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Clinical Management of COVID-19 Patients

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Hong Kong COVID-19 Symposium: From Prevention to Control

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Disclosures

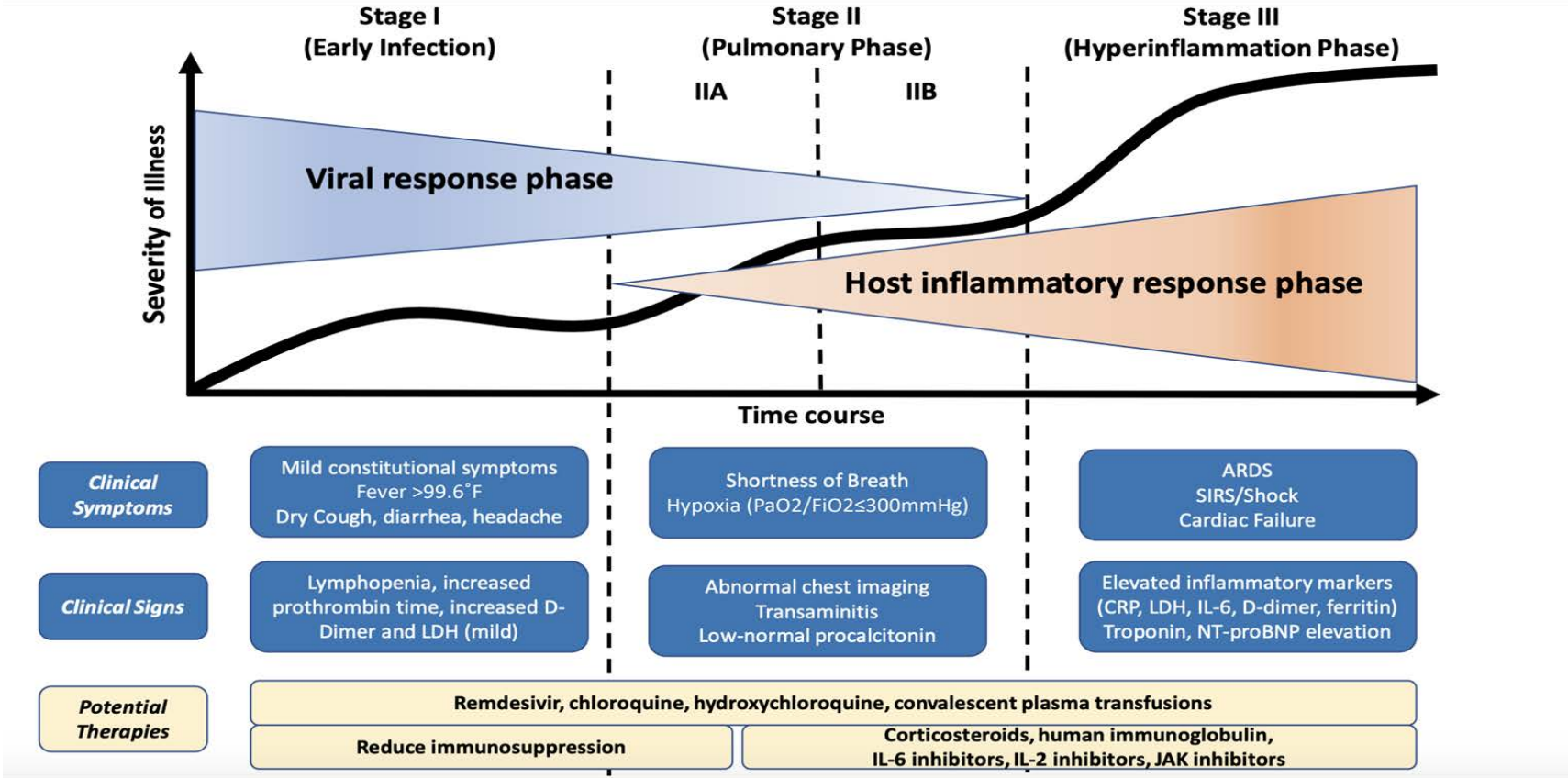
- Research Support°
  - AiCuris, Janssen, Shire
- Paid Consultation
  - Adagio, AlloVir, Celltrion, Cidara, Genentech/Roche, Janssen, Shionogi, Viracor Eurofins
- Unpaid Consultation
  - Romark
- Data & Safety Monitoring Board Participation
  - NIH, Janssen, Merck, SAB Biotherapeutics, Sequiris, Takeda, Vitaeris

As of 10/19/20; ° Paid to Northwestern University.

Clinical Management of COVID-19 Patients

- Course of COVID-19
- Potential Targets for Treatment of COVID-19
- Outpatient Management
- Antiviral Approaches
- Immunmodulatory Approaches
- Convalescent Plasma

COVID-19: *How and When to Intervene?*



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

Outpatient Management of COVID-19: *Preventing Hospitalization*

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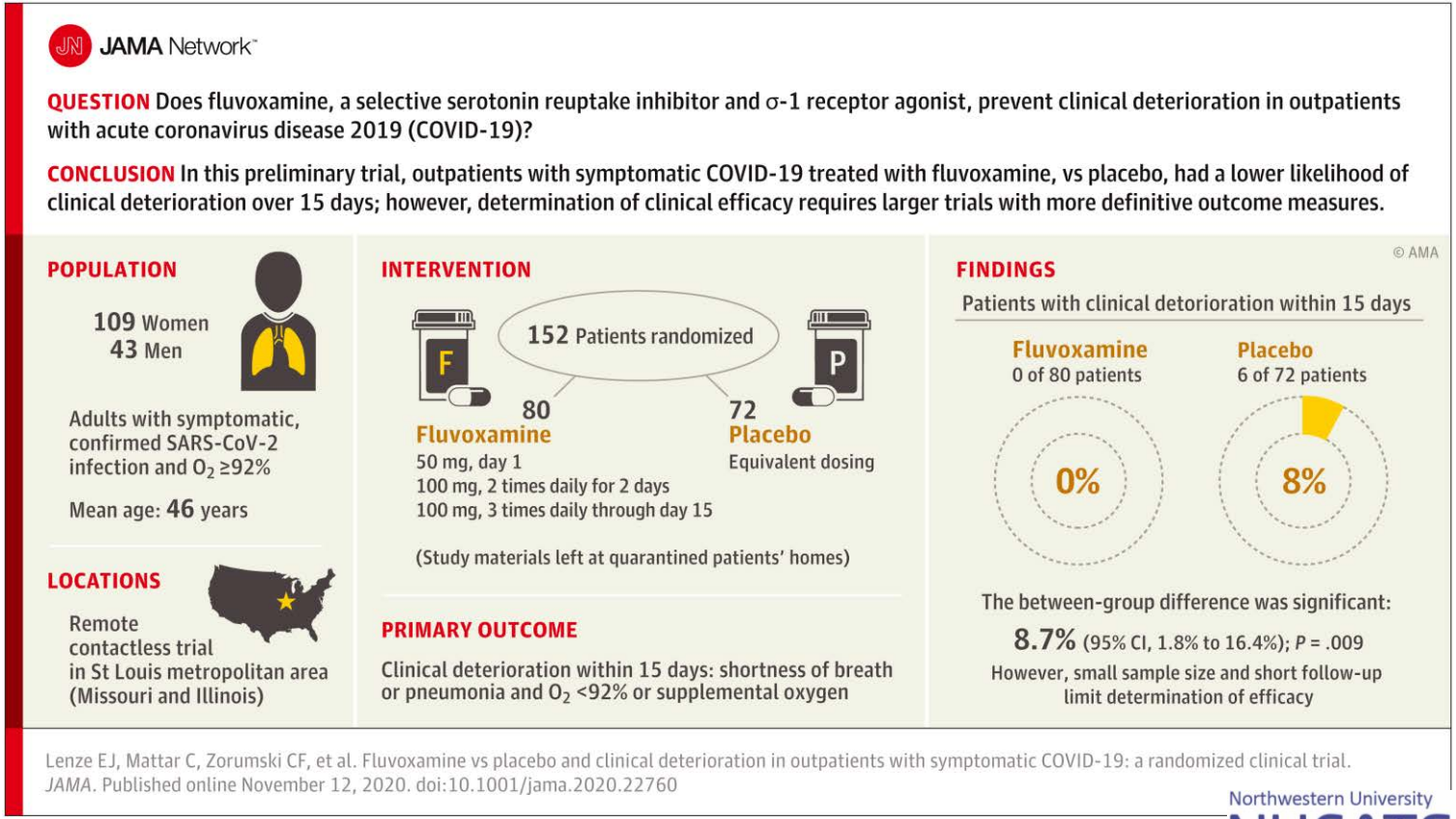
Fluvoxamine: *Outpatient Management of COVID-19*



Lenze EJ, Mattar C, Zorumski CF, et al. Fluvoxamine vs placebo and clinical deterioration in outpatients with symptomatic COVID-19: a randomized clinical trial. *JAMA*. Published online November 12, 2020. doi:10.1001/jama.2020.22760

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

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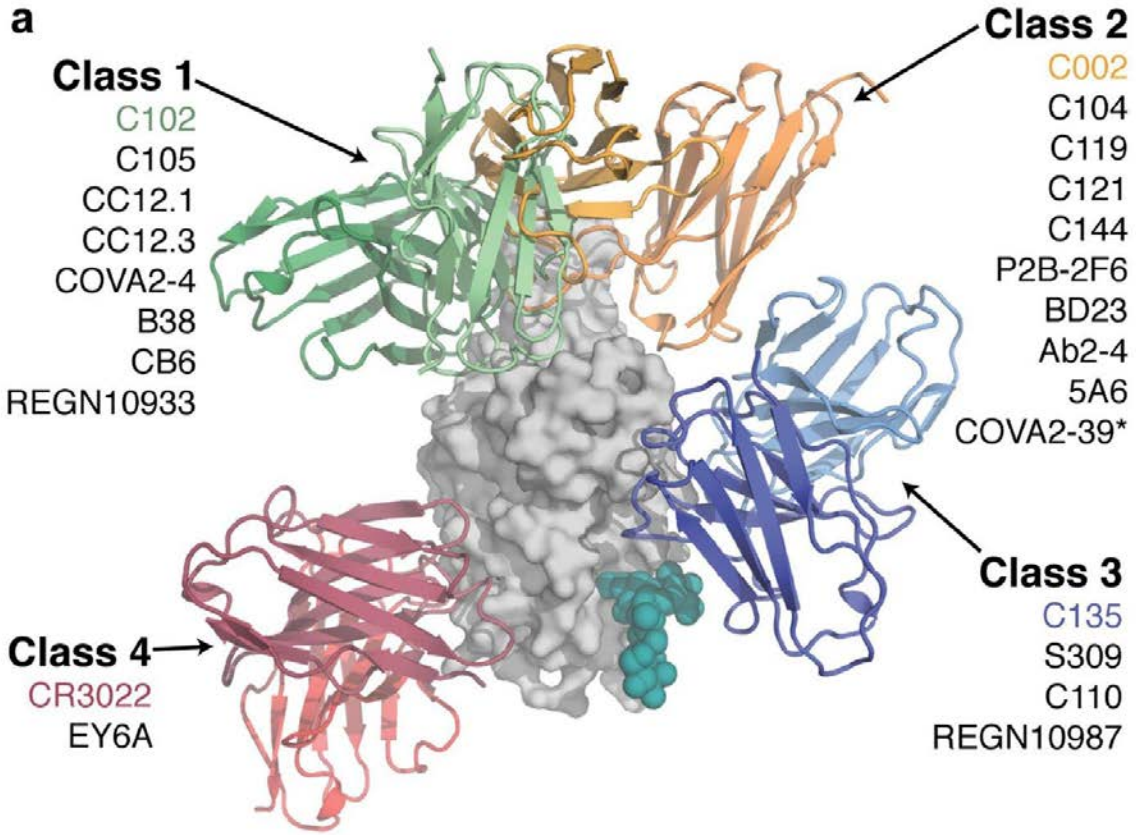
COVID-19: *Monoclonal Antibodies*



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COVID-19: *Bamlanivimab*

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

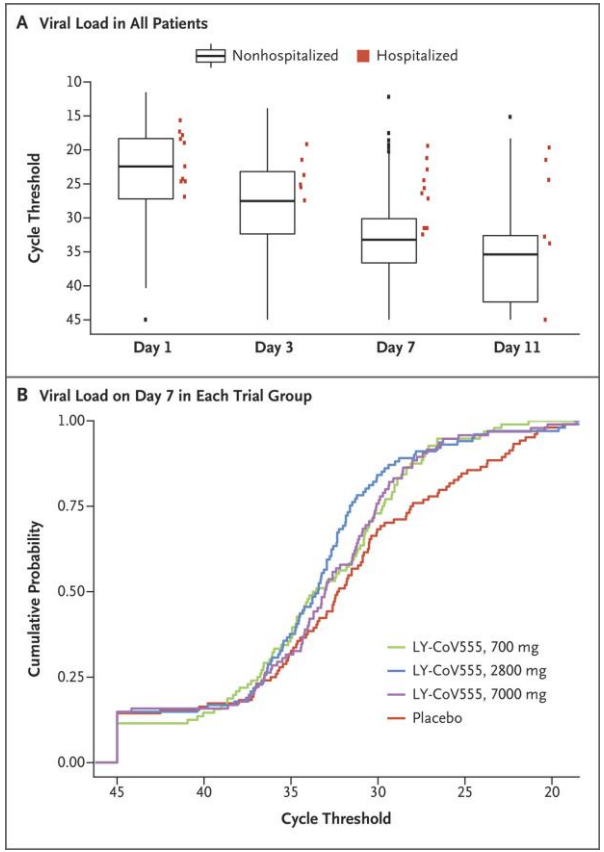

Table 2. Change from Baseline in Viral Load.

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)

EC_{50} value = 0.03 µg/mL

* Data regarding hospitalization, another key secondary outcome, are provided in Table 3.

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

COVID-19: *Bamlanivimab*

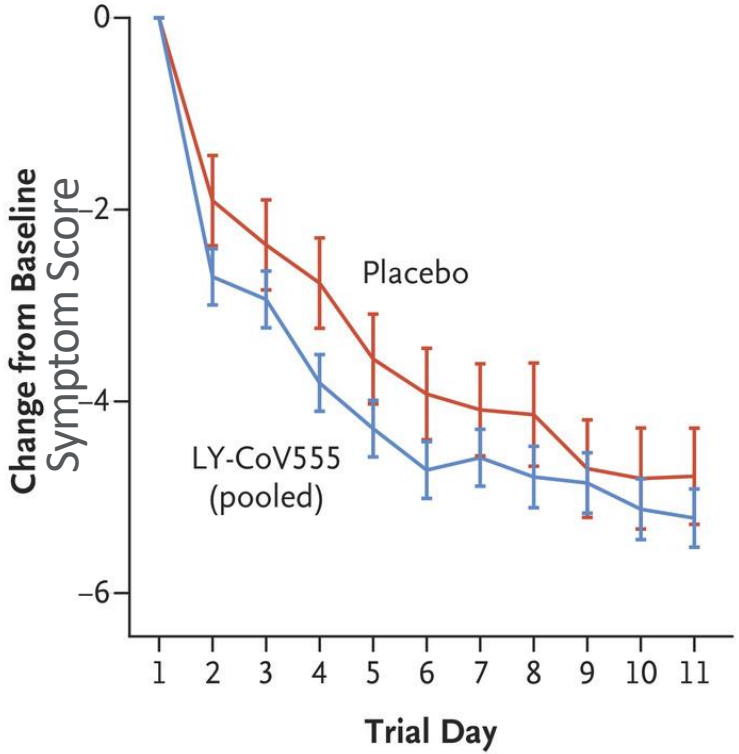


Table 3. Hospitalization.*

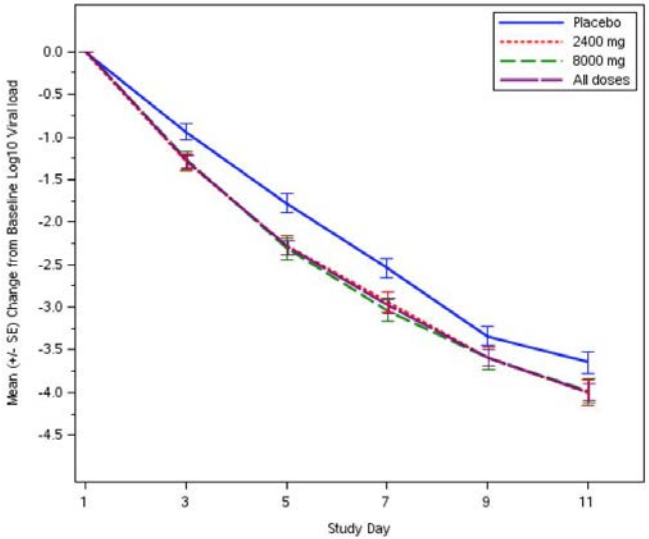
Key Secondary Outcome	LY-CoV555	Placebo	Incidence
	no. of patients/total no.		%
Hospitalization		9/143	6.3
	700 mg, 1/101		1.0
	2800 mg, 2/107		1.9
	7000 mg, 2/101		2.0
	Pooled doses, 5/309		1.6

* 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

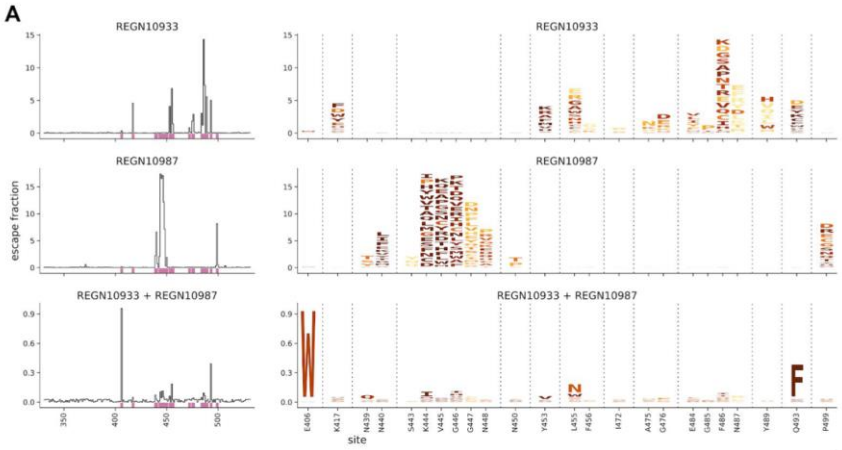
COVID-19: *Casirivimab and Imdevimab*

- EC_{50} values of 37.4 pM (0.006 µg/mL), 42.1 pM (0.006 µg/mL), and 31.0 pM (0.005 µg/mL)
- Resistance: 3/66 subjects
  - Two at baseline in subjects from placebo
  - One at day 25 from high dose combination therapy (135 fold increase EC_{50})
- Efficacy (N = 799: Approved Dose N=266, High Dose N=267, Placebo N = 266)

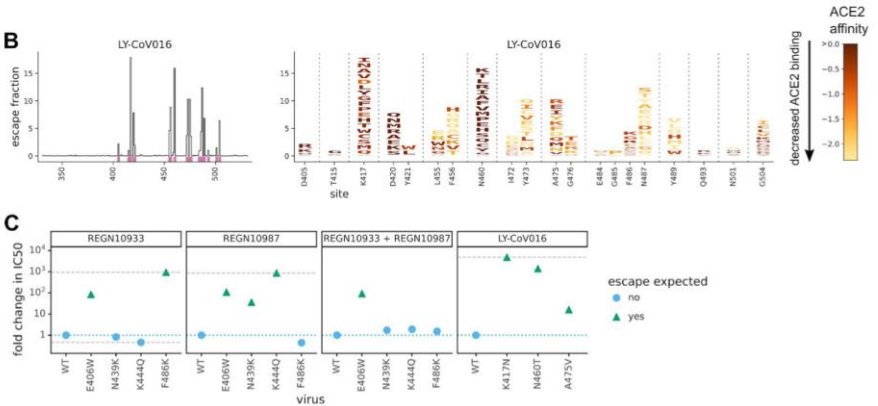


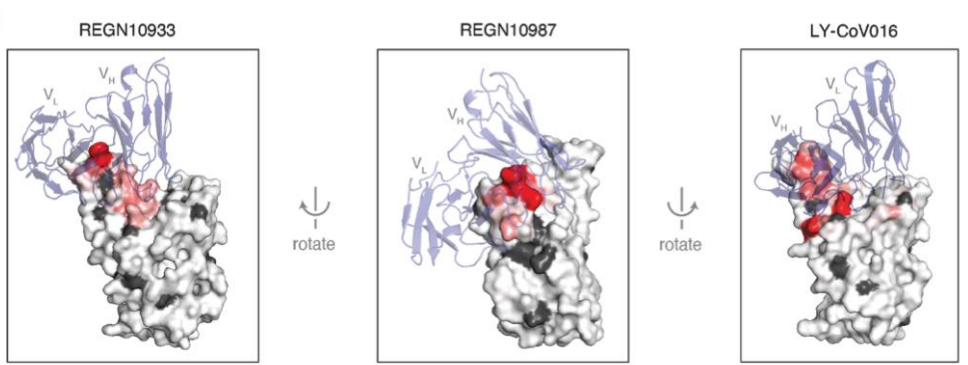
Arm	All Enrolled			High Risk Subjects		
	N	Events	%	N	Events	%
Placebo	231	10	4%	78	7	9%
1200mg	215	4	2%	70	2	3%
4000mg	219	4	2%	81	2	2%

Monoclonal Antibodies and Resistance Emergence



antibody	mutations
REGN10933	K417E, Y453F, L455Y, F486V, Q493K
REGN10987	K444Q, V445A
REGN10933 + REGN10987	none





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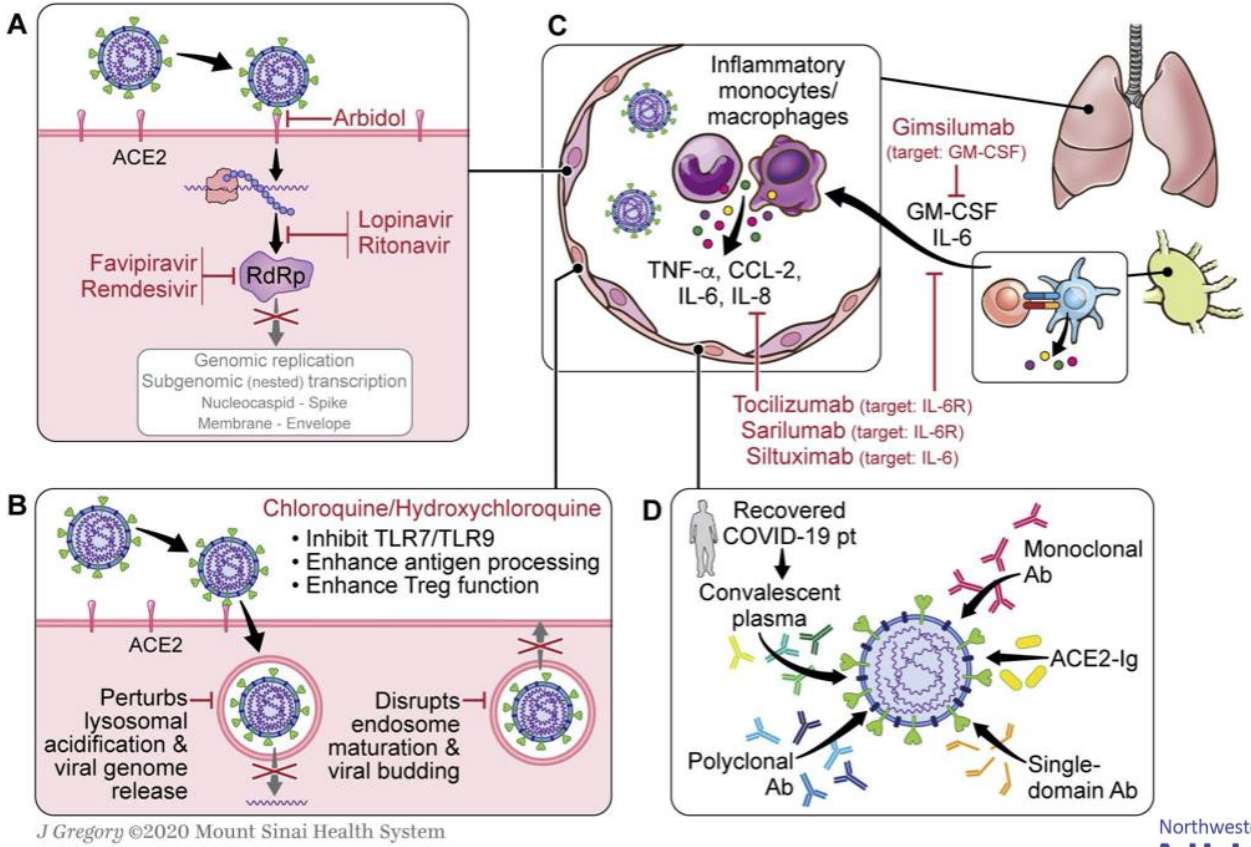
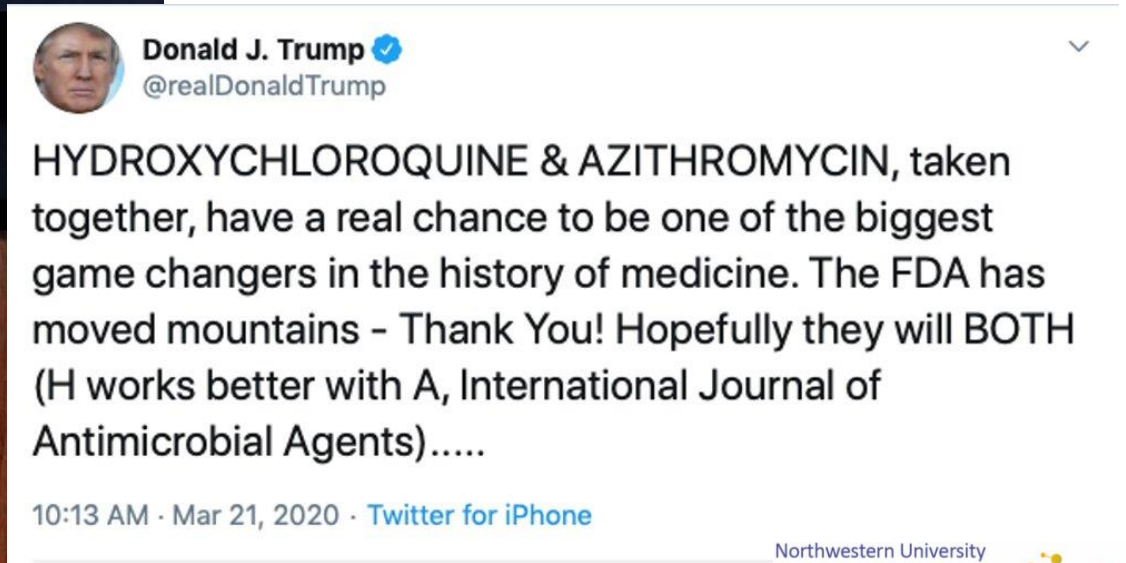
Starr *et al*. bioRxiv 2020.11.30.405472; doi: https://doi.org/10.1101/2020.11.30.405472

COVID-19: *Management Options*

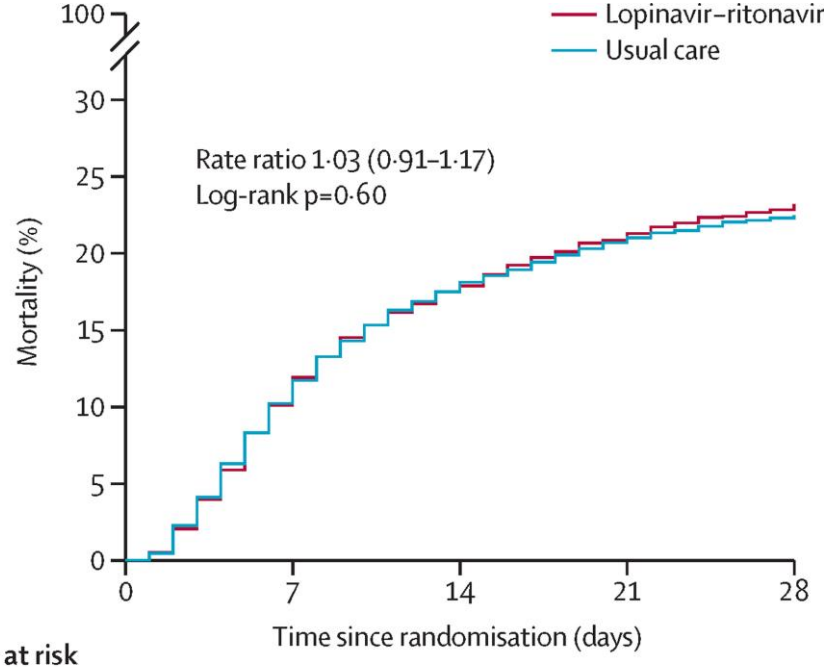


Shi *et al*. ***Cell Death Differentiation***. 2020;27: 1451-1454.

Early Studies Focused on Mostly Therapies that Failed

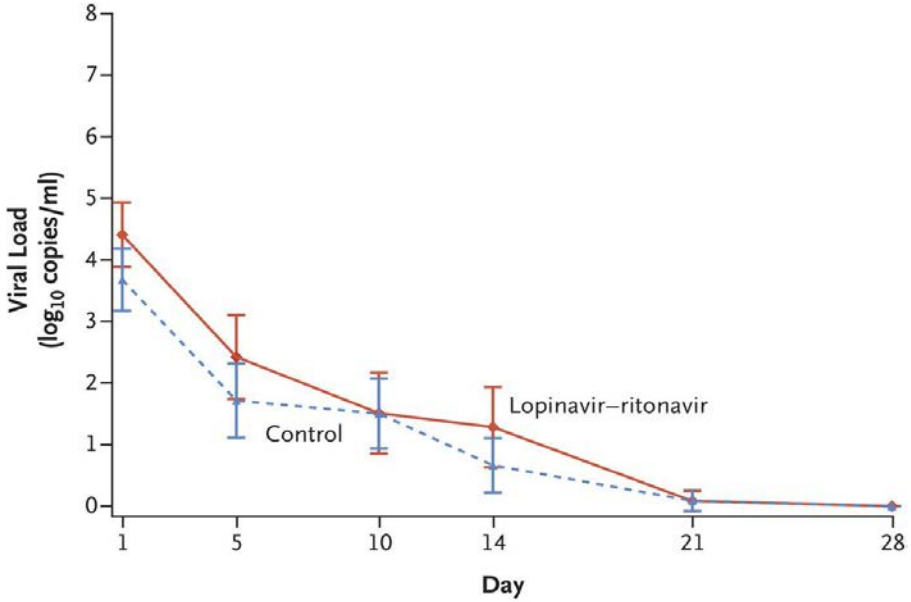


Early Studies Focused on Mostly Therapies that Failed



Number at risk

Active	1616	1422	1325	1269	1238
Control	3424	3018	2799	2700	2650



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Cao *et al*. ***New Eng J Med***. 2020: DOI: 10.1056/NEJMoa2001282.

Horby *et al*. ***Lancet***. 2020; DOI: 10.1016/S0140-6736(20)32013-4.

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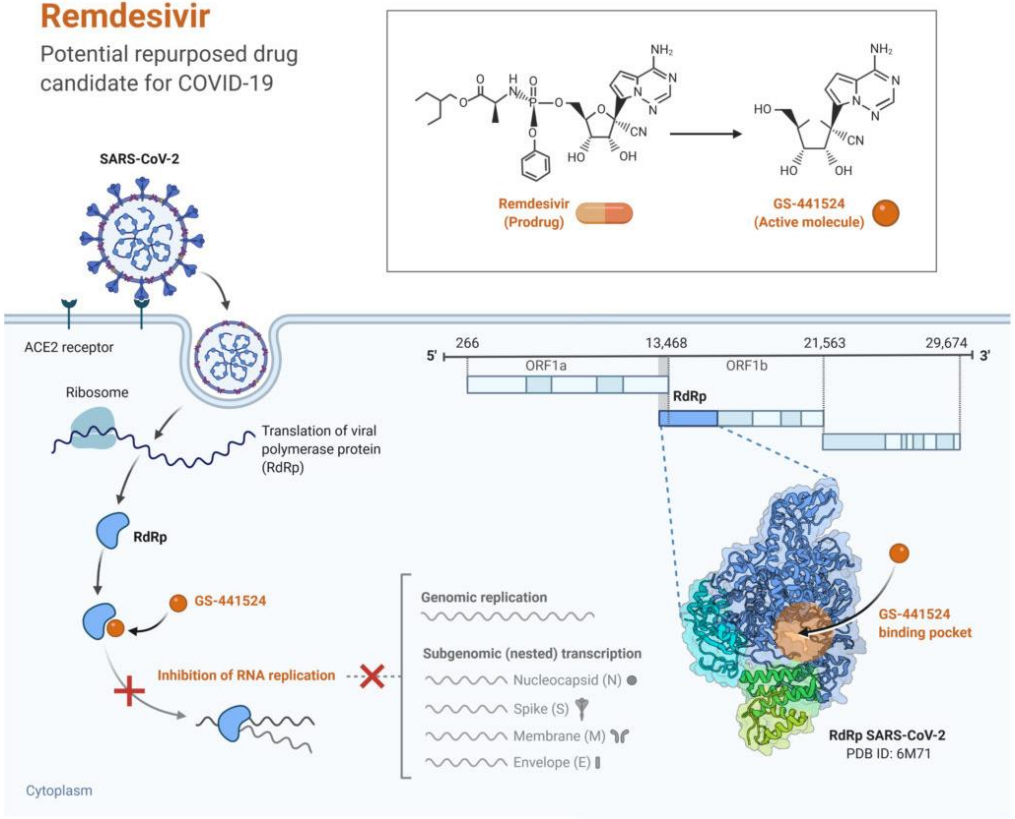
Remdesivir (GS-5734): *IV Antiviral Drug for SARS-CoV-2*



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

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

- NIH Adaptive COVID-19 Treatment Trial (ACTT)
  - Goal of 572 patients with 400 patients recovered to assess outcome
  - DSMB allowed over enrollment: 1063 patients enrolled
  - Randomized, placebo controlled trial (1:1 - RDB 200mg then 100mg BID vs Placebo for 10 days)
  - Primary endpoint: Time to Recovery
    - Day of recovery is defined as the first day on which the subject satisfies one of the following three categories from the ordinal scale:
      1. Hospitalized, not requiring supplemental oxygen - no longer requires ongoing medical care;
      2. Not hospitalized, limitation on activities and/or requiring home oxygen;
      3. Not hospitalized, no limitations on activities.

Beigel *et al*. ***N Eng J Med***. 2020: doi.org/10.1056/NEJMoa2007764.

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	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)	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)	

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

Remdesivir (GS-5734): *NIAID ACTT*

Table 3. Additional Secondary Outcomes.

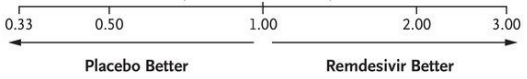
	Remdesivir (N=541)	Placebo (N=521)	Rate Ratio (95% CI)
Median time to clinical improvement (95% CI) — days			
Improvement of one category on ordinal scale	7.0 (6.0 to 8.0)	9.0 (8.0 to 11.0)	1.23 (1.08 to 1.41)
Improvement of two categories on ordinal scale	11.0 (10.0 to 13.0)	14.0 (13.0 to 15.0)	1.29 (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)

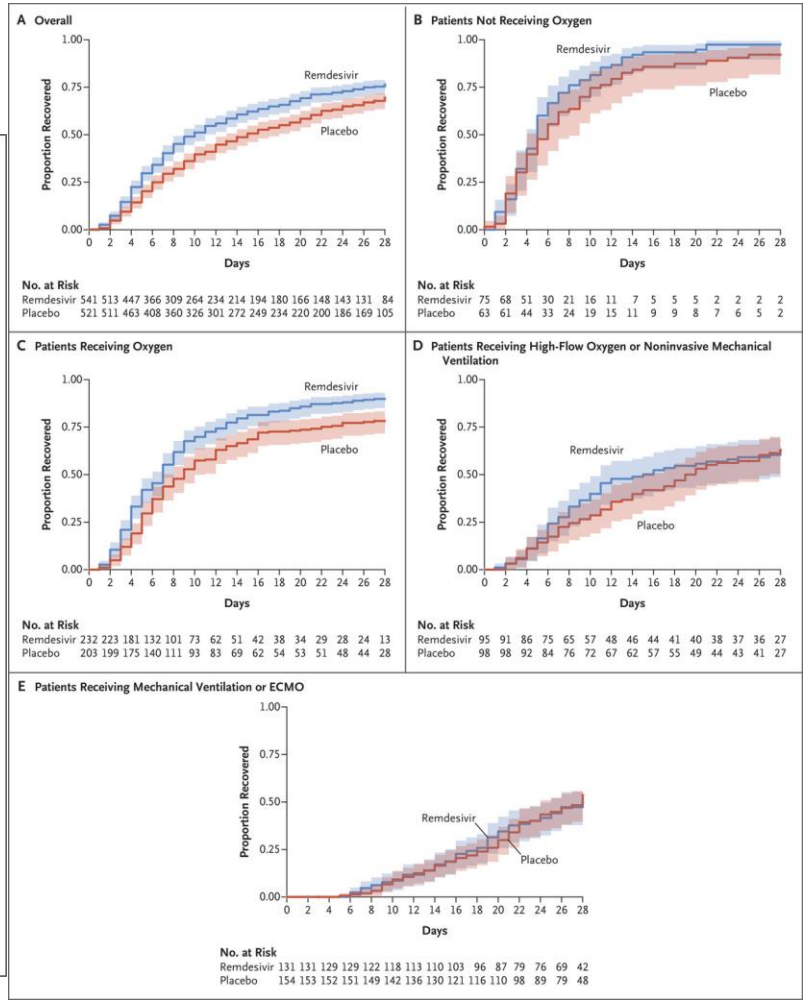
* The National Early Warning Score includes six physiological measures; total scores range from 0 to 20, with higher scores indicating greater clinical risk.
† The duration of initial hospitalization for patients who died was imputed as 28 days.

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

Remdesivir (GS-5734): *ACTT*

Subgroup	No. of Patients	Recovery Rate Ratio (95% CI)
All patients	1062	1.29 (1.12–1.49)
Geographic region		
North America	847	1.30 (1.10–1.53)
Europe	163	1.30 (0.91–1.87)
Asia	52	1.36 (0.74–2.47)
Race		
White	566	1.29 (1.06–1.57)
Black	226	1.25 (0.91–1.72)
Asian	135	1.07 (0.73–1.58)
Other	135	1.68 (1.10–2.58)
Ethnic group		
Hispanic or Latino	250	1.28 (0.94–1.73)
Not Hispanic or Latino	755	1.31 (1.10–1.55)
Age		
18 to <40 yr	119	1.95 (1.28–2.97)
40 to <65 yr	559	1.19 (0.98–1.44)
≥65 yr	384	1.29 (1.00–1.67)
Sex		
Male	684	1.30 (1.09–1.56)
Female	278	1.31 (1.03–1.66)
Symptoms duration		
≤10 days	676	1.37 (1.14–1.64)
>10 days	383	1.20 (0.94–1.52)
Baseline ordinal score		
4 (not receiving oxygen)	138	1.29 (0.91–1.83)
5 (receiving oxygen)	435	1.45 (1.18–1.79)
6 (receiving high-flow oxygen or noninvasive mechanical ventilation)	193	1.09 (0.76–1.57)
7 (receiving mechanical ventilation or ECMO)	285	0.98 (0.70–1.36)





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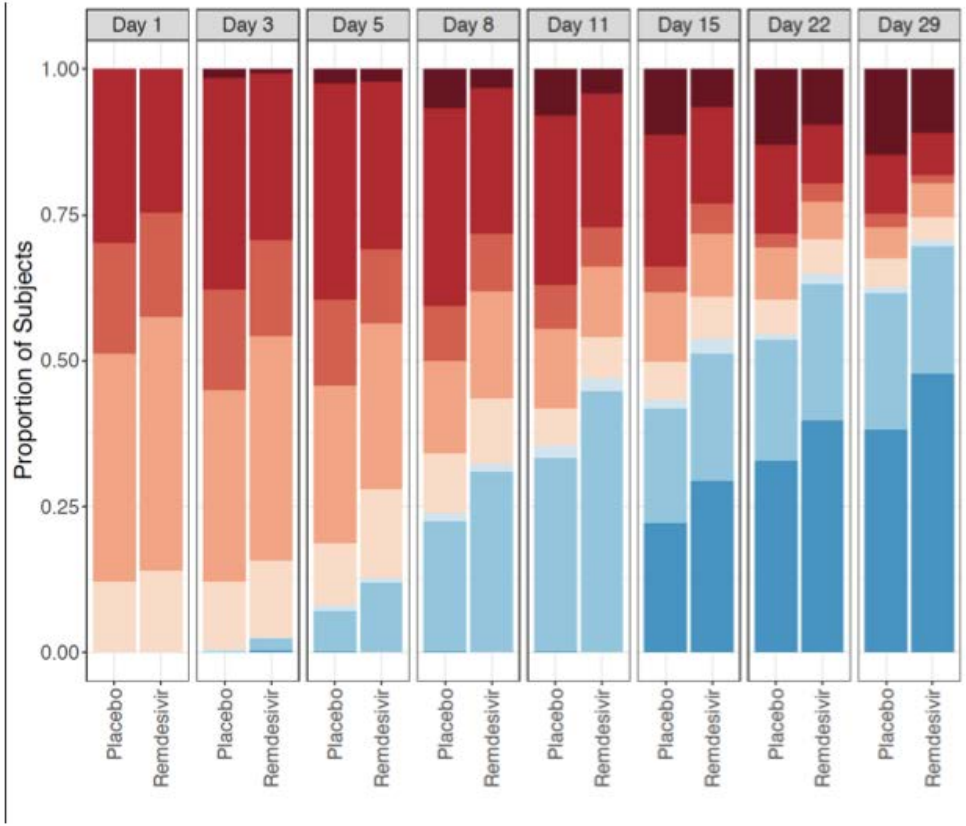
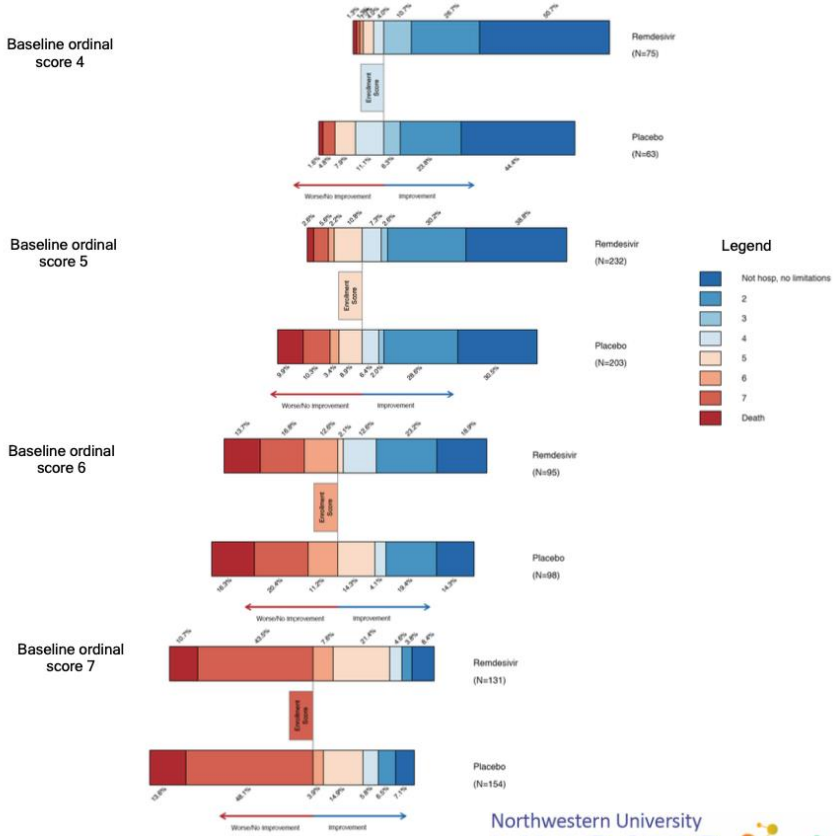
Remdesivir (GS-5734): *NIAID ACTT*





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

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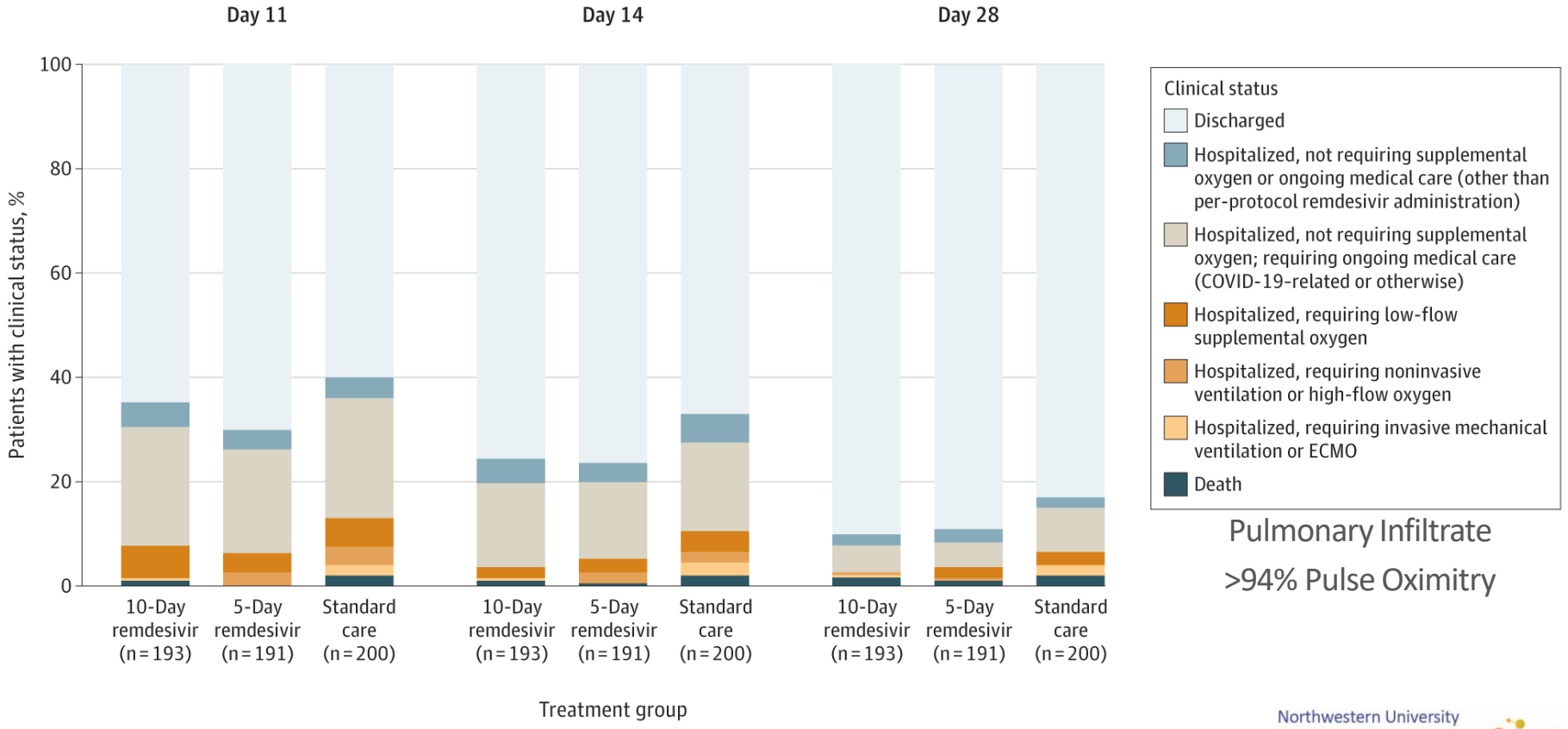
Remdesivir (GS-5734): *Therapy Moderate COVID-19*



Pulmonary Infiltrate

>94% Pulse Oximitry

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Spinner *et al*. ***JAMA***. 2020. DOI: 10.1001/jama.2020.16349.

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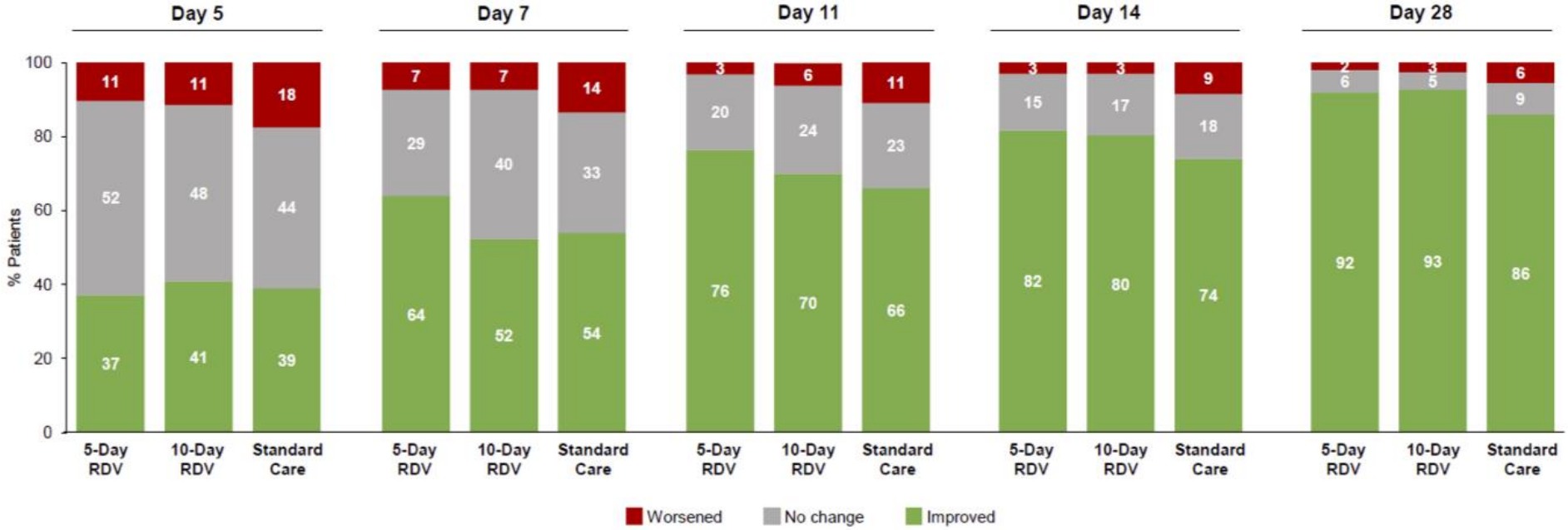
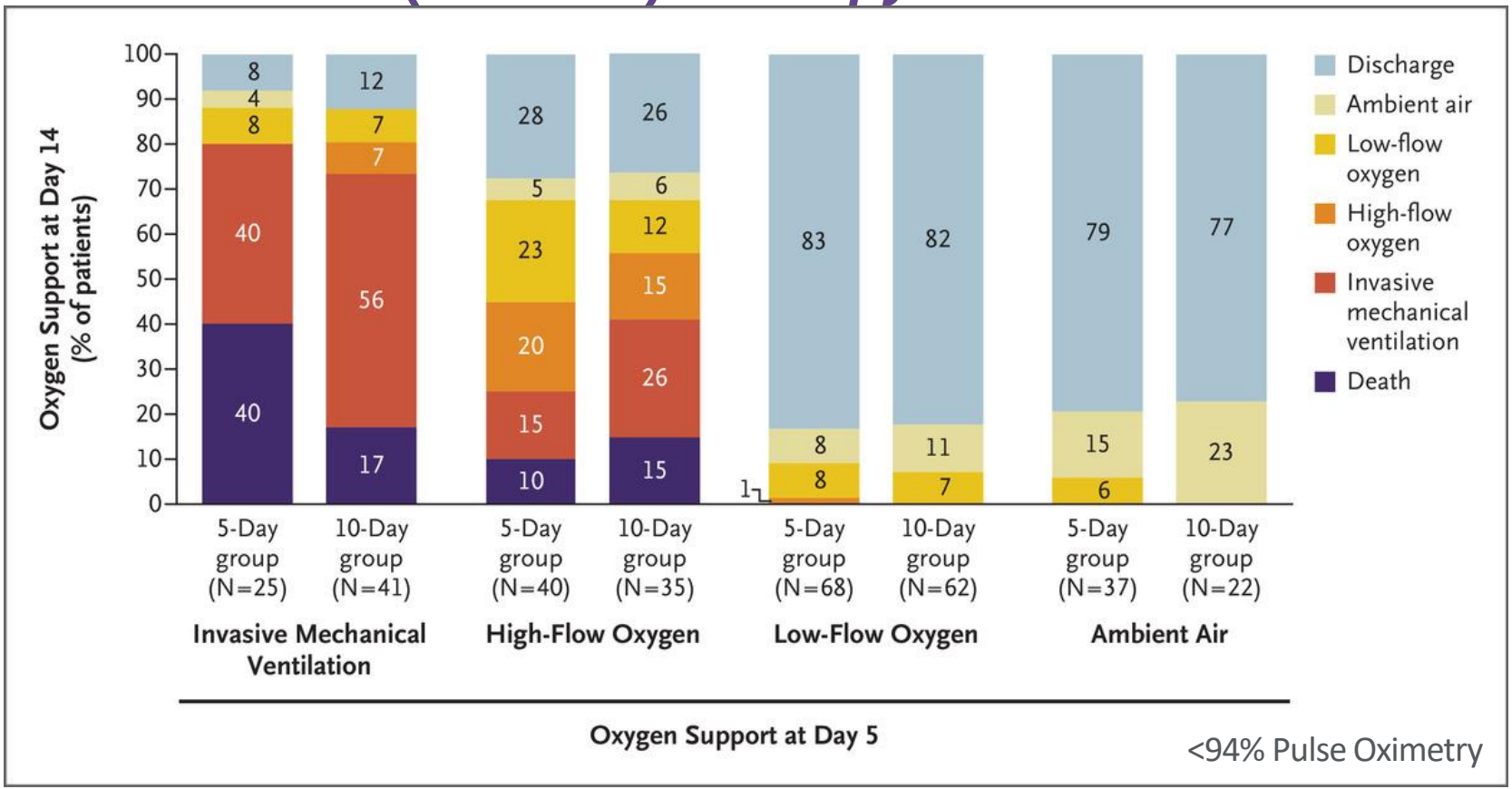
Remdesivir (GS-5734): *Therapy Moderate COVID-19*



Spinner *et al*. ***JAMA***. 2020. DOI: 10.1001/jama.2020.16349.

Remdesivir (GS-5734): *Therapy with Severe COVID-19*



<94% Pulse Oximetry

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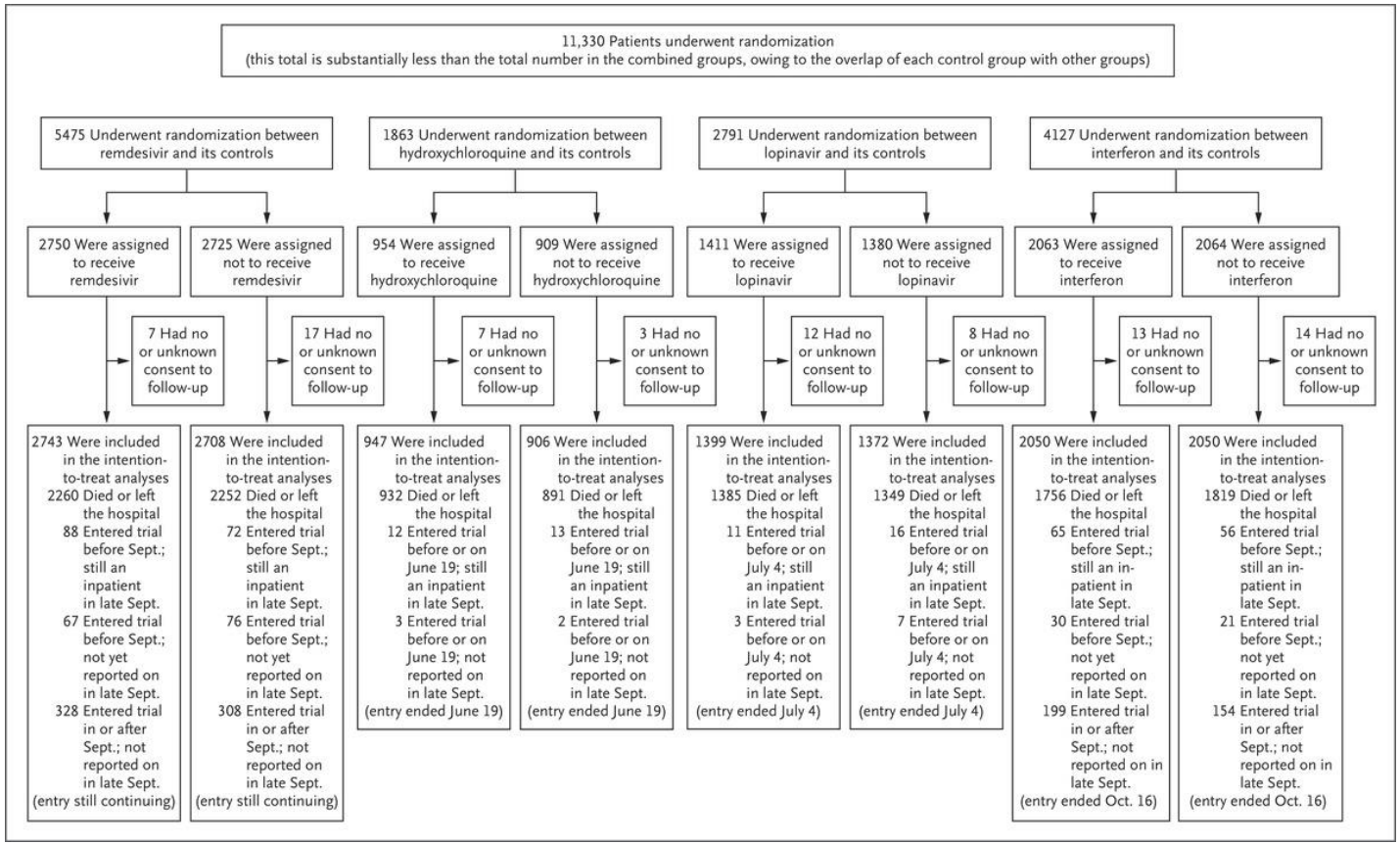
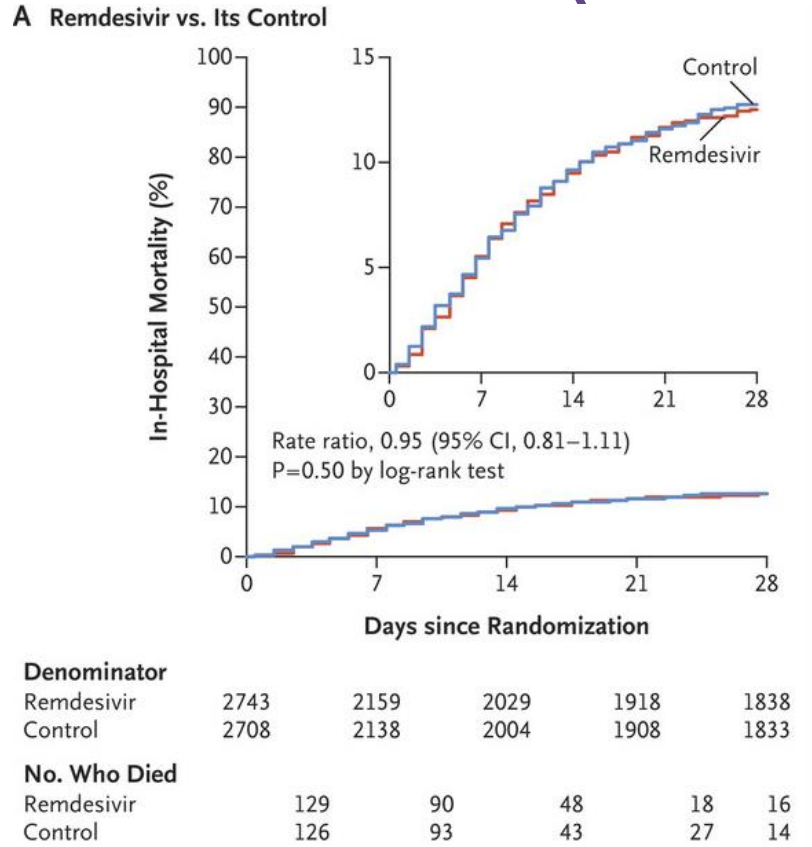
Goldman *et al*. ***N Engl J Med***. 2020. DOI: 10.1056/NEJMoa2015301.

Remdesivir (GS-5734): *SOLIDARITY Trial*

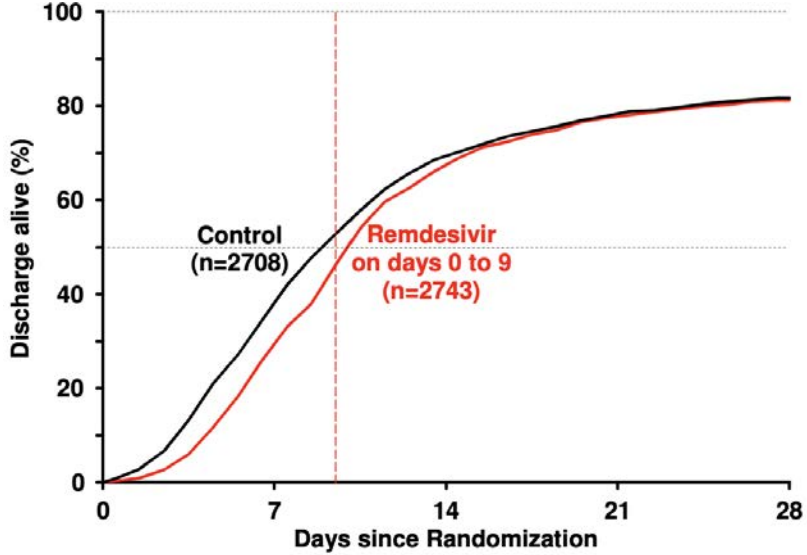


WHO Solidarity Trial Consortium. ***N Engl J Med***. 2020. DOI: 10.1056/NEJMoa2023184

Remdesivir (GS-5734): *SOLIDARITY Trial*

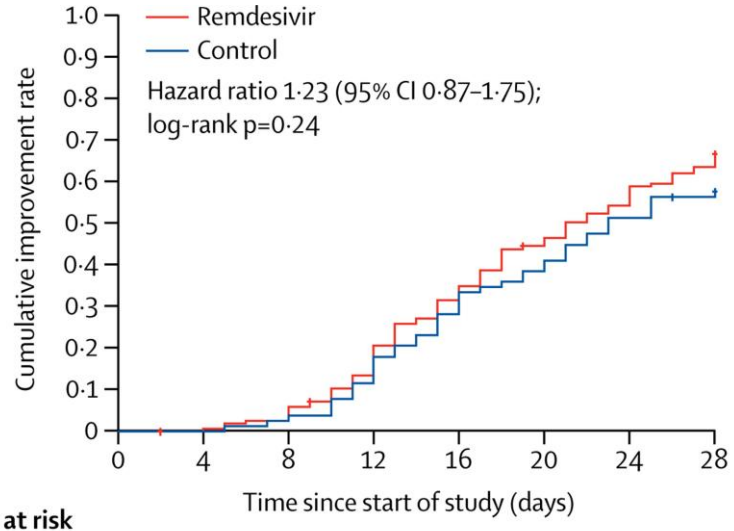


- Secondary Outcomes
  - New Onset Mechanical Ventilation
    - 295 remdesivir patients vs 284 control patients
  - Hospital Discharge

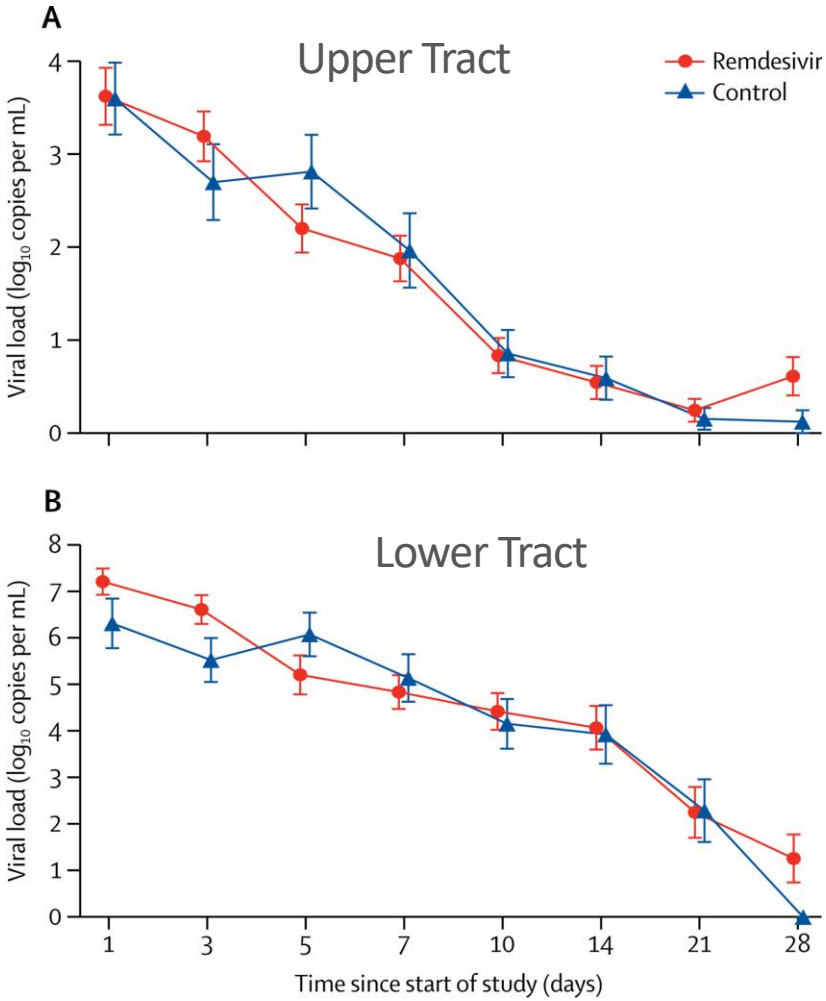


WHO Solidarity Trial Consortium. ***N Engl J Med***. 2020. DOI: 10.1056/NEJMoa2023184

Remdesivir: *Antiviral Activity*



Number at risk (number censored)								
Remdesivir	158	155	147	123	101	82	63	25
	(0)	(2)	(0)	(1)	(0)	(1)	(0)	(26*)
Control	78	78	75	64	52	46	38	17
	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(16*)



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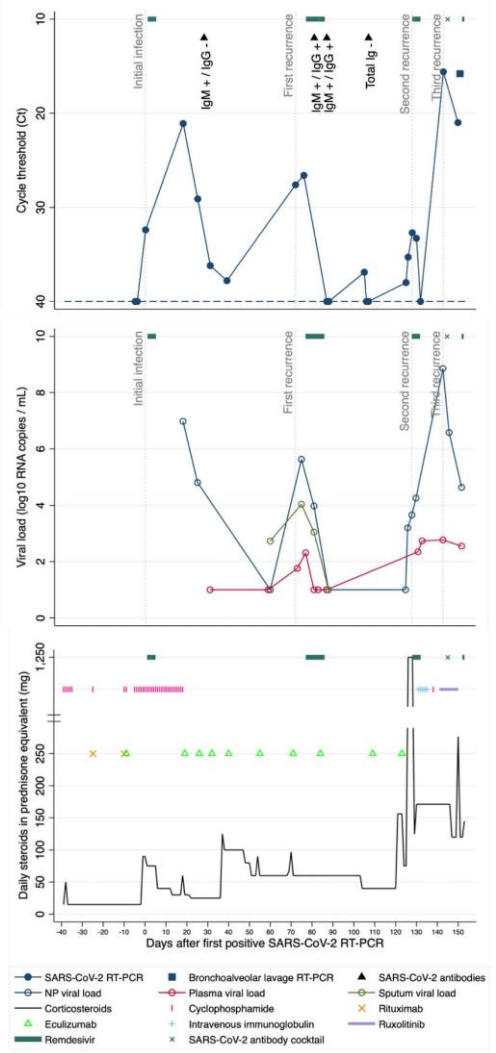
Wang *et al*. ***Lancet***. 2020: doi.org/10.1016/S0140-6736(20)31022-9.

Remdesivir: *Remaining Questions*

- Is mortality all that matters?
- Key data to understand utility is missing
  - Virology
  - Resistance emergence (esp w/ shorter course therapy)
  - Biomarkers
- Use in selected populations
  - Immunocompromised
    - Longer duration, balance with onging IS, addition to dexamethasone
  - Renal dysfunction



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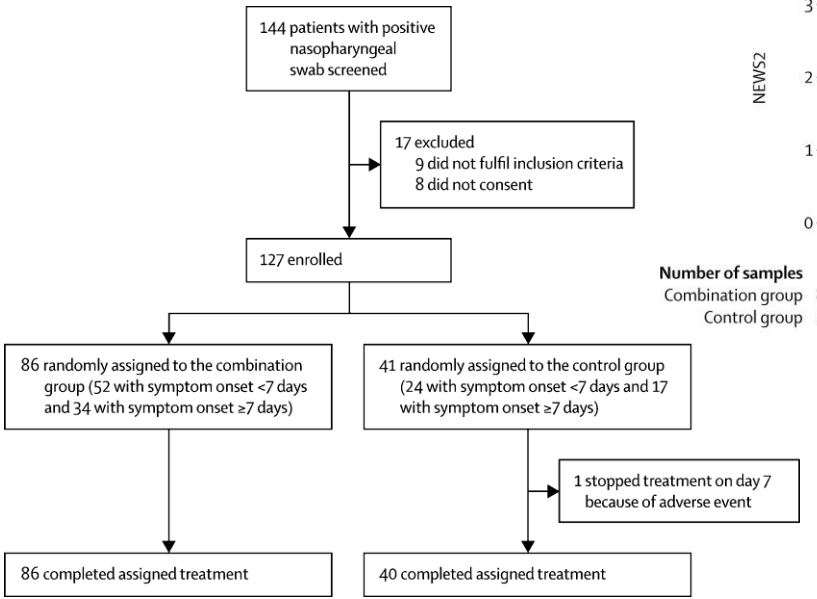
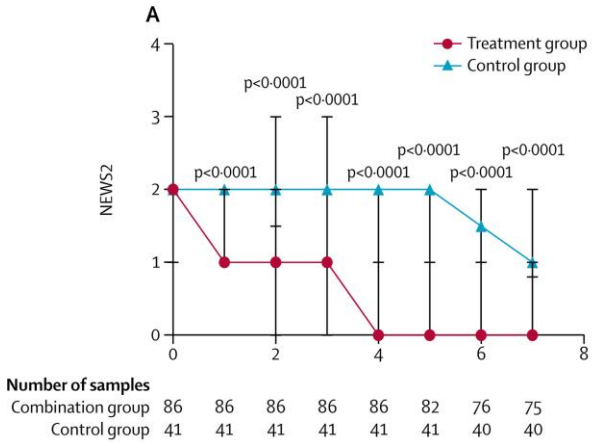
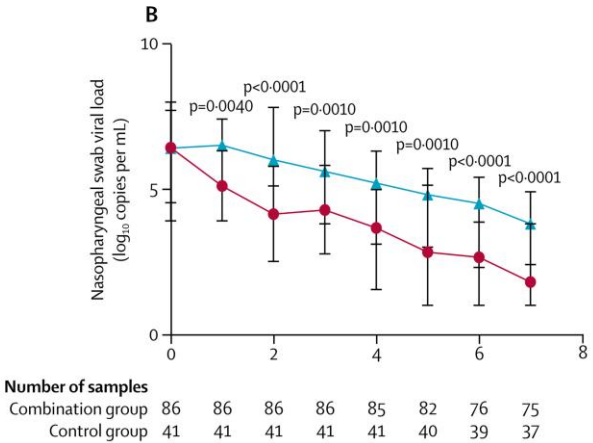
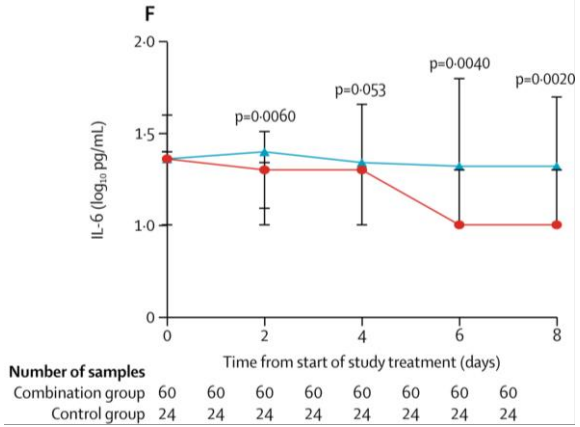
Choi *et al*. ***N Engl J Med***. 2020;383:2291-2293.

Interferon-Lopinavir-Ritonavir-Ribavirin









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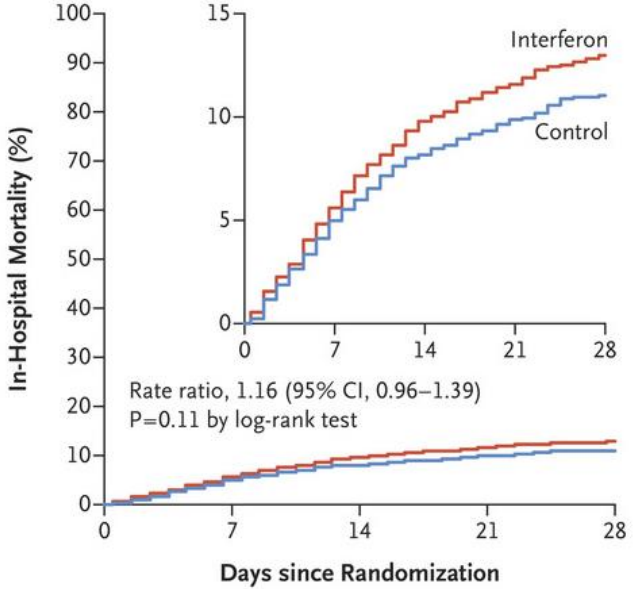
Hung *et ai*. ***Lancet***. 2020: doi.org/10.1016/ S0140-6736(20)31042-4.

Interferon

D Interferon vs. Its Control



Denominator					
Interferon	2050	1669	1554	1483	1410
Control	2050	1725	1636	1563	1498
No. Who Died					
Interferon	101	73	31	24	14
Control	91	58	31	21	15

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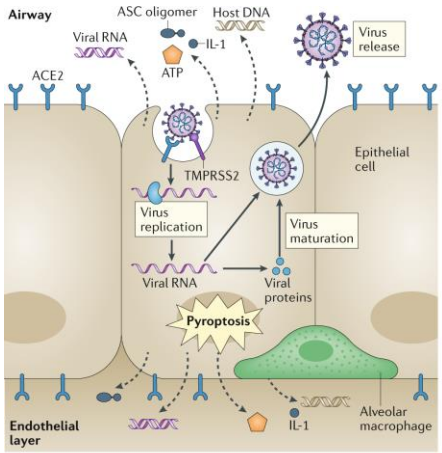
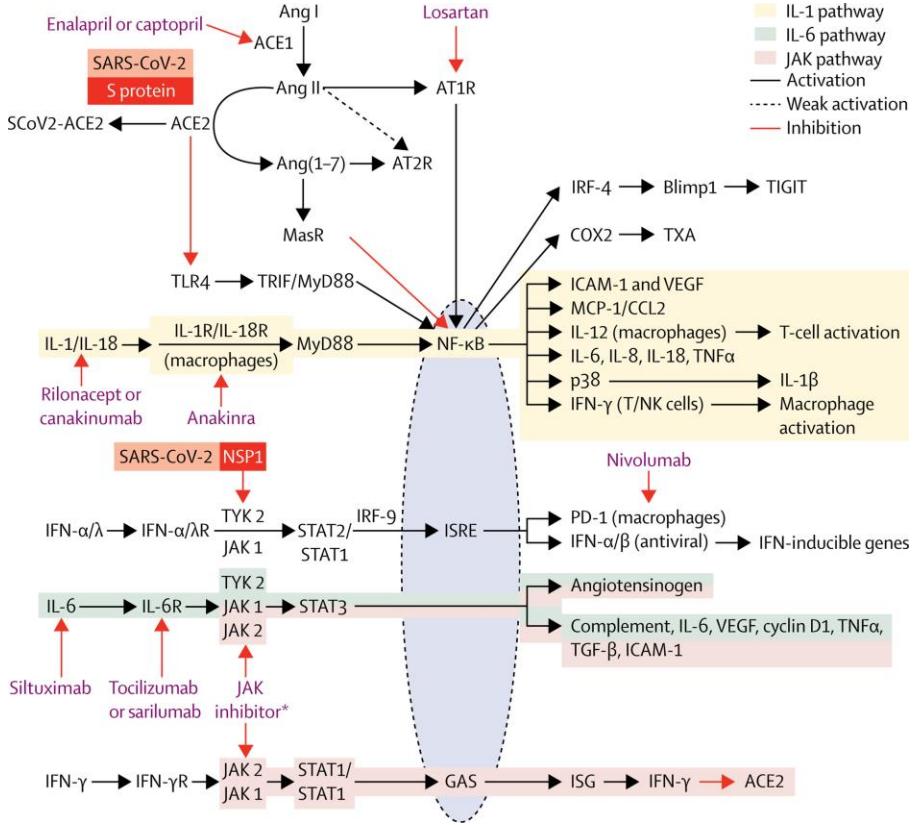
WHO Solidarity Trial Consortium. ***N Engl J Med***. 2020. DOI: 10.1056/NEJMoa2023184

COVID-19: *Immune Modulation Therapy*



- IL6R: Tocilizumab, Sarilumab
- JAK: Barcitinib, 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.

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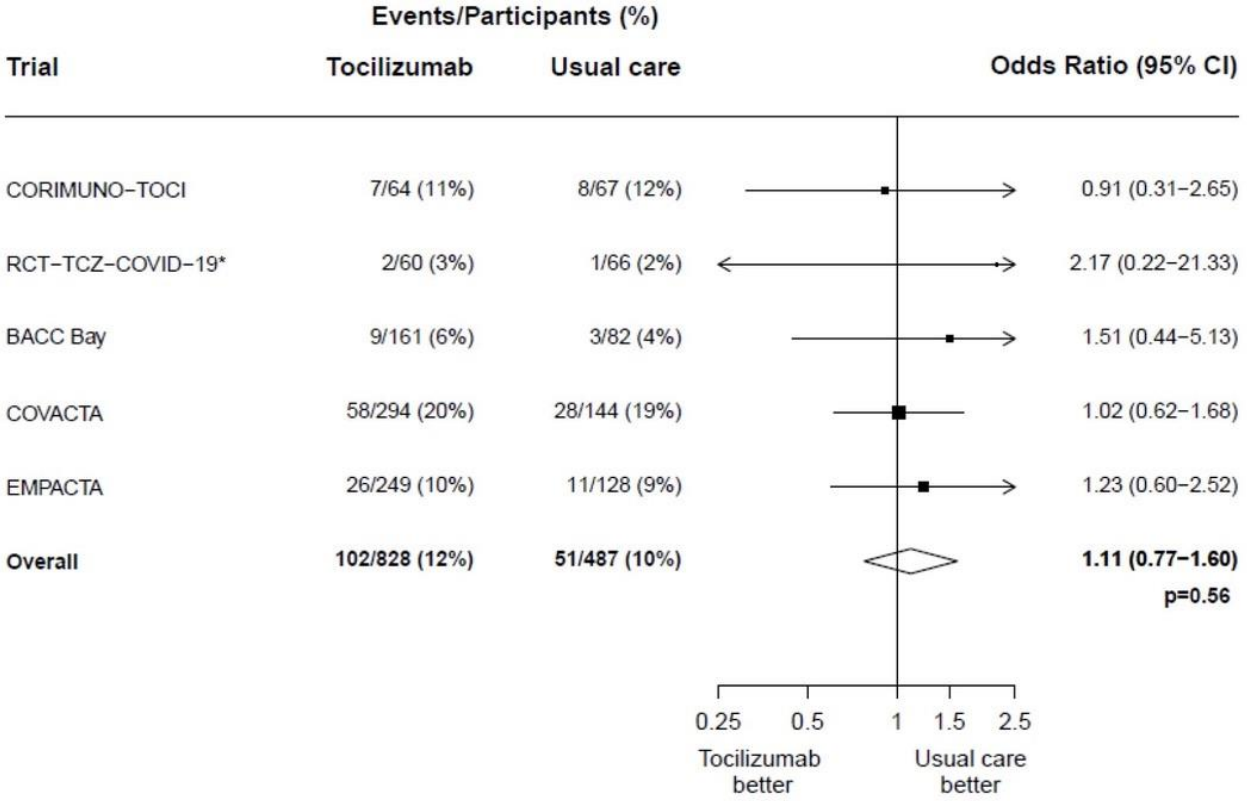
IL-6 Inhibition: *Tocilizuamb*



* RCT-TCZ-COVID-19 reported 30-day mortality.

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Lan *et al*. ***Int J Antimicrob Agents***. 2020; 56: 106103.

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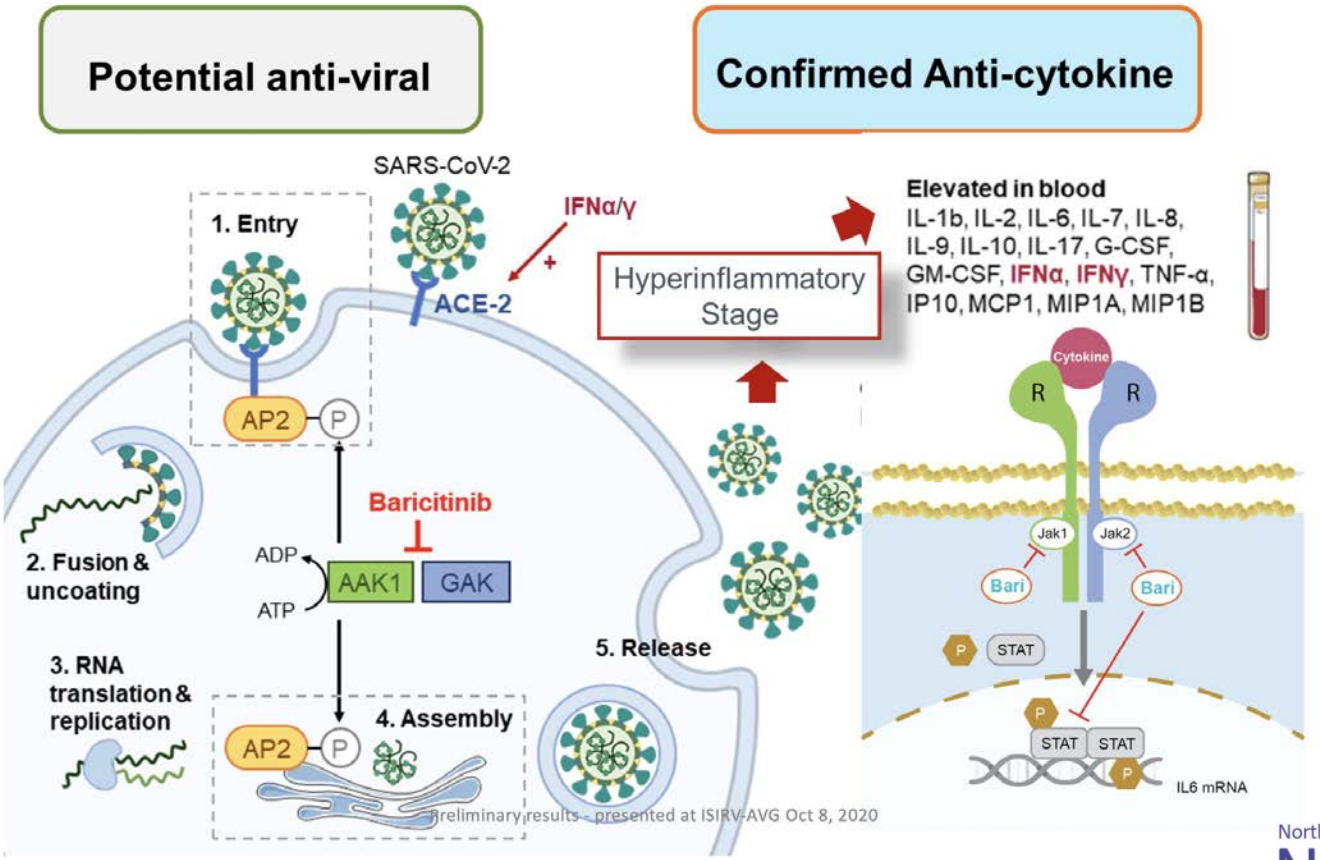
Barcitinib: *NIAID ACTT2*



Barcitinib: *NIAID ACTT2*

	Overall		4 Not on oxygen		5 Low flow oxygen		6 High flow oxygen / NIMV		7 Mechanical ventilation/ECMO	
Ordinal Score at Baseline										
	Bari + RDV (n=515)	Placebo + RDV (n=518)	Bari + RDV (n=70)	Placebo + RDV (n=72)	Bari + RDV (n=287)	Placebo + RDV (n=276)	Bari + RDV (n=104)	Placebo + RDV (n=113)	Bari + RDV (n=54)	Placebo + RDV (n=57)
Recovery										
No. of recoveries	433	406	67	69	261	243	83	73	22	21
Median time to recovery (95% CI) - days	7 (6, 8)	8 (7, 9)	5 (4, 6)	4 (4, 6)	5 (5, 6)	6 (5, 6)	10 (9, 13)	18 (13, 21)	NE (25, NE)	NE (26, NE)
Rate ratio (95% CI)	1.16 (1.01, 1.32); p=0.04		0.88 (0.63, 1.23)		1.17 (0.98, 1.39)		1.51 (1.10, 2.08)		1.08 (0.59, 1.97)	

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Beigel J. ISIRV AVG COVID-19 Therapeutics Symposium. Sept 2020

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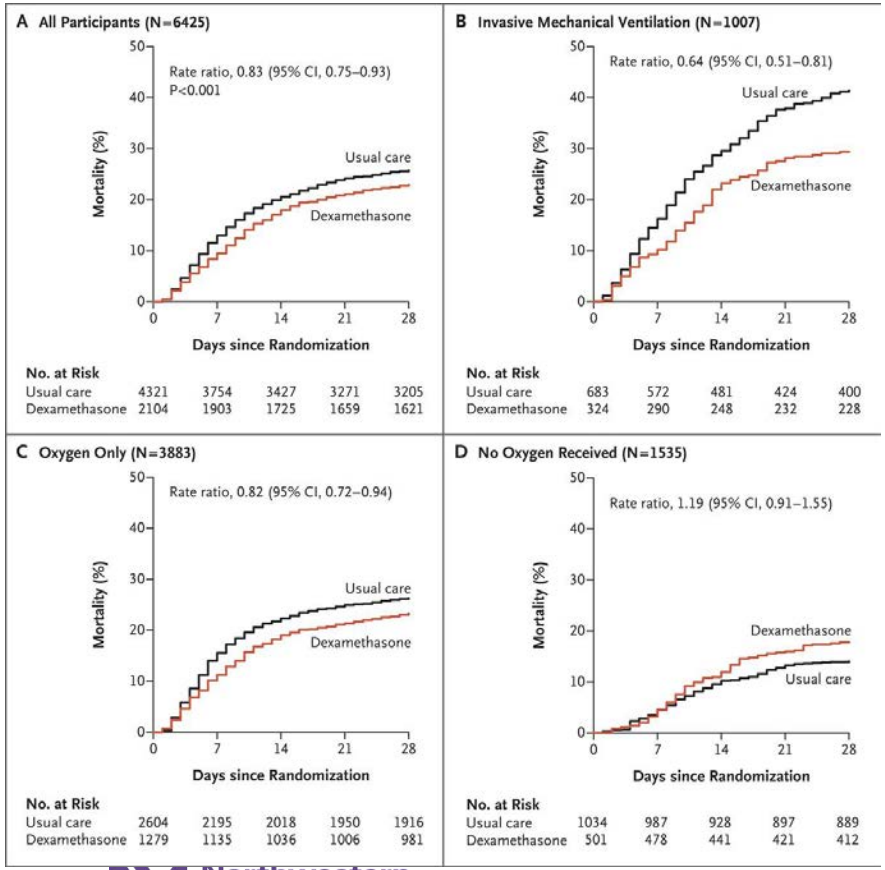
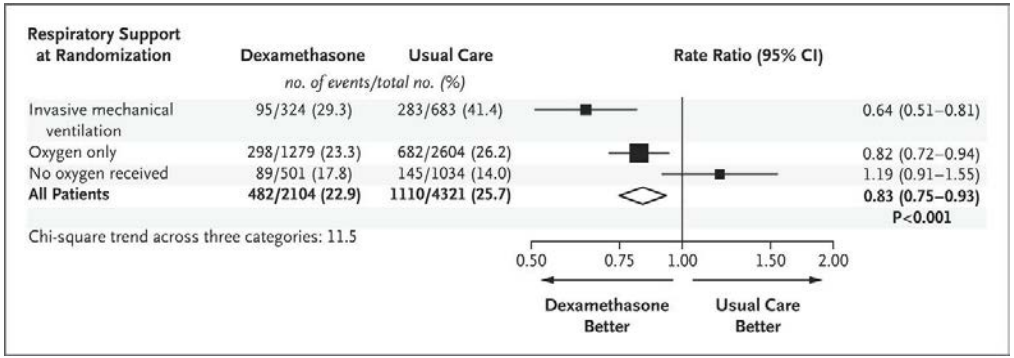
Barcitinib: *NIAID ACTT2*

	Overall		Ordinal Score at Baseline							
			4 Not on oxygen		5 Low flow oxygen		6 High flow oxygen / NIMV		7 Mechanical ventilation/ECMO	
	Baricitinib + RDV (n=515)	Placebo + RDV (n=518)	Baricitinib + RDV (n=70)	Placebo + RDV (n=72)	Baricitinib + RDV (n=287)	Placebo + RDV (n=276)	Baricitinib + RDV (n=104)	Placebo + RDV (n=113)	Baricitinib + RDV (n=54)	Placebo + RDV (n=57)
Mortality over entire study period										
Hazard ratio (95% CI) over entire study period	0.65 (0.39, 1.08); p=0.09		NE		0.4 (0.14, 1.14)		0.55 (0.22, 1.37)		1.00 (0.45, 2.22)	
Number of deaths by day 28	24	37	0	0	5	12	7	13	12	12
Kaplan-Meier estimate of mortality by day 28 – % (95% CI)	5.1 (3.5, 7.6)	7.8 (5.7, 10.6)	0 (NE, NE)	0 (NE, NE)	1.9 (0.8, 4.4)	4.7 (2.7, 8.1)	7.4 (3.6, 15.0)	12.9 (7.7, 21.3)	23.1 (13.8, 37.1)	22.6 (13.5, 36.4)

COVID-19: *Dexamethasone*

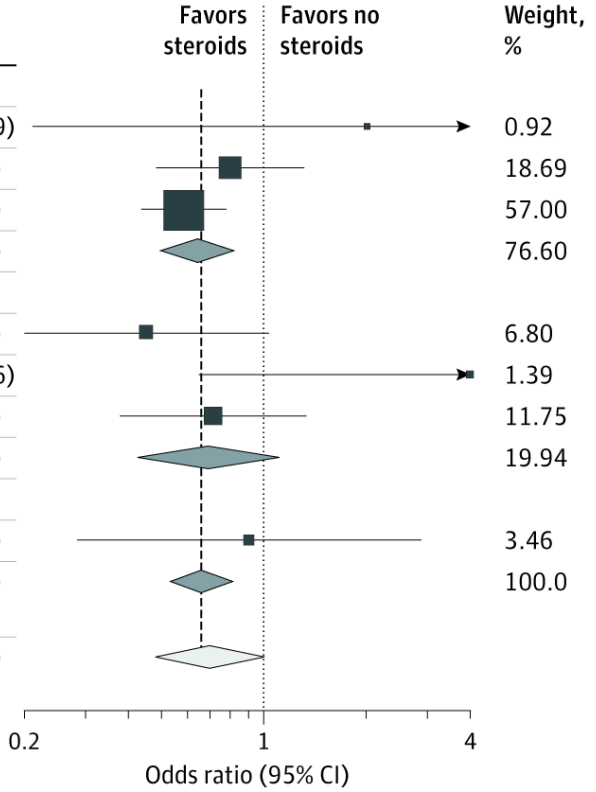




RECOVERY Collaborative Group. ***N Eng J Med.*** 2020. DOI: 10.1056/NEJMoa2021436.

COVID-19: *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)	



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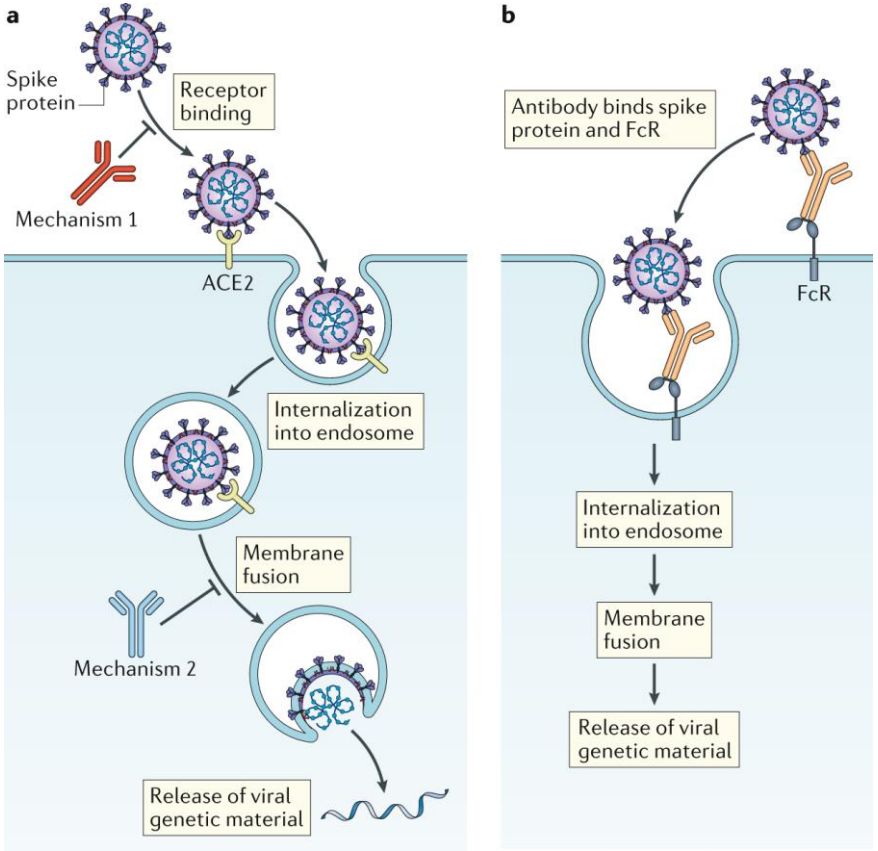
WHO REACT Group. ***JAMA.*** 2020. DOI: 10.1001/jama.2020.17023.

Passive Antibody Therapy: *Advantages and Disadvantages*



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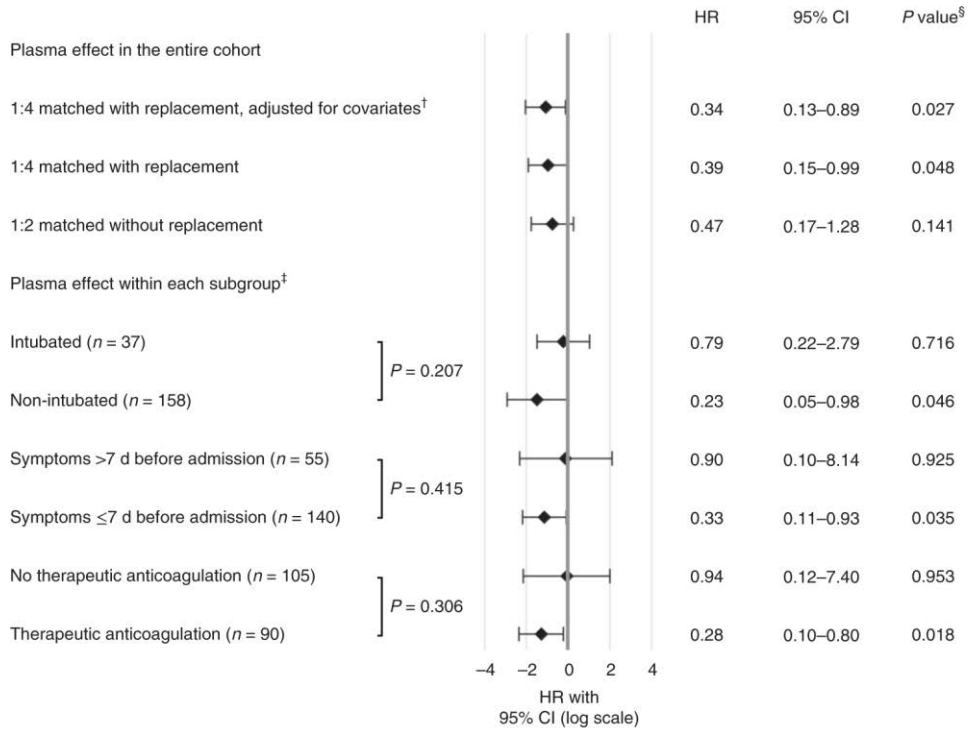
Abraham, J. ***Nat Rev Immunol***. 2020: doi.org/10.1038/s41577-02—0365-7.

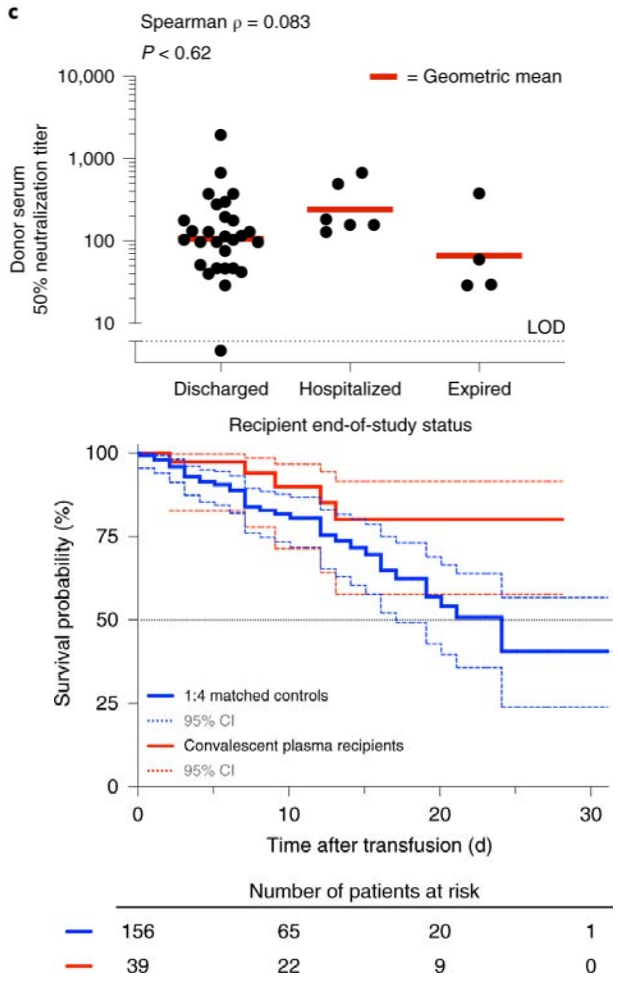
COVID-19: *Convalescent Plasma*



§*P* value by chi-square test

†Covariates: duration of symptoms before admission, therapeutic anticoagulation and broad-spectrum antibiotics

‡*P* value by chi-square test for homogeneity



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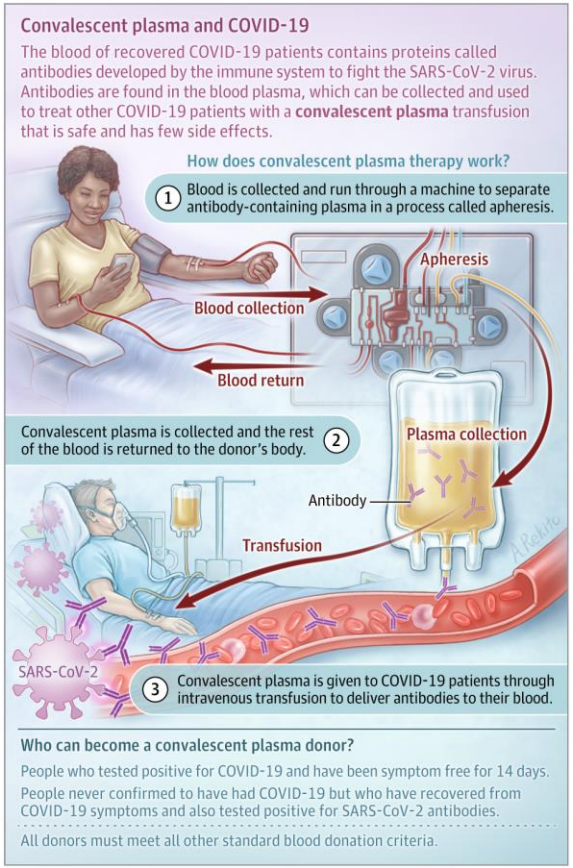
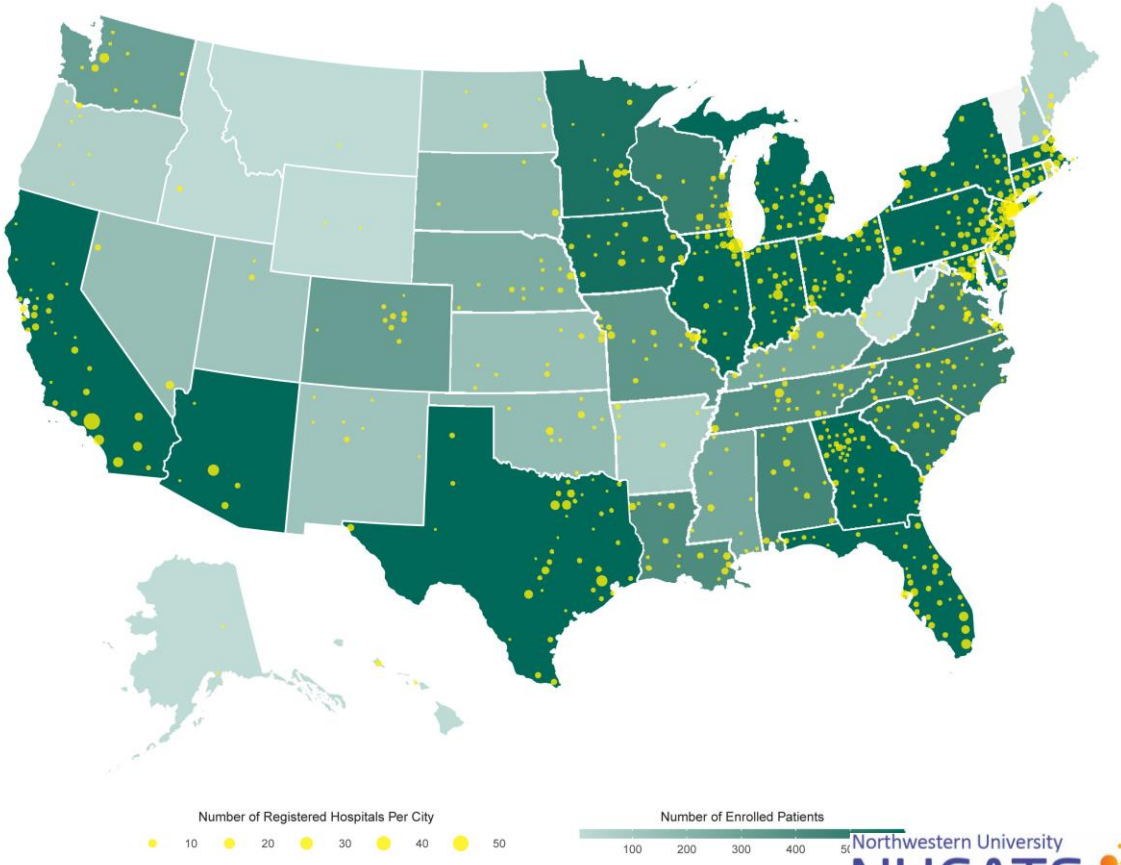
Liu *et al*. ***Nat Med.*** 2020: doi.org/10.1038/s41591-020-1088-9.

COVID-19: *Convalescent Plasma*





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Joyner *et al*. ***Mayo Clin Proc***. 2020:95: 1888-1892.

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COVID-19: *Convalescent Plasma - Safetv*

TABLE 1. Patient Characteristics Stratified by Month of COVID-19 Convalescent Plasma Transfusion[a]

	April	May	Total
Characteristic			
N	6214	13,786	20,000
Age, y			
18-39	449 (7.2)	1083 (7.9)	1,532 (7.7)
40-59	2056 (33.1)	4320 (31.3)	6,376 (31.9)
60-69	1798 (28.9)	3611 (26.2)	5,409 (27.0)
70-79	1260 (20.3)	2859 (20.7)	4,119 (20.6)
≥80	651 (10.5)	1913 (13.9)	2,564 (12.8)
Sex			
Female	2262 (36.4)	5499 (39.9)	7761 (38.8)
Male	3924 (63.2)	8241 (59.8)	12,165 (60.8)
Intersex or transgender	22 (0.4)	35 (0.3)	57 (0.3)
Undisclosed	6 (0.1)	11 (0.1)	17 (0.1)
Weight status[b]			
Underweight	61 (1.2)	249 (1.8)	310 (1.7)
Normal weight	868 (17.3)	2454 (18.0)	3322 (17.8)
Overweight	1502 (30.0)	3802 (27.8)	5304 (28.4)
Obese	2587 (51.6)	7166 (52.4)	9753 (52.2)
Race			
Asian	408 (6.6)	591 (4.3)	999 (5.0)
Black	1132 (18.2)	2784 (20.2)	3916 (19.6)
White	2993 (48.2)	6741 (48.9)	9734 (48.7)
Other or unknown	1681 (27.1)	3670 (26.6)	5351 (26.8)
Ethnicity			
Hispanic or Latino	2142 (34.5)	4794 (34.8)	6936 (34.7)
Not Hispanic or Latino	4072 (65.5)	8992 (65.2)	13,064 (65.3)
Clinical status			
Current severe or life-threatening COVID-19	4963 (79.9)	9274 (67.3)	14,237 (71.2)
High risk of severe or life-threatening COVID-19	1251 (20.1)	4512 (32.7)	5763 (28.8)
Intensive care unit admission	4038 (65.0)	7522 (55.0)	11,560 (58.1)
Mechanical ventilation[c]	2709 (48.5)	4155 (30.4)	6864 (35.6)
Clinical symptoms[d]			
Respiratory failure	3574 (72.0)	6155 (66.4)	9729 (68.3)
Dyspnea	3152 (63.5)	6561 (70.7)	9713 (68.2)
Blood oxygen saturation <93%	3092 (62.3)	6663 (71.8)	9755 (68.5)
Lung infiltrates >50% within 24 to 48 h	2105 (42.4)	4021 (43.4)	6126 (43.0)
Respiratory frequency ≥30/min	1937 (39.0)	4014 (43.3)	5951 (41.8)
$P_aO_2:FiO_2$[e] <300	1642 (33.1)	3014 (32.5)	4656 (32.7)
Multiple organ dysfunction or failure	936 (18.9)	1212 (13.1)	2148 (15.1)
Septic shock	734 (14.8)	987 (10.6)	1721 (12.1)

TABLE 2. SAE Characteristics in Patients Transfused With COVID-19 Convalescent Plasma (N=20,000)[a]

SAE: Transfusion reactions	Reported	Related	% Estimate[b] (95% CI)
Mortality within four hours of transfusion	63	10	0.05 (0.03-0.09)
TACO	36	36	0.18 (0.13-0.25)
TRALI	21	21	0.10 (0.07-0.16)
Severe allergic transfusion reaction	21	21	0.10 (0.07-0.16)
7-day SAE reports			
Thrombolic or thromboembolic complication	113	38	0.19 (0.14-0.26)
Sustained hypotension[c]	457	54	0.27 (0.21-0.35)
Cardiac events[d]	677	80	0.40 (0.32-0.50)
7-day mortality	Reported		
Crude Estimate	2592		12.96 (12.50-13.44)
Clinical status			
No ICU admission (n=8323)	772		9.28 (8.67-9.92)
ICU admission (n=11,560)	1806		15.62 (14.97-16.30)
No mechanical ventilation (n=12,147)	1220		9.85 (9.34-10.38)
Mechanical ventilation (n=6864)	1258		18.33 (17.43-19.26)
Clinical symptoms			
No MOF or septic shock (n=17,081)	1952		11.45 (10.98-11.94)
MOF or septic shock (n=2919)	640		21.72 (20.27-23.24)

[a]ICU = intensive care unit; MOF = multiple organ failure or dysfunction; SAE = severe adverse event; TACO = transfusion-associated circulatory overload; TRALI = transfusion-related acute lung injury.
[b]Point estimate of related serious adverse event incidence relative to 20,000 transfusions.
[c]Sustained hypotension included events requiring intravenous pressor support.
[d]Cardiac events included ventricular or atrial fibrillation or arrhythmia requiring treatment, and cardiac arrest.

Joyner *et al*. ***Mayo Clin Proc***. 2020:95: 1888-1892.

COVID-19: *Convalescent Plasma - Efficacy*

Table 1. Patient Characteristics Stratified by Time Period of COVID-19 Convalescent Plasma Transfusion.

	Apr 04 - May 01 (N=6,990)	May 01 - Jun 04 (N=14,846)	Jun 04 - Jul 04 (N=13,486)	Total Patients (N=35,322)	P value
Age at Enrollment (years)					**<0.001**
18 to 39	539 (7.7%)	1,337 (9.0%)	1,596 (11.8%)	3,472 (9.8%)	
40 to 59	2,424 (34.7%)	4,938 (33.3%)	4,806 (35.6%)	12,168 (34.4%)	
60 to 69	2,007 (28.7%)	3,791 (25.5%)	3,170 (23.5%)	8,968 (25.4%)	
70 to 79	1,358 (19.4%)	2,879 (19.4%)	2,467 (18.3%)	6,704 (19.0%)	
80 or older	662 (9.5%)	1,901 (12.8%)	1,447 (10.7%)	4,010 (11.4%)	
Gender					**<0.001**
Female	2,546 (36.5%)	5,961 (40.2%)	5,489 (40.8%)	13,996 (39.7%)	
Male	4,416 (63.4%)	8,838 (59.7%)	7,961 (59.1%)	21,215 (60.2%)	
Undisclosed	6 (0.1%)	11 (0.1%)	11 (0.1%)	28 (0.1%)	
Weight Status					**<0.001**
Underweight	69 (1.2%)	286 (1.9%)	156 (1.2%)	511 (1.5%)	
Normal Weight	1,010 (17.4%)	2,601 (17.6%)	1,744 (12.9%)	5,355 (15.7%)	
Overweight	1,723 (29.7%)	4,096 (27.8%)	3,647 (27.1%)	9,466 (27.8%)	
Obese	2,997 (51.7%)	7,761 (52.6%)	7,926 (58.8%)	18,684 (54.9%)	
Race					**<0.001**
White	3,330 (47.6%)	7,299 (49.2%)	7,178 (53.2%)	17,807 (50.4%)	
Asian	456 (6.5%)	628 (4.2%)	390 (2.9%)	1,474 (4.2%)	
Black or African American	1,301 (18.6%)	2,971 (20.0%)	2,379 (17.6%)	6,651 (18.8%)	
Other or Unknown	1,903 (27.2%)	3,948 (26.6%)	3,539 (26.2%)	9,390 (26.6%)	
Ethnicity					**<0.001**
Hispanic/Latino	2,391 (34.2%)	5,297 (35.7%)	5,875 (43.6%)	13,563 (38.4%)	
Not Hispanic/Latino	4,599 (65.8%)	9,549 (64.3%)	7,611 (56.4%)	21,759 (61.6%)	
Clinical Status					
Current severe or life-threatening COVID-19	5,584 (79.9%)	9,761 (65.7%)	8,157 (60.5%)	23,502 (66.5%)	**<0.001**
Intensive Care Unit (ICU) care prior to infusion	4,601 (65.8%)	7,908 (53.3%)	5,952 (44.1%)	18,461 (52.3%)	**<0.001**
Mechanical Ventilation prior to infusion	3,217 (49.9%)	4,143 (27.9%)	2,213 (16.4%)	9,573 (27.5%)	**<0.001**
Severe Risk Factors[a]					
Respiratory failure	4,063 (72.8%)	6,352 (65.1%)	4,760 (58.4%)	15,175 (64.6%)	**<0.001**
Dyspnea	3,543 (63.4%)	6,976 (71.5%)	6,476 (79.4%)	16,995 (72.3%)	**<0.001**
Blood oxygen saturation ≤ 93%	3,507 (62.8%)	7,063 (72.4%)	6,394 (78.4%)	16,964 (72.2%)	**<0.001**
Lung infiltrates > 50% within 24 to 48 hours	2,415 (43.2%)	4,151 (42.5%)	3,015 (37.0%)	9,581 (40.8%)	**<0.001**
Respiratory frequency ≥ 30/min	2,205 (39.5%)	4,174 (42.8%)	3,366 (41.3%)	9,745 (41.5%)	**<0.001**
PaO2:FiO2 ratio < 300	1,905 (34.1%)	3,075 (31.5%)	1,952 (23.9%)	6,932 (29.5%)	**<0.001**
Multiple organ dysfunction or failure	1,062 (19.0%)	1,200 (12.3%)	560 (6.9%)	2,822 (12.0%)	**<0.001**
Septic shock	844 (15.1%)	960 (9.8%)	475 (5.8%)	2,279 (9.7%)	**<0.001**

Table 1. Patient Characteristics Stratified by Time Period of COVID-19 Convalescent Plasma Transfusion.

	Apr 04 - May 01 (N=6,990)	May 01 - Jun 04 (N=14,846)	Jun 04 - Jul 04 (N=13,486)	Total Patients (N=35,322)	P value
Medications during hospital stay					
Angiotensin Receptor Blocker	397 (5.7%)	839 (5.7%)	779 (5.8%)	2,015 (5.7%)	0.90
Ace Inhibitor	467 (6.7%)	1,130 (7.6%)	1,023 (7.6%)	2,620 (7.4%)	**0.032**
Azithromycin	3,811 (54.5%)	5,717 (38.5%)	5,456 (40.5%)	14,984 (42.4%)	**<0.001**
Remdesivir	329 (4.7%)	4,066 (27.4%)	6,240 (46.3%)	10,635 (30.1%)	**<0.001**
Steroids	3,736 (53.4%)	6,137 (41.3%)	7,735 (57.4%)	17,608 (49.8%)	**<0.001**
Chloroquine	33 (0.5%)	22 (0.1%)	6 (0.0%)	61 (0.2%)	**<0.001**
Hydroxychloroquine	4,356 (62.3%)	2,437 (16.4%)	245 (1.8%)	7,038 (19.9%)	**<0.001**
Time to Transfusion					**<0.001**
0 days	141 (2.0%)	598 (4.0%)	625 (4.6%)	1,364 (3.9%)	
1 to 3 days	1,590 (22.7%)	5,748 (38.7%)	6,705 (49.7%)	14,043 (39.8%)	
4 to 10 days	2,843 (40.7%)	6,244 (42.1%)	5,271 (39.1%)	14,358 (40.6%)	
11+ days	2,416 (34.6%)	2,256 (15.2%)	885 (6.6%)	5,557 (15.7%)	

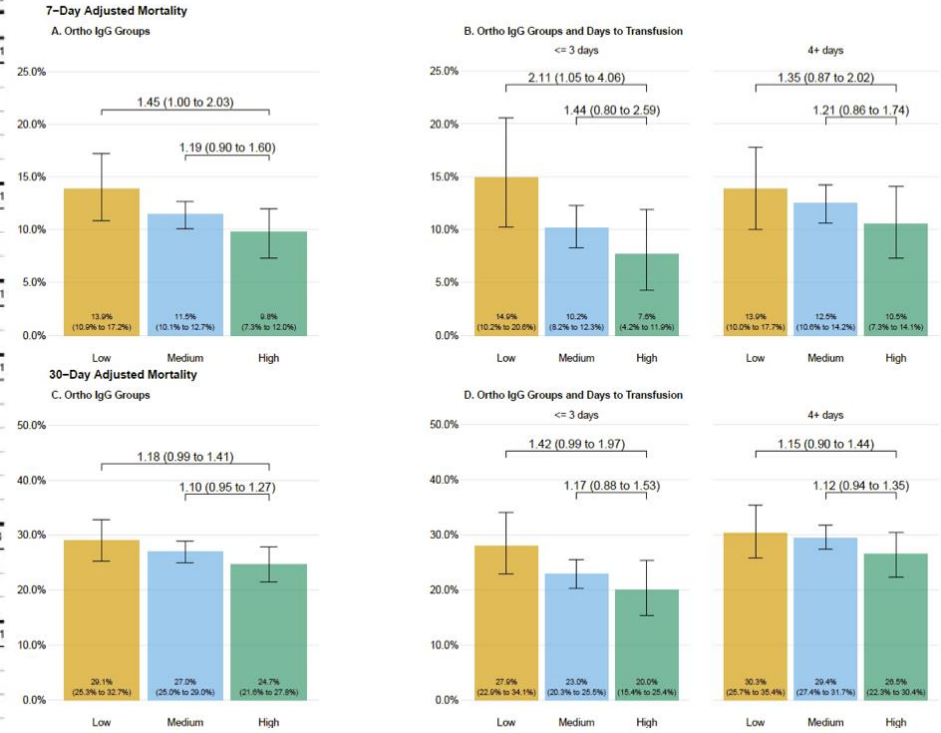
[a]These data include a subset of the sample (n = 23,502), only those patients that currently have severe or life-threatening COVID-19 Data was not available for Gender (n=83), Weight Status (n=1,306) and Mechanical Ventilation prior to infusion (n=544).

Joyner *et al*. ***medRxiv***. 2020: doi.org/10.1101/2020.08.12.20169359.

COVID-19: *Convalescent Plasma - Efficacy*

Table 2. Crude Mortality (7 and 30 day) of patients transfused with COVID-10 Convalescent Plasma.

	Seven-day Mortality				Thirty-day Mortality			
	Sample, No	Events, No	Estimate, 95% CI	P-value	Sample, No	Events, No	Estimate, 95% CI	P-value
Overall Mortality	35,322	3,706	10.5% (10.2%, 10.8%)		35,322	8,652	24.5% (24.0%, 24.9%)	
Age				<0.0001				<0.0001
18 - 39 y	3,472	109	3.1% (2.6%, 3.8%)		3,472	261	7.5% (6.7%, 8.4%)	
40 - 59 y	12,168	662	5.4% (5.1%, 5.9%)		12,168	1,837	15.1% (14.5%, 15.7%)	
60 - 69 y	8,968	897	10.0% (9.4%, 10.6%)		8,968	2,431	27.1% (26.2%, 28.0%)	
70 - 79 y	6,704	1,023	15.3% (14.4%, 16.1%)		6,704	2,367	35.3% (34.2%, 36.5%)	
80 y or older	4,010	1,015	25.3% (24.0%, 26.7%)		4,010	1,756	43.8% (42.3%, 45.3%)	
On Ventilator Prior to Infusion				<0.0001				<0.0001
No	25,205	1,932	7.7% (7.3%, 8.0%)		25,205	4,523	17.9% (17.5%, 18.4%)	
Yes	9,573	1,685	17.6% (16.9%, 18.4%)		9,573	3,924	41.0% (40.0%, 42.0%)	
Missing	544	89	16.4% (13.5%, 19.7%)		544	205	37.7% (33.7%, 41.8%)	
Days to Transfusion				<0.0001				<0.0001
<= 3 days	15,407	1,340	8.7% (8.3%, 9.2%)		15,407	3,329	21.6% (21.0%, 22.3%)	
4+ days	19,915	2,366	11.9% (11.4%, 12.3%)		19,915	5,323	26.7% (26.1%, 27.3%)	
Study Period and Days to Transfusion				<0.0001				<0.0001
Apr 04 - May 01 (<= 3 days)	1,731	232	13.4% (11.9%, 15.1%)		1,731	526	30.4% (28.3%, 32.6%)	
Apr 04 - May 01 (4+ days)	5,259	853	16.2% (15.2%, 17.2%)		5,259	1,821	34.6% (33.4%, 35.9%)	
May 01 - Jun 04 (<= 3 days)	6,346	659	10.4% (9.7%, 11.2%)		6,346	1,452	22.9% (21.9%, 23.9%)	
May 01 - Jun 04 (4+ days)	8,500	1,060	12.5% (11.8%, 13.2%)		8,500	2,260	26.6% (25.7%, 27.5%)	
Jun 04 - Jul 04 (<= 3 days)	7,330	449	6.1% (5.6%, 6.7%)		7,330	1,351	18.4% (17.6%, 19.3%)	
Jun 04 - Jul 04 (4+ days)	6,156	453	7.4% (6.7%, 8.0%)		6,156	1,242	20.2% (19.2%, 21.2%)	
Ortho IgG				0.0483				0.0208
Low	561	77	13.7% (11.1%, 16.8%)		561	166	29.6% (26.0%, 33.5%)	
Medium	2,006	233	11.6% (10.3%, 13.1%)		2,006	549	27.4% (25.5%, 29.4%)	
High	515	46	8.9% (6.8%, 11.7%)		515	115	22.3% (18.9%, 26.1%)	
IgG - Time to Transfusion				0.0500				<0.0001
<= 3 days (Low)	190	25	13.2% (9.1%, 18.7%)		190	48	25.3% (19.6%, 31.9%)	
<= 3 days (Medium)	727	73	10.0% (8.1%, 12.4%)		727	166	22.8% (19.9%, 26.0%)	
<= 3 days (High)	180	11	6.1% (3.4%, 10.6%)		180	30	16.7% (11.9%, 22.8%)	
4+ days (Low)	371	52	14.0% (10.9%, 17.9%)		371	118	31.8% (27.3%, 36.7%)	
4+ days (Medium)	1,279	160	12.5% (10.8%, 14.4%)		1,279	383	29.9% (27.5%, 32.5%)	
4+ days (High)	335	35	10.4% (7.6%, 14.2%)		335	85	25.4% (21.0%, 30.3%)	



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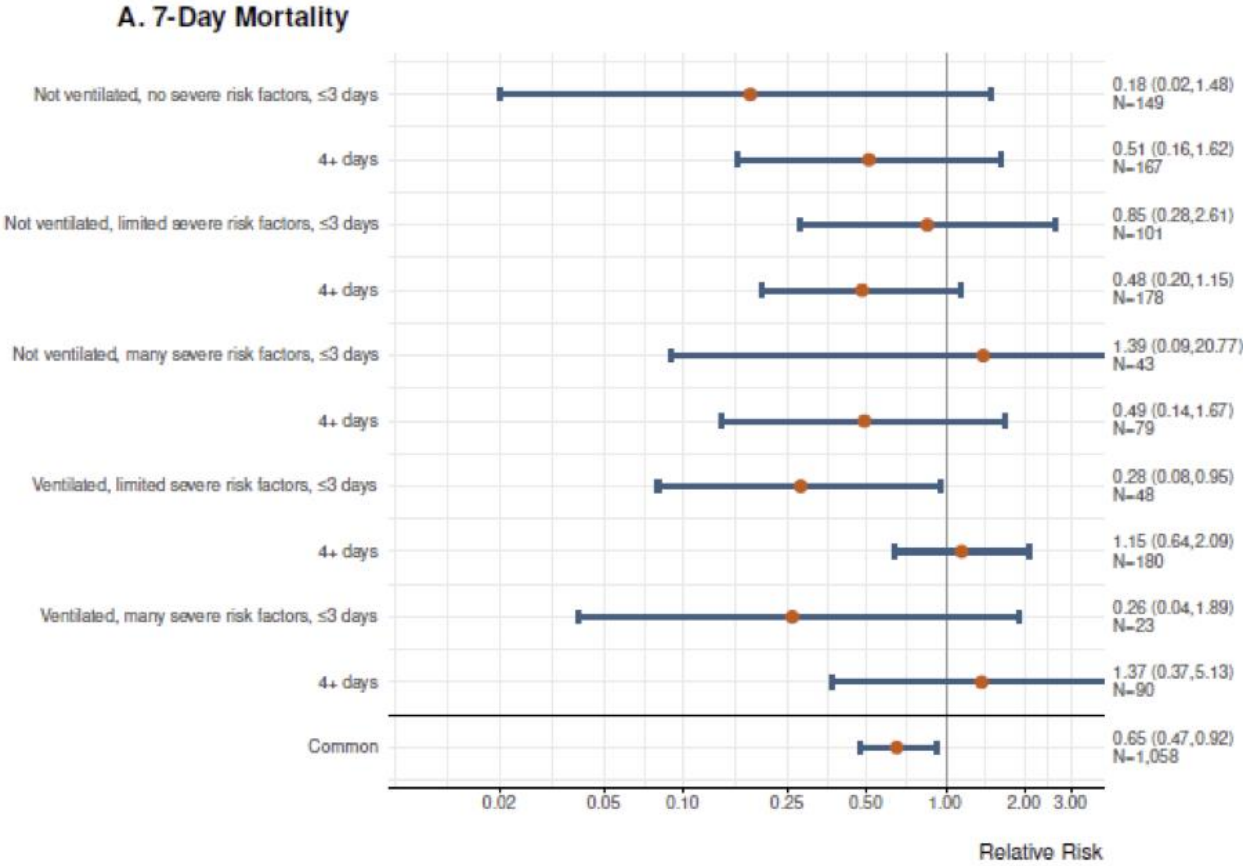
Joyner *et al*. ***medRxiv***. 2020: doi.org/10.1101/2020.08.12.20169359.

COVID-19: *Convalescent Plasma - Efficacy*



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Joyner *et al*. ***medRxiv***. 2020: doi.org/10.1101/2020.08.12.20169359.

COVID-19: *Convalescent Plasma*

Table 2 | Clinical and laboratory findings in study participants with moderate coronavirus disease 2019 assigned to convalescent plasma therapy (intervention arm) or to best standard of care (control arm) at baseline and drugs received during hospital stay. Values are numbers (percentages) unless stated otherwise

Clinical and laboratory findings	Intervention arm	Control arm
Shortness of breath	215/235 (91)	208/229 (91)
Fever	77/235 (32)	85/229 (37)
Cough	149/235 (63)	167/229 (73)
Fatigue	183/234 (78)	182/229 (79)
Radiography findings (n=432):		
Ground glass opacity	27/218 (12)	29/224 (13)
Local patchy shadows	12/218 (5)	9/224 (4)
Bilateral patchy shadows	140/218 (64)	139/224 (65)
Interstitial abnormalities	3/218 (1)	4 /224 (2)
Bilateral white out lung	2/218 (1)	2/224 (1)
Others	34/218 (16)	31/224 (14)
Mean (SD) SpO_2 on room air (%)	88.1 (4)	88.5 (4)
Mean (SD) FiO_2 required to maintain SpO_2 >92%	39.04 (13)	37.4 (11)
Mean (SD) $PaO_2/FiO2$	255.4 (42)	251.6 (39.5)
Mean (SD) haemoglobin (g/L)	125 (21)	125 (18)
Median (interquartile range) WBC count (cells/mm^3)	8480 (6110-11 460)	8500 (6500-11 200)
Median (interquartile range) neutrophil:lymphocyte ratio	5.5 (3.5-10)	5.5 (3.4-9.4)
Median (interquartile range) ferritin (ng/mL)	529.8 (278.6-956)	539.5 (328.3-873)
Median (interquartile range) LDH (IU/L)	473.5 (335-661)	458.6 (342.5-638.5)
Median (interquartile range) C reactive protein (mg/L)	41.6 (14.2-90)	41.7 (12-126)
Median (interquartile range) D-dimer (mg/L)	0.8 (0.5-2.1)	0.7 (0.4-1.5)
WHO ordinal scale (n=463):		
4	180/234 (7)	181/229 (79)
5	54/234 (23)	47/229 (21)
6	0	1/229 (0.4)
Drug treatments:		
Hydroxychloroquine	159/235 (68)	155/229 (68)
Remdesivir	7/235 (3)	13/229 (6)
Lopinavir/ritonavir	36/235 (15)	30/229 (13)
Methylprednisolone	123/235 (52)	114/229 (50)
Dexamethasone	23/235 (10)	30/229 (13)
Hydrocortisone	4/235 (2)	5/229 (2)
Tocilizumab	16/235 (7)	26/229 (11)
Heparin (UFH/LMWH)	178/235 (76)	170/229 (74)
Azithromycin	156/235 (66)	140/229 (61)
Intravenous immunoglobulin	1/235 (0.4)	0
Other antibiotics	204/235 (87)	196/229 (86)

SpO_2=peripheral capillary oxygen saturation; FiO_2=fraction of inspired oxygen; PaO_2=partial pressure of oxygen in arterial blood; WBC=white blood cells; LDH=lactate dehydrogenase; WHO=World Health Organization; UFH=unfractionated heparin; LMWH=low molecular weight heparin.

Table 3 | Comparison of primary outcomes between convalescent plasma therapy (intervention arm) and best standard of care (control arm) in intention-to-treat analysis

Composite outcome	No (%) in intervention arm (n=235)	No (%) in control arm (n=229)	Unadjusted risk difference (95% CI)	Unadjusted risk ratio (95% CI)	Adjusted risk ratio (95% CI)
All cause mortality at 28 days or progression to severe disease	44 (19)	41 (18)	0.008 (−0.062 to 0.078)	1.04 (0.71 to 1.54)	1.07 (0.73 to 1.58)

Adjusted for trial sites and presence of diabetes mellitus.

Table 4 | Comparison of secondary outcomes between convalescent plasma therapy (intervention arm) and best standard of care (control arm) in per protocol analysis (n=451). Values are numbers (percentages) unless stated otherwise

Secondary outcomes	Intervention arm	Control arm	Unadjusted risk ratio (95% CI)
Resolution of symptoms on day 7:			
Shortness of breath (n=362)	140/183 (76)	119/181 (66)	1.16 (1.02 to 1.32)
Fever (n=138)	66/67 (98)	65/71 (92)	1.08 (0.99 to 1.16)
Cough (n=274)	102/127 (80)	111/147 (76)	1.06 (0.94 to 1.2)
Fatigue (n=306)	114/156 (73)	92/153 (60)	1.21 (1.02 to 1.42)
Negative conversion of SARS-CoV-2 RNA:			
Day 3 (n=367)	79/184 (43)	67/183 (37)	1.2 (0.9 to 1.5)
Day 7 (n=342)	117/173 (68)	93/169 (55)	1.2 (1.04 to 1.5)
Median (interquartile range) total hospital stay (days); No with event	14 (10-19); n=227	13 (10-18); n=224	0.2*
Median (interquartile range) total days of respiratory support; No with event	9 (6-13); n=227	10 (6-13); n=224	0.7*
Median (interquartile range) days of respiratory support post-enrolment; No with event	6 (3-9); n=227	6 (4-10); n=224	0.5*
Type of mechanical ventilation during hospital stay:			
Invasive	19/227 (8)	19/224 (8)	0.99 (0.54 to 1.81)
Non-invasive	31/227 (14)	37/224 (16)	0.8 (0.5 to 1.3)
Vasopressor support after enrolment	10/225 (4)	8/221 (4)	1.2 (0.5 to 3.05)

SARS-CoV-2=severe acute respiratory syndrome coronavirus 2; RNA=ribonucleic acid.
*Continuous variables—Mann-Whitney U test applied and P values reported. All changes are measured from day of enrolment.

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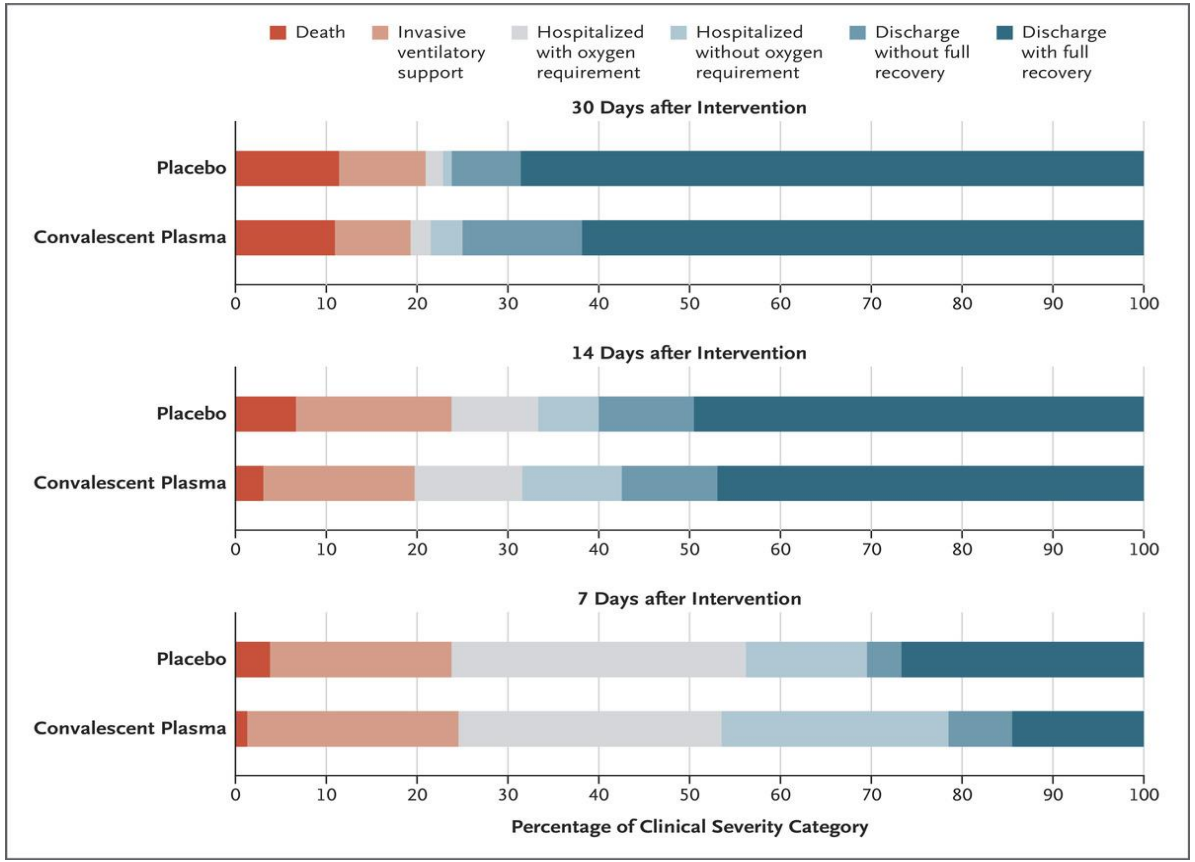
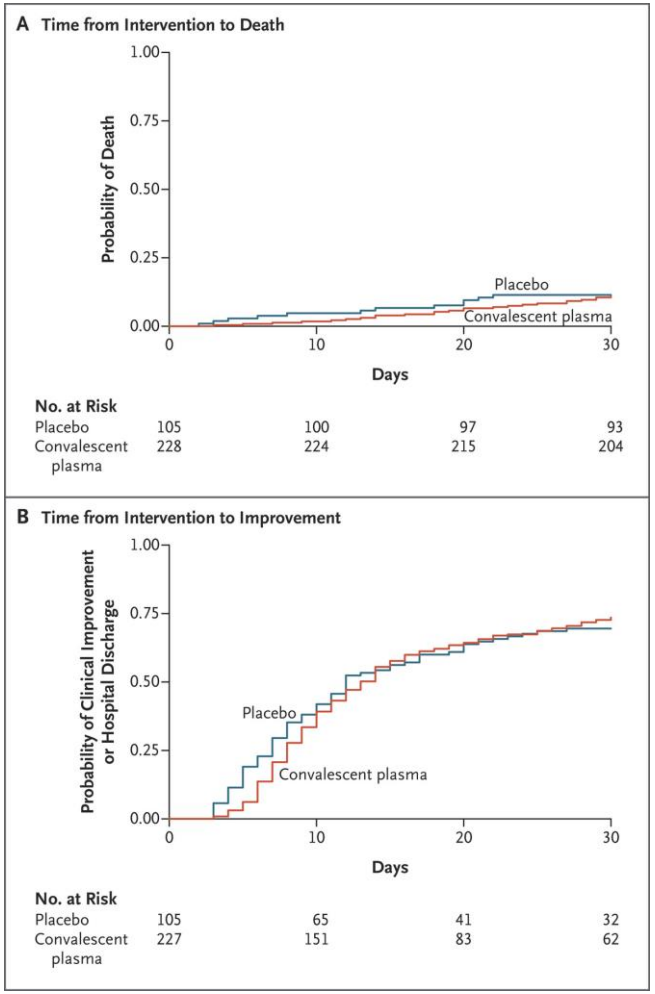
Agarwal *et al*. ***BMJ.*** 2020: doi.org/10.1136/bmj.m3939.

COVID-19: *Convalescent Plasma*





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

Approach to Management of COVID-19 at Northwestern Medicine

- Our overarching premise is that the definitive approach to treating patients with COVID-19 remains to be determined
  - We attempt to enroll patients in clinical trials instead of empiric therapy
- Outpatients Setting
  - Healthcare workers who test positive: Offered MAb
  - Patients with 3+ Co-Morbid Conditions: Offered MAb at MD discretion
- Inpatient Setting
  - 2+L Oxygen: Remdesivir, Dexamethason (if >7 days after onset) – 5 vs. 10 days
  - Immunocompromised: Remdesivir (10 days) +/- dexamethasone
  - Rapid progression within 3 days of admission: Consider convalescent plasma
  - Attempt to enroll in clinical trials: *ACTT-4, ACTIV-1, ACTIV-4, PAI-1 inhibitor*

Approach to COVID-19: *Gaps in Our Understanding*

- We need to identify ideal study endpoints
  - Initial enthusiasm for ordinal scale; challenges noted
  - There's more to drugs than prevention of death
- We need to know more about impact of interventions
  - Serial virology and resistance emergence
  - Biomarkers and the clinical correlates of their change
- We need to figure out how to learn from EUA/EAP
- We need more personalized approach to therapy
  - Especially true for immunmodulation
- Better therapies for outpatient care and more potent antivirals

Are you a registered organ donor?

I am!

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Questions?

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