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) by the US FDA. Ongoing studies suggest that these therapies may be effective in reducing viral load, symptoms, and the risk of hospitalization in patients recently diagnosed with mild to moderate Covid-19. Application of these guidelines will require and depend on physician judgment at the point of patient care. 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.

Scope of this Document

Why: The EUA clinical criteria identify a larger eligible population, comprising more than 27% of positive patients in Utah. However, because the initial available supply of monoclonal antibody therapies was sufficient to treat only 2% of positive cases, an accurate and flexible method was needed to prioritize limited drug to patients at highest risk of hospitalization who are most likely to benefit. 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.

Where: These triage guidelines apply to all healthcare professionals, clinics, facilities and patients in the state of Utah. 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 SARSCoV-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 we recommend exclusive use of combination monoclonal antibody therapies.

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)
- Laboratory-confirmed COVID-19 (PCR or Antigen)
- 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 B-cell immunodeficiency** [primary or acquired (e.g. rituximab therapy, certain types of cancer treatment that are B-cell depleting therapies)]

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.

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
- Laboratory-confirmed COVID-19 (PCR or Antigen)
- Symptomatic, with no more than 7 days from symptom onset
- Utah COVID-19 Risk Score greater 5.5 (current threshold listed on the Utah Novel Therapeutics site: *https://coronavirus.utah.gov/noveltherapeutics*)
- 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*

* 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. We realize though that there may be rare 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.

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	

Use during Pregnancy: Monoclonal antibody therapy may be considered on a case by case basis for pregnant patients at high risk for progression to severe COVID-19 disease after discussion of potential benefits and unknown risks. Placental transfer of antibodies is likely to occur, but no data exists estimating potential treatment benefit or harm to the fetus.

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 has been identified as 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 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. We now endorse expanding clinical criteria to the threshold in the Utah COVID Risk Score that most closely approximates the EUA criteria. In late February 2021, the threshold has been lowered to greater than 5.5 (6 or more). Please see the Utah Novel Therapeutics site (https://coronavirus.utah.gov/noveltherapeutics) for the current threshold.

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. 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.

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.