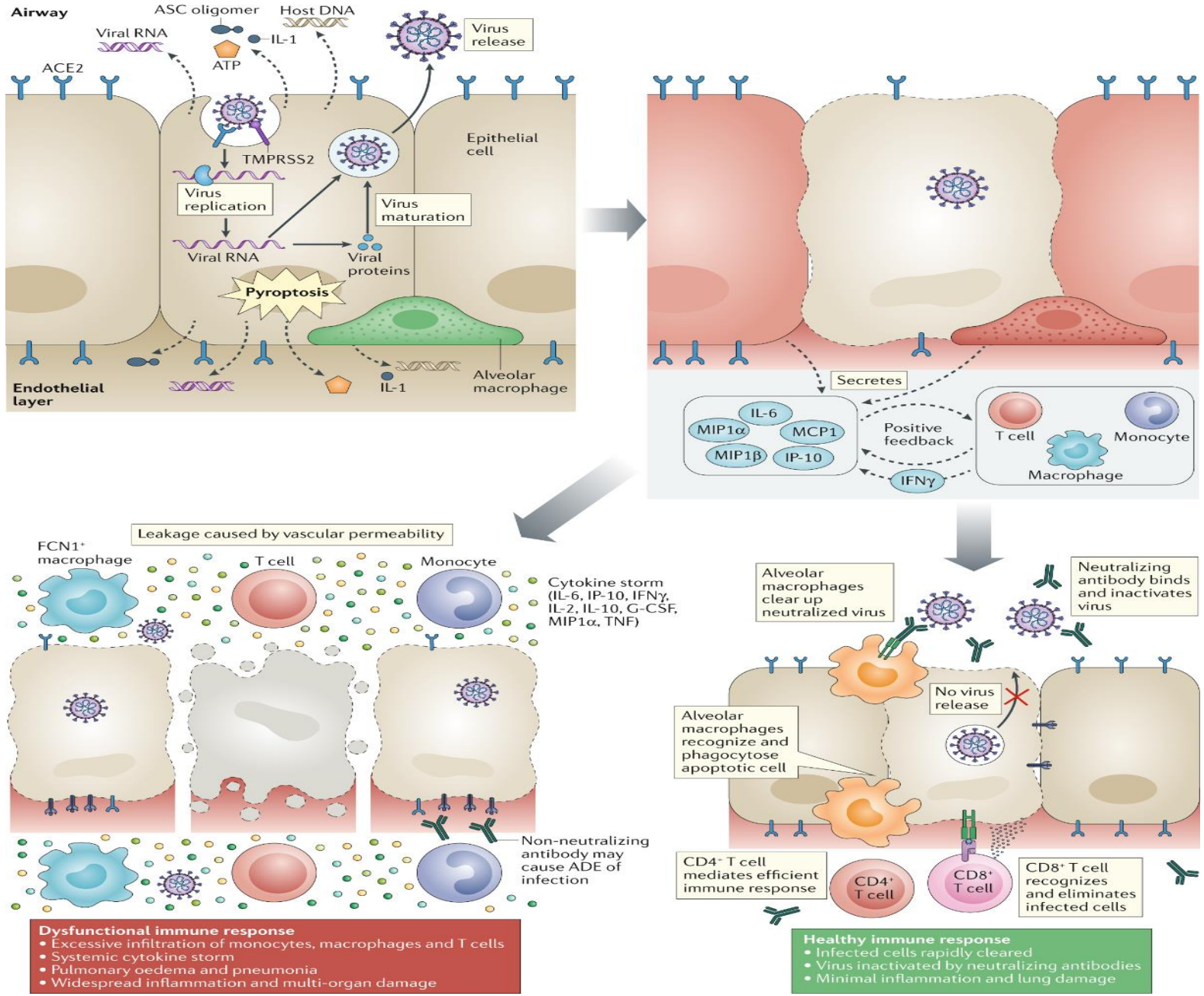
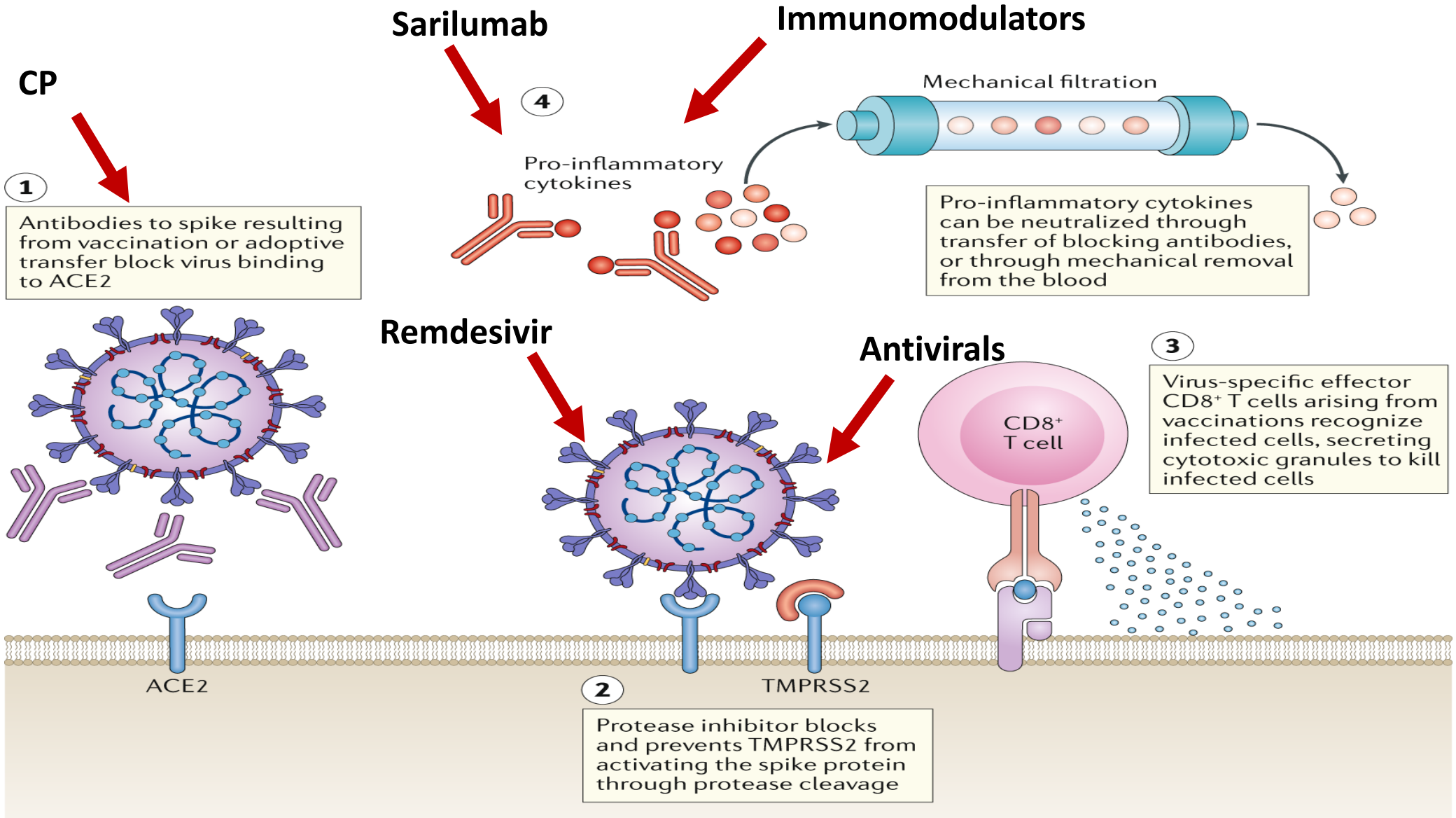
COVID-19 Clinical Trials

Sanjay Sethi MD
Professor and Division Chief
Pulmonary, Critical Care and Sleep Medicine
Assistant Vice President for Health Sciences
Director, Clinical Research office
Deputy Director, Clinical and Translational Science Institute
University at Buffalo, SUNY
ssethi@buffalo.edu

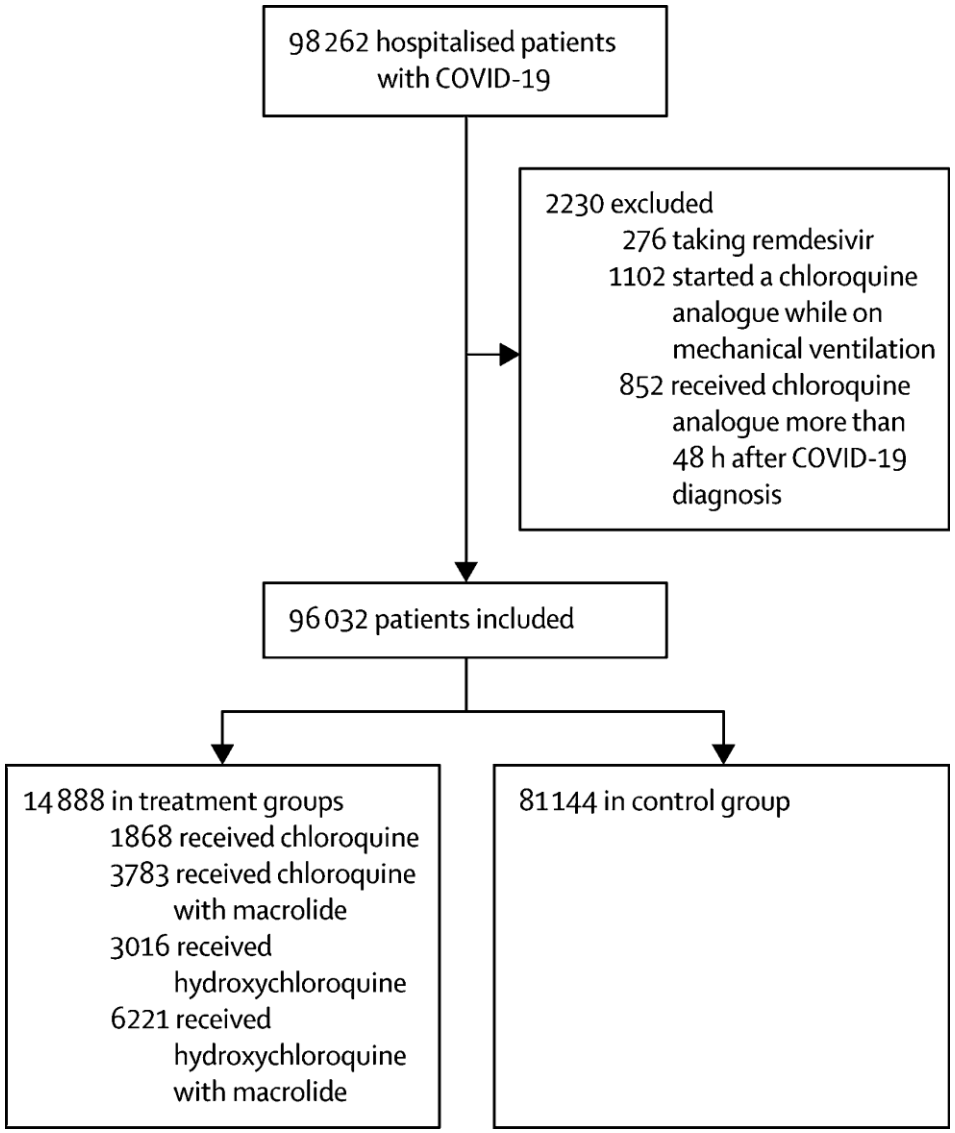
COVID-19 Pathogenesis

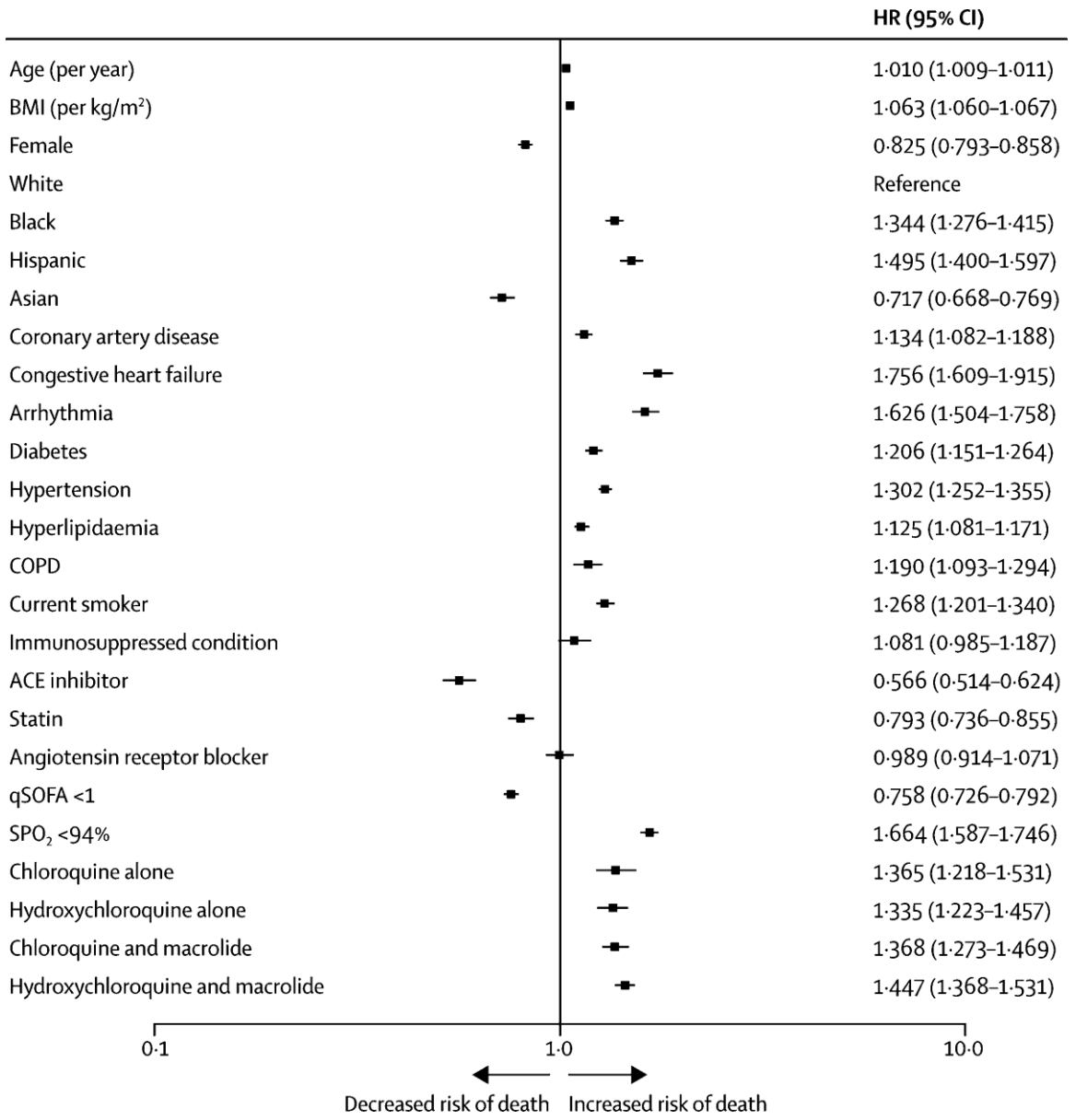


COVID-19 Potential Interventions



Hydroxychloroquine or chloroquine with or without a macrolide for treatment of COVID-19: a multinational registry analysis *M Mehra et al, The Lancet* DOI: 10.1016/S0140-6736(20)31180-6



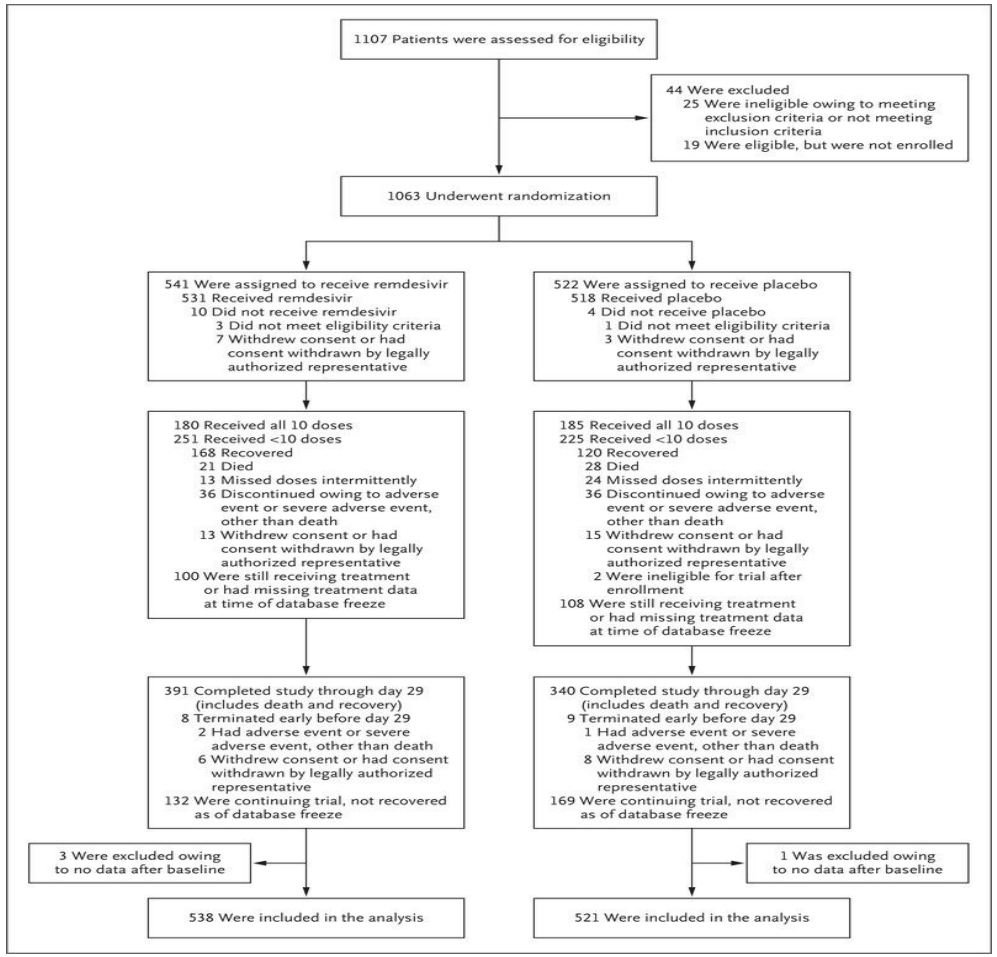


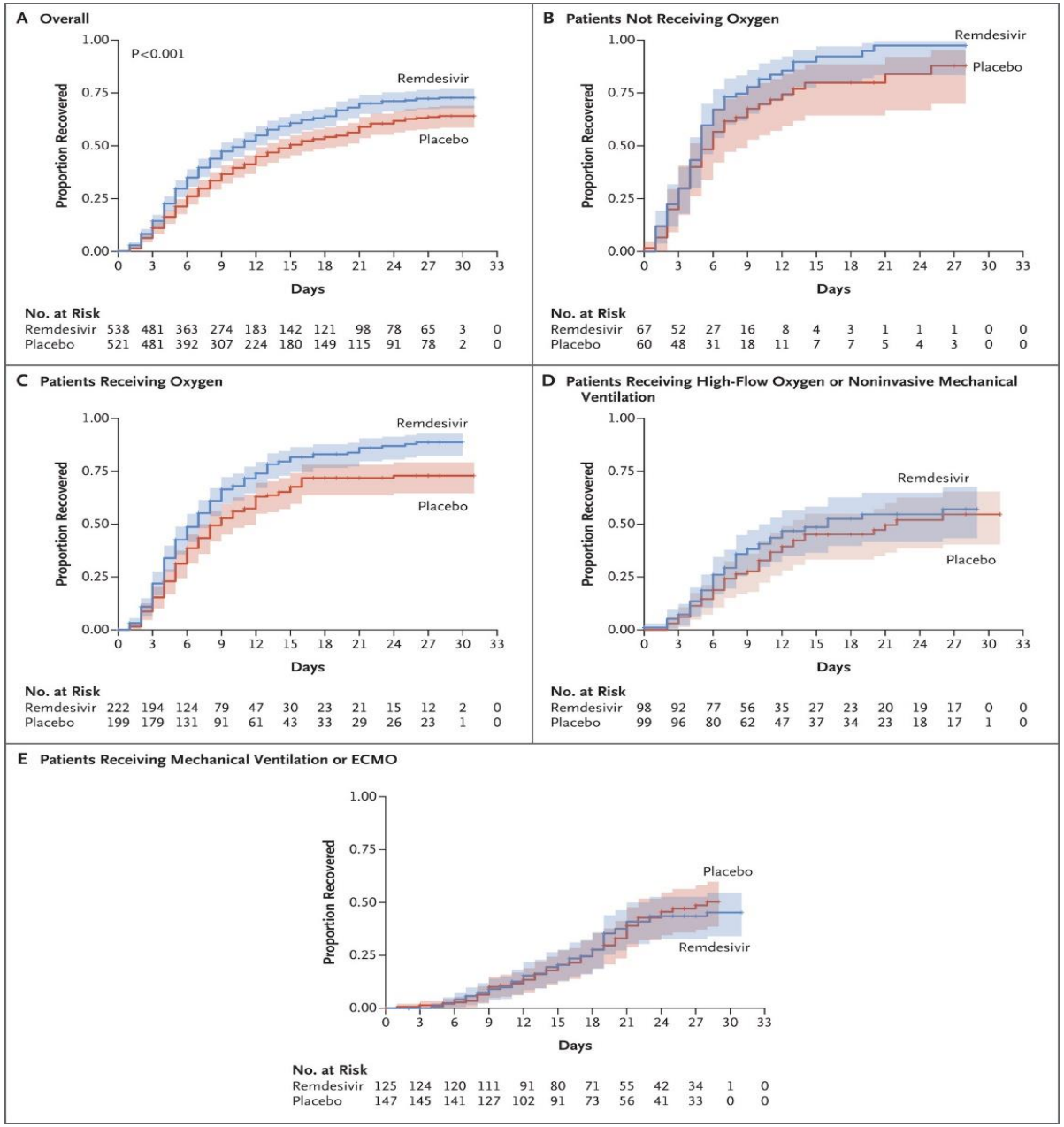
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Remdesivir for the Treatment of Covid-19 — Preliminary Report

J.H. Beigel, K.M. Tomashek, L.E. Dodd, A.K. Mehta, B.S. Zingman, A.C. Kalil,



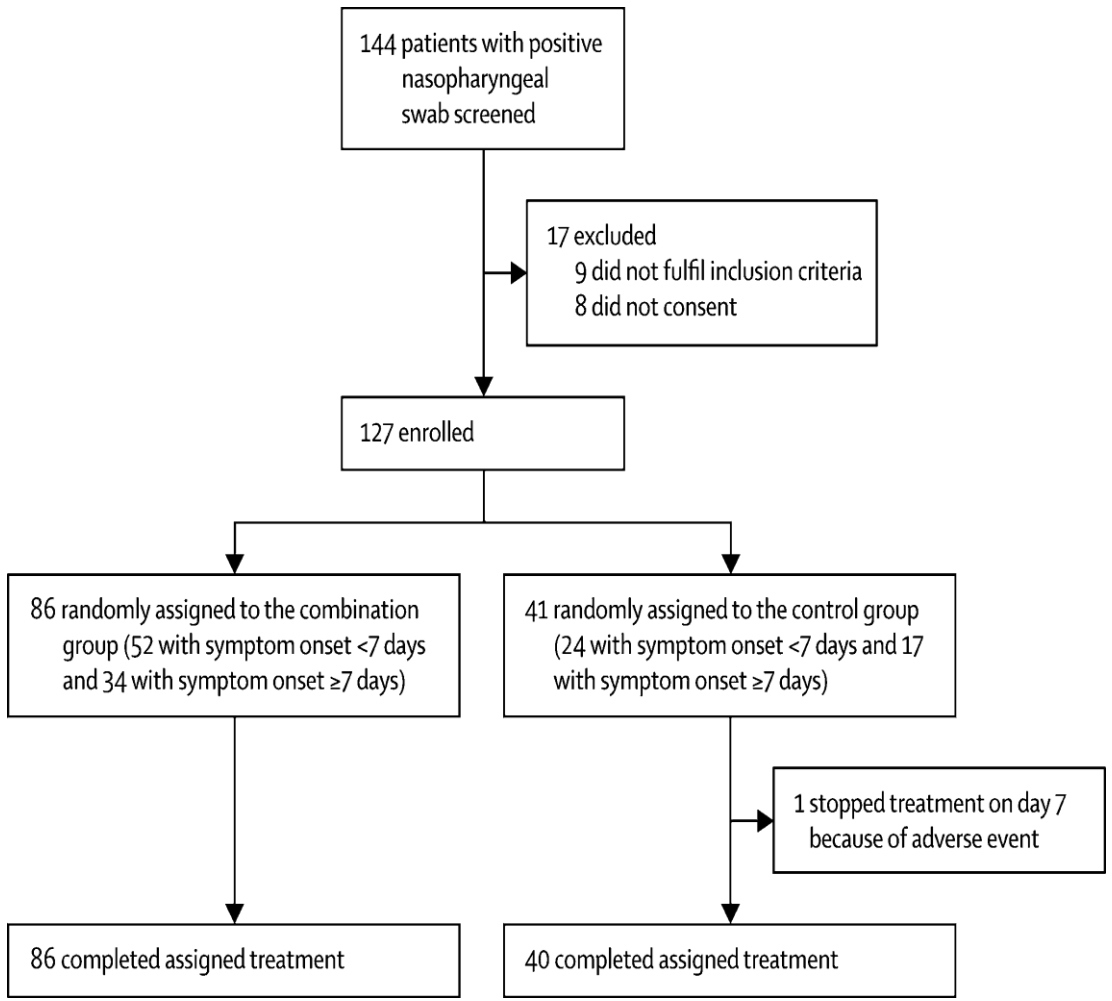


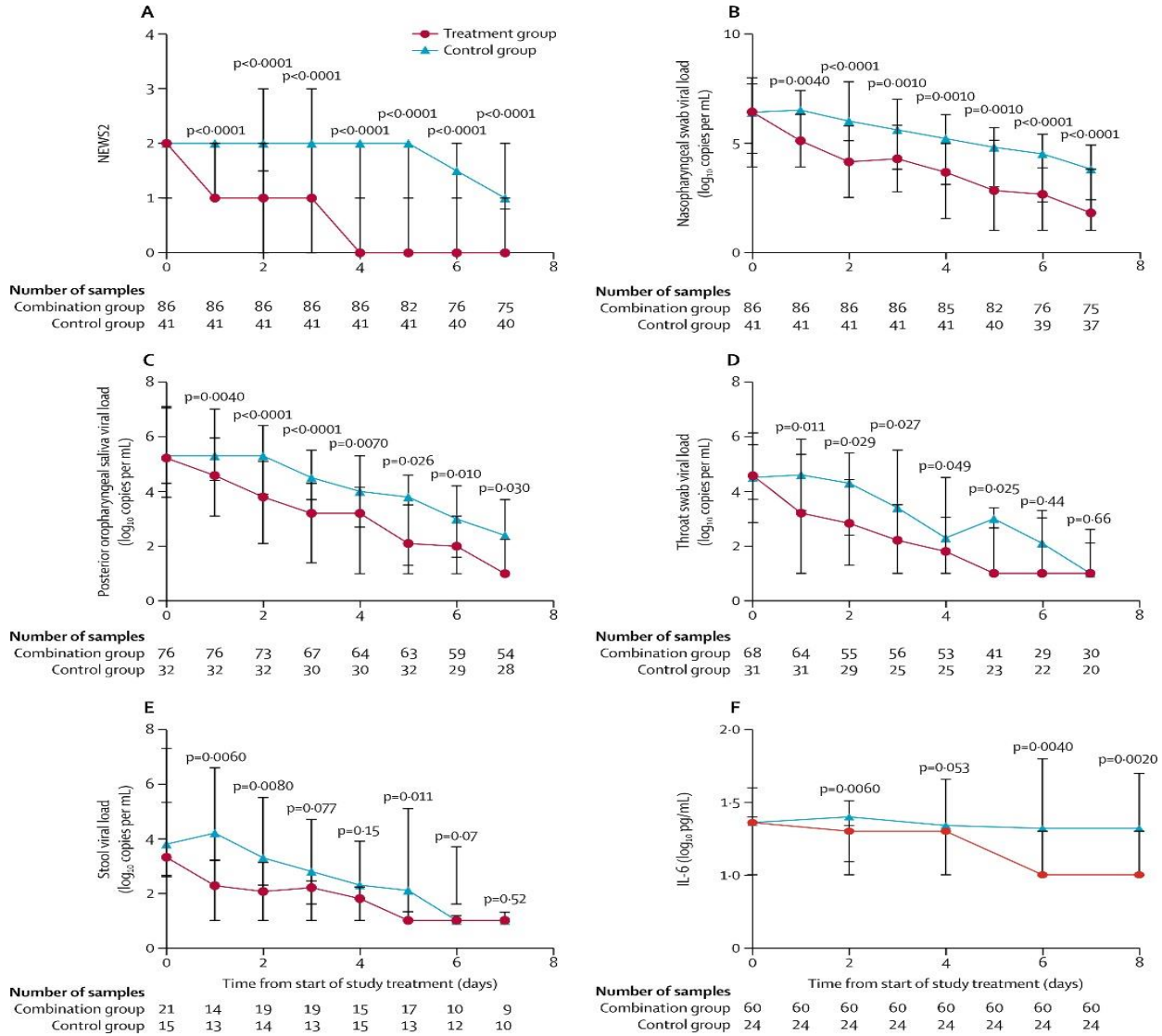
Remdesivir: Local Results

- Expanded access program (EAP)
- N=4
- Baseline severity: All intubated
- Outcomes
  - 1 died
  - 2 extubated
  - 1 intubated

- Emergency use authorization (EUA)
- Gilead donated 144,000 courses of Remdesivir
- Substantial increase in supply
- Can be used in earlier disease

Triple combination of interferon beta-1b, lopinavir–ritonavir, and ribavirin in the treatment of patients admitted to hospital with COVID-19: an open-label, randomised, phase 2 trial *Prof Ivan Fan-Ngai Hung, The Lancet* DOI: 10.1016/S0140-6736(20)31042-4





Convalescent Plasma: Mayo/BARDA Program

Table 1. Patient Characteristics.

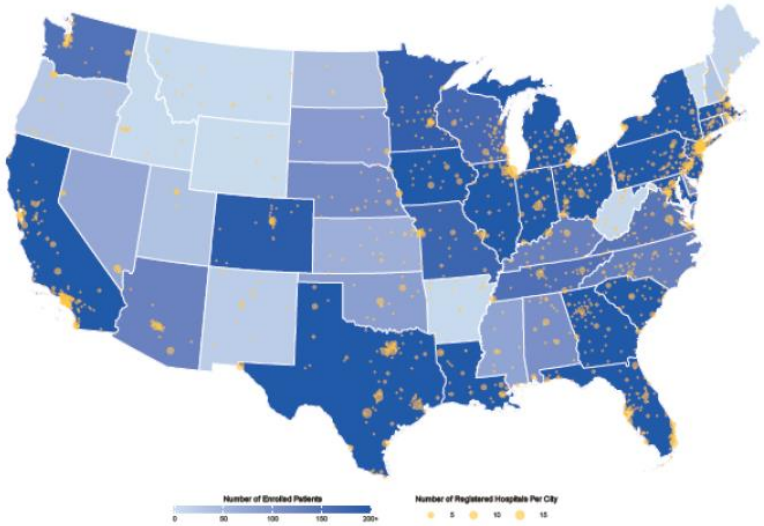
	n = 5,000
Age	
Median (Range)	62.3 (18.5, 97.8)
Gender	
Women	1,824 (36.5%)
Men	3,153 (63.1%)
Intersex or Transgender	17 (0.3%)
Undisclosed	6 (0.1%)
Race	
Asian	317 (6.3%)
American Indian or Alaska Native	40 (0.8%)
Black or African American	915 (18.3%)
White	2,438 (48.8%)
Native Hawaiian or Other Pacific Islander	17 (0.3%)
Multiracial	23 (0.5%)
Other or Unknown	1,250 (24.8%)
Ethnicity	
Hispanic or Latino	1,733 (34.7%)
Not Hispanic or Latino	3,267 (65.3%)
Clinical Status	
Current severe or life-threatening COVID-19	4,051 (81.0%)
High risk of severe or life-threatening COVID-19	949 (19.0%)
Intensive Care Unit (ICU) admission	3,316 (66.3%)
Clinical Symptoms[a]	***n* = 4,051**
Respiratory failure	2,912 (71.9%)
Dyspnea	2,550 (62.9%)
Blood oxygen saturation ≤ 93%	2,519 (62.2%)
Lung infiltrates > 50% within 24 to 48 hours	1,721 (42.5%)
Respiratory frequency ≥ 30/min	1,546 (38.2%)
P_aO_2:F_iO_2 ratio[b] < 300	1,365 (33.7%)
Multiple organ dysfunction or failure	745 (18.4%)
Septic shock	600 (14.8%)

Footnotes

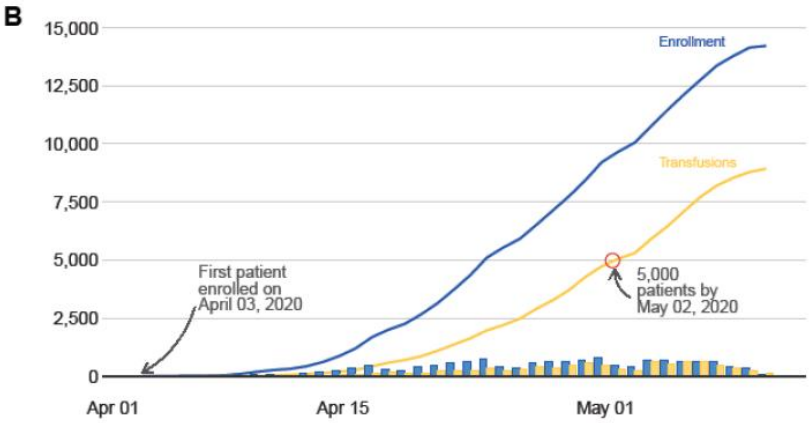
[a]These data include only patients with current severe or life-threatening COVID-19 (*n* = 4,051).

[b]The ratio of partial pressure of arterial oxygen to fraction of inspired oxygen ratio.

A



B



Convalescent Plasma: Safety and ?Efficacy

Table 2. Serious Adverse Event (SAE) Characteristics. (n=5,000)

Four Hour Reports	Reported *(n = 36)*	Related[a] *(n = 25)*	Estimate (95% CI)
Mortality	15	4	0.08% (0.03%, 0.21%)
Transfusion-Associated Circulatory Overload (TACO)	7	7	0.14% (0.07%, 0.29%)
Transfusion-Related Acute Lung Injury (TRALI)	11	11	0.22% (0.12%, 0.39%)
Severe allergic transfusion reaction	3	3	0.06% (0.02%, 0.18%)
Seven Day Reports	**Reported**		**Estimate (95% CI)[b]**
Mortality	602		14.9% (13.8%, 16.0%)

Convalescent Plasma: Safety and ?Efficacy

Convalescent plasma treatment of severe COVID-19: A matched control study

Sean T. H. Liu, M.D., Ph.D., Icahn School of Medicine at Mount Sinai

Supplemental oxygen requirement prior to initiation of transfusion	
Standard nasal cannula – no. (%)	7 (18)
2 liters – no. (%)	0
3 liters – no. (%)	2 (5)
4 liters – no. (%)	2 (5)
≥5 liters – no. (%)	3 (8)
High-flow oxygen, high-flow nasal cannula or BiPAP – no. (%)	27 (69)
Mechanical ventilation – no. (%)	4 (10)

Pharmacologic interventions	**Patients (N = 39)**	**1:4 matching Controls (N=156)**	**1:2 matchin Controls (N=74)**
Antimicrobial agents – no. (%)			
Azithromycin	31 (79)	133 (85)	63 (85)
Broad spectrum antibiotics	29 (74)	112 (72)	57 (77)
Hydroxychloroquine	36 (92)	148 (95)	69 (93)
Investigational antivirals	1 (3)	9 (6)	4 (5)
Therapeutic anticoagulation – no. (%)	26 (67)	64 (41)	32 (43)
Anti-inflammatory agents – no. (%)			
Corticosteroids	22(56)	90 (58)	38 (51)
Interleukin-1 inhibitors	0	0	0
Interleukin-6 inhibitors	3 (8)	13 (8)	6 (8)

Convalescent Plasma: Safety and ?Efficacy

Convalescent plasma treatment of severe COVID-19: A matched control study

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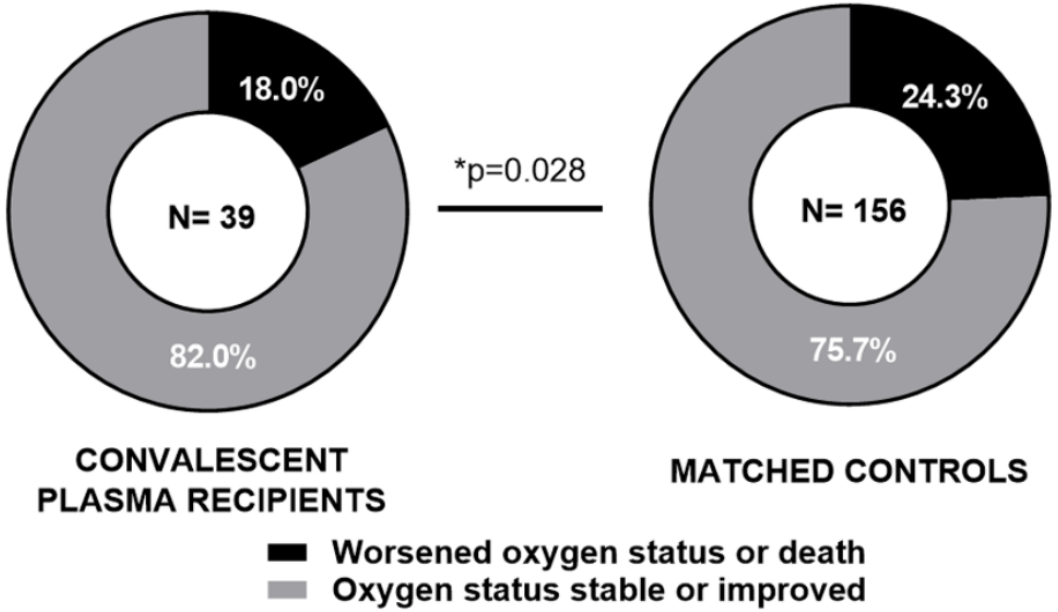
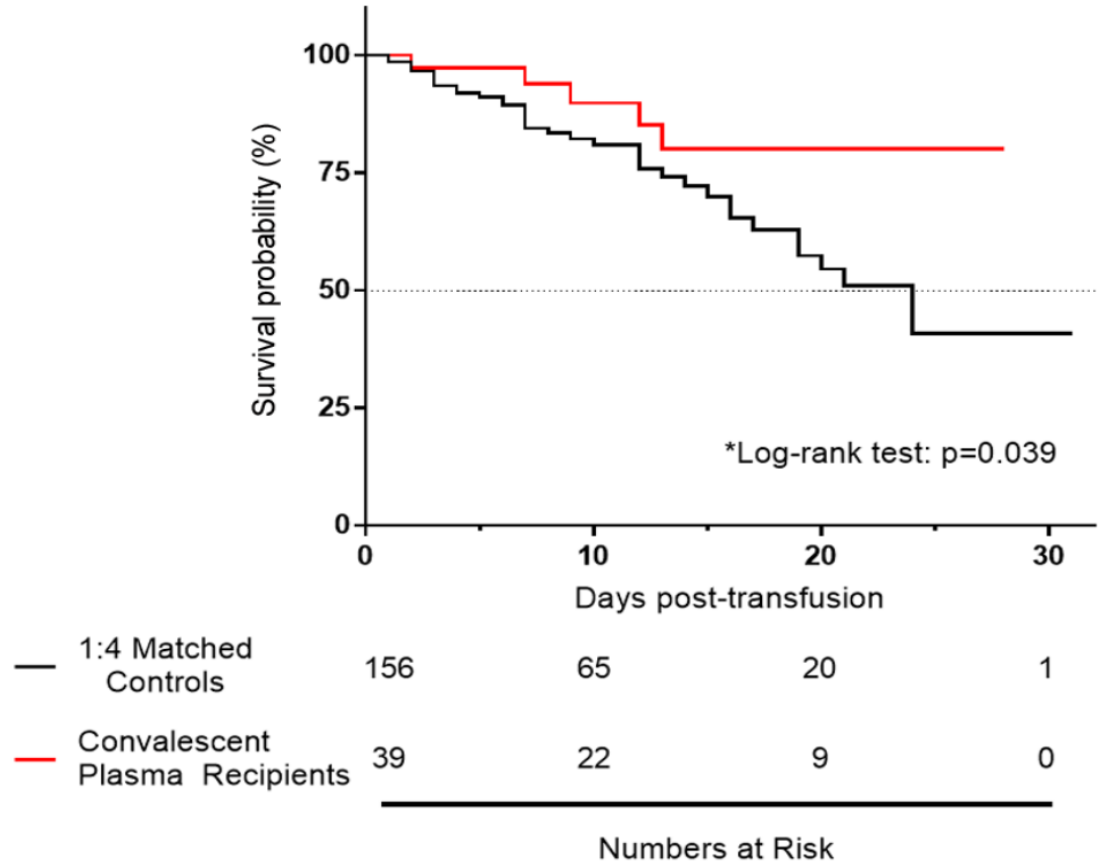
Figure 1. Comparison of oxygen requirements between Day 14 versus Day 0.



*** Covariates adjusted. No significant differences were observed at day 1 (p=0.444) or day 7 (p=0.425).**

Figure 2. Survival Probability



Convalescent plasma; Local Results

Ordinal Scale for Clinical Improvement, 7 Days Post-transfusion			Ordinal Scale for Clinical Improvement, 4 Hours Post-Transfusion					
			Hospitalized, critical, multi-system organ failure	Hospitalized, critical (ICU), on vent, in shock	Hospitalized, critical (ICU), on vent	Hospitalized, critical (ICU), high-flow oxygen	Hospitalized, severe (medical floor)	Hospitalized, mild
			(N=5)	(N=3)	(N=13)	(N=14)	(N=15)	(N=0)
			7	6	5	4	3	2
	Death	8	2 (40%)	1 (33%)	2 (15%)	3 (21.4%)	2 (13.3%)	0
	Hospitalized, critical, multi-system organ failure	7	3 (60%)	0	2 (15%)	0	0	0
	Hospitalized, critical (ICU), on vent, in shock	6	0	0	0	1 (7.1%)	0	0
	Hospitalized, critical (ICU), on vent	5	0	1 (33%)	3 (23%)	3 (21.4%)	0	0
	Hospitalized, critical (ICU), high-flow oxygen	4	0	1 (33%)	3 (23%)	3 (21.4%)	1 (6.7%)	0
	Hospitalized, severe (medical floor)	3	0	0	2 (15%)	3 (21.4%)	9 (60%)	0
	Hospitalized, mild	2	0	0	1 (7.6%)	0	0	0
	Discharged	1	0	0	0	1 (7.1%)	3 (20%)	0
	Improvement		0	2	6	7	3	0

Key	
	Worsened Condition
	No Change
	Improvement

Sarilumab: Anti-IL6 Inhibitor

Regeneron and Sanofi Provide Update on U.S. Phase 2/3 Adaptive-Designed Trial of Kevzara® (sarilumab) in Hospitalized COVID-19 Patients

	Placebo	Kevzara 200 mg	Kevzara 400 mg
PRIMARY ENDPOINT (REDUCTION IN C-REACTIVE PROTEIN)			
	(n=77)	*(n=136)*	*(n=145)*
% change from baseline in CRP (Patients with high baseline IL-6, where data was available)	-21%	-77%	-79%
EXPLORATORY CLINICAL ENDPOINTS IN "CRITICAL" GROUP			
	(n=44)	*(n=94)*	*(n=88)*
Died or "On a ventilator"	24 (55%)	43 (46%)	28 (32%)
Died	*12 (27%)*	*34 (36%)*	*20 (23%)*
On a ventilator	*12 (27%)*	*9 (10%)*	*8 (9%)*
Clinical improvement (Achieved ≥2 point improvement on 7-point scale)[1]	18 (41%)	48 (51%)	52 (59%)
Off oxygenation	18 (41%)	40 (43%)	51 (58%)
Discharged	18 (41%)	37 (39%)	47 (53%)

1. 7-point scale consists of: 1) death; 2) hospitalized, requiring invasive mechanical ventilation or extracorporeal membrane oxygenation (ECMO); 3) hospitalized, requiring non-invasive ventilation or high flow oxygen devices; 4) hospitalized, requiring supplemental oxygen; 5) hospitalized, not requiring supplemental oxygen – requiring ongoing medical care (COVID-19 related or otherwise); 6) hospitalized, not requiring supplemental oxygen – no longer requires ongoing medical care; 7) discharged from hospital.

Sarilumab: Local Results

- 18 patients randomized
- 17 of 18 were intubated at baseline
- MFS: 6 patients
  - 4 discharged, 2 died
- ECMC: 8 patients
  - 1 discharged, 7 still intubated
- BGH: 4 patients
  - 3 discharged, 1 died

New Trials

- Apellis

APL9-COV-201

A RANDOMIZED, DOUBLE-BLIND, VEHICLE-CONTROLLED, MULTICENTER, PARALLEL-GROUP STUDY OF APL-9 IN MILD TO MODERATE ACUTE RESPIRATORY DISTRESS SYNDROME DUE TO COVID-19

- Covis

A Phase 3, Multicenter, Randomized, Double-Blind, Placebo-Controlled Study to Assess the Safety and Efficacy of Ciclesonide Metered-Dose Inhaler in Non-Hospitalized Patients 12 Years of Age and Older With Symptomatic COVID-19 Infection

Planned Trials

- **Adjunctive Photobiomodulation (PBM) treatment to prevent progression of COVID-19 in hospitalized patients.**
  - Arany and Sethi co-PIs
- **A Pilot Randomized, Double-Blind, Placebo-Controlled Clinical Trial of the Safety and Efficacy of Melatonin for the Treatment of COVID-19 in OutPatients**
  - Dubocovich and Sethi co-PIs
- **The use of non-specific HOST protective effects of oral polio vaccine to prevent COVID-19 (SHIELD Trial)**
  - Morse, Hicar, Gomez co-Is

Trials Being Considered

- Monoclonal antibodies for prophylaxis
- Monoclonal antibodies for treatment
- Immunomodulation
- Vaccine trials

- Need Investigators
- Need Research coordinators
- ‘With challenges, come opportunities’

COVID: Multimodality Therapy

- Prevention
  - Vaccination
  - Control Risk Factors
  - Immune enhancement (Vitamin D)
  - Monoclonal antibodies
- Outpatient
  - Antiviral (Ivermectin)
  - Immunomodulation (Melatonin, Ciclesonide)
  - ?Convalescent plasma
  - ?Monoclonal Antibodies
- Inpatient
  - Antiviral
  - Convalescent plasma
  - Immunomodulation
  - Block cytokine storm

Acknowledgements

- Clinical Research Office
  - Pam Anderson
  - Kim Brunton
  - Lynn Jagodzinski
  - Conor Flynn
- CTSA
  - Tim Murphy
- Office Of Research Compliance
  - Rich Karalus
  - Stan Halverson
- Kaleida Health
  - Ken Snyder
  - Ashlee Lang
- ECMC
  - Brian Murray
  - Sally Algera
- Investigators
  - Jamie Nadler
  - Manoj Mammen
  - John Crane
  - Joseph Izzo
  - Kim Zammit
  - Carla Frederick
  - Alberto Monegro
  - Karin Provost
  - Archana Mishra
  - Brian Clemency
- Research coordinators
  - Catherine Wrona
  - Ryan Haley
  - Judith Wilkins
  - Nancy Desu
  - Deanna Coleman
  - Chris Roach
- RPCCC Donor Center
  - Joanne Becker
  - Maria Turner
- JSMBS
  - Daniel Zinkovsky (MS3)