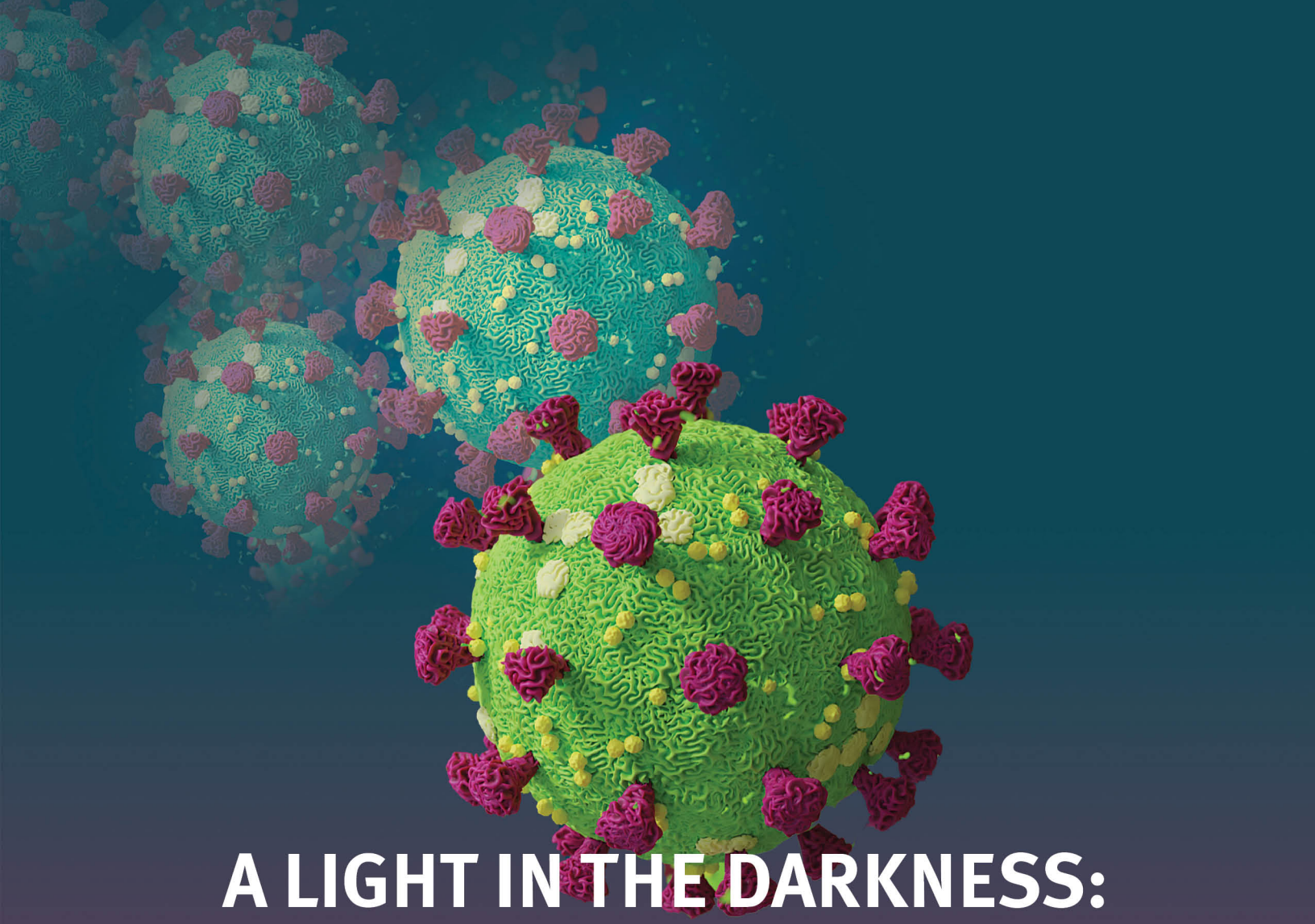

A LIGHT IN THE DARKNESS:

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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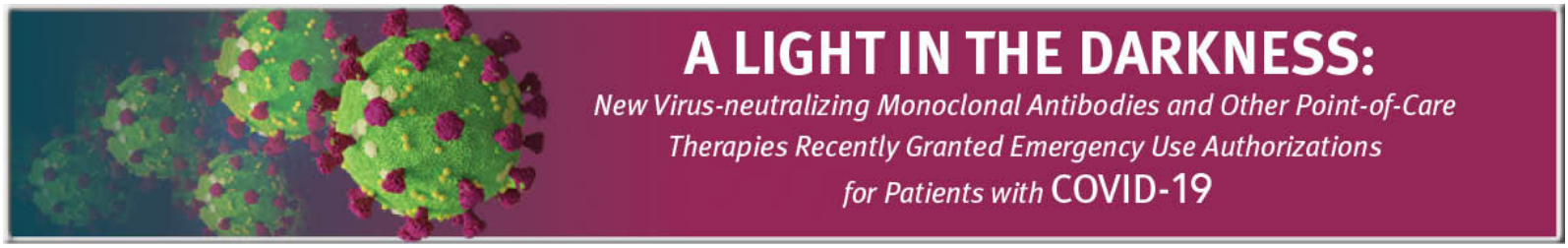
This activity is supported by an educational grant from Lilly.



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

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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 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

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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 trials, as well he has received research funds paid to the university from Merck Inc, Gilead Sciences and Arbutus Pharmaceuticals. He has also provided contracted research for Regeneron, Eli Lilly, and air Pharmaceuticals, as well as serving on the advisory board for hepatitis b functional cure program at Merck Inc.
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

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2. Participate in the live virtual activity.
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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
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Disclosures

- Pleases see Program Overview for specific speaker disclosure information.
- During this lecture, the faculty may mention the use of medications for both FDA-approved and nonapproved indications.

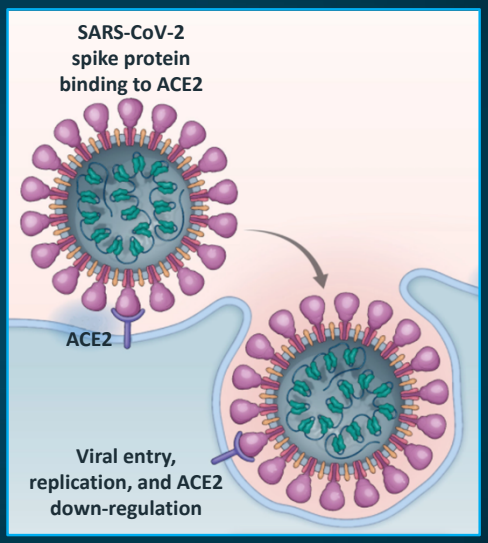
This activity is supported by an independent medical education grant from Lilly.

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]



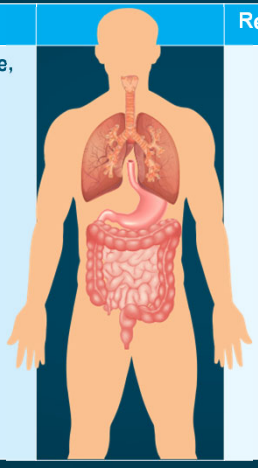
SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; COVID-19 = coronavirus disease 2019; ACE = angiotensin-converting enzyme.

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, cough, fatigue, sputum production, headache	Rhinorrhea, sneezing, sore throat
Hemoptysis, acute cardiac injury	Pneumonia
Hypoxemia	Ground-glass opacities
Dyspnea, Lymphopenia	RNAemia, acute respiratory distress syndrome
Diarrhea	



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

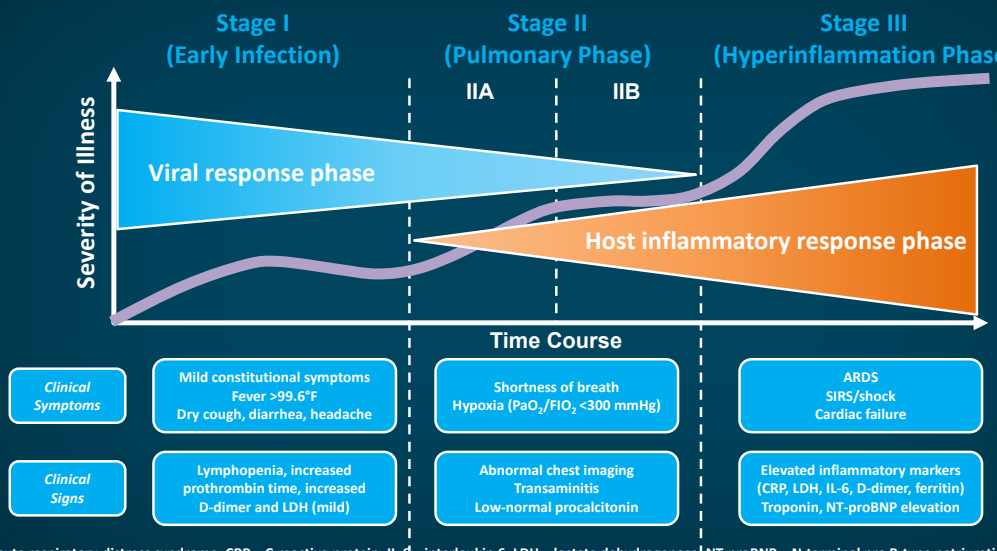
A large study of 44,672 confirmed COVID-19 cases identified by the Chinese Centers for Disease Control and Prevention found that 81% of cases were mild-to-moderate, 13.8% were severe, and 6.1% were critical

	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.

Risk Factors for Severe Disease

Case series of 5700 hospitalized patients in NYC, Long Island, and Westchester County, NY found:

- Median number of total comorbidities at admission: 4 (IQR: 2–8)
- 88% of patients had more than one comorbidity
- Most common comorbidities were hypertension (56.6%), obesity (41.7%), and diabetes (33.8%)

Risk Factors for Severe COVID-19

- Older age
- Chronic obstructive pulmonary disease
- Cardiovascular disease (eg, heart failure, coronary artery disease, or cardiomyopathy)
- Type 2 diabetes mellitus
- Obesity (body-mass index >30)
- Sickle cell disease
- Chronic kidney disease
- Immunocompromised state from solid-organ transplantation
- Cancer

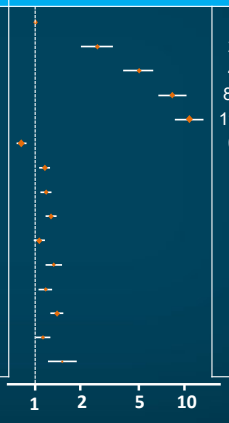
IQR = interquartile range.

Richardson S, et al. *JAMA*. 2020;323:2052-2059. NIH. COVID-19 treatment guidelines (https://files.covid19treatmentguidelines.nih.gov/guidelines/covid19treatmentguidelines.pdf). Accessed 12/2/2020.

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

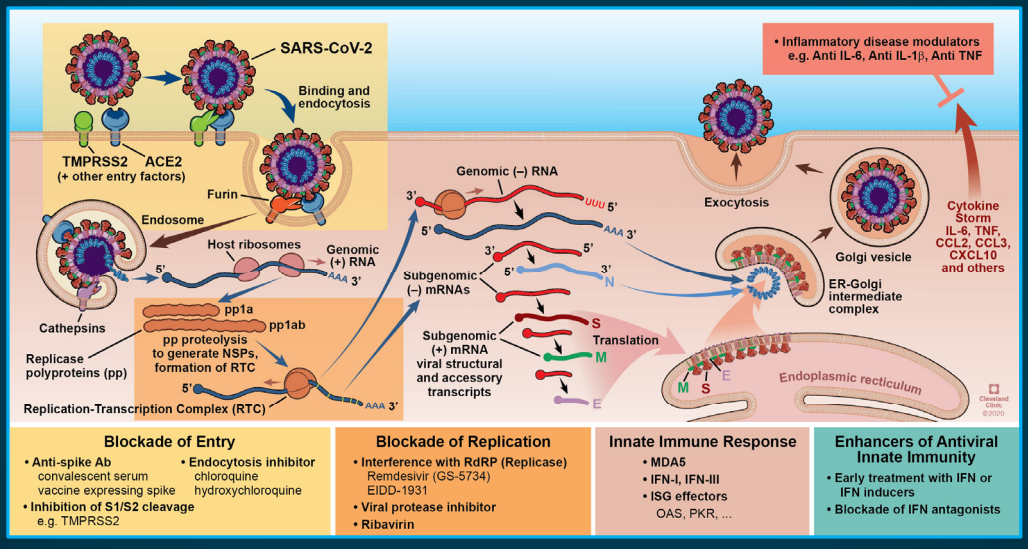
		HR (95% CI)	*P*- value
Age on admission (years)	<50		
	50–59	2.63 (2.06–3.35)	<.001
	60–69	4.99 (3.99–6.25)	<.001
	70–79	8.51 (6.85–10.57)	<.001
	≥80	11.09 (8.93–13.77)	<.001
Sex at birth	Female	0.81 (0.75–0.86)	<.001
Chronic cardiac disease	Yes	1.16 (1.08–1.24)	<.001
Chronic pulmonary disease	Yes	1.17 (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.

Viral Targets



TMPRSS2 = transmembrane serine protease 2; NSP = non-structural proteins; mRNA = messenger RNA; Ab = antibody; CCL = C-C motif chemokine ligand; C-X-C motif chemokine ligand; TNF = tumor necrosis factor; IFN = interferon; ISG = interferon-stimulated genes; OAS = 29 59 –oligoadenylate synthetases; PKR = RNA-dependent protein.

Bergmann CC, Silverman RH. *Cleve Clin J Med*. 2020;87:321-327

Antibody Therapies for the Management of COVID-19

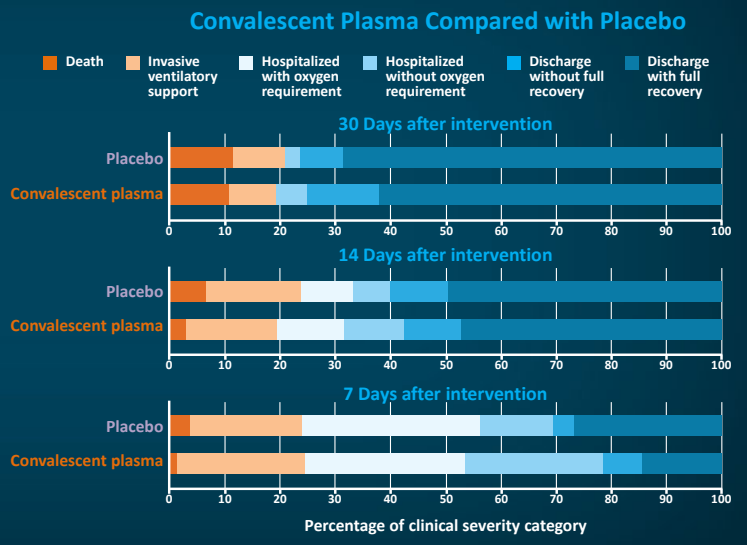
Antibody Therapy in Mild-to-Moderate COVID-19

	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

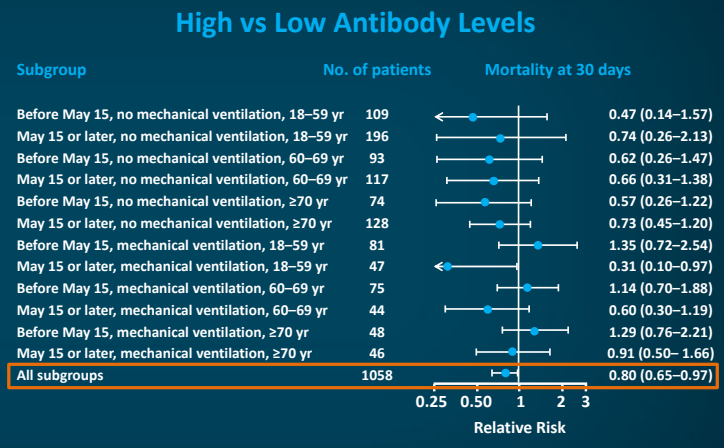


ICU = intensive care unit.

Simonovich VA, et al. *N Engl J Med.* 2020;Nov 24: Epub ahead of print.

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;Jan 13: Epub ahead of print.

Emergence 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 (EUA)

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

Bamlanivimab 700 mg

Administer as a single IV infusion over minimum of 16–60 minutes

Bamlanivimab 700 mg AND Etesevimab 1400 mg

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

Casirivimab 1200 mg AND Imdevimab 1200 mg

Must be administered together as a single IV infusion over minimum of 60 minutes

IV = intravenous.

Bamlanimab EUA. (http://pi.lilly.com/eua/bamlanivimab-eua-factsheet-hcp.pdf). Bamlanivimab and etesevimab EUA. (www.fda.gov/media/145802/download). Casirivimab and imdevimab EUA. (www.fda.gov/media/143892/download). URLs accessed 2/12/2021.

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

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

Identifying High-Risk Candidates for mAb Therapy

High risk is defined as a patient who meets ≥1 of the following criteria

Patients of any age with:
- BMI ≥35
- Chronic kidney disease
- Diabetes
- Immunosuppressive disease
- Current immunosuppressive therapy

Patients aged ≥65 years

Patients ≥55 years of age with:
- Cardiovascular disease, OR
- Hypertension, OR
- Chronic obstructive pulmonary disease/ other chronic respiratory condition

Patients aged 12–17 years with:
- BMI >85th percentile for age and gender
- Sickle cell disease
- Congenital or acquired heart disease
- Neurodevelopmental disorders (eg, cerebral palsy)
- Asthma, reactive airway, or other chronic respiratory disease that requires daily medication for control
- A medical-related technological dependence (eg, tracheostomy, gastrostomy, positive-pressure ventilation (not related to COVID-19)

BMI = body-mass index.

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

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 PCR test is positive for SARS-CoV-2.
- Nora's prior medical history is significant for hypertension and depression. Her BMI is 36 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

PCR = polymerase-chain reaction.

Is Nora a Candidate for Monoclonal Antibody Therapy?

High risk is defined as a patient who meets ≥1 of the following criteria

Patients of any age with:
- BMI ≥35
- Chronic kidney disease
- Diabetes
- Immunosuppressive disease
- Current immunosuppressive therapy

Patients aged ≥65 years

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Casirivimab and imdevimab EUA. (www.fda.gov/media/143892/download). Bamlanivimab EUA. (http://pi.lilly.com/eua/bamlanivimab-eua-factsheet-hcp.pdf). URLs accessed 1/18/2021.

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

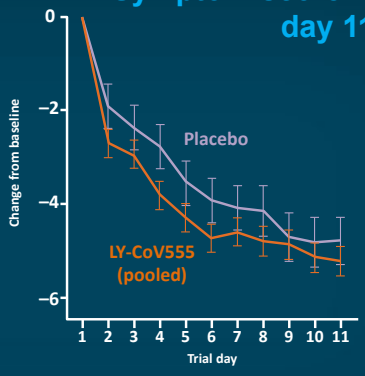
Chen P, et al. *N Engl J Med*. 2020;Oct 28: Epub ahead of print.

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)

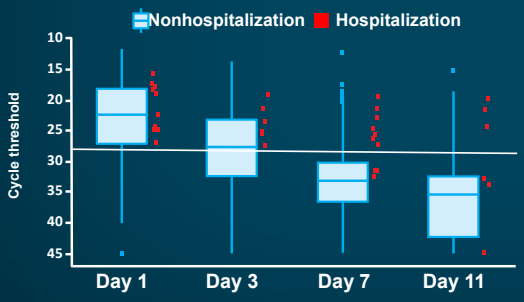
- Symptom scores ranged from 0 to 24 and included eight domains, each of **which** was graded on a scale of 0 (no symptoms) to 3 (severe symptoms)

Chen P, et al. *N Engl J Med*. 2020;Oct 28: Epub ahead of print.

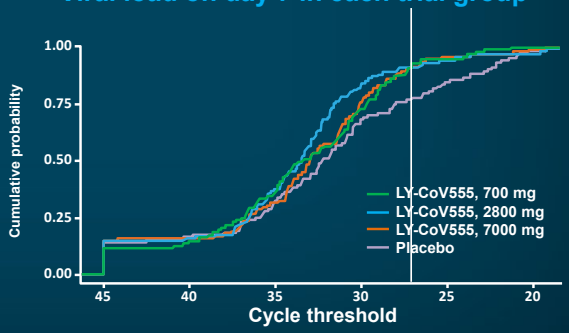
BLAZE-1: Viral Loads Over Time

- 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*. 2020;Oct 28: Epub ahead of print.

BLAZE-1: Bamlanivimab Safety

- No serious AEs reported with bamlanivimab use

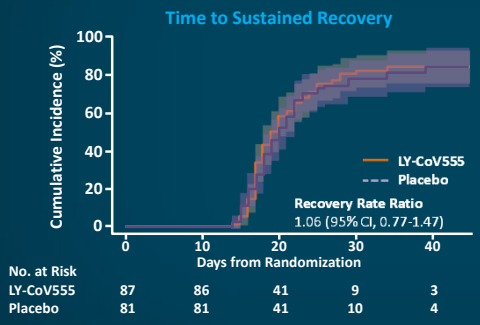
	LY-CoV555 (N=309)				Placebo (n = 143)
	700 mg (n = 101)	2800 mg (n = 107)	7000 mg (n = 101)	Pooled Doses (n = 309)	
Adverse Event	Number of patients (%)				
Serious adverse event*	0	0	0	0	1 (0.7)
Adverse events					
Any	24 (23.8)	23 (21.5)	22 (21.8)	69 (22.3)	35 (24.5)
Mild	16 (15.8)	18 (16.8)	10 (9.9)	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

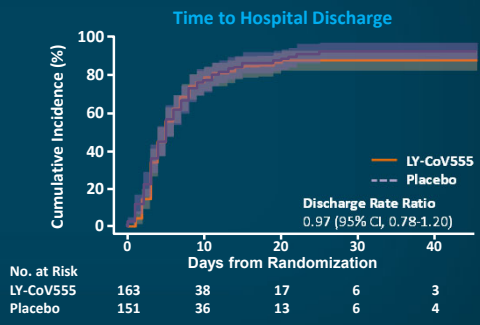
- Infusion-related reactions were reported in 2.3% of patients receiving bamlanivimab and 1.4% of patients in the placebo group
  - Most reactions were mild and occurred during the infusion

Chen P, et al. *N Engl J Med*. 2020;Oct 28: Epub ahead of print.

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

ACTIV-3/TICO LY-CoV555 Study Group. *N Engl J Med.* 2020;Dec 22: Epub ahead of print.

Case Study 2: Sandy

- Sandy is a 79-year-old woman who was tested for COVID-19 after her husband began to experience symptoms.
- Her past medical history is significant for COPD and type 2 diabetes. She has a 20-pack-year history of cigarette smoking.
- Sandy tested positive for COVID-19 five days ago, but she is not experiencing shortness of breath. She reports a mild headache and fatigue over the last 2 days.
- **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

COPD = chronic obstructive pulmonary disease.

Is Sandy a Candidate for Monoclonal Antibody Therapy?

High risk is defined as a patient who meets ≥1 of the following criteria

Patients of any age with:
- BMI ≥35
- Chronic kidney disease
- Diabetes
- Immunosuppressive disease
- Current immunosuppressive therapy

Patients aged ≥65 years

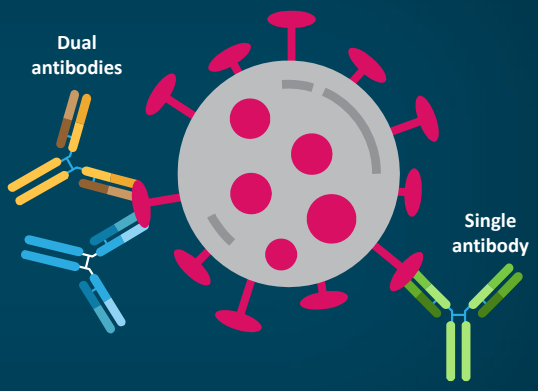
Patients ≥55 years of age with:
- Cardiovascular disease, OR
- Hypertension, OR
- Chronic obstructive pulmonary disease/ other chronic respiratory condition

	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

Casirivimab and imdevimab EUA. (www.fda.gov/media/143892/download). Bamlanivimab EUA. (http://pi.lilly.com/eua/bamlanivimab-eua-factsheet-hcp.pdf). NIH treatment guidelines (https://files.covid19treatmentguidelines.nih.gov/ guidelines/covid19treatmentguidelines.pdf). URLs accessed 1/18/2021.

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.

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;Jan 21: Epub ahead of print.

Casirivimab and Imdevimab (REGN-COV2)

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

Inclusion criteria:

- ≥18 years
- ≥1 symptom of COVID-19
- Positive SARS-CoV-2 test <72 hours prior to randomization
- Symptoms consistent with COVID-19 with onset <7 days before randomization
- No hospitalization due to COVID-19

R

- 2.4 g casirivimab and imdevimab (1.2 g each)
- 8.0 g casirivimab and imdevimab (4.0 g each)
- Placebo

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*. 2020;Dec 17: Epub ahead of print.

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

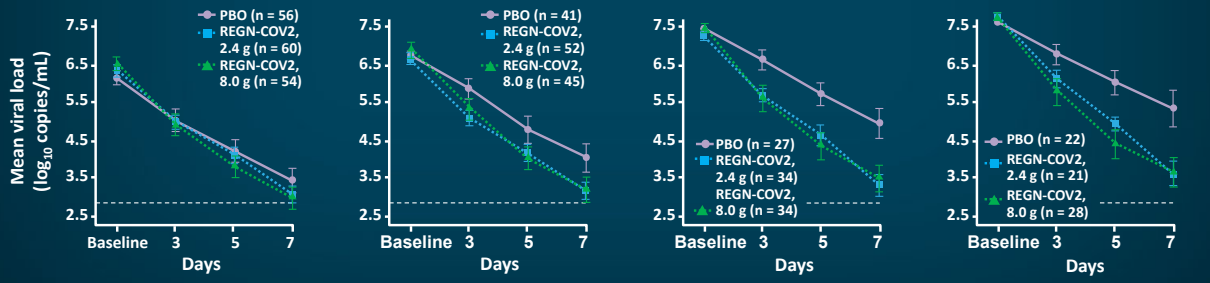
Viral load over time according to baseline viral-load category

	>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*. 2020;Dec 17: Epub ahead of print.

Casirivimab/Imdevimab Safety

Event	REGN-COV2			Placebo (n = 93)
	2.4 g (n = 88)	8.0 g (n = 88)	Combined (n = 176)	
	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.* 2020;Dec 17: Epub ahead of print.

Top-line Results on mAb Therapies

- **BLAZE-2: Bamlanivimab in SARS-CoV-2-negative nursing home residents**
  - Phase 3 trial of 965 participants (299 residents and 666 nursing home staff) who tested negative for SARS-CoV-2 at baseline
  - Residents randomized to bamlanivimab may have up to 80% lower risk of contracting COVID-19
- **BLAZE-1: Bamlanivimab plus etesivimab**
  - Phase 3 trial of 1035 patients recently diagnosed with COVID-19 and at high risk of severe COVID-19 or hospitalization showed that therapy with bamlanivimab and etesevimab reduced COVID-19-related hospitalizations and deaths by 70% (*P*= .0004) compared with placebo
- **Casirivimab and imdevimab**
  - 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

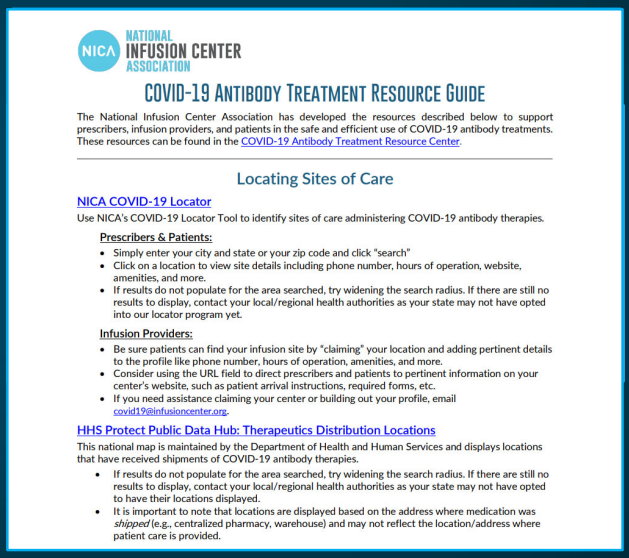
OR = odds ratio.

Lilly BLAZE-2 press release. 1/21/2121. (https://investor.lilly.com/node/44291/pdf). Lilly BLAZE-1 press release. 1/26/2021. (https://investor.lilly.com/node/44331/pdf). Regeneron press release. 1/26/21. (https://newsroom.regeneron.com/news-releases/news-release-details/regeneron-reports-positive-interim-data-regen-covtm-antibody)

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 92%.
- He reports that his shortness of breath has progressively worsened since his COVID-19 diagnosis 13 days ago.
- His past medical history is significant for diabetes and a prior myocardial infarction.

- **Is Gary a candidate for monoclonal antibody therapy?**

  A. Yes, he should receive monoclonal antibody therapy.

  B. No, he should not receive monoclonal antibody therapy.

Is Gary a Candidate for Monoclonal Antibody Therapy?

- Monoclonal antibodies are authorized for use within 10 days of symptom onset in patients with mild-to-moderate COVID-19.
- Gary is not a candidate since he has severe COVID-19 (SpO_2 <94% on room air) and his symptoms began 13 days ago.

	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

Casirivimab and imdevimab EUA. (www.fda.gov/media/143892/download). Bamlanivimab EUA. (http://pi.lilly.com/eua/bamlanivimab-eua-factsheet-hcp.pdf). https://files.covid19treatmentguidelines.nih.gov/guidelines/covid19treatmentguidelines.pdf URLs accessed 1/18/2021.

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

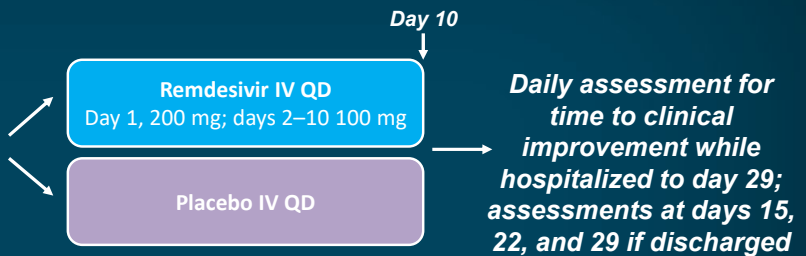
IDSA = Infectious Diseases Society of America; ECMO = extracorporeal membrane oxygenation; PO = by mouth.

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.

COVID-19 Clinical Status Ordinal Scale

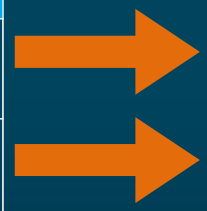
Clinical Status Ordinal Scale	Clinical Status Description for Assessment
1	Not hospitalized, no limitations on activities
2	Not hospitalized, limitation on activities, and/or requiring home oxygen
3	Hospitalized, not requiring supplemental oxygen, and no longer requires ongoing medical care (if hospitalization extended for infection-control purposes)
4	Hospitalized, not requiring supplemental oxygen; requiring ongoing medical care (COVID-19 related or otherwise)
5	Hospitalized, requiring supplemental oxygen
6	Hospitalized, on noninvasive ventilation or high-flow oxygen devices
7	Hospitalized, on invasive mechanical ventilation or ECMO
8	Death

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)



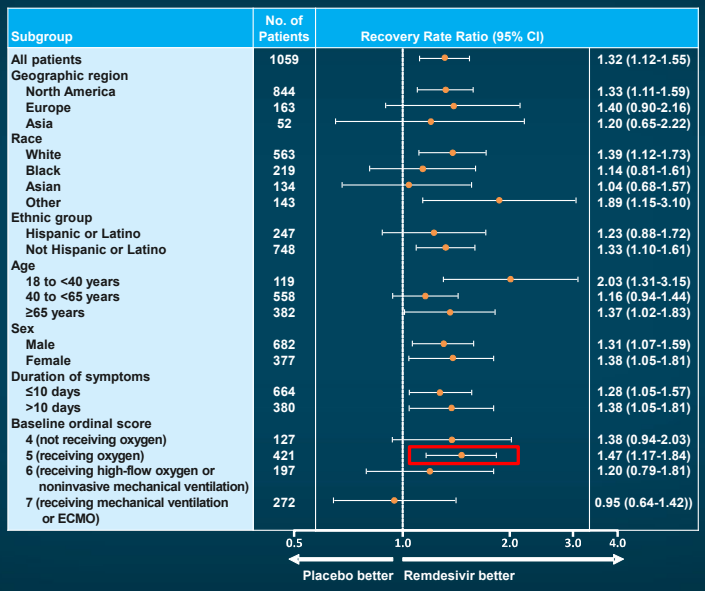
An ICU bed becomes available 5 days earlier
Benefit is in early disease

~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.

SIMPLE-Moderate Study: Trial Design

- Multicenter, randomized, open-label phase 3 trial of remdesivir in patients with moderate COVID-19

Inclusion criteria (N = 584)

- Patients ≥12 years of age
- Hospitalized with SARS-CoV-2 infection confirmed by RT-PCR
- Radiographic infiltrates by imaging
- SpO_2 >94% on room air

Remdesivir IV QD
Day 1, 200 mg; days 2–5, 100 mg
(n = 191)

Remdesivir IV QD
Day 1, 200 mg; days 2–10 100 mg
(n = 193)

SoC
(n = 200)

- Primary endpoint: improvement on 7-point ordinal scale on day 11
- Secondary endpoint: treatment-emergent adverse events

RT-PCR = reverse transcriptase-polymerase chain reaction; SoC = standard of care.

Spinner CD, et al. *JAMA*. 2020;324:1048-1057.

SIMPLE-Moderate Study: Efficacy

Patients receiving 5-day remdesivir were 65% more likely to have clinical improvement at day 11 vs SoC (OR = 1.65; 95% CI: 1.09–2.48; *P* = .017)

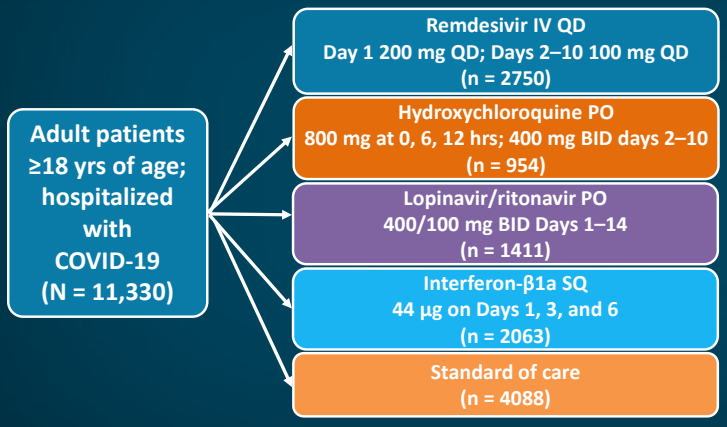
- No significant improvement noted with 10-day remdesivir vs SoC; OR = 1.31; 95% CI, 0.88–1.95; *P*= .18)

Clinical efficacy at day 11	Remdesivir 5-Day (n = 191) n (%)	Remdesivir 10-Day (n = 193) n (%)	SoC (n = 200) n (%)
Clinical improvement	134 (70)	126 (65)	121 (61)
Requiring any oxygen support	12 (6)	13 (7)	22 (11)
Recovery	141 (74)	132 (68)	128 (64)
Death	0	2 (1)	4 (2)

Spinner CD, et al. *JAMA*. 2020;324:1048-1057.

WHO SOLIDARITY Trial: Antiviral Drugs in Hospitalized Patients

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



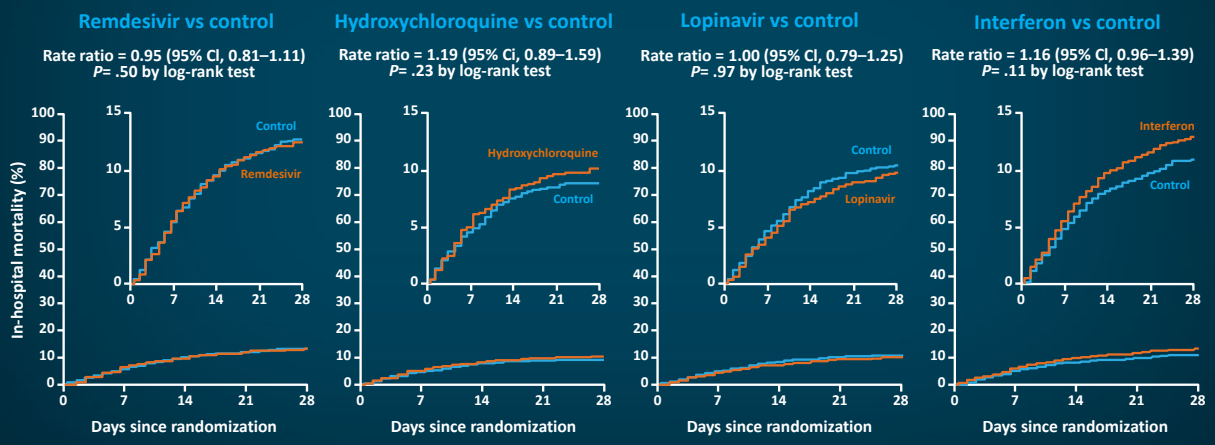
- **Primary endpoint**
  28-day in-hospital mortality
- **Secondary endpoints**
  - Initiation of ventilation
  - Duration of hospitalization

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**

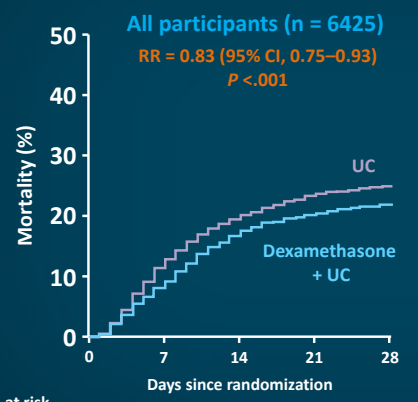
- Primary endpoint: 28-day mortality
- Patients with progressive disease (hypoxia and an inflammatory state) may undergo second randomization to no additional treatment or **tocilizumab**
- Current RECOVERY trials are investigating **baricitinib, casirivimab/imdevimab, aspirin, dexamethasone** (in children),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

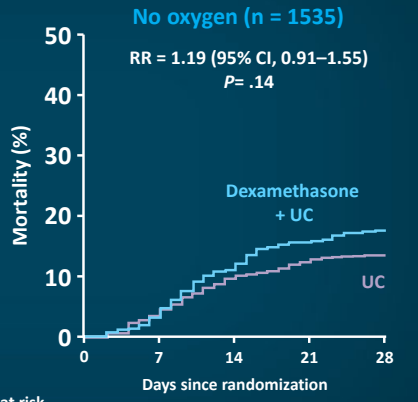
RECOVERY Trial

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



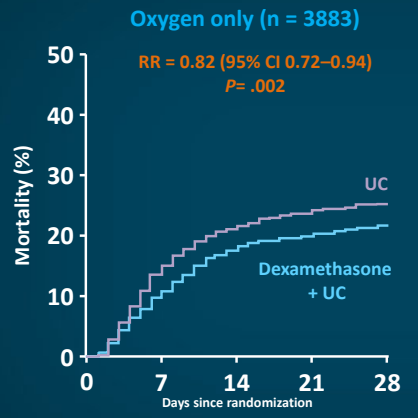
No. at risk					
UC	501	463	420	394	383
Dexamethasone/UC	1034	969	890	856	832

UC = usual care; RR = relative risk.

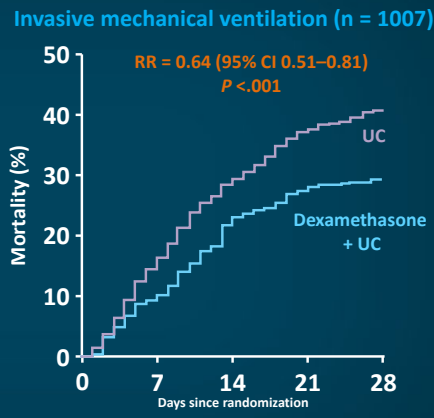
Horby P, et al; RECOVERY Collaborative Group. *N Engl J Med.* 2020;Jul 17:Epub ahead of print.

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

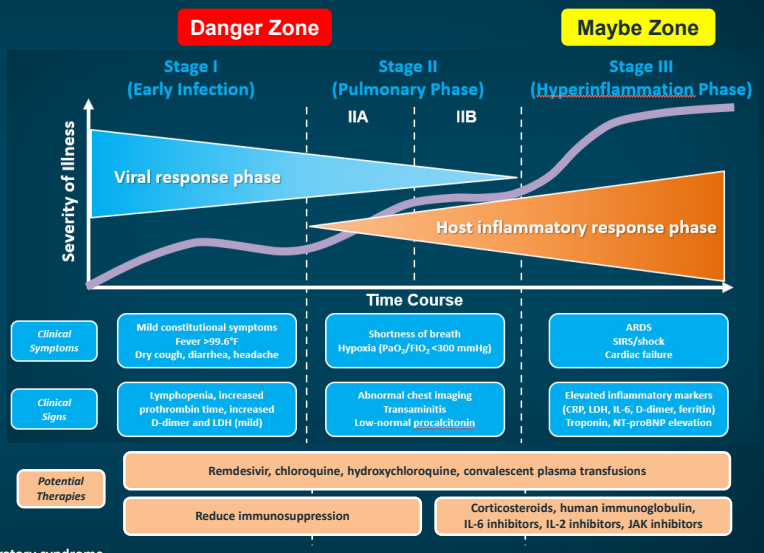


No. at Risk					
Dexamethasone/UC	324	290	248	232	228
UC	683	572	481	424	400

Horby P, et al; RECOVERY Collaborative Group. *N Engl J Med.* 2020;Jul 17:Epub ahead of print.

Corticosteroids for Respiratory Syndromes

- Corticosteroid use for SARS and MERS patients
  - Higher plasma RNA levels at weeks 2–3 into illness (likely prolonged viremia)
  - Increased 30-day mortality **(adjusted OR = 1.87, 95% CI, 1.02–3.44).**
- Corticosteroid use for severe influenza pneumonia
  - Higher rates of secondary bacterial infection and **mortality (OR = 3.06, 95% CI, 1.58–5.92)**

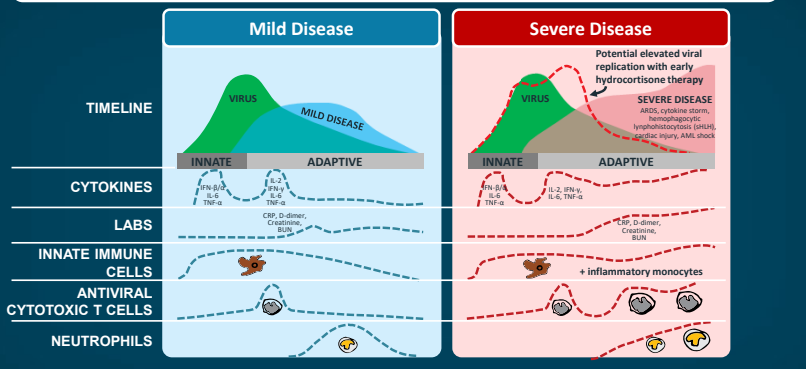


SARS = severe acute respiratory syndrome; MERS = Middle East respiratory syndrome.

Arabi YM et al. *Am J Respir Crit Care Med.* 2018;197:757-767. Rodrigo C, et al. *Cochrane Database Syst Rev.* 2016;3:CD010406. Adapted from Siddiqi HK, Mehra MR. *J Heart Lung Transplant.* 2020;39:405-407.

Corticosteroids for COVID-19

What is the **immune response to SARS-CoV-2,** and how does this inform our treatment strategies?

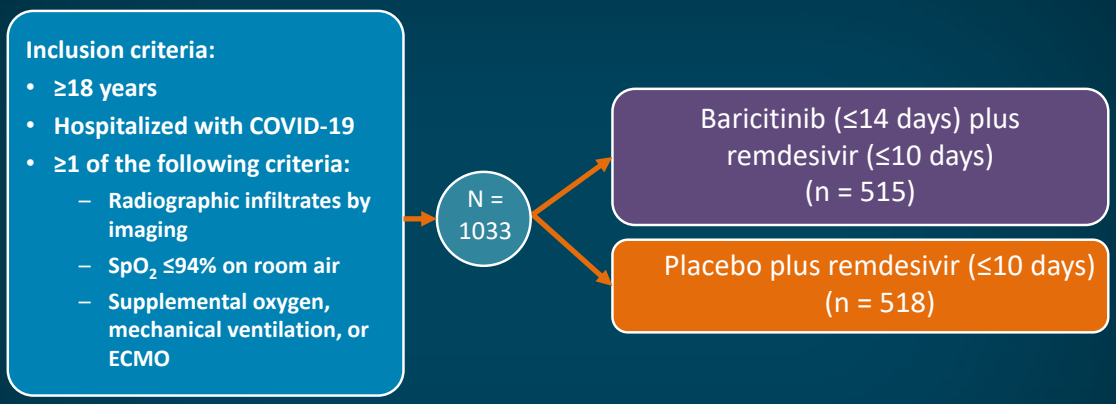


Current evidence **DOES NOT support early corticosteroid use** in mild-moderate COVID-19 without comorbidities.

Thevarajan I, et al. *Nat Med.* 2020;26:453-455. Wang D, et al. *JAMA.* 2020;323:1061-1069. Ruan Q, et al. *Intensive Care Med.* 2020;Mar 3: 1-3. Lee N, et al. *J Clin Virol.* 2004;31:304-309. Chen J, et al. *J Virol.* 2010;84:1289-1301. Russell CD, et al. *Lancet.* 2020;395:473-475. Liao M, et al. *MedRxiv.* 2020.

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.* 2020;Epub ahead of print.

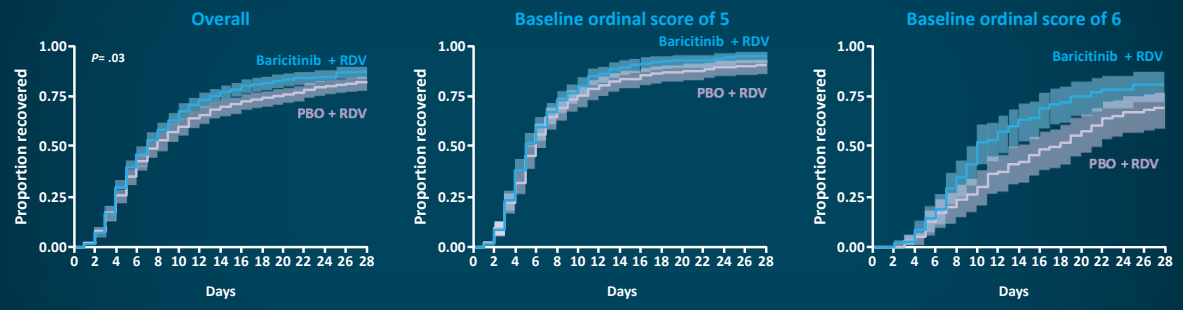
ACTT-2: Ordinal Scale

Ordinal Scale Used for Outcome Measures	
Recovered	
1	Not hospitalized, no limitations on activities
2	Not hospitalized, limitation on activities and/or requiring home oxygen
3	Hospitalized, not requiring supplemental oxygen—no longer requiring ongoing medical care
Population enrolled	
4	Hospitalized, not requiring supplemental oxygen—requiring ongoing medical care
5	Hospitalized, requiring supplemental oxygen
6	Hospitalized, on non-invasive ventilation or high-flow oxygen devices
7	Hospitalized, on mechanical ventilation or ECMO
8	Death

Kalil AC, et al. *N Engl J Med.* 2020;Dec 11:Epub ahead of print.

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.* 2020;Dec 11:Epub ahead of print.

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.* 2020;Dec 11:Epub ahead of print.

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.* 2020;Dec 11:Epub ahead of print 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.

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

Case Study 4: Tom

- Tom is a 66-year-old man with diabetes and COPD who presents to the ED with increasing weakness and progressive exertional dyspnea. His SpO_2 was 92% on room air at arrival, and he was admitted.
- His O_2 saturation would remain >90% while at rest, but Tom would desaturate to 88% while ambulating.
- He was placed on supplemental oxygen.
- **Which of the following is NOT an option to treat Tom's COVID-19?**

  A. Baricitinib plus remdesivir for 14 days

  B. Dexamethasone for 5 days

  C. Remdesivir for 5 days

Treatment Options for Hospitalized Patient with COVID-19

Treatment Option	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 • Recommended daily monitoring: serum chemistries, hematology, ALT, AST, renal function tests, bilirubin, ALP • Discontinue immediately at signs of clinically significant infusion reaction or if ALT ≥5 x ULN
Glucocorticoids	• Recommended for hospitalized patients with severe COVID-19 • Dexamethasone 6 mg IV or PO or equivalent for 10 days • Not recommended for hospitalized patients without hypoxemia requiring supplemental oxygen
Baricitinib plus remdesivir	• 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

ALT = alanine aminotransferase; AST = aspartate aminotransferase; ALP = alkaline phosphatase; ULN = upper limit of normal.

Bhimraj A, et al. IDSA Guidelines. V2.1.0 (www.idsociety.org/COVID19guidelines). Remdesivir EUA provider fact sheet. Baricitinib EUA provider fact sheet. Accessed 1/18/2021.

Summary

- Bamlanivimab, bamlanivimab/etesevimab and casirivimab/imdevimab have emergency use authorization for the treatment of mild-to-moderate COVID-19 in patients ≥12 years (and ≥40 kg) who are 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 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.