United States are aged >50 years, and many have comorbidities that are associated with more severe illness with COVID-19, including hypertension, diabetes mellitus, cardiovascular disease, tobacco use disorder, chronic lung disease, chronic liver disease, and cancer.

There are a number of case reports and case series that describe the clinical presentation of COVID-19 in persons with HIV. These studies indicate that the clinical presentation of COVID-19 is similar in persons with and without HIV. Most of the published reports describe populations in which most of the individuals with HIV are on ART and have achieved virologic suppression. Consequently, the current understanding of the impact of COVID-19 in persons with advanced HIV who have low CD4 counts or persistent HIV viremia is limited.

**Management of COVID-19 in People With HIV**

Recommendations for the triage and management of COVID-19 in people with HIV are the same as those for the general population (AIII).

The treatment of COVID-19 in persons with HIV is the same as that for persons without HIV (AIII). In outpatients, people with HIV who are immunosuppressed or who have certain underlying comorbidities are candidates for the monoclonal antibodies that are available through EUAs. In hospitalized patients, the appropriate treatment strategy depends on disease severity (see Therapeutic Management of Adults With COVID-19).

When starting treatment for COVID-19 in patients with HIV, clinicians should pay careful attention to potential drug-drug interactions and overlapping toxicities among COVID-19 treatments, ARV medications, antimicrobial therapies, and other medications (AIII). Both tocilizumab and dexamethasone, which are recommended for some patients with severe or critical COVID-19, are immunosuppressive agents. The safety of using these drugs in immunocompromised patients, including those with advanced HIV, has not been studied. Therefore, patients with advanced HIV who are receiving these drugs should be closely monitored for secondary infections. Dexamethasone is a dose-dependent inducer of cytochrome P450 3A4 and could potentially lower the levels of certain coadministered ARV drugs. More than a single dose of dexamethasone is not recommended for patients who are receiving rilpirivirine as part of their ARV regimen. Clinicians should consult an HIV specialist before administering dexamethasone to these patients. Whether administering up to 10 days of dexamethasone impacts the clinical efficacy of other ARV drugs is unknown. Patients with HIV who are receiving dexamethasone for COVID-19 should follow up with their HIV providers to assess virologic response.

Although some ARV drugs are being studied for the prevention and treatment of COVID-19, no agents have been shown to be effective.
People with HIV should be offered the opportunity to participate in clinical trials of vaccines and potential treatments for COVID-19. A variety of immunomodulatory therapies are prescribed empirically or administered as part of a clinical trial to treat severe COVID-19. Data about whether these medications are safe to use in patients with HIV are lacking. If a medication has been shown to reduce the mortality of patients with COVID-19 in the general population, it should also be used to treat COVID-19 in patients with HIV, unless data indicate that the medication is not safe or effective in this population.

Management of HIV in People With SARS-CoV-2/HIV Coinfection

Below are some general considerations regarding the management of HIV in people with SARS-CoV-2/HIV coinfection.

- Whenever possible, ART and opportunistic infection prophylaxis should be continued in a patient with HIV who develops COVID-19, including in those who require hospitalization (AIII). ARV treatment interruption may lead to rebound viremia, and, in some cases, the emergence of drug resistance. If the appropriate ARV drugs are not on the hospital’s formulary, administer medications from the patient’s home supplies (if available).

- Clinicians who are treating COVID-19 in people with HIV should consult an HIV specialist before adjusting or switching a patient’s ARV medications. An ARV regimen should not be switched or adjusted (i.e., by adding ARV drugs to the regimen) for the purpose of preventing or treating SARS-CoV-2 infection (AIII). Many drugs, including some ARV agents (e.g., lopinavir/ritonavir, boosted darunavir, tenofovir disoproxil fumarate/emtricitabine), have been or are being evaluated in clinical trials or are prescribed for off-label use for the treatment or prevention of SARS-CoV-2 infection. To date, lopinavir/ritonavir and darunavir/ritonavir have not been found to be effective (see Lopinavir/Ritonavir and Other HIV Protease Inhibitors). Two retrospective studies have suggested that tenofovir disoproxil fumarate/emtricitabine may play a role in preventing SARS-CoV-2 acquisition or hospitalization or death associated with COVID-19; however, the significance of these findings is unclear, as neither study adequately controlled for confounding variables such as age and comorbidities.

- For patients who are taking an investigational ARV medication as part of their ARV regimen, arrangements should be made with the investigational study team to continue the medication, if possible.

- For critically ill patients who require tube feeding, some ARV medications are available in liquid formulations, and some ARV pills may be crushed. Clinicians should consult an HIV specialist and/or pharmacist to assess the best way for a patient with a feeding tube to continue an effective ARV regimen. Information may be available in the drug product label or in this document.

- For people who present with COVID-19 and have either a new diagnosis of HIV or a history of HIV but are not taking ART, the optimal time to start or restart ART is currently unknown. For people with HIV who have not initiated ART or who have been off therapy for >2 weeks before presenting with COVID-19, the Panel recommends consulting an HIV specialist regarding initiation or re-initiation of ART as soon as clinically feasible. If ART is started, maintaining treatment and linking patients to HIV care upon hospital discharge is critical. If an HIV specialist is not available, clinical consultation is available by phone through the National Clinical Consultation Center, Monday through Friday, 9 am to 8 pm EST.

Special Considerations in Children and Pregnant Women With HIV Who Develop COVID-19

Currently, there is limited information about pregnancy and maternal outcomes in women with HIV who have COVID-19 and in children with HIV and COVID-19. Please see the sections in these Guidelines...
that discuss the management of COVID-19 during pregnancy and in children, and the HHS Interim Guidance for COVID-19 and Persons With HIV.

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Influenza and COVID-19

Last Updated: October 22, 2020

Summary Recommendations

Influenza Vaccination
• Although data are lacking on influenza vaccination for persons with COVID-19, on the basis of practice for other acute respiratory infections, the Panel recommends that persons with COVID-19 should receive an inactivated influenza vaccine (BIII). The Centers for Disease Control and Prevention (CDC) has provided guidance on the timing of influenza vaccination for inpatients and outpatients with COVID-19 (see Interim Guidance for Routine and Influenza Immunization Services During the COVID-19 Pandemic).

Diagnosis of Influenza and COVID-19 When Influenza Viruses and SARS-CoV-2 Are Cocirculating
• Only testing can distinguish between severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and influenza virus infections and identify SARS-CoV-2 and influenza virus coinfection.
• When SARS-CoV-2 and influenza viruses are cocirculating, the Panel recommends testing for both viruses in all hospitalized patients with acute respiratory illness (AIII).
• When SARS-CoV-2 and influenza viruses are cocirculating, the Panel recommends influenza testing in outpatients with acute respiratory illness if the results will change clinical management of the patient (BIII).
• Testing for other pathogens should be considered depending on clinical circumstances, especially in patients with influenza in whom bacterial superinfection is a well-recognized complication.
• See the CDC Information for Clinicians on Influenza Virus Testing and the Infectious Diseases Society of America (IDSA) Clinical Practice Guidelines for more information.

Antiviral Treatment of Influenza When Influenza Viruses and SARS-CoV-2 Are Cocirculating
• The treatment of influenza is the same in all patients regardless of SARS-CoV-2 coinfection (AIII).
• The Panel recommends that hospitalized patients be started on empiric treatment for influenza with oseltamivir as soon as possible without waiting for influenza testing results (AIIb).
• Antiviral treatment of influenza can be stopped when influenza has been ruled out by nucleic acid detection assay in upper respiratory tract specimens for nonintubated patients and in both upper and lower respiratory tract specimens for intubated patients.
• For influenza treatment in hospitalized and non-hospitalized patients, see the CDC and IDSA recommendations on antiviral treatment of influenza.

Rating of Recommendations: A = Strong; B = Moderate; C = Optional
Rating of Evidence: I = One or more randomized trials without major limitations; Ia = Other randomized trials or subgroup analyses of randomized trials; IIb = Nonrandomized trials or observational cohort studies; III = Expert opinion

Introduction

Influenza activity in the United States during the 2020–2021 influenza season is difficult to predict and could vary geographically and by the extent of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) community mitigation measures. During early 2020, sharp declines in influenza activity coincided with implementation of SARS-CoV-2 control measures in the United States and several Asian countries. Very low influenza virus circulation was observed in Australia, Chile, and South Africa during the typical Southern Hemisphere influenza season in 2020. Clinicians should monitor local influenza and SARS-CoV-2 activity (e.g., by tracking local and state public health surveillance data and testing performed at health care facilities) to inform evaluation and management of patients with acute respiratory illness.

Influenza Vaccination

There are no data on the safety, immunogenicity, or effectiveness of influenza vaccines in patients...
with mild COVID-19 or those who are recovering from COVID-19. Therefore, the optimal timing for influenza vaccination in these patients is unknown. The safety and efficacy of vaccinating persons who have mild illnesses from other etiologies have been documented. On the basis of practice following other acute respiratory infections, the Panel recommends that persons with COVID-19 should receive an inactivated influenza vaccine (BIII). The Centers for Disease Control and Prevention (CDC) has provided guidance on the timing of influenza vaccination for inpatients and outpatients with COVID-19 (see Interim Guidance for Routine and Influenza Immunization Services During the COVID-19 Pandemic). It is not known whether dexamethasone or other immunomodulatory therapies for COVID-19 will affect the immune response to influenza vaccine. However, despite this uncertainty, as long as influenza viruses are circulating, an unvaccinated person with COVID-19 should receive the influenza vaccine once they have substantially improved or recovered from COVID-19. See influenza vaccine recommendations from CDC and the Advisory Committee on Immunization Practices.

Clinical Presentation of Influenza Versus COVID-19

The signs and symptoms of uncomplicated, clinically mild influenza overlap with those of mild COVID-19. Ageusia and anosmia can occur with both diseases, but these symptoms are more common with COVID-19 than with influenza. Fever is not always present in patients with either disease, particularly in patients who are immunosuppressed or elderly. Complications of influenza and COVID-19 can be similar, but the onset of influenza complications and severe disease typically occurs within a week of illness onset whereas the onset of severe COVID-19 usually occurs in the second week of illness. Because of the overlap in signs and symptoms, when SARS-CoV-2 and influenza viruses are cocirculating, diagnostic testing for both viruses in people with an acute respiratory illness is needed to distinguish between SARS-CoV-2 and influenza virus, and to identify SARS-CoV-2 and influenza virus coinfection. Coinfection with influenza A or B viruses and SARS-CoV-2 has been described in case reports and case series, but the frequency, severity, and risk factors for coinfection with these viruses versus for infection with either virus alone are unknown.

Which Patients Should be Tested for SARS-CoV-2 and influenza?

When influenza viruses and SARS-CoV-2 are cocirculating in the community, SARS-CoV-2 testing and influenza testing should be performed in all patients hospitalized with suspected COVID-19 or influenza (see Testing for SARS-CoV-2 Infection) (AIII). When influenza viruses and SARS-CoV-2 are cocirculating in the community, SARS-CoV-2 testing should be performed in outpatients with suspected COVID-19, and influenza testing can be considered in outpatients with suspected influenza if the results will change clinical management of the illness (BIII). Several multiplex assays that detect SARS-CoV-2 and influenza A and B viruses have received Food and Drug Administration Emergency Use Authorization and can provide results in 15 minutes to 8 hours on a single respiratory specimen. For information on available influenza tests, including clinical algorithms for testing of patients when SARS-CoV-2 and influenza viruses are cocirculating, see the CDC Information for Clinicians on Influenza Virus Testing and recommendations of the Infectious Diseases Society of America (IDSA) on the use of influenza tests and interpretation of testing results.

Which Patients Should Receive Antiviral Treatment of Influenza?

When SARS-CoV-2 and influenza viruses are cocirculating in the community, patients who require hospitalization and are suspected of having either or both viral infections should receive influenza antiviral treatment with oseltamivir as soon as possible without waiting for influenza testing results (AIIb). Treatment for influenza is the same for all patients regardless of SARS-CoV-2 coinfection (AIII). See the CDC Influenza Antiviral Medications: Summary for Clinicians, including clinical algorithms for antiviral treatment of patients with suspected or confirmed influenza when SARS-CoV-2
and influenza viruses are cocirculating, and the IDSA Clinical Practice Guidelines recommendations on antiviral treatment of influenza.

If a diagnosis of COVID-19 or another etiology is confirmed and if the result of an influenza nucleic acid detection assay from an upper respiratory tract specimen is negative:

- **In a Patient Who is Not Intubated**: Antiviral treatment for influenza can be stopped.
- **In a Patient Who is Intubated**: Antiviral treatment for influenza should be continued and if a lower respiratory tract specimen (e.g., endotracheal aspirate) can be safely obtained, it should be tested by influenza nucleic acid detection. If the lower respiratory tract specimen is also negative, influenza antiviral treatment can be stopped.

### Treatment Considerations for Hospitalized Patients With Suspected or Confirmed SARS-CoV-2 and Influenza Virus Coinfection

- Corticosteroids, which may be used for the treatment of COVID-19, may prolong influenza viral replication and viral RNA detection and may be associated with poor outcomes.\(^{14,15}\)
- Oseltamivir has no activity against SARS-CoV-2.\(^{16}\) Oseltamivir does not have any known interactions with remdesivir.
- Standard-dose oseltamivir is well absorbed even in critically ill patients. For patients who cannot tolerate oral or enterically administered oseltamivir (e.g., because of gastric stasis, malabsorption, or gastrointestinal bleeding), intravenous peramivir is an option.\(^{14}\) There are no data on peramivir activity against SARS-CoV-2.
- CDC does not recommend inhaled zanamivir and oral baloxavir for the treatment of influenza in hospitalized patients because of insufficient safety and efficacy data (see the CDC Influenza Antiviral Medications: Summary for Clinicians). There are no data on zanamivir activity against SARS-CoV-2. Baloxavir has no activity against SARS-CoV-2.\(^{16}\)
- Based upon limited data, the co-occurrence of community-acquired secondary bacterial pneumonia with COVID-19 appears to be infrequent and may be more common with influenza.\(^{17,18}\) Typical bacterial causes of community-acquired pneumonia with severe influenza are *Staphylococcus aureus* (methicillin-resistant *S. aureus* [MRSA] and methicillin-susceptible *S. aureus* [MSSA]), *Streptococcus pneumoniae*, and group A *Streptococcus*.\(^{14}\)
- Patients with COVID-19 who develop new respiratory symptoms with or without fever or respiratory distress, and without a clear diagnosis, should be evaluated for the possibility of nosocomial influenza.

### References


