Suggested Criteria for the Use of Outpatient Antiviral Therapy for COVID-19 in Children

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This document provides guidance on clinical conditions for providers to consider when prescribing outpatient antiviral therapies for COVID-19 in children.

Antivirals for treatment of COVID-19

Oral antivirals

Since December 2021, the Food and Drug Administration (FDA) has issued Emergency Use Authorizations (EUAs) to permit the emergency use of oral antiviral therapies for the treatment of mild to moderate COVID-19 in adult and pediatric patients. Currently authorized oral antiviral therapies are:

- Nirmaltrelvir/ritonavir (Paxlovid™) (Pfizer) EUA issued Dec. 22, 2021[1]
- Molnupiravir (Merck) EUA issued Dec. 23, 2021[2]

Of these, only Paxlovid™ is currently authorized for use in pediatric patients ages 12 to 17. Patients should weigh ≥ 40 kg to qualify for Paxlovid™.

Molnupiravir is authorized ONLY FOR PATIENTS AGES 18 AND OLDER.

Paxlovid™ is authorized for use in patients ages 12 to 17 who weigh at least 40 kilograms and are at **high risk** for progressing to severe COVID-19 including hospitalization or death. Paxlovid™ is not recommended for use in patients with severe renal impairment (eGFR less than 30 milliliters per minute) or severe hepatic impairment (Child-Pugh Class C); in addition, the ritonavir component of Paxlovid™ may result in significant drug interactions when co-administered with drugs that affect the CYP3A metabolic pathway. Please refer to the FDA: Fact Sheet for Healthcare Providers: EUA for Paxlovid (www.fda.gov/media/155050/download) for prescribing information.

Intravenous antivirals

On Dec. 23, 2021, the National Institutes of Health COVID-19 Treatment Guidelines Panel issued a recommendation to consider the use of remdesivir, an intravenous antiviral, for outpatient treatment of patients

[1] FDA: Letter to Karen Baker, Pfizer, Dec. 22, 2021. (www.fda.gov/media/155049/download)

[2] FDA: Letter to Sushma Kumar, Merck, Dec. 23, 2021. (www.fda.gov/media/155053/download)

with mild to moderate COVID-19 at high risk of clinical progression.[3] This recommendation is based on results from the PINETREE clinical trial[4] showing that three consecutive days of IV remdesivir resulted in a significant reduction in hospitalizations and deaths compared to placebo. Remdesivir is currently FDA-approved for treatment of COVID-19 in both hospitalized and nonhospitalized patients, including pediatric patients 28 days of age and older who weigh at least 3 kilograms (about 6.6 pounds).

For patients aged between 28 days and 12 years old who weigh at least 3 kilograms, remdesivir is the only currently approved antiviral option for treatment of COVID-19 of any severity. When used for nonhospitalized patients, remdesivir is administered intravenously once daily for three consecutive days.[5] Refer to Veklury prescribing information (remdesivir) (www.gilead.com/-/media/files/pdfs/medicines/covid-19/veklury/veklury_pi.pdf) for details.

Monoclonal antibodies

Due to lack of effectiveness against currently circulating variants of SARS-CoV-2, there are currently no monoclonal antibodies authorized for use for the treatment or prevention of COVID-19 in the U.S.

High-risk conditions

The EUA for Paxlovid™ specifies that use is authorized for patients with mild-to-moderate COVID-19 who are at **high risk** for progression to severe COVID-19, including hospitalization or death. For complete information on medical conditions and demographic factors associated with increased risk for progression to severe COVID-19, refer to Underlying Medical Conditions Associated with Higher Risk for Severe COVID-19: Information for Healthcare Professionals | CDC. Demographic factors include age, race, and ethnicity.

The above website also lists the following medical conditions that are associated with higher risk of severe illness from COVID-19 with conclusive or suggestive evidence (in alphabetical order, not in order of risk):

- Asthma
- Cancer
- Cerebrovascular disease
- Children with certain underlying conditions
- Chronic kidney disease
- Chronic liver diseases
- Chronic lung diseases
- Cystic fibrosis
- Diabetes (Type 1 or Type 2)
- Disabilities, including Down syndrome
- Heart conditions

[3] National Institutes of Health: COVID-19 Treatment Guidelines. Statement on the Use of Anti-SARS-CoV-2 Monoclonal Antibodies or Remdesivir for the Treatment of COVID-19 in Nonhospitalized Patients When Omicron is the Predominant Circulating Variant (files.covid19treatmentguidelines.nih.gov/guidelines/archive/statement-on-anti-sars-cov-2--12-23-2021.pdf).

[4] PINETREE Clinical Trial NEJM 2021. Accessed March 23, 2023.

[5] FDA New Release: FDA Approves First COVID-19 Treatment for Young Children. April 25, 2022.

- HIV infection
- Mental health conditions
- Neurologic conditions
- Obesity
- Overweight
- Physical inactivity
- Pregnancy or recent pregnancy
- Primary immunodeficiencies
- Sickle cell disease
- Smoking, current or former
- Solid organ or blood stem cell transplant
- Substance use disorders
- Tuberculosis
- Use of corticosteroids or other immunosuppressive medications

Most children with COVID-19 experience asymptomatic or mild illness, but some children are at risk of developing severe illness. Studies have found that some underlying medical conditions including obesity; diabetes; cardiac, lung, and neurologic disorders; and medical complexity increase the risk of severe outcomes from COVID-19, and having more than one pre-existing comorbidity is associated with an increased risk of severe illness. Age may also be associated with risk of severe illness with infants and adolescent patients making up a disproportionate number of severe COVID-19 cases among pediatric patients. For more information see https://www.cdc.gov/coronavirus/2019-ncov/hcp/pediatric-hcp.html

Suggested clinical criteria for use of outpatient antiviral therapy in pediatric patients

The suggested **high risk** clinical criteria listed below for the use of outpatient antiviral therapies in pediatric patients are designed to assist providers with clinical decision-making. The criteria were developed by an advisory group consisting of clinicians from Children's Minnesota, Mayo Clinic, and the University of Minnesota, in collaboration with the Minnesota Department of Health. The list does not supersede the current EUA eligibility criteria. The list below is a resource for providers to help identify **pediatric** patients **most at risk** for severe disease and hospitalization who may be **most likely to benefit** from treatment based on expert clinical opinion.

There are no currently authorized monoclonal antibodies or oral antivirals for patients younger than 12 years of age. For patients aged between 28 days and 12 years old who weigh at least 3 kilograms, the only currently approved option for treatment of COVID-19 is remdesivir.

Cardiology

- Single ventricle physiology (Fontan physiology or similar, and/or presence of protein-losing enteropathy or plastic bronchitis).
- Complex conotruncal disease (interrupted aortic arch, pulmonary atresia, truncus).
- Cardiac failure/transplant (decision-making in conjunction with heart failure/transplant team).
- Pulmonary hypertension (HTN) on oral or inhaled therapy (decision-making in conjunction with pulmonary and/or pulmonary HTN team).

- Significant secondary immunosuppression due to pharmacologic agents (refer to Immunology).

Complex conditions

- Medical complexity with respiratory technology dependence (includes but is not limited to baseline requirement for oxygen, ventilator-dependent chronic lung disease, neuromuscular disease, or presence of tracheostomy).

Endocrinology

- Obesity (BMI greater than 95% percentile for age/sex).
- Type 1 diabetes mellitus.
- Type 2 diabetes mellitus.
- Significant secondary immunosuppression due to pharmacologic agents (refer to Immunology).

Gastroenterology

- Significant secondary immunosuppression due to pharmacologic agents (refer to Immunology).

Hematology/oncology

- Allogeneic stem cell transplant within the previous 12 months.
- Acute myeloid leukemia (AML) on therapy.
- High risk and relapsed acute lymphoblastic leukemia (ALL) or lymphoblastic lymphoma on intensive therapy.
- Sickle cell disease with significant pulmonary disease and/or greater than one hospitalization for confirmed or suspected acute chest episode.
- Significant secondary immunosuppression due to pharmacologic agents (refer to Immunology).

Immunology

- Primary or secondary cellular (T cell) immunodeficiency.
- HIV infection with history of opportunistic infection or with severe CD4 lymphocytopenia (CD4 percentage less than 15% if under age 14; CD4 count less than 200 lymphocytes/mm3 if older than age 14).
- Antibody disorders requiring immunoglobulin replacement.
- Combined immunodeficiency associated with immune dysregulation, with or without current immunosuppression (e.g., APD3, STATE3 GOF, ALPS).
- Primary immune regulatory disorders with or without immune deficiency (e.g., APECED, XIAP).
- Significant secondary immunosuppression due to pharmacologic agents:

    1. Agents used for malignant conditions and related complications.
        a. Chemotherapeutic agents (e.g., cyclophosphamide, methotrexate, mycophenolate).
        b. Anti-B lymphocyte monoclonal antibodies (e.g., rituximab), or anti-T lymphocyte monoclonal antibodies (e.g., alemtuzumab).
        c. Cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) inhibitors (e.g., abatacept).
        d. Tumor necrosis factor-alpha (TNF-α) antagonists (e.g., adalimumab, certolizumab, infliximab, etanercept, and golimumab).
        e. Select anti-cytokine antagonists (e.g., tocilizumab, ustekinumab, secukinumab, ixekizumab).*
    2. Immunosuppressive agents used for solid organ transplant and rheumatologic and other autoimmune conditions (e.g., inflammatory bowel disease, hemolytic uremic syndrome).

   a. Conventional immunosuppression: mycophenolate, sirolimus, tacrolimus, azathioprine.**
   b. Anti-B lymphocyte monoclonal antibodies or inhibiting agents (e.g., rituximab or belimumab).
   c. Cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) inhibitors (e.g., abatacept).
   d. Anti-C5 monoclonal antibody (e.g., eculizumab).
   e. Tumor necrosis factor-alpha (TNF-α) antagonists (e.g., adalimumab, certolizumab, infliximab, etanercept, and golimumab).
   f. Select anti-cytokine antagonists (e.g., tocilizumab, ustekinumab, secukinumab, ixekizumab).*
3. Daily corticosteroid therapy at a dose greater than 20 milligrams of prednisone or equivalent for longer than 14 days.

*Does not include anakinra when used as monotherapy as there is no significant increase in the risk of severe infection. Tocilizumab is included because it can cause neutropenia and generally is associated with more infections.

**Does not include low-dose methotrexate, hydroxychloroquine, colchicine, or leflunomide as used in rheumatic conditions.

Infants under 1 year of age (remdesivir only)

- History of prematurity (gestational age under 29 weeks).
- Qualifying comorbidities listed under organ system headings (e.g., chronic lung disease, congenital heart disease, neuromuscular conditions, Trisomy 21).

Nephrology

- Dialysis (peritoneal or hemodialysis).
- Significant secondary immunosuppression due to pharmacologic agents (refer to Immunology).

Neurology

- Oxygen- or ventilator-dependent neuromuscular disease.
- Cerebral palsy/spastic quadriplegia.
- Congenital chromosomal abnormality (e.g., trisomy 21, trisomy 18, 22q11del, or other chromosome abnormalities, on an individual basis as recommended by a geneticist).
- Mitochondrial disease and other inborn errors of metabolism with risk of metabolic decompensation (e.g., maple syrup urine disease (MSUD), organic acidemias, urea cycle disorders).
- Significant secondary immunosuppression due to pharmacologic agents (refer to Immunology).

Obstetrics

- Pregnancy.

Pulmonology

- Oxygen- or ventilator-dependent chronic lung disease or neuromuscular disease.
- High-risk (severe or poorly controlled) asthma.
- History of bronchopulmonary dysplasia with lung function impairment or other fixed obstructive lung disease.
- Cystic fibrosis, primary ciliary dyskinesia, and other causes of bronchiectasis (e.g., primary immunodeficiency).
- Significant secondary immunosuppression due to pharmacologic agents (refer to Immunology section above).

Rheumatology

- Significant secondary immunosuppression due to pharmacologic agents (refer to Immunology section above).

The FDA has provided guidance that other medical conditions or factors may also place individual patients at high risk for progression to severe COVID-19. Authorization of treatments currently available under EUA are not limited to the medical conditions or factors listed above. Health care providers should consider the benefit-risk for an individual patient.

Use of outpatient therapy in hospitalized patients

Paxlovid™ is authorized for the treatment of patients hospitalized with mild to moderate COVID-19, such as patients admitted for monitoring of drug-drug interactions. Paxlovid™ is not authorized for **initiation** of treatment in patients requiring hospitalization due to severe or critical COVID-19 but may be **continued** in patients hospitalized for severe or critical COVID-19 after starting treatment with Paxlovid™. Paxlovid™ is also authorized for use in patients hospitalized for reasons other than COVID-19 provided the terms of the authorization are otherwise met. Refer to FDA: Frequently Asked Questions on the Emergency Use Authorization for Paxlovid for Treatment of COVID-19 (www.fda.gov/media/155052/download).

Fact sheets for providers

The fact sheets below contain full prescribing information, including EUA criteria where applicable; eligibility criteria; contraindications; dosing and monitoring recommendations; and safety information on adverse reactions and hypersensitivity. These fact sheets are subject to revision as additional data emerges, and providers are encouraged to review them regularly.

- Fact Sheet for Health Care Providers: Emergency Use Authorization for Paxlovid (www.fda.gov/media/155050/download)
- Veklury Prescribing Information (remdesivir) (www.gilead.com/-/media/files/pdfs/medicines/covid-19/veklury/veklury_pi.pdf)

Additional resources

- Therapeutic Options for COVID-19 Patients (www.health.state.mn.us/diseases/coronavirus/hcp/therapeutic.html)
- COVID-19 Medication Options (www.health.state.mn.us/diseases/coronavirus/meds.html)
- CDC: Underlying Medical Conditions Associated with Higher Risk for Severe COVID-19: Information for Healthcare Professionals (www.cdc.gov/coronavirus/2019-ncov/hcp/clinical-care/underlyingconditions.html)
- American Academy of Pediatrics: Management Strategies in Children and Adolescents with Mild to Moderate COVID-19 (www.aap.org/en/pages/2019-novel-coronavirus-covid-19-infections/clinical-guidance/outpatient-covid-19-management-strategies-in-children-and-adolescents/)

- NIH COVID-19 Treatment Guidelines for Nonhospitalized Children: Framework for Assessing Risk of Progression to Severe COVID-19 Basedon Patient Conditions and COVID-19 Vaccination Status (www.covid19treatmentguidelines.nih.gov/tables/assessing-risk/)
- Checking drug interactions for Paxlovid™: University of Liverpool: COVID-19 Drug Interactions (covid19-druginteractions.org/checker)