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GUIDELINES

Updated Guidance on Use and Prioritization of Monoclonal Antibody Therapy for Treatment of COVID-19 in Adolescents

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Background. Starting in November 2020, the US Food and Drug Administration (FDA) has issued Emergency Use Authorizations (EUAs) for multiple novel virus-neutralizing monoclonal antibody therapies, including bamlanivimab monotherapy (now revoked), bamlanivimab and etesivimab, casirivimab and imdevimab (REGEN-COV), and sotrovimab, for treatment or postexposure prophylaxis of Coronavirus disease 2019 (COVID-19) in adolescents (≥12 years of age) and adults with certain high-risk conditions. Previous guidance is now updated based on new evidence and clinical experience.

Methods. A panel of experts in pediatric infectious diseases, pediatric infectious diseases pharmacotherapy, and pediatric critical care medicine from 18 geographically diverse US institutions was convened. Through a series of teleconferences and web-based surveys, a guidance statement was developed and refined based on a review of the best available evidence and expert opinion.

Results. The course of COVID-19 in children and adolescents is typically mild, though more severe disease is occasionally observed. Evidence supporting risk stratification is incomplete. Randomized controlled trials have demonstrated the benefit of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2)-specific monoclonal antibody therapies in adults, but data on safety and efficacy in children or adolescents are limited. Potential harms associated with infusion reactions or anaphylaxis are reportedly low in adults.

Conclusions. Based on evidence available as of August 31, 2021, the panel suggests a risk-based approach to administration of SARS-CoV-2 monoclonal antibody therapy. Therapy is suggested for the treatment of mild to moderate COVID-19 in adolescents (≥12 years of age) at the highest risk of progression to hospitalization or severe disease. Therapeutic decision-making about those at moderate risk of severe disease should be individualized. Use as postexposure prophylaxis could be considered for those at the highest risk who have a high-risk exposure but are not yet diagnosed with COVID-19. Clinicians and health systems should ensure safe and timely implementation of these therapeutics that does not exacerbate existing healthcare disparities.

Key words. bamlanivimab and etesevimab; COVID-19; pediatric; REGEN-COV (casirivimab and imdevimab); sotrovimab.

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Note: Since completion of this guidance, the emergence of Omicron as the predominant SARS-CoV-2 variant causing infections in the US has made bamlanivimab/etesevimab and casivimab/imdevimab likely ineffective as treatment or post-exposure prophylaxis. Consideration of risk stratification for use of sotrovimab and other therapeutics remains appropriate.

The Coronavirus disease 2019 (COVID-19) pandemic caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) has been met with rapid development of novel therapeutics [1]. As new therapies become available for use, careful evaluation of evidence is essential to provide guidance for safe and effective use [2, 3]. Important components of the COVID-19 armamentarium are virus-neutralizing monoclonal antibodies (mAb), which are human or humanized antibodies administered by intravenous (IV) infusion or subcutaneous (SQ) injection that bind to virus or to infected cells to treat or prevent SARS-CoV-2 infection. The Food and Drug Administration (FDA) has active Emergency Use Authorizations (EUAs) for 3 products: bamlanivimab and etesevimab [4], casirivimab and imdevimab (REGEN-COV) [5], and sotrovimab [6]. Bamlanivimab was the first agent authorized for use in the United States under an EUA issued on November 9, 2020, but withdrawn on April 16, 2021, because of a sustained increase of resistant SARS-CoV-2 viral variants [7]. The combination product, bamlanivimab and etesevimab, was authorized on February 9, 2021, but it is currently authorized for use only in states, territories, and US jurisdictions in which the most recently published combined frequency of resistant variants is ≤5% [4]. Casirivimab and imdevimab (REGEN-COV) were authorized for use on November 21, 2020 [5]. The EUAs for casirivimab and imdevimab and for bamlanivimab and etesevimab were expanded to include the indication of postexposure prophylaxis (PEP) as of July and September 2021, respectively [4, 5]. The FDA issued an EUA for sotrovimab on May 26, 2021 [6]. Information on current availability and ordering for these mAb products is provided by the Department of Health and Human Services [8].

All of these mAb products are authorized for use in pediatric patients ≥12 years of age and weighing ≥40 kg who are at high risk for progressing to severe COVID-19 and/or hospitalization. For treatment, all mAb products must be administered within 10 days of symptom onset. For PEP, eligible individuals must (1) be incompletely vaccinated or not expected to mount an adequate immune response to vaccination and (2) have been exposed to an individual infected with SARS-CoV-2 or be at high risk of exposure due to SARS-CoV-2 transmission in an institutional setting (eg, long-term care facility). For the treatment of COVID-19, individuals must have a positive direct SARS-CoV-2 viral test, and COVID-19 must be mild to moderate, not requiring hospitalization or new/increased supplemental oxygen. It should be noted that administration is not precluded for those who are hospitalized for another reason but develop symptomatic COVID-19 during hospitalization. The criteria for defining those at high risk are defined identically in the EUAs for all of the mAb products and are discussed later. No mAb products are authorized for use in patients hospitalized or requiring supplemental oxygen therapy for COVID-19, but initial data have suggested benefits in seronegative adults being treated with supplemental oxygen [9]. Initial guidance on the use of these products was published by this group in January 2021 and is updated herein based on new evidence and expert consensus [10]. It is important to note that although immunization with an approved COVID-19 vaccine remains the most effective strategy for prevention of infection or severe disease, some adolescents may not mount an adequate immune response, and others may be exposed before vaccination is complete.

APPROACH

To update guidance on the use of mAb products for the treatment of mild to moderate COVID-19 or PEP in high-risk adolescents as authorized by the current EUAs, we re-convened a panel of experts in pediatric infectious diseases, pediatric infectious diseases pharmacotherapy, and pediatric intensive care medicine from 18 geographically diverse US institutions to evaluate the evidence for safety and efficacy in pediatric patients. This consensus statement has been reviewed and approved by all panelists and endorsed by the Pediatric Infectious Diseases Society, and it replaces previous guidance [10].

A statement of "recommend" reflects the panel's view that the evidence base for or against a therapy is sufficiently strong that departures from these recommendations could be viewed as outside the range of usual practice. A statement of "suggest" reflects the panel's view that there is weighting toward risk or benefit from the therapy. A statement of "consider" reflects the panel's uncertainty about the risk or benefit from the therapy.

GUIDANCE STATEMENT

Based on evidence available as of August 31, 2021, the panel suggests the following for *treatment* of adolescents who meet age, weight, and risk factor criteria under the EUAs (**Table 1**):

- The panel suggests the use of mAb products for the treatment of mild to moderate COVID-19 in adolescents at the highest risk of severe disease (see COVID-19 risk factor section later).
- The use of mAb products for the treatment of mild to moderate COVID-19 could be considered in adolescents with moderate risk of severe disease based on individualized risk assessment and shared decision-making.
- The panel does not suggest routine use of mAb products for treatment in adolescents at lower risk of severe disease.
- The use of mAb products as PEP could be considered in adolescents at the highest risk of severe disease following high-risk exposures (eg, household).
- The choice of product should take into consideration local epidemiology of SARS-CoV-2 variants and resistance.
- Early administration is advised for optimal clinical response. Clinicians and health systems should ensure the implementation of a system for safe and timely administration that does not exacerbate existing healthcare disparities.

Table 1. Summary of Recommendations for Administration of Monoclonal Antibodies

Risk for Severe COVID-19	Condition	Recommendation	
		Treatment	Postexposure Prophylaxis
Highest risk	• Obesity • Severe immunocompromise[a] • Medical complexity with respiratory technology dependence	Suggest use	Consider if high-risk exposure and unvaccinated or unlikely to mount an adequate response to vaccine
Moderate risk	• Mild to moderate immunocompromise[a] • Chronic respiratory conditions • Congenital heart disease • Sickle cell disease	Consider use	Insufficient evidence
Lower risk	• Diabetes • Chronic kidney disease	Suggest no routine use	

[a]Refer to text for examples of severe or mild to moderate immunocompromise.

RATIONALE

This guidance statement is based on balancing the beneficial impact on mortality and hospitalizations seen in adult studies, against the generally lower risk of progression to severe disease in adolescents—even among those with risk factors specifically mentioned in the EUAs—and the scarcity of pediatric evidence. While the FDA has authorized use for adolescents at high risk of severe COVID-19, there are limited data to support such a designation among adolescents belonging to many of the risk groups mentioned in the EUA. While the safety profile of these agents in adult studies is deemed acceptable, they have not been studied systematically in younger age groups; furthermore, whether these agents provide protection against multisystem inflammatory syndrome in children (MIS-C) or post-COVID conditions is unknown.

The intent of this guidance is not to suggest routine use in all adolescent patients or preclude use in any specific group but to clarify that pediatric use should be guided by best available evidence on the potential trajectory of SARS-CoV-2 infection in an individual adolescent. The guidance should supplement and not replace instructions from state health departments on the use of these products.

EVIDENCE SUMMARY

Available clinical evidence for the benefit of these agents from phase III studies is summarized later, with an emphasis on products currently available in the United States.

The authorization for bamlanivimab and etesevimab was based on an interim analysis of the phase 3 Blocking Viral Attachment and Cell Entry with SARS-CoV-2 Neutralizing Antibodies (BLAZE-1) study, which included 1035 ambulatory patients with mild to moderate COVID-19 at risk for progression to severe disease. The mean (±SD) age of the patients was 53.8 ± 16.8 years. The composite outcome of hospitalization or death occurred in 2% of patients (11/518) in the mAb arm vs 7% of patients (36/517) in the placebo arm, corresponding with a 70% risk reduction of hospitalization or death ($P = .0004$) [4, 11].

The efficacy of casirivimab and imdevimab (REGEN-COV) for COVID-19 treatment was tested in a phase 3 placebo-controlled study [COV-2067(NCT04425629)] that recruited 4567 participants while simultaneously comparing dosing regimens [12]. The efficacy analysis included participants aged ≥18 years who had a positive SARS-CoV-2 PCR no more than 72 hours before randomization, symptom onset no more than 7 days before randomization, and ≥1 risk factor for progression to severe COVID-19. The primary outcome was COVID-19-related hospitalizations or death from any cause. At baseline, in all randomized subjects with ≥1 risk factor, the median age was 50 years (with 13% of subjects ≥65 years of age). Two dosing arms were studied: 1200 mg (casirivimab 600 mg and imdevimab 600 mg) and 2400 mg (casirivimab 1200 mg and imdevimab 1200 mg). In the 1200-mg dosing arm, the primary outcome was reported in 1.0% in the intervention arm compared with 3.2% in the placebo arm (7/736 vs 24/748, $P = .0024$), a 2.2% absolute reduction, and a 70% relative reduction in death and/or hospitalization. These results were comparable to those in the 2400-mg dosing arm, where the primary endpoint was reported in 1.3% of participants compared with 4.6% in the placebo group (18/1335 vs 62/1341, $P < .0001$). Serious adverse events (SAEs) were more common in the placebo group (4%) compared with the 1200-mg group (1.1%) or 2400-mg group (1.3%). In pooled phase 1/2/3 analysis, infusion-related reactions of grade 2 or higher severity were observed in 10/4206 (0.2%) of those who received REGEN-COV at the authorized dose or a higher dose [5]. Previous studies reported a greater time-weighted average reduction in viral load by day 7 for those treated with casirivimab and imdevimab vs placebo (difference 0.56 $\log_{10}$ copies/mL), with those participants who had a higher viral load and seronegative status at baseline showing the greatest reduction [13]. An SQ formulation has been studied but should only be used for the treatment of COVID-19 when IV administration is not feasible and would result in treatment delay. The mortality benefit noted in outpatients has been preliminarily replicated in adults patients who are hospitalized for COVID-19, treated with supplemental oxygen, and seronegative

at admission. Among seronegative patients, 396 (24%) of 1633 patients allocated to casirivimab and imdevimab and 451 (30%) of 1520 patients allocated to usual care died within 28 days (rate ratio 0.80, 95% confidence interval [CI] 0.70-0.91; P = .0010) [9].

Sotrovimab efficacy was evaluated in the phase 3 COMET-ICE trial (ClinicalTrials.gov Identifier NCT04545060), which recruited 583 adult outpatients with mild to moderate COVID-19 who were at high risk for progression to severe disease and/or hospitalization [6]. Participants had a median age of 53 years. The primary endpoint, defined as the proportion who were hospitalized (for ≥24 hours) or died within 29 days of randomization, was higher in the placebo arm (21/292 [7%]) compared with the intervention arm (3/291 [1%]) (P = .002), translating to a 6% absolute reduction and an 85% relative reduction in hospitalizations or death [6, 14].

Common features of all of these treatment trials are the older ages of adult participants and the higher rates of hospitalization and death among participants when compared with adolescents with acute COVID-19, even within high-risk groups. While the EUAs allow for a 10-day window from symptom onset to administration, time to therapy for patients in these trials was typically shorter, within 3 days of the positive test. Certain risk factors of particular interest for pediatric patients (eg, neurodevelopmental disorders, genetic syndromes, or medical-related technological dependence [eg, tracheostomy, gastrostomy, or positive-pressure ventilation not related to COVID-19]) were poorly represented in recruited patients in all of these trials. The most significant type of adverse event reported across the trials was infusion reactions, and these were rare and generally mild.

The evidence for use for casirivimab and imdevimab as PEP was a randomized, double-blind, placebo-controlled phase 3 trial of asymptomatic individuals ≥12 years of age exposed to a SARS-CoV-2 reverse transcriptase polymerase chain reaction (RT-PCR)-positive household contact (index case) within the previous 96 hours [15]. Study participants had to be SARS-CoV-2 negative at entry and live with the index case during the 29-day follow-up period. The study group received casirivimab 600 mg plus imdevimab 600 mg (four 2.5-mL SQ injections). Casirivimab plus imdevimab significantly reduced the risk of symptomatic SARS-CoV-2 infection compared with placebo (81.4% relative risk reduction: 11/753 [1.5%] vs 59/752 [7.8%] with odds ratio [OR] of 0.17, P < .001) and also reduced hospitalizations (4 in placebo vs none in treatment arm) in the primary analysis of 1505 participants (mean age was 42.9 years). Adolescents were not well-represented in this trial (n = 67) [15].

Authorization of use of bamlanivimab and etesevimab as PEP was based on a randomized, double-blind, placebo-controlled phase 3 trial of a single 4200-mg dose of bamlanivimab (without etesevimab) to prevent symptomatic SARS-CoV-2 infection within 8 weeks of randomization among residents and staff, negative at baseline for SARS-CoV-2 infection and serology, in 74 US skilled nursing and assisted living facilities with ≥1 confirmed index case. The median age of the 966 subjects (484 in the bamlanivimab group and 482 in the placebo group) was 53.0 (range 18-104) years. Bamlanivimab significantly decreased the incidence of COVID-19 compared with placebo (8.5% vs. 15.2%, for an absolute risk difference of −6.6 [95% CI −10.7 to −2.6] percentage points; OR 0.43, P < 0.001) [16].

Ongoing reviews of the data supporting the use of these products are available from the National Institutes of Health and the Infectious Diseases Society of America [17, 18].

Defining a Risk-Based Approach for Monoclonal Antibody Administration in Adolescents

Under the EUAs, mAb products are authorized only for patients with mild to moderate COVID-19 who are at high risk for progression to severe COVID-19, including hospitalization or death. Risk factors specifically mentioned in the EUAs include older age (eg, ≥65 years); obesity or overweight (body mass index [BMI] ≥ 25, or ≥85th percentile for age and gender in adolescents); pregnancy; chronic kidney disease; diabetes; immunosuppressive disease or immunosuppressive treatment; sickle cell disease; congenital or acquired heart disease; neurodevelopmental disorder; medical-related technology dependence; and asthma, reactive airway disease, or other chronic respiratory disease that requires daily medication for control. However, the EUAs state that authorization is not limited to these criteria.

In general, children and adolescents are at low risk for hospitalization or severe disease with COVID-19, with approximately 2% of infected patients requiring hospitalization [19]; however, among hospitalized patients, intensive care unit (ICU) admission rates in children are similar to adults (~30%) [20]. Among hospitalized adolescents, nearly one-third have required ICU admission, and 5% have required invasive mechanical ventilation, even though mortality has been uncommon [21]. However, the impact of emerging variants or the presence of co-infections on the severity of pediatric disease is not yet established. Because the absolute risk of adverse outcomes with SARS-CoV-2 infection is much lower in children and adolescents, the benefit of mAb therapy is likely greatest in those with the highest risk of severe COVID-19.

We evaluated available evidence on conditions that might be associated with increased risk of severe disease in adolescents. Severe disease was not defined in the EUAs; in our analysis, we considered "severe COVID-19" as a disease requiring supplemental oxygen or ICU admission [10, 22]. We reviewed data from published literature, where available, and registry data if sufficient published data were lacking. With respect to chronic respiratory conditions, we considered asthma separately from other conditions (eg, cystic fibrosis). We interpreted "medical device dependence" to be a surrogate for "medical complexity" as discussed in our earlier guidance although this may not hold true for some patients, such as those with only gastrostomy tubes. Due to relative rarity of some of these conditions, clinical experience of treating patients with COVID-19 by panel members was also taken into consideration.

Conditions Associated With Highest Risk of Severe COVID-19.

Conditions that predispose most strongly to severe COVID-19 in adolescents include obesity, medical complexity with respiratory technology dependence, and specific severe immunocompromising conditions. Based on available evidence, among the population authorized for use, adolescents with these underlying conditions are likely to benefit the most from mAb administration.

Obesity.

Currently available evidence suggests that obesity (BMI ≥ 95th percentile for age and gender) is an independent risk factor for severe COVID-19 in adolescents. Obesity is well characterized as a risk factor for severe COVID-19 in adults and is a prevalent comorbidity in national cohorts of pediatric COVID-19 hospitalizations with both acute infection and MIS-C [21, 23]. In a large cohort of 577 children with severe COVID-19, 36.2% were obese [24], while a recent national estimate of obesity prevalence in adolescents was 21.2% [25]. In a multistate cohort of 281 children and youth, multivariable analysis showed obesity to be independently predictive of severe respiratory disease (OR 3.39, 95% CI 1.26-9.10; $P = .02$) [26], aligning with previous observations from single-center studies [27].

Medical Complexity With Respiratory Technology Dependence.

There is evidence that children and adolescents with medical complexity, defined as multiple underlying conditions (eg, genetic or neurodevelopmental syndromes, often with associated respiratory technology dependence), are at increased risk of hospitalization or severe disease following infection with SARS-CoV-2 [28, 29]. A cross-sectional analysis of an all-payer database that included 43 465 children with COVID-19 across 900 US hospitals showed that children with medical complexity, as a group, were at significantly greater risk for both hospitalization and progression to severe disease (risk ratio [RR] 7.86, 95% CI 6.91-8.95 and RR 2.86, 95% CI 2.47-3.32, respectively) [28]. Children with neurodevelopmental disorders had a 64% greater risk of hospitalization (RR 1.64, 95% CI 1.47-1.88), yet when hospitalized, they had a significantly lower risk of developing severe illness (RR 0.83, 95% CI 0.70-0.98) than other hospitalized children [28], suggesting that the presence of often multiple comorbidities in children with neurodevelopmental delay could be potentially driving earlier hospitalization and more aggressive therapy that may minimize severe outcomes. These children have also featured prominently in multicenter cohorts of ICU admissions [30, 31].

Severe Immunocompromise.

Immunocompromising conditions that predispose to decreased neutralizing antibody production are associated with failure of viral clearance and severe or persistent disease [32, 33]. Correspondingly, the efficacy of mAb therapy appears to be higher in adults who are slow to produce endogenous neutralizing antibodies [13]. While outcomes are not universally poor for immunocompromised children with SARS-CoV-2 infection [34, 35], patients receiving high-intensity chemotherapy for newly diagnosed or relapsed leukemia, as well as those with profound antibody deficiency or very low lymphocyte counts (especially <100 cells/μL), appear to be at highest risk [36–40] and should be prioritized for mAb administration. Chimeric antigen receptor (CAR) T-cell therapy causes prolonged B-cell aplasia and resulting hypogammaglobulinemia following cell infusion, placing patients potentially at risk for prolonged and severe COVID-19 [41].

Data on the impact of COVID-19 on patients with primary immune deficiencies include primarily adult patients, which may overestimate the risk of severe disease for children, but the rate of severe outcomes seems higher compared with the general population [42, 43]. Based on clinical experience and limited published data, patients with severe antibody deficiency or lymphocyte dysfunction appear to be at the highest risk, and mAb therapy for adolescents with these conditions is suggested [44].

Limited information is available on the impact of SARS-CoV-2 in pediatric hematopoietic cell transplant (HCT) recipients. In cohorts of predominantly adult HCT recipients, overall mortality was 30% at 30 days after the diagnosis of COVID-19 [45]. Older age (>50), male sex, and COVID-19 within 12 months of transplantation are associated with a higher risk of mortality in allogeneic HCT recipients, and a diagnosis of lymphoma is associated with a higher risk of mortality in autologous HCT recipients. Pediatric mortality appears to be significantly lower at ~7% [46, 47]. However, although pediatric case series have shown good outcomes in some patients, some developed respiratory failure or other serious complications [48, 49]. Additionally, pediatric HCT recipients, especially those who are early post-transplant (eg, <100 days) or receiving high levels of immunosuppressive therapy (eg, active immunosuppression for graft vs host disease), share many characteristics associated with high risk of severe COVID-19, including T-cell deficiency or dysfunction, and decreased antibody production. Therefore, they are considered to be at high risk for the purposes of considering mAb therapy.

Conditions Associated With Moderate Risk of Severe COVID-19.

Monoclonal antibody use for children with risk factors in this category could be considered based on individualized risk assessment and shared decision-making among subspecialists, primary care providers, caregivers, and patients. Factors to consider in decision-making for each group include the stage and severity of the underlying condition and the presence of multiple risk factors in the same patient.

Chronic Respiratory Conditions (eg, asthma, cystic fibrosis, and chronic lung disease).

Asthma is prevalent in hospitalized children and adolescents with COVID-19 [21], but studies that have specifically analyzed asthma as a risk factor for severe pediatric COVID-19 have not

shown a consistent association with worse outcomes [26, 50]. The incidence of asthma exacerbations has also decreased substantially during the pandemic. In a single-center study of 454 pediatric patients with SARS-CoV-2 infection, asthma was an independent predictor of hospital admission and respiratory support (adjusted OR 2.2; $P = .04$) [29]. The lack of data on specific measures of underlying asthma severity or control limits inference from these studies, and the role of allergic asthma at all severity classifications as a risk factor for severe COVID-19 in adults is also not established [51]. Based on available data, moderate to severe asthma or poorly controlled disease could be a potential risk factor for pediatric hospitalization with COVID-19, particularly if accompanied by another risk factor (eg, obesity). There are limited data on COVID-19 in patients with other chronic respiratory diseases. In a case series of 105 children with cystic fibrosis, SARS-CoV-2 infection was most often associated with mild illness in those who did not have preexisting severe lung disease [52]. When evaluating individual patients with chronic respiratory conditions for mAb therapy, it is reasonable to take into consideration the severity of underlying lung disease.

Congenital or Acquired Heart Disease.

Data on the course of COVID-19 in children with congenital heart disease are limited, but these patients have been represented in case series of severe diseases [24, 53]. While severe outcomes seem rare, the presence of a genetic syndrome has been shown to increase the risk of severe disease among those with congenital heart disease [53]. An analysis of administrative data suggested cardiac and circulatory congenital anomalies to be an independent risk factor for severe disease (adjusted RR 1.72, 95% CI 1.48-1.99) [28]. A triaged approach to estimating risk for severe COVID-19 in this group has been advised by the American College of Cardiology, with the highest risk in patients with single-ventricle physiology after Fontan operation, those with chronic cyanosis and depressed ventricular function, individuals with severe pulmonary hypertension, immunocompromised patients (including those who have undergone heart transplantation), infants with unrepaired significant congenital heart disease, and older adolescents with congenital heart disease complicated by coronary artery disease or systemic hypertension [54].

Sickle Cell Disease.

Severe COVID-19 has been reported in adults with sickle cell disease, but outcomes in pediatrics are variable [55]. Monoclonal antibodies could be considered for patients who have severe sickle cell disease, specifically those with a history of acute chest syndrome, recurrent pain crises, other end-organ damage such as renal or cardiac dysfunction, or other risk factors such as obesity [56].

Other Immunocompromising Conditions.

Based on observational studies, most pediatric patients with cancer who develop SARS-CoV-2 infection seem overall to be at low risk of severe disease [57, 58] although their risk is higher than that of the general pediatric population [35, 59]. These less severe outcomes may be driven partly by the predominance of patients with mild to moderate immunosuppression in these studies, such as patients with leukemia in remission, or solid tumors not receiving intensive chemotherapy [57]. Compared with patients with hematologic malignancies receiving more intensive therapy, these patients are likely able to rapidly generate a sufficient immune response to the virus [60].

Compared with adult solid organ transplant recipients (SOTRs), pediatric SOTRs seem to be at lower risk for morbidity and mortality following COVID-19 infection. Multicenter series of pediatric SOTRs with COVID-19 have shown low rates of severe respiratory disease, ICU admission, or death due to COVID-19 [61, 62]. While individual cases of severe COVID-19 have been reported among pediatric SOTR, and comorbidities such as obesity and/or severe immunosuppressive regimens (eg, lymphocyte-depleting therapy) may exacerbate risk, current evidence suggests that consideration of monoclonal therapy should be individualized for pediatric SOTRs.

Conditions With Lower Risk of Severe COVID-19.

Administration of mAb products is not suggested on a routine basis for patients in this category. While this statement does not preclude administration to any patient group, hospitals should ensure that equitable supply and resources exist to offer mAb therapy to children with the more well-established risk factors above before expanding to other populations with less defined risk for COVID-19.

Diabetes Mellitus and Chronic Kidney Disease.

Data are limited on the association between diabetes mellitus (DM), both type I and II, and severe pediatric COVID-19. Evidence is mixed on whether patients with DM are at increased risk of hospitalization or outcomes such as ICU admission or death [28, 63]. Furthermore, associations between diabetic ketoacidosis and SARS-CoV-2 infection have been observed, which complicates inference from studies that report a higher rate of hospitalization or severe outcomes in children with DM [64]. It is unclear whether pediatric DM predisposes to severe respiratory outcomes in the absence of additional risk factors (eg, obesity) and if so, whether degree of glycemic control modifies this relationship or mAb therapy would mitigate the risk. Evidence suggesting that chronic kidney disease or dialysis is an independent risk factor for severe COVID-19 in children in high-income countries is limited [65].

COVID-19 and Healthcare Disparities

The current pandemic has highlighted longstanding disparities in healthcare, with a disproportionately negative effect on communities of color. Adults and children of racial and/or ethnic minority groups have, on average, a SARS-CoV-2 infection rate

that is >4 times higher than that non-Hispanic whites [66–68]. Disparities in disease severity have also been well documented. Several studies have revealed that, on average, 3 out of every 4 children hospitalized with COVID-19 and/or MIS-C come from racial or ethnic minority groups [69, 70]. Given these disparities, equitable distribution of novel therapeutics such as mAb products is especially important and will require the investment of human resources, space, and informatics support by hospital leadership. Specific efforts to improve equitable distribution to minority groups could include active screening of all newly positive COVID patients or educating primary care clinicians in community clinics on referral criteria.

SARS-COV-2 Variants, Resistance, and Choice of Specific Monoclonal Antibody Product

The presence of certain substitutions or combinations of substitutions in the SARS-CoV-2 spike protein can decrease the efficacy of specific mAb products for COVID-19, and resistance to these therapeutic agents is a consideration when designating a SARS-CoV-2 variant to be a variant of concern. Details on in vitro resistance are included in the EUAs. Up-to-date information on circulating variants and implications for therapy are available from the Centers for Disease Control and Prevention (CDC) [71]. Decreased susceptibility for certain variants has been noted for casirivimab and imdevimab, bamlanivimab alone and for bamlanivimab and etesevimab, thereby rendering that these products are no longer reliable options in regions where these variants are common. Sotrovimab, which targets an epitope in the receptor-binding domain of the spike glycoprotein that does not overlap with the ACE-2-binding site, appears to be effective against currently circulating variants.

Use for Postexposure Prophylaxis

As discussed above, evidence on the efficacy of mAb products for PEP is derived from largely adult data on the use of casirivimab and imdevimab to prevent symptomatic disease. The number of adolescents enrolled in the trial was small, and considering the higher rates of mild and asymptomatic disease in adolescents, the absolute risk reduction for this endpoint may be lower in adolescents. Exposures to SARS-CoV-2 also vary in their propensity to cause infection, with prolonged exposures in household and other communal settings associated with the highest risk of secondary transmission [72]. While evidence currently does not support the universal use of mAb products as PEP in adolescents who qualify under the EUA, casirivimab and imdevimab or bamlanivimab and etesevimab for PEP should be considered, supposing predominant circulating variants are susceptible, in those adolescents with the highest risk of severe disease and who are exposed recently in settings where there is a high risk of transmission such as prolonged indoor exposure without the use of adequate personal protective equipment. The expertise of infection prevention and control professionals should be solicited to adjudicate the risk of specific exposures in healthcare settings. Patients who are fully vaccinated against SARS-CoV-2 are not eligible for PEP unless they are not expected to mount an adequate immune response to SARS-CoV-2 vaccination.

Other Considerations

It is imperative that pediatric-specific data for use of mAb therapy are collected. In weighing the risk-benefit ratio across all risk factors, there is still clinical equipoise for preferential enrollment in controlled clinical trials for lower and moderate risk populations when available for these products. Since currently available vaccines largely retain effectiveness for dominant variants in the United States against severe disease and hospitalization in adults [73], the risk of severe breakthrough disease in completely vaccinated, non-immunocompromised adolescents is likely low. While providers can use vaccination status to adjudicate the risk of severe disease in vaccinated high-risk adolescents, current evidence is insufficient to suggest for or against the use of mAb products for the treatment of breakthrough infections in this population.

CONCLUSIONS AND RESEARCH PRIORITIES

Based on current data on safety and efficacy, mAb treatment for mild to moderate COVID-19 is suggested for SARS-CoV-2-infected adolescents who are at the highest risk of hospitalization or severe disease and could be considered in those with moderate risk. The use of mAb products for PEP could be considered in adolescents who have the highest risk of severe disease and are exposed in settings associated with a high risk of transmission. Routine use of mAb products in all adolescents with potential risk factors is not recommended as data specifically supporting safety and efficacy in children or adolescents remain limited. More research is needed to identify pediatric patients at high absolute risk of severe COVID-19 and to determine the impact of mAb therapies in this population. The use of these products in younger children with risk factors who are not currently eligible under the EUA also needs to be studied. This guidance will be reevaluated as more evidence becomes available.

Notes

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