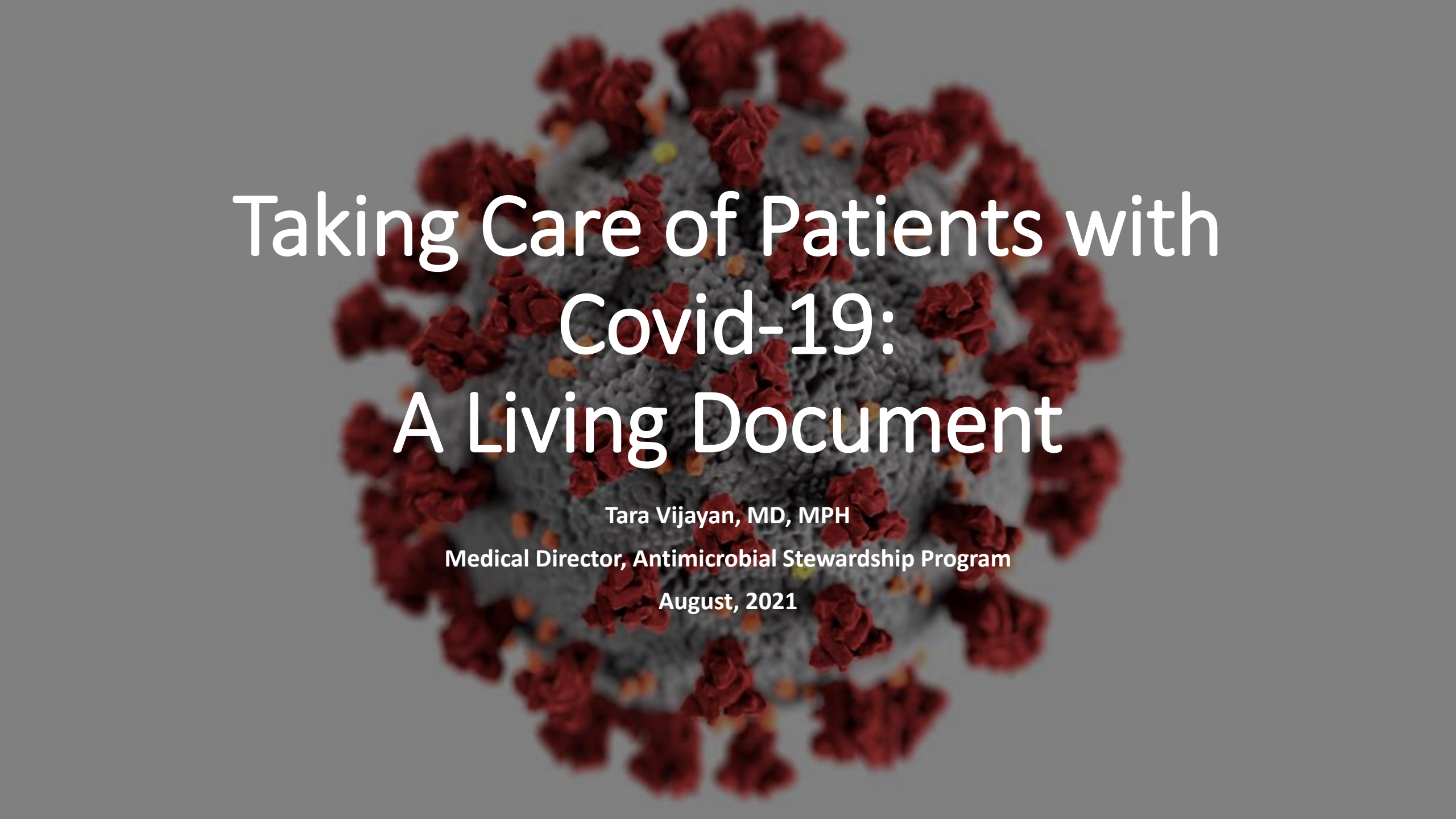


Taking Care of Patients with Covid-19: A Living Document

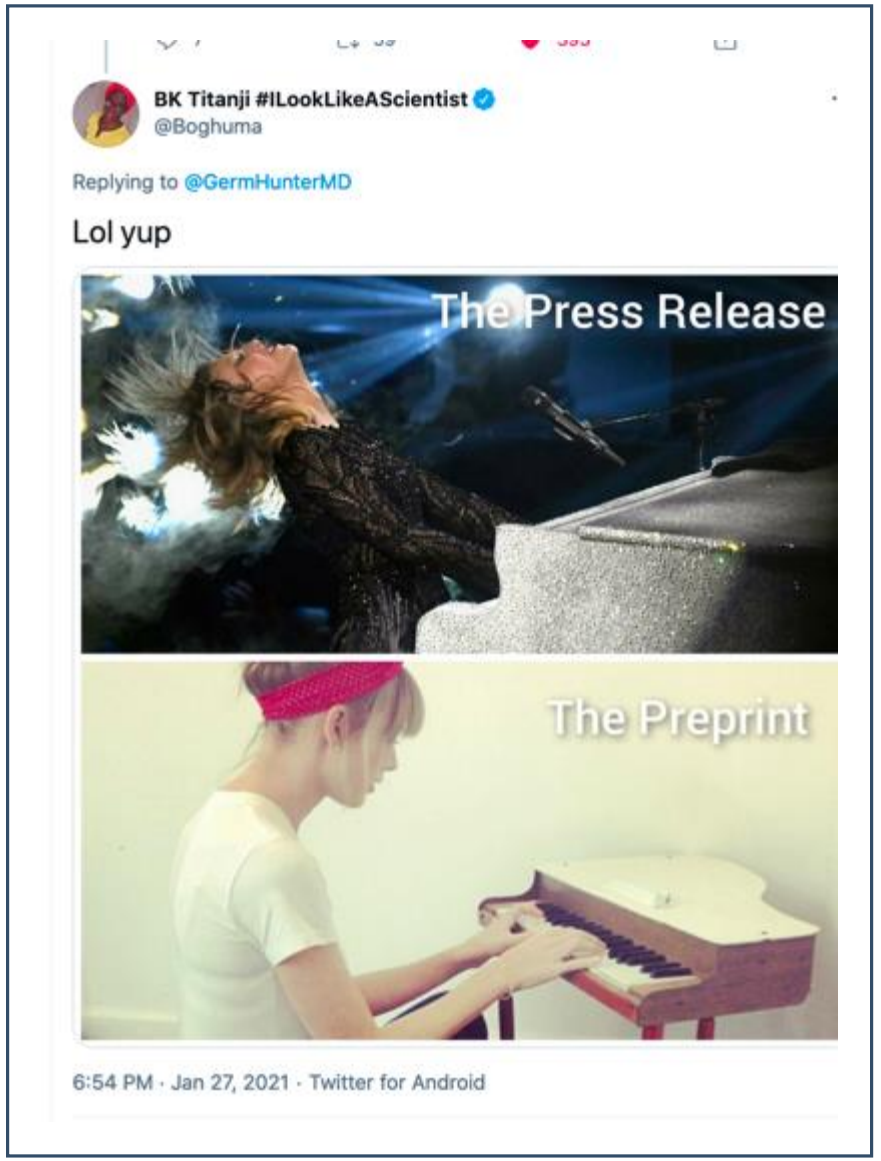
Tara Vijayan, MD, MPH

Medical Director, Antimicrobial Stewardship Program

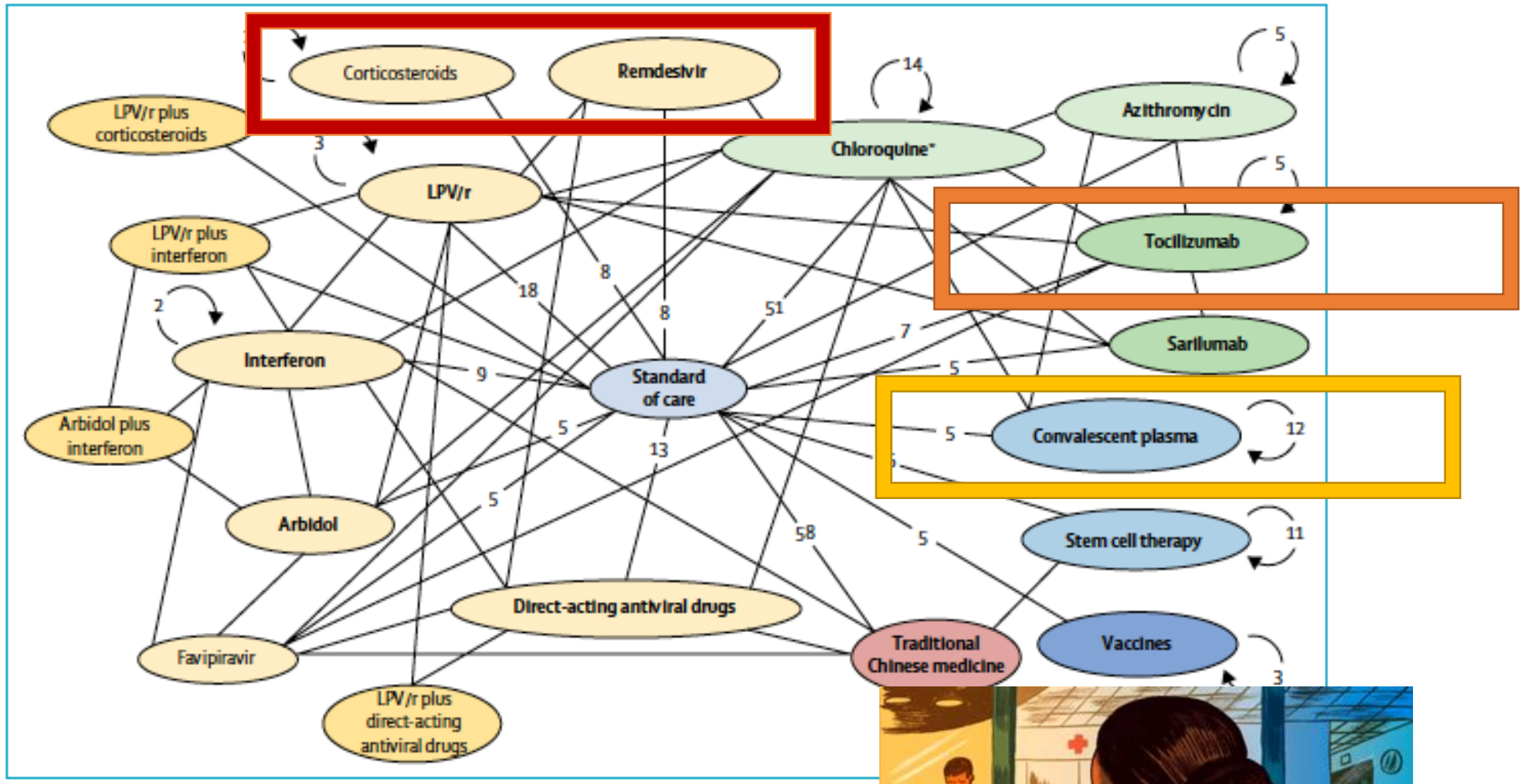
August, 2021

Overview

- Antiviral treatment
- Immunomodulator therapies
- Monoclonal antibody therapy
- Timing is everything



Therapeutics



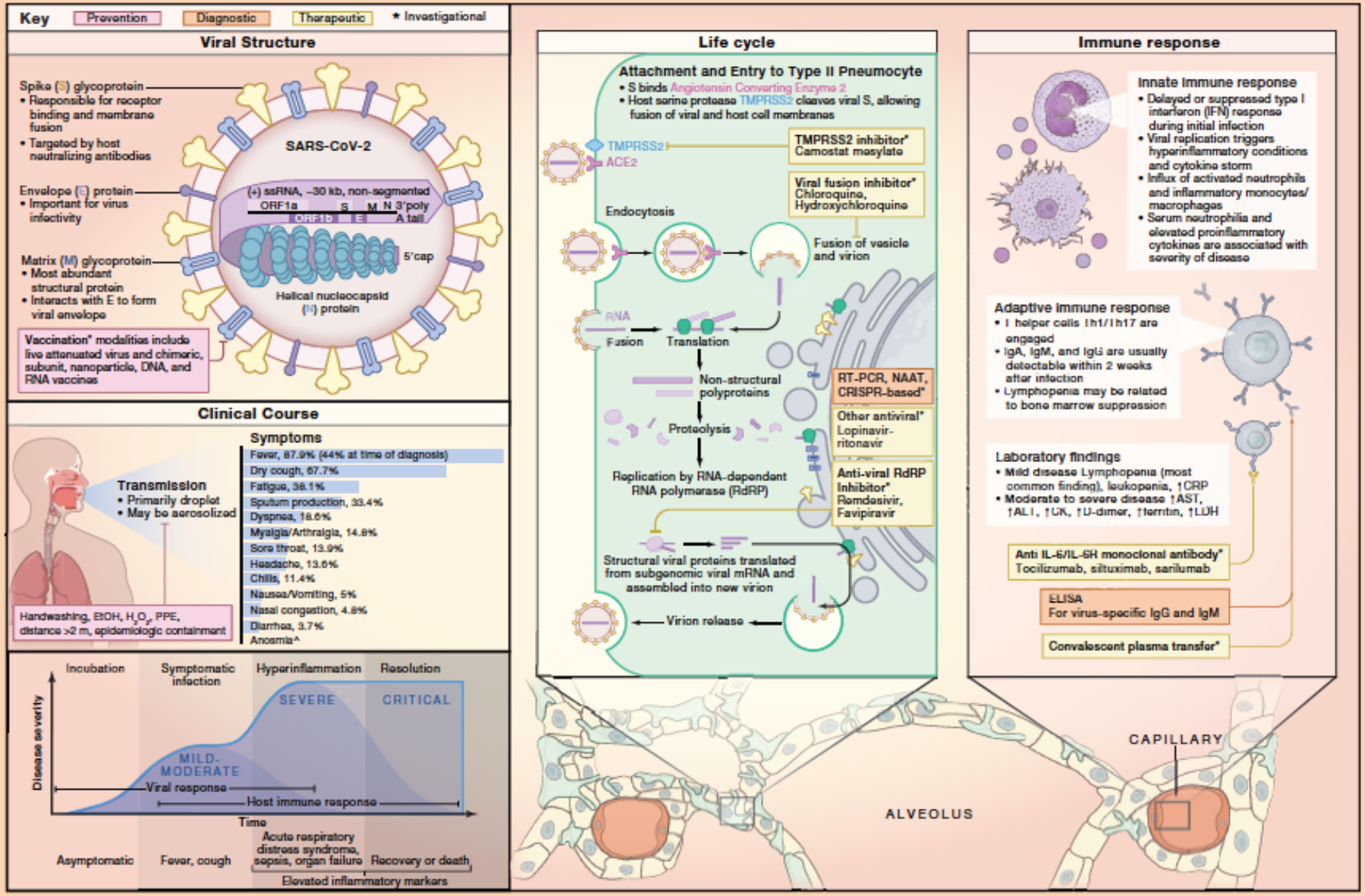
Lancet Digital Health, April 2020

Mike Reddy, StatNews

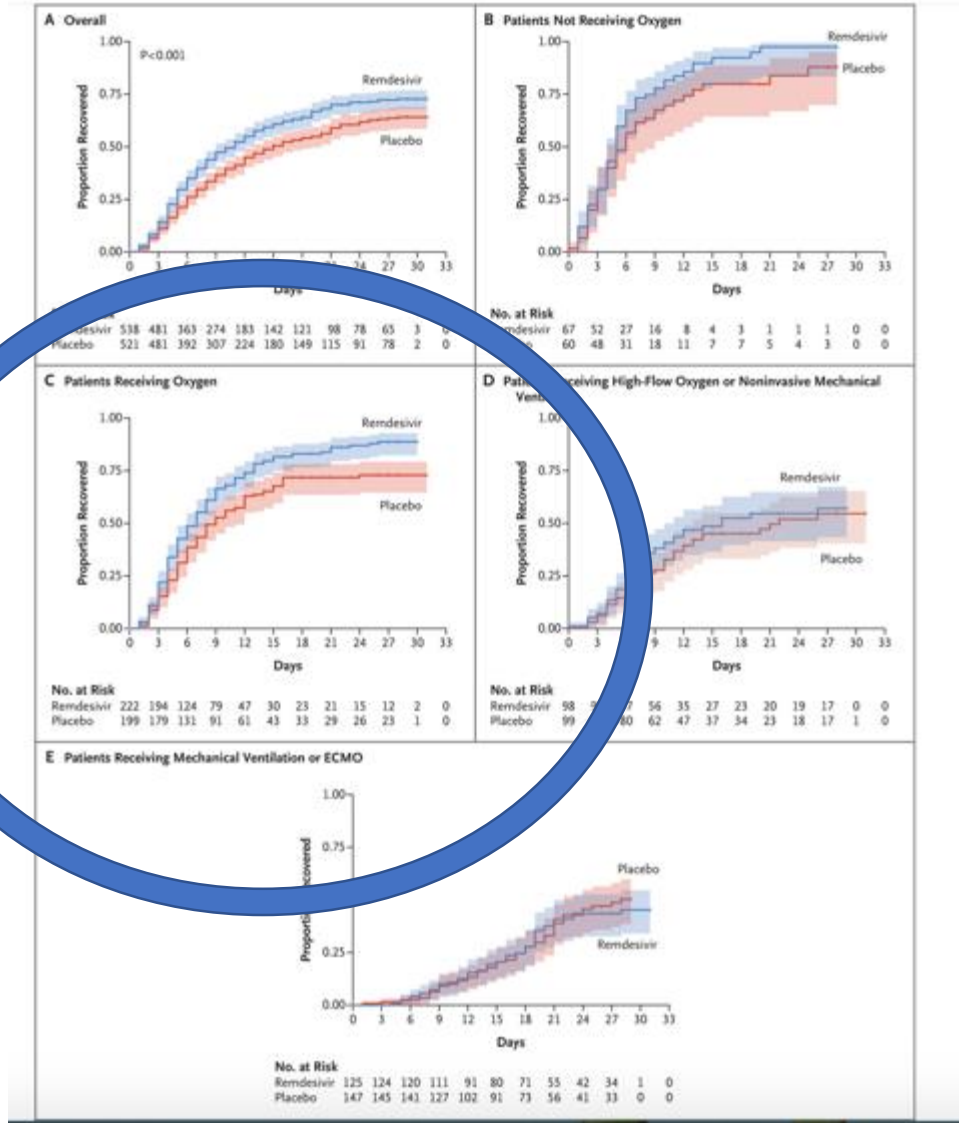
SnapShot: COVID-19

Blake Oberfeld,[1] Aditya Achanta,[1] Kendall Carpenter,[1] Pamela Chen,[1] Nicole M. Gilette,[1] Pinky Langat,[1] Jordan T. Said,[1] Abigail E. Schiff,[1,2] Allen S. Zhou,[1] Amy K. Barczak,[1,2] and Shiv Pillai[1,2]
[1]Harvard Medical School, Boston, MA 02115, USA; [2]Ragon Institute of MGH, MIT, and Harvard, Cambridge, MA 02139, USA

Cell

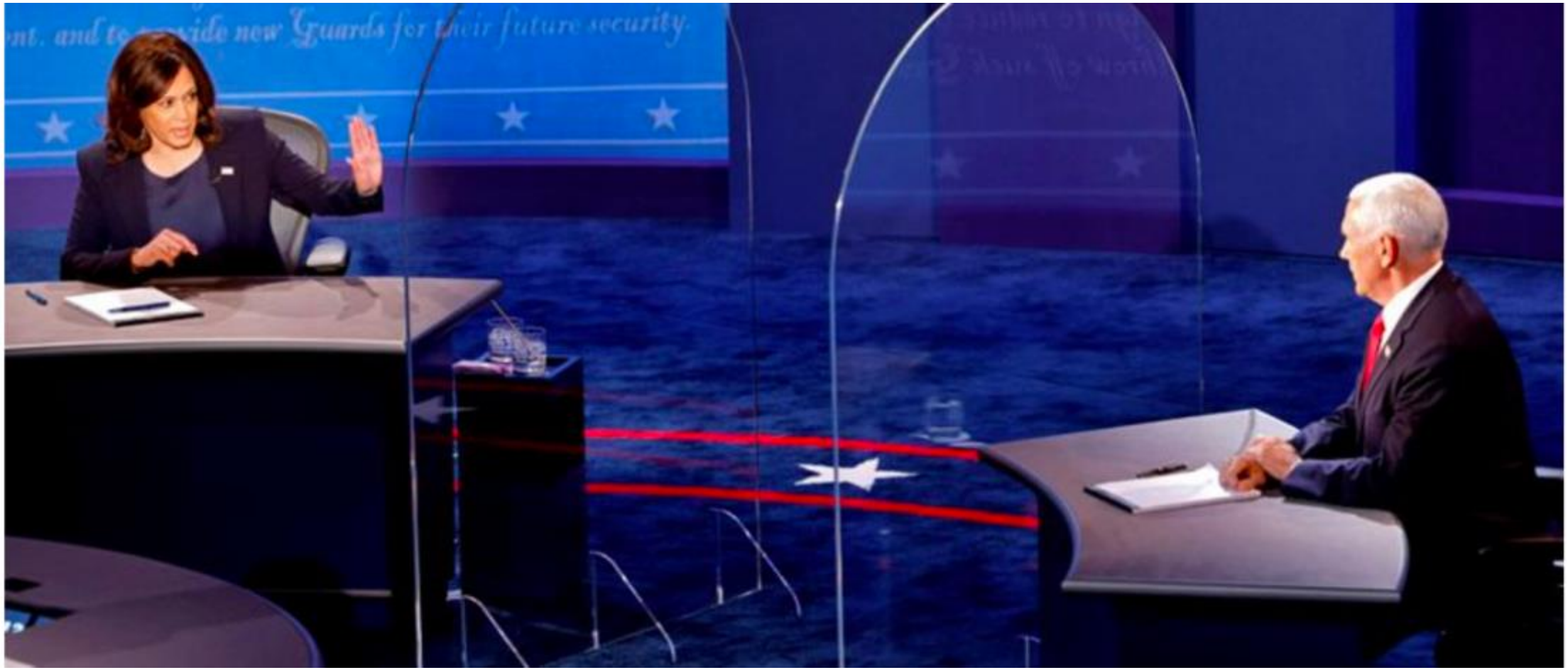


The data to date: remdesivir



Beigel, NEJM, May 22, 2020

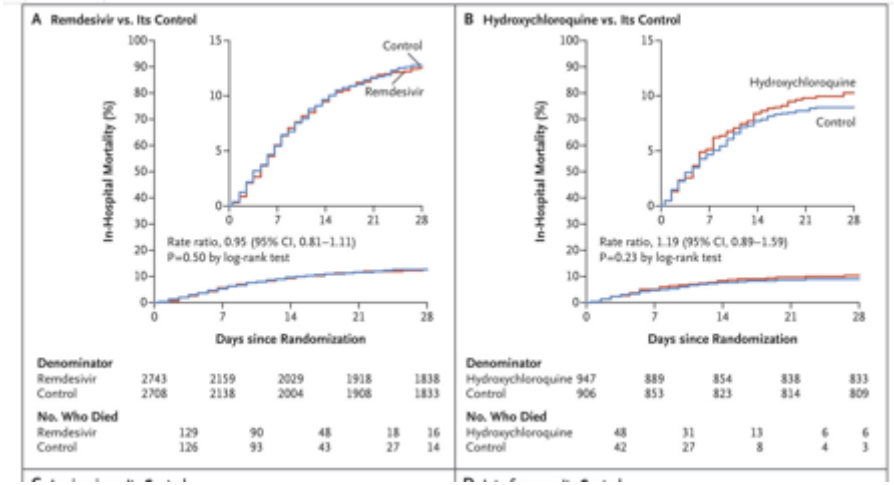
Solidarity Trial and other controversies



Reuters, October 2020

Solidarity Trial, WHO
Preprint Oct 15
NEJM Dec 2, 2020

- A pragmatic trial design: Lop/r, RDV, IFN-b, HCQ, local standard
- SARS CoV2 PCR positivity not required



Subgroup	Active Treatment	Control	Log-Rank Statistics for No. of Deaths in Active-Treatment Group O−E	Variance	Rate Ratio for Death (99% CI; 95% CI for total)
	no. of deaths reported/no. of patients (%)				
Remdesivir					
Age at entry					
<50 yr	61/961 (6.9)	59/952 (6.8)	2.3	29.8	1.08 (0.67–1.73)
50–69 yr	154/1282 (13.8)	161/1287 (14.2)	−7.6	77.5	0.91 (0.68–1.21)
≥70 yr	86/500 (20.5)	83/469 (21.6)	−2.9	41.5	0.93 (0.63–1.39)
Respiratory support at entry					
No mechanical ventilation	203/2489 (9.4)	232/2475 (10.6)	−15.8	108.0	0.86 (0.67–1.11)
Mechanical ventilation	98/254 (43.0)	71/233 (37.8)	7.6	40.8	1.20 (0.80–1.80)
Total	**301/2743 (12.5)**	**303/2708 (12.7)**	**−8.3**	**148.8**	**0.95 (0.81–1.11)**
Heterogeneity around total: χ^2_3=3.9					P=0.50
Hydroxychloroquine					
Age at entry					
<50 yr	19/335 (5.7)	19/317 (5.8)	0.9	9.2	1.10 (0.47–2.57)
50–69 yr	55/410 (12.1)	31/396 (7.1)	10.8	21.2	1.66 (0.95–2.91)
≥70 yr	30/202 (14.0)	34/193 (17.8)	−3.5	15.8	0.80 (0.42–1.53)
Respiratory support at entry					
No mechanical ventilation	69/862 (7.4)	57/824 (6.6)	4.7	31.4	1.16 (0.73–1.84)
Mechanical ventilation	35/85 (39.2)	27/82 (32.3)	3.4	14.8	1.26 (0.65–2.46)
Total	**104/947 (10.2)**	**84/906 (8.9)**	**8.1**	**46.2**	**1.19 (0.89–1.59)**
Heterogeneity around total: χ^2_3=5.0					P=0.23

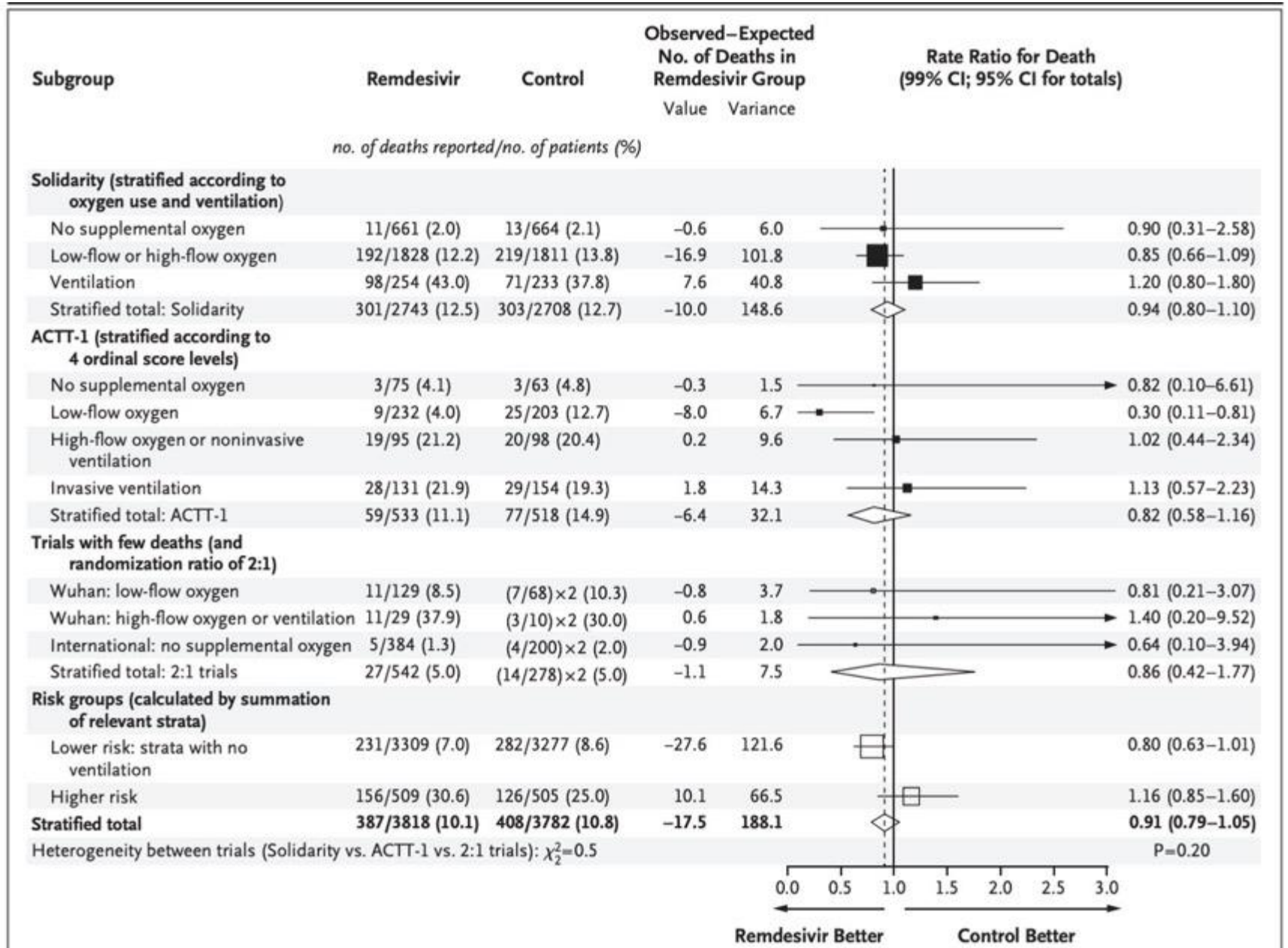


Figure 4. Meta-Analysis of Mortality in Trials of Random Assignment of Remdesivir or Its Control to Hospitalized Patients with Covid-19.

VA RDV study (T3) JAMA, July 15, 2021

- Retrospective cohort study
- 5898 patients, 123 hospitals
- 79% received CST
- No formal guidance on stopping RDV once better

Figure 3. Distribution of Days to Remdesivir Treatment Completion Among Recipients and Days to Hospital Discharge Among Recipients and Controls

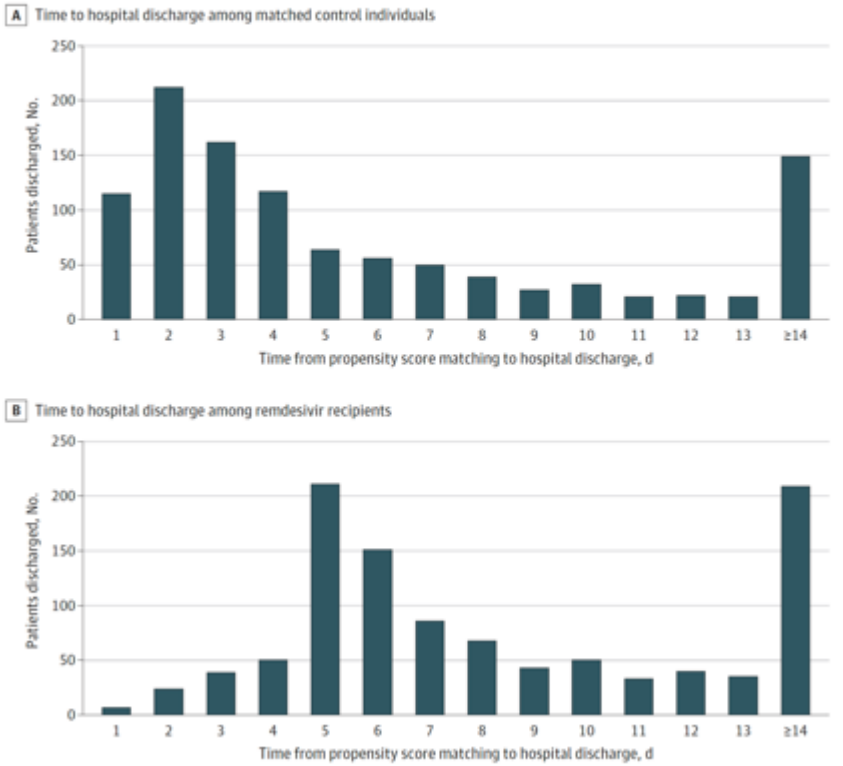
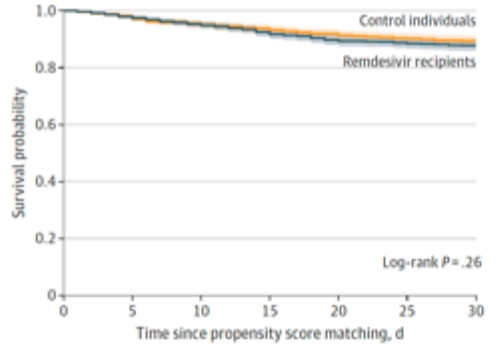


Figure 2. Kaplan-Meier Survival Curves for Remdesivir Recipients and Control Individuals in the Propensity Score–Matched Cohort



No. at risk							
Control individuals	1172	1129	1098	1075	1054	1041	1030
Remdesivir recipients	1172	1142	1112	1075	1047	1034	1034

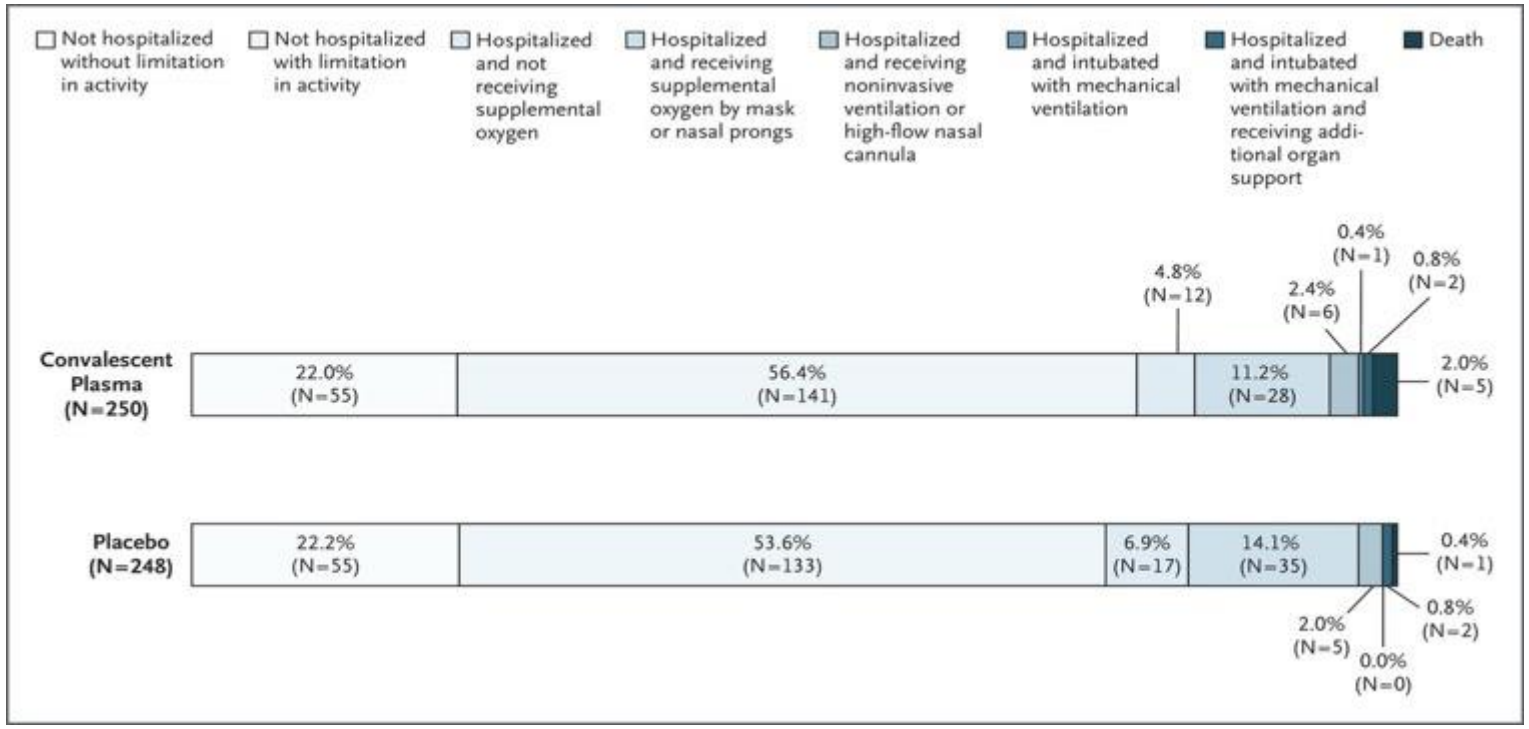
Day 0 is the day of matching (ie, day of remdesivir initiation or corresponding hospital day for controls).

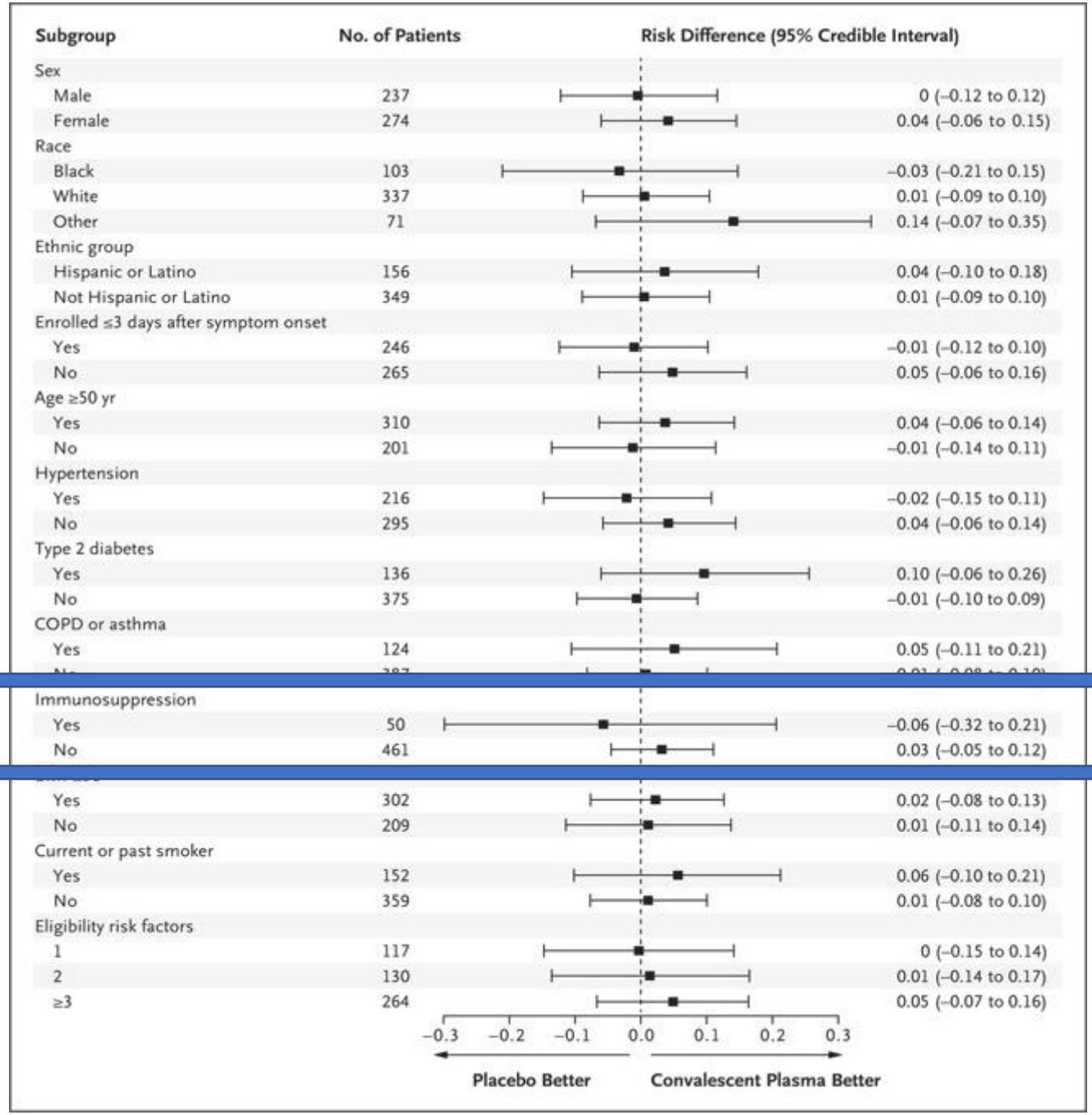
Convalescent Plasma: The Data Remain Mixed

- Ling, L and colleagues (JAMA June 2020) published RCT showing improvement in clinical recovery in those with severe disease:
  - 91.3% (21/23) in treatment vs 68.2% (15/22) in control
- NEJM Nov 2020: ⊘ benefit in severe disease, median time to dose 8d
- NEJM Feb 2021: >75 years old, or >65 + co-morbid, ↓ 48% in severity
- At this time, UCLA is using at least FDA minimum titer standard, prioritizing higher titer plasma if possible, within 3 days sx onset
  - High titer defined as 1:250 or more

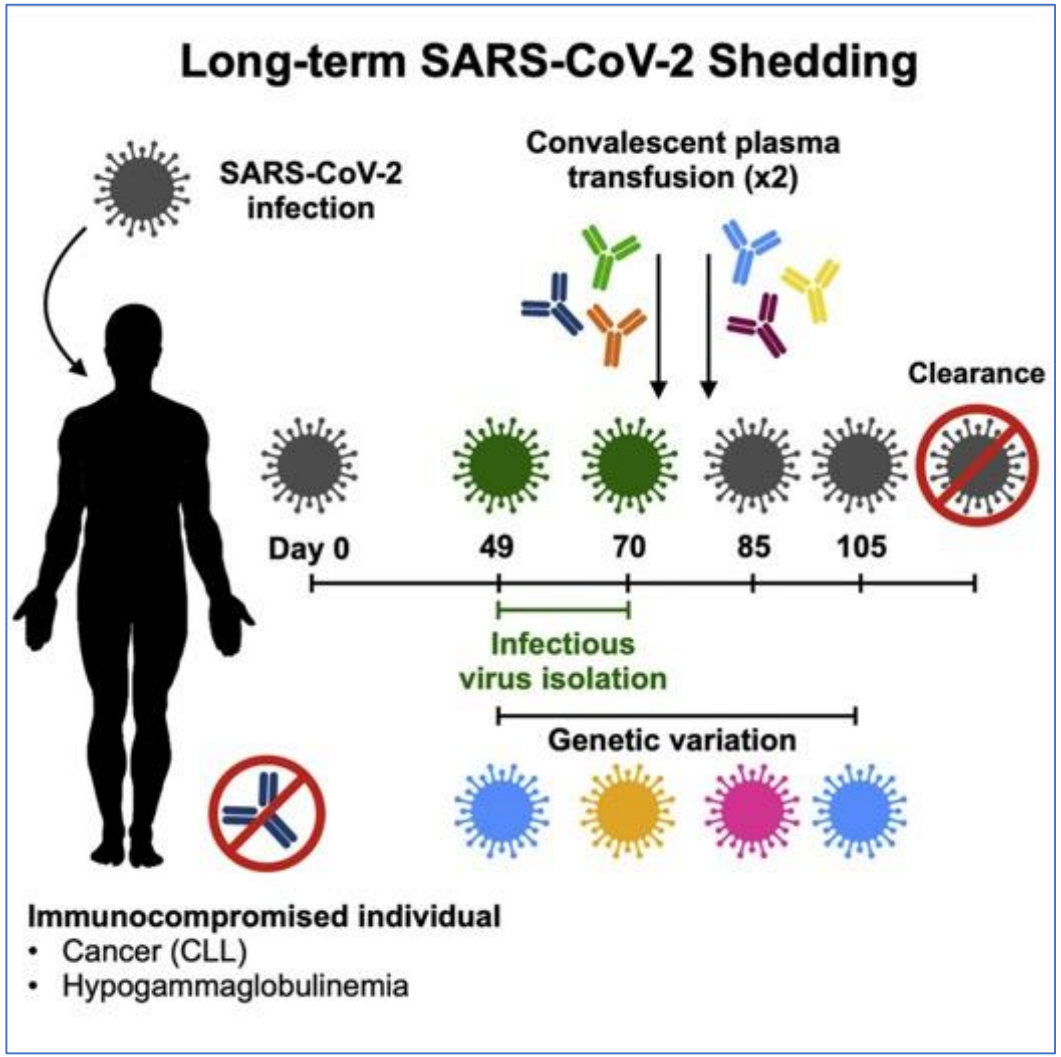
C3PO RCT: 511 patients enrolled NEJM Aug 2021, Korley and colleagues

- Primary outcome was disease progression d15 (no difference)
- Secondary outcome: worst rating within 30 days



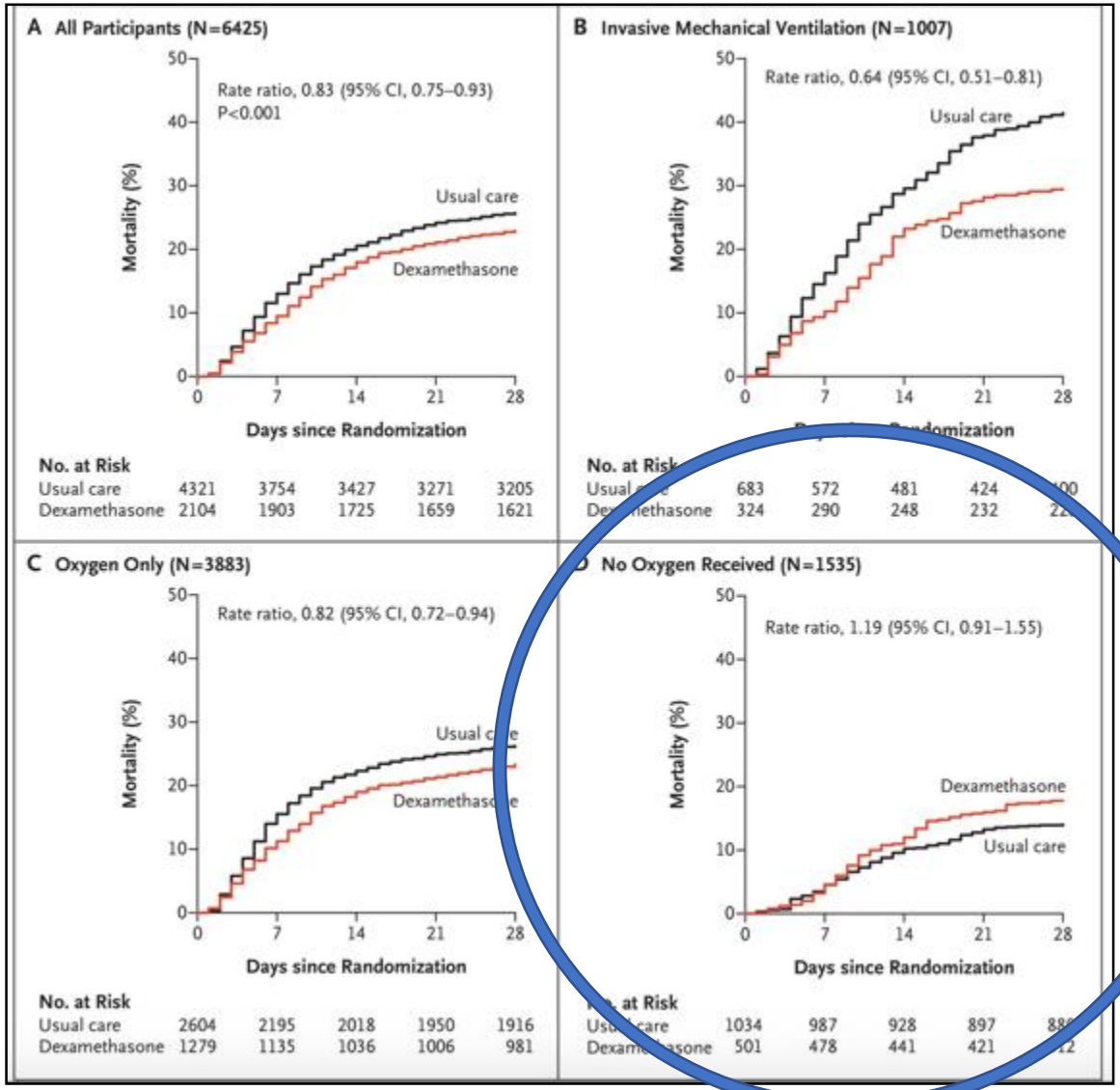

Subgroup
No. of Patients
Risk Difference (95% Credible Interval)
Sex
Male 237 0 (–0.12 to 0.12)
Female 274 0.04 (–0.06 to 0.15)
Race
Black 103 –0.03 (–0.21 to 0.15)
White 337 0.01 (–0.09 to 0.10)
Other 71 0.14 (–0.07 to 0.35)
Ethnic group
Hispanic or Latino 156 0.04 (–0.10 to 0.18)
Not Hispanic or Latino 349 0.01 (–0.09 to 0.10)
Enrolled ≤3 days after symptom onset
Yes 246 –0.01 (–0.12 to 0.10)
No 265 0.05 (–0.06 to 0.16)
Age ≥50 yr
Yes 310 0.04 (–0.06 to 0.14)
No 201 –0.01 (–0.14 to 0.11)
Hypertension
Yes 216 –0.02 (–0.15 to 0.11)
No 295 0.04 (–0.06 to 0.14)
Type 2 diabetes
Yes 136 0.10 (–0.06 to 0.26)
No 375 –0.01 (–0.10 to 0.09)
COPD or asthma
Yes 124 0.05 (–0.11 to 0.21)
Immunosuppression
Yes 50 –0.06 (–0.32 to 0.21)
No 461 0.03 (–0.05 to 0.12)
Yes 302 0.02 (–0.08 to 0.13)
No 209 0.01 (–0.11 to 0.14)
Current or past smoker
Yes 152 0.06 (–0.10 to 0.21)
No 359 0.01 (–0.08 to 0.10)
Eligibility risk factors
1 117 0 (–0.15 to 0.14)
2 130 0.01 (–0.14 to 0.17)
≥3 264 0.05 (–0.07 to 0.16)
–0.3 –0.2 –0.1 0.0 0.1 0.2 0.3
Placebo Better
Convalescent Plasma Better

Exceptions…



Cell 2020 1831901-1912.e9DOI: (10.1016/j.cell.2020.10.049) (December 2020)

The data to date: steroids

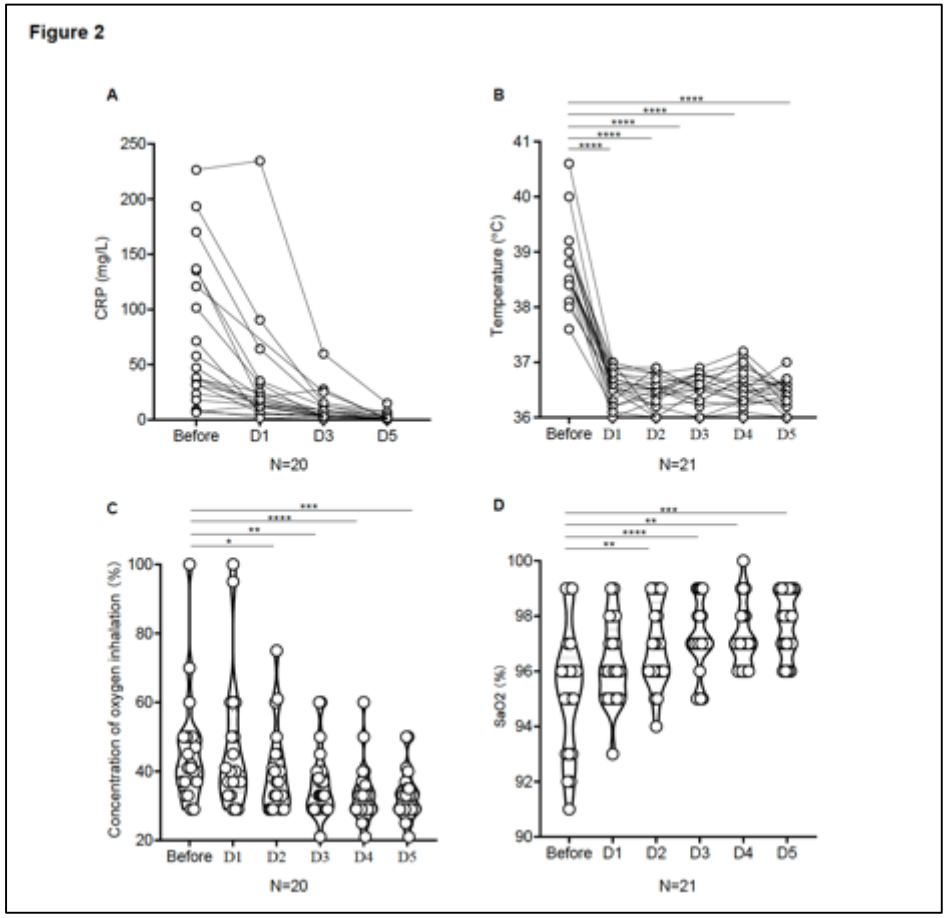


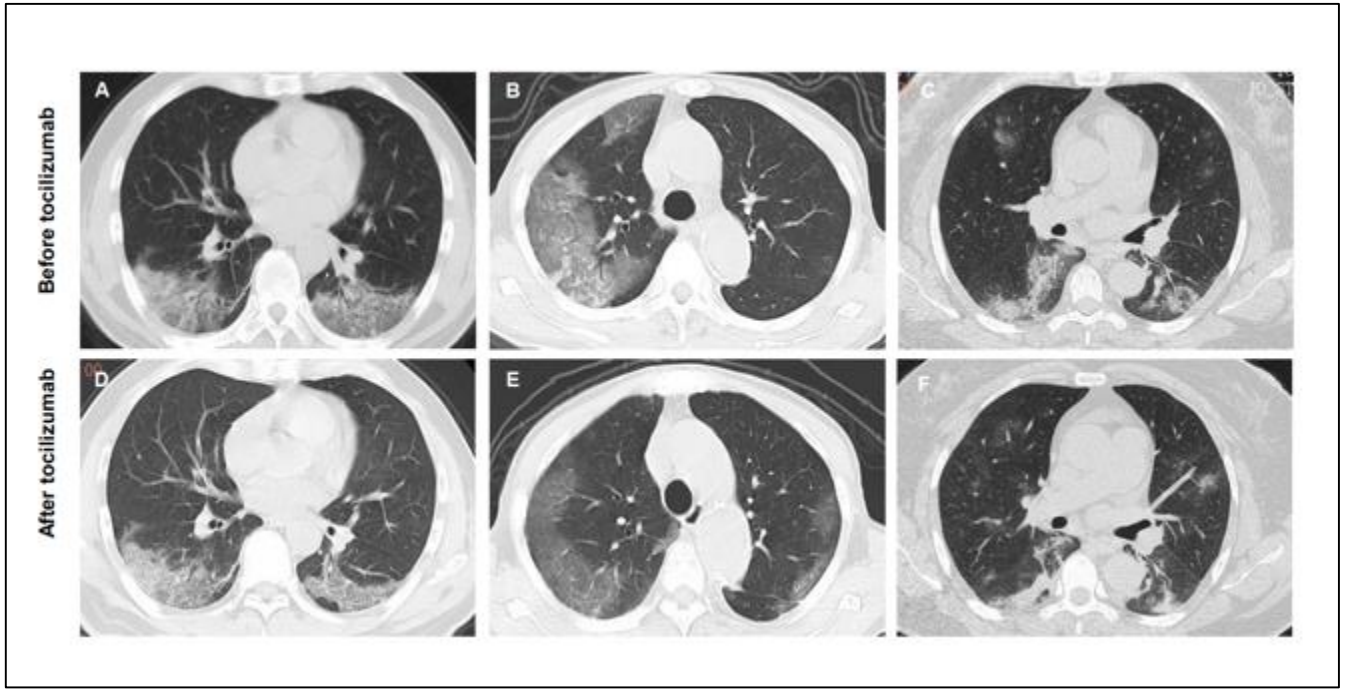
RECOVERY:

- Dexamethasone
- Tocilizumab
- Colchicine
- Convalescent Plasma
- REGN-CoV2
- Aspirin

Recovery, NEJM, July 17, 2020

Tocilizumab: theory





Xu X, Han M, Li T, Sun W, Wang D, Fu B, Zhou Y, Zheng X, Yang Y, Li X, Zhang X, Pan A, Wei H. Effective treatment of severe COVID-19 patients with tocilizumab. Proc Natl Acad Sci U S A. 2020 May 19;117(20):10970-10975. doi: 10.1073/pnas.2005615117. Epub 2020 Apr 29. PMID: 32350134;

BRIGHAM HEALTH
BRIGHAM AND WOMEN'S HOSPITAL

MAGNET RECOGNIZED

HARVARD MEDICAL SCHOOL TEACHING HOSPITAL

Tocilizumab RCT Summary as of Feb 17th, 2021

Study (n)	n	Severity	Tocilizumab Mortality	Control Mortality	Steroid Use	Time from Symptom Onset	Comments
RCT-TCZ-COVID-19	126	Severe	30-day 3.3%	1.5%	9.8%	8 (6-11)	Open label, underpowered
CORIMUNO-TOCI-1	131	Moderate-Severe	28-day 10.9%	11.9%	33% vs. 61%	10 (7-13)	Open label
BACC Bay	243	Severe	28-day 5.6%	3.7%	9.5%	9 (6-13)	Underpowered?
COVACTA	438	Severe-critically ill	28-day 19.7%	19.4%	36.1% vs. 54.9%	11 vs. 10 (no IQR)	Shorter LOS in toci arm
EMPACTA	377	Severe	28-day 10.4%	8.6%	82.8%	8 (no IQR)	Toci reduced % patients intubated
REMAP-CAP	755	Critically ill	Hospital 27.8%	35.3%	85% *(maybe)*	?, <24 hours from organ support	Open label
TOCIBRAS	129	Severe-critically ill	28-day 21.5%	9.4%	83.6% vs. 88.7%	10 vs. 9.5 (no IQR)	Open label, underpowered
RECOVERY	4,116	Severe-critically ill	28-day 29.5%	33.1%	82%	9 (7-13) vs. 10 (7-14)	Open label
All RCTs	6,315		24.8%	27.5%	OR 0.87 (0.79-0.96) *per Horby et al*		

Jeff Pearson
@jeffpears0n

Salvarani et al. JAMA Intern Med. 2020;181(1):24-31. doi: 10.1001/jamainternmed.2020.6615
Hermine et al. JAMA Intern Med. 2020;181(1):32-40. doi: 10.1001/jamainternmed.2020.6820
Stone et al. N Engl J Med. 2020; 383:2333-2344. doi: 10.1056/NEJMoa2028836
Rosas et al. medRxiv preprint. 2020. doi:10.1101/2020.08.27.20183442
Salama et al. N Engl J Med. 2021;384:20-30. doi:10.1056/NEJMoa2030340
Gordon et al. medRxiv preprint. 2020. doi:10.1101/2021.01.07.21249390
Veiga et al. BMJ. 2021; 372:n84. doi:10.1136/bmj.n84
Horby et al. medRxiv preprint. 2021. doi:10.1101/2021.02.11.21249258

Timing is everything

TOCIBRAS

- Primary Outcome:
  - ordinal scale at d15
- <24h MV
- Only 7% CST at enrollment
- >80% CST over course of tx

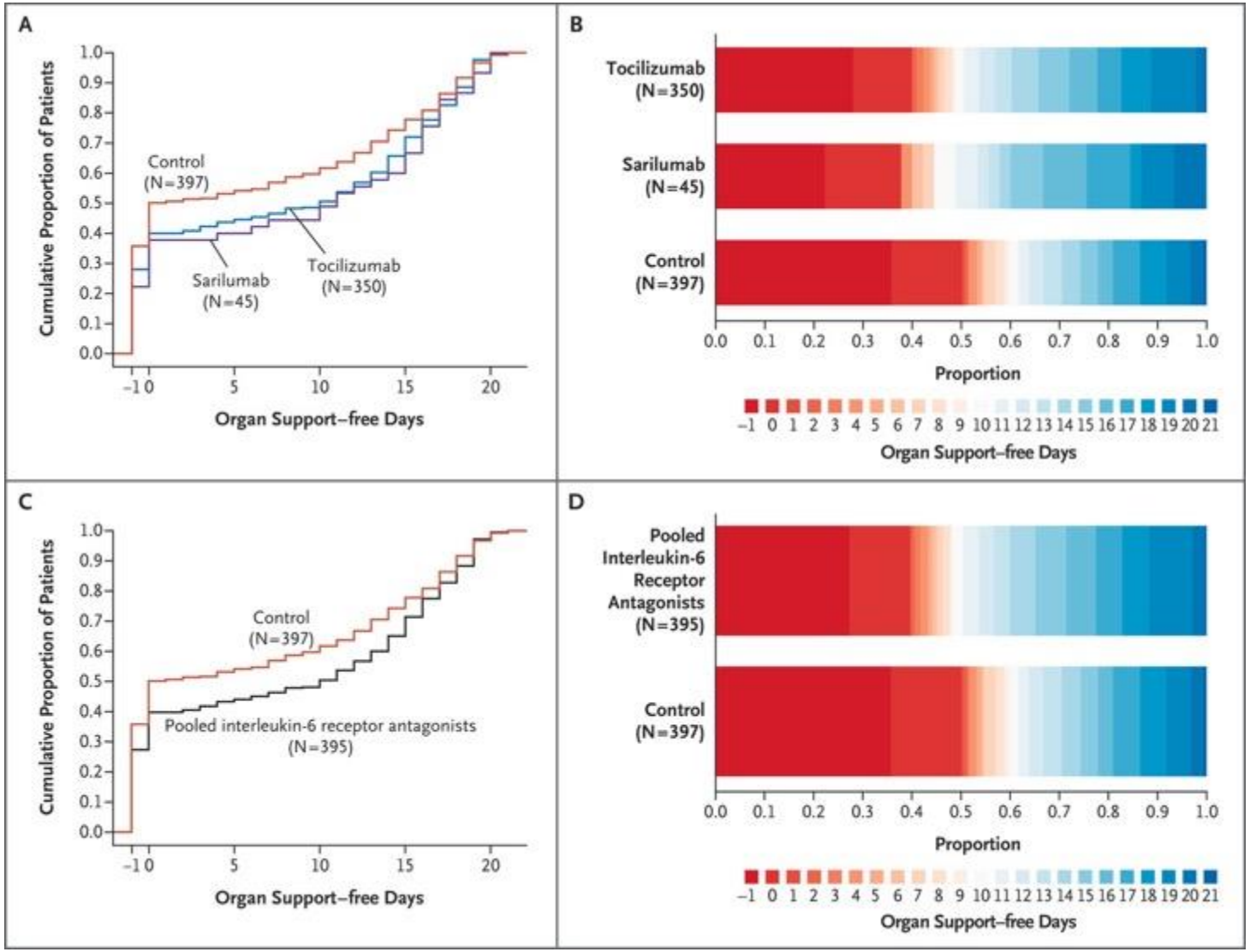
REMAP-CAP

- Primary Outcome:
  - # organ support free days at d21
- <24 MV
- 93% on CST at enrollment

BMJ, Jan, 2021
NEJM April, 202

Sarilumab v tocilizumab: primary outcomes

- 350 included in toci arm in REMAP-CAP
  - OR 1.64 (95% credible interval, 1.25 to 2.14)
- 45 included in in sari arm in REMAP-CAP
  - OR 1.76 (95% credible interval, 1.17 to 2.91)



NEJM April 2021

A history of Emergency Use Authorization

- March 28, 2020 FDA issued EUA for hydroxychloroquine
- May 3, 2020 FDA issued EUA for remdesivir
- June 15, 2020 FDA retracts EUA for hydroxychloroquine
- August 23, 2020 FDA issues EUA for convalescent plasma
- November 9 & 21, 2020: EUA for bamlanivimab and casi/imdevimab
- November 19, 2020 FDA issues EUA for baracitinib with RDV
- June 21, 2021: FDA issues EUA for tocilizumab

April 15, 2021

The NEW ENGLAND JOURNAL of MEDICINE

Baricitinib + Remdesivir for Hospitalized Adults with Covid-19

DOUBLE-BLIND, MULTICENTER, RANDOMIZED, CONTROLLED TRIAL

1033
Patients hospitalized with Covid-19

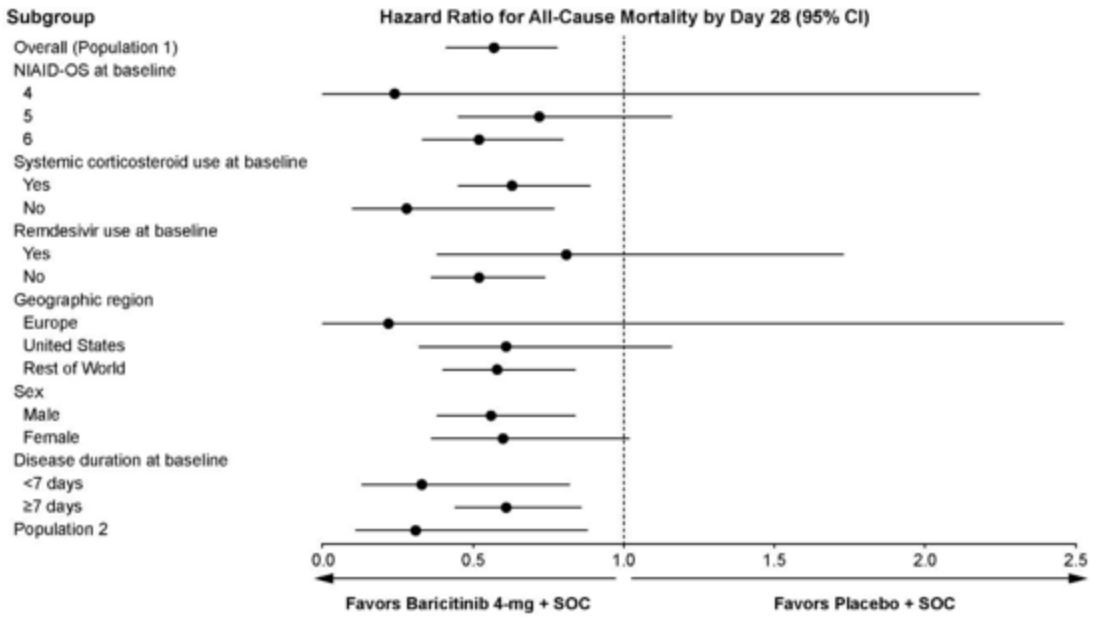
	Baricitinib + Remdesivir (N=515)	Placebo + Remdesivir (N=518)
Median time to recovery	7 Days	8 Days
	Rate ratio for recovery, 1.16; 95% CI, 1.01 to 1.32; P=0.03	
Time to recovery among patients receiving high-flow oxygen or noninvasive ventilation	10 Days	18 Days
	Rate ratio for recovery, 1.51; 95% CI, 1.10 to 2.08	
Serious adverse events	16%	21%

Baricitinib + remdesivir reduced recovery time and accelerated improvement in clinical status.

A.C. Kalil et al. 10.1056/NEJMoa2031994

Baricitinib, COV-Barrier, preprint May 2021

- 1525 patients enrolled, 79% on CST at enrollment
- Primary outcome: progression to HFNC, NIPPV, MV, Death at d28
- 38% reduction in mortality
  - 48% reduction among those on HFNC, NIPPV



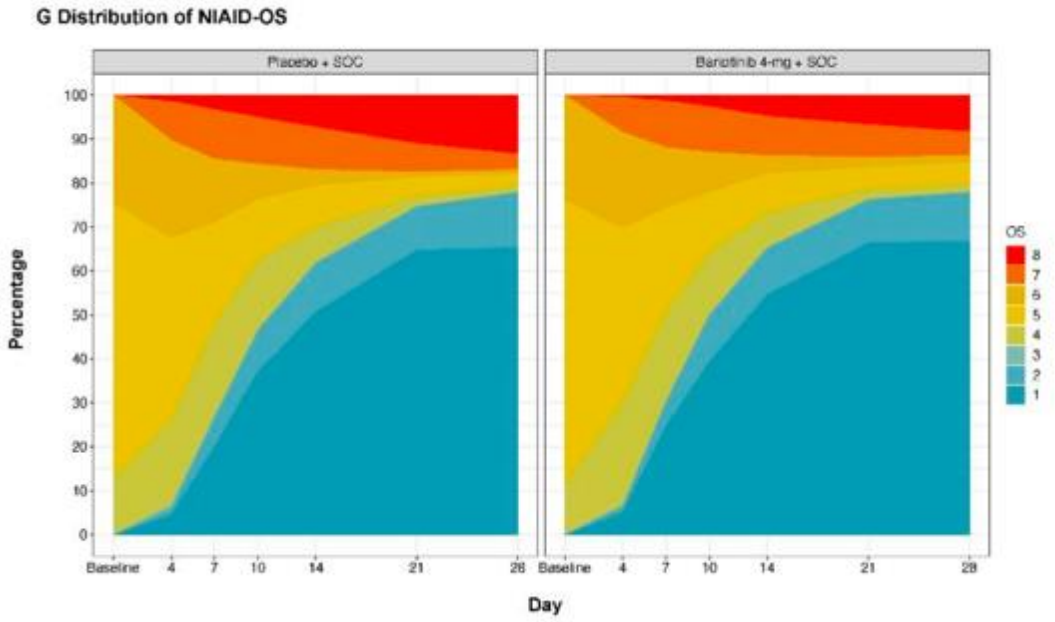


Figure 3. Mortality according to subgroup.

Side effects:

- Antivirals
  - Remdesivir: elevated liver enzymes (allowing 10x ULN)
  - Convalescent plasma: transfusion reaction, need to type and screen first
- Immunomodulators
  - Dexamethasone: hyperglycemia, immunosuppression (low dose less likely)
  - Baricitinib: increased risk of thrombosis
  - IL-6r blockade: bacterial infections, fungal and TB reactivation

Monoclonal Antibodies: LyCoV555 and REGN-CoV antibodies

	Bamlanivimab	Casirivimab/Imdevimab
Randomization	452, 1:1:1:1 700mg, 2400mg, 7[illegible]0mg, placebo	275, 1:1:1 2.4g, 8g, placebo
Inclusion criter	Symptomatic [illegible] [illegible]S-CoV2 [illegible]om infusion	Symptomatic ≤7d from randomization SARS-CoV2 PCR+≤3d SpO2>93%
Patient character	[illegible], Age ≥65, BMI ≥35	45% already Ab positive
Primary outcome	[illegible]1: no difference seen	VL reduction at d7- demonstrated More significant in Ab negative
Secondary o	[illegible]nitalizations: [illegible]→1.6% [illegible]eduction) 15%→4% amo[illegible]5 or BMI ≥35	Medically attended visit: 6→3% 15%→4% if antibody neg (-9, 95%CI -29,11)
Other notes	Reduction in sympt[illegible]ns No difference in any of doses EUA specifies 700mg dose	No difference in doses EUA specifies 2400mg dose

Chen P, Nirula A, Heller B, and colleagues on behalf of the BLAZE-1 Investigators. N Engl J Med. 2020 Oct 28. doi: 10.1056/NEJMoa2029849.
DM Weinreich et al. N Engl J Med 2021;384:238-251.

Adverse Events- not different than placebo

- Infusion reactions
  - We have seen several “delayed” infusion reactions marked by rigors
  - 2 cases of pregnant women with fetal heart deceleration
- Nausea, Vomiting
- Headache
- Pruritis
- Diarrhea

California variant B. 1429/27

- Likely predominant strain December 2020-Feb 2021
- Bamlanivimab was not effective against it

State of California—Health and Human Services Agency
California Department of Public Health

TOMÁS J. ARAGÓN, M.D., Dr.P.H.
Director and State Public Health Officer

GAVIN NEWSOM
Governor

Health Alert:
Concerns re: the Use of Bamlanivimab Monotherapy in the Setting of SARS-CoV2 Variants

March 19, 2021

Bamlanivimab is an investigational monoclonal antibody product that received emergency use authorization (EUA) from the U.S. Food and Drug Administration (FDA) in November 2020 for the treatment of mild-to-moderate COVID-19 in non-hospitalized adult and pediatric patients who are at high risk for progression to severe disease.

The California Department of Public Health recommends facilities and providers stop administering bamlanivimab monotherapy in California. Below is updated information regarding federal concerns of decreased clinical effectiveness for bamlanivimab monotherapy in the setting of emerging SARS-CoV2 variants. This notice also includes information on alternative monoclonal antibody products that are still authorized for use and how to acquire these products.

The COVID-19 Treatment Guidelines Panel (the Panel) currently recommends that nonhospitalized patients with COVID-19 who are at high risk for disease progression receive one of three authorized anti-SARS-CoV-2 monoclonal antibody regimens (see the Panel's Statement on the Emergency Use Authorizations of Anti-SARS-CoV-2 Monoclonal Antibodies for the Treatment of COVID-19). The Panel has reviewed the data that were provided in the updated EUA for casirivimab plus imdevimab and reported publicly.[2,3] For the casirivimab plus imdevimab combination regimen (if selected from the three authorized regimens), the Panel recommends:

- Using the dose of **casirivimab 600 mg plus imdevimab 600 mg (AIIa)**.
- Using IV infusion of **casirivimab plus imdevimab (AIIa)**.
- When IV infusion is not feasible or would lead to delay in treatment, SQ injection of **casirivimab plus imdevimab** can be used as an alternative route of administration **(BIII)**.

NIH COVID-19 Guidelines, June 2021

UCLA Criteria: non hospitalized and hospitalized

- No new oxygen requirement (SpO2>93%, unless baseline O2)
- Symptom onset ≤ 7 days
- SARS CoV2 PCR positive ≤ 7 days
- Risk Factors for Progression

Risk Factors for Progression: Point System

Point	
3	❑ ≥6
3	❑ BM
2	❑ ≥5 HTN or chronic
2	lur
2	❑ Dia
2	❑ Ch
	❑ Im
1	❑ Medi-Cal recipient (or VFC patient)

Added:

- >12 years, at least 40kg
- cardiovascular disease/lung disease with any age
- BMI >30
- Neurologic disease
- Liver disease
- Pregnancy* (only if other high-risk criteria met)
- Smoking
- Sickle cell/thalassemia
- Medical technological dependence (trach, peg)

Other oral agents studied

- Colchicine: small studies, Recovery stopped arm due to no benefit
- Fluvoxamine 100mg po daily x 15 days v placebo
  - Sigma-1 receptor agonism
    - modulates cytokine production in endoplasmic reticulum
  - 0 of 80 v 6 of 72 met primary end point of clinical deterioration (delta 8.7%)
- Ivermectin
  - Used extensively in Latin America, Africa
  - Pooled risk ratio for very small studies outside the US 0.17 (95% CI 0.08, 0.35)
  - Remains controversial

RCT: Effect of Early Treatment with Fluvoxamine on Risk of Emergency Care and Hospitalization Among Patients with COVID-19

POPULATION

182 Men, 241 Women

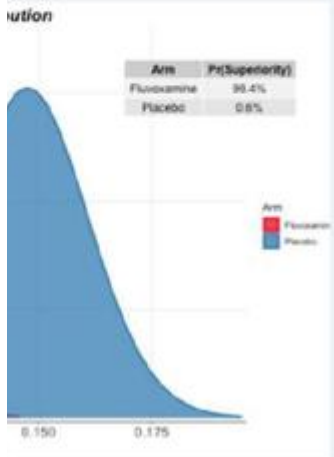
Patients with COVID-19 a
hospitalization
Median 50y (18-102y)

INTERVENTION

1472 Patients Randomized

FINDINGS

The proportion of patients with extended ER
tion was 77/739
e group and 108/733
up



Regional Warmist @SandyPattz · 3h

Replying to @boulware_dr and @TogetherTrial

Here's why I think this is meaningless.
Fluvoxamine is a med I've been on long term.
Principle side effect early on is sleepiness. Last several months in my experience.
2x100mg is a high dose so > S/E.
Sleepy people don't go out much hence don't catch infectious diseases inc C-19

SETTINGS/LOCATION

10 Clinical sites,
Minas Gerais, Brazil

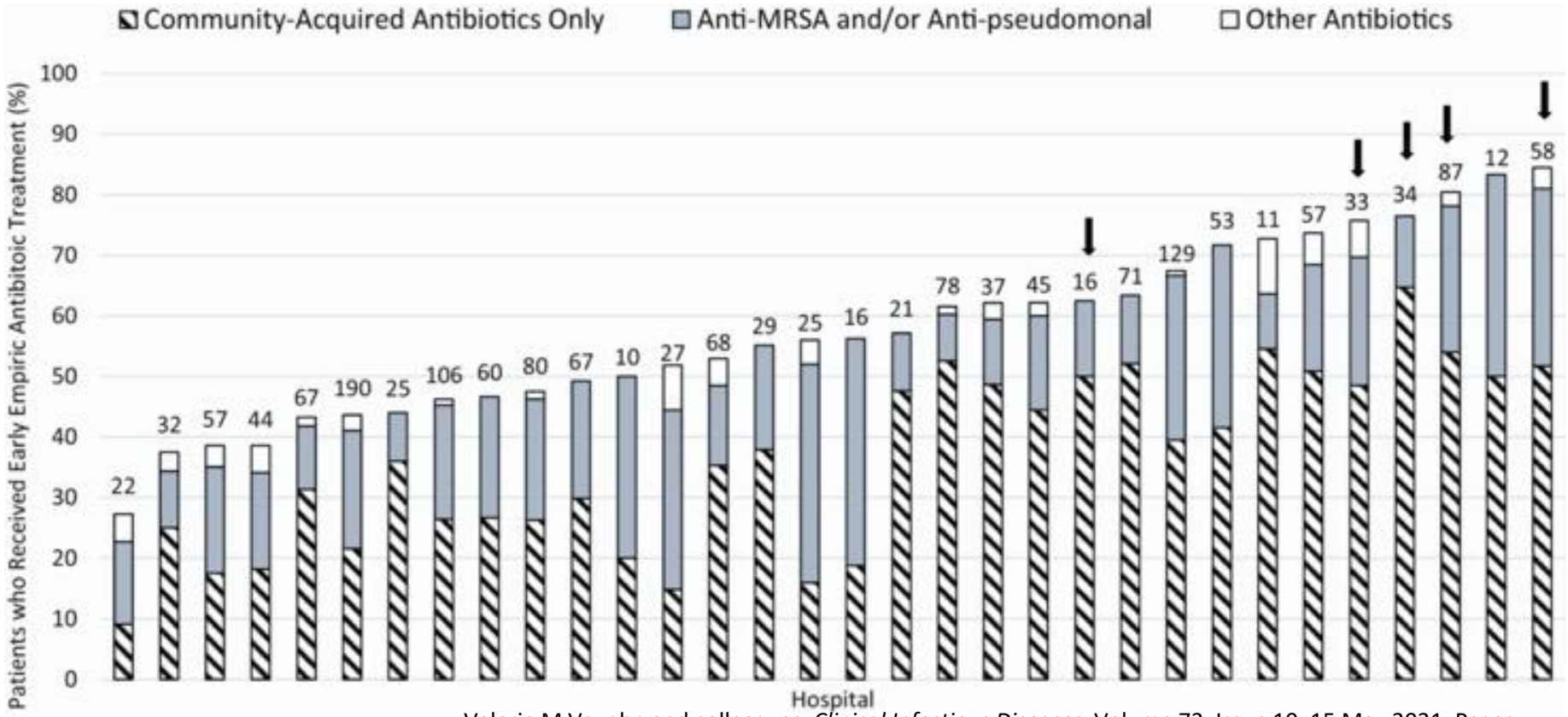
PRIMARY OUTCOMES

A composite of emergency room visits due to clinical worsening of COVID-19 (requiring observation for > 6 hours) or hospitalization due to the progression of COVID-19 within 28 days of randomization.

together • COVID-19 clinical trials

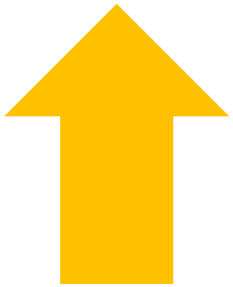
When are antibiotics needed in Covid-19?

- Of 1705 patients with COVID-19, 56.6% were prescribed early empiric antibacterial therapy; 3.5% (59/1705) had a confirmed community-onset bacterial infection.



Valerie M Vaughn and colleagues, *Clinical Infectious Diseases*, Volume 72, Issue 10, 15 May 2021, Pages e533–e541, https://doi.org/10.1093/cid/ciaa1239

For patients with COVID-19

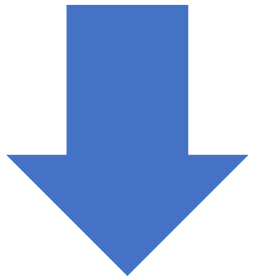


Not Hypoxic

- Consider monoclonal antibodies if high-risk, including BMI ≥30 (Casirivimab/Imdevimab, can give subcutaneous)
- AVOID steroids (associated with increased risk of mortality)
- AVOID antibiotics

Steroids

Hypoxic



- Remdesivir (sx <24d)
- Dexamethasone
- AVOID antibiotics unless clear bacterial infection
- If worsening, baricitinib if HFNC, toci/sarilumab if MV <24h

Steroids

For COVID-19 clinical guidance, visit: asp.mednet.ucla.edu/pages/asp-resources

Summary

- Outpatient treatment: monoclonal antibodies (combo only), trials
- Inpatient treatment if not hypoxic but high risk: Mab
  - May consider checking antibodies to maximize benefit
  - If outside EUA, apply for compassionate use
- Inpatient treatment if hypoxic: RDV + Steroids: BUT send home if better
- Consider baricitnib if worsening and not MV
- Consider sarilumab/tociluzumab if HFNC/MV in ICU
- Plasma? Maybe for patients w BMT/Heme malignancies who are Ab neg
- Remember Fact Sheets for IL6r blockers, baricitinib
- Avoid antibiotics, not needed 99% of the time
- Not discussed: treat pregnant women the same under MFM guidance

Resources

- ASP website: asp.mednet.ucla.edu
- IDSA: https://www.idsociety.org/practice-guideline/covid-19-guideline-treatment-and-management/
- NIH treatment guidelines: https://www.covid19treatmentguidelines.nih.gov/whats-new/