Clinical Prioritization of Antispike Monoclonal Antibody Treatment of Mild to Moderate COVID-19

Raymund R. Razonable, MD; Ravindra Ganesh, MBBS, MD; and Dennis M. Bierle, MD

From the Division of Infectious Diseases (R.R.R) and Division of General Internal Medicine (R.G and D.M.B), Mayo Clinic, Rochester, MN.

The 2021 summer surge of coronavirus disease 2019 (COVID-19) in the United States is predominantly fueled by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) delta variant that is dominant in most communities.[1] The SARS-CoV-2 delta variant has increased transmissibility, resulting in an uptick of cases with a corresponding increased rate of hospitalization across many locations, especially in communities with low COVID-19 vaccination rates.[1] Efforts to curtail this surge include vaccination and other public health mitigation strategies such as masking and social distancing. In addition, early outpatient treatment of mild to moderate COVID-19 is recommended to reduce the risk of progression to severe COVID-19 in patients at high risk so as to reduce the need for hospitalization.

Antispike monoclonal antibodies are authorized by the US Food and Drug Administration (FDA) for the early treatment of mild to moderate COVID-19 in high-risk patients.[2] In November 2020, Mayo Clinic established a Monoclonal Antibody Treatment Program (MATRx) to provide these therapies to high-risk patients outside the hospital setting.[3] By October 22, 2021, the program had infused antispike monoclonal antibodies to more than 13,800 patients. Analysis of the program's outcomes revealed significant reduction in hospital and intensive care unit admission and mortality in 2335 patients who received bamlanivimab infusion compared with a propensity score—matched cohort of 2335 untreated patients.[4] Given the emergence of SARS-CoV-2 delta and other variants with resistance to bamlanivimab and etesevimab, MATRx currently uses casirivimab-imdevimab for treatment, as it maintains efficacy against SARS-CoV-2 variants of concern including delta.[2] The hospitalization rate was significantly lower in 696 patients treated with casirivimab-imdevimab combination than in 696 high-risk patients who did not receive monoclonal antibodies.[5]

By leveraging the electronic health record, MATRx developed the Monoclonal Antibody Screening Score (MASS), which is composed of the FDA Emergency Use Authorization (EUA) eligibility criteria issued in November 2020 (Table 1, footnote d), to rapidly identify and stratify eligible patients according to the risk of hospitalization.[6,7] The clinical performance of MASS has been reported.[6,7] There was a direct relationship between MASS and hospitalization rates—patients with higher MASS have higher rates of hospitalization.[6,7] By stratifying patients into risk strata, MASS was originally designed to identify patients that will be prioritized for monoclonal antibody treatment during periods of scarcity. Resource scarcity may result from limited product supply, limited infusion capacity, or staffing shortages. As it turned out, MATRx was able to keep up with the demand for monoclonal antibody treatment and thus MASS was mainly used to screen and identify all eligible patients. On May 14, 2021, the US FDA expanded the eligibility criteria for monoclonal antibody therapy, most notably the reduction in the body mass index threshold from 35 to 25 kg/m^2 and the removal of the age restriction for hypertension, cardiovascular diseases, and chronic lung diseases. Adopting the new expanded FDA EUA criteria, MATRx

TABLE 1. Demographic and Clinical Characteristics of 1141 Patients With COVID-19 at Mayo Clinic in the Midwest, May and June 2021[a,b]

Characteristic	Casirivimab-imdevimab treatment (n=132)	No antibody treatment (n=1009)	P value
Age (y)	55.6±15.9	44.8±18.0	<.0001
Male gender	50.8	45.5	.25
Body mass index (kg/m^2)	34.3±8.4	30.9±7.2	<.0001
Medical comorbidities			
Coronary artery disease	12 (9.1)	60 (6.0)	.18
Congestive heart failure	10 (7.6)	36 (3.6)	.0316
Chronic kidney disease	12 (9.1)	50 (5.0)	.052
Diabetes	28 (21.2)	100 (9.9)	.0002
Hypertension	60 (45.5)	188 (18.6)	<.0001
Organ transplant	4 (3.0)	3 (0.3)	.0023
Pulmonary disease	21 (15.9)	97 (9.6)	.0272
Allocation criteria			
CAST score[c]	3.1±1.9	1.8±1.8	<.0001
MASS[d]	3.1±2.6	1.3±2.2	<.0001

[a]BMI = body mass index; CAST = COVID-19 Antibody Screening Tool; COVID-19 = coronavirus disease 2019; EUA = Emergency Use Authorization; FDA = Food and Drug Administration; MASS = Monoclonal Antibody Screening Score.

[b]Data are presented as mean ± SD or as No. (percentage).

[c]COVID-19 Antibody Screening Tool assigned 1 point to each of the expanded US FDA EUA criteria (released in May 2021) as follows: age ≥ 65 y, BMI ≥ 35 kg/m^2, diabetes mellitus, hypertension, cardiovascular disease, pulmonary disease, dialysis or chronic kidney disease, bone marrow or organ transplant or immunosuppressive medication or disease, pregnancy, sickle cell disease, neurological or neuro-developmental disorders, genetic or congenital metabolic disorder, liver disease, or use of medical devices.

[d]Monoclonal Antibody Screening Score assigned a score to each of the original US FDA EUA criteria (released in November 2020) as follows: age ≥ 65 y (2), BMI ≥ 35 kg/m^2 (2), diabetes mellitus (2), chronic kidney disease (3), cardiovascular disease in a patient 55 y and older (2), chronic respiratory disease in a patient 55 y and older (3), hypertension in a patient 55 y and older (1), and immuno-compromised status (3). The maximum score is 18.

developed a new score, the COVID-19 Antibody Screening Tool (CAST; Table 1, footnote c), in an effort to expand MASS to capture the additional newly eligible patients using the electronic health record.

The expansion of the FDA EUA eligibility criteria coincided with the rapid spread of the SARS-CoV-2 delta variant, initially causing COVID-19 surge in southern states but soon progressed throughout the United States, including the upper Midwest. On July 30, 2021, the US FDA further expanded the clinical indication of casirivimab-imdevimab to include postexposure prophylaxis in high-risk unvaccinated or partially vaccinated patients and in immunocompromised individuals. Collectively, the expansion of the clinical indication and eligibility criteria, coupled with the rapid spread of the more communicable SARS-CoV-2 delta variant, have resulted in a marked increase in the number of patients who are eligible for casirivimab-imdevimab infusion. The increase in demand for monoclonal antibody treatments raises the potential concern for scarcity—when the supply of the product or the capacity to infuse does not meet the increasing demand.

In this article, we offer our perspectives in addressing antispike monoclonal antibody allocation during periods of scarcity by using the data gathered from MATRx's clinical prioritization approaches. Specifically, we establish that MASS and CAST scores can be used effectively to determine clinical priority and guide allocation by identifying the subgroups of eligible patients who are at highest risk of hospitalization and therefore would benefit most from prioritization for casirivimab-imdevimab treatment.

After institutional review board approval, we assessed the clinical outcomes of a total of 1141 patients in the Midwest who tested positive for COVID-19 and met the FDA

TABLE 2. Crude All-Cause Hospitalization Rates, by Day 28, in 1141 Patients With COVID-19 Based on the Clinical Eligibility for Antispike Monoclonal Antibody Therapy as Assessed by the Original (MASS) and Expanded (CAST) FDA EUA Criteria, May and June 2021[a,b]

	CAST[c]		MASS[d]	
Score	No treatment	Casirivimab-imdevimab	No treatment	Casirivimab-imdevimab
1	6.4	3.2	10.6	0
2	12.9	0	13.5	5.9
3	13.5	6.9	25.3	3.7
4	31.0	4.8	22.9	0
≥5	46.9	12.0	40.7	16.7

[a]BMI = body mass index; CAST = COVID-19 Antibody Screening Tool; EUA = Emergency Use Authorization; FDA = Food and Drug Administration; MASS = Monoclonal Antibody Screening Score.

[b]Data are presented as percentage.

[c]COVID-19 Antibody Screening Tool assigned 1 point to each of the expanded US FDA EUA criteria (released in May 2021) as follows: age ≥ 65 y, BMI ≥ 35 kg/m^2, diabetes mellitus, hypertension, cardiovascular disease, pulmonary disease, dialysis or chronic kidney disease, bone marrow or organ transplant or immunosuppressive medication or disease, pregnancy, sickle cell disease, neurological or neurodevelopmental disorders, genetic or congenital metabolic disorder, liver disease, or use of medical devices.

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EUA eligibility criteria for monoclonal antibody therapy in May and June 2021. The characteristics of this population are listed in Table 1. The crude rate of all-cause hospitalization was 5.3% in 132 patients who were treated with casirivimab-imdevimab compared with 12.9% in 1009 patients who did not receive the therapy (P=.015). This significant difference in the outcomes is even more clinically relevant because those who received casirivimab-imdevimab treatment had more high-risk medical comorbidities, such as obesity, hypertension, diabetes, and immunosuppression (Table 1). There was a significantly higher MASS (3.1±2.6 vs 1.3±2.2; P<.0001) and CAST (3.1±1.9 vs 1.8±1.8; P<.0001) scores in patients who received casirivimab-imdevimab than in those who did not receive monoclonal antibody. These data are similar to our previous report describing that patients with higher comorbidity scores were more likely to consent to monoclonal antibody therapy and likely reflects the patients' awareness of their multiple comorbidities as risk factors for COVID-19 complications.[6,7]

As shown in Table 2, the rates of hospitalization in our patients increased directly with CAST and MASS, especially in those who did not receive monoclonal antibodies. A CAST score of 1 or greater is more sensitive (sensitivity, 96.9%; specificity, 26.5%) whereas a MASS of 1 or greater is more specific (sensitivity, 73.1%; specificity, 63.4%) for hospitalization. We further emphasize that patients with a CAST score of 1 (without fulfilling any of stricter MASS eligibility criteria, ie, MASS, 0) were unlikely to require COVID-19 hospitalization; the latter group consists of additional patients who were captured using the expanded EUA criteria enacted in May 2021. In our population of 218 untreated patients who belonged to this stratum (CAST score, 1; MASS, 0), the all-cause and COVID-19 hospitalization rates were 7.8% and 0.1%, respectively; notably, two-thirds of all-cause hospitalizations in this group were for childbirth. Adjusting for pregnancy yields an all-cause hospitalization rate of only 1.8%, which compares favorably with the hospitalization rates in patients without any qualifying high-risk condition (ie, CAST score of 0: 1.6% all-cause hospitalization; odds ratio, 1.09; P=.90 and 0.4% COVID-19−related hospitalization; odds ratio, 1.09; P=.95).

Accordingly, during periods when there is resource scarcity (ie, when there is limited product supply or infusion appointment slots), this group of eligible but lower-risk patients may be given lower priority to ensure access for those with higher CAST and MASS scores.

The new data presented here add to our collective observations since the start of MATRx in November 2020 that there is indeed a direct correlation between the number of medical comorbidities and the rate of hospitalization in high-risk patients with mild to moderate COVID-19. Persons with multiple medical comorbidities (higher MASS and CAST scores) should therefore be given priority for monoclonal antibody allocation during periods of scarcity as may occur during overwhelming surges of SARS-CoV-2 infection within the United States or in other countries where antispike monoclonal antibody supplies are far from abundant. This strategy is an effort to reduce the risk for disease progression, thereby relieving the potential burden to the already overburdened hospital systems. This prioritization strategy should also be extended to patients with mild to moderate COVID-19 and were already admitted to the hospital for another cause to reduce their risk of disease progression that may lead to the need for intensive care unit admission.

We further propose that during periods of scarcity, treatment of high-risk patients with symptomatic COVID-19 should be given priority over postexposure prophylaxis, with the exception of the exposed unvaccinated or immunocompromised essential or critical workers. High-risk patients who are already having mild to moderate COVID-19 have a limited time to receive these lifesaving monoclonal antibody therapies and therefore should be prioritized over the exposed asymptomatic high-risk persons who will have a second chance at monoclonal antibody infusion, if they develop symptoms. For the eligible high-risk patients who were not given postexposure prophylaxis because of scarcity, they should be monitored closely, and be treated early, only if they develop symptoms after their exposure. Because of society's dependence on our critical workers, they should be given priority for postexposure prophylaxis if they remain at risk because of an underlying immunocompromised status or are not yet fully vaccinated.

Although MASS and CAST scores are integral in the implementation of Mayo's MATRx, there was no period of resource scarcity since the program started in November 2020. There has always been sufficient supply of monoclonal antibody products from the federal government, and our institutional capacity for infusion had adequately met the overall demand for these lifesaving therapies. Nonetheless, the program remains at risk of resource scarcity because SARS-CoV-2 transmission and infection remains high in our communities and our product supply is not guaranteed, as it remains dependent on the allocation provided by the federal and state governments.

During periods of resource scarcity, the clinical criteria for monoclonal antibody allocation should be based on patient need (defined by high-risk medical comorbidities as stratified by MASS and CAST) and likelihood of benefit (defined by lack of clinical progression and hospitalization). In our program, we have found that MASS and CAST as paired screening tools are clinically useful in achieving this goal.[6,7] We encourage the use of MASS and CAST to identify and stratify patients who would benefit the most from antispike monoclonal antibodies, thereby reducing COVID-19–related admissions and decompressing an already overwhelmed hospital system. As the SARS-CoV-2 delta variant continues to surge and the demand for antispike monoclonal antibodies continues to increase, these 2 clinical tools for monoclonal antibody allocation should be strongly considered to complement other strategies that will also ensure equity among essential and critical workers and the underserved and underrepresented populations.[6]

Correspondence: Address to Raymund R. Razonable, MD, Division of Infectious Diseases, Mayo Clinic, 200 First St SW, Rochester, MN 55905 (Razonable.raymund@mayo.edu).

ORCID
Raymund R. Razonable: https://orcid.org/0000-0001-5248-0227; Ravindra Ganesh: https://orcid.org/0000-0002-6877-1712

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