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CME Information

COVID19
Keeping Up with a Moving Target

Jointly provided by

Postgraduate Institute for Medicine, DKBmed, and the Institute for Johns Hopkins Nursing.

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The faculty reported the following financial relationships or relationships they or their spouse/life partner have with commercial interests related to the content of this continuing education activity:

Name of Faculty or Presenter	Reported Financial Relationship
Michael G. Ison, MD MS FIDSA FAST	**Consulting:** Adagio, AlloVir, Celltrion, Cidara, Genentech/Roche, Janssen, Shionogi, Viracor Eurofins **Contracted Research:** AiCuris, Janssen, Shire **Other DSMB:** NIH, Janssen, Merck, SAB Biotherapeutics, Sequiris, Takeda, Vitaeris

Dr. Ison has indicated that he will be referencing the unlabeled or unapproved use of agents currently being investigated in on-going studies and trials, including several vaccine platforms.

All activity, content, and materials have been developed solely by the activity directors, planning committee members, and faculty presenters, and are free of influence from a commercial entity.

Commercial Support

This educational activity is supported by independent medical educational grants from Gilead Sciences, Inc., Regeneron Pharmaceuticals, Inc., and Eli Lilly and Company.

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Learning Objectives

1. Appraise the efficacy, safety and indications for treatments for patients with COVID requiring hospitalization.
2. Evaluate management strategies for outpatients with mild to moderate COVID-19.
3. Explain mechanisms of action of monoclonal antibodies (mAbs) and other current and in-development treatments for COVID-19.
4. Describe best practices for managing patients with COVID-19 with mAbs and other agents.


COVID19
Keeping Up with a Moving Target
PRE-TEST

Pre-Test Question 1

How confident are you in describing current management strategies for mild to moderate COVID-19?

1. Not confident
2. Slightly confident
3. Moderately confident
4. Highly confident

Pre-Test Question 2

According to the ACTT-1 trial, which group of included patients benefitted the most from remdesivir?

1. All included patients benefitted equally
2. Patients not receiving oxygen
3. Patients receiving noninvasive mechanical ventilation
4. Patients receiving mechanical ventilation or ECMO

Pre-Test Question 3

A 22-year-old previously healthy patient with no underlying conditions has mild COVID-19. Which of following is/are recommended for this patient?

1. Home isolation
2. Symptom monitoring
3. Dexamethasone
4. Monoclonal antibodies
5. 1 and 2
6. 1 and 3

Pre-Test Question 4

Monoclonal antibodies are thought to primarily work by blocking the virus' ability to attach to and enter human cells.

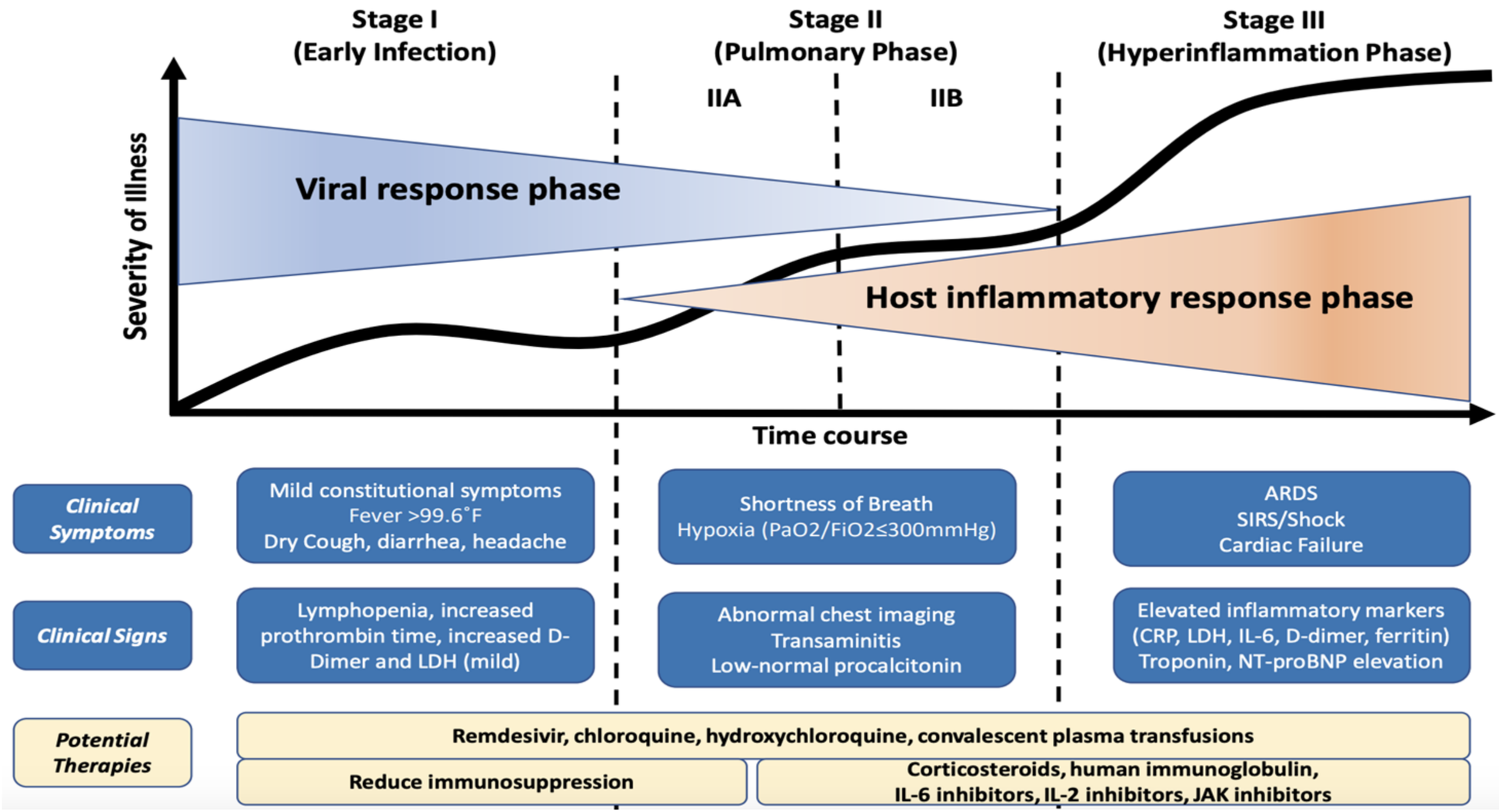
1. True
2. False

Pre-Test Question 5

Monoclonal antibody products are authorized to treat which group of patients with confirmed COVID-19?

1. Any patient
2. Any non-hospitalized patient ≥ 18 years of age
3. Non-hospitalized patients ≥ 12 years of age at high risk for severe disease
4. Hospitalized patients for COVID-19 ≥ 12 years of age requiring oxygen support

How and When to Intervene?



Siddiqi et al. J Heart Lung Transplant. 2020. doi:10.1016/j.healun.2020.03.012

Outpatient Management of COVID-19: Preventing Hospitalization

Home Care

- Monitor symptoms
- Supportive care
- Infection prevention and control measures

Isolation for People with COVID-19

May be discontinued under these conditions:

- At least 10 days since symptom onset, *and*
- At least 24 hours since resolution of fever without fever-reducing meds, *and*
- Other symptoms have improved

Quarantine for Close Contacts

Recommended for 14 days, but can end early:

- After day 10 without testing if no symptoms
- After day 7 if testing is negative and no symptoms

Symptom monitoring and masking through day 14 still required.

Source: CDC

Fluvoxamine

JAMA Network™

QUESTION Does fluvoxamine, a selective serotonin reuptake inhibitor and σ-1 receptor agonist, prevent clinical deterioration in outpatients with acute coronavirus disease 2019 (COVID-19)?

CONCLUSION In this preliminary trial, outpatients with symptomatic COVID-19 treated with fluvoxamine, vs placebo, had a lower likelihood of clinical deterioration over 15 days; however, determination of clinical efficacy requires larger trials with more definitive outcome measures.

POPULATION

109 Women
43 Men

Adults with symptomatic, confirmed SARS-CoV-2 infection and O_2 ≥92%

Mean age: **46** years

LOCATIONS

Remote contactless trial in St Louis metropolitan area (Missouri and Illinois)

INTERVENTION

152 Patients randomized

80
Fluvoxamine
50 mg, day 1
100 mg, 2 times daily for 2 days
100 mg, 3 times daily through day 15

72
Placebo
Equivalent dosing

(Study materials left at quarantined patients' homes)

PRIMARY OUTCOME

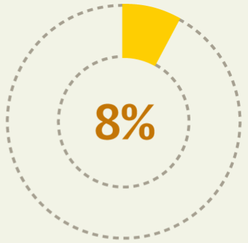
Clinical deterioration within 15 days: shortness of breath or pneumonia and O_2 <92% or supplemental oxygen

FINDINGS

Patients with clinical detorioration within 15 days

Fluvoxamine
0 of 80 patients

Placebo
6 of 72 patients



The between-group difference was significant:

8.7% (95% CI, 1.8% to 16.4%); P = .009

However, small sample size and short follow-up limit determination of efficacy

Lenze et al. JAMA. 2020; DOI:10.1001/jama.2020.22760.

Bamlanivimab

Resistance: 9.2% (9/98) vs 6.1% (6/98)

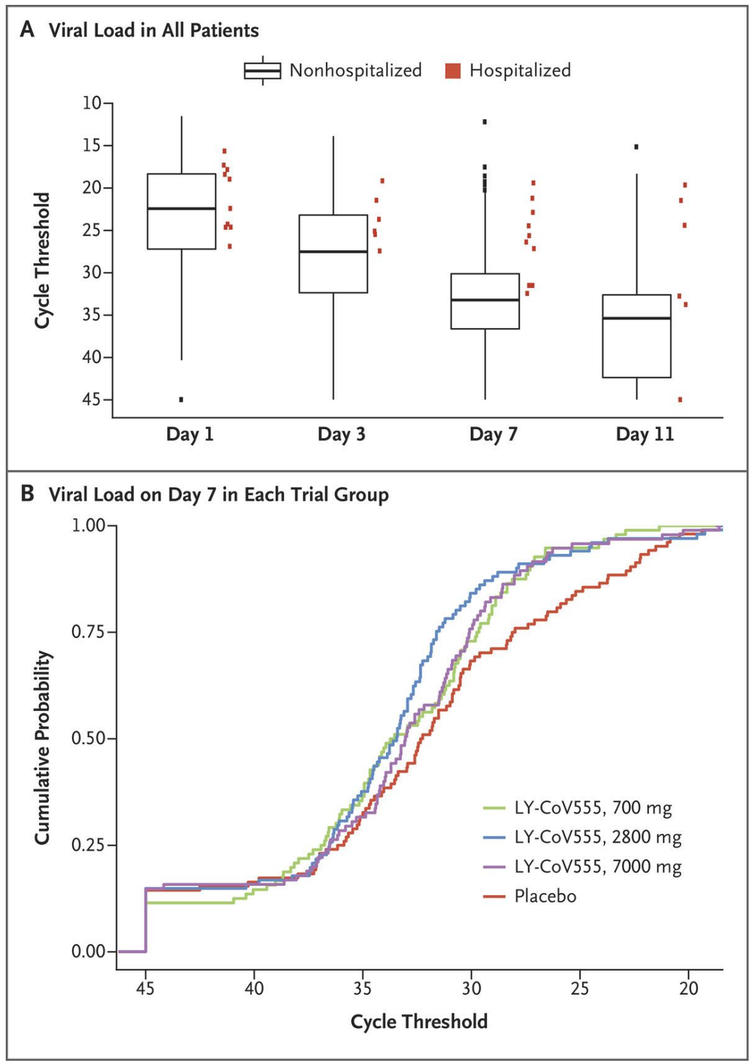


Table 2. Changes from Baseline in Viral Load

Variable	LY-CoV555 (N=309)	Placebo (N=143)	Difference (95% CI)
Primary outcome			
Mean change from baseline in viral load at day 11		−3.47	
	700 mg, −3.67		−0.20 (−0.66 to 0.25)
	2800 mg, −4.00		−0.53 (−0.98 to −0.08)
	7000 mg, −3.38		0.09 (−0.37 to 0.55)
	Pooled doses, −3.70		−0.22 (−0.60 to 0.15)
Secondary outcomes*			
Mean change from baseline in viral load at day 3		−0.85	
	700 mg, −1.27		−0.42 (−0.89 to 0.06)
	2800 mg, −1.50		−0.64 (−1.11 to −0.17)
	7000 mg, −1.27		−0.42 (−0.90 to 0.06)
	Pooled doses, −1.35		−0.49 (−0.87 to −0.11)
Mean change from baseline in viral load at day 7		−2.56	
	700 mg, −2.82		−0.25 (−0.73 to 0.23)
	2800 mg, −3.01		−0.45 (−0.92 to 0.03)
	7000 mg, −2.85		−0.28 (−0.77 to 0.20)
	Pooled doses, −2.90		−0.33 (−0.72 to 0.06)

EC50 value = 0.03 µg/mL

Chen et al. N Engl J Med. 2020. DOI: 10.1056/NEJMoa2029849.

Bamlanivimab

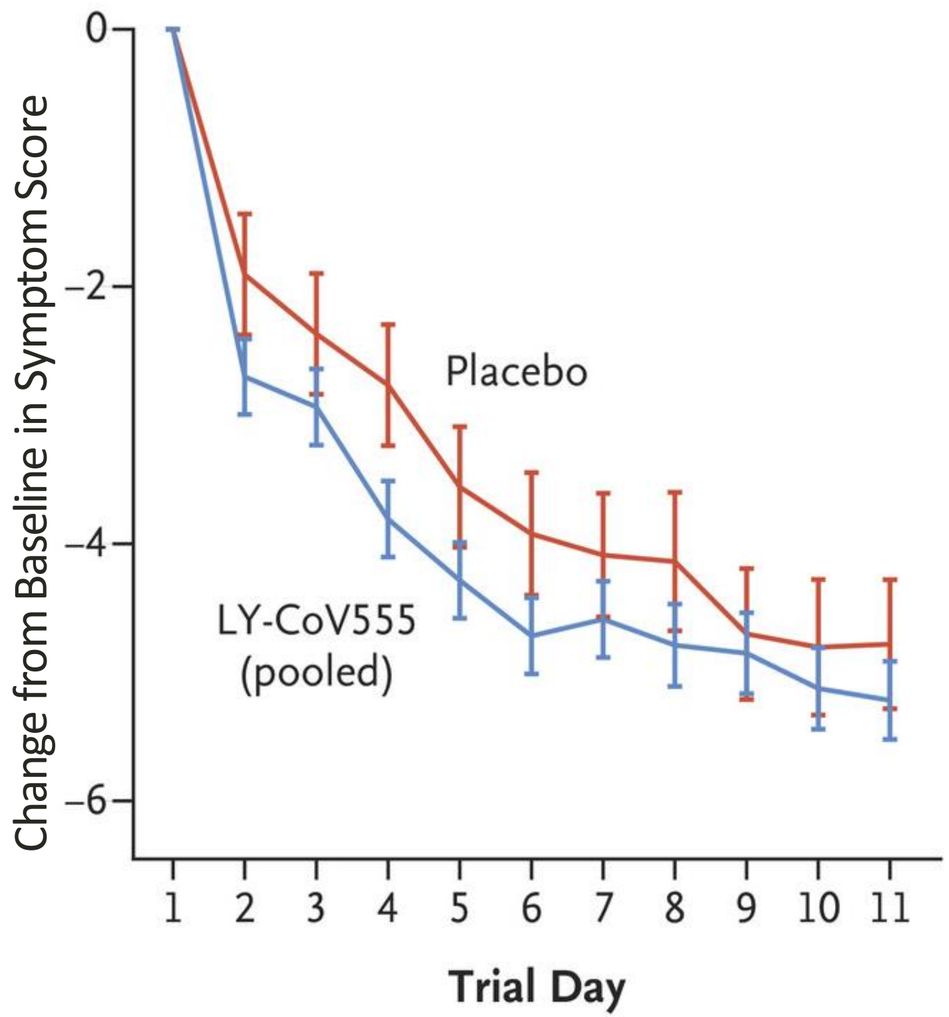


Table 3. Hospitalization.*

Key Secondary Outcome	LY-CoV555	Placebo	Incidence
	no. of patients/total no.		%
Hospitalization		9/143	6.3
	700 mg, 1/101		1.0
	2800 mg, 2/107		1.9
	7000 mg, 2/101		2.0
	Pooled doses, 5/309		1.6

* Data for patients who presented to the emergency department are included in this category.

Chen et al. N Engl J Med. 2020. DOI: 10.1056/NEJMoa2029849.

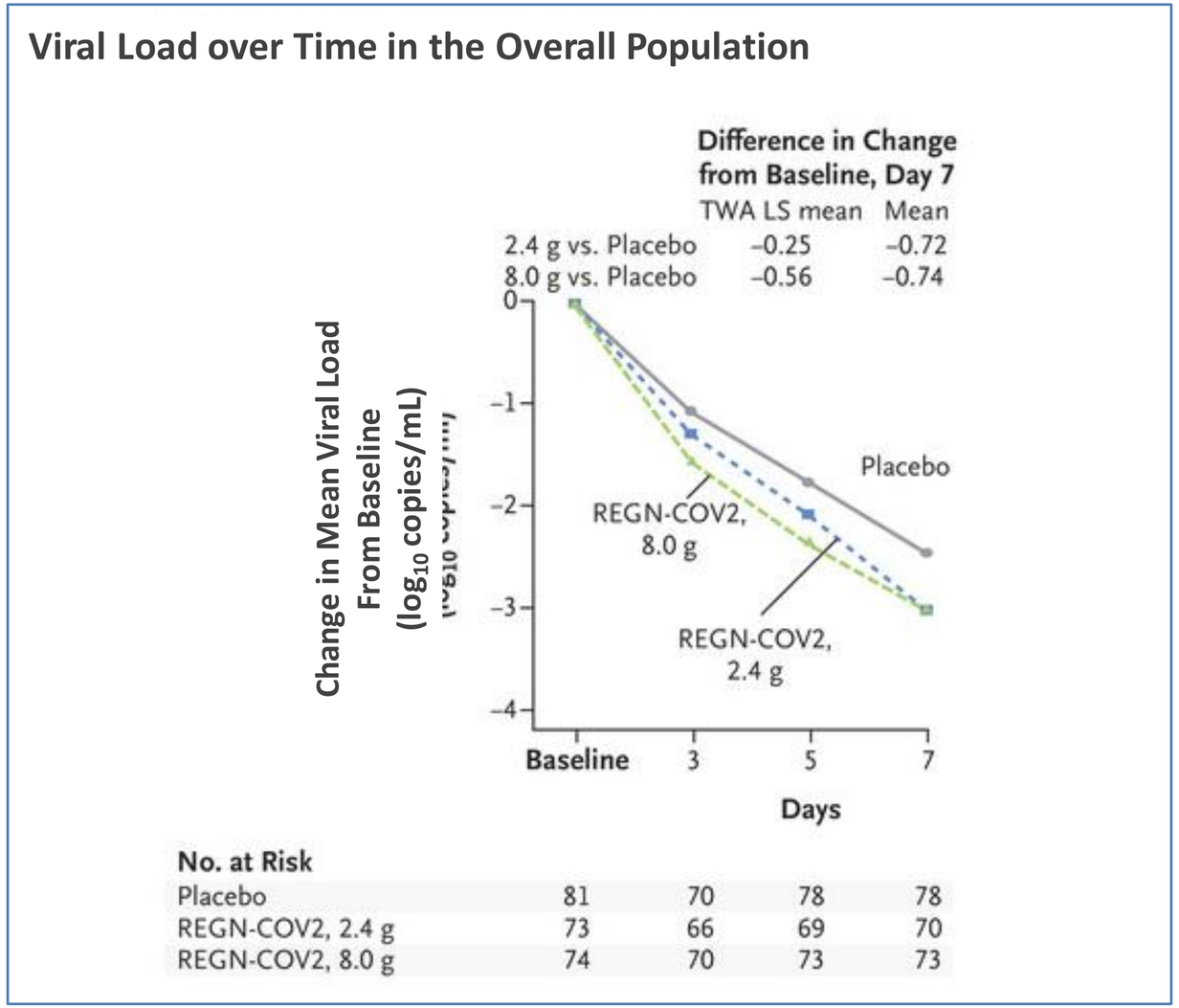
Casirivimab and Imdevimab: Key Endpoints

End Point	REGN-COV2			Placebo
	2.4	8.0	Combined	
Time-weighted average change in viral load from day 1 through day 7				
Modified full analysis set				
No. of patients	70	73	143	78
Least-squares mean change – log_{10} copies/mL	-1.60±0.14	-1.90±0.14	-1.74±0.11	-1.34±0.13
95% CI	-1.87 to -1.32	-2.18 to -1.62	-1.95 to - -1.53	-1.60 to -1.08
Difference vs placebo at day 7 – log10 copies/mL				
Least-squares mean change	-0.25±0.18	-0.56±0.18	-0.41±0.15	
95% CI	-0.60 to 0.10	-0.91 to -0.21	-0.71 to -0.10	
Baseline serum antibody status: Negative				
No. of patients	34	35	69	28
Least-squares mean change – log10 copies/mL	-1.89±0.18	-1.96±0.18	-1.94±0.13	-1.37±0.20
95% CI	-2.24 to -1.53	-2.33 to -1.60	-2.20 to -1.67	-1.76 to -0.98
Difference vs placebo at day 7 – log_{10} copies/mL				
Least-squares mean change	-0.52±0.26	-0.60±0.26	-0.56±0.23	
95% CI	-1.04 to 0.00	-1.12 to -0.08	-1.02 to -0.11	

End Point	REGN-COV2			Placebo
	2.4	8.0	Combined	
Time-weighted average change in viral load from day 1 through day 7				
Baseline serum antibody status: Positive				
No. of patients	27	29	56	37
Least-squares mean change – log10 copies/mL	-1.24±0.19	-1.63±0.20	-1.45±0.13	-1.24±0.16
95% CI	-1.61 to -0.86	-2.03 to – 1.24	-1.71 to -1.18	-1.55 to -0.93
Difference vs placebo at day 7 – log_{10} copies/mL				
Least-squares mean change	0.00±0.24	-0.39±0.25	-0.21±0.20	
95% CI	-0.48 to 0.49	-0.89 to 0.11	-0.62 to 0.20	
Baseline serum antibody status: Unknown				
No. of patients	9	9	18	13
Least-squares mean change – log10 copies/mL	-0.95±0.56	-1.98±0.60	-1.43±0.44	-1.49±0.63
95% CI	-2.12 to 0.22	-3.22 to -0.73	-2.34 to -0.51	-2.79 to -0.19
Difference vs placebo at day 7 – log_{10} copies/mL				
Least-squares mean change	0.54±0.84	-0.49±0.86	0.06±0.76	
95% CI	-1.20 to 2.28	-2.27 to 1.30	-1.51 to 1.63	

DM Weinreich et al. N Engl J Med. 2020. DOI: 10.1056/NEJMoa2035002.

Casirivimab and Imdevimab

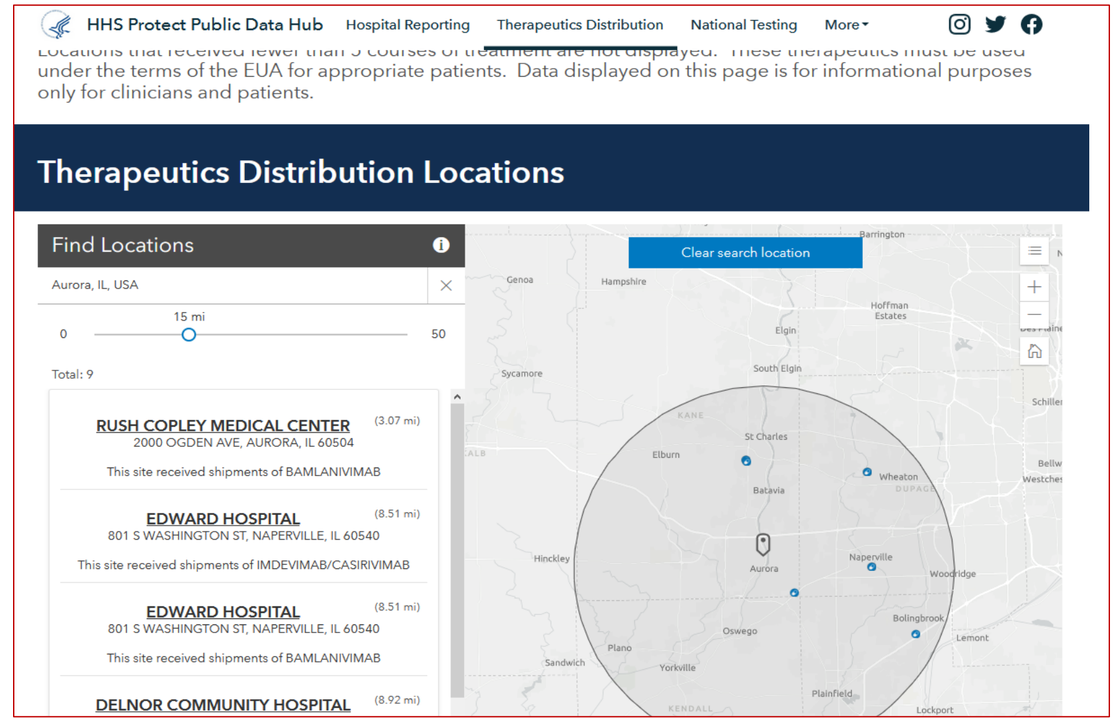


DM Weinreich et al. N Engl J Med. 2020. DOI: 10.1056/NEJMoa2035002.

Facilitating mAb Treatments

- Identify patients: must be at risk of severe disease **per EUA fact sheets** (eg, BMI ≥35, age ≥65 years, diabetes, CKD, etc) but not currently in hospital or requiring oxygen because of COVID.
- Discuss benefits, risks, and process with patients:
  - One-hour IV infusion
  - One-hour monitoring after infusion
  - Continue self-isolation and infection control measures
- ONLY administer in settings in which health care providers have immediate access to medications to treat a severe infusion reaction, such as anaphylaxis, and the ability to activate the emergency medical system as necessary.
- Check state department of health

Finding Antibodies



Covid.infusioncenter.org

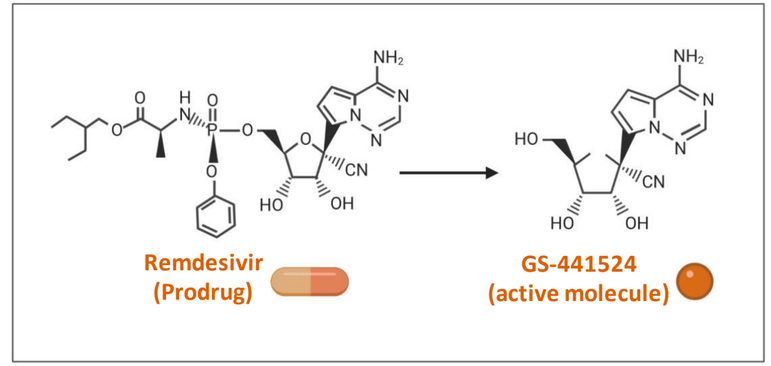
https://protect-public.hhs.gov/pages/therapeutics-distribution#distribution-locations

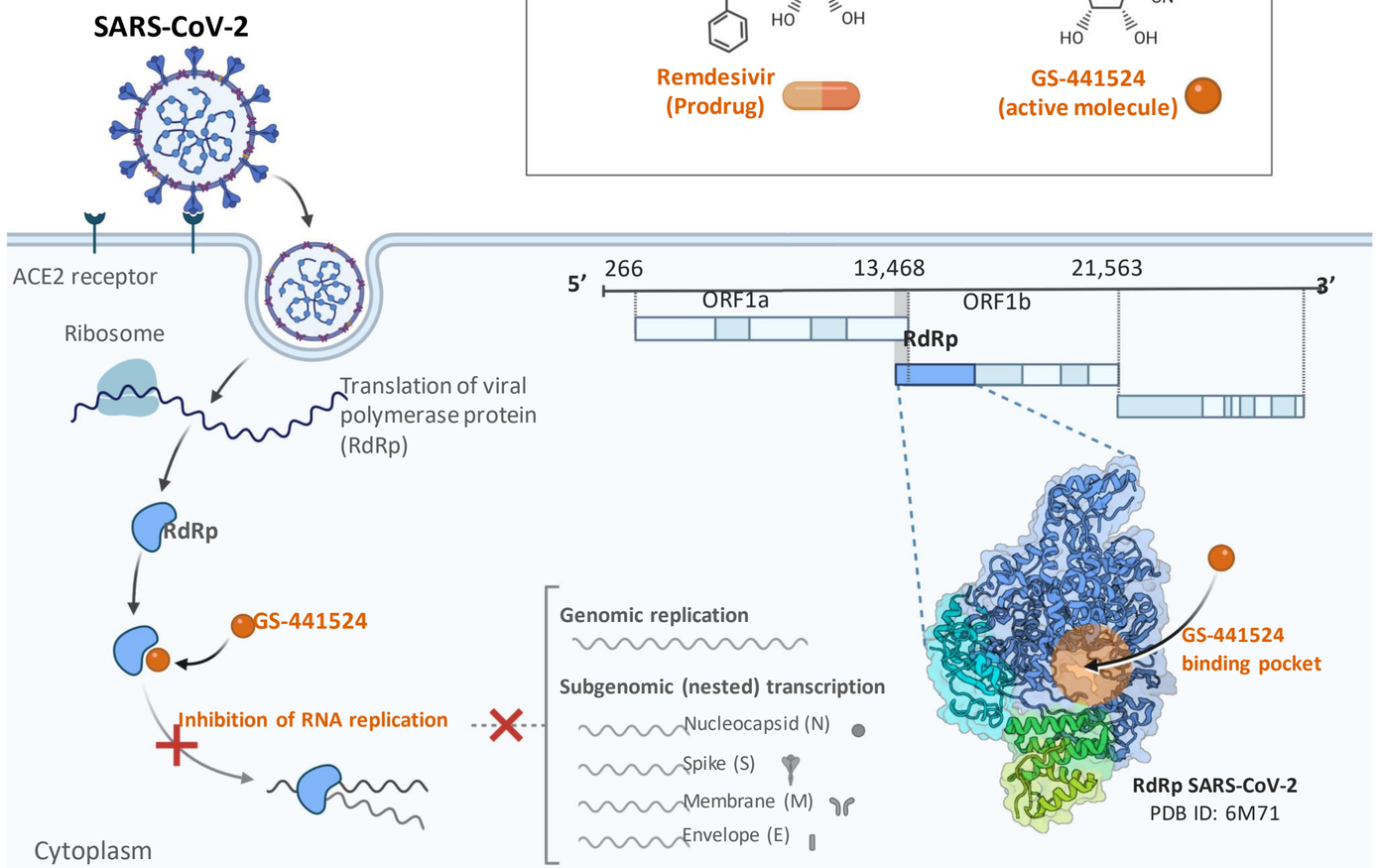
HOSPITALIZED PATIENTS

Remdesivir (GS-5734): IV Antiviral Drug for SARS-CoV-2

Remdesivir

Potential repurposed drug candidate for COVID-19





https://microbenotes.com/remdesivir/. Accessed 4 July 2020.

Remdesivir (GS-5734): NIAID ACTT

Table 2. Outcomes Overall and According to Score on the Ordinal Scale in the Intention-to-Treat Population.*	Overall		Ordinal Score at Baseline							
			4		5		6		7	
	Remdesivir (N=541)	Placebo (N=521)	Remdesivir (N=75)	Placebo (N=63)	Remdesivir (N=232)	Placebo (N=203)	Remdesivir (N=95)	Placebo (N=98)	Remdesivir (N=131)	Placebo (N=154)
Recovery										
No. of recoveries	399	352	73	58 58	206	156	57	61	63	77
Median time to recovery (95% CI) — days	10 (9–11)	15 (13–18)	5 (4–6)	6 (4–7) 6 (4–7)	7 (6–8)	9 (7–10)	15 (10–27)	20 (14–26)	29 (24–NE)	28 (24–NE)
Rate ratio (95% CI)†	1.29 (1.12–1.49 [P<0.001])		1.29 (0.91–1.83)		1.45 (1.18–1.79)		1.09 (0.76–1.57)		0.98 (0.70–1.36)	
Mortality through day 14‡										
Hazard ratio for data through day 15 (95% CI)	0.55 (0.36–0.83)		0.42 (0.04–4.67)		0.28 (0.12–0.66)		0.82 (0.40–1.69)		0.76 (0.39–1.50)	
No. of deaths by day 15	35	61	1	2	7	21	13	17	14	21
Kaplan–Meier estimate of mortality by day 15 — % (95% CI)	6.7 (4.8–9.2)	11.9 (9.4–15.0)	1.3 (0.2–9.1)	3.2 (0.8–12.1)	3.1 (1.5–6.4)	10.5 (7.0–15.7)	14.2 (8.5–23.2)	17.3 (11.2–26.4)	10.9 (6.6–17.6)	13.8 (9.2–20.4)
Mortality over entire study period‡										
Hazard ratio (95% CI)	0.73 (0.52–1.03)		0.82 (0.17–4.07)		0.30 (0.14–0.64)		1.02 (0.54–1.91)		1.13 (0.67–1.89)	
No. of deaths by day 29	59	77	3	3	9	25	19	20	28	29
Kaplan–Meier estimate of mortality by day 29 — % (95% CI)	11.4 (9.0–14.5)	15.2 (12.3–18.6)	4.1 (1.3–12.1)	4.8 (1.6–14.3)	4.0 (2.1–7.5)	12.7 (8.8–18.3)	21.2 (14.0–31.2)	20.4 (13.7–29.8)	21.9 (15.7–30.1)	19.3 (13.8–26.5)
Odds ratio (95% CI)	1.5 (1.2–1.9)		1.5 (0.8–2.7)		1.6 (1.2–2.3)		1.4 (0.9–2.3)		1.2 (0.8–1.9)	

* P values and confidence intervals have not been adjusted for multiple comparisons. NE denotes not possible to estimate.

† Recovery rate ratios and hazard ratios were calculated from the stratified Cox model; the P value for this ratio was calculated with the stratified log-rank test (overall model stratified by actual disease severity). Recovery rate ratios greater than 1 indicate a benefit with remdesivir; hazard ratios less than 1 indicate a benefit with remdesivir.

Beigel et al. N Eng J Med. 2020: doi.org/10.1056/NEJMoa20007764.

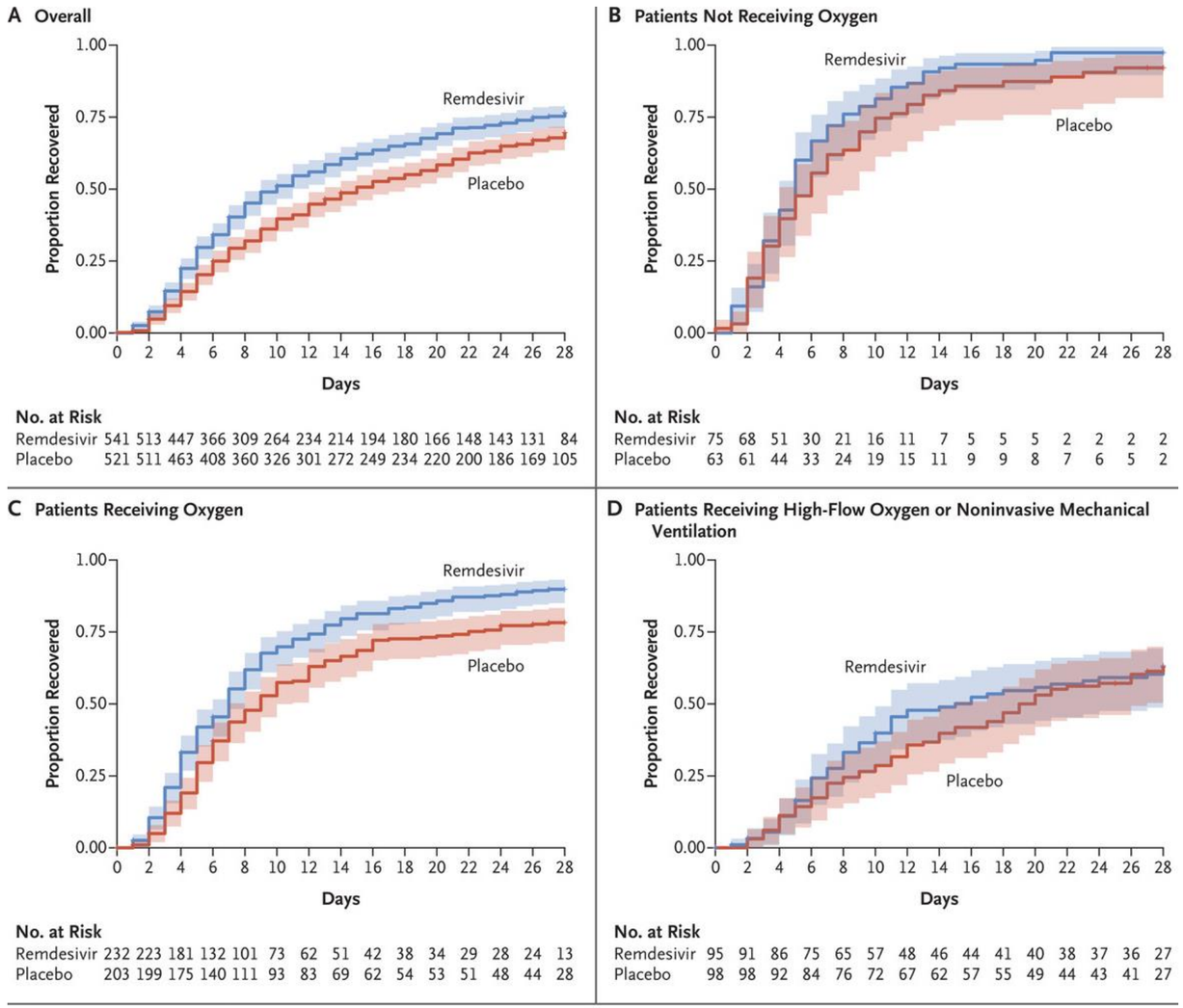
Remdesivir (GS-5734): NIAID ACTT

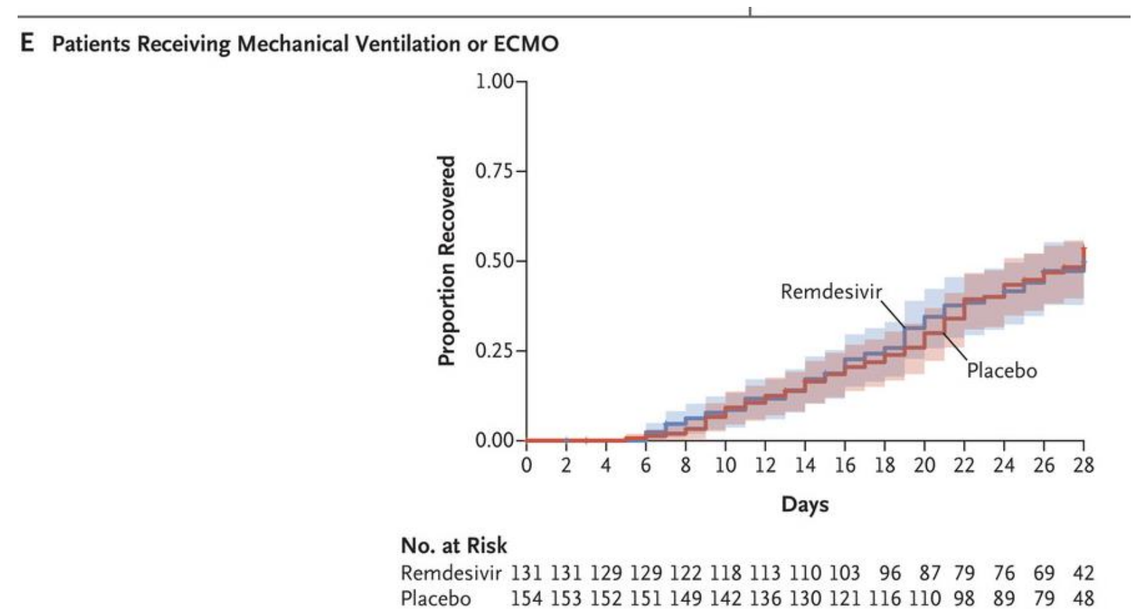
Table 3. Additional Secondary Outcomes	Remdesivir (N=541)	Placebo (N=521)	Rate Ratio (95% CI)
Median time to clinical improvement (95% CI) — days			
Improvement of one category on ordinal scale	7.0 (6.0 to 8.0)	9.0 (8.0 to 11.0)	1.23 (1.08 to 1.41)
Improvement of two categories on ordinal scale	11.0 (10.0 to 13.0)	14.0 (13.0 to 15.0)	1.29 (1.12 to 1.48)
Discharge or National Early Warning Score ≤2 for 24 hr*	8.0 (7.0 to 9.0)	12.0 (10.0 to 15.0)	1.27 (1.10 to 1.46)
			Difference (95% CI)
Hospitalization			
Median duration of initial hospitalization (IQR) — days†	12 (6 to 28)	17 (8 to 28)	−5.0 (−7.7 to −2.3)
Median duration of initial hospitalization among those who did not die (IQR) — days	10 (5 to 21)	14 (7 to 27)	−4.0 (−6.0 to −2.0)
Patients rehospitalized — % (95% CI)	5 (3 to 7)	3 (2 to 5)	2 percentage points (0 to 4)
Oxygen			
Median days receiving oxygen if receiving oxygen at baseline (IQR)	13 (5 to 28)	21 (8 to 28)	−8.0 (−11.8 to −4.2)
New use of oxygen			
No. of patients/total no.	27/75	28/63	
Percent of patients (95% CI)	36 (26 to 47)	44 (33 to 57)	−8 (−24 to 8)
Median days receiving oxygen (IQR)	4 (2 to 12)	5.5 (1 to 15)	−1.0 (−7.6 to 5.6)

* Plus–minus values are means ±SD. Percentages may not total 100 because of rounding. IQR denotes interquartile range, and ECMO extracorporeal membrane oxygenation. The full table of baseline characteristics is available in the Supplementary Appendix.
† Race and ethnic group were reported by the patients. The number of patients in other races and ethnic groups are listed in Table S1 in the Supplementary Appendix.

Beigel et al. N Eng J Med. 2020: doi.org/10.1056/NEJMoa20007764.

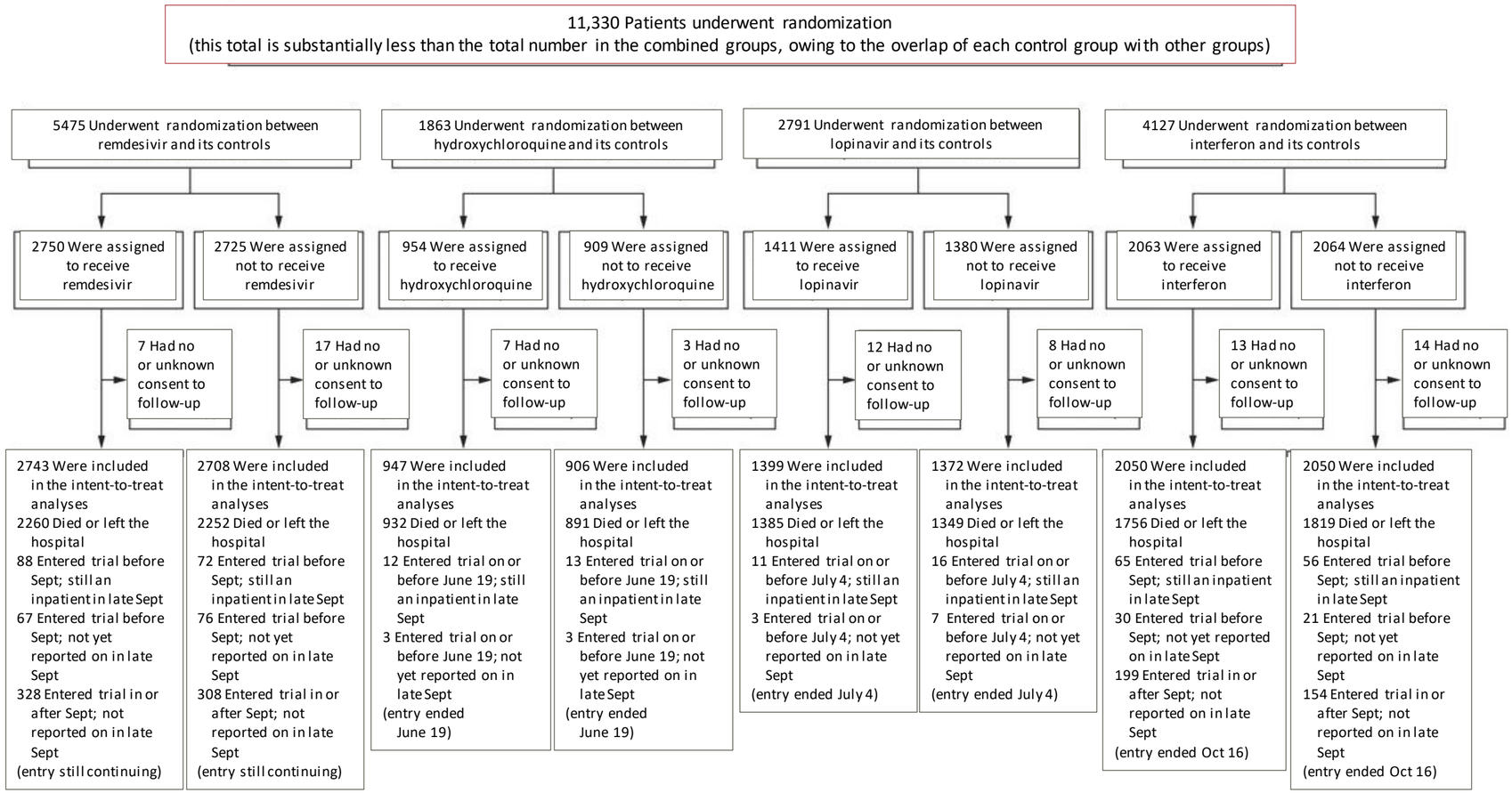
Remdesivir (GS-5734): ACTT





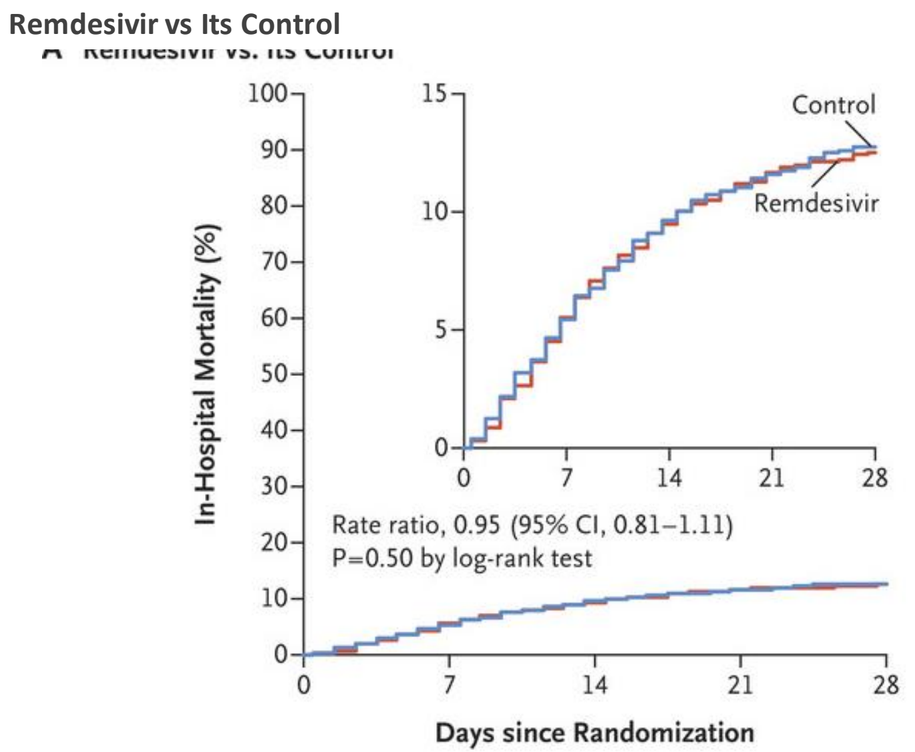
Beigel et al. N Eng J Med. 2020: doi.org/10.1056/NEJMoa20007764.

Remdesivir (GS-5734): SOLIDARITY Trial



WHO Solidarity Trial Consortium. N Engl J Med. 2020. DOI: 10.1056/NEJMoa2023184.

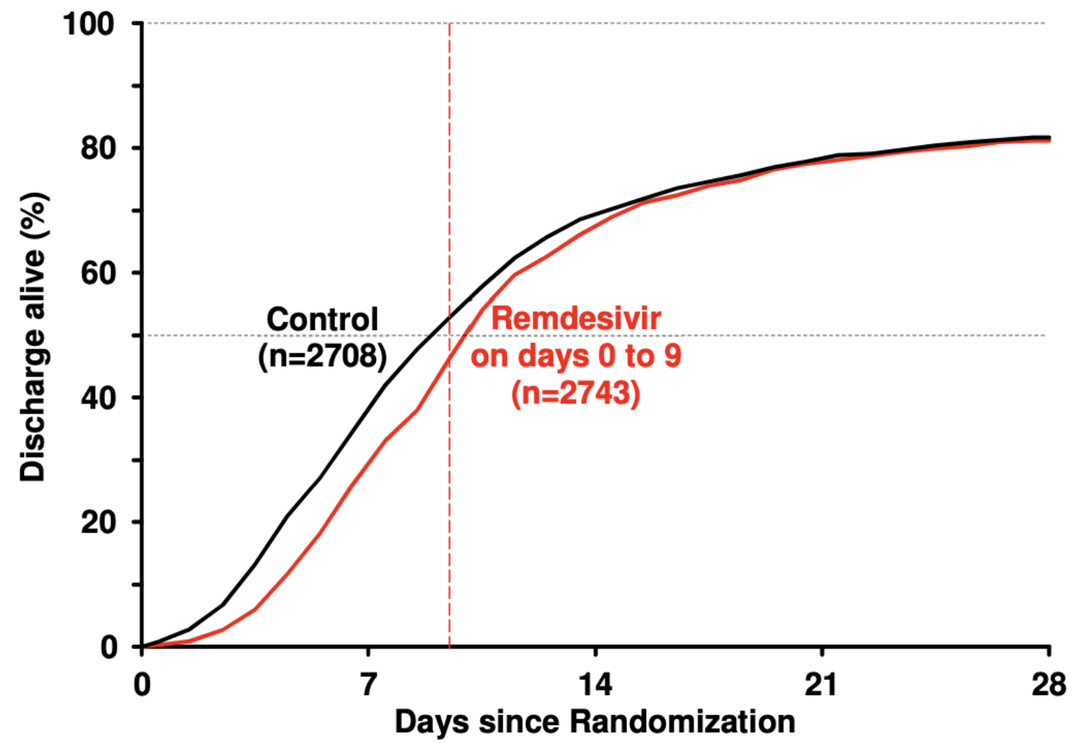
Remdesivir (GS-5734): SOLIDARITY Trial



Denominator					
Remdesivir	2743	2159	2029	1918	1838
Control	2708	2138	2004	1908	1833
No. Who Died					
Remdesivir	129	90	48	18	16
Control	126	93	43	27	14

Secondary Outcomes

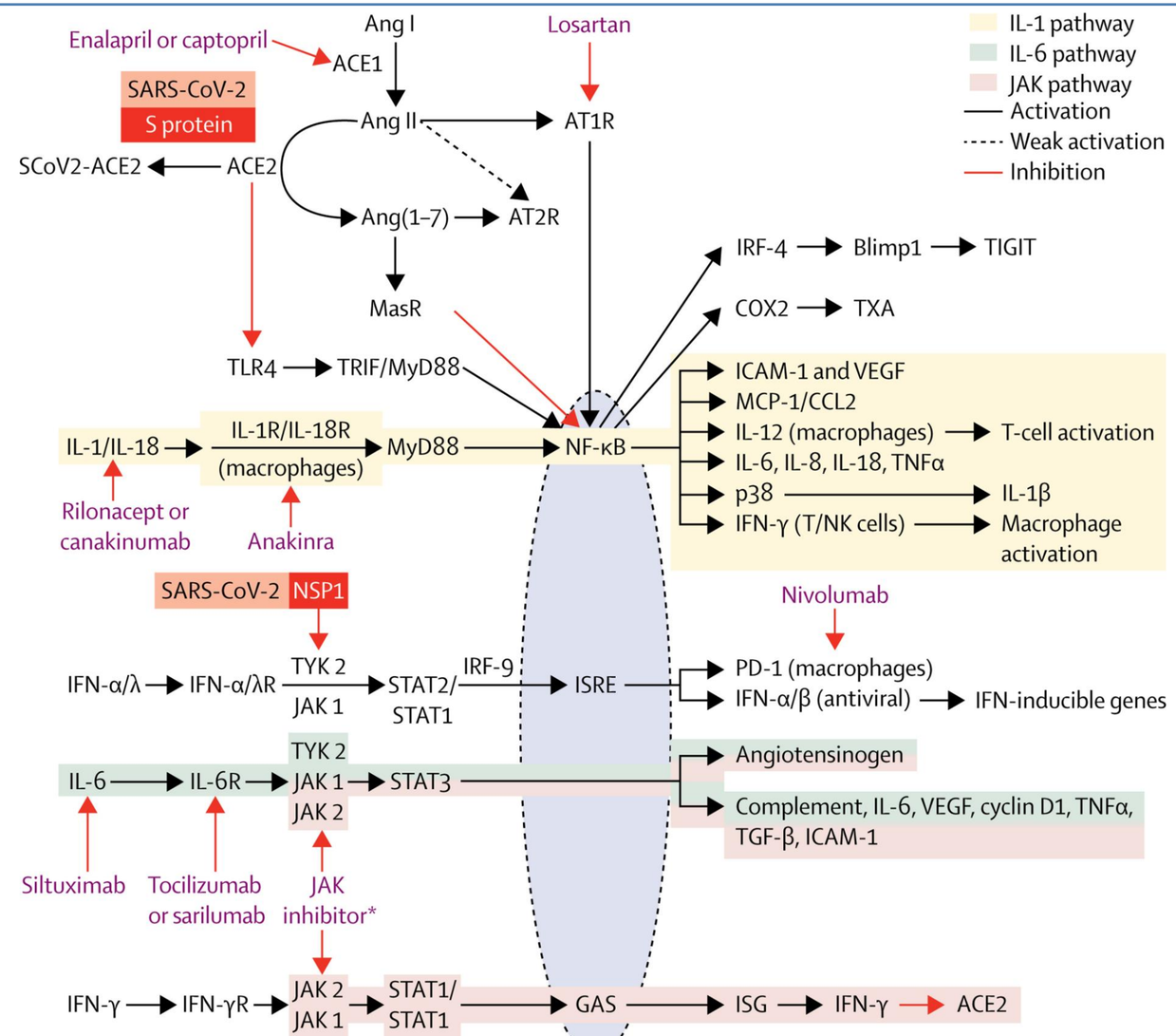
- New-onset mechanical ventilation
  - 295 remdesivir patients vs 284 control patients
- Hospital discharge



WHO Solidarity Trial Consortium. N Engl J Med. 2020. DOI: 10.1056/NEJMoa2023184.

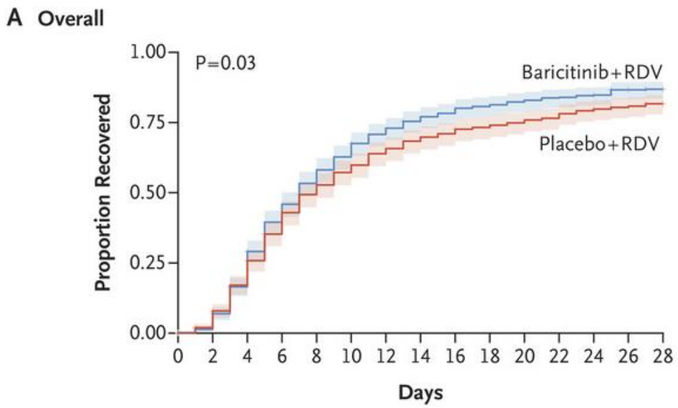
Immune Modulation Therapy

- IL6R: Tocilizumab, Sarilumab
- JAK: Baricitinib, Ruxolitinib
- IL-1: Canakinumab, Anakinra
- BTK Inhibitor: Ibrutinib
- Steroids



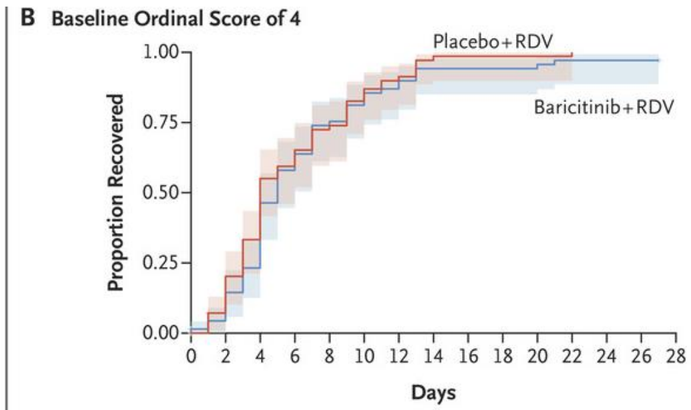
Ingraham et al. Lancet Resp Med. 2020: DOI.org/10.1016/s2213-2600(20)30226-5.
Tay et al. Nat Rev Immunolo. 2020: doi.org/10.1038/s41577-020-0311-8.

Baricitinib: NIAID ACTT2



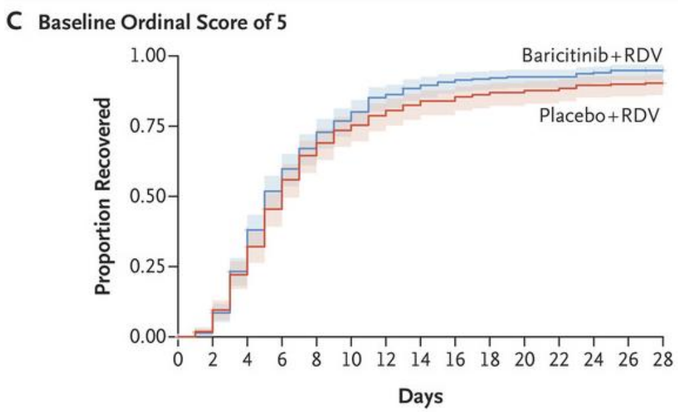
No. at Risk

Baricitinib+RDV	515	497	418	302	233	186	145	121	107	95	87	80	76	63	30
Placebo+RDV	518	495	417	322	251	211	178	156	143	131	123	115	102	92	44



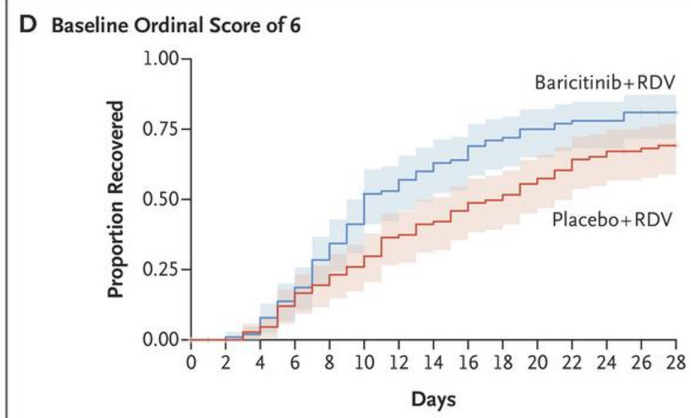
No. at Risk

Baricitinib+RDV	70	66	53	29	18	13	9	4	4	4	4	2	2	2	0
Placebo+RDV	72	64	46	28	19	12	7	2	1	1	1	1	0	0	0



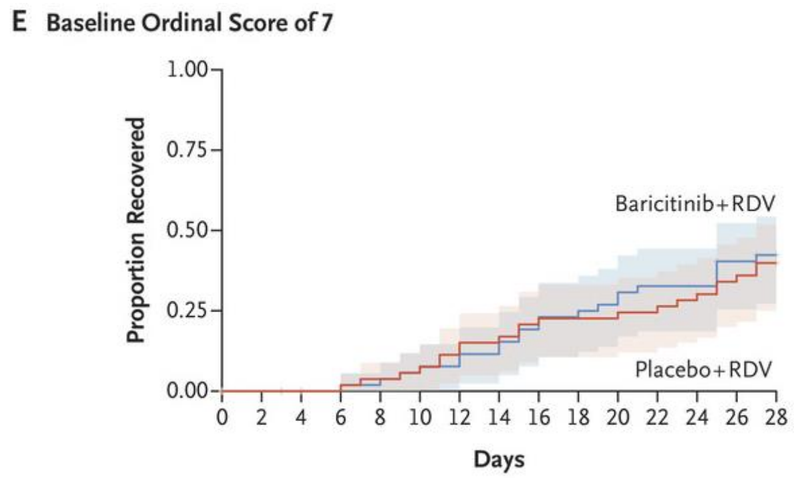
No. at Risk

Baricitinib+RDV	288	276	213	133	91	64	41	31	25	22	20	20	17	12	5
Placebo+RDV	276	267	211	146	95	71	57	47	43	37	35	33	28	26	12



No. at Risk

Baricitinib+RDV	103	102	100	88	73	60	47	40	36	29	25	23	22	19	10
Placebo+RDV	113	110	106	95	86	78	67	62	57	52	46	41	36	32	16

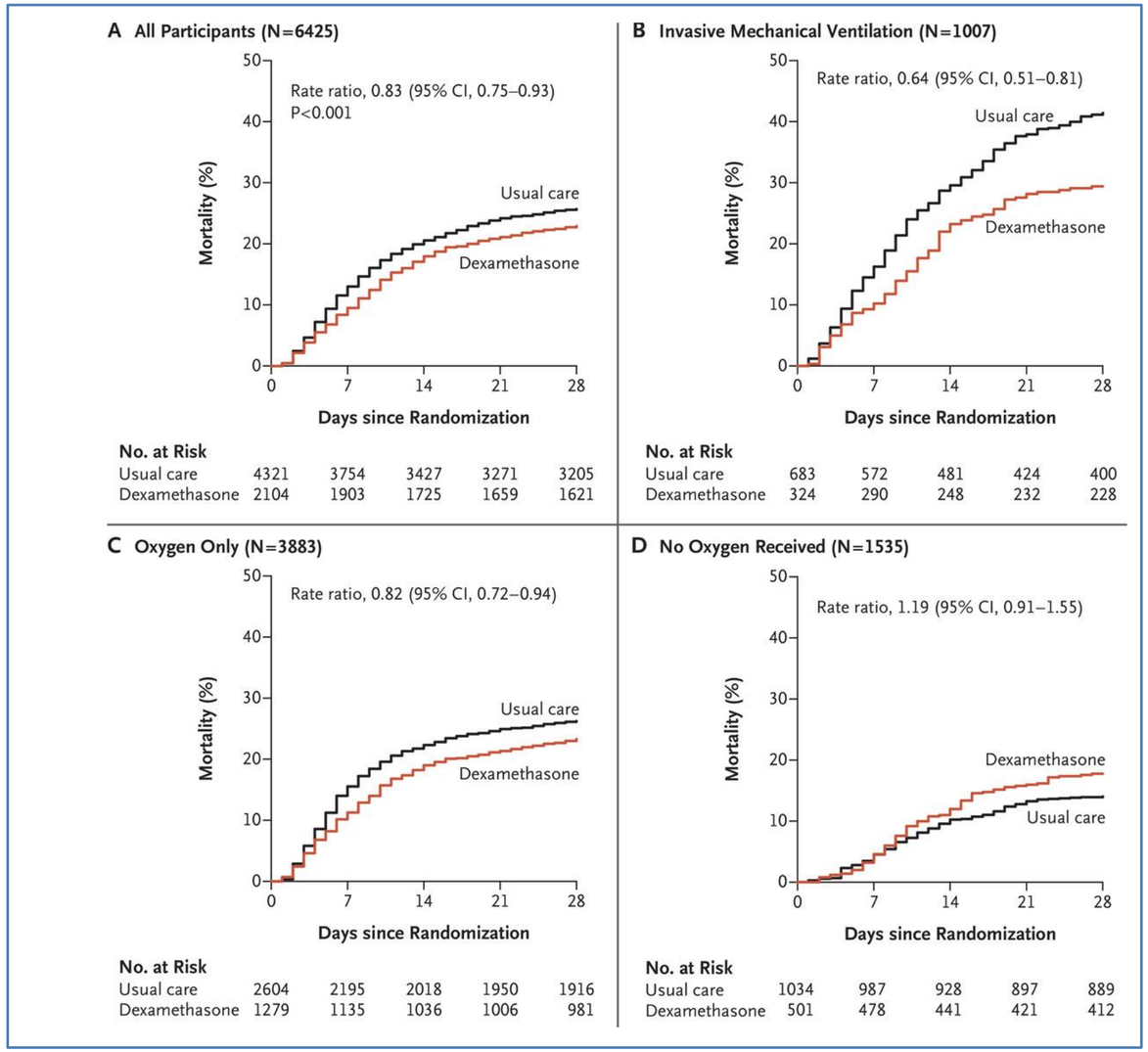


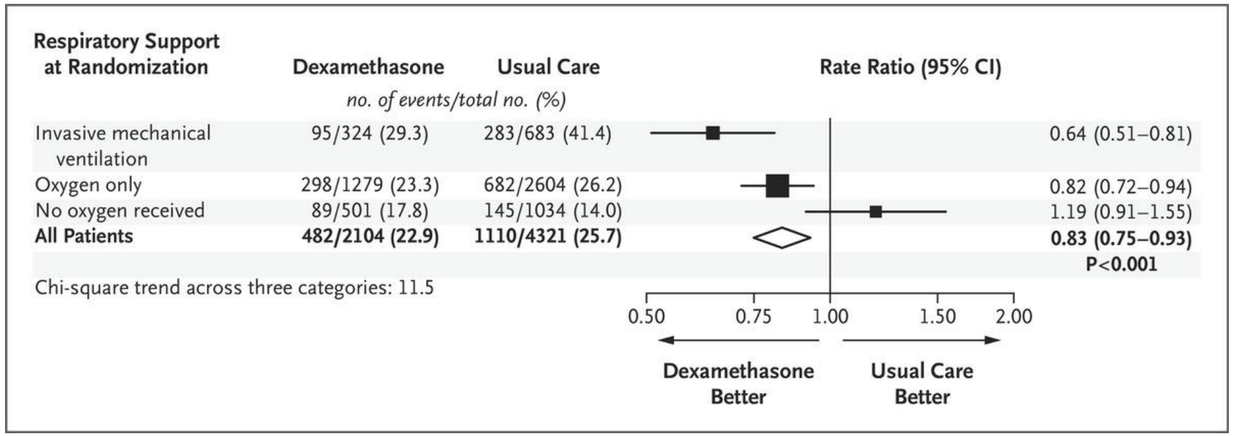
No. at Risk

Baricitinib+RDV	54	53	52	52	51	49	48	46	42	40	38	35	35	30	15
Placebo+RDV	57	54	54	53	51	50	47	45	42	41	41	40	38	34	16

Kalil et al. N Eng J Med. 2020: DOI: 10.1056/NEJMoa2031994.

Dexamethasone

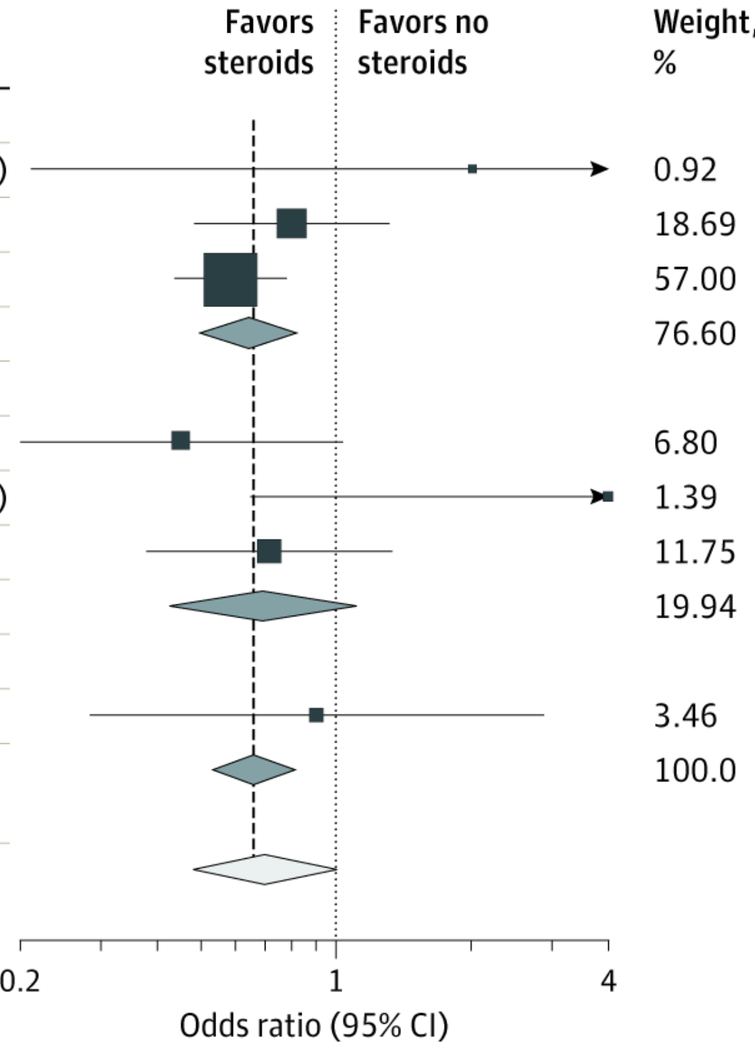




RECOVERY Collaborative Group. N Eng J Med. 2020. DOI: 10.1056/NEJMoa2021436.

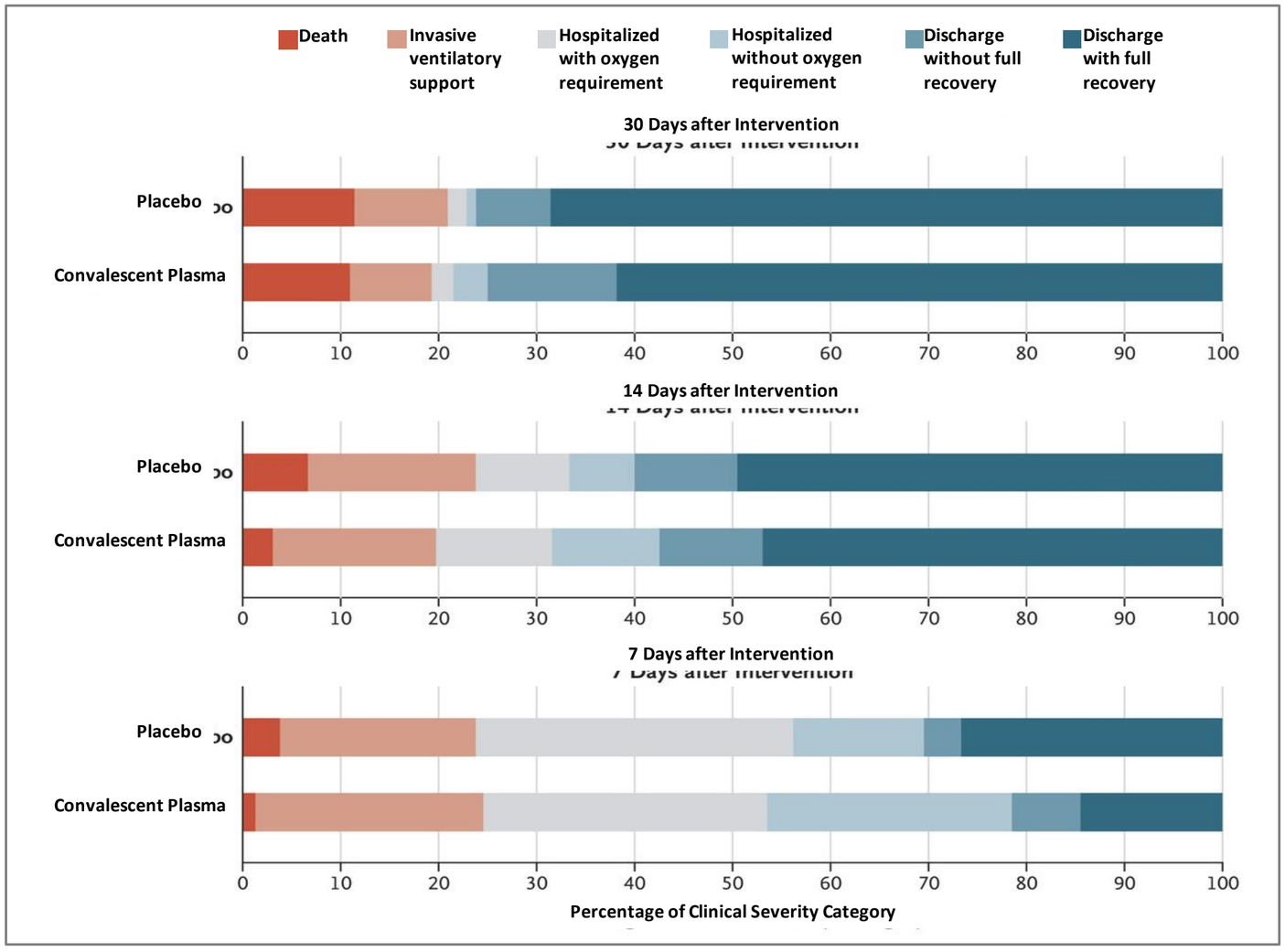
Steroids

Drug and trial	ClinicalTrials.gov identifier	Initial dose and administration	No. of deaths/total No. of patients: Steroids	No. of deaths/total No. of patients: No steroids	Odds ratio (95% CI)	Weight, %
Dexamethasone						
DEXA-COVID 19	NCT04325061	High: 20 mg/d intravenously	2/7	2/12	2.00 (0.21-18.69)	0.92
CoDEX	NCT04327401	High: 20 mg/d intravenously	69/128	76/128	0.80 (0.49-1.31)	18.69
RECOVERY	NCT04381936	Low: 6 mg/d orally or intravenously	95/324	283/683	0.59 (0.44-0.78)	57.00
Subgroup fixed effect			166/459	361/823	0.64 (0.50-0.82)	76.60
Hydrocortisone						
CAPE COVID	NCT02517489	Low: 200 mg/d intravenously	11/75	20/73	0.46 (0.20-1.04)	6.80
COVID STEROID	NCT04348305	Low: 200 mg/d intravenously	6/15	2/14	4.00 (0.65-24.66)	1.39
REMAP-CAP	NCT02735707	Low: 50 mg every 6 h intravenously	26/105	29/92	0.71 (0.38-1.33)	11.75
Subgroup fixed effect			43/195	51/179	0.69 (0.43-1.12)	19.94
Methylprednisolone						
Steroids-SARI	NCT04244591	High: 40 mg every 12 h intravenously	13/24	13/23	0.91 (0.29-2.87)	3.46
Overall (fixed effect)			222/678	425/1025	0.66 (0.53-0.82)	100.0
$P = .31$ for heterogeneity; $I^2 = 15.6\%$						
Overall (random effects[a])			222/678	425/1025	0.70 (0.48-1.01)	

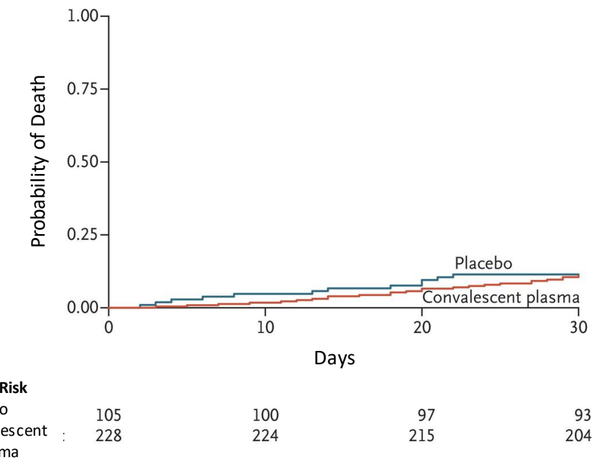


WHO REACT Group. JAMA. 2020. DOI: 10.1001/jama.2020.17023.

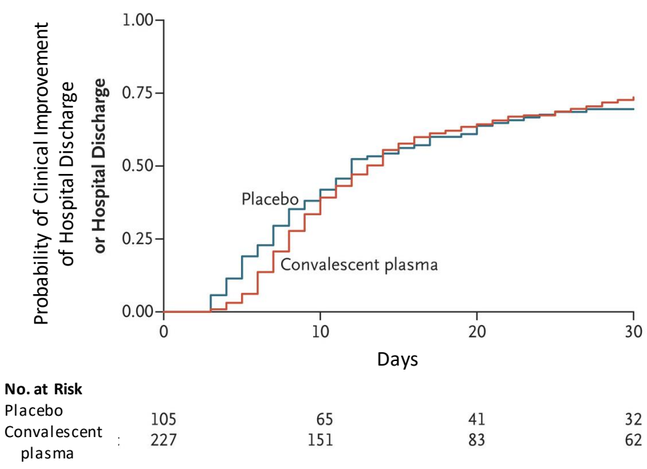
Convalescent Plasma



Time from Intervention to Death



Time from Intervention to Improvement



Simonovich et al. N Engl J Med. 2020. DOI: 10.1056/NEJMoa2031304.

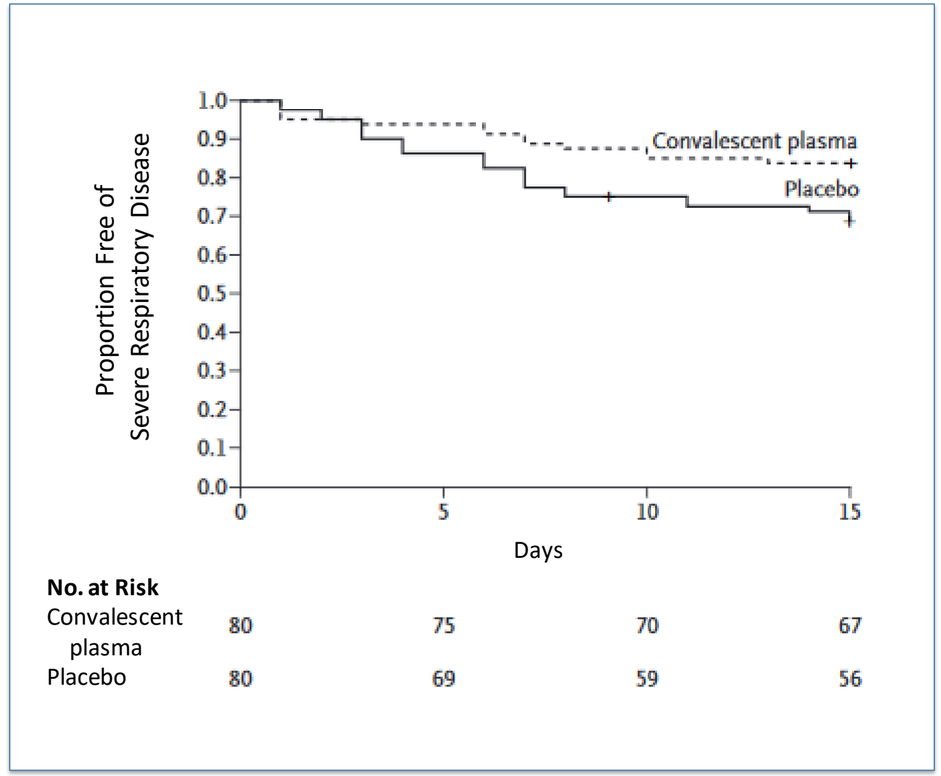
Convalescent Plasma

- Early high-titer plasma
- Administered within 72 hours after symptom onset
- Older adults

Table 3. Primary Endpoint, According to Donor SARS-CoV-2 S IgG Titer

Patient Group	Patients with Severe Respiratory Disease no./total no. (%)	Relative Risk (95% CI)	Relative Risk Reduction percent
Placebo	25/80 (31)	1.00	
Recipient of SARS-CoV-2 S IgG in donor plasma*			
At a titer at or above median concentration	3/36 (8)	0.27 (0.08-0.68)	73.3
At a titer below median concentration	9/42 (21)	0.69 (0.34-1.31)	31.4

*The median concentration is a SARS-CoV-2 S IgG titer of 1:3200.



Libster et al. N Engl J Med. 2021. DOI: 10.1056/NEJMoa2033700.

Treatment Eligibility

Treatment	Status	Eligibility
Monoclonal antibodies: Bamlanivimab Casirivimab + imdevimab	EUA	Outpatients (≥12 yrs) with confirmed COVID at risk for severe disease, based on established criteria, within 10 days of symptom onset; Excluding: patients requiring oxygen because of COVID
Remdesivir	Approved	Patients (≥12 yrs and ≥40 kg) requiring hospitalization
Dexamethasone	Off label	Patients requiring supplemental oxygen
Convalescent plasma	EUA	Hospitalized patients
Remdesivir + baricitinib	EUA	Hospitalized patients (≥2 yrs) requiring supplemental oxygen, invasive mechanical ventilation, or ECMO

POST-TEST

Post-Test Question 1

How confident are you in describing current management strategies for mild to moderate COVID-19?

1. Not confident
2. Slightly confident
3. Moderately confident
4. Highly confident

Post-Test Question 2

According to the ACTT-1 trial, which group of included patients benefitted the most from remdesivir?

1. All included patients benefitted equally
2. Patients not receiving oxygen
3. Patients receiving noninvasive mechanical ventilation
4. Patients receiving mechanical ventilation or ECMO

Post-Test Question 3

A 22-year-old previously healthy patient with no underlying conditions has mild COVID-19. Which of following is/are recommended for this patient?

1. Home isolation
2. Symptom monitoring
3. Dexamethasone
4. Monoclonal antibodies
5. 1 and 2
6. 1 and 3

Post-Test Question 4

Monoclonal antibodies are thought to primarily work by blocking the virus' ability to attach to and enter human cells.

1. True
2. False

Post-Test Question 5

Monoclonal antibody products are authorized to treat which group of patients with confirmed COVID-19?

1. Any patient
2. Any non-hospitalized patient ≥ 18 years of age
3. Non-hospitalized patients ≥ 12 years of age at high risk for severe disease
4. Hospitalized patients for COVID-19 ≥ 12 years of age requiring oxygen support


COVID19
Keeping Up with a Moving Target
Q&A


COVID19
Keeping Up with a Moving Target
Thank You!