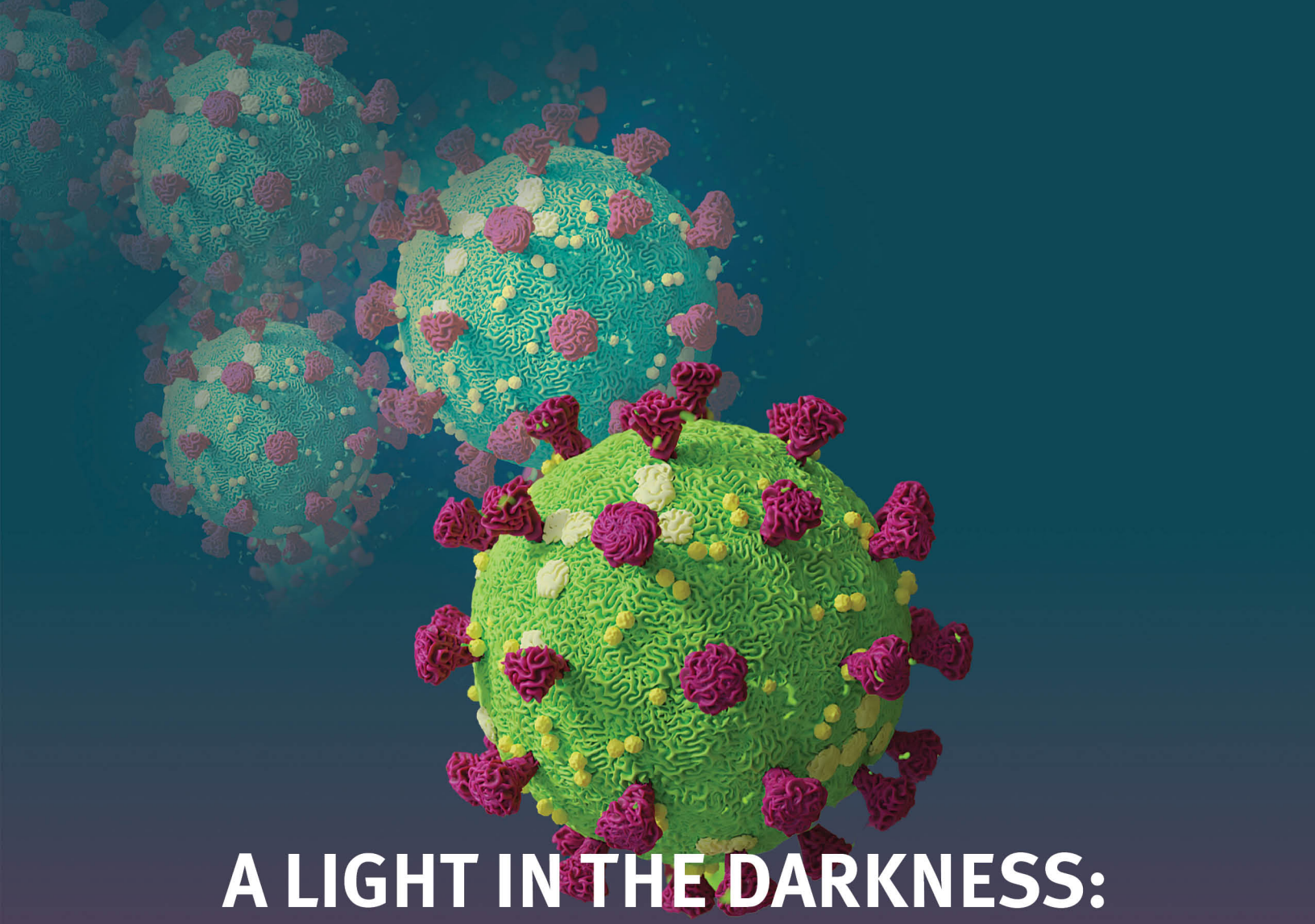

A LIGHT IN THE DARKNESS:

New Virus-neutralizing Monoclonal Antibodies and Other Point-of-Care Therapies Recently Granted Emergency Use Authorizations for Patients with COVID-19

This activity is provided by Med Learning Group.
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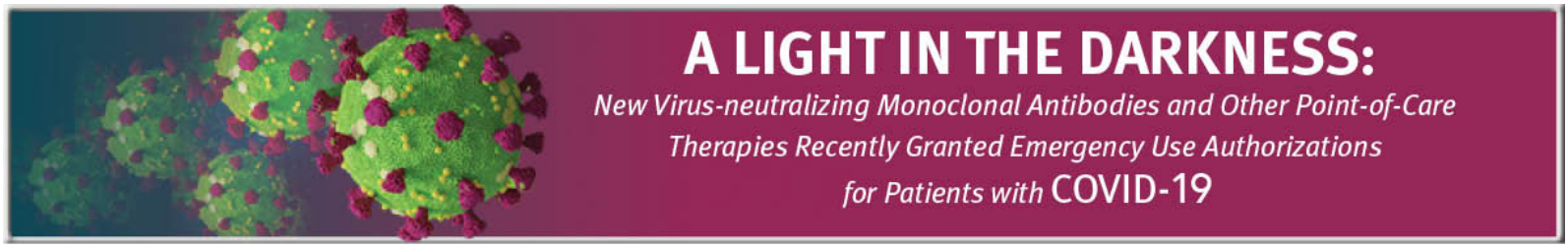
This activity is supported by an educational grant from Lilly.



1. **The COVID-19 Pandemic**
    a. Clinical presentation of patients with COVID-19
    b. Recognizing disease severity in infected patients
    c. Phases of COVID-19: from early infection to hyperinflammation
    d. Risk factors for severe disease

2. **Monoclonal Antibody Therapies Authorized for Emergency Use**
    a. Identifying candidates for monoclonal antibody therapy
        i. When to administer monoclonal antibody therapies
        ii. Recognizing patients who are at high risk for severe COVID-19 or hospitalization
    b. *Case study 1: Impact of comorbidities on management of COVID-19*
    c. *Case study 2: Patient with very mild disease*
    d. Clinical trial data on the efficacy and safety of:
        i. Convalescent plasma
        ii. Casirivimab and imdevimab
        iii. Bamlanivimab
    e. Resources on setting up or finding infusion centers
    f. *Case study 3: Delay in therapy*

3. **Management of Hospitalized Patients with COVID-19**
    a. Selecting patients with COVID-19 who would benefit from pharmacologic therapy
    b. Clinical trial data on the efficacy and safety of:
        i. Remdesivir
        ii. Dexamethasone
        iii. Baricitinib plus remdesivir
    c. Recommended dosing and duration of therapy
    d. *Case study 4: Choosing therapy for a patient with severe COVID-19*

4. **Conclusions**

A Light in the Darkness: New Virus-neutralizing Monoclonal Antibodies and Other Point-of-Care Therapies Recently Granted Emergency Use Authorizations for Patients with COVID-19

PROGRAM CHAIR

Shyam Kottilil, MD, PhD (PROGRAM CHAIR)
Professor of Medicine
Chief, Division of Infectious Diseases
Institute of Human Virology
University of Maryland
Baltimore, MD

FACULTY PRESENTERS

Timothy Albertson, MD, MPH, PhD
Distinguished Professor and Chair of Internal Medicine
School of Medicine
University of California, Davis
Sacramento, CA

Roger Bedimo, MD, MS
Professor of Medicine
University of Texas Southwestern Medical Center
Dallas, TX

Danny Branstetter, MD
Infectious Disease
Wellstar Medical Group
Marietta, GA

Joel Chua, MD
Assistant Professor of Medicine
Chief, Surgical Infectious Diseases, UMMC
Institute of Human Virology
University of Maryland School of Medicine
Baltimore, MD

William A. Fischer II, MD
Associate Professor of Medicine, Pulmonary and Critical Care Medicine
Director of Emerging Pathogens
Institute for Global Health and Infectious Diseases
The University of North Carolina
Chapel Hill, NC

Michael G. Ison, MD MS FIDSA FAST
Professor, Northwestern University Feinberg School of Medicine
Chicago, IL

Poonam Mathur, DO, MPH
Institute of Human Virology, University of Maryland School of Medicine
Baltimore, MD

Richard Martinello, MD
Associate Professor
Departments of Internal Medicine and Pediatrics, Infectious Diseases
Yale School of Medicine
New Haven, CT

PROGRAM OVERVIEW

The COVID-19 FRONTLINE Grand Rounds series provides a comprehensive and up-to-date perspective on the ever-changing management of patients with COVID-19. Each Grand Rounds session features in-depth case studies to encourage retention of the lessons and provide new perspectives on the management of patients during the COVID-19 pandemic. This program will focus on optimizing outcomes for hospitalized and nonhospitalized patients with COVID-19 through the use of novel agents authorized for emergency use.

TARGET AUDIENCE

This CME initiative is designed for HCPs who are involved in the care and treatment of patients with COVID-19 in an outpatient setting, including physicians, NPs, PAs, nurses, pharmacists, and paramedics.

LEARNING OBJECTIVES

Upon the completion of this program, attendees should be able to:

- Assess the rationale for the use of new virus-neutralizing monoclonal antibodies to mitigate the risk of viral resistance to therapy
- Critique the efficacy and safety of new virus-neutralizing monoclonal antibody therapies and other therapies approved for emergency use in all patients who test positive for COVID-19
- Develop in-clinic infusion capability in order to administer new virus-neutralizing monoclonal antibodies to patients with COVID-19 at the point-of-care

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NURSING CREDIT INFORMATION

Purpose: This program would be beneficial for nurses involved in the care of patients with Covid-19.
CNE Credits: 1.0 ANCC Contact Hour.

CNE ACCREDITATION STATEMENT

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Faculty Member	Disclosures
Shyama Kottilil, MD, Ph.D.	Discloses that the University of Maryland has received funds to participate in clinical trials using monoclonal antibodies for treatment of COVID-19. He has received research funds paid to the University from Merck Inc, Gilead Sciences, and Arbutus Pharmaceuticals. He has served on the scientific advisory board for the Hepatitis B Functional Cure Program at Merck Inc and for COVID-19 at Regeneron Pharmaceuticals.
Timothy E. Albertson, MD, MPH, PhD	Discloses he has worked as a Consultant for Johnson & Johnson and he has provided research support for Pfizer and Regeneron
Roger Bedimo, MD, MS	Discloses that he has worked as a Consultant for Merck & Co, Viiv Healthcare and Theratechnologies
Joel Chua, MD	Has nothing to disclose
William A. Fischer II, MD	Discoloses that he has been contracted for research for Ridgeback Biopharmaceuticals for COVID-19 research, as well as worked as Consulted for Merck and Roche. He also worked for Syneos and Janssen for adjudication of AE in RSV and Influenza studies respectively, and served as the site PI for the Phase I Lilly study of - Bamlanivimab and for the Phase II study of Casirivimab/Imdevimab at University of North Carolina.
Michael G. Ison, MD, MS, FIDSA, FAST	Discloses that he has received royalties from UpToDate, and has worked as a consultant for Roche, Janssen and Celltrion
Poonam Mathur, DO, MPH	Has nothing to disclose
Richard Martinello, MD	Discloses that he has worked as a Consultant for Genetech and has worked on the Data Safety Monitoring Board for Noveome phase 1 COVID study

CME Content Review

The content of this activity was independently peer reviewed.
The reviewer of this activity has nothing to disclose.

CNE Content Review

The content of this activity was peer reviewed by a nurse reviewer.
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2. Participate in the live virtual activity.
3. Complete the online post-test and evaluation.

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COVID-19 FRONTLINE

A Light in the Darkness: New Virus-Neutralizing Monoclonal Antibodies and Other Point-of-Care Therapies Recently Granted Emergency Use Authorizations for Patients with COVID-19

Shyam Kottilil MD, PhD
Professor of Medicine
Chief, Division of Infectious Diseases
University of Maryland
Baltimore, MD

Accreditation

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- This educational activity is applicable for CME and CNE credit. Please complete the necessary electronic evaluation to receive credit.

Disclosures

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- During this lecture, the faculty may mention the use of medications for both FDA-approved and nonapproved indications.

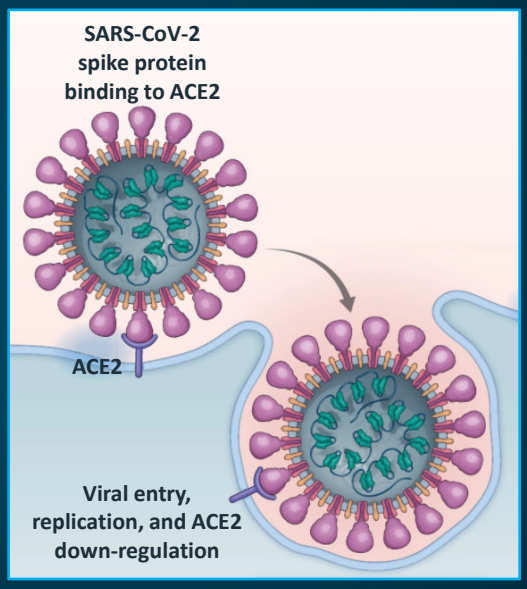
This activity is supported by an educational grant from Lilly.

Learning Objectives

- Assess the rationale for the use of neutralizing monoclonal antibody therapies in recently diagnosed COVID-19 patients to prevent the development of severe disease
- Critique the efficacy and safety of new virus-neutralizing monoclonal antibody therapies and other therapies approved for emergency use in all patients who test positive for COVID-19
- Develop in-clinic infusion capability in order to administer new virus-neutralizing monoclonal antibodies to patients with COVID-19 at the point-of-care

SARS-CoV-2

- COVID-19 is caused by the SARS-CoV-2 virus[1–3]
- The virus is spread primarily via respiratory droplets during face-to-face contact[2]
- Spike protein on viral surface binds to ACE2 receptor on target cells, facilitating viral entry into host cells[2,3]



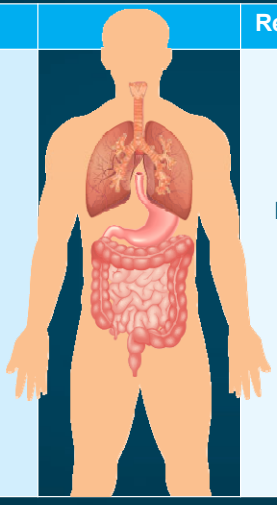
SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; COVID-19 = coronavirus disease 2019; ACE = angiotensin-converting enzyme.

1. Adapted from Vaduganathan M, et al. *N Engl J Med*. 2020;382:1653-1659. 2. Wiersinga WJ, et al. *JAMA*. 324:782-793. 3. Baum A, et al. *Science*. 2020;369:1014-1018.

Clinical Presentation of COVID-19

Systemic and respiratory disorders caused by COVID-19

Systemic Disorders	Respiratory Disorders
Fever, fatigue, Headache	Cough, rhinorrhea, sneezing, sore throat, sputum production
Diarrhea	Dyspnea, hypoxemia
Hemoptysis, acute cardiac injury	Pneumonia
Coagulopathies	Ground-glass opacities
Lymphopenia	Acute respiratory distress syndrome
RNAemia	



Most common symptoms of COVID-19 at presentation

Symptom	Patients Presenting with Symptom (N = 1420)
Headache	70.3%
Loss of smell	70.2%
Nasal obstruction	67.8%
Asthenia	63.3%
Cough	63.2%
Myalgia	62.5%
Rhinorrhea	60.1%
Taste dysfunction	54.2%
Sore throat	52.9%
Fever (>38°C)	45.4%

RNA = ribonucleic acid; C = Celsius.

Guan WJ, et al. *N Engl J Med*. 2020;382:1708-1720. Rothan HA, et al. *J Autoimmun*. 2020;109:102433. Lechien JR , et al. *J Intern Med*. 2020;288:335-344. Wang WW, et al. *J Med Virol*. 2020;92:441-447.

COVID-19 Disease Severity

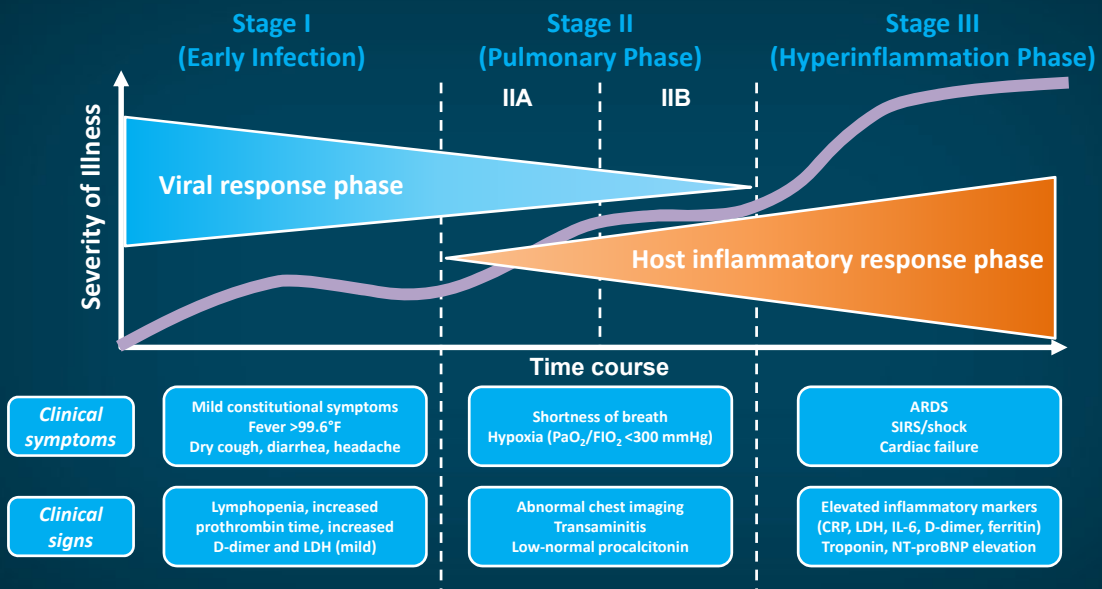
A large study of 44,672 confirmed COVID-19 cases identified by the Chinese Centers for Disease Control and Prevention found that 81% of cases were mild-to-moderate, 14% were severe, and 6% were critical

	Disease Characteristics—NIH
Mild illness	Various symptoms (eg, fever, cough, sore throat, headache, malaise, muscle pain) without shortness of breath, dyspnea, or abnormal chest imaging
Moderate illness	SpO_2 ≥94% on room air and lower respiratory disease evidenced by clinical assessment or imaging
Severe illness	SpO_2 <94% on room air, PaO_2/FiO_2 <300, respiratory rate >30 breaths/min, or lung infiltrates >50%
Critical illness	Respiratory failure, septic shock, and/or multiorgan dysfunction

SpO_2 = oxygen saturation; PaO_2 = arterial partial pressure of oxygen; FiO_2 = fraction of inspired oxygen; NIH = National Institutes of Health.

Wu Z, McGoogan JM. *JAMA*. 2020;323:1239-1242. NIH. COVID-19 treatment guidelines (https://files.covid19treatmentguidelines.nih.gov/guidelines/covid19treatmentguidelines.pdf). Accessed 12/2/2020.

Phases of COVID-19



ARDS = acute respiratory distress syndrome; CRP = C-reactive protein; IL-6 = interleukin 6; LDH = lactate dehydrogenase; NT-proBNP = N-terminal pro B-type natriuretic peptide; SIRS = systemic inflammatory response syndrome.

Adapted from Siddiqi HK, Mehra MR. *J Heart Lung Transplant.* 2020;39:405-407.

Association Between Pre-existing Characteristics and COVID-19 Survival

- Prospective cohort study of 20,133 patients in UK hospitalized with COVID-19
- Increasing age, male sex, and chronic comorbidities, including obesity, were identified as independent risk factors for mortality

		HR (95% CI)	*P*- value
Age on admission (years)	<50		
	50–59	2.63 (2.06–3.35)	<.001
	60–69	4.99 (3.99–6.25)	<.001
	70–79	8.51 (6.85–10.57)	<.001
	≥80	11.09 (8.93–13.77)	<.001
Sex at birth	Female	0.81 (0.75–0.86)	<.001
Chronic cardiac disease	Yes	1.16 (1.08–1.24)	<.001
Chronic pulmonary disease	Yes	1.17 (1.09–1.27)	<.001
Chronic kidney disease	Yes	1.28 (1.18–1.39)	<.001
Diabetes	Yes	1.06 (0.99–1.14)	.087
Obesity	Yes	1.33 (1.19–1.49)	<.001
Chronic neurological disorder	Yes	1.17 (1.06–1.29)	.001
Dementia	Yes	1.40 (1.28–1.52)	<.001
Malignancy	Yes	1.13 (1.02–1.24)	.017
Moderate/severe liver disease	Yes	1.51 (1.21–1.88)	<.001

UK = United Kingdom; HR = hazard ratio; CI = confidence interval.

Docherty AB, et al. *BMJ*. 2020;369:m1985.

Increased Risk of Hospitalization and Death with Certain Comorbidities

Factors that increase the risk of progressing to severe COVID-19	
• Cancer	• Overweight or obesity
• Cardiovascular disease	• Older age (≥65 years of age)
• Chronic kidney disease	• People from racial and ethnic minority groups
• Chronic lung diseases	• People with disabilities
• Dementia or other neurologic conditions	• Pregnancy
• Diabetes (type 1 or 2)	• Sickle cell disease or thalassemia
• Down syndrome	• Smoking, current or former
• HIV infection	• Solid-organ or blood stem-cell transplant
• Immunocompromised state	• Stroke or cerebrovascular disease
• Liver disease	• Substance-use disorders

HIV = human immunodeficiency virus.

US Centers for Disease Control and Prevention (CDC). Medical conditions (www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/people-with-medical-conditions.html). Accessed 6/2/2021.

Antibody Therapies for the Management of COVID-19

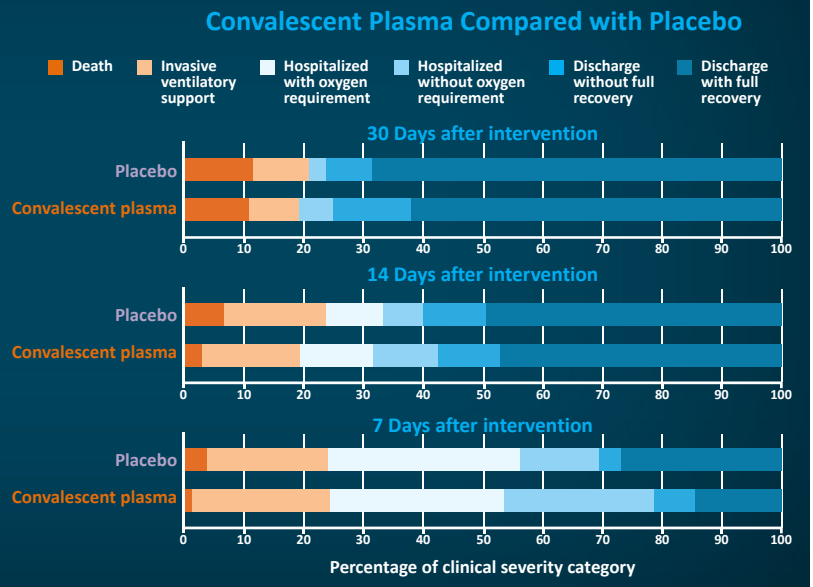
Antibody Therapy in Mild-to-Moderate COVID-19

	Asymptomatic or presymptomatic	Mild illness	Moderate illness	Severe illness	Critical illness
Features	Positive SARS-CoV-2 test; no symptoms	Mild symptoms (eg, fever, cough, or change in taste or smell); no dyspnea	Clinical or radiographic evidence of lower respiratory tract disease; oxygen saturation ≥94%	Oxygen saturation <94% respiratory rate ≥30 breaths/min; lung infiltrates >50%	Respiratory failure, shock, and multiorgan dysfunction or failure
Testing	Screening testing; if patient has known exposure, diagnostic testing	Diagnostic testing	Diagnostic testing	Diagnostic testing	Diagnostic testing
Isolation	Yes	Yes	Yes	Yes	Yes
Proposed disease pathogenesis	Viral replication				
	Inflammation				
Potential treatment	Antiviral therapy				
	Antibody therapy				
	Anti-inflammatory therapy				
Management considerations	Monitoring for symptoms	Clinical monitoring and supportive care	Clinical monitoring; if patient hospitalized and at high risk for deterioration, possibly remdesivir	Hospitalization, oxygen therapy, and specific therapy (remdesivir, dexamethasone)	Critical care and specific therapy (dexamethasone, possibly remdesivir)

Adapted from Gandhi RT, et al. *N Engl J Med*. 2020;383:1757-1766

Convalescent Plasma in Severe COVID: Not Highly Effective

- Convalescent plasma had no impact on survival at 30 days in severe COVID-19 in 333 hospitalized patients
  - >98% on convalescent plasma and 95% on placebo with oxygen saturation <93% on room air at baseline
  - 29% on convalescent plasma and 24% on placebo in ICU at baseline
  - 92% on convalescent plasma and 96% on placebo given steroids during trial

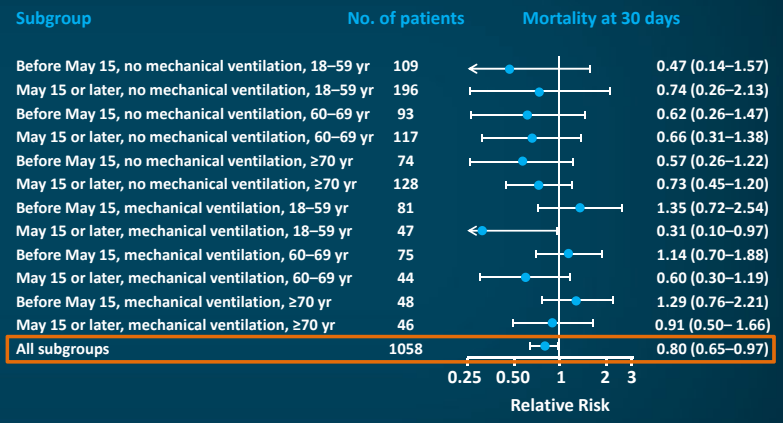


ICU = intensive care unit.

Simonovich VA, et al. *N Engl J Med.* 2021;384:619-629.

Effect of Anti-SARS-CoV-2 Antibody Level on 30-Day Mortality

- Death within 30 days after plasma transfusion in 3 titer groups
  - High-titer: 22.3% (115/515)
  - Medium-titer: 27.4% (549/2006)
  - Low-titer: 29.6% (166/561)
- Significantly lower risk of death within 30 days among patients who had not received mechanical ventilation before transfusion in high-titer group compared with low-titer group (RR = 0.66; 95% CI, 0.48–0.91)



RR = relative risk; yr = year(s).

Joyner MJ, et al. *N Engl J Med.* 2021;384:1015-1027.

Emergency Use Authorization (EUA) for Convalescent Plasma

- EUA issued for **high-titer** convalescent plasma
- Authorized for the treatment of hospitalized patients with COVID-19 early in the disease course and for hospitalized patients with impaired humoral immunity
- Early disease generally means prior to respiratory failure requiring intubation and mechanical ventilation

US Food and Drug Administration (FDA). Convalescent plasma fact sheet (www.fda.gov/media/141478/download). Accessed 2/25/2021.

mAb Therapies With Emergency Use Authorization

These therapies must be given as soon as possible and within 10 days of symptom onset

Bamlanivimab 700 mg AND Etesevimab 1400 mg

Administer together as single IV infusion over a minimum of 21–60 minutes

Casirivimab 1200 mg AND Imdevimab 1200 mg

Must be administered together as a single IV infusion over a minimum of 20–52 minutes

Sotrovimab 500 mg

Administer as an IV infusion over a minimum of 30 minutes

The EUA for bamlanivimab monotherapy was revoked due to prevalence of resistant SARS-CoV-2 variants

IV = intravenous.

FDA. Bamlanivimab and etesevimab EUA, rev 5/2021 (www.fda.gov/media/145802/download). FDA. Casirivimab and imdevimab EUA, rev 5/2021 (www.regeneron.com/downloads/treatment-covid19-eua-fact-sheet-for-hcp.pdf). FDA. Sotrovimab EUA, 2021. (www.fda.gov/media/149534/download). FDA. Bamlanivimab monotherapy EUA revoked, 4/16/2021 (www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-revokes-emergency-use-authorization-monoclonal-antibody-bamlanivimab). URLs accessed 6/2/2021.

Emergency Use Authorization of COVID-19 mAb Therapy

- EUA for the treatment of mild-to-moderate COVID-19 in patients:
  - Who are at least 12 years of age and weigh at least 40 kg
  - Have positive results of direct SARS-CoV-2 viral testing
  - Who are at high risk of progressing to severe COVID-19 or hospitalization
- No benefit in patients hospitalized due to COVID-19
- These therapies may be associated with worse clinical outcomes in hospitalized COVID-19 patients requiring high-flow oxygen or mechanical ventilation

FDA. Casirivimab and imdevimab EUA. (www.fda.gov/media/143892/download). FDA. Bamlanivimab EUA. (http://pi.lilly.com/eua/bamlanivimab-eua-factsheet-hcp.pdf). URLs accessed 12/2/2020.

High-Risk Factors Listed in the EUA

The following conditions place patients at higher risk for severe COVID-19

- **Older age** (≥65 years)
- **Obesity or being overweight** (adults BMI >25 kg/m^2, or BMI ≥85th percentile for patients 12–17 years)
- **Pregnancy**
- **Chronic kidney disease**
- **Diabetes**
- **Immunosuppressive disease or immunosuppressive treatment**
- **Cardiovascular disease** (including congenital heart disease)
- **Hypertension**
- **Chronic lung diseases** (such as COPD, moderate-to-severe asthma, interstitial lung disease, cystic fibrosis, and pulmonary hypertension)
- **Sickle cell disease**
- **Neurodevelopmental disorders** (eg, cerebral palsy) or other medically complex conditions (eg, genetic or metabolic syndromes and severe congenital anomalies)
- **Medical-related technological dependence** (eg, tracheostomy, gastrostomy, positive-pressure ventilation (not related to COVID-19))

BMI = body-mass index; COPD = chronic obstructive pulmonary disease.

FDA. Bamlanivimab and etesevimab EUA, rev 5/2021 (www.fda.gov/media/145802/download). FDA. Casirivimab and imdevimab EUA, rev 5/2021 (www.regeneron.com/downloads/treatment-covid19-eua-fact-sheet-for-hcp.pdf). FDA. Sotrovimab EUA, 2021. (www.fda.gov/media/149534/download). URLs accessed 6/2/2021.

Identifying Other High-Risk Candidates for mAb Therapy

- Other medical conditions or factors can increase a person's risk of progression to severe COVID-19
- Authorization of monoclonal antibodies is not limited to medical conditions listed in EUA
- Healthcare providers should consider the benefit-risk for each patient
- List of additional high-risk factors can be found on the CDC website: www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/people-with-medical-conditions.html

Additional risk factors for progression to severe COVID-19

- Cancer
- Dementia
- Down syndrome
- HIV infection
- Liver disease
- Smoking, current or former
- Stroke or cerebrovascular disease
- Thalassemia
- Substance-use disorders
- Racial and ethnic minority groups
- People with disabilities
- Other factors increasing risk of progression to COVID-19

FDA. Bamlanivimab and etesevimab EUA, rev 5/2021 (www.fda.gov/media/145802/download). FDA. Casirivimab and imdevimab EUA, rev 5/2021 (www.regeneron.com/downloads/treatment-covid19-eua-fact-sheet-for-hcp.pdf). FDA. Sotrovimab EUA, 2021. (www.fda.gov/media/149534/download). CDC. Medical conditions (www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/people-with-medical-conditions.html). URLs accessed 6/2/2021.

Case Study 1: Nora

- Nora is a 45-year-old woman who presents with shortness of breath and cough that began 3 days ago. Her SpO_2 is 95% with a heart rate of 98 bpm. Her PCR test is positive for SARS-CoV-2.
- Nora's prior medical history is significant for hypertension and depression. Her BMI is 26 kg/m^2 and she has elevated triglycerides.
- **Is Nora a candidate for treatment with a monoclonal antibody therapy?**

  A. Yes, she should receive monoclonal antibody therapy

  B. No, she should not receive monoclonal antibody therapy

bpm = beats per minute; PCR = polymerase-chain reaction; SpO2 = oxygen saturation.

BLAZE-1: Phase 2 Trial of Bamlanivimab (LY-CoV555)

- Interim results from phase 2 trial of bamlanivimab in patients with mild-to-moderate COVID-19
- Risk factors for severe COVID-19 in 70% of bamlanivimab and 66% of placebo patients at baseline

Inclusion criteria:
- ≥18 years of age
- Not hospitalized
- Sample collection for 1st positive SARS-CoV-2 viral infection determination ≤3 days prior to start of infusion
- ≥1 mild or moderate symptom of COVID-19 (fever, cough, sore throat, malaise, headache, muscle pain, gastrointestinal symptoms, or shortness of breath with exertion)

R

N = 452

- LY-CoV555 700 mg monotherapy (n = 101)
- LY-CoV555 2800 mg monotherapy (n = 107)
- LY-CoV555 7000 mg monotherapy (n = 101)
- Placebo (n = 143)

Interim analysis
- Positive SARS-CoV-2 test ≤3 days before infusion
- Mild or moderate COVID-19 symptoms
- Primary endpoint: change from baseline to day 11 (±4 days) in SARS CoV-2 viral load
- Secondary endpoints include safety, symptom severity, hospitalization, and time points for viral clearance

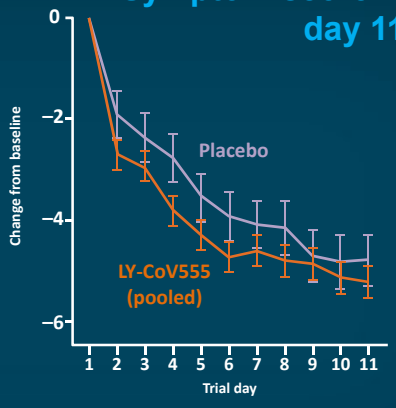
Chen P, et al. *N Engl J Med*. 2021;384:229-237.

BLAZE-1 Interim Results

Treatment	Patients Hospitalized/ Total No.	Incidence of Hospitalization (%)
Placebo	9/143	6.3
Bamlanivimab 700 mg	1/101	1.0
Bamlanivimab 2800 mg	2/107	1.9
Bamlanivimab 7000 mg	2/101	2.0
Bamlanivimab pooled doses	5/309	1.6

- In subjects ≥65 years and/or with a BMI ≥35, day 29 hospitalization was 4% in treated patients and 15% in those receiving placebo

Symptom score from day 2 to day 11



	Delta value (95% CI)
Day 2	–0.79 (–1.35 to –0.24)
Day 3	–0.57 (–1.12 to –0.01)
Day 4	–1.04 (–1.60 to –0.49)
Day 5	–0.73 (–1.28 to –0.17}
Day 6	–0.79 (–1.35 to –0.23)
Day 7	–0.50 (–1.06 to 0.07)
Day 8	–0.65 (–1.28 to –0.02)
Day 9	–0.15 (–0.75 to 0.45)
Day 10	–0.32 (–0.94 to 0.29)
Day 11	–0.44 (–1.02 to 0.15)

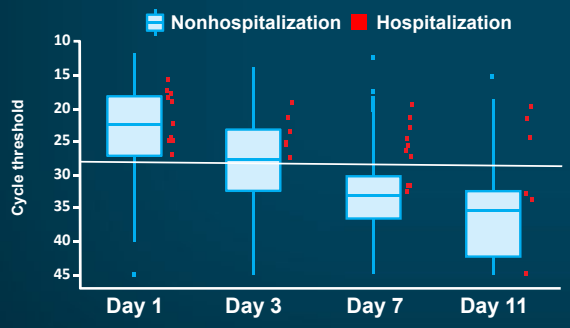
- Symptom scores ranged from 0 to 24 and included eight domains, each of **which** was graded on a scale of 0 (no symptoms) to 3 (severe symptoms)

Chen P, et al. *N Engl J Med*. 2021;384:229-237.

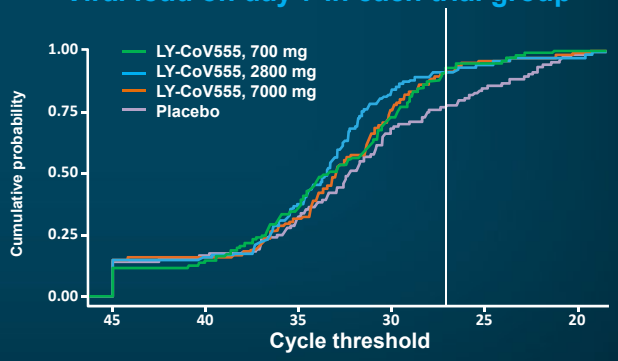
BLAZE-1: Viral Loads Over Time

- Correlation between high viral load and hospitalization
- At day 7, the frequency of hospitalization was 12% (7 of 56 patients) among those who had a Ct value of less than 27.5, as compared with a frequency of 0.9% (3 of 340 patients) among those with a lower viral load.

Viral load in all patients



Viral load on day 7 in each trial group



Ct = PCR cycle threshold (higher viral load = lower Ct value).

Chen P, et al. *N Engl J Med*. 2021;384:229-237.

BLAZE-1: Bamlanivimab Safety

- No serious AEs reported with bamlanivimab use

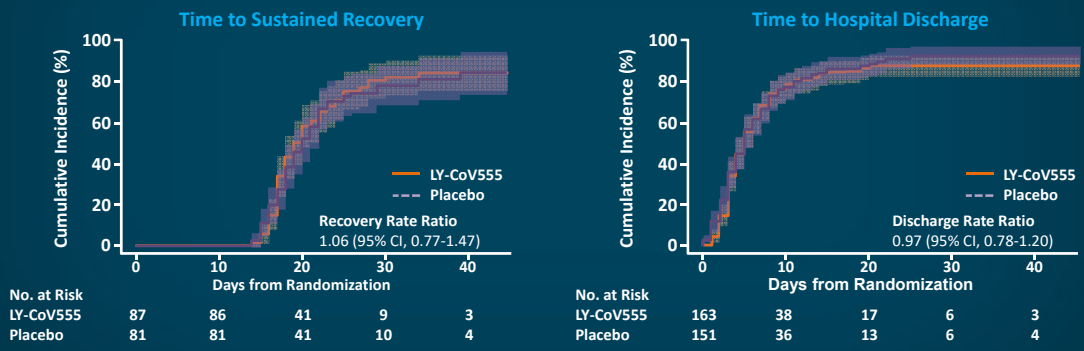
	LY-CoV555 (N=309)				Placebo (n = 143)
	700 mg (n = 101)	2800 mg (n = 107)	7000 mg (n = 101)	Pooled Doses (n = 309)	
Adverse Event	Number of patients (%)				
Serious adverse event*	0	0	0	0	1 (0.7)
Adverse events					
Any	24 (23.8)	23 (21.5)	22 (21.8)	69 (22.3)	35 (24.5)
Mild	16 (15.8)	18 (16.8)	10 (9.9)	44 (14.2)	18 (12.6)
Moderate	7 (6.9)	3 (2.8)	8 (7.9)	18 (5.8)	16 (11.2)
Severe	0	2 (1.9)	3 (3.0)	5 (1.6)	1 (0.7)
Missing data	1 (1.0)	0	1 (1.0)	2 (0.6)	0

- Infusion-related reactions were reported in 2.3% of patients receiving bamlanivimab and 1.4% of patients in the placebo group
  - Most reactions were mild and occurred during the infusion

Chen P, et al. *N Engl J Med*. 2021;384:229-237.

ACTIV-3 Trial: Bamlanivimab in Hospitalized Patients

- Hospitalized patients were randomized to receive bamlanivimab or placebo in addition to high-quality supportive care, including remdesivir and, when indicated, supplemental oxygen and glucocorticoids



- Trial was paused when bamlanivimab was not shown to improve outcomes in hospitalized patients with COVID-19 who did not have end-organ failure

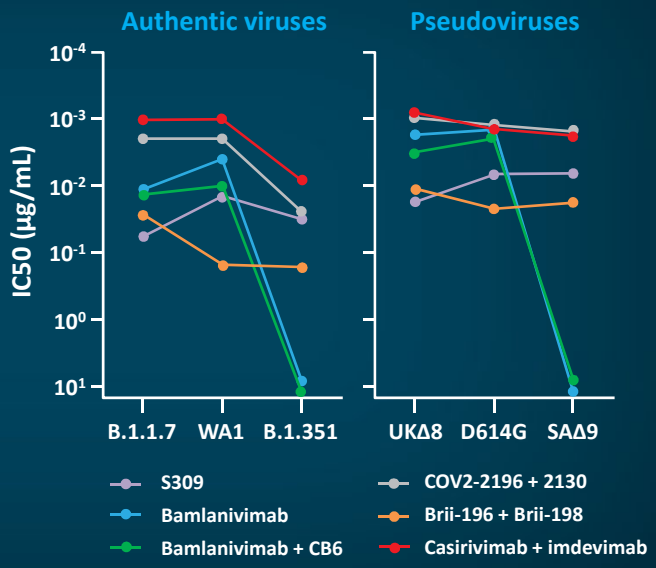
Lundgren JD, et al: ACTIV-3/TICO LY-CoV555 study group. *N Engl J Med.* 2021;384:905-914.

Case Study 2: Ellie

- Ellie is a 29-year-old woman who was tested for SARS-CoV-2 after her husband began to experience symptoms. She initially developed a cough and headache 13 days ago and complains of worsening shortness of breath over the last week. Her SpO_2 is 93%.
- She is 32 weeks pregnant with her second child
- **Is Sandy a candidate for therapy with monoclonal antibodies?**
  - A. Yes, she should receive monoclonal antibody therapy
  - B. No, she should not receive monoclonal antibodies

Emergence of SARS-CoV-2 Variants

- Several SARS-CoV-2 variants with enhanced transmissibility have emerged
  - B.1.1.7 contains 8 spike mutations and emerged in the UK
  - B.1.351 from South Africa has 9 spike mutations
- Activity against the B.1.351 variant is:
  - Reduced with casirivimab
  - Absent with bamlanivimab

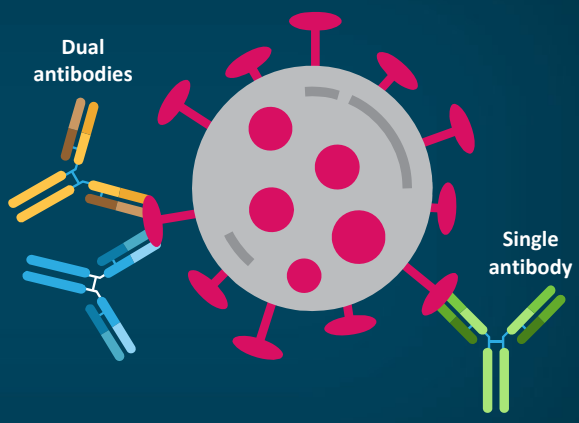


WA1 = wild-type strain; UKΔ8 = pseudovirus with 8 B.1.1.7 mutations; SAΔ9 = pseudovirus with 9 B.1.351 mutations; IC50 = half maximal inhibitory concentration

Wang P, et al. *Nature*. 2021;593:130-135.

Mechanism of Action of mAb Therapies Against SARS-CoV-2

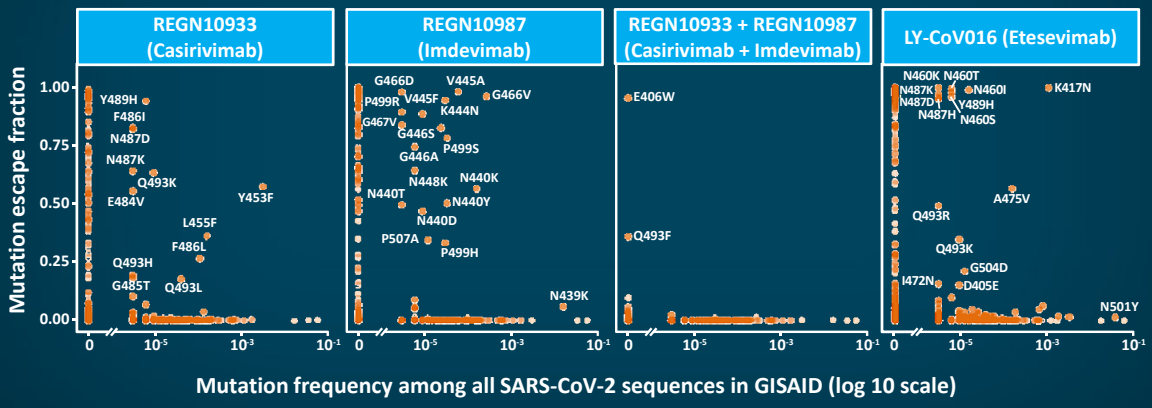
- Neutralizing monoclonal antibodies against SARS-CoV-2 bind to the receptor-binding domain (RBD) of the spike protein and prevent host-cell entry
- Dual monoclonal antibody cocktail contains 2 potent antibodies that simultaneously and noncompetitively bind to different regions of the RBD
  - Use of 2 individual antibodies prevents generation of escape mutants and therapy failure



Hansen J, et al. *Science*. 2020;369:1010-1014.

Antibody Escape Mutations in Circulating SARS-CoV-2

- Many variants that can escape a single monoclonal antibody are currently in circulation
- Very few variants are capable of escaping dual monoclonal-antibody therapies



GISAID = Global Initiative on Sharing Avian Influenza Data.

Starr TN, et al. *Science.* 2021;371:850-854.

Bamlanivimab Plus Etesevimab

- Etesevimab is a neutralizing monoclonal antibody that binds to a different epitope on the spike protein than bamlanivimab
- 577 nonhospitalized patients with mild-to-moderate COVID-19 were randomized to bamlanivimab (700 mg, 2800 mg, or 7000 mg), combination therapy (bamlanivimab 2800 mg + etesevimab 2800 mg), or placebo

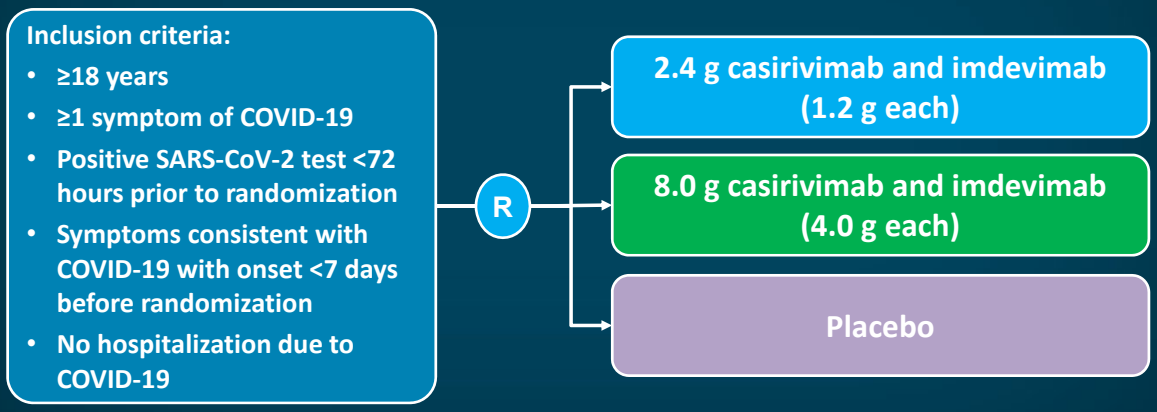
	Bamlanivimab 700 mg	Bamlanivimab 2800 mg	Bamlanivimab 7000 mg	Bamlanivimab 2800 mg + Etesevimab 2800 mg	Placebo
Change in log viral load from baseline to day 11	–3.72 *P* = 0.69	–4.08 *P* = 0.21	–3.49 *P* = 0.16	–4.37 *P* = 0.01	–3.80
COVID-19-related hospitalizations or ED visits	1.0%	1.9%	2.0%	0.9%	5.8%

ED = emergency department.

Gottlieb RL, et al. *JAMA.* 2021;325:632-644.

Casirivimab and Imdevimab (REGN-COV2)

Ongoing phase 1–3 trial of casirivimab and imdevimab in non-hospitalized adults with mild-to-moderate COVID-19



FDA. Casirivimab and imdevimab EUA. (www.fda.gov/media/143892/download). Accessed 1/7/2021.

Casirivimab and Imdevimab: Interim Results

Interim analysis of 275 nonhospitalized patients with mild-to-moderate COVID-19

At Least 1 COVID-19-Related Medical Visit Within 29 Days		
Treatment	**Events/Total Patients**	**Incidence**
All patients		
Placebo	6/93	6%
Casirivimab and imdevimab 2.4 g	3/92	3%
Casirivimab and imdevimab 8.0 g	3/90	3%
All doses casirivimab and imdevimab	6/182	3%
Seronegative patients		
Placebo	5/33	15%
Casirivimab and imdevimab 2.4 g	2/41	5%
Casirivimab and imdevimab 8.0 g	3/39	8%
All doses casirivimab and imdevimab	5/80	6%

Weinreich DM, et al. *N Engl J Med*. 2021;384:238-251.

Casirivimab/Imdevimab: Efficacy by Baseline Viral Load

Casirivimab/imdevimab (REGN-COV2) provided greater reduction in viral load in those patients with higher viral load at baseline

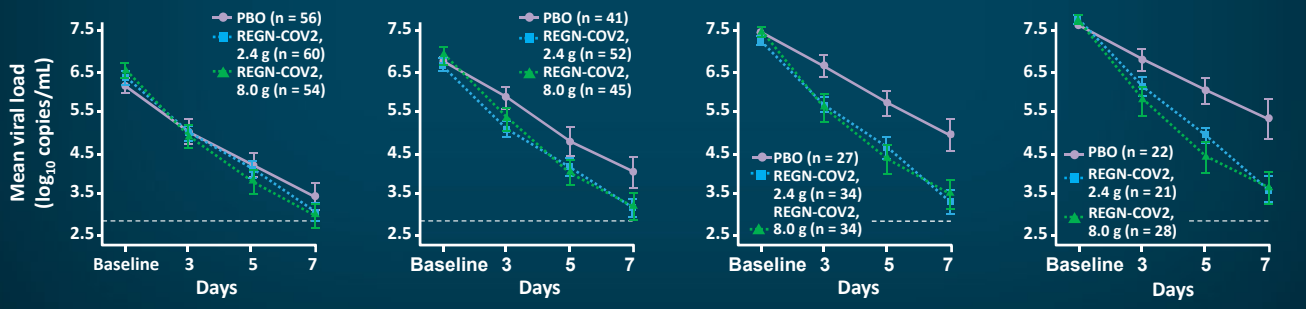
Viral load over time according to baseline viral-load category

	>10^4 copies/mL	
	Difference in Change from Baseline, Day 7	
	TWA LS mean	Mean
2.4 g vs PBO	–0.36	–0.64
8.0 g vs PBO	–0.59	–0.90

	>10^5 copies/mL	
	Difference in Change from Baseline, Day 7	
	TWA LS mean	Mean
2.4 g vs PBO	–0.59	–0.83
8.0 g vs PBO	–0.75	–1.12

	>10^6 copies/mL	
	Difference in Change from Baseline, Day 7	
	TWA LS mean	Mean
2.4 g vs PBO	–0.81	–1.46
8.0 g vs PBO	–1.14	–1.54

	>10^7 copies/mL	
	Difference in Change from Baseline, Day 7	
	TWA LS mean	Mean
2.4 g vs PBO	–1.03	–1.84
8.0 g vs PBO	–1.32	–1.75



TWA = time-weighted average; LS = least-squares.

Weinreich DM, et al. *N Engl J Med*. 2021;384:238-251.

Casirivimab/Imdevimab Safety

Event	REGN-COV2 2.4 g (n = 88)	REGN-COV2 8.0 g (n = 88)	REGN-COV2 Combined (n = 176)	Placebo (n = 93)
	Number of patients (%)			
Any serious adverse event	1 (1)	0	1 (1)	2 (2)
Any adverse event of special interest* (Grade 2 or higher hypersensitivity or infusion-related reactions)	0	2 (2)	2 (1)	2 (2)
Any serious adverse event of special interest*	0	0	0	0
Grade ≥2 infusion-related reaction within 4 days	0	2 (2)	2 (1)	1 (1)
Grade ≥2 hypersensitivity reaction within 29 days	0	1 (1)	1 (1)	2 (2)
Adverse events that occurred or worsened during the observation period†				
Grade 3 or 4 event	1 (1)	0	1 (1)	1 (1)
Event that led to death	0	0	0	0
Event that led to withdrawal from the trial	0	0	0	0
Event that led to infusion interruption*	0	1 (1)	1 (1)	1 (1)

*Events were grade 2 or higher hypersensitivity reactions or infusion-related reactions.
†Events listed here were not present at baseline or were an exacerbation of a preexisting condition that occurred during the observation period, which is defined as the time from administration of REGN-COV2 or placebo to the last study visit.

Weinreich DM, et al. *N Engl J Med*. 2021;384:238-251.

COMET-ICE Trial: Sotrovimab

Interim analysis of 583 patients with mild-to-moderate COVID-19 at high-risk of progressing to severe COVID-19

- 58% of subjects received sotrovimab within 3 days of COVID-19 symptom onset and 42% within 4 to 5 days

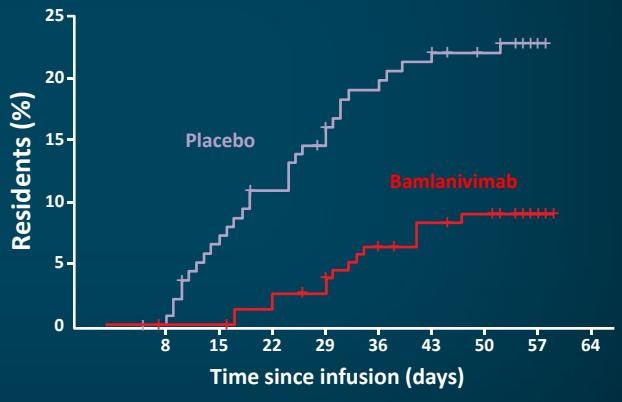
	Sotrovimab n = 291	Placebo n = 292
Progression of COVID-19 at day 29 (hospitalization for >24 hours for acute management of any illness or death from any cause)		
Proportion, n (%)	3 (1%)	21 (7%)
Adjusted relative risk reduction (97.24% CI)	85% (44–96)	
P-value	0.002	
All-cause mortality (up to day 29)		
Proportion, n (%)	0	1 (<1%)

FDA. Sotrovimab EUA, 2021 (www.fda.gov/media/149534/download). Accessed 6/2/2021.

Bamlanivimab in Nursing-Home Setting

- 966 participants, including 266 nursing-home residents considered at high-risk for severe COVID-19, were administered a single-dose of bamlanivimab or placebo if a case of SARS-CoV-2 was confirmed in nursing home
- Compared with placebo, bamlanivimab was associated with:
  - Significantly lower proportion of residents with mild or worse COVID-19 by day 57 (OR = 0.20; 95% CI, 0.08–0.49; *P* <.001)
  - Significant reductions in incident SARS-CoV-2 infection by day 29 (OR = 0.23; CI, 0.11–0.48; *P* <.001)
- 5 COVID-19-related deaths (all in placebo group)

Time since treatment to development of mild or worse COVID-19 in residents



OR = odds ratio.

Cohen M, et al. CROI 2021: abstract 121LB. Lilly BLAZE-2 press release, 1/21/2121. (https://investor.lilly.com/node/44291/pdf). Accessed 3/25/2021.

Top-line Results on mAb Therapies

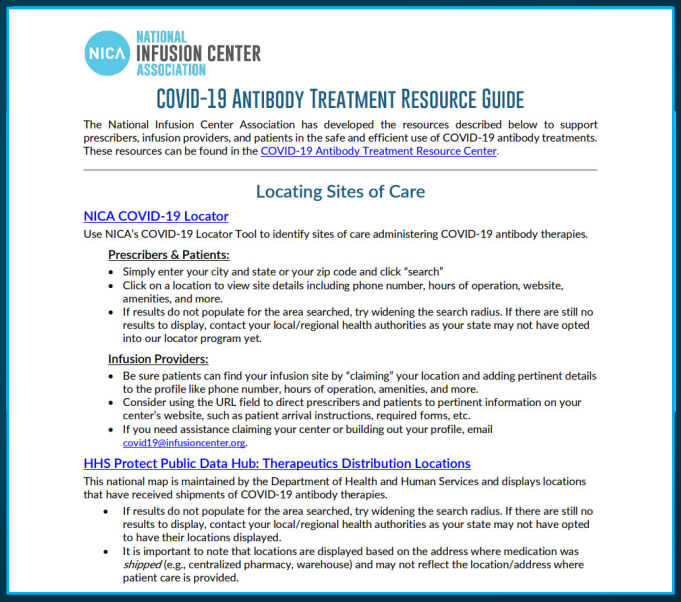
- **BLAZE-1: Bamlanivimab plus etesivimab**
  - Phase 3 trial of 769 high-risk, recently diagnosed COVID-19 patients showed that therapy with bamlanivimab and etesevimab reduced hospitalizations and deaths by **87%** (*P*= .0001)
- **Casirivimab and imdevimab for COVID-19 treatment**
  - 70% reduction in risk of hospitalization or death in 4567 high-risk, non-hospitalized COVID-19 patients
- **Casirivimab and imdevimab for COVID-19 prevention**
  - Interim analysis found 100% prevention of symptomatic infection and 50% reduction in rate of COVID-19 infection in a phase 3 trial of 400 individuals with household exposure to COVID-19

Lilly press release. 3/10/2021. (https://investor.lilly.com/news-releases/news-release-details/lillys-bamlanivimab-and-etesevimab-together-reduced). Regeneron press release. 1/26/21. (https://newsroom.regeneron.com/news-releases/news-release-details/regeneron-reports-positive-interim-data-regen-covtm-antibody). Regeneron press release. 3/23/21. (https://investor.regeneron.com/news-releases/news-release-details/phase-3-trial-shows-regen-covtm-casirivimab-imdevimab-antibody). URLs accessed 3/25/2021.

COVID-19 Antibody Treatment Resource Guide

National Infusion Center Association

- Infusion center locator
- Resources for providers
  - Bamlanivimab playbook
  - Casirivimab + imdevimab guidebook
- Patient education resources
- Treatment indication checklist
- Plus, other resources



NATIONAL INFUSION CENTER ASSOCIATION

COVID-19 ANTIBODY TREATMENT RESOURCE GUIDE

The National Infusion Center Association has developed the resources described below to support prescribers, infusion providers, and patients in the safe and efficient use of COVID-19 antibody treatments. These resources can be found in the COVID-19 Antibody Treatment Resource Center.

Locating Sites of Care

NICA COVID-19 Locator

Use NICA's COVID-19 Locator Tool to identify sites of care administering COVID-19 antibody therapies.

Prescribers & Patients:

- Simply enter your city and state or your zip code and click "search"
- Click on a location to view site details including phone number, hours of operation, website, amenities, and more.
- If results do not populate for the area searched, try widening the search radius. If there are still no results to display, contact your local/regional health authorities as your state may not have opted into our locator program yet.

Infusion Providers:

- Be sure patients can find your infusion site by "claiming" your location and adding pertinent details to the profile like phone number, hours of operation, amenities, and more.
- Consider using the URL field to direct prescribers and patients to pertinent information on your center's website, such as patient arrival instructions, required forms, etc.
- If you need assistance claiming your center or building out your profile, email covid19@infusioncenter.org.

HHS Protect Public Data Hub: Therapeutics Distribution Locations

This national map is maintained by the Department of Health and Human Services and displays locations that have received shipments of COVID-19 antibody therapies.

- If results do not populate for the area searched, try widening the search radius. If there are still no results to display, contact your local/regional health authorities as your state may not have opted to have their locations displayed.
- It is important to note that locations are displayed based on the address where medication was *shipped* (e.g., centralized pharmacy, warehouse) and may not reflect the location/address where patient care is provided.

National Infusion Center Association (https://infusioncenter.org/infusion_resources/covid-19-antibody-treatment-resource-center/). Accessed 1/18/2021.

Case Study 3: Gary

- Gary is a 67-year-old man who presents to the ED with cough, nausea, and shortness of breath. His SpO_2 is 94% on room air.
- His past medical history is significant for diabetes and a prior myocardial infarction. After receiving an infusion of bamlanivimab/etesevimab, his symptoms improve over the next 2 days.
- Gary received his first COVID-19 vaccine 3 weeks before his mAb infusion and is scheduled to receive a second dose of the vaccine in 1 week
- **Should Gary receive his second vaccine dose next week?**
  - A. Yes, he should receive his vaccine dose as scheduled
  - B. No, he should wait 1 month after mAbs to receive a vaccine dose
  - C. No, he should wait 3 months after mAbs to receive a vaccine dose
  - D. A second vaccine dose is not needed in patients who test positive for SARS-CoV-2

Decision-Making With Monoclonal Antibody Infusions and SARS-CoV-2 Vaccination

- For people who develop COVID-19 after SARS-CoV-2 vaccination, prior vaccination should not affect treatment decisions, including the use and timing of treatment with mAbs
- SARS-CoV-2 vaccination should be deferred for ≥90 days after receipt of anti-SARS-CoV-2 mAbs
  - Monoclonal antibody infusions may interfere with the immune response to vaccines
  - If patient receives mAbs after receipt of first vaccine (but before second dose), second dose should be deferred for at least 90 days
  - "Receipt of passive antibody therapy in the past 90 days is not a contraindication to receipt of COVID-19 vaccine."
  - COVID-19 vaccine doses that are given within 90 days after receipt of mAb therapy do not need to be repeated

CDC. Monoclonal antibody COVID-19 infusion, 2021. (www.cdc.gov/vaccines/covid-19/info-by-product/clinical-considerations.html). Accessed 6/2/2021.

Management of Hospitalized Patients with COVID-19

IDSA: Recommended Treatment Options for Hospitalized Patients

Treatment	Guidance
Remdesivir	• Recommended for hospitalized patients with severe COVID-19 • Most benefit seen in those with severe COVID-19 on supplemental oxygen rather than patients on mechanical ventilation or ECMO • 5 days of treatment recommended for patients on supplemental oxygen • 10 days of treatment recommended for patients on mechanical ventilation or ECMO
Glucocorticoids	• Recommended for hospitalized patients with severe COVID-19 • Dexamethasone 6 mg IV or PO for 10 days or equivalent • Not recommended for hospitalized patients without hypoxemia (SpO_2 >94%) requiring supplemental oxygen
Baricitinib plus remdesivir	• Baricitinib plus remdesivir recommended over remdesivir alone in hospitalized patients with severe COVID-19 who cannot receive corticosteroids because of a contraindication
Tocilizumab	• Recommended in addition to standard of care in hospitalized patients with progressive severe or critical COVID-19 who have elevated markers of systemic inflammation

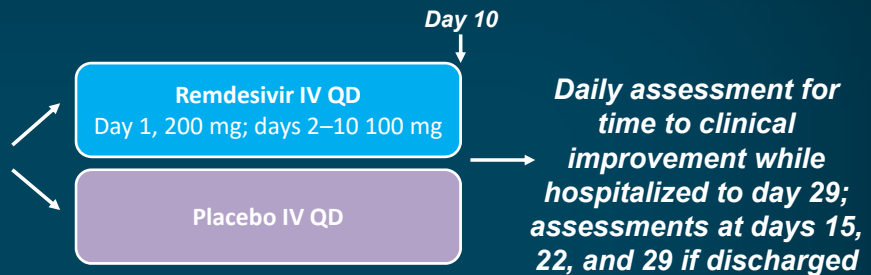
IDSA = Infectious Diseases Society of America; ECMO = extracorporeal membrane oxygenation; PO = by mouth.

Bhimraj A, et al. IDSA Guidelines. V3.9.0. (www.idsociety.org/practice-guideline/covid-19-guideline-treatment-and-management/).

Adaptive COVID-19 Treatment Trial (NIAID ACTT-1): Trial Design

- Multicenter, adaptive, randomized, double-blind, placebo-controlled phase 3 trial

Inclusion criteria (N = 1062)
- Adult patients ≥18 years of age
- Hospitalized with symptoms of COVID-19/SARS-CoV-2 infection and ≥1 of following:
  - Radiographic infiltrates by imaging
  - SpO_2 ≤94% on room air
  - Requiring supplemental oxygen
  - Requiring mechanical ventilation



- Primary endpoint: time to recovery by day 29 according to 8-point ordinal scale
- Secondary endpoints: treatment-related improvements in ordinal scale at day 15

QD = each day.

Beigel JH, et al. *N Engl J Med*. 2020;383:1813-1826.

Remdesivir: NIAID ACTT Clinical Trial

- 1062 patients in 68 sites randomized 1:1 to remdesivir or placebo
- Independent data safety monitoring board found that remdesivir shortened time to recovery compared with placebo

	Remdesivir	Placebo	*P*-value
Time to recovery	10 days	15 days	*P* <.001
Mortality	6.7% day 15 11.4% day 29	11.9% day 15 15.2% day 29	*P* = .07 (day 29)

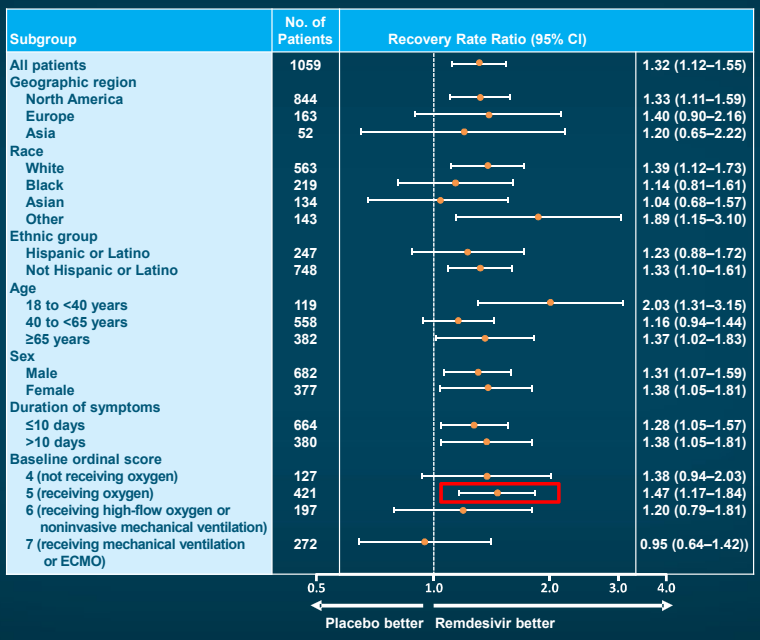
An ICU bed becomes available 5 days earlier
Benefit is in early disease

~30% reduction in mortality
Not statistically significant

NIAID = National Institute of Allergy and Infectious Diseases.

Beigel JH et al. *N Engl J Med*. 2020;383:1813-1826 plus supplement.

Remdesivir: NIAID ACTT Clinical Trial



Beigel JH, et al. *N Engl J Med.* 2020;383:1813-1826.

WHO SOLIDARITY Trial: Antiviral Drugs in Hospitalized Patients

Open-label, randomized phase 3 trial conducted in 405 hospitals in 30 countries

Adult patients ≥18 yrs of age; hospitalized with COVID-19 (N = 11,330)

- **Remdesivir IV QD**
  Day 1 200 mg QD; Days 2–10 100 mg QD
  (n = 2750)
- **Hydroxychloroquine PO**
  800 mg at 0, 6, 12 hrs; 400 mg BID days 2–10
  (n = 954)
- **Lopinavir/ritonavir PO**
  400/100 mg BID Days 1–14
  (n = 1411)
- **Interferon-β1a SQ**
  44 µg on Days 1, 3, and 6
  (n = 2063)
- **Standard of care**
  (n = 4088)

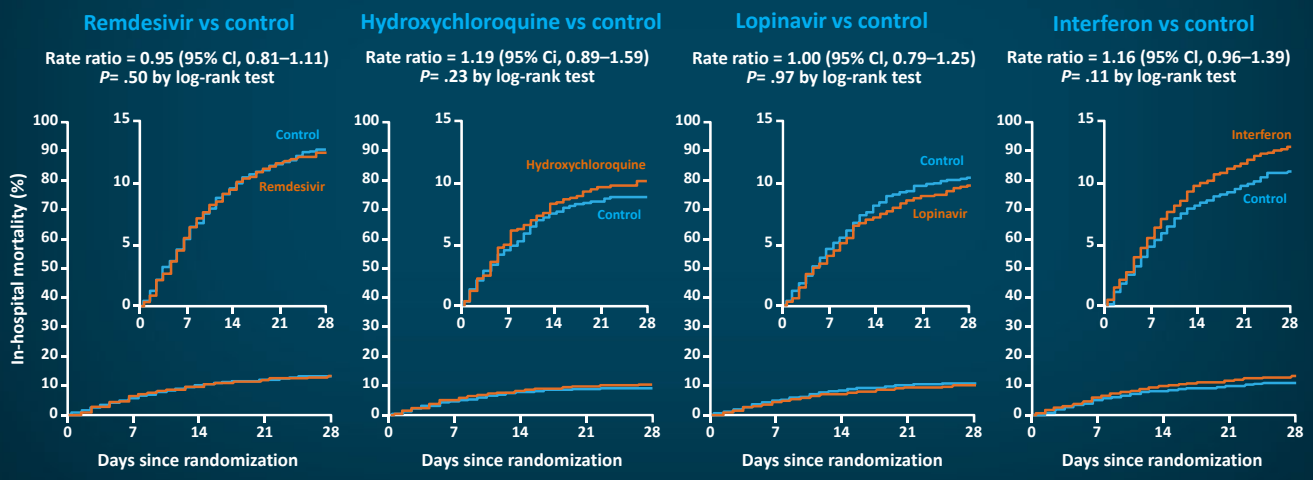
- **Primary endpoint**
  28-day in-hospital mortality
- **Secondary endpoints**
  - Initiation of ventilation
  - Duration of hospitalization

BID = twice daily; SQ = subcutaneous.

Pan H, et al; WHO (World Health Organization) Solidarity Trial Consortium. *N Engl J Med.* 2021;384:497-511.

WHO SOLIDARITY Trial: Results

Remdesivir, hydroxychloroquine, lopinavir, and interferon regimens had little to no effect on overall mortality, initiation of ventilation, or duration of hospital stay in hospitalized patients with COVID-19



Pan H, et al; WHO Solidarity Trial Consortium. *N Engl J Med.* 2021;384:497-511.

RECOVERY Trial Design

- Eligible patients (hospitalized with clinically suspected or laboratory-confirmed SARS-CoV-2 infection) were randomized to:

No additional treatment | **Dexamethasone** | **Hydroxychloroquine**

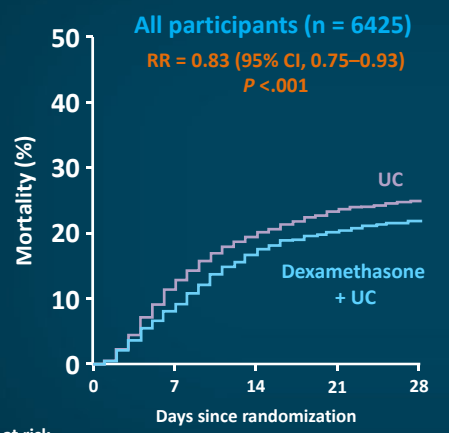
Lopinavir/ritonavir | **Azithromycin**

- Primary endpoint: 28-day mortality
- Patients with progressive disease (hypoxia and an inflammatory state) may undergo second randomization to no additional treatment or **tocilizumab**
- Current RECOVERY trials are investigating **baricitinib, casirivimab/imdevimab, aspirin, dexamethasone** (in children), and **colchicine**

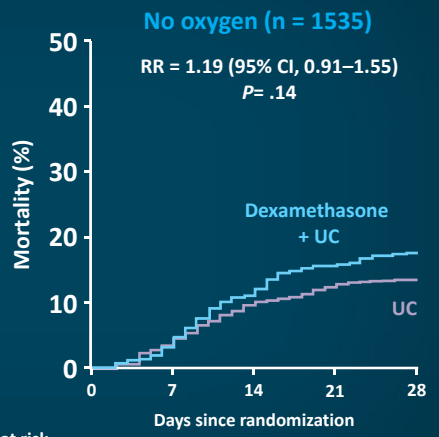
Randomized Evaluation of COVID-19 Therapy—RECOVERY (www.recoverytrial.net/files/recovery-protocol-v7-0-2020-06-18.pdf). Accessed 2/12/2021.

RECOVERY Trial: Mortality With Dexamethasone + UC vs UC Alone

2104 patients randomized to dexamethasone 6 mg QD for up to 10 days; 4321 patients received UC alone



No. at risk					
UC	4321	3754	3427	3271	3205
Dexamethasone/UC	2104	1903	1725	1659	1621



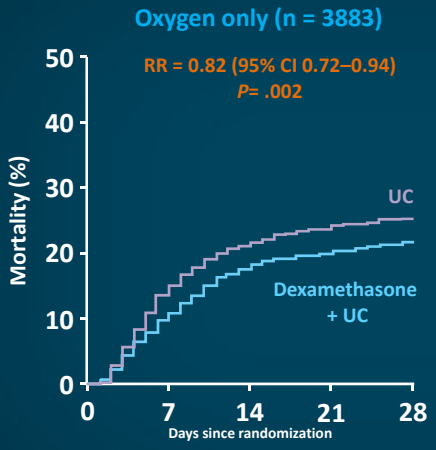
No. at risk					
UC	501	463	420	394	383
Dexamethasone/UC	1034	969	890	856	832

UC = usual care; RR = relative risk.

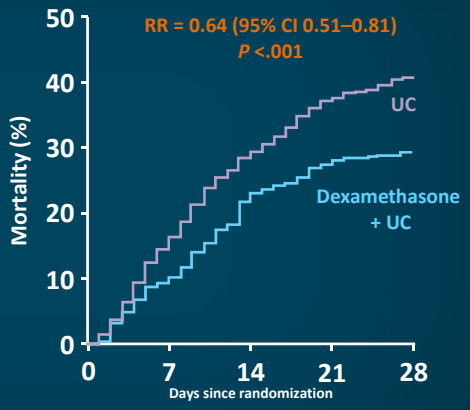
Horby P, et al; RECOVERY Collaborative Group. *N Engl J Med.* 2021;384:693-704.

RECOVERY Trial

Mortality in Patients On Oxygen or Mechanical Ventilation ± Dexamethasone



No. at risk					
Dexamethasone/UC	1279	1135	1036	1006	981
UC	2604	2195	2018	1950	1916

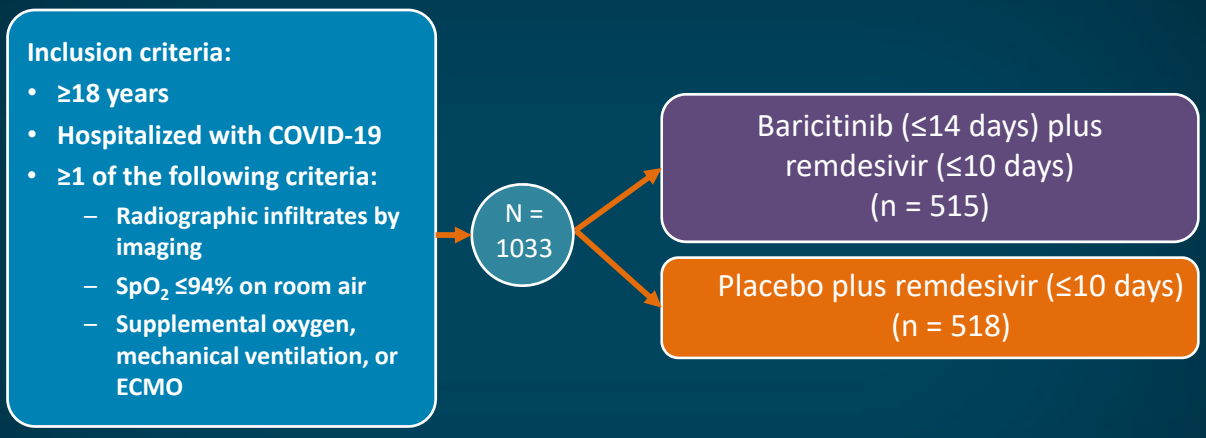


No. at Risk					
Dexamethasone/UC	324	290	248	232	228
UC	683	572	481	424	400

Horby P, et al; RECOVERY Collaborative Group. *N Engl J Med.* 2021;384:693-704.

EUAs for Hospitalized Patients

ACCT-2: Baricitinib Plus Remdesivir in Hospitalized Patients

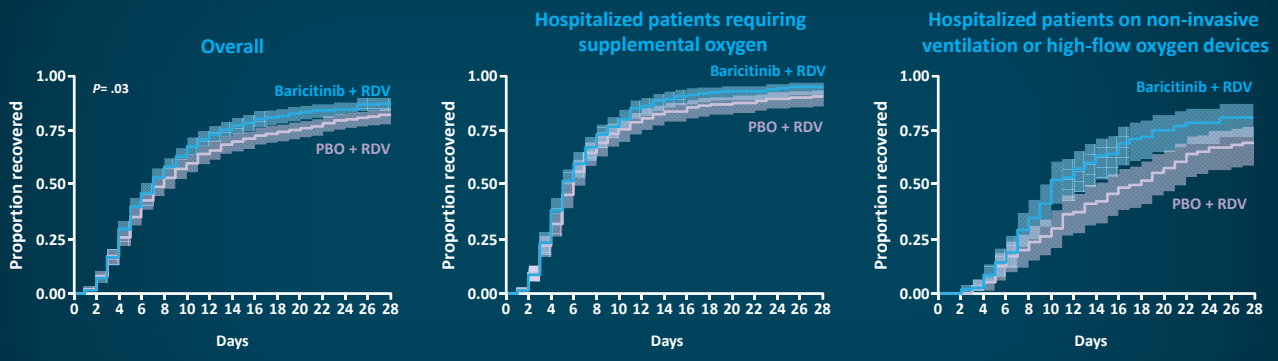


- Primary outcome: time to recovery
- Key secondary outcome: clinical status at day 15

Kalil AC, et al. *N Engl J Med.* 2021;384:795-807.

Baricitinib Plus Remdesivir: Recovery Time

- Recovery time was reduced with baricitinib vs placebo (7 days vs 8 days; rate ratio for recovery = 1.16; 95% CI, 1.01–1.32; *P*= .03)



- Time to recovery was significantly lower with baricitinib in patients receiving high-flow oxygen or noninvasive ventilation at enrollment (10 days vs 18 days; rate ratio for recovery = 1.51)

RDV = remdesivir.

Kalil AC, et al. *N Engl J Med.* 2021;384:795-807.

Baricitinib Plus Remdesivir: Results

- Baricitinib was associated with 30% higher odds of improvement in clinical status at day 15 (OR = 1.3)
- 28-day mortality was 5.1% in the combination group and 7.8% in the control group (HR for death = 0.65)

Overall Outcomes

Outcomes	Baricitinib + RDV (n = 515)	Placebo + RDV (n = 518)
Recovery		
No. of recoveries	433	406
Median time to recovery (95% CI), days	7 (6–8)	8 (7–9)
Rate ratio (95% CI)	1.16 (1.01–1.32), *P*= .03	
Mortality over first 14 days		
No. of deaths by day 14	8	15
Kaplan-Meier estimate of mortality by day 14, % (95% CI)	1.6 (0.8–3.2)	3.0 (1.8–5.0)
HR (95% CI) for data through day 14	0.54 (0.23–1.28)	
Mortality over entire trial period		
No. of deaths by day 28	24	37
Kaplan-Meier estimate of mortality by day 28, % (95% CI)	5.1 (3.5–7.6)	7.8 (5.7–10.6)
HR (95% CI)	0.65 (0.39–1.09)	

Kalil AC, et al. *N Engl J Med.* 2021;384:795-807.

ACTT-2: Adverse Events

Treatment-Emergent Adverse Events in ACTT-2		
	Baricitinib + RDV (n = 508) No. (%)	Placebo + RDV (n = 509) No. (%)
Grade 3 or 4 AEs	207 (40.7)	238 (46.8)
Hyperglycemia	25 (4.9)	40 (7.9)
Anemia	25 (4.9)	33 (6.5)
Decreased lymphocyte count	24 (4.7)	35 (6.9)
Acute kidney injury	20 (3.9)	36 (7.1)
Venous thromboembolism	21 (4.1)	16 (3.1)

AE = adverse event.

Kalil AC, et al. *N Engl J Med.* 2021;384:795-807 supplement.

Emergency Use Authorization for Baricitinib

- Baricitinib plus remdesivir was authorized for emergency use in hospitalized adults and pediatric patients ≥2 years of age requiring supplemental oxygen, invasive mechanical ventilation, or ECMO with suspected or confirmed COVID-19
- Recommended dosage:
  - Patients ≥9 years of age: 4 mg baricitinib once daily
  - Patients 2 to 9 years of age: 2 mg baricitinib once daily
- Recommended treatment duration is 14 days or until hospital discharge, whichever comes first
- Evaluate baseline eGFR, liver enzymes, and complete blood count to determine treatment suitability and dose

eGFR = estimated glomerular filtration rate.

FDA. Baricitinib EUA. (www.fda.gov/media/143823/download). Accessed 1/18/2021.

Summary of Agents Authorized for Emergency Use for COVID-19

- Several neutralizing mAb therapies are authorized for treatment of mild-to-moderate COVID-19 in patients at high risk of progressing to severe COVID-19 or hospitalization
  - mAbs against SARS-CoV-2 reduced the risk of COVID-19-related hospitalization
  - These therapies may be associated with worse clinical outcomes in hospitalized COVID-19 patients requiring high-flow oxygen or mechanical ventilation
  - Therapy should be provided as soon as possible and within 10 days of symptoms onset
- Baricitinib plus remdesivir is authorized for emergency use in hospitalized adults and pediatric patients ≥2 years of age requiring supplemental oxygen, invasive mechanical ventilation, or ECMO with suspected or confirmed COVID-19
  - Recommended treatment duration is 14 days or until hospital discharge, whichever comes first
  - Baricitinib plus remdesivir associated with improvements in recovery time

Thank you!

COVID-19 Frontline

A Light in the Darkness: New Virus-neutralizing Monoclonal Antibodies and Other Point-of-Care Therapies Recently Granted Emergency Use Authorizations for Patients with COVID-19

Resource	Address
National Infusion Center Association (NICA). **COVID-19 Antibody Therapies Resource Center.** Accessed January 21, 2021.	https://infusioncenter.org/infusion_resources/covid-19-antibody-treatment-resource-center/
Joost Wiersinga W, et al. **Pathophysiology, transmission, diagnosis, and treatment of coronavirus disease 2019 (COVID-19): A review.** *JAMA.* 2020;324:782-793.	https://pubmed.ncbi.nlm.nih.gov/32648899/
Guan WJ, et al. **Clinical characteristics of coronavirus disease 2019 in China.** *N Engl J Med*. 2020;382:1708-1720.	https://pubmed.ncbi.nlm.nih.gov/32109013/
Rothan HA, et al. **The epidemiology and pathogenesis of coronavirus disease (COVID-19) outbreak.** *J Autoimmun*. 2020;109:102433.	https://pubmed.ncbi.nlm.nih.gov/32113704/
Lechien JR, et al. **Clinical and epidemiological characteristics of 1420 European patients with mild-to-moderate coronavirus disease 2019.** *J Intern Med*. 2020;288:335-344.	https://pubmed.ncbi.nlm.nih.gov/32352202/
Wang W, et al. **Updated understanding of the outbreak of 2019 novel coronavirus (2019-nCoV) in Wuhan, China.** *J Med Virol*. 2020;92:441-447.	https://pubmed.ncbi.nlm.nih.gov/31994742/
Wu Z, et al. **Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China: Summary of a report of 72 314 cases from the Chinese Center for Disease Control and Prevention.** *JAMA*. 2020;323:1239-1242.	https://jamanetwork.com/journals/jama/fullarticle/2762130
Richardson S, et al. **Presenting characteristics, comorbidities, and outcomes among 5700 patients hospitalized with COVID-19 in the New York City area.** *JAMA*. 2020;323:2052-2059.	https://pubmed.ncbi.nlm.nih.gov/32320003/
Docherty AB, et al. **Features of 20,133 UK patients in hospital with COVID-19 using the ISARIC WHO Clinical Characterisation Protocol: Prospective observational cohort study.** *BMJ.* 2020;369:m1985.	https://www.bmj.com/content/bmj/369/bmj.m1985.full.pdf
Yuan X, et al. **Changes of hematological and immunological parameters in COVID-19 patients.** *Int J Hematol*. 2020;112:553-559.	https://pubmed.ncbi.nlm.nih.gov/32656638/
Bhimraj A, et al. **Infectious Diseases Society of America Guidelines on the Treatment and Management of Patients with COVID-19**. *IDSA Guidelines*. V3.6.0. Last updated January 8, 2021. Accessed January 21, 2021.	https://www.idsociety.org/practice-guideline/covid-19-guideline-treatment-and-management/
Alhazzani W, et al. **Surviving Sepsis Campaign: Guidelines on the management of critically ill adults with coronavirus disease 2019 (COVID-19).** *Intensive Care Med*. 2020;46:854-887.	https://pubmed.ncbi.nlm.nih.gov/32222812/

World Health Organization (WHO). **Clinical management of COVID-19.** Interim Guidance. May 27, 2020. Accessed January 21, 2021.	https://www.who.int/publications/i/item/clinical-management-of-covid-19
National Institutes of Health (NIH). **Coronavirus Disease 2019 (COVID-19) Treatment Guidelines.** Accessed January 21, 2021.	https://www.covid19treatmentguidelines.nih.gov/
Beigel JH, et al. **Remdesivir for the treatment of COVID-19 – Final Report.** *N Engl J Med.* 2020;383:1813-1826.	https://www.nejm.org/doi/full/10.1056/NEJMoa2007764
Spinner CD, et al. **Effect of remdesivir vs standard care on clinical status at 11 days in patients with moderate COVID-19: A randomized clinical trial.** *JAMA.* 2020;324:1048-1057.	https://jamanetwork.com/journals/jama/fullarticle/2769871
Horby P, et al. **Dexamethasone in hospitalized patients with COVID-19 – Preliminary report** [published online ahead of print, 2020 Jul 17]. *N Engl J Med.* 2020;NEJMoa2021436.	https://pubmed.ncbi.nlm.nih.gov/32678530/
Siddiqi HK, et al. **COVID-19 illness in native and immunosuppressed states: A clinical-therapeutic staging proposal.** *J Heart Lung Transplant.* 2020;39:405-407.	https://www.jhltonline.org/article/S1053-2498(20)31473-X/fulltext
Li L, et al. **Effect of convalescent plasma therapy on time to clinical improvement in patients with severe and life-threatening COVID-19: A randomized clinical trial.** *JAMA*. 2020;324:460-470.	https://pubmed.ncbi.nlm.nih.gov/32492084/
Kalil AC, et al. **Baricitinib plus remdesivir for hospitalized adults with COVID-19** [published online ahead of print, 2020 Dec 11]. *N Engl J Med.* 2020;NEJMoa2031994.	https://www.nejm.org/doi/full/10.1056/NEJMoa2031994
Baum A, et al. **Antibody cocktail to SARS-CoV-2 spike protein prevents rapid mutational escape seen with individual antibodies.** *Science*. 2020;369:1014-1018.	https://pubmed.ncbi.nlm.nih.gov/32540904/
Gandhi RT, et al. **Mild or moderate COVID-19**. *N Engl J Med.* 2020;383:1757-1766.	https://pubmed.ncbi.nlm.nih.gov/32329974/
Simonovich VA, et al. **A randomized trial of convalescent plasma in Covid-19 severe pneumonia** [published online ahead of print, 2020 Nov 24]. *N Engl J Med*. 2020;NEJMoa2031304.	https://pubmed.ncbi.nlm.nih.gov/33232588/
US Food and Drug Administration (FDA). Fact Sheet for Health Care Providers. **Emergency Use Authorization (EUA) of Baricitinib.** Issued November, 2020.	https://www.fda.gov/media/143823/download
US Food and Drug Administration (FDA). Fact Sheet for Health Care Providers. **Emergency Use Authorization (EUA) of Bamlanivimab.** Revised December 2020.	https://www.fda.gov/media/143603/download
US Food and Drug Administration (FDA). Fact Sheet for Health Care Providers. **Emergency Use Authorization (EUA) of Casirivimab and Imdevimab.** Revised December 2020.	https://www.fda.gov/media/143892/download

Weinreich DM, et al. **REGN-COV2, a neutralizing antibody cocktail, in outpatients with COVID-29** [published online ahead of print, 2020 Dec 17]**.** *N Engl J Med.* 2020;NEJMoa2035002.	https://www.nejm.org/doi/pdf/10.1056/NEJMoa2035002
Chen P, et al. **SARS-CoV-2 Neutralizing Antibody LY-CoV555 in Outpatients with Covid-19** [published online ahead of print, 2020 Dec 17]**.** *N Engl J Med.* 2020;NEJMoa2035002.	https://www.nejm.org/doi/full/10.1056/NEJMoa2029849
ACTIV-3/TICO LY-CoV555 Study Group, Lundgren JD, Grund B, et al. **A neutralizing monoclonal antibody for hospitalized patients with COVID-19** [published online ahead of print, 2020 Dec 22]**.** *N Engl J Med.* 2020;NEJMoa2033130.	https://www.nejm.org/doi/full/10.1056/NEJMoa2033130
Hansen J, et al. **Studies in humanized mice and convalescent humans yield a SARS-CoV-2 antibody cocktail**. *Science.* 2020;369:1010-1014.	https://science.sciencemag.org/content/369/6506/1010
Callaway E. **The coronavirus is mutating – does it matter?** *Nature.* 2020;585:174-177.	https://www.nature.com/articles/d41586-020-02544-6

For more information from the National Infusion Center Association, please visit: https://infusioncenter.org/

NATIONAL INFUSION CENTER ASSOCIATION

COVID-19 Antibody Treatment Resource Guide

The National Infusion Center Association has developed the resources described below to support prescribers, infusion providers, and patients in the safe and efficient use of COVID-19 antibody treatments. These resources can be found in the COVID-19 Antibody Treatment Resource Center.

Locating Sites of Care

NICA COVID-19 Locator

Use NICA's COVID-19 Locator Tool to identify sites of care administering COVID-19 antibody therapies.

Prescribers & Patients:

- Simply enter your city and state or your zip code and click "search"
- Click on a location to view site details including phone number, hours of operation, website, amenities, and more.
- If results do not populate for the area searched, try widening the search radius. If there are still no results to display, contact your local/regional health authorities as your state may not have opted into our locator program yet.

Infusion Providers:

- Be sure patients can find your infusion site by "claiming" your location and adding pertinent details to the profile like phone number, hours of operation, amenities, and more.
- Consider using the URL field to direct prescribers and patients to pertinent information on your center's website, such as patient arrival instructions, required forms, etc.
- If you need assistance claiming your center or building out your profile, email covid19@infusioncenter.org.

HHS Protect Public Data Hub: Therapeutics Distribution Locations

This national map is maintained by the Department of Health and Human Services and displays locations that have received shipments of COVID-19 antibody therapies.

- If results do not populate for the area searched, try widening the search radius. If there are still no results to display, contact your local/regional health authorities as your state may not have opted to have their locations displayed.
- It is important to note that locations are displayed based on the address where medication was *shipped* (e.g., centralized pharmacy, warehouse) and may not reflect the location/address where patient care is provided.

Resources for Prescribers

COVID-19 Antibody Treatment Indication Checklist

This checklist is intended to help prescribers determine if treatment with COVID-19 antibodies is authorized for use in accordance with the Emergency Use Authorization (EUA) requirements.

- If COVID-19 antibody treatment is not indicated, the checklist can be included in the medical record to document the clinical decision-making process.
- If COVID-19 antibody treatment is indicated, the checklist can accompany the medication order to document eligibility criteria and support medical necessity.†

† Individual infusion site documentation requirements may vary

COVID-19 Antibody Treatment Order Set

An order set is developed for each approved COVID-19 antibody therapy and serves as the prescription for treatment.

- Facilitates proper prescribing by capturing the necessary elements of a valid, complete COVID-19 antibody treatment infusion order
- Captures criteria for authorized use mandatory reporting requirements per EUA.
- Guides infusion clinician in safe administration by prompting best practices and adherence to administration requirements.
- Supports continuity of care by prompting the infusion provider to send records of completed treatment to the prescriber.

Coding Guide

List of common diagnosis codes that may apply to eligible patients.‡

- Provides prescriber with easy access to codes needed to complete order set and indications checklist
- ICD-10 data helps public health officials understand which patient populations are receiving COVID-19 therapeutics to support efforts aimed at equitable allocation and distribution of COVID-19 therapeutics.

Referral Checklist

Many HCPs prescribing COVID-19 antibody treatments may be unfamiliar with the infusion referral process. As COVID-19 antibody treatments are thought to be most effective when given as early as possible in the disease course, it is critical to streamline the referral process to reduce unnecessary delays to expedite access to treatment and optimize outcomes. This checklist provides a template overview of necessary steps to refer a patient for COVID-19 antibody treatment.

- Infusion sites of care are encouraged to download and modify this checklist to create a custom checklist including any unique, site-specific requirements.

Patient Education: Preparing for a COVID-19 Antibody Infusion

Prescribers can provide and review this handout with patients to help them understand and prepare for their infusion to promote treatment acceptance and adherence.

- Includes a field for prescriber to indicate facility name and phone number where referral/order was sent, with instruction for patient to call if they have not received an appointment promptly. This is intended to reduce treatment delays or patients "timing out" of treatment eligibility due to communication challenges.

Resources for Infusion Providers

Casirivimab + Imdevimab Flowsheet / Bamlanivimab Flowsheet

The flowsheet, sometimes called a treatment note, is used to document all care associated with administration of COVID-19 antibody therapies.

- Guides the clinician to follow industry standards and best practices as well as adhere to administration and documentation requirements under the EUA.

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‡ This is not an all-inclusive list of diagnoses meeting EUA criteria for high risk for progressing to severe COVID-19 and/or hospitalization.

- Provides a detailed record to fax to the referring prescriber for inclusion in the patient's medical record
- Especially helpful for temporary sites of care or other infusion providers using paper documentation.

Drip Rate Tables

In sites of care administering infusions by gravity (as opposed to with an infusion pump or other rate-control device), HCPs will be required to calculate the appropriate drip rate using the volume to be infused and drop factor of the administration set used (infusion tubing). As many HCPs may be unfamiliar with the calculations required, these tables provide the appropriate drip rates for administration of both products using administration sets with any drop factor.

Casirivimab + Imdevimab Medication Safety Alert

Casirivimab and Imdevimab are supplied in multiple packaging configurations and have unique preparation requirements that may increase risk for medication errors.

- Provides considerations and strategies to reinforce use of proper quantities/combinations of product to prepare a single dose.

Patient Education: COVID-19 Antibody Treatment Discharge Instructions

This patient handout explains signs and symptoms to watch for and report following a COVID-19 antibody infusion.

- Provides home care instructions for discomfort at the IV site
- Reinforces the need to continue isolation to prevent disease transmission
- Lists emergency warning signs that necessitate seeking medical attention

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Additional Resources

NICA Standards for In-Office Infusion

View NICA's minimum standards for the administration of intravenous and injectable medication in an outpatient setting.

Eli Lilly Bamlanivimab Playbook

NICA collaborated with Eli Lilly to develop this playbook with in-depth information about preparation and administration of bamlanivimab as well as other considerations for operationalizing an infusion site.

Regeneron Casirivimab + Imdevimab Emergency Use Authorization (EUA) Guidebook

NICA collaborated with Regeneron to develop this playbook with in-depth information about preparation and administration of casirivimab + imdevimab as well as other considerations for operationalizing an infusion site.

Report an Adverse Event to MedWatch

Healthcare providers must submit a report on all medication errors and all serious adverse events potentially related to COVID-19 antibody therapy.

Multilingual COVID-19 Resources

The CDC has developed the COVID-19 Communication Toolkit: For Migrants, Refugees, and Other Limited-English-Proficient Populations in various languages. Resources are available in Spanish, Simplified Chinese, Korean, Tagalog, Hmoob (Hmong), Af Soomaali (Somali), and Vietnamese.