COVID-19 FRONTLINE - A New Light in the Darkness:

Therapies Recently Granted Emergency Use Authorizations for Patients with **COVID-19**

Monday, February 1, 2021

FACULTY

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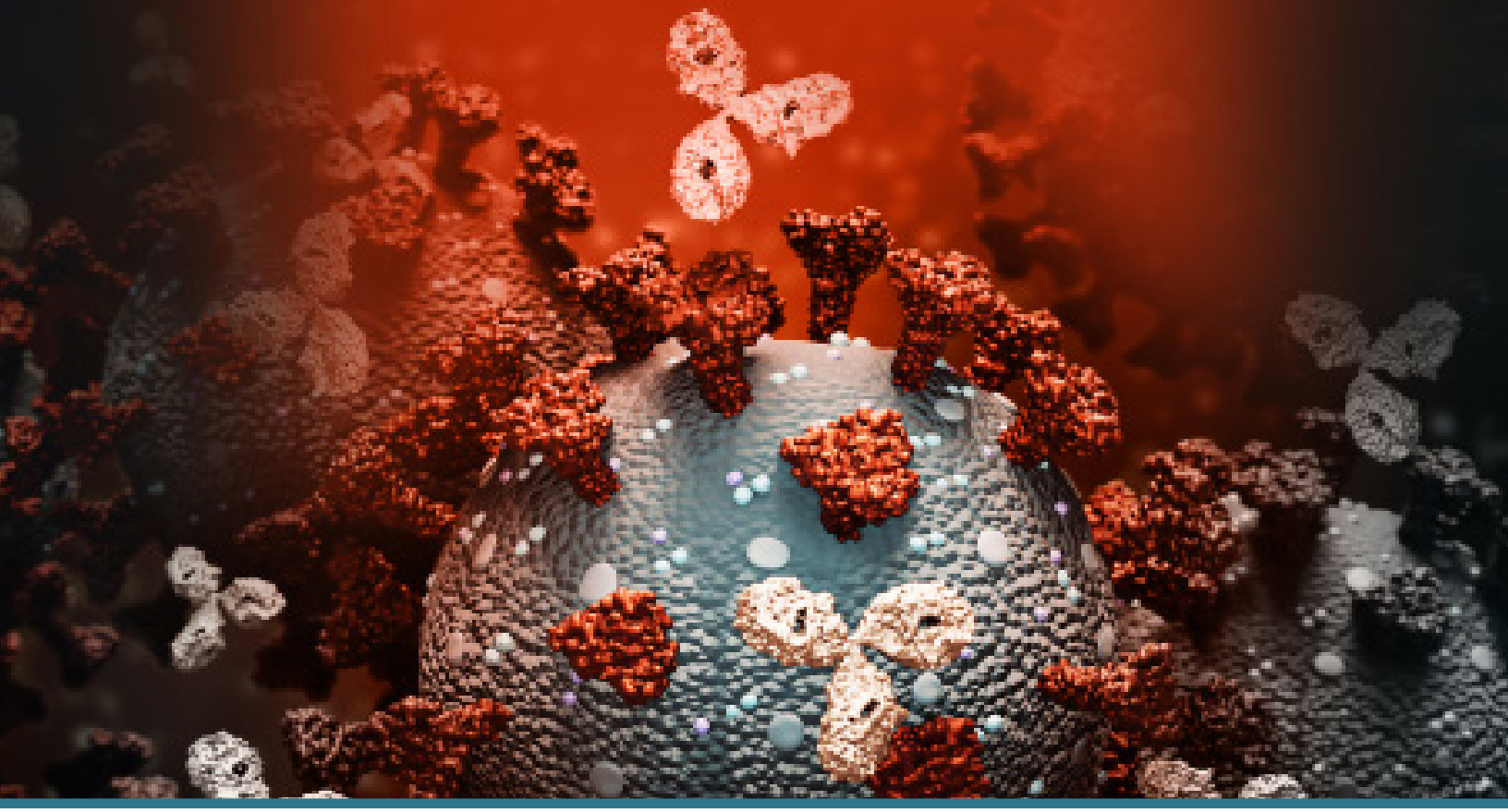

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AGENDA

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 of severe COVID-19 or hospitalization
    b. Clinical trial data on the efficacy and safety of:
        i. Convalescent plasma
        ii. Casirivimab and imdevimab
        iii. Bamlanivimab
    c. Resources on setting up or finding infusion centers

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

4. **Case studies**

5. **Conclusions**

COVID-19 Frontline - A New Light in the Darkness: Therapies Recently Granted Emergency Use Authorizations for Patients with COVID-19

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PROGRAM OVERVIEW

The COVID-19 FRONTLINE TeleECHO series provides a comprehensive and up-to-date perspective on the ever-changing management of patients with COVID-19. Each TeleECHO 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. The case studies will focus on different issues facing clinicians, such as identifying patients who would benefit from monoclonal antibody therapy and best practices for incorporating agents authorized for emergency use into the care of hospitalized and non-hospitalized patients with COVID-19.

TARGET AUDIENCE

This activity is intended for pulmonologists, critical care specialists, infectious disease specialists, hospitalists, and hospital pharmacists to help support them in their effort to optimize care of patients with COVID-19.

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 therapies recently granted EUAs for patients with COVID-19

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Purpose: This program would be beneficial for nurses involved in the treatment of patients with COVID-19.

Credits: 1.0 ANCC Contact Hour.

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CME Content Review

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The reviewer of this activity has nothing to disclose.

CNE Content Review

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2. Participate in the web-based live activity.
3. Submit the evaluation form to Med Learning Group.

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COVID-19 FRONTLINE

A New Light in the Darkness: Therapies Recently Granted Emergency Use Authorizations for Patients with COVID-19

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1

Disclosures

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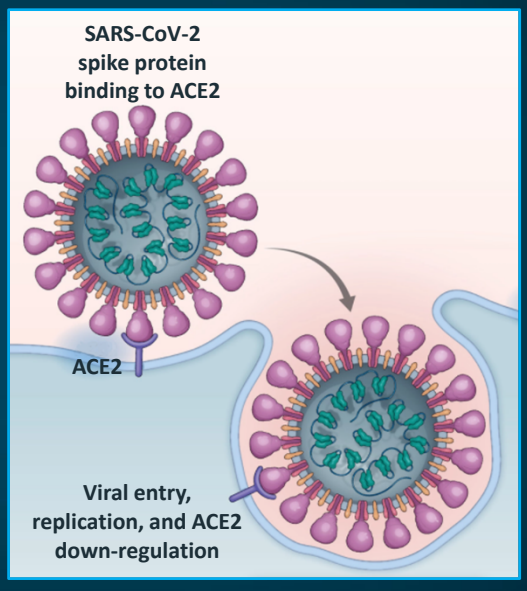
Learning Objectives

- Assess the rationale for the use of antibody therapies to mitigate the risk of viral resistance to therapy
- Critique the efficacy and safety of therapies recently granted emergency use authorizations (EUAs) for patients with COVID-19

3

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.

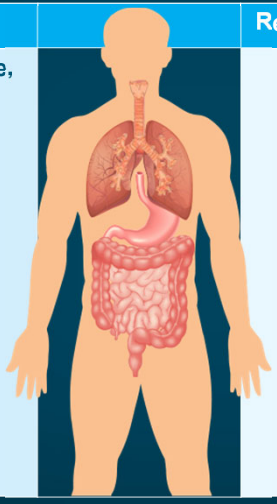
1. Adapted from Vaduganathan M, et al. *N Engl J Med*. 2020;382:1653-1659. 2. Wiersinga WJ, et al. *JAMA*. 324:782-793. 3. Baum A, et al. *Science*. 2020;369:1014-1018.

4

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.

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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

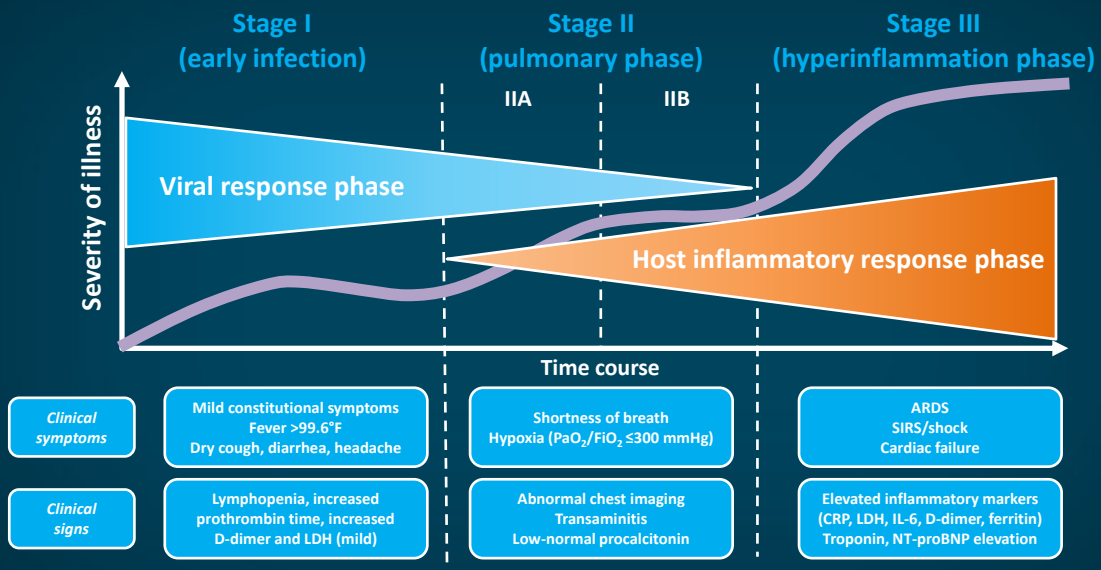
	Disease Characteristics—NIH
Mild illness	Various symptoms (eg, fever, cough, sore throat, headache, malaise, muscle pain) without shortness of breath, dyspnea, or abnormal chest imaging
Moderate illness	SpO_2 ≥94% on room air and lower respiratory disease evidenced by clinical assessment or imaging
Severe 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.

6

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.

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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.

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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.

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Monoclonal Antibody Therapies Authorized for Emergency Use

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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)

According to the Centers for Disease Control and Prevention (CDC), diagnostic testing for SARS-CoV-2 is intended to identify current infection in individuals and is performed when a person has signs or symptoms consistent with Covid-19 or when a person is asymptomatic but has recent known or suspected exposure to SARS-CoV-2. Screening testing for SARS-CoV-2 is intended to identify infected persons who are asymptomatic and without known or suspected exposure to SARS-CoV-2. Screening testing is performed to identify persons who may be contagious so that measures can be taken to prevent further transmission.

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

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Convalescent Serum Antibodies in Severe COVID: Not Highly Effective

Convalescent serum antibodies had no impact on survival at 30 days in severe COVID-19 in hospitalized patients.

- 333 randomized: 228 antibody, 105 placebo
- Median of 8 days from onset of symptoms
- >98% on convalescent serum and 95% on placebo with oxygen saturation <93% on room air at baseline
- 29% on convalescent serum and 24% on placebo in ICU at baseline
- 92% on convalescent serum 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.

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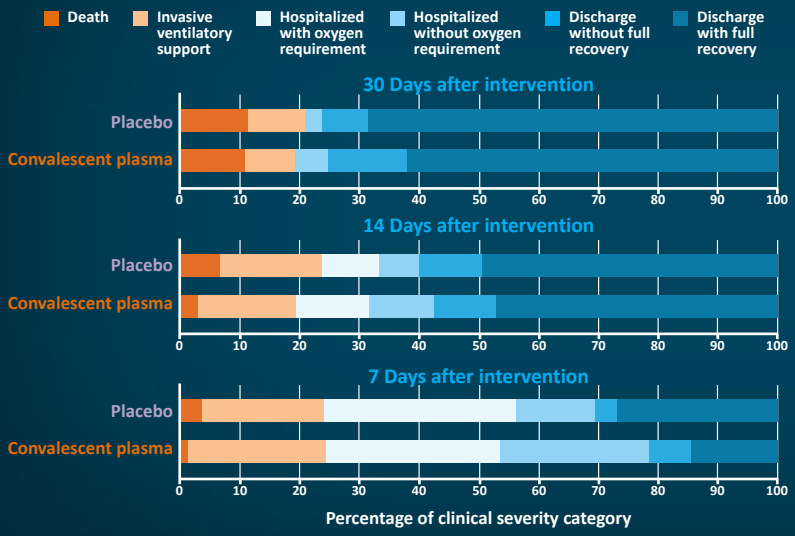
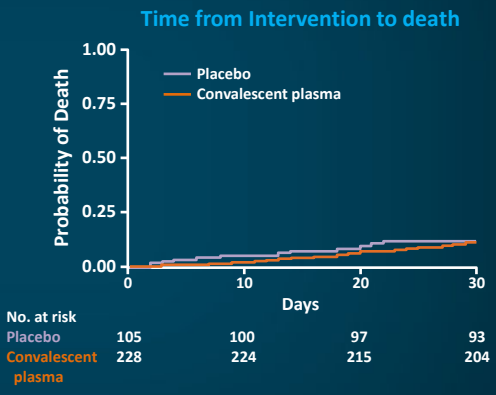
Convalescent Serum Antibodies in Severe COVID: Not Highly Effective

Clinical Outcomes

Convalescent Plasma Compared with Placebo





No. at risk				
Placebo	105	100	97	93
Convalescent plasma	228	224	215	204

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

13

mAb Therapies With Emergency Use Authorization (EUA)

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

Dual monoclonal antibody cocktail

Casirivimab 1200 mg AND

Imdevimab 1200 mg

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

Single monoclonal antibody therapy

Bamlanivimab 700 mg

Administer as a single IV infusion over 60 minutes

IV = intravenous.

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

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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). Bamlanimab EUA. (http://pi.lilly.com/eua/bamlanivimab-eua-factsheet-hcp.pdf). URLs accessed 12/2/2020.

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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)

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

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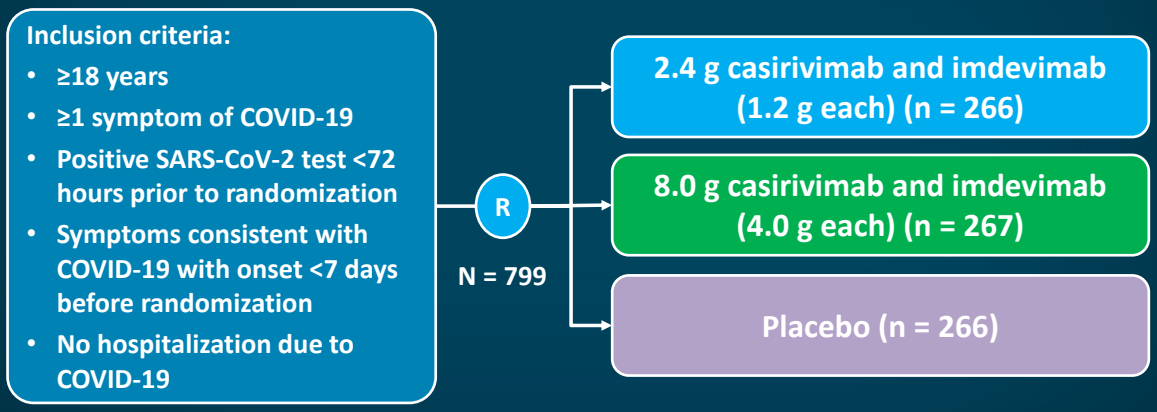
Casirivimab and Imdevimab (REGN-COV2)

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



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

17

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.

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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

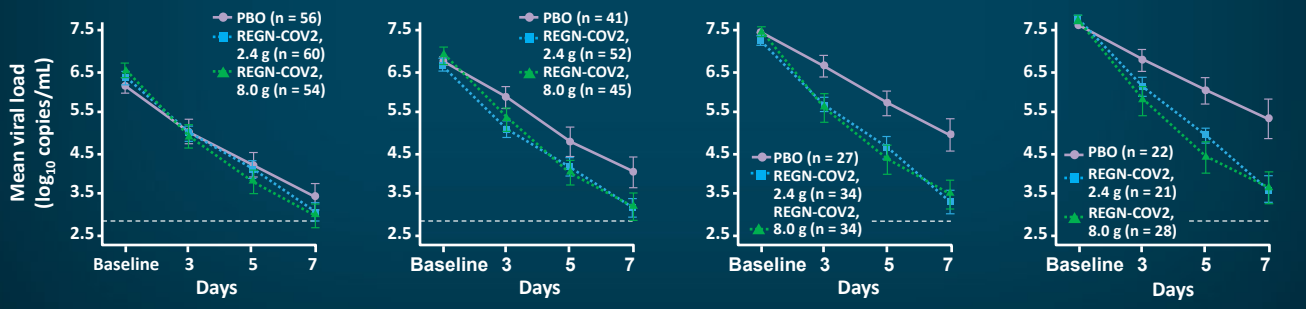
Viral load over time according to baseline viral-load category

	>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.

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

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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.

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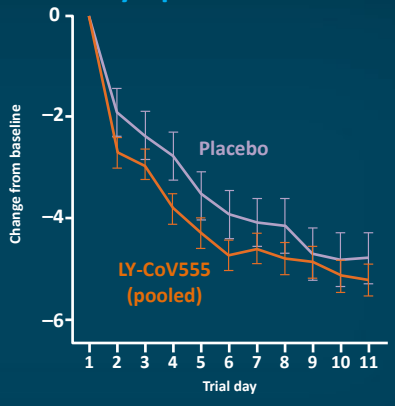
BLAZE-1 Interim Results

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)

BMI = body-mass index.

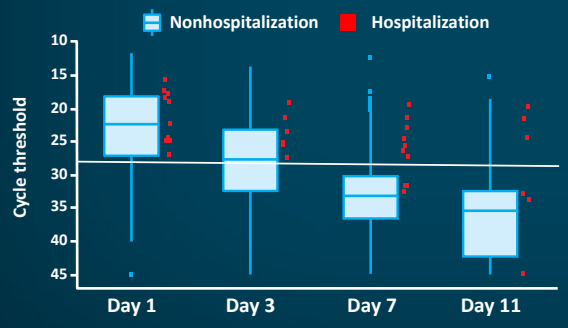
Chen P, et al. *N Engl J Med*. 2020;Oct 28: Epub ahead of print.

22

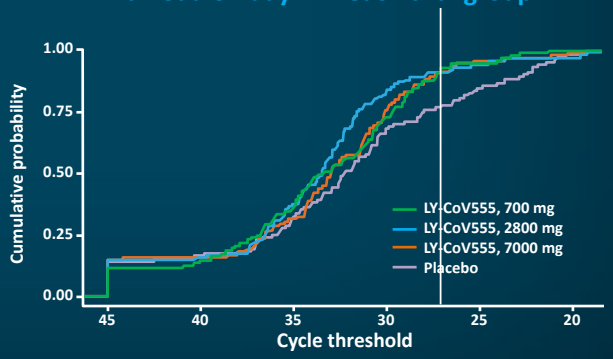
BLAZE-1: Viral Loads Over Time

- 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 (polymerase-chain reaction) cycle threshold (higher viral load = lower Ct value).

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

23

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

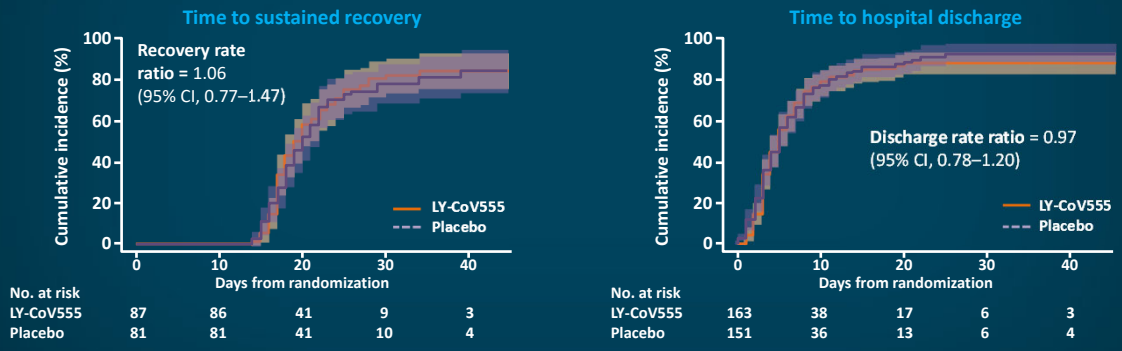
- Infusion-related reactions were reported in 2.3% of patients receiving bamlanivimab and 1.4% of patients in the placebo group
  - Most reactions were mild and occurred during the infusion

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

24

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.

25

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.

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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)

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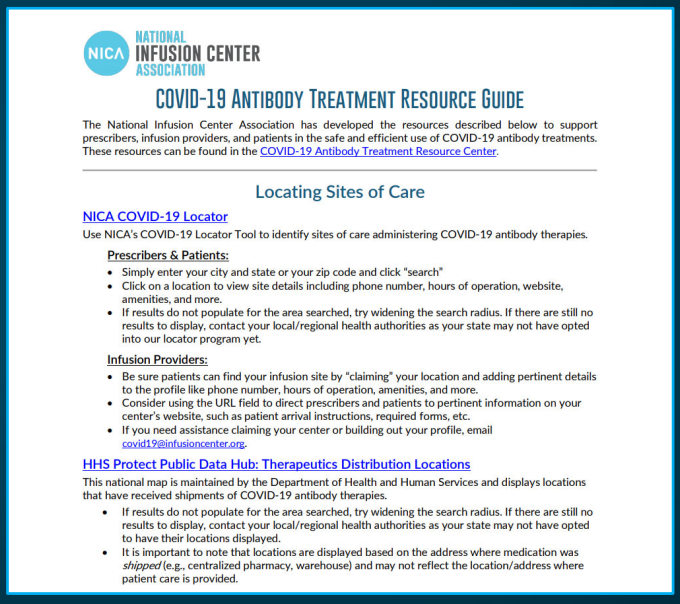
COVID-19 Antibody Treatment Resource Guide

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.

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Management of Hospitalized Patients with COVID-19

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IDSA: Recommended Treatment Options

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
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

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

Bhimraj A, et al. IDSA Guidelines. V3.5.1. (www.idsociety.org/practice-guideline/covid-19-guideline-treatment-and-management/).

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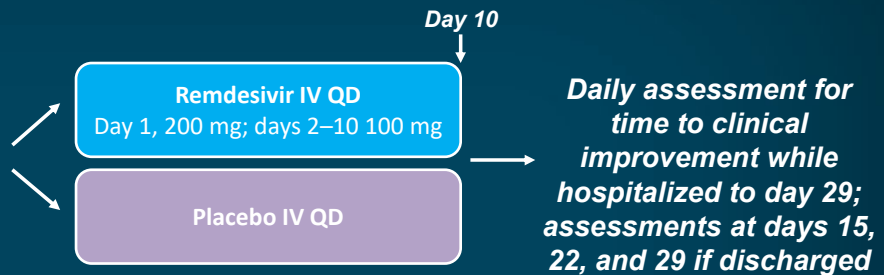
Adaptive COVID-19 Treatment Trial (NIAID ACTT-1): Trial Design

- 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.

31

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.

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Remdesivir: NIAID ACTT Clinical Trial

- 1062 patients in 60 sites randomized 1:1 to remdesivir or placebo
- Independent data safety monitoring board found that remdesivir shortened time to recovery compared with placebo

	Remdesivir n = 541	Placebo n = 521	*P*-value
Time to recovery	11 days	15 days	<.001
Mortality	6.7% on day 15 11.4% on day 29	11.9% on day 15 15.2% on day 29	.07 (day 29)

An ICU bed becomes available 4 days earlier
Benefit is in early disease

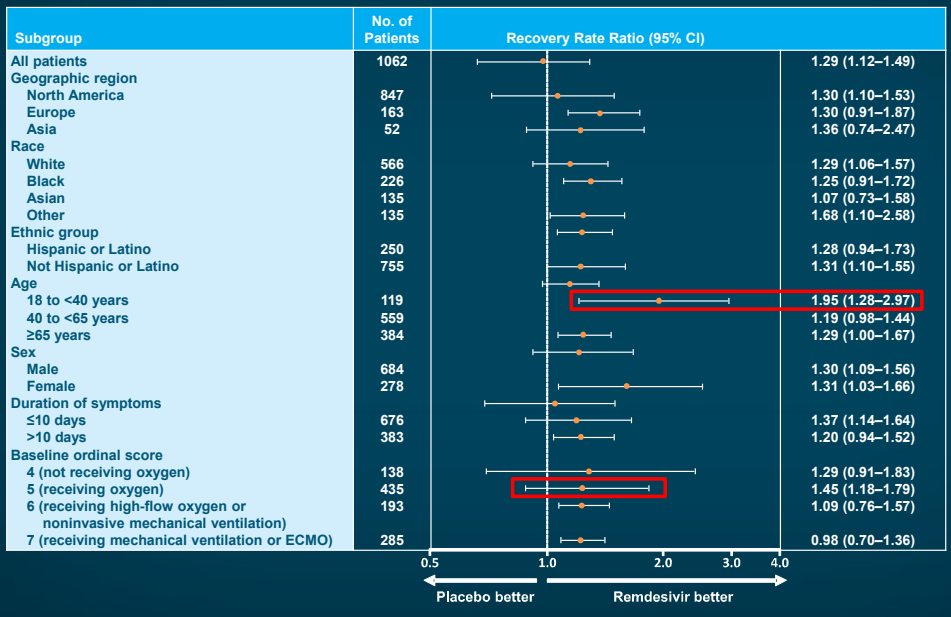
A 3.8% mortality benefit (or a 27% reduction in mortality)
Not statistically significant

NIAID = National Institute of Allergy and Infectious Diseases.

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

33

Remdesivir: NIAID ACTT Clinical Trial

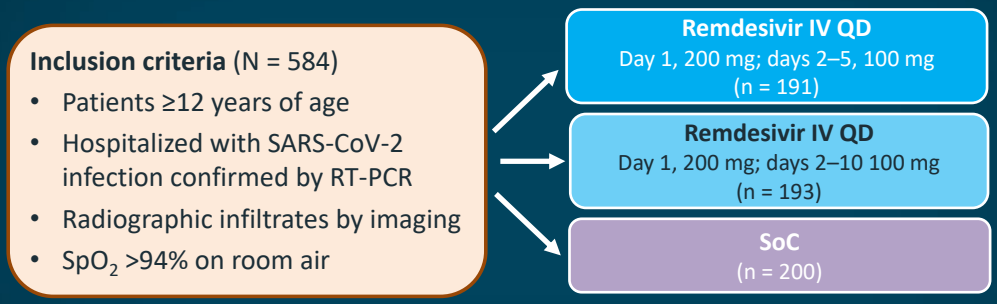


Beigel JH, et al. *N Engl J Med*. 2020;383:1813-1826.

34

SIMPLE-Moderate Study: Trial Design

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



- 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.

35

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.

36

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**

- Factorial design with simultaneous randomization to no additional therapy or **convalescent plasma**
- Patients with progressive disease (hypoxia and an inflammatory state) may undergo second randomization to no additional treatment or **tocilizumab**
- Primary endpoint: 28-day mortality

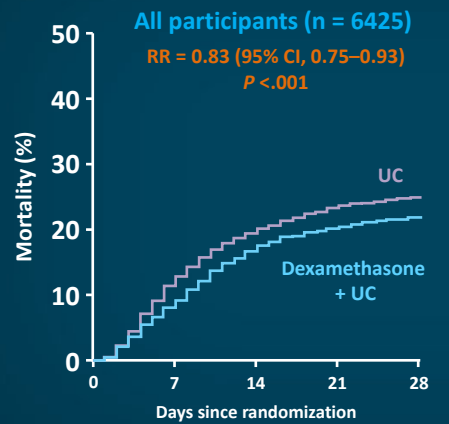
Randomized Evaluation of COVID-19 Therapy—RECOVERY (www.recoverytrial.net/files/recovery-protocol-v7-0-2020-06-18.pdf). Accessed 1/20/2021.

37

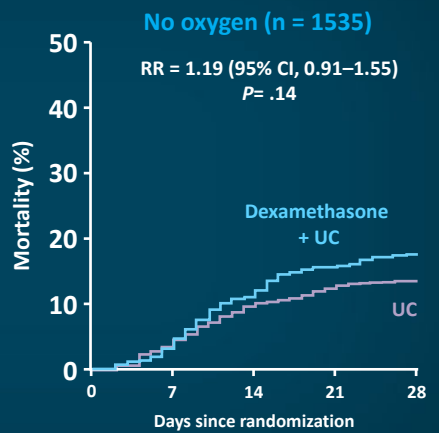
RECOVERY Trial

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.

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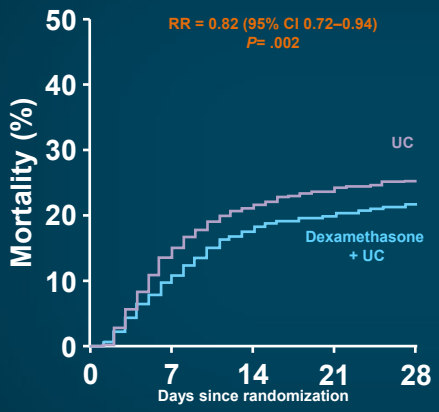
RECOVERY Trial

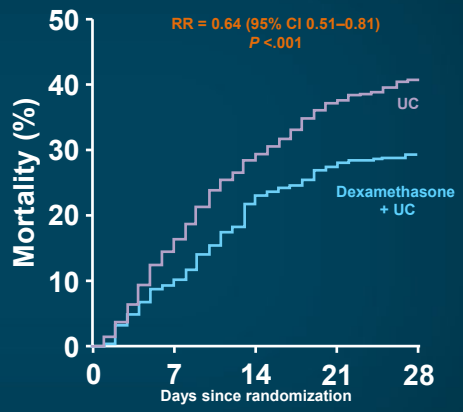
Mortality in Patients On Oxygen or Mechanical Ventilation ± Dexamethasone

Oxygen only (n = 3883)



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

Invasive mechanical ventilation (n = 1007)



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.

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EUAs for Hospitalized Patients

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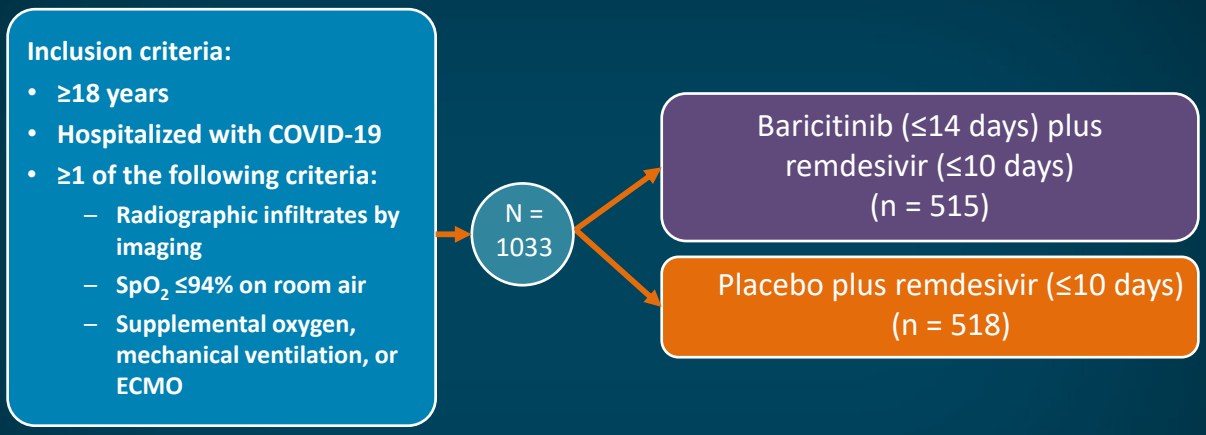
ACCT-2: Baricitinib Plus Remdesivir in Hospitalized Patients



- 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.

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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.

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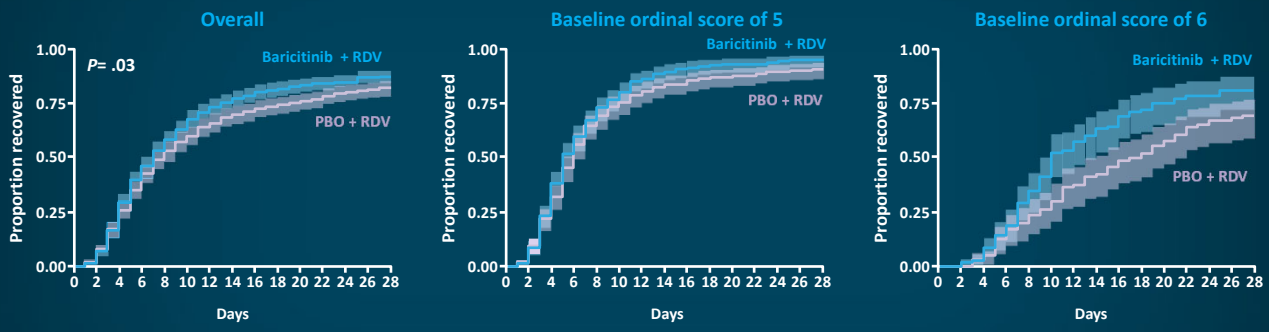
Baricitinib Plus Remdesivir: Recovery Time

- 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.

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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.

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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.

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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

Baricitinib EUA. (www.fda.gov/media/143823/download). Accessed 1/20/2021.

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Case Study

Avoiding Disease Progression

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Initial Presentation

- CD is a 50-year-old male with mild obesity, HTN, G6PD deficiency (treated with sulfa drugs, quinine, hydroxychloroquine), hypothyroid s/p thyroiditis with ocular manifestations and a history of Bells palsy (10 years ago) and bacterial pneumonia (December 2019)
- He presents with 1 week of fatigue, fever, and cough and is found to have a positive SARS-CoV-2 PCR with known COVID-19 exposure

Is CD a candidate for monoclonal antibody therapy?

HTN = hypertension; G6PD = glucose-6-phosphate dehydrogenase; s/p = status post; PCR = polymerase chain reaction; LLL = left-lower lobe (lung); L = liter; NC = nasal cannula.

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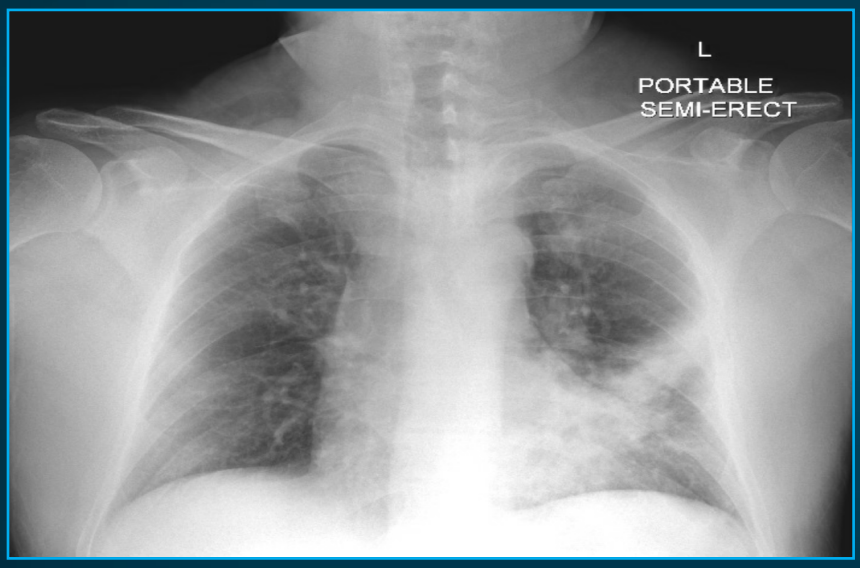
CXR of Moderate COVID-19



- CD was not given monoclonal antibodies.
- He was admitted to the ED with an O_2 saturation of 92% at room air.

How would you manage CD?

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Further Management

- CD's CXR showed LLL infiltrate
- Hospital course: he had desaturation, requiring oxygen at 1–4L NC
  - Given 5 days of ceftriaxone, azithromycin/doxycycline
  - Given 5 days of remdesivir and 7 days of dexamethasone (6 mg daily) to complete a 10-day course as an outpatient
- Given apixaban in hospital and on discharge, with plan to reevaluate as an outpatient

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Case Study

Moderate COVID-19 in an Immunocompromised Patient

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Moderate COVID-19 in an Immunocompromised Patient

- JL is a 28-year old male with AML diagnosed in August 2020 who was treated with 7+3 as induction therapy. He was started on consolidation therapy with HiDAC (high-dose cytarabine) on 10/21/20 and received a 2nd cycle on 11/23/20.
- On 11/28/20, he experiences fevers, chills, shortness of breath, sore throat, and congestion.
  - On 12/1/20, he tested positive for COVID-19.

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Admitted for COVID-19

- He was admitted on 12/3/20 due to persistent fever, nausea, vomiting and new cough.
- On admission, he was afebrile, not hypoxic, and had tachycardia.
- Labs: WBC 0.2, AST 70, ALT 120

Is JL a candidate for monoclonal antibody therapy?

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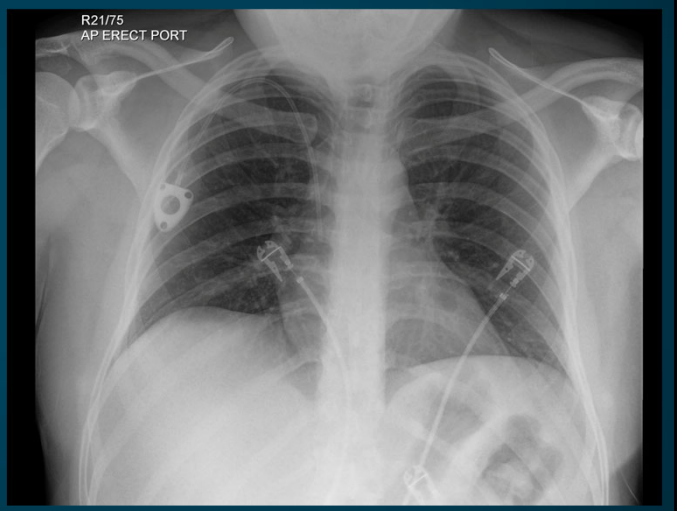
Imaging Results

- Chest CT with contrast showed peripheral ground glass opacities thought to be consistent with COVID-19 and no PE.
- O_2 saturations were continuously monitored and remained >90% while at rest.

How would you manage JL?



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Further Management

- JL did not experience episodes of hypoxia and was not given remdesivir, steroids, and/or baricitinib.
- On 12/9, his absolute neutrophil count (ANC) was >500.
- On 12/14, he was afebrile. His ambulatory saturation was assessed and >90% so he was discharged 24 hours later.
- Following discharge, JL's COVID-19 symptoms completely resolved and he was readmitted on 1/16 for cycle 3 of HiDAC.

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Summary

- Casirivimab/imdevimab and bamlanivimab 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

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Thank you!

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COVID-19 Frontline website

Med Learning Group - COVID-19 Frontline

https://covid-frontline.com

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COVID-19 Frontline - A New Light in the Darkness: Therapies Recently Granted Emergency Use Authorizations for Patients with COVID-19

Resource	Address
National Infusion Center Association. **COVID-19 Antibody Therapies Resource Center.**	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;10.1001/jama.2020.12839.	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.** [published online ahead of print, 2020 Apr 30]. *J Intern Med*. 2020; 10.1111/joim.13089.	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 May 26;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/369/bmj.m1985
Yuan X, et al. **Changes of hematological and immunological parameters in COVID-19 patients.** [published online ahead of print, 2020 Jul 12]. *Int J Hematol*. 2020;1-7.	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*. V2.1.0.	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. 2020 May 27.	https://www.who.int/publications/i/item/clinical-management-of-covid-19
National Institutes of Health (NIH). **COVID-19 Treatment Guidelines.**	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.** *N Engl J Med.* 2020;Epub ahead of print.	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.** [published online ahead of print, 2020 Jun 3]*JAMA*. 2020;e2010044..	https://pubmed.ncbi.nlm.nih.gov/32492084/
Kalil AC, et al. **Baricitinib plus remdesivir for hospitalized adults with COVID-19.** *N Engl J Med.* 2020;Epub ahead of print.	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/
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://pubmed.ncbi.nlm.nih.gov/32444460/
Simonovich VA, et al. **A Randomized Trial of Convalescent Plasma in Covid-19 Severe Pneumonia.** *N Engl J Med*. 2020;Epub ahead of print.	https://pubmed.ncbi.nlm.nih.gov/33232588/

Fact Sheet for Health Care Providers **Emergency Use Authorization (EUA) of Baricitinib**	https://www.fda.gov/media/143823/download
Fact Sheet for Health Care Providers **Emergency Use Authorization (EUA) of Bamlanivimab**	http://pi.lilly.com/eua/bamlanivimab-eua-factsheet-hcp.pdf
Fact Sheet for Health Care Providers **Emergency Use Authorization (EUA) of Casirivimab and Imdevimab**	https://www.fda.gov/media/143892/download
Weinreich DM, et al. **REGN-COV2, a neutralizing antibody cocktail, in outpatients with COVID-29.** *N Engl J Med.* 2020;Epub ahead of print.	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.** *N Engl J Med.* 2020;Epub ahead of print.	https://www.nejm.org/doi/full/10.1056/NEJMoa2029849
ACTIV-3/TICO LY-CoV555 Study Group. **A neutralizing monoclonal antibody for hospitalized patients with COVID-19.** *N Engl J Med.* 2020;Epub ahead of print.	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