Outpatient COVID-19 Management Strategies in Children and Adolescents

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American Academy of Pediatrics Interim Clinical Guidance

General pediatricians, pediatric subspecialists, and pediatric surgeons have a crucial role in providing frontline medical care to children and adolescents during the COVID-19 pandemic. As of September 16, 2021, >5.5 million children and adolescents have laboratory-confirmed SARS-CoV-2 infection, representing 15.7% of all reported COVID-19 cases in the United States.[1,2] Starting in July-August 2021, rates of pediatric COVID-19 hospitalizations have increased[3,4]; overall, 0.1% to 1.9% of COVID-19 cases in children and adolescents resulted in hospitalization and ≤0.03% resulted in death.[5] Presently, children and adolescents with COVID-19 have less disease severity and overall, good clinical outcomes when compared with their adult counterparts.[6,7] On the basis of current evidence, children and adolescents with certain host factors and underlying medical conditions may be at increased risk for severe illness from SARS-CoV-2 infection.[8-16]
Given rapidly emerging data, recent increasing rate of COVID-19 hospitalizations,[3,4] and the fact that many children and adolescents are presenting for medical attention in the outpatient/ambulatory setting, this interim guidance is intended to navigate treatment considerations and challenges and summarize currently available recommendations for the outpatient management of COVID-19 in children and adolescents.

Which children and adolescents qualify for outpatient treatment with SARS-CoV-2 monoclonal antibodies?

Data from randomized studies demonstrate that timely outpatient monoclonal antibody (mAb) therapy that targets SARS-CoV-2 spike protein reduced the risk for hospitalization and death in adults with COVID-19.[17,18] Although clinical experience[19] and data on efficacy and safety of mAb therapy are emerging, these therapies remain investigational in children and adolescents at present. The absence of proven risk factors that reliably identify and predict poor clinical outcomes in children and adolescents with COVID-19, precludes the routine use of mAb in all children and adolescents with COVID-19. Instead, an individual risk/benefit assessment should be performed when considering mAb for a child/adolescent with COVID-19.

The US Food and Drug Administration (FDA) has authorized an Emergency Use Authorization (EUA) of SARS-CoV-2 mAb in **high-risk** individuals in outpatient settings for both (1) the **treatment**[20-22] of mild to moderate COVID-19; and (2) **postexposure prophylaxis**.[23,24]

(1) **FDA EUA for SARS-CoV-2 mAb for <u>Treatment</u>**[20,21,25,26]
- Child/adolescent ≥12 years and weighing ≥40 kg, **and**
- Non-hospitalized patient, **and**
- Laboratory confirmed SARS-CoV-2 infection, **and**
- **Mild to moderate** COVID-19, **and**
- Within 10 days of symptom onset, **and**
- **High risk** for progressing to severe COVID-19 and/or hospitalization.

mAb therapies are <u>NOT</u> authorized for use in:
- Patients hospitalized for COVID-19 (unless admitted to the hospital for reasons other than COVID-19 and otherwise meet EUA criteria for treatment);
- Patients who require oxygen therapy for COVID-19; or
- Patients who require an increase in baseline oxygen flow rate in those already receiving chronic oxygen therapy for other, non–COVID-19 related, underlying conditions.

(2) FDA EUA Criteria for SARS-CoV-2 mAb for COVID-19 <u>Postexposure Prophylaxis</u>[23]
- Child/adolescent ≥12 years and weighing ≥40 kg, **and**

- Non-hospitalized patient, **and**
- Not fully vaccinated or are fully vaccinated but are not expected to have an adequate immune response (eg, underlying immunocompromising conditions or receiving immunosuppressive medications)
- **Close contact** (following Centers for Disease Control and Prevention [CDC] definitions) with an individual with laboratory-confirmed SARS-CoV-2.[23]

Which patients are considered "high risk"?
High-risk criteria in the FDA EUA for COVID-19 mAb are described as:

- **Body mass index (BMI) ≥85th percentile** for their age and gender based on the Centers for Disease Control and Prevention growth charts;
- **Immunosuppressive disease or receipt of immunosuppressive therapies**[a];
- Neurodevelopmental disorders (eg, cerebral palsy, trisomy 21);
- A medical-related technological dependence that is not related to COVID-19 (eg, **tracheostomy, positive pressure ventilation**, gastrostomy);
- Sickle cell disease;
- Congenital or acquired heart disease;
- Asthma or other chronic respiratory disease that requires daily medication for control;
- Diabetes;
- Chronic kidney disease; *or*
- Pregnancy.

Proven risk factors for disease severity and poor outcomes from COVID-19 in children and adolescents have not been confirmed. The **bolded** conditions in the FDA EUA for mAb have been described in observational studies of children with severe COVID-19. It is reasonable to consider preferential SARS-CoV-2 mAb therapy in adolescents 12 to 17 years old who may be at highest risk for severe disease and progression, especially those with **bolded** conditions, including adolescents with obesity, those who are severely immunocompromised, and medically complex children/adolescents with dependence on respiratory technology.

Routine SARS-CoV-2 mAb therapies are not indicated for children/adolescents with COVID-19 at low risk for progression or hospitalization.

Which mAB therapy should I choose for my eligible patient?
There are FDA Emergency Use Authorizations for multiple mAb therapies for outpatient treatment: (1) **casirivimab and imdevimab** administered together; (2) **bamlanivimab and etesevimab** administered together; or (3) **sotrovimab**. See Table 1 for additional information.

Local circulating variant susceptibility needs to be considered when choosing the most appropriate mAb therapy[27,28]; given changing epidemiology, pediatricians should refer to the most up-to-date guideline recommendations in their area. SARS-CoV-2 variants with mutations that affect the spike protein may result in reduced susceptibility to available mAb therapies.

[a] Regarding assessment of immunosuppression: Immunosuppressive therapies leading to severe immunocompromise include receipt of: T cell-depleting (eg, leading to CD4 count < 100-300 cells/mm3 or CD4 <15% for children) and B cell-depleting (eg, rituximab) agents; high-intensity chemotherapy or recent transplantation (1–3 months after solid organ transplantation, 1–6 months after hematopoietic stem cell transplantation) or augmented immunosuppression in the preceding 30 days for therapy of graft rejection or graft-versus-host disease; daily systemic corticosteroids with a prednisone dose equivalent of ≥20 mg/day (or ≥2 mg/kg/day in children who weigh <10 kg) for ≥2 weeks; and/or combination immunosuppressive therapies.

Casirivimab-imdevimab (either subcutaneous injection or intravenous infusion) or bamlanivimab-etesivimab (intravenous infusion) are the mAb therapies currently authorized by the FDA for the indication of COVID-19 Post-exposure Prophylaxis (PEP). See Tables 1 and 2 for additional information.

When should mAb therapy be initiated?
Treatment with SARS-CoV-2 mAb should be started as quickly as possible following positive SARS-CoV-2 test and within 10 days of symptom onset for an eligible individual.
If an individual is a candidate for mAb for SARS-CoV-2 postexposure prophylaxis, casirivimab-imdevimab or bamlanivimab-etesivimab should be prescribed as soon as possible, and **optimally within 96 hours** and maximally within 7 days after the confirmed SARS-CoV-2 exposure, on the basis of results of randomized controlled trials.[23,30]

Are there precautions my practice should take when administering mAb?
Monoclonal antibodies should only be administered in settings in which health care clinicians have immediate access to medications to treat a severe infusion reaction, such as anaphylaxis, and the ability to activate the emergency medical system (EMS), as necessary. It may be necessary for pediatricians to collaborate and to coordinate with community healthcare settings to provide mAb therapy.

Patients should be clinically monitored during administration and observed for at least 1 hour following administration.

What adverse reactions[25] have been reported after SARS-CoV-2 mAb therapies?

- Local injection site reactions are the most frequently reported events (4%-12%). Infusion-related reactions, including fever, chills, shortness of breath, dizziness, abdominal pain, nausea, vomiting and flushing, and pruritus, have been reported to occur during and up to 24 hours after administration. Serious hypersensitivity reactions, including anaphylaxis, may also occur.
- Pediatricians should report all medication errors and serious adverse reactions potentially related to mAb to the FDA MedWatch Adverse Event Reporting program at www.fda.gov/medwatch/report.htm or by calling 1-800-FDA-1088 to request a reporting form. Refer to the https://www.fda.gov/media/145611/download for more details.

What are additional considerations for children receiving SARS-CoV-2 mAb?

- Despite receiving SARS-CoV-2 mAb therapy, clinical worsening of COVID-19 has been reported and may include fever, hypoxia or increased respiratory distress, dysrhythmias, and altered mental status. Pediatricians should advise parents/caregivers on how to monitor for clinical worsening, occurring most frequently in the first 7 to 10 days after symptom onset, and provide further instructions on when to seek emergency medical attention.
- Children/adolescents who receive mAb for treatment or as post-exposure prophylaxis should continue to isolate or quarantine and adhere to public health department policies and local recommendations for discontinuing isolation and quarantine precautions.
- Receipt of mAb does not preclude the need to continue to follow preventive measures, including wearing an appropriately fitted mask in children and adolescents ≥2 years of age, physical distancing, and performing hand hygiene.
- Neither acute SARS-CoV-2 infection nor treatment with mAb are substitutes for COVID-19 vaccination. Eligible adolescents ≥12 years of age and their household contacts should be vaccinated optimally as soon as the COVID-19 vaccine is available to them. After SARS-CoV-2 infection, COVID-19 vaccination can be provided once symptoms resolve and at **least 90 days after receiving mAb**.

- Pediatricians are encouraged to discuss participation in anti-SARS-CoV-2 mAb clinical trials with patients who have mild to moderate COVID-19, if available locally (https://clinicaltrials.gov/ct2/results?cond=COVID-19+monoclonal&term=children&cntry=US&state=&city=&dist).

What are potential options for prescribing SARS-CoV-2 mAb to eligible children and adolescents at highest risk?

- Availability of SARS-CoV-2 mAb therapy may vary geographically. Pediatricians are encouraged to partner with their local pediatric hospitals and health departments to inquire about the availability of mAb therapies and help establish a reliable process for safe and timely administration of SARS-CoV-2 mAb to eligible patients.
- In an effort to reduce COVID-19-related healthcare resource burden on hospitals, some facilities (eg, infusion centers, urgent care centers), medical practices, and home health companies may be equipped and able to provide subcutaneous administration of SARS-CoV-2 mAb; these sites are required to follow quality standards and clinically monitor patients for at least 1 hour after therapy, including having a reaction management kit, providing basic life support, and activating emergency medical services, if needed.[31-34] Additional resources for health professions administering mAb can be found at https://www.phe.gov/emergency/events/COVID19/therapeutics/Pages/administration-sites.aspx and https://www.phe.gov/emergency/mAbs-calculator/Pages/default.aspx.
- Information regarding availability and access to SARS-CoV-2 mAb therapies by location are available on the following sites: https://protect-public.hhs.gov/pages/therapeutics-distribution and https://covid.infusioncenter.org/.

What strategies may be considered in communities with resource constraints or limited access to SARS-CoV-2 mAb?

- The American Academy of Pediatrics (AAP) strongly supports the equitable distribution and availability of therapeutic medications and vaccinations to eligible children and adolescents. Hispanic and Latino, non-Hispanic Black, and Non-Hispanic American Indian/Alaska Native children and adolescents have higher COVID-19 hospitalization rates than non-Hispanic white and Asian children and adolescents.[35,36] In areas of limited access to COVID-19 mAb where further prioritization may be required, additional risk stratification based on host and situational factors may need to be considered when assessing COVID-19 risk and appropriateness of mAb therapies for an individual patient, including:
    - Accessibility and availability of mAb products
    - Prioritizing the treatment of SARS-CoV-2 infection over post-exposure prophylaxis
    - Continuing to prioritize for patients deemed at highest risk for COVID-19 complications
    - Individual comorbidities, including the presence of multiple high-risk criteria
    - Underlying host factors: Obesity, defined as BMI ≥ 95th percentile for age and gender in children or BMI ≥ 30 kg/m^2 in older adolescents, has been described in children and adolescents with severe COVID-19[14,37] and may need to be used preferentially over the overweight criterion in the EUA (BMI 85th-95th percentile for age and gender or BMI 25-29.9 kg/m^2)
    - COVID-19 vaccination status: individuals who are unvaccinated against COVID-19 are at higher risk for hospitalization than fully vaccinated individuals[38] and vaccinated individuals not expected to mount an adequate vaccine immune response (eg immunocompromised children)
    - Details of COVID-19 exposure: type and extent of exposure (eg, highest risk of transmission with prolonged and household exposures) and time post-exposure

Are there additional adjunctive therapies or interventions to treat or prevent the progression of COVID-19 in children and adolescents?

- Data are emerging regarding the clinical utility of inhaled corticosteroids in treating mild acute COVID-19 in older adults with mild, acute SARS-CoV-2 to prevent progression to severe COVID-19.[39,40] There are no data regarding the safety and efficacy of this approach in children and adolescents to recommend their routine use presently.
- There is **NO** conclusive evidence to support the efficacy and safety of the following medications for routine use in the treatment or prevention of COVID-19 in children and adolescents. It is strongly recommended that these unproven interventions be avoided, not be prescribed, and parents counseled against their use. In addition to showing no efficacy against COVID-19, inappropriate use of these antimicrobials cause significant harm.[41,42] The following **are NOT recommended** to be prescribed for COVID-19**:**
    - Azithromycin: Results of randomized trials in ambulatory subjects conclude that azithromycin did not result in more or faster COVID-19 symptom improvement compared with placebo and had no meaningful benefit in preventing COVID-19 hospitalizations.[43,44]
    - Ivermectin[45]: In addition, inappropriate use of this anti-parasitic for COVID-19 is causing increased reports of severe illness to poison control centers and has prompted a CDC Health Advisory.[46]
    - Hydroxychloroquine/chloroquine: moderate-quality evidence suggests that these agents lack efficacy in reducing short-term mortality or need for hospitalization in patients with COVID-19[47]; in addition, serious cardiac events, including QTc prolongation, have been reported.[48]

There is much misinformation on the internet/social media. Pediatricians are encouraged to refer patients and families to reputable, up-to-date COVID-19 resources:

- National Institutes of Health NIH COVID-19 Treatment Guidelines
- Infectious Diseases Society of America IDSA Guidelines on the Treatment and Management of Patients with COVID-19 (see recommendation 14)
- AAP *Red Book* chapter: Coronaviruses, Including SARS-CoV-2 and MERS-CoV

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Table 1. SARS-CoV-2 Monoclonal Antibodies Authorized for Use in Eligible Children ≥12 Years of Age and Weighing ≥40 kg

Monoclonal Antibody (mAb)	COVID-19 Indication, per EUA	Dosage	Route of Administration	Additional Dosing Information	mAb Fact Sheet for Health Care Providers	mAb Fact Sheet for Patients (English and Spanish)
Sotrovimab	Treatment	500 mg	IV	Provide ASAP after positive SARS-CoV-2 test and within 10 days of symptom onset	• https://www.fda.gov/media/149534/download	• https://gskpro.com/content/dam/global/hcpportal/en_US/Prescribing_Information/Sotrovimab/pdf/SOTROVIMAB-PATIENT-FACT-SHEET.PDF • Sotrovimab Patient Fact Sheet (Spanish) - Emergency Use Authorization (FUA)
Bamlanivimab/ etesevimab[28]	Treatment[#], depending on geographic location and travel history[49]	700 mg/ 1400 mg	IV	Provide ASAP after positive SARS-CoV-2 test and within 10 days of symptom onset	• https://www.fda.gov/media/145802/download	• http://pi.lilly.com/eua/bam-and-ete-eua-factsheet-patient.pdf • http://pi.lilly.com/eua/span/bam-and-ete-eua-factsheet-patient-span.pdf
	PEP[#], depending on geographic location and travel history[49]	700 mg/ 1400 mg	IV	Provide ASAP after exposure to SARS-CoV-2 and within 96 hours to max of 7 days after exposure	• https://www.fda.gov/media/145802/download	• http://pi.lilly.com/eua/bam-and-ete-eua-factsheet-patient.pdf • http://pi.lilly.com/eua/span/bam-and-ete-eua-factsheet-patient-span.pdf
Casirivimab/ imdevimab	Treatment	600 mg/ 600 mg	IV (preferred), SC (alternative if IV not feasible or available)	Provide ASAP after positive SARS-CoV-2 test and within 10 days of symptom onset	• https://www.fda.gov/media/145611/download	• Fact Sheet for Patients, Parents, and Caregivers: Emergency Use Authorization (EUA) of casirivimab and imdevimab for COVID-19 (fda.gov) • Regeneron Recipient Fact Sheet Spanish Language (fda.gov)
	PEP	600 mg/ 600 mg	IV or SC	Provide ASAP and within 96 hours[*] to max of 7 days after exposure	• https://www.fda.gov/media/145611/download	• Fact Sheet for Patients, Parents, and Caregivers: Emergency Use Authorization (EUA) of casirivimab and

				A second dose of 300 mg/300 mg may be indicated for high risk individuals with ongoing SARS-CoV-2 exposure for >4 weeks who are not expected to mount an antibody response. This dosing may be repeated every 4 weeks for the duration of exposure.	Refer to PEP prescribing information for further details: https://www.regeneron.com/downloads/treatment-covid19-eua-preventing-medication-errors.pdf	imdevimab for COVID-19 (fda.gov) • Regeneron Recipient Fact Sheet Spanish Language (fda.gov)

ASAP indicates as soon as possible; EUA, Emergency Use Authorization; IV, intravenous; PEP, postexposure prophylaxis; SC, subcutaneous.

Bamlanivimab and etesevimab, administered together, are not to be used in states in which the combined frequency of variants resistant to these monoclonals is >5% or if the patient has traveled to a state with >5% resistance to this mAb in the preceding 2 weeks.[49]

*Time window for mAb prescribing from the phase 3 clinical trial was within 96 hours after positive SARS-CoV-2 diagnostic test result in index case.

Table 2. Subcutaneous (SC) Dosing and Administration of Casirivimab/Imdevimab[50]

	Initial Dosing	**Subsequent Dosing**
Casirivimab dose/imdevimab dose	**600 mg/600 mg**	**300 mg/300 mg**, if needed
Co-formulated vials	Withdraw 2.5 mL solution/syringe **into 4 separate syringes**	Withdraw 2.5 mL solution/syringe into **2 separate syringes**
Individual vials and dose packs	Casirivimab: withdraw 2.5 mL solution/syringe into **2 separate syringes** *plus* Imdevimab: withdraw 2.5 mL solution/syringe into 2 separate syringes For a total of **4 separate syringes**	Casirivimab: withdraw 2.5 mL solution/syringe into **1 syringe** *plus* Imdevimab: withdraw 2.5 mL solution/syringe into **1 syringe** For a total of 2 **separate syringes**
Administration instructions	Administer SC injections consecutively, at 4 different injection sites (thighs, upper arms, abdomen, but avoiding the 2 inches around the navel and waistline) Observe patient for at least 1 hour after injection	Administer SC injections consecutively, at 2 different injection sites (thighs, upper arms, abdomen, but avoiding the 2 inches around the navel and waistline) Observe patient for at least 1 hour after injection
Materials needed	3-mL or 5-mL polypropylene Luer lock syringes with Luer connection and 21-gauge 1½-inch transfer needles; 25-gauge or 27-gauge needle for SC injection	
Dispensing	Product is preservative free and should be dispensed immediately after preparation.	
Storage	Refrigerate unopened vials at 2°C to 8°C (36°F to 46°F) in the individual original carton to protect from light. Do NOT freeze, shake, or expose to direct light. Remove product from refrigerated storage and allow to equilibrate to room temperature for approximately 20 minutes before use.	

The COVID-19 clinical interim guidance provided here has been updated based on current evidence and information available at the time of publishing. Guidance will be regularly reviewed with regards to the evolving nature of the pandemic and emerging evidence. All interim guidance will be presumed to expire December 31, 2021, unless otherwise specified.