

Therapeutic Management of Nonhospitalized Children With COVID-19

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This section outlines the COVID-19 Treatment Guidelines Panel's (the Panel) recommendations for the therapeutic management of nonhospitalized children (i.e., pediatric patients aged <18 years) with mild to moderate COVID-19. These recommendations are also for children who have mild to moderate COVID-19 and are hospitalized for reasons other than COVID-19. For patients aged ≥18 years, see [Therapeutic Management of Nonhospitalized Adults With COVID-19](#). Throughout this section, the term "COVID-19" refers to the acute, primarily respiratory illness due to infection with SARS-CoV-2. For the Panel's recommendations for managing multisystem inflammatory syndrome in children (MIS-C), see [Therapeutic Management of Hospitalized Children With MIS-C, Plus a Discussion on MIS-A](#).

Treatment Considerations

Currently, no results from pediatric clinical trials that evaluated the treatment of COVID-19 have been published. Data evaluating the use of pharmacologic therapy in children with COVID-19 are limited largely to descriptive reports.¹⁻³ Therefore, more high-quality randomized trials, observational studies, and pharmacokinetic studies are urgently needed. Whenever possible, clinical trials of therapeutics and multicenter observational cohorts should enroll children with COVID-19.

Published guidance on the treatment of COVID-19 in children has been extrapolated mostly from recommendations for adults with COVID-19, recommendations for children with other viral infections, and expert opinion.⁴⁻⁶ Applying adult data from COVID-19 trials to children is a unique challenge because most children experience a mild course of illness with COVID-19. Relative to adults, children with COVID-19 have substantially lower mortality and less need for hospitalization.⁷⁻⁹ Because of these differences in epidemiology and disease severity, the effect sizes of treatments for children are likely to be smaller than those observed in adults. Therefore, to produce a beneficial outcome in children, the number needed to treat is higher. Collectively, these factors influence the risk versus benefit balance for pharmacologic therapies in children.

Other challenges are the uncertainty about which comorbid conditions place children at the highest risk of severe COVID-19 and the uncertainty about the absolute magnitude of the increased risk from those comorbid conditions. For children with COVID-19, the type, number, and severity of comorbid conditions influence decisions about pharmacologic treatments. For more information on risk factors for children with COVID-19, see [Special Considerations in Children](#).

Recommendations

In the absence of sufficient clinical trial data on the treatment of children with COVID-19, the Panel's recommendations for the therapeutic management of nonhospitalized children are based largely on safety and efficacy data from clinical trials in adults (see Table 3a). No pediatric comparative studies have been published; therefore, all the quality of evidence ratings for the Panel's recommendations in this section are based on expert opinion (i.e., a **III** rating).

The majority of children with mild to moderate COVID-19 will not progress to more severe illness; therefore, the Panel recommends managing these patients with supportive care alone (**AIII**). The risks and benefits of therapy should be assessed based on COVID-19 disease severity, age, vaccination status,

and the presence of underlying medical conditions that may place the patient at high risk of severe COVID-19.

Table 3a. Therapeutic Management of Nonhospitalized Children With COVID-19

Risk of Severe COVID-19	Panel's Recommendations	
	Aged 12–17 Years	Aged <12 Years
Symptomatic, Regardless of Risk Factors	<ul style="list-style-type: none"> • Provide supportive care (AIII). 	<ul style="list-style-type: none"> • Provide supportive care (AIII).
High Risk^{a,b}	<ul style="list-style-type: none"> • Use 1 of the following options (listed in order of preference):^c <ul style="list-style-type: none"> • Ritonavir-boosted nirmatrelvir (Paxlovid) within 5 days of symptom onset (BIII) • Remdesivir within 7 days of symptom onset (CIII) 	<ul style="list-style-type: none"> • Ritonavir-boosted nirmatrelvir is not authorized by the FDA for use in children aged <12 years. • There is insufficient evidence to recommend either for or against the routine use of remdesivir. Consider treatment based on age and other risk factors.
Intermediate Risk^{b,d}	<ul style="list-style-type: none"> • There is insufficient evidence to recommend either for or against the use of any antiviral therapy. Consider treatment based on age and other risk factors. 	<ul style="list-style-type: none"> • There is insufficient evidence to recommend either for or against the routine use of remdesivir.
Low Risk^{b,e}	<ul style="list-style-type: none"> • Manage with supportive care alone (AIII). 	<ul style="list-style-type: none"> • Manage with supportive care alone (AIII).

Each recommendation in the Guidelines receives a rating for the strength of the recommendation (A, B, or C) and a rating for the evidence that supports it (I, IIa, IIb, or III). See [Guidelines Development](#) for more information.

^a Molnupiravir is not authorized by the FDA for use in children aged <18 years and should not be used.

^b See Table 3b for the Panel's framework for assessing the risk of progression to severe COVID-19 based on patient conditions and COVID-19 vaccination status.

^c Initiate treatment as soon as possible after symptom onset.

^d The relative risk of severe COVID-19 for intermediate-risk patients is lower than the risk for high-risk patients but higher than the risk for low-risk patients.

^e Low-risk patients include those with comorbid conditions that have a weak or unknown association with severe COVID-19. Patients with no comorbidities are included in this group.

Key: FDA = Food and Drug Administration; the Panel = the COVID-19 Treatment Guidelines Panel

Table 3b. The Panel’s Framework for Assessing the Risk of Progression to Severe COVID-19 Based on Patient Conditions and COVID-19 Vaccination Status

Conditions	Risk Level by Vaccination Status	
	Not Up to Date ^{a,b}	Up to Date ^a
Strong or Consistent Association With Progression to Severe COVID-19		
<ul style="list-style-type: none"> Moderately or severely immunocompromised (see Special Considerations in People Who Are Immunocompromised) 	High	
<ul style="list-style-type: none"> Obesity (BMI ≥95th percentile for age), especially severe obesity (BMI ≥120% of 95th percentile for age)^c Medical complexity with dependence on respiratory technology^d Severe neurologic, genetic, metabolic, or other disability that results in impaired airway clearance or limitations in self-care or activities of daily living Severe asthma or other severe chronic lung disease requiring ≥2 inhaled or ≥1 systemic medications daily Severe congenital or acquired cardiac disease Multiple moderate to severe chronic diseases Pregnancy 	High	Intermediate
Moderate or Inconsistent Association With Progression to Severe COVID-19		
<ul style="list-style-type: none"> Aged <1 year Prematurity in children aged ≤2 years Sickle cell disease Diabetes mellitus (poorly controlled) Chronic kidney disease Nonsevere cardiac, neurologic, or metabolic disease^e 	Intermediate	
Weak or Unknown Association With Progression to Severe COVID-19		
<ul style="list-style-type: none"> Mild asthma Overweight Diabetes mellitus (well controlled) 	Low	

^a See the current [COVID-19 vaccination schedule](#) from the CDC.

^b Recent SARS-CoV-2 infection (i.e., within 3–6 months) may confer substantial immunity against closely related variants. A patient’s recent infection history should be factored into the risk assessment.

^c The degree of risk conferred by obesity in younger children is less clear than it is in older adolescents.

^d This includes patients with a tracheostomy and those who require NIV.

^e The data for this group are particularly limited.

Key: BMI = body mass index; CDC = Centers for Disease Control and Prevention; NIV = noninvasive ventilation; the Panel = the COVID-19 Treatment Guidelines Panel

Rationale for the Panel's Framework for Assessing the Risk of Progression to Severe COVID-19

Although mortality associated with COVID-19 in children is low overall, severe disease can occur, especially in those with risk factors.¹⁰ Risk stratification for severe disease in children remains challenging. Imprecise definitions of comorbid conditions, insufficient granularity for differentiating the severity of comorbidities (e.g., mild vs. severe lung disease, poorly controlled vs. well-controlled diabetes), and small sample sizes limit the conclusions that can be drawn from individual studies and make comparing findings across studies difficult.

Furthermore, asymptomatic SARS-CoV-2 infection detected during admission screening of children who are hospitalized for reasons other than COVID-19 may affect the estimated risk of severe COVID-19, particularly for patient groups that may have protocolized admissions (e.g., children with febrile neutropenia, infants aged <90 days with fever). In addition, the published studies that have evaluated these associations in children are limited largely to case series without control groups and observational studies with methodologic limitations.

Despite these challenges, a risk-stratification framework needs to be developed that will allow clinicians to identify the patients who are most likely to benefit from receiving treatment. These patients can be prioritized in situations where supply or logistical constraints make it impossible to offer therapy to all eligible patients. Both the Pediatric Infectious Diseases Society and the American Academy of Pediatrics advocate for a risk-stratified approach to identifying the patients who are at the highest risk of progression to severe COVID-19 among those eligible for therapies under Food and Drug Administration (FDA) Emergency Use Authorizations (EUAs).^{11,12}

The Panel's approach to risk stratification and prioritization considers COVID-19 vaccination status, immune function, clinical risk factors, the strength of the evidence that demonstrates an association between each clinical risk factor and severe disease, and expert opinion.^{7-10,13-27} See [Special Considerations in Children](#) for more information on clinical risk factors. The Panel suggests that decisions regarding treatment be individualized, particularly for patients in the intermediate risk category. Clinicians should consider the type, number, and severity of comorbid conditions, the child's vaccination status, and the time since vaccination.

Comorbid conditions associated with severe COVID-19 are separated into the following categories in Table 3b:

- *Strong or Consistent Association With Progression to Severe COVID-19:* Comorbid conditions for which the published literature most consistently supports an increased risk of severe COVID-19. Patients in this category are moderately or severely immunocompromised, at risk of severe COVID-19, and not expected to develop an adequate immune response to COVID-19 vaccination.
- *Moderate or Inconsistent Association With Progression to Severe COVID-19:* Comorbid conditions and ages for which the published literature supports an association with severe COVID-19, but the association may be moderate or inconsistent across studies. In addition, the absolute risk of progression to severe disease or death is likely modest for any of the patients in this category.
- *Weak or Unknown Association With Progression to Severe COVID-19:* Comorbid conditions for which the data suggesting an association with severe COVID-19 are weak or for which an association is unknown. Patients with no comorbidities are included in this category.

Vaccination Status

Because COVID-19 vaccines are highly effective in preventing severe disease, individuals who are not immunocompromised and are up to date on their vaccines²⁸ are likely to have a low absolute risk of severe disease. Therefore, the potential benefit from antiviral treatment is less clear for these patients. Patients who are not up to date may have a lower level of protection against severe disease than patients who are up to date, but the data comparing these groups are limited. Evidence suggests that vaccine protection against severe COVID-19 wanes over time, particularly protection against the Omicron variant and its subvariants.²⁹⁻³² Several studies suggested that people who have had SARS-CoV-2 infection and were vaccinated have more durable protection than those who have had only an infection or only been vaccinated.^{33,34} Clinicians should consider the time since a child's vaccination when making treatment decisions.

Health Disparities

COVID-19–related outcomes are worse among medically underserved populations, although this factor is not strictly a comorbid condition. Some racial and ethnic minority groups experience disproportionate rates of COVID-19 hospitalization and are less likely to receive specific therapies.^{23,35-37} These factors may be relevant when making clinical decisions about treatment.^{38,39} See [Special Considerations in Children](#) for more information.

Rationale for the Panel's Recommendations

Ritonavir-Boosted Nirmatrelvir (Paxlovid)

Ritonavir-boosted nirmatrelvir has received an FDA EUA for the treatment of mild to moderate COVID-19 in nonhospitalized adolescents aged ≥ 12 years and weighing ≥ 40 kg who are at high risk of progression to severe COVID-19.⁴⁰

The EPIC-HR trial enrolled adults aged ≥ 18 years who were at high risk of severe COVID-19.⁴¹ They were randomized to receive ritonavir-boosted nirmatrelvir or placebo. The primary outcome of COVID-19–related hospitalization or all-cause mortality occurred in 8 of 1,039 patients (0.8%) who received ritonavir-boosted nirmatrelvir and in 66 of 1,046 patients (6.3%) who received placebo, an 89% relative risk reduction. No pediatric patients were included in the trial, and no pediatric safety data were made available.

Ritonavir has been used extensively in pediatric patients as a pharmacokinetic booster for the treatment of HIV and hepatitis C virus infection, and it has a known and tolerable side effect profile. In the FDA EUA, the dose of ritonavir-boosted nirmatrelvir authorized for adolescents aged ≥ 12 years and weighing ≥ 40 kg is expected to result in a drug exposure similar to that observed in adults.⁴⁰

Given the high efficacy of ritonavir-boosted nirmatrelvir in adults, its overall manageable side effect profile, the pediatric clinical experience with ritonavir, and the convenience of an oral medication, the Panel recommends the use of **ritonavir-boosted nirmatrelvir (Paxlovid)** for nonhospitalized adolescents aged ≥ 12 years and weighing ≥ 40 kg who have mild to moderate COVID-19 and are at the highest risk of progression to severe COVID-19 (**BIII**). Ritonavir-boosted nirmatrelvir is expected to be active against circulating variants, although clinical efficacy data are currently limited in children.⁴²⁻⁴⁴

Because of the potential for significant drug-drug interactions with some concomitant medications, ritonavir-boosted nirmatrelvir may not be the safest choice for some patients. See [Ritonavir-Boosted Nirmatrelvir \(Paxlovid\)](#) and [Drug-Drug Interactions Between Ritonavir-Boosted Nirmatrelvir \(Paxlovid\) and Concomitant Medications](#) for more information.

Remdesivir

Remdesivir is approved by the FDA for use in hospitalized and nonhospitalized pediatric patients aged ≥ 28 days and weighing ≥ 3.0 kg.⁴⁵ Remdesivir is expected to be active against circulating variants, although clinical efficacy data are currently limited in children.^{44,46-48}

In a study that included nonhospitalized adults with mild to moderate COVID-19 who were at high risk of progression to severe disease, administering an intravenous infusion of remdesivir once daily for 3 days resulted in an 87% relative reduction in the risk of hospitalization or death when compared with placebo.⁴⁹ Although adolescents aged ≥ 12 years were eligible for inclusion, the trial included only 8 patients aged < 18 years. Therefore, no conclusions regarding the efficacy of remdesivir in children can be made from this trial. In addition, clinical experience data from hospitalized children with COVID-19 who received remdesivir through a compassionate use program have been reported.^{2,50} Given the demonstrated efficacy of remdesivir in the overall study population, its overall favorable side effect profile, and clinical experience with remdesivir in hospitalized children, **remdesivir**, as an alternative to ritonavir-boosted nirmatrelvir, can be considered for children aged ≥ 12 years who are at the highest risk of progression to severe COVID-19 (CIII).

There is insufficient evidence to recommend either for or against the routine use of remdesivir for the treatment of COVID-19 in nonhospitalized children aged < 12 years who are at the highest risk of progression to severe disease or who are at intermediate risk of severe disease. Administering remdesivir requires performing an intravenous infusion once daily for 3 days, so logistical constraints may preclude the use of remdesivir in many settings.

Pharmacologic Therapies Not Recommended

Molnupiravir

The FDA EUA for molnupiravir is limited to people aged ≥ 18 years, and there are no data on the safety of using molnupiravir in children.⁵¹ The mechanism of action of molnupiravir has raised concerns about potential mutagenesis in mammalian cells. See [Molnupiravir](#) and [Therapeutic Management of Nonhospitalized Adults With COVID-19](#) for additional information.

Corticosteroids

Corticosteroids are not indicated for the treatment of COVID-19 in nonhospitalized children. However, corticosteroids should be used per usual standards of care in children with asthma and croup triggered by SARS-CoV-2 infection. Children with COVID-19 who are receiving corticosteroids for an underlying condition should continue this therapy as directed by their health care providers.

Other Therapeutic Agents

For other therapies that have been studied or are under investigation for the treatment of COVID-19, see [Therapies](#).

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