Utah Crisis Standards of Care Monoclonal Antibody Allocation Guidelines

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Produced in cooperation with

UHA UTAH HOSPITAL ASSOCIATION

UTAH DEPARTMENT OF HEALTH

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About the Guidelines

The purpose of this document is to guide the allocation of monoclonal antibody therapies while they are a scarce patient care resource, and after being issued an Emergency Use Authorization (EUA), with updates, by the US FDA. Ongoing studies suggest that these therapies are effective in reducing viral load, symptoms, and the risk of hospitalization in patients recently diagnosed with mild to moderate Covid-19 and in preventing infection in high risk individuals who have had a direct exposure to someone with COVID-19. This document will be updated as needed.

A committee process to determine ethical allocation frameworks within states is recommended by the U.S. Department of Health and Human Services. The Scarce Medications Allocation Subcommittee of the Utah Crisis Standards of Care Workgroup has developed additional criteria beyond the EUA to ensure that the drug is prescribed fairly and to patients who are most likely to benefit from it. This subcommittee consists of physicians trained in critical care, infectious disease, pediatrics, and internal medicine; hospital pharmacists, and experts in allocation frameworks and ethics. The foundation of our approach to crisis standards of care is that allocation decisions must be based on criteria that ensure that every patient has equitable access to any care from which they might benefit. This protocol meets the CSC ethical goals of fairness, duty to care, transparency, consistency, proportionality, and accountability.

This committee is acutely aware of the pressure that COVID is placing on our hospitals, caregivers, and society. We are very supportive of expanding eligibility to all patients that might benefit, as outlined in the EUA. However, we continue to deliver this therapy primarily within existing and already stressed healthcare systems. Expanding eligibility without first expanding capacity will only lead to more eligible patients being turned away, which will only dilute the effectiveness of monoclonal antibodies in preventing hospitalization. Instead, we need to first expand the capacity to deliver this therapy, through mechanisms that include earlier and more widely accessible testing with collocated treatment capacity. Expansion of eligibility should only occur after that capacity to deliver the therapy is equal and greater to the numbers of eligible patients.

Scope of this Document

Why: Monoclonal antibody infusions designed to neutralize SARS-CoV-2 are effective at reducing viral levels, attenuating progression of disease and preventing hospitalization or death when administered to high-risk patients early in their symptom course. However, during surge phases of the current pandemic, FDA EUA criteria identify an eligible population that far exceeds maximum statewide capacity to provide monoclonal antibody infusions. To equitably prioritize limited drug to patients at highest risk of hospitalization who are most likely to benefit, an accurate risk-assessment tool was developed using Utah data. Depending on community transmission levels and infusion capacity statewide, eligibility threshold can be adjusted to allow dynamic demand-capacity matching. As infusion capacity increases, the eligibility criteria will be expanded to provide access to a larger group of progressively lower-risk patients. The health systems have agreed to administer these therapies according to the criteria set forth in this state guideline. We rely on each system's antimicrobial stewardship programs to encourage and verify adherence to the guideline.

As of August 2021, given COVID-19 vaccination provides strong protection against severe disease and need for hospitalization, we recommend targeting monoclonal antibody therapy to patients with COVID-19 who are either not previously fully vaccinated or those who remain at high risk for hospitalization or death despite vaccination.

The rationale for this decision is based on the following factors:

1) Capacity to provide monoclonal antibody infusions remains limited compared to the number of new COVID-19 cases occurring daily.
2) The primary objective of monoclonal antibody therapy remains to prevent hospitalization and death.
3) Risk of hospitalization and mortality is dramatically decreased in fully vaccinated individuals with breakthrough COVID-19. Vaccinated patients who are ultimately admitted tend to be immunocompromised and those with advanced age and multiple medical comorbidities, with an average COVID Risk Score of 9(https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8261136)
4) Data from more than one hundred thousand Utah COVID cases analyzed by this committee show that compared to the very strong benefit in unvaccinated, the effect of MAbs in fully vaccinated individuals is not significant.

Where: These eligibility guidelines apply to all healthcare professionals, clinics, facilities and patients in the state of Utah EXCEPT those in Long Term Care Facilities. Patients in these facilities have increased risk of infection due to cohabitation and shared caregivers, have higher risk of hospitalization, and can often be treated simultaneously through our outreach teams. Monoclonal antibody therapies may only be administered in settings in which health care providers 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.
Within the constraints of scarce medication delivery, maintaining equitable access to this and other drugs is top priority to the committee. Patients access care in many ways. To that end we recommend a layered approach to outreach and referral. Where available, prospective screening for eligible patients at the time of test notification is ideal, but logistically challenging. We will work with test providers in the state to include links on test result notifications directing patients to testing locations as well as signage at testing locations. Emergency departments, urgent care and primary care clinics are also important outreach venues where information on drug availability should be posted. We will work with health systems to educate providers on this new resource, eligibility criteria and referral pathways. Finally, community outreach groups may be best positioned to raise awareness in disadvantaged populations.

When: Monoclonal antibody therapies should be given as soon as possible after a positive direct SARS-CoV-2 viral test and within 7 days of symptom onset. Patients receiving monoclonal antibody therapy should consider waiting 90 days before receiving SARS-CoV vaccine.

What: Due to increased incidence of variant forms of SARS-CoV-2 which have greater resistance to monoclonal antibody monotherapies, as of March 23, 2021 and in alignment with HHS guidance, we currently recommend exclusive use of either casirivimab-imdevimab or sotrovimab, Because bamlanivimab-etesevimab is effective against the Delta variant, this agent may be authorized by HHS and FDA if drug supply becomes limited. Please see the Utah Novel Therapeutics site (https://coronavirus.utah.gov/noveltherapeutics) for the current recommended MAbs.

Post-Exposure Prevention

Current evidence suggests that when given within 4 days of exposure, monoclonal antibody therapy is effective at reducing the risk of developing COVID-19 (https://www.nejm.org/doi/full/10.1056/NEJMoa2109682). On August 1st, based on this data, the FDA expanded the EUA to authorize use of casirivimab-imdevimab for post-exposure prophylaxis (PEP) in select high-risk patients who have recently had a direct exposure to an individual with confirmed COVID-19:

FDA EUA Inclusion Criteria for Prophylaxis:

1. Adult and pediatric individuals (12 years of age and older weighing at least 40 kg) in individuals who are at high risk for progression to severe COVID-19, including hospitalization or death, and are:

- Not fully vaccinated or who are not expected to mount an adequate immune response to complete SARS-CoV-2 vaccination (for example, individuals with immunocompromising conditions including those taking immunosuppressive medications) **and *either***
  1) have recently* been exposed to an individual infected with SARS-CoV-2 consistent with close contact criteria per Centers for Disease Control and Prevention (CDC).
  OR
  2) who are at high risk of exposure to an individual infected with SARS- CoV-2 because of occurrence of SARS-CoV-2 infection in other individuals in the same institutional setting (for example, nursing homes, prisons).

* In the Phase III randomized trial that resulted in the EUA PEP indication, patients were only eligible for up to 4 days after exposure. Patients who develop symptoms after exposure should be tested for COVID-19 before receiving monoclonal antibody infusion. (https://www.nejm.org/doi/full/10.1056/NEJMoa2109682)

Principles for Prioritizing Limited Capacity for PEP: Because many infections must be prevented in order to prevent hospitalization or death, post-exposure prophylaxis is not an efficient method for preventing these outcomes. Data from clinical trials suggest that if applied by EUA criteria, approximately >100 post-exposure infusions would be required to prevent one hospitalization. For this reason, health systems in the state of Utah will prioritize treatment of infected patients over PEP when capacity is limited. Health care providers and local health care facilities should work together to determine availability on a case by case basis. Post-exposure prophylaxis with monoclonal antibody therapy is not a substitute for vaccination.

Because of the ongoing limited capacity to deliver monoclonal antibodies, we recommend that post-exposure prophylaxis under the EUA should be prioritized to patients most likely to benefit including:

1) severely immunocompromised patients who are unlikely to mount an adequate immune response to vaccination**
2) individuals with relative or absolute contraindications to vaccination
3) unvaccinated patients at very high risk for hospitalization and death (E.g. Utah COVID Risk of >8)
4) patients in congregate living facilities with active COVID-19 outbreaks.

**Solid organ or hematopoietic stem cell recipients, patients with cancer on active chemotherapy, patients on biologics and other immunosuppressive medications that impair humoral or cell mediated immunity (including chronic steroids >20mg/day prednisone equivalent), hypogammaglobulinemia, and patients with HIV with CD4 <200.

Connecting Eligible Patients with Treatment

For adult patients age 18 years or greater, go to the UDOH Novel Therapeutics site (*https://coronavirus.utah.gov/noveltherapeutics*) for updated delivery locations. Patient eligibility must be confirmed by the ordering provider by calculating the presenting patient's risk score with reference to comorbidity definitions listed in the appendix.

For pediatric patients from 12 years of age but less than age 18 years, please talk with your child's specialist physician (e.g. rheumatologist, immunologist, or oncologist). If your child's provider determines that your child meets the eligibility criteria, the provider should send an email regarding eligible pediatric patients to: Pediatric.MonoclonalAntibodies@imail.org

Patient < 16 yo Selection Criteria

Children must meet ALL Inclusion Criteria:

- Must be at least 12 years and up to and including 15 years of age
- At least 88 pounds (40 kg)
- Test confirmed COVID-19 (PCR or Antigen; home or lab)
- Symptomatic, with no more than 7 days from symptom onset
- NOT being admitted or already admitted to an acute care hospital for COVID-19 specifically, or for COVID related complications
- **Must have EITHER:**
    - **B-cell immunodeficiency** [primary or acquired (e.g. rituximab therapy, certain types of cancer treatment that are B-cell depleting therapies)]
    - **BMI greater than or equal to 35**

Pediatric Criteria Rationale: Children have a lower risk of hospitalization from COVID-19 infection than adults and therefore are less likely to benefit from monoclonal antibody therapy. Studies using COVID-19 monoclonal antibody therapy have NOT included children. Although rare, there is a risk of anaphylaxis and infusion related reaction with the administration of the COVID-19 antibody therapy. Given that children are less likely to benefit from COVID-19 monoclonal antibody than adults (even adolescents with high-risk conditions), the unknown benefit and the lack of safety information for this drug in children, monoclonal antibody therapy should be considered experimental and should only be considered for children at highest risk of serious complication. Our hospitalization data supports the use of Mab only in the two groups of patients listed above.

A serious effect of COVID-19 in children is multisystem inflammatory syndrome in children (MIS-C). This is a condition where multiple organs such as the heart, lungs, brain, kidneys, skin, eyes, and gastrointestinal system become inflamed. We do NOT know the effect of COVID-19 monoclonal antibody therapy on risk of MIS-C.

Patient ≥ 16 yo Selection Criteria

Older adolescents/Adults must meet ALL Inclusion Criteria:

- Age ≥ 16 yo
- Test confirmed COVID-19 (PCR or Antigen; home or lab)
- Symptomatic, with no more than 7 days from symptom onset
- NO new hypoxemia (SpO2<90% on room air or receiving new/increased supplemental oxygen)
- NOT being admitted or already admitted to an acute care hospital for COVID-19 specifically, or for COVID-19 related complications[1]

IF meeting above inclusion criteria AND pregnant, then the patient is eligible.[2]

IF meeting above inclusion criteria AND NOT pregnant, determine eligibility based on vaccination status:

- IF NOT fully vaccinated[3] against COVID-19, the patient must have a Utah COVID-19 Risk Score greater than 4.5 (5 or more)[4].
- IF fully vaccinated[3], the patient must have a Utah COVID-19 Risk Score greater than 8 (8.5 or more) OR be severely immunocompromised. This includes solid organ or hematopoietic stem cell recipients, patients with cancer on active chemotherapy, patients on biologics and other immunosuppressive medications that impair humoral or cell mediated immunity (including chronic steroids >20mg/day prednisone equivalent), hypogammaglobulinemia, and patients with HIV with CD4 <200[5].

Utah COVID-19 Risk Score

Demographic Risk Factors	**Points**
Male	**1**
Age	**0.5 for every decade:** 16-20=**1**, 21-30=**1.5**, 31-40=**2**, 41-50=**2.5**, 51-60=**3**, 61-70=**3.5**, 71-80=**4**, 81-90=**4.5**, 91-100=**5**, >100=**5.5**
Non-White race or Hispanic/Latinx ethnicity	**2**
Highest-Risk Comorbidities	
Diabetes mellitus	**2**
Severely immunocompromised	**2**
Obesity (BMI>30)	**2**
Other High-Risk Comorbidities	
Hypertension	**1**
Coronary artery disease	**1**
Cardiac arrhythmia	**1**
Congestive heart failure	**1**
Chronic kidney disease	**1**
Chronic pulmonary disease	**1**
Chronic liver disease	**1**
Cerebrovascular disease	**1**
Chronic neurologic disease	**1**
Symptom Risk Factor	
New shortness of breath	**1**
Total	

1. Monoclonal antibodies should NOT be used in patients hospitalized for COVID or COVID related issues because trials have shown that they are not useful for patients hospitalized for COVID. There may be circumstances where a patient may be admitted for non-COVID reasons, and incidentally is found to have acute COVID with mild symptoms developing within prior 7 days but no new hypoxia, and is at moderate to high risk of developing severe disease according to the Risk Score, in whom treatment with MAbs may be justifiable.
2. We strongly recommend that monoclonal antibody therapy be considered for pregnant patients, given their greater risk for progression to severe COVID-19 disease and the continued lack of evidence of harm to the mother or fetus.
3. Fully vaccinated is defined as having one dose of the Johnson and Johnson vaccine, or 2 doses of an mRNA vaccine (Pfizer or Moderna).
4. Please see the Utah Novel Therapeutics site (https://coronavirus.utah.gov/noveltherapeutics) for the current threshold.
5. Please refer to the "Why" section under Scope of This Document on page 2 for background.

Adult Risk Score Rationale: The Scarce Medications Allocation Subcommittee proposes this as an evidence-based alternative to the EUA, that recognizes that other comorbidities not included in the EUA also increase risk, such as chronic liver disease, congestive heart failure and chronic neurologic disease. In addition, race/ethnicity continues to be a risk factor for severe COVID-19 disease, and the Utah COVID Risk Score is one approach to address equitable access to hard hit communities. Providers may choose to use the EUA criteria, recognizing that the potential for benefit may be lower in older individuals with minimal comorbidities.

Tool Development: Risk factors for hospitalization and mortality are now well-recognized and include age, cumulative comorbidities, male gender, shortness of breath, and importantly, but for reasons not well-understood, non-white race/ethnicity. In order to identify a model that would perform well in our state, the committee validated a modified version of a published risk stratification tool in a population of >22,000 consecutive unvaccinated Utahns with COVID-19. The test performance of the tool is reported below.

Utah COVID-19 Risk Score Threshold: As novel therapeutics for COVID-19 have emerged, strategies that focus treatment on patients whose clinical and demographic features place them at highest risk of developing severe disease and poor outcomes have proven effective in optimizing clinical efficacy and minimizing harm. In the case of MAbs, a risk-targeted approach has been very successful in delivering infusions to patients who are most likely to derive the greatest clinical benefit. The threshold above which patients are eligible for treatment with monoclonal antibody therapies was initially determined based on supply of the therapy relative to patient demand. We strove to maximize its effectiveness in the community, while ensuring fair and equitable allocation. The initial threshold chosen was a score greater than 8. As case counts in our community have decreased, our infusion capacity with respect to demand has increased. In June 2021, the threshold has been lowered to greater than 4.5 (5 or more) to more closely approximate the EUA criteria. As of August 2021, given COVID-19 vaccination provides strong protection against severe disease and need for hospitalization, we recommend targeting monoclonal antibody therapy to patients with COVID-19 who are either not previously fully vaccinated or those whom are at greatest risk despite full vaccination.

Patient Features/Comorbidity Definitions: Please see the Appendix for definitions for each patient feature and comorbidity. To ensure recommended use of this scarce resource, providers must verify patient eligibility, including adherence to the definitions, prior to ordering treatment.

Ethical Justification for Using Race/Ethnicity in Patient Selection: COVID-19 has had a disproportionate impact on low income communities and certain racial/ ethnic minorities in the United States. Equity calls attention to the systematic differences in health outcomes and opportunities to be healthy that adversely affect socially discounted and/or marginalized groups. For COVID-19, these inequities may arise from higher burdens of preexisting comorbid disease, poor health care access, or not having the option for social distancing due to living in densely populated neighborhoods or households. There are also more economically disadvantaged individuals working essential jobs during the pandemic, and many are unable to perform job functions from the safety of their home. This puts them at greater risk of interacting with others who may transmit COVID-19. Utah Data from more than one hundred thousand patients with COVID-19 confirms that even after controlling for age and comorbidities, Utahns who identify from communities of color have a significantly higher risk of severe disease requiring hospitalization. Public health interventions may be used to attempt to mitigate these disparities in COVID-19 by recognizing the structural inequities that underlie them. One way to do this is to include race/ethnicity in the patient selection criteria. The FDA Emergency Use Authorization for monoclonal antibodies specifically states that race and ethnicity may be considered when identifying patients most likely to benefit from this lifesaving treatment.

Risk Score Accuracy

Derivation Cohort, n=16,030				Validation Cohort, n=5976			
Hospitalization		28-day Mortality		Hospitalization		28-day Mortality	
AUROC	95% CI	AUROC	95% CI	AUROC	95% CI	AUROC	95% CI
0.82	0.81-0.84	0.91	0.83-0.94	0.8	0.78-0.82	0.8	0.69-0.9

Point Threshold	Sensitivity	Specificity	PPV	NPV	% of Positives
3	95.0%	28.5%	7.5%	98.9%	72.8%
4	89.1%	45.7%	9.3%	98.5%	56.3%
5	80.6%	62.8%	12.1%	98.1%	39.8%
6	71.1%	76.2%	16.6%	97.5%	26.7%
7	60.9%	84.1%	20.6%	97.0%	18.7%
8	51.4%	89.2%	24.4%	96.4%	13.4%
9	41.4%	92.8%	28.2%	95.9%	9.4%
10	32.3%	95.2%	31.7%	95.4%	6.5%
11	25.0%	97.0%	36.1%	94.9%	4.4%
12	17.4%	98.1%	38.5%	94.6%	2.9%

Appendix – Patient Features/Comorbidity Definitions

Feature	Detailed Definition
Male gender	Does the patient identify as "male?" Male gender is associated with increased risk of severe COVID-19 for reasons that are not fully understood; non-binary and transgender patients may choose to answer this question with that background information.
Non-white race or Hispanic/Latinx ethnicity	Does the patient identify as *either* a race other than "White" or as Hispanic/Latinx?
Shortness of Breath	Applies to patients with symptomatic COVID-19 who are experiencing shortness of breath *beyond their usual baseline*.
Diabetes mellitus	Diagnosed with type I, type II or gestational diabetes by a physician. Pre-diabetes does not qualify.
High Blood Pressure	Diagnosed with high blood pressure by a physician, whether on medications or not.
Cardiovascular Disease	Has the patient had a heart attack or been diagnosed with cardiovascular disease by a physician?
Cardiac Arrhythmia	Has the patient been diagnosed with a supraventricular or ventricular arrhythmia by a physician? Premature ventricular contractions (PVCs) do not qualify.
Chronic Lung Disease	Has the patient been diagnosed with COPD, emphysema, asthma or other less common chronic pulmonary diseases by a physician?
Chronic Kidney Disease	Has the patient been diagnosed with Chronic Kidney Disease Stage III or worse?
Congestive Heart Failure	Has the patient been diagnosed with any type of heart failure (reduced or preserved ejection fraction) or cardiomyopathy by a physician?
Chronic Liver Disease	Has the patient been diagnosed with a chronic liver disease, such as cirrhosis of any stage, non-alcoholic steatohepatitis (fatty liver), chronic viral hepatitis, or other less common disorder by a physician?
Obesity	Does the patient currently have a body mass index of >30 https://www.nhlbi.nih.gov/health/educational/lose_wt/BMI/bmicalc.htm
Severely Immunocompromised	Does the patient have any of the following immunocompromised features: Recipient of a solid organ or hematopoietic (bone marrow) transplant; taking immunosuppressive drugs including calcineurin inhibitors, anti-proliferative agents like mycophenolate or azathioprine, TNF-alpha or other drugs used for autoimmune conditions or systemic steroids of more than 20mg prednisone-equivalent per day for more than 4 weeks; HIV with AIDS; Receiving active chemotherapy; B cell immunodeficiency such as common variable immunodeficiency.
Cerebrovascular disease	Has the patient had a stroke or transient ischemic attack?
Neurological Disease	Has the patient been diagnosed with a systemic neurologic disease such as multiple sclerosis, Parkinson's disease, dementia and other neurodegenerative conditions, myasthenia gravis, or other less common conditions by a physician? Migraines, local neuropathies, and fibromyalgia do not qualify.