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COVID Commentary

SARS-CoV-2 Monoclonal Antibodies in Children: Ethical Considerations

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ABSTRACT

The use of monoclonal antibodies in children with certain conditions and at high risk for severe COVID-19 has been approved by the US Food and Drug Administration under the Emergency Use Authorization mechanism of the Federal Food, Drug, and Cosmetic Act. No data on the tolerability or efficacy of these therapies in persons <18 years of age are available; there is risk. Whether they will work is unknown, but they could. A disproportionate number of these children who meet the criteria for treatment with mAbs are from communities of black, Native American, and other race. How should health systems, hospitals, and clinicians balance the tensions between being seen as experimenting with an untested drug as opposed to withholding a potentially lifesaving treatment? This article identifies, analyzes, and makes recommendations on the methods by which health systems, hospitals, and individual clinicians can ethically balance these tensions. (Clin Ther. 2021;43:e157–e162.) © 2021 Elsevier Inc.

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INTRODUCTION

An interim analysis of data from the BLAZE-1 study (Effect of Bamlanivimab as Monotherapy or in Combination With Etesevimab on Viral Load in Patients With Mild to Moderate COVID-19),1 an ongoing Phase II trial of the efficacy and tolerability of bamlanivimab + etesevimab in adults with recently diagnosed mild to moderate coronavirus disease 2019 (COVID-19) in the outpatient setting, has demonstrated a reduction in progression to related hospitalizations. Of participants who received bamlanivimab + etesevimab combination therapy, only 0.9% required emergency department visits and hospitalization compared to 5.8% in the placebo group.1 Similarly, an interim analysis of the data from a trial of a monoclonal antibody (mAb) cocktail, casirivimab/imdevimab,* demonstrated a lower rate of subsequent COVID-19-related medically attended visits, at 3% of those who received REGN-COV2 versus 6% receiving placebo.2 While these findings were preliminary and showed modest effects in reducing progression to severe disease, these drugs may be beneficial for high-risk patients and may reduce the burden on the health care system, particularly given that other therapeutic options are limited.

*Trademark: REGN-COV2 (Regeneron Pharmaceuticals Inc, Tarrytown, New York).

Both products have been approved by the US Food and Drug Administration (FDA) under the Emergency Use Authorization (EUA) mechanism of the Federal Food, Drug, and Cosmetic Act for use in children 12 to 17 years of age and of >40 kg body weight.3 The clinical eligibility criteria include several high-risk pediatric chronic conditions despite both agents lacking evidence of efficacy in those <18 years of age. The Infectious Diseases Society of America and the Pediatric Infectious Diseases Society have recommended against the routine use of mAbs in children (but with consideration in individual cases of high-risk patients evidenced by pediatric-specific data),
and the National Institutes of Health has not made recommendation for or against its use in children due to insufficient data.3,4 These 3 organizations have not fully opposed the use of mAbs in children.

This situation is complex, and ethical considerations might differ between the federal, state, and hospital levels.5–7 States are allocating mAbs under the EUA (Figure 1) for use in the treatment children aged 12 to 17 who test positive for and are symptomatic with COVID-19, with no available data from pediatric trials but with possible expected benefit, raising 2 important and ethically challenging questions for health care systems, hospitals, and clinicians: (1) Should a treatment with preliminary data on tolerability and efficacy from studies exclusively in adults be given to children?; and (2) If so, how does one balance risk and benefit, equity and harm, while striving for trustworthiness? This article identifies, analyzes, and makes recommendations on organizational and individual clinicians’ obligations in prescribing mAb therapies for the treatment of COVID-19 in children.

**DETERMINING UTILITY IN PEDIATRICS**

The EUA lists comorbidities for eligibility for treatment with mAbs in the 12- to 17-year age group (Figure). Chronic conditions associated with COVID-19–related hospitalization in children include technology dependence, obesity, immune suppression/malignancy, neurologic disorders, cardiac disease, and chronic lung disease.3,4,8,9 However, pediatric reports on the impact of these risk factors have varied, limited by fewer patients and lower absolute risk than in adult studies.6 Furthermore, many of the descriptors are vague. For example, technology dependence is a spectrum, from intermittent use of a feeding pump to total dependence on a mechanical ventilator, and immune suppression encompasses a range of conditions.

Diagnoses associated with hospital admission, such as respiratory failure, may not reflect COVID-19 severity, as COVID-19 diagnosis may not be the primary driver of hospitalization in children with chronic medical conditions. It may be difficult to distinguish disease progression or complication from COVID-19 severity. Thus, risk stratification for progression to severe disease in children is inherently difficult. How the perceived benefits of mAbs in children are balanced with the risks is unclear. A national clinical trial would be ideal to ensure adequate patient protections, tolerability, equitable access, and informed consent. Absent this, hospitals and state departments of health will have to carefully balance risk and benefit.

**OBLIGATIONS WITH ALLOCATION**

Children’s hospitals or entities that will be distributing and administering mAb therapy to eligible children are confronted by a difficult decision of whether to participate. Children do not progress to severe disease as often as adults, but serious morbidity and mortality are possible, and thus potential individual and community benefits exist.

It would be reasonable to not participate, from an ethical stance, given the lack of data in children; the
potential for harm; and the positions of Infectious Diseases Society of America, Pediatric Infectious Diseases Society, and National Institutes of Health; the risks and burdens may outweigh the benefits in some areas. New and innovative therapies require a delicate balance between beneficence and non-maleficence (do no harm). If a hospital takes the stance that mAbs should not be administered in children due to insufficient benefit over risk, then they have no ethical obligation to refer elsewhere and must make this stance known to their respective departments of health. However, some patients followed up by pediatric specialists may be >18 years of age and might benefit, and efforts to assist these patients in gaining access to mAbs should be made.

There are also many logistical challenges. Infusion centers will need to be set up, requiring physical and technological resources. Children receiving mAbs will need to be fully assessed, including a medical history and physical examination. If primary health care systems choose not to participate, some children who might benefit from receiving a mAb will have to go to an unfamiliar institution. These drugs must be administered at facilities that have the capacity to safely monitor pediatric patients during and after infusion and to respond to any potential adverse reactions, including anaphylaxis. As mAbs are funded and allocated through federal and state public health agencies, children may be referred from other facilities or regions, and full medical records may not be available. Adherence to distancing and mitigation strategies may be challenging. COVID-19–positive children will be accompanied by parents or guardians who also may be infected or have been exposed.

Given the amount of resources this administration will require, the lack of data in children, and the documented benefit of mAbs in the adult population, it would be reasonable to choose not to allocate them to children. If these challenges preclude a hospital from participating in allocation despite a belief in some benefit in children, then the hospital is obligated to consider whether this decision will prohibit access by their pediatric patient population, particularly if other centers are not offering infusion in children.

Given the disparate effects of COVID-19 on certain communities, there is a need to consider how the principle of justice is applied. While Hispanic/Latino and black children make up 25% and 14% of the US child population, respectively, and white children, 50%,10 the proportion of children progressing to disease severe enough to require intensive care unit (ICU) admission is inverse. According to the Virtual Pediatric Systems (VPS) COVID-19 dashboard, as of March 22, 2021, discharge surveys for reporting North American pediatric ICUs showed that 26% of COVID-19 patients were white, 27% were black, and 35% were Hispanic/Latino.11 This trend is similar to results published in 2020.12

If a hospital chooses to participate in allocation, it has an obligation to not only their patients but also their state department of health, who is trusting them to allocate mAbs to the public. This allocation requires hospitals to consider a unique set of duties, notably, whether individual clinicians within the hospital has a duty to offer it (patient–provider relationship), and whether they should strictly adhere to the EUA, which may not represent the actual population of children progressing to severe illness (hospital–community relationship).

Clinicians are not ethically obligated to provide a treatment that is nonstandard. However, as with other recommendations on preventing and treating COVID-19 during the pandemic, standards of therapy have rapidly evolved and the burden of scientific proof is lower than normal. When there are questions about benefits, and reasonable people might choose either option, it becomes the obligation of clinicians to provide adequate information on the risks and benefits and the context in which those risks and benefits were determined for a child, and to make a recommendation, but also to ultimately respect a parent’s decision.

Another ethical obligation of clinicians is to assist families with understanding the decision to treat (transparency), including providing information on studies and their limitations, and on EUAs. The reason for transparency is not only ethical but practical. In the context of an EUA without data in children, mAbs may appear to be experimental in the eyes of patients and their parents. Given the lack of data on tolerability and efficacy in children, there is an important tension between using an unproven, but potentially beneficial, therapy (innovation), and withholding it from those who might benefit (exclusion). An improper balance or lack of appreciation of this tension may lead to a hospital and its clinicians to be viewed as untrustworthy.
On one side of this tension, a hospital might appear as experimenting in populations that historically have lower trust in medical and scientific institutions due to a history of racism, abuse, and mistreatment. COVID-19-related hospitalizations and the chronic medical conditions listed in the mAb eligibility criteria of the EUA disproportionately affect black, Native American, and Hispanic/Latino children. Yet while Hispanic/Latino patients composed 43% and 56% of the patients in the BLAZE-1 and REGN-COV2 trials, respectively, black patients made up roughly 7% and 13%.1,2 On the opposite side of the tension, a hospital could be seen as being exclusionary if it denies minority populations access to a potentially beneficial therapy, or if the therapy is distributed inequitably.

To balance this tension, transparency emerges as a hospital's *prima facie* obligation to meet the duty of trustworthiness.13 A hospital must be transparent about the limitations of the data available. When families are apprehensive and information is being disseminated rapidly—and not always reliably or comprehensibly—hospitals must manage these complicating factors and be steadfast in their dedication to ensuring appropriate transparent consideration of data on treatments. Clinicians must provide knowledge and recommendations to each individual patient consistent with shared decision-making norms.

**RECOMMENDATIONS**

Clinical eligibility for treatment with mAbs in pediatric patients must be developed not solely based on the EUA but supplemented with systematically collected data from within each organization or region on which 12- to 17-year-olds are progressing to severe disease, what the common comorbidities are, and who will most likely benefit. Eligibility criteria, education, and outreach should prioritize minority communities, which have borne the brunt of the COVID-19 epidemic.

If a children's hospital chooses to allocate a mAb to the community, it is as a public resource and it must be offered to all children who fit carefully thought-out eligibility criteria developed specifically for the pediatric population most likely to benefit, and ideally in conjunction with other pediatric facilities in the state. Mandating clinicians to offer mAbs to all who fit the agreed upon eligibility criteria may seem intrusive to individual obligations clinicians feel towards their patients and professional autonomy. Clinicians may feel conflicted given the lack of efficacy and tolerability data. This feeling is reasonable. But their obligations have not disappeared. Clinicians should offer their opinion and recommendation to families and weigh the risks and benefits in each child, even if they advise parents against use of the treatment. Another, more burdensome, option is convening *ad hoc* discussions between specialists and primary care clinicians to determine the benefit and risk prior to offering treatment with an mAb. Absent data from a national pediatric clinical trial in conjunction with allocation, hospitals and departments of health should treat mAb infusions for COVID-19 as a clinical trial in order to ensure ethically acceptable tolerability, access, and informed consent.

Hospitals and clinicians must consider the potential power shift with regard to parents' concerns about their children progressing to severe disease, and must ensure that they have scrutinized the EUA criteria to meet their ethical and clinical obligations to patients in conjunction with their departments of health to in turn ensure consistency with other pediatric infusion centers. Given the broad criteria of the EUA, health care systems and children's hospitals should convene workgroups to further clarify eligibility criteria. Discussion between specialists about each patient may be needed for assessing risks and benefits. Criteria should be tailored using clinical data from institutions or regions. Once the criteria are set, mAbs must be offered equally to all patients meeting those criteria, with an equitable amount of time for the decision-making process shared by the patients/parents and their clinicians.

There is a clear lack of data on the tolerability and efficacy of mAbs in children, a likely high number needed to treat, and the important consideration of a potentially greater risk from untested therapies than from COVID-19 itself in the pediatric population. There may be a reasonable utilitarian argument, from a public health standpoint, for diverting all mAb supplies to the adult population, given the likely greater benefit, especially as supply becomes limited. It appears that an amount is held specifically for allocation to children's hospitals; however, the guidance from the National Governors Association has not addressed whether allotments are specific to populations or allocated based on need.14 Orders for mAbs are placed through the federal government; utilization data are required, and subsequent orders are subject to previous orders and utilization.15 Scare resources should generally
maximize benefit by going to those in greatest need and most likely to benefit the most; however, there does not appear to be a limited supply of mAbs so far, possibly due in part to a low demand, and so this argument is currently ethically unsupportable.16

When offering mAb therapy in children, pediatric health care providers will likely identify parents or grandparents concurrently having COVID and high-risk conditions. Certainly some of those adults will be eligible for mAb therapy but may experience language-, socioeconomic-, or race-based construct barriers to access to care. To address this ethical concern, formal processes for referring ill family members to a non-pediatrician health care provider should be developed.

Hospitals and clinicians need to move away from asking why certain populations do not trust them and toward striving to be trustworthy.17 mAbs may pose difficulty to children’s hospitals with regard to balancing competing priorities and children’s best interests.

AUTHOR CONTRIBUTIONS
Drs. Wolfe and Patel conceptualized the work, drafted the initial manuscript, and reviewed and revised the manuscript. Both of the authors approved the final manuscript as submitted and agreed to be accountable for all aspects of the work.

DISCLOSURES
The authors have indicated that they have no conflicts of interest with regard to the content of this article.

REFERENCES
1. Gottlieb RL, Nirula A, Chen P, et al. Effect of bamlanivimab as monotherapy or in combination with etesevimab on viral load in patients with mild to moderate COVID-19: A randomized clinical trial. JAMA. 2021;325:632–644.
2. Weinreich DM, Sivapalasingam T, Norton T, et al. REGN-COV2, a neutralizing antibody cocktail, in outpatients with Covid-19. N Engl J Med. 2021;384:238–251.
3. Infectious Diseases Society of America (IDSA), Centers for Disease Control and Prevention. COVID-19 Real-Time Learning Network: Monoclonal Antibodies [IDSA website]. Updated December 7, 2020. Available at: https://www.idsociety.org/covid-19-real-time-learning-network/therapeutics-and-interventions/monoclonal-antibodies. Accessed December 19, 2020.
4. Wolf J, Abzug MJ, Wattier RL, et al. Initial guidance on use of monoclonal antibody therapy for treatment of COVID-19 in children and adolescents. J Pediatr Infect Dis Soc. 2021 Jan 3 pii:a175 [Epub ahead of print].
5. Laventhal N, Basak R, Dell ML, Diekema D, Elster N, Geis G, Mercurio M, Opel D, Shalowitz D, Statter M, Macauley R. The ethics of creating a resource allocation strategy during the COVID-19 pandemic. Pediatrics. 2020;146.
6. Emanuel EJ, Persad G, Upshur R, et al. Fair allocation of scarce medical resources in the time of Covid-19. N Engl J Med. 2020;382:2049–2055.
7. Persad G, Peek ME, Emanuel EJ. Fairly prioritizing groups for access to COVID-19 vaccines. JAMA. 2020;324:1601–1602.
8. Shekerdemian LS, Mahmood NR, Wolfe KK, et al. Characteristics and outcomes of children with coronavirus disease 2019 (COVID-19) infection admitted to US and Canadian pediatric intensive care units. JAMA Pediatr. 2020;174:868–873.
9. Williams N, Radia T, Harman K, Agrawal P, Cook J, Gupta A. COVID-19 Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection in children and adolescents: a systematic review of critically unwell children and the association with underlying comorbidities. Eur J Pediatr. 2020;1–9.
10. Annie E. Casey Foundation (AECF). What the Data Say About Race, Ethnicity and American Youth [AECF website]. Updated September 4, 2020. Available at: https://www.aecf.org/blog/what-the-data-say-about-race-ethnicity-and-american-youth. Accessed March 22, 2021.
11. Virtual Pediatric Systems (VPS). COVID-19 Data: North American Pediatric ICUs [VPS website]. Updated daily. Available at: https://covid19.myvps.org. Accessed March 22, 2021.
12. Sachdeva R, Rice TB, Reisner B, Brundage N, Hulbert C, Kaminski A, Wetzel RC. The impact of coronavirus disease 2019 pandemic on US and Canadian PICUs. Pediatr Crit Care Med. 2020;21:e643–e650.
13. Schuklenk U. COVID19: Why justice and transparency in hospital triage policies are paramount. Bioethics. 2020;34:325–327.
14. National Governors Association (NGS). Monoclonal Antibody Therapies For COVID-19: What Governors Need To Know [NGS website]. Updated November 2, 2020. Available at: https://www.nga.org/center/publications/monoclonal-antibody-therapies-covid-19. Accessed March 22, 2021.
15. Public Health Emergency (PHE). Overview of Direct Order Process for COVID-19 Therapeutics [PHE website]. Updated March 17, 2021. Available at: https://www.phe.gov/emergency/events/COVID19/investigation-MCM/Documents/Overview%20of%20Direct%20Order%20Process%20Fact%20Sheet-508.pdf. Accessed March 22, 2021.

16. Public Health Emergency (PHE). Allocation of Casirivimab/Imdevimab by Jurisdiction [PHE website]. Updated February 2, 2021. Available at: https://www.phe.gov/emergency/events/COVID19/investigation-MCM/cas_imd/Pages/allocation.aspx. Accessed March 22, 2021.

17. Baker DW. Trust in health care in the time of COVID-19. JAMA. 2020;324:2373–2375.

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