STAY SAFE MN

Suggested Criteria for the Use of Monoclonal Antibody Therapy for COVID-19 in Children

1/12/2022

Monoclonal antibodies for treatment

Since November 2020, the U.S. Food and Drug Administration (FDA) has issued several Emergency Use Authorizations (EUAs) to permit the emergency use of investigational monoclonal antibody (mAb) therapies for the treatment of mild to moderate COVID-19 in adult and pediatric patients. The currently authorized mAbs are:

- Casirivimab and imdevimab (Regeneron) EUA issued November 21, 2020[1]
- Bamlanivimab and etesevimab (Lilly) EUA issued February 9, 2021[2]
- Sotrovimab (GlaxoSmithKline) EUA issued May 26, 2021[3]

Both casirivimab/imdevimab and sotrovimab are authorized for use in pediatric patients with positive results from direct SARS-CoV-2 viral testing and who are ages 12 to 17, weigh at least 40 kg., and are at ***high risk*** for progressing to severe COVID-19 and/or hospitalization. On Dec. 6, 2021, the FDA expanded the EUA for bamlanivimab/etesevimab to include use for treatment of COVID-19 in pediatric patients under 12 years of age, including neonates weighing at least 1 kg, using standard dosing for patients aged 40 kg and more and weight-based dosing for patients weighing less than 40 kg.[4]

PLEASE NOTE: Certain circulating SARS-CoV-2 viral variants may be associated with resistance to monoclonal antibodies. Health care providers should review the viral neutralization data in the authorized fact sheets for

1 US Food and Drug Administration (FDA). Nov 21, 2020. Letter to Yunji Kim, PharmD, Regeneron Pharmaceuticals, Inc. (https://www.fda.gov/media/143891/download)

2 US Food and Drug Administration (FDA). September 16, 2021. Letter to Christine Phillips, PhD, RAC, Eli Lilly and Company. (https://www.fda.gov/media/145801/download)

3 US Food and Drug Administration (FDA). October 8, 2021. Letter to Debra Lake, GlaxoSmithKline. (https://www.fda.gov/media/149532/download)

4 FDA: Fact Sheet for Health Care Providers Emergency Use Authorization of Bamlanivimab and Etesevimab. https://www.fda.gov/media/145802/download

each mAb under EUA for details regarding specific variants and resistance (fact sheets are below). Information on the proportion of SARS-CoV-2 variants circulating in the U.S. is available on CDC COVID Data Tracker: Variant Proportions (https://covid.cdc.gov/covid-data-tracker/#variant-proportions) and is updated regularly. Additional updates on current treatment recommendations are available at Therapeutic Options for COVID-19 Patients (www.health.state.mn.us/diseases/coronavirus/hcp/therapeutic.html). Providers should review these resources before providing monoclonal antibody treatment. Note that currently, the omicron variant is dominant in Minnesota and casirivimab/imdevimab and bamlanivimab/etesevimab are not thought to have good activity against this variant. Sotrovimab is thought to retain effectiveness against the omicron variant.

For updated information on treatment of pediatric patients with sotrovimab and the new oral antiviral agent nirmatrelvir/ritonavir (Paxlovid), please refer to Interim Guidance for Use of Sotrovimab and Nirmatrelvir/Ritonavir (Paxlovid) for Pediatric Patients (www.health.state.mn.us/diseases/coronavirus/hcp/sotpaxpeds.pdf).

Monoclonal antibodies for post-exposure prophylaxis

On Sept. 9 and Sept. 16, 2021, respectively, the FDA updated and expanded the EUAs[5] for casirivimab/imdevimab and bamlanivimab/etesevimab to include post-exposure prophylaxis (PEP). Eligibility criteria for PEP is the same as the criteria for treatment, in that the child must be age 12 to 17, weigh at least 40 kg., and be at ***high risk*** for progression to severe COVID-19. Those eligible for PEP must also meet the following criteria:

- They must not be fully vaccinated or are not expected to mount an adequate immune response to complete SARS-CoV-2 vaccination (for example, people with immunocompromising conditions, including those taking immunosuppressive medications).
- They must have had an exposure to someone infected with SARS-CoV-2 consistent with close contact criteria per Centers for Disease Control and Prevention (CDC) or at high risk of exposure to an individual infected with SARS-CoV-2 because of occurrence of SARS-CoV-2 infection in other individuals in the same institutional setting (for example, group homes, shelters, etc.).

The expanded EUA for bamlanivimab/etesevimab on Dec 6, 2021, to include pediatric patients less than 12 years of age also authorized use of bamlanivimab/etesevimab for post-exposure prophylaxis in this age group.

Casirivimab/imdevimab is authorized to be given either through IV infusion or subcutaneously for PEP. In contrast, bamlanivimab/etesevimab is authorized only for IV infusion, and is NOT authorized for subcutaneous administration.

The use of monoclonal antibodies for PEP is NOT a substitute for vaccination, nor is it authorized for pre-exposure prophylaxis.

[5] US Food and Drug Administration (FDA). September 9, 2021. Letter to Yunji Kim, PharmD, Regeneron Pharmaceuticals, Inc. (https://www.fda.gov/media/145610/download)

Use of monoclonal antibody therapy in hospitalized patients

Each of the three currently authorized monoclonal antibodies for the treatment of COVID-19 are indicated for use in outpatients **or** patients who are hospitalized for reasons other than COVID-19. Bamlanivimab/etesevimab **may** be used in patients 2 years and older who are hospitalized due to COVID-19; casirivimab/imdevimab and sotrovimab are not authorized in this situation. Regardless of age, none of these three monoclonal antibody therapies are authorized for use in patients who require oxygen therapy and/or respiratory support due to COVID-19 or who require an increase in baseline oxygen flow rate and/or respiratory support due to COVID-19 and are on chronic oxygen therapy and/or respiratory support due to underlying non-COVID-19 related comorbidity.

High-risk conditions

Per each EUA, **high risk** is defined as meeting at least one of the following criteria:

- Older age (for example, aged 65 years or older).
- Less than 1 year of age (NOTE: This applies only to bamlanivimab/etesevimab at this time).
- Obesity or being overweight (for example, adults with BMI greater than 25 kg/m2, or if age 12-17, have BMI greater than or equal to the 85th percentile for their age and gender, based on CDC growth charts).
- Pregnancy.
- Chronic kidney disease.
- Diabetes.
- Immunosuppressive disease or immunosuppressive treatment.
- Cardiovascular disease (including congenital heart disease) or hypertension.
- Chronic lung diseases (for example, chronic obstructive pulmonary disease, asthma (moderate-to-severe), interstitial lung disease, cystic fibrosis, and pulmonary hypertension).
- Sickle cell disease.
- Neurodevelopmental disorders (for example, cerebral palsy) or other conditions that confer medical complexity (for example, genetic or metabolic syndromes and severe congenital abnormalities).
- Medical-related technological dependence (for example, tracheostomy, gastrostomy, or positive pressure ventilation (not related to COVID-19)).

Other medical conditions or factors may also place patients at high risk for progression to severe COVID-19 and authorization of mAbs under these EUAs is **not limited to the medical conditions or factors listed above**. For additional information on medical conditions and factors associated with increased risk for progression to severe COVID-19, visit CDC: People with Certain Medical Conditions (www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/people-with-medical-conditions.html). Clinicians and institutions may choose to administer these agents on a case-by-case basis to pediatric patients who meet EUA criteria.

For information regarding administration of monoclonal antibody therapy in children and adolescents, visit the American Academy of Pediatrics Outpatient COVID-19 Management Strategies in Children and Adolescents (www.aap.org/en/pages/2019-novel-coronavirus-covid-19-infections/clinical-guidance/outpatient-covid-19-management-strategies-in-children-and-adolescents/). Health care providers should consider the benefit-risk for each patient.

Fact sheets for providers

The U.S. Food and Drug Administration has issued revised fact sheets for health care providers to include additional information on susceptibility of SARS-CoV-2 variants for each of the mAb currently available. These fact sheets contain full EUA prescribing information, including 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 for details regarding specific variants and potential resistance that may make the authorized mAb therapies less effective.

- Fact Sheet for Health Care Providers: Emergency Use Authorization of Regeneron (www.fda.gov/media/145611/download)
- Fact Sheet for Health Care Providers: Emergency Use Authorization for Bamlanivimab/Etesevimab (www.fda.gov/media/145802/download)
- Fact Sheet for Health Care Providers: Emergency Use Authorization for Sotrovimab (www.fda.gov/media/149534/download)

Suggested clinical criteria for use of monoclonal antibody therapy for treatment or post-exposure prophylaxis

The suggested clinical criteria listed below for the use of mAbs in pediatric patients are designed to assist providers with clinical decision-making and 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, nor is the use of mAbs in pediatric patients in Minnesota restricted to these clinical criteria. The list is a resource for providers to help identify patients most at risk for severe disease and hospitalization who may be most likely to benefit from mAb treatment based on expert clinical opinion. MDH gratefully acknowledges the assistance of this advisory group in the development of these criteria.

Please note that these are suggested criteria for **pediatric patients only, not adults**.

For conditions listed that refer to pediatric patients aged less than 12 years, bamlanivimab/etesevimab is currently the **only** monoclonal antibody authorized for use in this age group.

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 (see Immunology).

Complex conditions

- Medical complexity with respiratory technology dependence (includes but 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 and 5 years of age or older).
- Type 1 diabetes mellitus.
- Type 2 diabetes mellitus.
- Significant secondary immunosuppression due to pharmacologic agents (see Immunology).

Gastroenterology

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

Immunology

- Primary or secondary cellular (T cell) immunodeficiency.
- HIV infection with history of opportunistic infection or with severe CD4 lymphocytopenia (CD4% less than 15% if under age 14; CD4 count less than 200 lymphocytes/mm3 if older than age 14).
- Primary immunodeficiency on immunoglobulin therapy.
- Combined immunodeficiency associated with immune dysregulation, with or without current immunosuppression.
- 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 mg 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 less than 1 year of age

- History of prematurity (gestational age less than 29 weeks) in patients less than 1 year of age.
- Qualifying comorbidities listed under other organ system headings in this guidance (e.g., chronic lung disease, congenital heart disease, neuromuscular conditions, Trisomy 21).

Nephrology

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

Race/ethnicity

- Black/African American
- Hispanic/Latino
- Asian
- Native Hawaiian or Pacific Islander
- American Indian or Alaskan Native

Rheumatology

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

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 and authorization of monoclonal antibodies under the EUA is not limited to the medical conditions or factors listed above. Health care providers should consider the benefit-risk for an individual patient.

Advisory Group: Children's Minnesota, Mayo Clinic, University of Minnesota (12/23/21)

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)