Special Considerations in Children

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<table>
<thead>
<tr>
<th>Summary Recommendations</th>
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<tr>
<td><strong>General Considerations</strong></td>
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<tr>
<td>• SARS-CoV-2 infection is generally milder in children than in adults, and a substantial proportion of children with the disease have asymptomatic infection.</td>
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<td>• Most children with SARS-CoV-2 infection will not require any specific therapy.</td>
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<td>• 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 non-White children and older teenagers may be at increased risk for severe disease.</td>
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<tr>
<td>• 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.</td>
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<tr>
<td><strong>Specific Therapy for Children</strong></td>
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<tr>
<td>• 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.</td>
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<td>• Most children with mild or moderate disease can be managed with supportive care alone (AIII).</td>
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<td>• Remdesivir is recommended for:</td>
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<tr>
<td>• 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).</td>
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<td>• Hospitalized children aged ≥16 years with COVID-19 who have an emergent or increasing need for supplemental oxygen regardless of whether they have risks factors for severe disease (BIII).</td>
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<td>• 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).</td>
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<td>• The COVID-19 Treatment Guidelines Panel (the Panel) recommends using dexamethasone for hospitalized children with COVID-19 who require high-flow oxygen, noninvasive ventilation, mechanical ventilation, or extracorporeal membrane oxygenation (BIII).</td>
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<tr>
<td>• There is insufficient pediatric evidence 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 1 criterion or are aged ≥16 years. The Panel recommends consulting a pediatric infectious disease specialist in such cases.</td>
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<tr>
<td>• The Panel <strong>recommends against</strong> 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 <strong>recommends against</strong> 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.</td>
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<tr>
<td>• There is insufficient evidence 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.</td>
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<tr>
<td>• There is insufficient evidence 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 <strong>recommends against</strong> the use of sarilumab for hospitalized children with COVID-19 or MIS-C, except in a clinical trial (AIII).</td>
</tr>
<tr>
<td>• MIS-C is a serious delayed complication of SARS-CoV-2 infection that may develop in a minority of children and young adults. See <a href="https://www.covid19treatmentguidelines.nih.gov/">Therapeutic Management of Hospitalized Pediatric Patients With Multisystem Inflammatory Syndrome in Children (MIS-C) (With Discussion on Multisystem Inflammatory Syndrome in Adults [MIS-A])</a> for the Panel’s recommendations for treating children with MIS-C.</td>
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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 units in a 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 neurological 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.\(^\text{21}\) A few reports have demonstrated a higher prevalence of asthma in pediatric COVID-19 cases, although the association between asthma and severe disease is not clearly defined.\(^\text{7,8}\) Congenital heart disease may be associated with an increased risk of severe COVID-19, but the condition has not been consistently identified as a risk factor.\(^\text{22,23}\) 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 (mAb) therapy for pediatric patients.\(^\text{24,25}\)

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 People 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.\(^\text{27-29}\) 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.\(^\text{30-33}\) Among 100 women with SARS-CoV-2 infection who delivered 101 infants, only 2 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.\(^\text{34}\)

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).\(^\text{35}\) 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.\(^\text{36}\) 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.\(^\text{37}\) 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.\(^\text{38}\) 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.\(^\text{39,40}\) 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 people with known or suspected SARS-CoV-2 infection is provided by CDC.

**Treatment Considerations**

There are no results available from clinical trials that evaluated treatments 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. 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 Nonhospitalized Adults With COVID-19 and Therapeutic Management of Hospitalized 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 (AIII). The risks and benefits of therapy should be assessed based on illness severity, age, and the presence of the 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 more 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. 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 conditions 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 Hospitalized Adults With COVID-19 for more information). The safety and effectiveness of dexamethasone or other corticosteroids for COVID-19 treatment have not been sufficiently evaluated in pediatric patients; 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, 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, casirivimab plus imdevimab, and sotrovimab 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 is insufficient evidence for the Panel to recommend either for or against the use of these anti-SARS-CoV-2 mAbs 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, anti-SARS-CoV-2 mAb 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 the efficacy and safety in children and adolescents, limited data with which to identify children who are at the highest risk of severe COVID-19, 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 mAbs in hospitalized children for COVID-19. Emerging data regarding the prevalence and clinical significance of SARS-CoV-2 variants, and the efficacy of mAbs against variants, may inform the choice of specific anti-SARS-CoV-2 mAb therapies 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 more information). The safety and efficacy of convalescent plasma have not been evaluated in pediatric patients with COVID-19. There is insufficient evidence 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, 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 is insufficient evidence 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 more information).

**Tocilizumab**

Data on the use of tocilizumab 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...
The use of tocilizumab for severe cases of acute COVID-19 has been described in pediatric case series.\(^4^6\) 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 is insufficient evidence 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 is insufficient evidence 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 the 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 that are 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 using these drugs in children and refer to Table 2f and Table 4f 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 PMIS-TS. MIS-C is consistent with a post-infectious inflammatory syndrome related to SARS-CoV-2. 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. 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. 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 non-White, and obesity was the most common comorbidity. 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,\(^a\) laboratory evidence of inflammation,\(^b\) and evidence of clinically severe illness that requires hospitalization with multisystem (i.e., >2) organ involvement (cardiac, renal, respiratory, hematologic, gastrointestinal, dermatologic, or neurological); and
- No alternative plausible diagnoses; and
- Positive for current or recent SARS-CoV-2 infection by RT-PCR, antigen test, or serology results; or COVID-19 exposure within the 4 weeks prior to the onset of symptoms.\(^5^4\)

\(^a\) Fever >38.0°C for ≥24 hours or report of subjective fever lasting ≥24 hours

\(^b\) Including, but not limited to, 1 or more of the following: an elevated C-reactive protein, erythrocyte sedimentation rate,
fibrinogen, procalcitonin, D-dimer, ferritin, lactate dehydrogenase, interleukin-6, or neutrophils, or reduced lymphocytes or albumin levels.

Distinguishing MIS-C from other febrile illnesses in the community setting remains challenging, but the 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 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 and coronary artery dilations, and rarely, coronary artery aneurysms. The 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 sequelae 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 interleukin-10) between MIS-C and acute COVID-19 in children.

Management

Please see Therapeutic Management of Hospitalized Pediatric Patients With Multisystem Inflammatory Syndrome in Children (MIS-C) (With Discussion on Multisystem Inflammatory Syndrome in Adults [MIS-A]) for the Panel’s recommendations for treating MIS-C in children.

References


43. Food and Drug Administration. Fact sheet for healthcare providers: emergency use authorization (EUA) of veklury (remdesivir) for hospitalized pediatric patients weighing 3.5 kg to less than 40 kg or hospitalized pediatric patients less than 12 years of age weighing at least 3.5 kg. 2020. Available at: https://www.fda.gov/media/137566/download.


