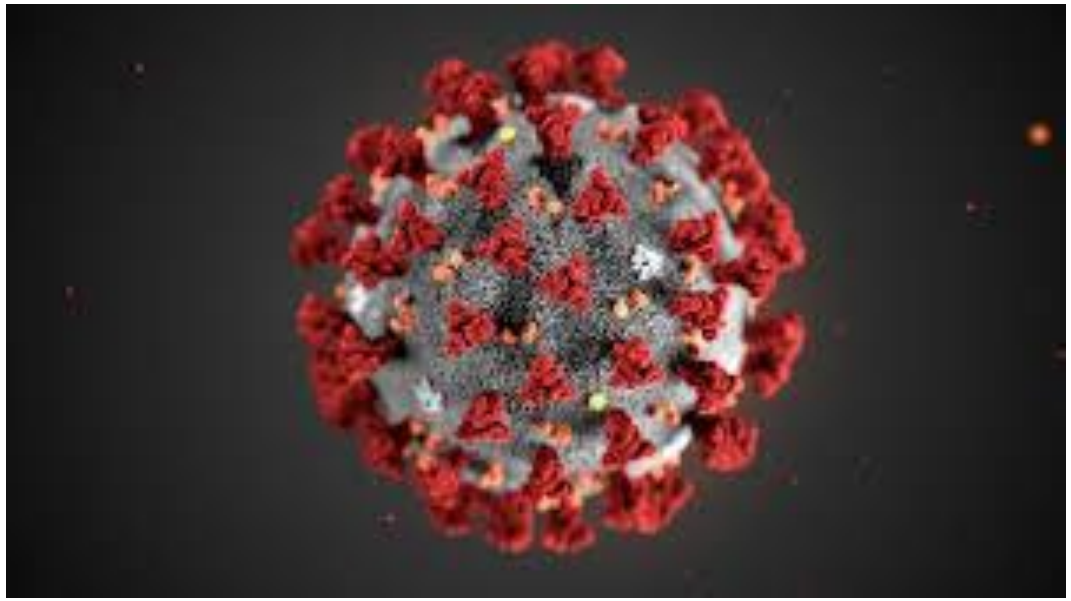
COVID-19 Therapeutics



Dave Dobrzynski Jr., MD

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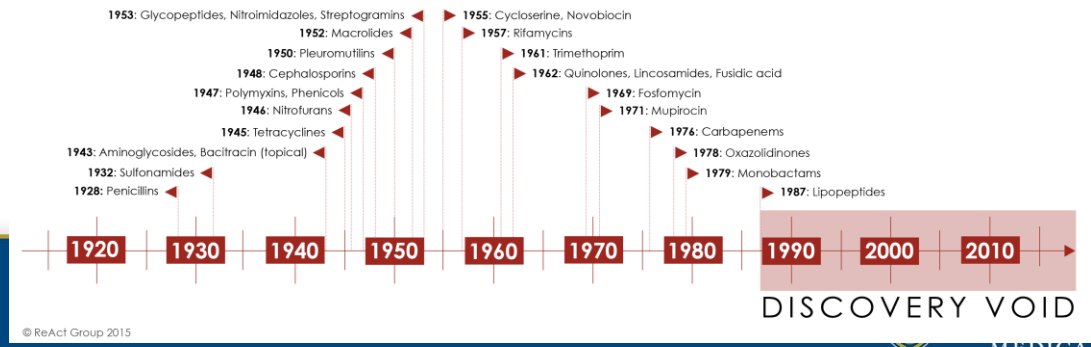
Outline

- What is antimicrobial stewardship?
- How has antimicrobial stewardship been involved in COVID-19 pandemic?
- What therapeutic options are available for COVID-19?
- What does the future of COVID-19 therapeutics hold?

Antimicrobial Stewardship

- Antibiotics have truly transformed medicine over the last century
- CDC estimates ~30% of all antibiotics are unnecessary or suboptimal
- Rise in resistance along with lack of antimicrobial development has driven this divide further

Antibiotic Approved or Released	Year Released	Resistant Germ Identified	Year Identified
Penicillin	1943	Penicillin-resistant *Streptococcus pneumoniae*[9,10]	1967
		Penicillinase-producing *Neisseria gonorrhoeae*[11]	1976
Vancomycin	1958	Plasmid-mediated vancomycin-resistant *Enterococcus faecium*[12,13]	1988
		Vancomycin-resistant *Staphylococcus aureus*[14]	2002
Amphotericin B	1959	Amphotericin B-resistant *Candida auris*[15]	2016
Methicillin	1960	Methicillin-resistant *Staphylococcus aureus*[16]	1960
Extended-spectrum cephalosporins	1980 (Cefotaxime)	Extended-spectrum beta-lactamase- producing *Escherichia coli*[17]	1983
Azithromycin	1980	Azithromycin-resistant *Neisseria gonorrhoeae*[18]	2011
Imipenem	1985	*Klebsiella pneumoniae* carbapenemase (KPC)-producing *Klebsiella pneumoniae*[19]	1996
Ciprofloxacin	1987	Ciprofloxacin-resistant *Neisseria gonorrhoeae*[20]	2007
Fluconazole	1990 (FDA approved)	Fluconazole-resistant *Candida*[21]	1988
Caspofungin	2001	Caspofungin-resistant *Candida*[22]	2004
Daptomycin	2003	Daptomycin-resistant methicillin-resistant *Staphylococcus aureus*[23]	2004
Ceftazidime-avibactam	2015	Ceftazidime-avibactam-resistant KPC-producing *Klebsiella pneumoniae*[24]	2015



Antimicrobial Resistance

- CDC has had call to action with 4 core actions:
    1. Preventing infections and spread of resistance
    2. Tracking resistant bacteria
    3. Improving the use of today's antibiotics
    4. Promoting the development of new antibiotics and new diagnostic tests for resistant bacteria

- On Feb 2nd, 2015, President Obama released fiscal budget for 2016 which included $1.2 billion to be allocated to improving antibiotic stewardship, strengthening risk assessment and reporting, and promoting research in health and agricultural sectors

Courtesy of Global Alliance for Infections in Surgery

Antimicrobial Stewardship Programs (ASPs)

- First described in 1996 by two Emory physicians(John McGowan and Dale Gerding)
  - Suggested “large scale, well controlled trials of antimicrobial use regulation…to determine the best methods to prevent and control this problem(antimicrobial resistance)”

- In 1997, SHEA and IDSA published first guidelines to prevent antimicrobial resistance

- In 2014, CDC recommended that all US hospitals have an antimicrobial stewardship program

- On January 1st, 2017, Joint Commission approved regulations that hospitals should have an Antimicrobial Stewardship team

What do ASPs do?

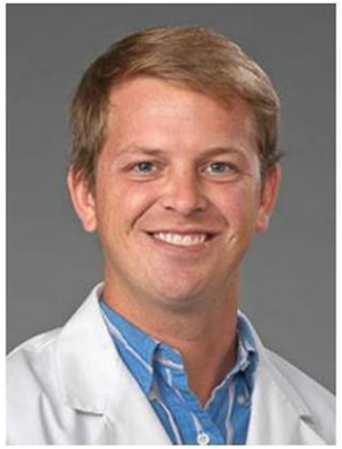
1. **Optimize** the treatment of infections
2. **Reduce** adverse events associated with antibiotic use
3. **Help** clinicians improve quality of patient care
4. **Improve** patient safety through increase cure rates, reduced treatment failures, and increased frequency of correct prescribing
5. **Cut** hospital rates of C. diff and antibiotic resistance

Core Principles of ASP

- **Leadership Commitment:** Dedicating necessary human, financial, and information technology resources.
- **Accountability:** Appointing a single leader responsible for program outcomes. Experience with successful programs shows that a physician leader is effective.
- **Drug Expertise:** Appointing a single pharmacist leader responsible for working to improve antibiotic use.
- **Action:** Implementing at least one recommended action, such as systemic evaluation of ongoing treatment need after a set period of initial treatment (e.g., an “antibiotic time out” after 48 hours).
- **Tracking:** Monitoring antibiotic prescribing and resistance patterns.
- **Reporting:** Regular reporting of information on antibiotic use and resistance to doctors, nurses, and relevant staff.
- **Education:** Educating clinicians about resistance and optimal prescribing

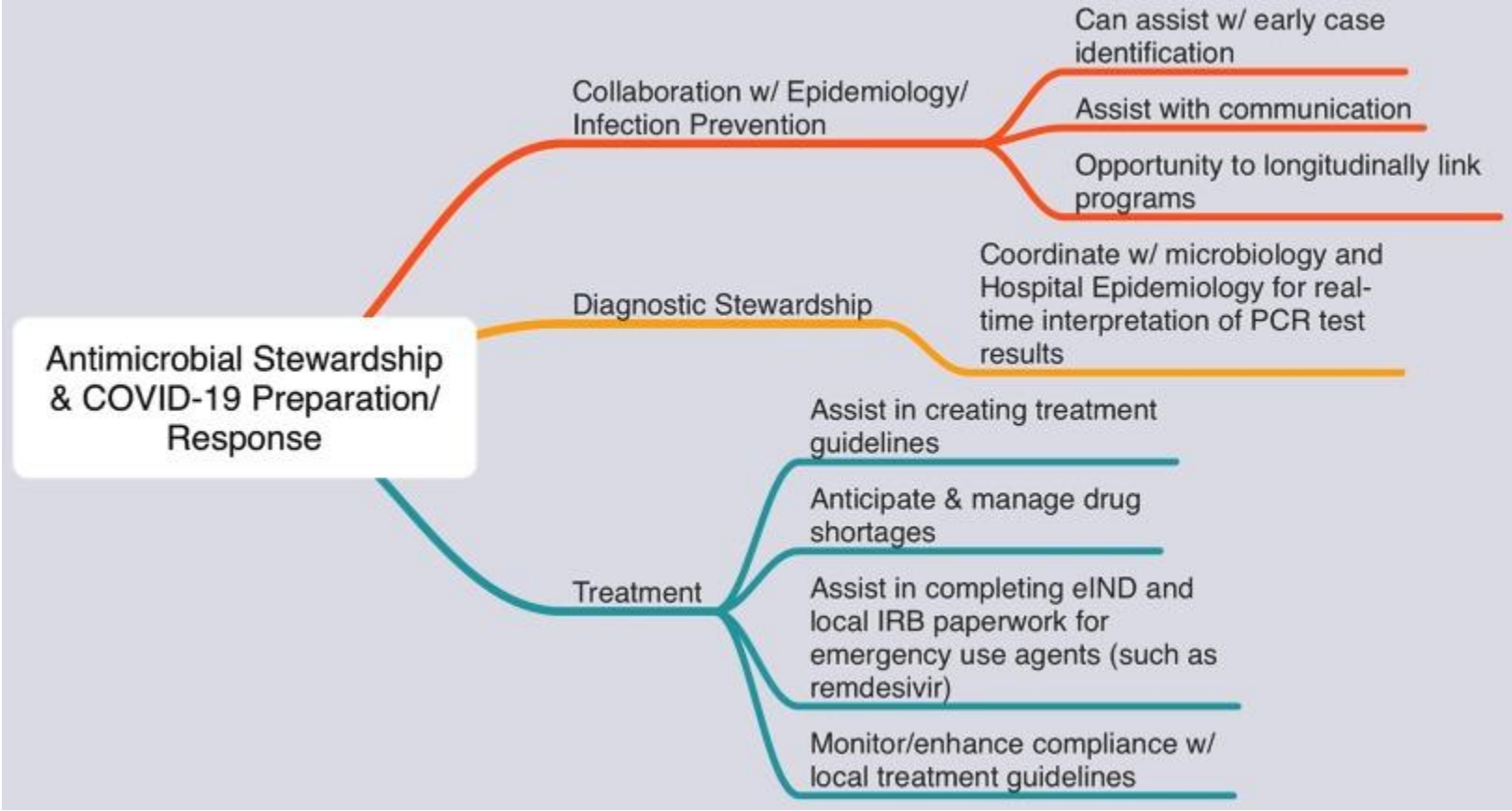
University of Rochester ASP Team

- Dr. Dave Dobrzynski, MD
- Dr. Paul Graman, MD
- Dr. Brenda Tesini, MD



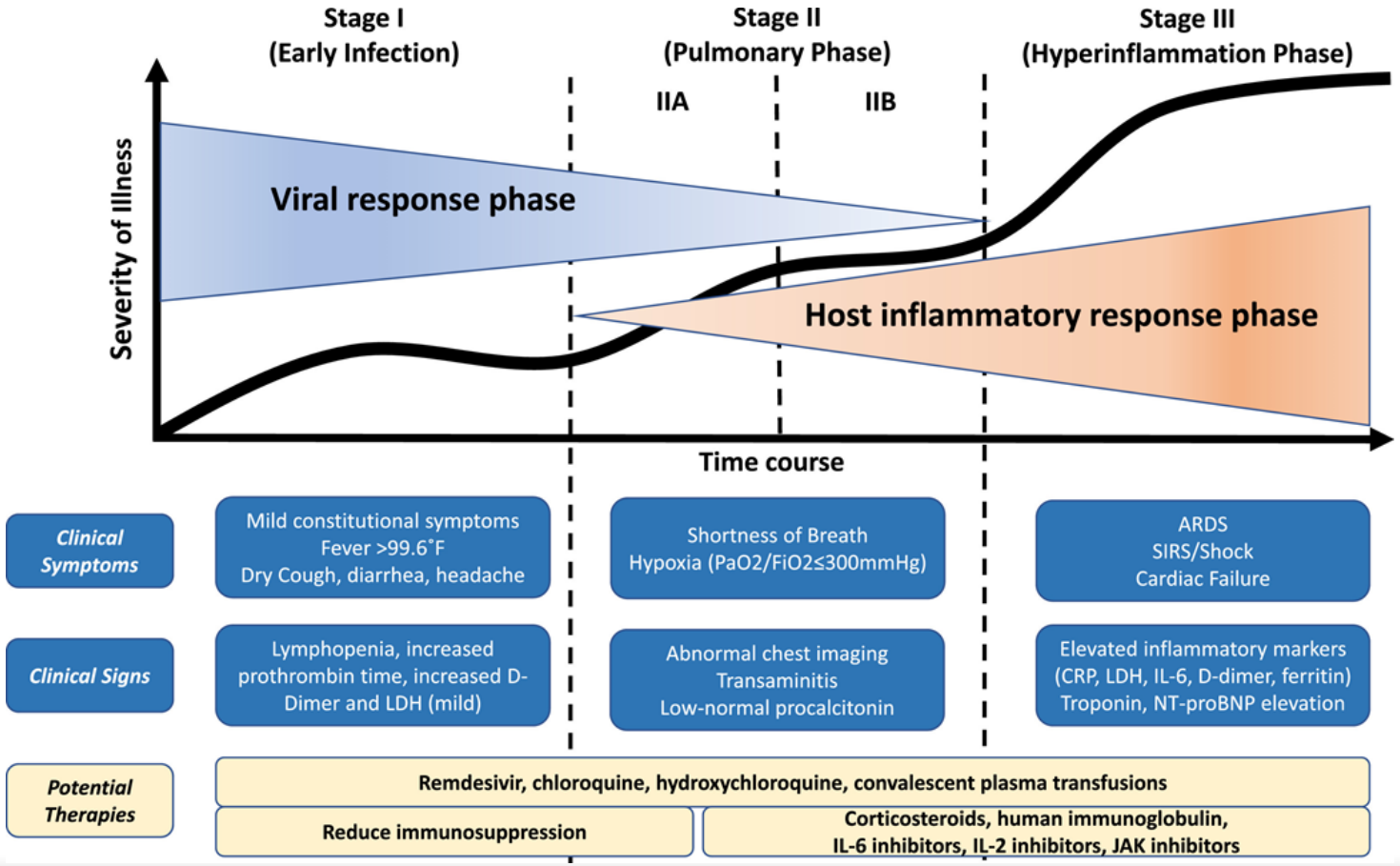
- Stephanie Shulder, PharmD
- Kelly Pillinger, PharmD
- Kate Quartuccio, PharmD (Highland)


How are ASPs equipped to help with COVID-19 Pandemic?



Nori P, et al. Involving antimicrobial stewardship programs in COVID-19 response efforts: All hands on deck. *Infect Control Hosp Epidemiol* 2020: March 13: 1-2

COVID-19: Clinical Therapeutic Staging



The Journal of Heart and Lung Transplantation DOI: (10.1016/j.healun.2020.03.012)

Early Therapeutics-Spring 2020

- Hydroxychloroquine
- Lopinavir/ritonavir (Kaletra)
- Tocilizumab

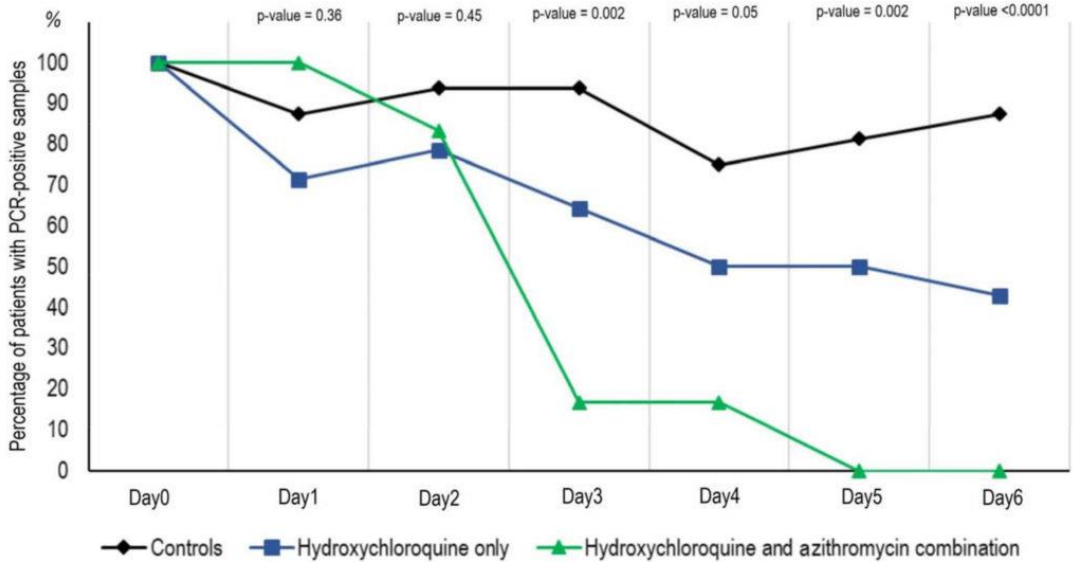
Chloroquine/Hydroxychloroquine

- FDA approved for treatment of SLE, RA, and malaria
- Early studies by Chinese researchers found viral replication inhibition and good penetration into lung tissues
  - Increases endosomal pH and interferes with the glycosylation of cellular receptor of SARS-CoV2 (ACE2)
- Gao and colleagues stated that in 100 patients treated in China, chloroquine was superior to placebo
  - Decreased exacerbation of pneumonia
  - Improved lung imaging findings
  - Promoted a virus negative conversion
  - Shortened the disease course

Gao et al Biosci Trends doi: 10.5582/bst.2020.01047
Zhonghua et al doi: 10.3760/cma.j.issn.1001-0939.2020.03.009
Colson et al Int J of Antimicrob Agents doi: 10.1016/j.ijantimicag.2020.105932
Corgegiani J of Crit Care doi:10.1016/j.jcrc.2020.03.0050
Yao et al. CID doi: 10.1093/cid/ciaa237

Hydroxychloroquine/azithromycin combination

- Study by Didier Raoult studied 36 patients
  - 16 controls
  - 14 HCQ
  - 6 HCQ + Azithromycin
- Conclusion suggested synergistic effect
- Caveats: Groups not balanced!, PCR – only results, no clinical data



Raoult Int J of Antimicrob Agents doi: 10.1016/j.ijantimicag.2020.105959

Supplementary Table 1.

Patient	Age (years)	Sex	Clinical status	Time between onset of symptoms and inclusion (days)	Hydroxychloroquine treatment	Hydroxychloroquine serum concentration µg/ml (day of dosage)	Azithromycin treatment	D0	D1	D2	D3	D4	D5	D6
1	10	M	Asymptomatic	-	No	-	No	31	NEG	NEG	NEG	NEG	NEG	NEG
2	12	F	Asymptomatic	-	No	-	No	26	ND	33	34	NEG	34	NEG
3	14	F	Asymptomatic	-	No	-	No	26	31	23	22	27	NEG	26
4	10	M	Asymptomatic	-	No	-	No	24	NEG	33	33	NEG	NEG	32
5	20	M	URTI	4	No	-	No	24	24	24	27	NEG	31	29
6	65	F	URTI	2	No	-	No	POS	ND	POS	ND	POS	ND	POS
7	46	M	URTI	Unknown	No	-	No	28	ND	ND	ND	26	ND	30
8	69	M	LRTI	2	No	-	No	POS	ND	POS	ND	POS	POS	POS
9	62	F	LRTI	10	No	-	No	POS	ND	POS	ND	POS	ND	POS
10	66	F	URTI	0	No	-	No	POS	ND	POS	ND	ND	ND	POS
11	75	F	URTI	3	No	-	No	POS	ND	POS	ND	POS	ND	ND
12	23	F	URTI	5	No	-	No	ND	ND	POS	ND	POS	ND	ND
13	45	F	URTI	Unknown	No	-	No	POS	ND	POS	ND	POS	ND	POS
14	16	M	URTI	2	No	-	No	POS	ND	POS	ND	ND	POS	ND
15	42	F	URTI	5	No	-	No	ND	ND	ND	POS	ND	POS	ND
16	23	F	URTI	6	No	-	No	POS	ND	ND	ND	ND	POS	ND
17	44	F	URTI	6	Yes	0.519 (D6)	No	30	ND	29	26	32	26	31
18	54	M	Asymptomatic	-	Yes	0.462 (D6)	No	29	NEG	NEG	NEG	NEG	NEG	NEG
19	25	M	URTI	3	Yes	0.419 (D6)	No	23	25	28	25	NEG	NEG	NEG
20	59	F	Asymptomatic	-	Yes	0.288 (D4)	No	30	NEG	NEG	NEG	NEG	NEG	NEG
21	49	F	URTI	1	Yes	0.621 (D6)	No	34	27	19	16	34	24	22
22	24	F	URTI	10	Yes	0.723 (D6)	No	28	NEG	32	34	NEG	NEG	NEG
23	81	F	LRTI	2	Yes	0.591 (D6)	No	22	21	30	NEG	32	28	NEG
24	85	F	LRTI	1	Yes	0.619 (D6)	No	17	21	23	21	26	24	24
25	40	M	URTI	3	Yes	0.418 (D6)	No	22	ND	28	21	15	20	17
26	53	M	URTI	5	Yes	0.515 (D6)	No	27	28	32	31	NEG	NEG	NEG
27	63	F	URTI	8	Yes	0.319 (D4)	No	34	NEG	30	NEG	NEG	NEG	NEG
28	42	F	URTI	1	Yes	0.453 (D6)	No	19	16	17	17	19	20	31
29	87	F	URTI	5	Yes	0.557 (D6)	No	25	30	NEG	NEG	NEG	ND	ND
30	33	M	URTI	2	Yes	0.194 (D2)	No	15	23	26	26	NF	32	32
31	53	F	LTRI	7	Yes	1.076 (D6)	Yes	28	31	34	NEG	34	NEG	NEG
32	48	M	URTI	2	Yes	0.57 (D6)	Yes	23	29	29	NEG	NEG	NEG	NEG
33	50	F	LRTI	5	Yes	0.827 (D6)	Yes	30	27	NEG	NEG	NEG	NEG	NEG
34	20	M	URTI	2	Yes	0.381 (D6)	Yes	27	31	29	NEG	NEG	NEG	NEG
35	54	M	LRTI	6	Yes	0.366 (D4)	Yes	24	ND	ND	29	NEG	NEG	NEG
36	60	M	LRTI	4	Yes	0.319 (D4)	Yes	29	31	31	NEG	NEG	NEG	NEG

URTI: upper tract respiratory infection, LRTI: lower tract respiratory infection, POS: positive PCR, NEG: negative PCR (CT value ≥35), ND: PCR not done

Controls

HCQ

HCQ + Azithro

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Observational Study of Hydroxychloroquine in Hospitalized Patients with Covid-19

Joshua Geleris, M.D., Yifei Sun, Ph.D., Jonathan Platt, Ph.D., Jason Zucker, M.D., Matthew Baldwin, M.D., George Hripcsak, M.D., Angelena Labella, M.D., Daniel K. Manson, M.D., Christine Kubin, Pharm.D., R. Graham Barr, M.D., Dr.P.H., Magdalena E. Sobieszczyk, M.D., M.P.H., and Neil W. Schluger, M.D.

- Observational study in a large NYC medical center
- 1376 consecutive patients were observed with 811 (58.9%) receiving HCQ
- End point was composite of intubation or death
- No significant association between HCQ use and decrease in intubation or death (HR 1.04, CI 0.82-1.32)

N Engl J Med. 2020 Jun 18;382(25):2411-2418. doi: 10.1056/NEJMoa2012410

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

A Randomized Trial of Hydroxychloroquine as Postexposure Prophylaxis for Covid-19

D.R. Boulware, M.F. Pullen, A.S. Bangdiwala, K.A. Pastick, S.M. Lofgren, E.C. Okafor, C.P. Skipper, A.A. Nascene, M.R. Nicol, M. Abassi, N.W. Engen, M.P. Cheng, D. LaBar, S.A. Lother, L.J. MacKenzie, G. Drobot, N. Marten, R. Zarychanski, L.E. Kelly, I.S. Schwartz, E.G. McDonald, R. Rajasingham, T.C. Lee, and K.H. Hullsiek

- Randomized, double-blind, placebo controlled trial in US and Canada
- Household or occupational high risk exposure in 821 patients
- No difference in new illness in HCQ vs placebo (11.8% vs 14.3%)
- Higher side effects in HCQ vs placebo (40.1% vs 16.8%)

N Engl J Med. 2020 Aug 6;383(6):517-525. doi: 10.1056/NEJMoa2016638

Lopinavir/ritonavir (Kaletra)

- Anti-retroviral drug for HIV/AIDS
  - Boosted protease inhibitor
- Cao et al conducted randomized-controlled, open label trial of 199 patients
  - 14 days of Lpv/r vs SOC
  - Primary outcome: 2 point change in time to clinical improvement on 7 point ordinal scale* or live discharge
- No difference in Time to Clinical Improvement
  - M-ITT (excluding 3 early deaths) showed modest improvement 15 vs 16 days
  - ~22% mortality!

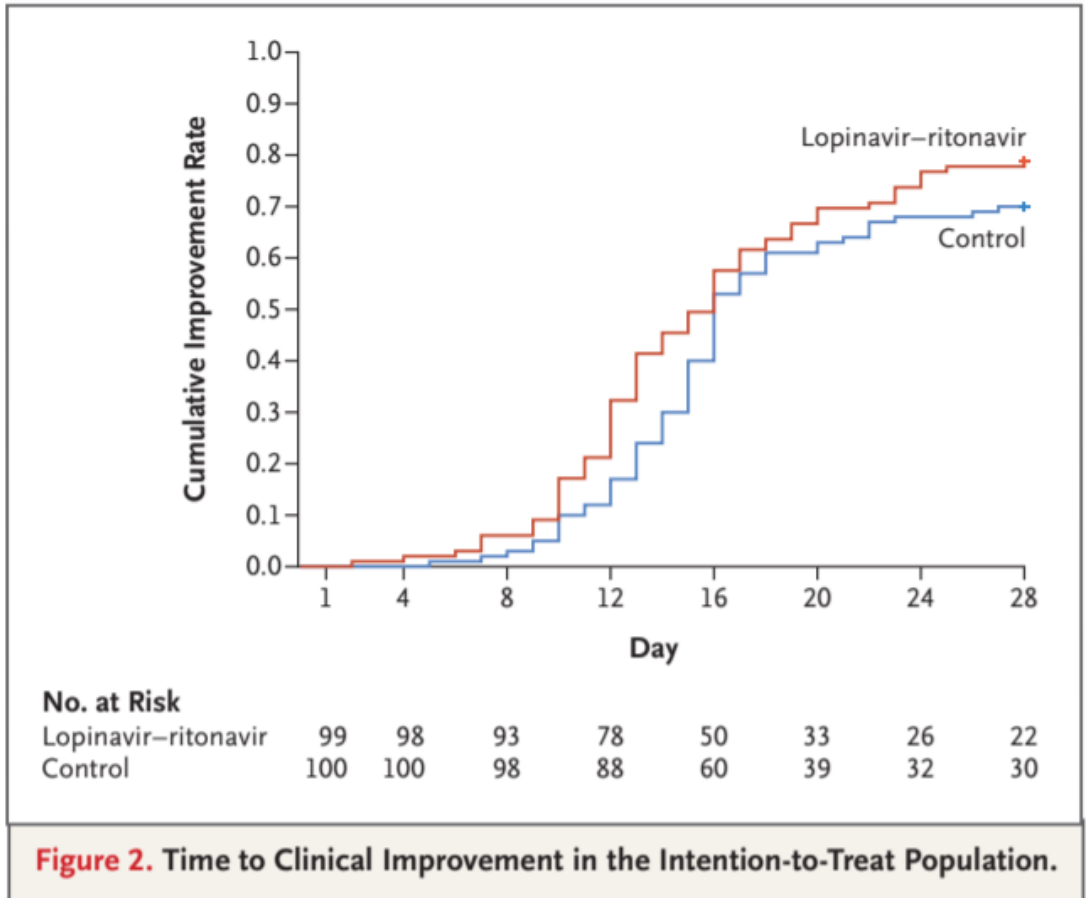


Figure 2. Time to Clinical Improvement in the Intention-to-Treat Population.

*Used in previous influenza studies

Cao B, Wang Y, Wen D, et al. A trial of lopinavir-ritonavir in adults hospitalized with severe Covid-19. N Engl J Med. March 18, 2020. DOI: 10.1056/NEJMoa2001282

Tocilizumab (Actemra)

- Used as immunomodulatory agent for RA, JIA, giant cell arteritis, and cytokine storm
  - Binds to soluble and membrane bound IL6 receptors inhibiting pro-inflammatory effects

- On March 6th, China included Tocilizumab in treatment guidelines for severe complications

- Since then there have been case series detailing possible benefit in cytokine storm

Luo P., et al. J Med Virol. 2020 Jul;92(7):814-818. doi: 10.1002/jmv.25801. Epub 2020 Apr 15.

Tocilizumab

- Early observational data showed possible promise
- More recent RCT's shed some doubt as all did not meet efficacy endpoint of 28 or 30 d mortality
  - Only 2 met efficacy of survival without non-invasive or mechanical ventilation
- Recent RCT from Mass Gen revealed no difference in prevention of intubation or death

Table. Comparison of Major Tocilizumab COVID-19 Studies Reported to Date

Study characteristic	Gupta et al[3] (STOP-COVID)	Salvarani et al[1] (RCT-TCZ-COVID-19)	Hermine et al[2] (CORIMUNO-TOCI-1)	COVACTA[12]	EMPACTA[13]
Design					
Type	Observational retrospective	Randomized prospective	Randomized prospective	Randomized prospective	Randomized prospective
Blinded	NA	No	No	Yes (double)	Yes (double)
Placebo-controlled	NA	No	No	Yes	Yes
Enrollment					
No. of sites	68	24	9	67	69
Countries	US	Italy	France	Canada, Denmark, France, Germany, Italy, the Netherlands, Spain, United Kingdom, US	Brazil, Kenya, Mexico, Peru, South Africa, US
No. of participants	3924	126	131	450	389
No. tocilizumab treated	433	60[a]	63	225[b]	194[b]
Clinical severity[c]					
Moderate	No	No	No	No	No
Severe	Yes	Yes	Yes	Yes	Yes
Critical	Yes	No	No	Yes	No
Intervention					
Tocilizumab	Within 2 d of ICU admission	8 mg/kg ×2 Doses, 12 h apart	8 mg/kg ×1, Possible second dose on day 3	8 mg/kg ×1, Possible second dose	8 mg/kg ×1, Possible second dose
Comparator	Usual care	Usual care	Usual care	Usual care plus placebo	Usual care plus placebo
Outcomes[d]					
Primary, effect size	Time to death: Threshold for efficacy met; HR, 0.71 (95% CI, 0.56 to 0.92) 30-d mortality: Threshold for efficacy met; RD, 9.6% (95% CI, 3.1% to 16.0%)	Pao_2:Fio_2 <150 mm Hg, ICU admission, or death: Threshold for efficacy not met; RR, 1.05 (95% CI, 0.59 to 1.86)[e]	WHO-CPS score >5 on day 4: Threshold for efficacy not met; ARD, −9.0% (90% CrI, −21.0% to 3.1%); posterior probability of ARD <0 of 89.0% Survival without NIV or MV by day 14: Threshold for efficacy met; HR, 0.58 (90% CrI, 0.33 to 1.00), posterior probability of HR<1 of 95.0%	Difference in clinical status using a 7-category scale at day 28: Threshold for efficacy not met; OR, 1.19 (95% CI, 0.81 to 1.76)	Death or MV by day 28: Threshold for efficacy met; HR, 0.56 (95% CI, 0.32 to 0.97)
28- or 30-d mortality, tocilizumab vs comparator, effect size[f]	27.5% vs 37.1%; RD, 9.6% (95% CI, 3.1% to 16.0%)	3.3% vs 1.6%; RR, 2.10 (95% CI, 0.20 to 22.6)	11.1% vs 11.9%; aHR, 0.92 (95% CI, 0.33 to 2.53)	19.7% vs 19.4%; ARD, 0.3% (95% CI, −7.6% to 8.2%)	10.4% vs 8.6%; ARD, 2.0% (95% CI, −5.2% to 7.8%)
Trial registration	NCT04343898	NCT04346355	NCT04331808	NCT04320615	NCT04372186

Stone JH. Efficacy of Tocilizumab in Patients Hospitalized with COVID-19. New Engl Journal. Oct 2020

Parr JB. Time to Reassess Tocilizumab's Role in COVID-19 Pneumonia. JAMA Internal Medicine. Oct 2020. doi:10.1001/jamainternmed.2020.6557

Newer Therapeutic Agents (Summer 2020)

- Remdesivir
- Dexamethasone
- Convalescent Plasma
- Baricitinib

Remdesivir

- Developed by Gilead Sciences initially for Ebola and Marburg virus
  - Interferes with RNA polymerase
  - Has activity against numerous single stranded RNA viruses (MERS, SARS, RSV, Nipah, Lassa)
- Rose to prominence after treatment of patient in Washington after he progressed to pneumonia and had rapid improvement
- IV formulation
- Main adverse effects are LFTs abnormalities

Remdesivir

- NIH sponsored Adaptive COVID Treatment Trial
  - Multi-center randomized, double blinded, placebo controlled trial including international sites (~75 sites)
  - URMC Site PIs: Ann Falsey MD and Angela Branche MD
- Primary endpoint: Time to clinical improvement on 8 point ordinal scale
- Inclusion fairly broad: + COVID PCR, adult >18 years of age
- Exclusion: LFTs >5x ULN, GFR <50, Pregnant
- Also available under FDA Emergency Use Program(EUA) for pediatrics and pregnant women

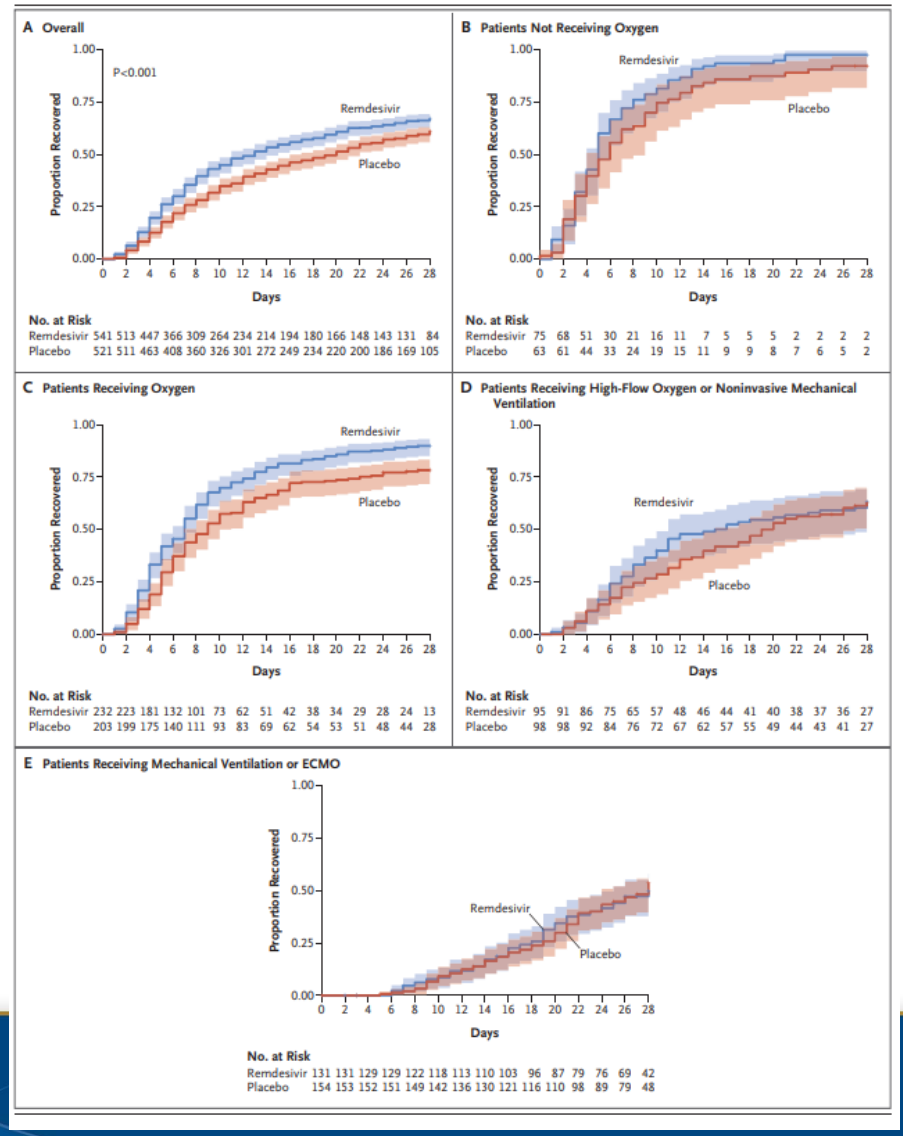
Patient Characteristics

Table 1. Demographic and Clinical Characteristics of the Patients at Baseline.*

Characteristic	All (N=1062)	Remdesivir (N=541)	Placebo (N=521)
Age — yr	58.9±15.0	58.6±14.6	59.2±15.4
Male sex — no. (%)	684 (64.4)	352 (65.1)	332 (63.7)
Race or ethnic group — no. (%)†			
American Indian or Alaska Native	7 (0.7)	4 (0.7)	3 (0.6)
Asian	135 (12.7)	79 (14.6)	56 (10.7)
Black or African American	226 (21.3)	109 (20.1)	117 (22.5)
White	566 (53.3)	279 (51.6)	287 (55.1)
Hispanic or Latino — no. (%)	250 (23.5)	134 (24.8)	116 (22.3)
Median time (IQR) from symptom onset to randomization — days‡	9 (6–12)	9 (6–12)	9 (7–13)
No. of coexisting conditions — no. /total no. (%)‡			
None	194/1048 (18.5)	97/531 (18.3)	97/517 (18.8)
One	275/1048 (26.2)	138/531 (26.0)	137/517 (26.5)
Two or more	579/1048 (55.2)	296/531 (55.7)	283/517 (54.7)
Coexisting conditions — no./total no. (%)			
Type 2 diabetes	322/1051 (30.6)	164/532 (30.8)	158/519 (30.4)
Hypertension	533/1051 (50.7)	269/532 (50.6)	264/519 (50.9)
Obesity	476/1049 (45.4)	242/531 (45.6)	234/518 (45.2)
Score on ordinal scale — no. (%)			
4. Hospitalized, not requiring supplemental oxygen, requiring ongoing medical care (Covid-19–related or otherwise)	138 (13.0)	75 (13.9)	63 (12.1)
5. Hospitalized, requiring supplemental oxygen	435 (41.0)	232 (42.9)	203 (39.0)
6. Hospitalized, receiving noninvasive ventilation or high-flow oxygen devices	193 (18.2)	95 (17.6)	98 (18.8)
7. Hospitalized, receiving invasive mechanical ventilation or ECMO	285 (26.8)	131 (24.2)	154 (29.6)
Baseline score missing	11 (1.0)	8 (1.5)	3 (0.6)

* 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.
‡ Data on symptom onset were missing for 3 patients; data on coexisting conditions were missing for 11 patients and were incomplete for 3 patients.

Time to Recovery Results



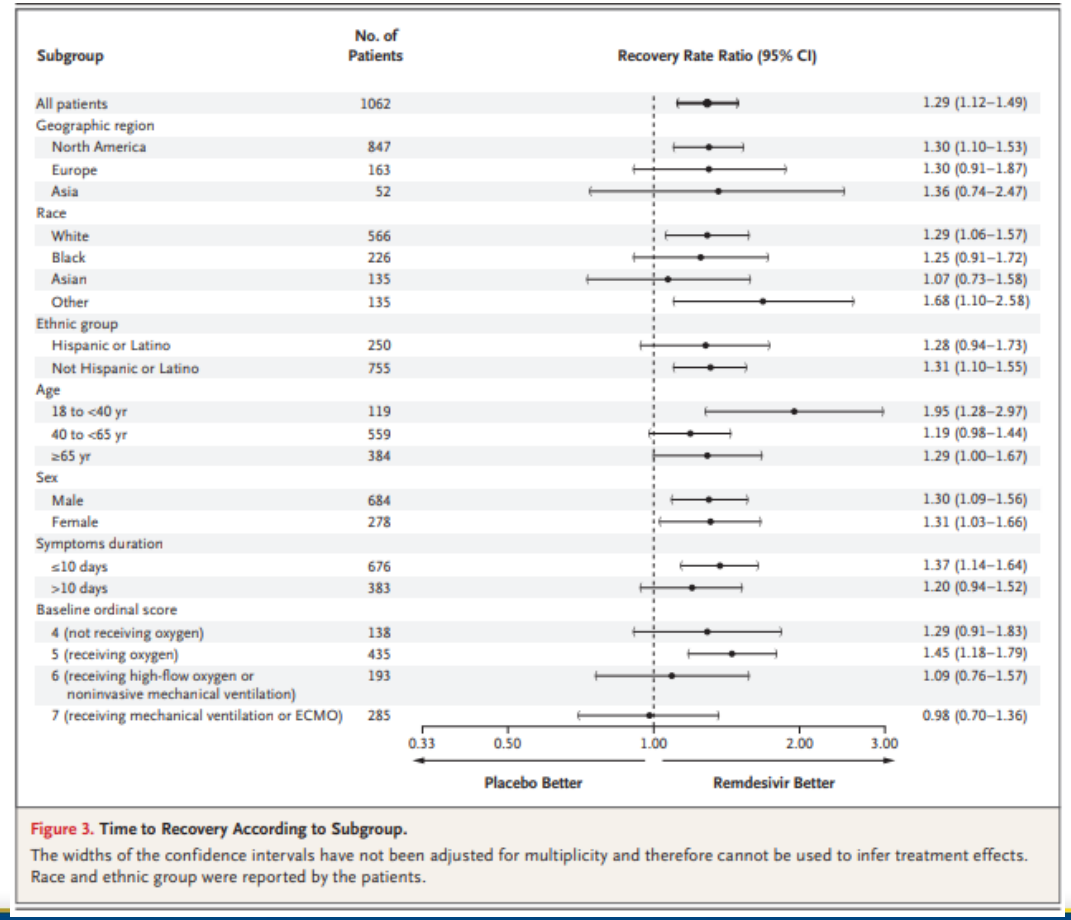


Figure 3. Time to Recovery According to Subgroup.

The widths of the confidence intervals have not been adjusted for multiplicity and therefore cannot be used to infer treatment effects. Race and ethnic group were reported by the patients.

Mortality Results

Table S5. Outcomes overall According to Score on the Ordinal Scale – ITT Population
(same as Table 2 of the main manuscript, but with additional analyses)

	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)	19.5 (14, 26)	29 (24, NE)	28 (24, NE)
Restricted Mean Recovery Time (95% CI) - days	14.1 (13.2,15.1)	16.9 (15.9,17.8)	6.7 (5.4,8.0)	8.6 (6.7,10.5)	9.9 (8.8,11.0)	13.1 (11.7,14.5)	17.5 (15.3,19.8)	19.0 (16.9,21.0)	23.5 (22.2,24.9)	23.8 (22.6,25.0)
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 over first 14 days‡										
Hazard ratio (95% CI) for data through Day 15	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)	
Number 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) over entire study period	0.73 (0.52, 1.03); p=0.07		0.82 (0.17, 4.07)		0.30 (0.14, 0.64)		1.02 (0.54, 1.91)		1.13 (0.67, 1.89)	
Number 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)
Restricted Mean Survival Time (95% CI) - days	26.2 (25.7,26.7)	25.3 (24.7,25.9)	27.5 (26.8,28.2)	27.3 (26.6,28.1)	27.3 (26.9,27.8)	25.6 (24.7,26.6)	24.4 (22.7,26.0)	24.1 (22.4,25.7)	24.9 (23.7,26.0)	24.9 (23.7,26.0)
Ordinal Scale at day 15 (±2 days) – no. (%)**										
1	157 (29.0)	115 (22.1)	38 (50.7)	28 (44.4)	90 (38.8)	62 (30.5)	18 (18.9)	14 (14.3)	11 (8.4)	11 (7.1)
2	117 (21.6)	102 (19.6)	20 (26.7)	15 (23.8)	70 (30.2)	58 (28.6)	22 (23.2)	19 (19.4)	5 (3.8)	10 (6.5)
3	14 (2.6)	8 (1.5)	8 (10.7)	4 (6.3)	6 (2.6)	4 (2.0)	0 (0)	0 (0)	0 (0)	0 (0)
4	38 (7.0)	33 (6.3)	3 (4.0)	7 (11.1)	17 (7.3)	13 (6.4)	12 (12.6)	4 (4.1)	6 (4.6)	9 (5.8)
5	58 (10.7)	60 (11.5)	3 (4.0)	5 (7.9)	25 (10.8)	18 (8.9)	2 (2.1)	14 (14.3)	28 (21.4)	23 (14.9)
6	28 (5.2)	24 (4.6)	1 (1.3)	0 (0)	5 (2.2)	7 (3.4)	12 (12.6)	11 (11.2)	10 (7.6)	6 (3.9)
7	95 (17.6)	121 (23.2)	1 (1.3)	3 (4.8)	13 (5.6)	21 (10.3)	16 (16.8)	20 (20.4)	57 (43.5)	74 (48.1)
8	34 (6.3)	58 (11.1)	1 (1.3)	1 (1.6)	6 (2.6)	20 (9.9)	13 (13.7)	16 (16.3)	14 (10.7)	21 (13.6)
Odds ratio (95% CI)	1.5 (1.2, 1.9); p<0.001		1.5 (0.8, 2.7)		1.6 (1.2, 2.3)		1.4 (0.9, 2.3)		1.2 (0.8, 1.9)	

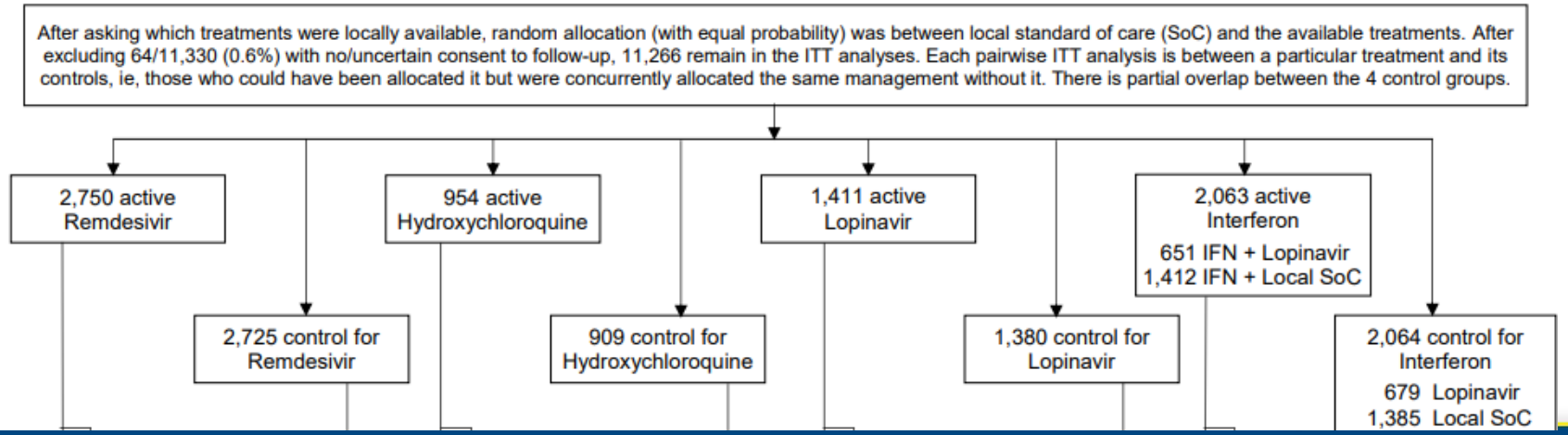
Key Takeaways

- 5 days shorter recovery time for all patients
- Lower progression to non-invasive and mechanical ventilation
- Mortality reduction at Day 14 and Day 28 for those receiving oxygen
- Mortality reduction not seen in “sickest patients”

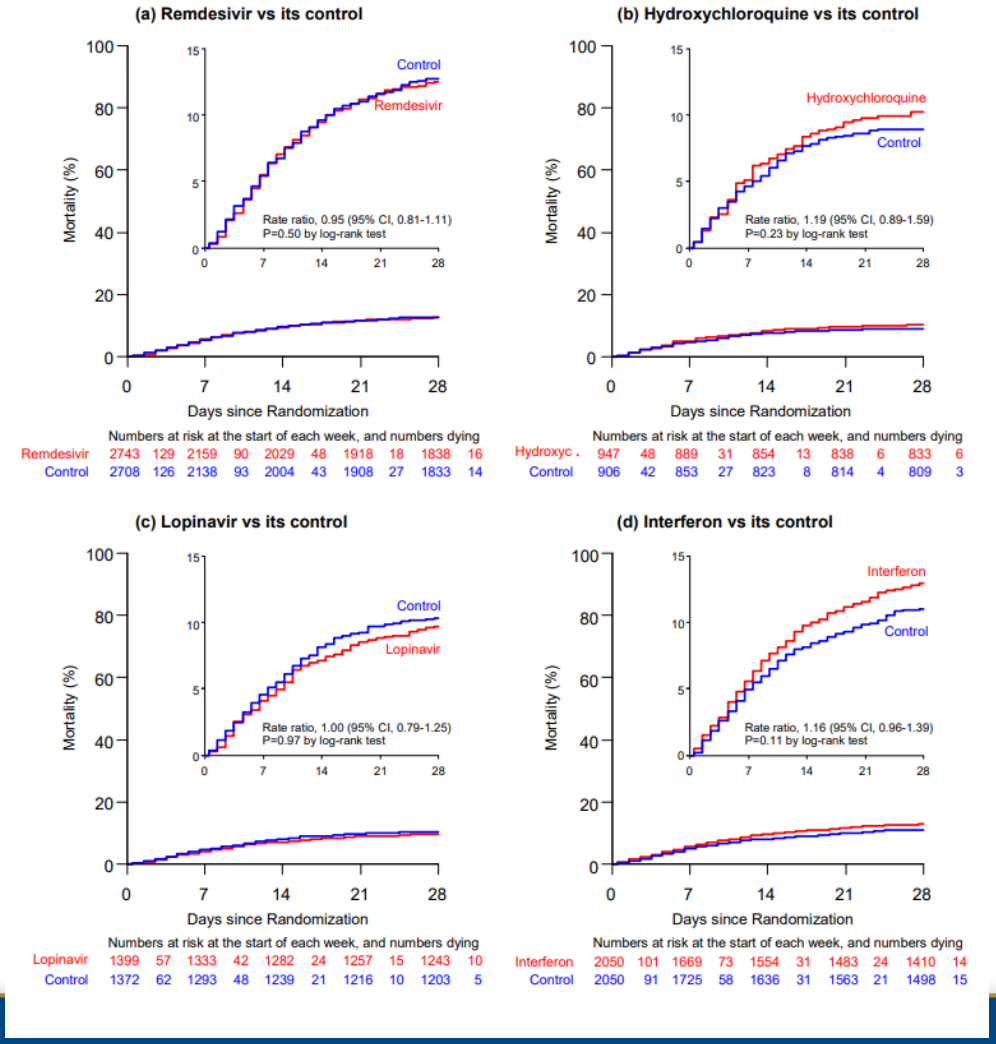
WHO Solidarity Trial

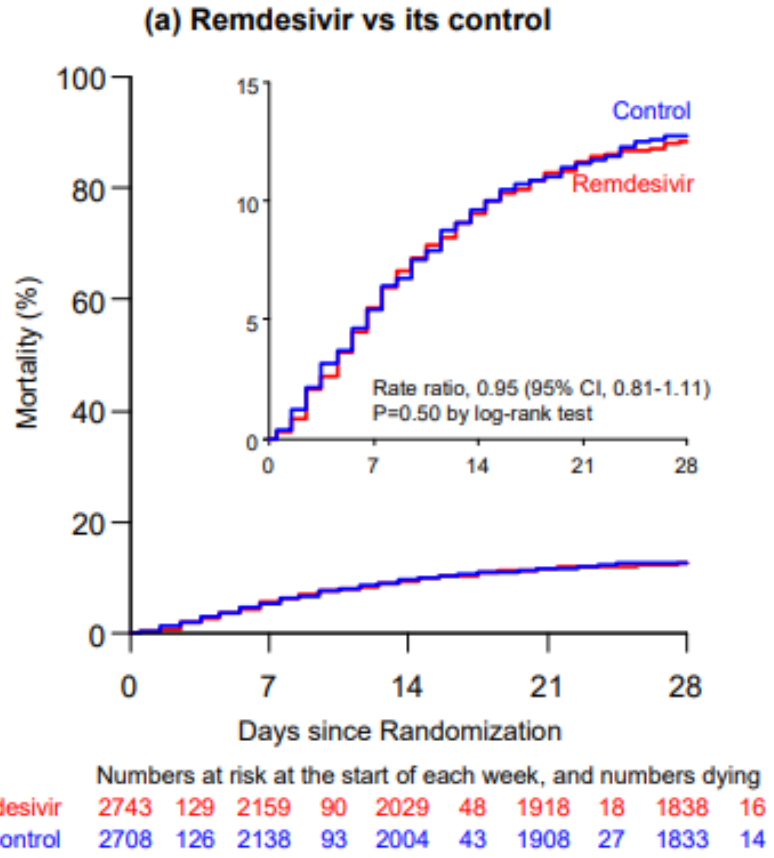
- Mortality trials in hospitalized COVID-19 patients in 4 re-purposed durgs:
  - Remdesivir, Hydroxychloroquine, Lopinavir/r, and Interferon
  - 405 hospitals
  - 30 countries
  - 11,266 randomized adults

Figure 1. WHO Solidarity Trial – information to October 4, 2020 on entry, follow-up (FU) and intent-to-treat (ITT) analyses



Results


(a) Remdesivir vs its control
Control
Remdesivir
Rate ratio, 0.95 (95% CI, 0.81-1.11)
P=0.50 by log-rank test
Mortality (%)
Days since Randomization
Numbers at risk at the start of each week, and numbers dying
Remdesivir 2743 129 2159 90 2029 48 1918 18 1838 16
Control 2708 126 2138 93 2004 43 1908 27 1833 14
(b) Hydroxychloroquine vs its control
Hydroxychloroquine
Control
Rate ratio, 1.19 (95% CI, 0.89-1.59)
P=0.23 by log-rank test
Mortality (%)
Days since Randomization
Numbers at risk at the start of each week, and numbers dying
Hydroxyc . 947 48 889 31 854 13 838 6 833 6
Control 906 42 853 27 823 8 814 4 809 3
(c) Lopinavir vs its control
Control
Lopinavir
Rate ratio, 1.00 (95% CI, 0.79-1.25)
P=0.97 by log-rank test
Mortality (%)
Days since Randomization
Numbers at risk at the start of each week, and numbers dying
Lopinavir 1399 57 1333 42 1282 24 1257 15 1243 10
Control 1372 62 1293 48 1239 21 1216 10 1203 5
(d) Interferon vs its control
Interferon
Control
Rate ratio, 1.16 (95% CI, 0.96-1.39)
P=0.11 by log-rank test
Mortality (%)
Days since Randomization
Numbers at risk at the start of each week, and numbers dying
Interferon 2050 101 1669 73 1554 31 1483 24 1410 14
Control 2050 91 1725 58 1636 31 1563 21 1498 15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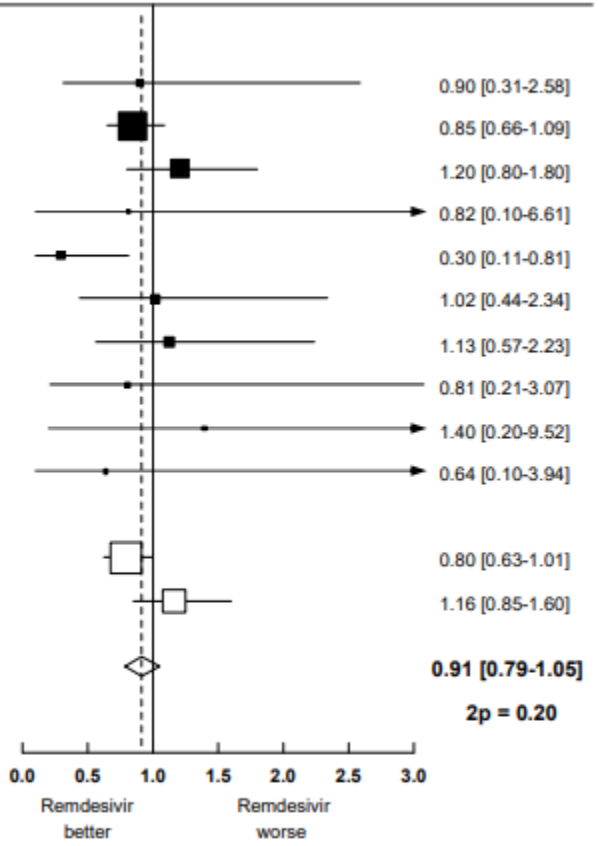
Mortality (%)
Days since Randomization
Numbers at risk at the start of each week, and numbers dying
Remdesivir 2743 129 2159 90 2029 48 1918 18 1838 16
Control 2708 126 2138 93 2004 43 1908 27 1833 14

Results

Trial name, and initial respiratory support	Deaths reported / Patients randomized in ITT analyses (28-day risk, K-M%) Remdesivir	Control	Remdesivir deaths: Observed-Expected (O-E)*	Var (O-E)	Ratio of death rates (RR), & 99% CI (or 95% CI, for total) Remdesivir : Control
Solidarity: no O_2	11/661 (2.0)	13/664 (2.1)	-0.6	6.0	0.90 [0.31-2.58]
Solidarity: low/hi-flow O_2	192/1828 (12.2)	219/1811 (13.8)	-16.9	101.8	0.85 [0.66-1.09]
Solidarity ventilation	98/254 (43.0)	71/233 (37.8)	7.6	40.8	1.20 [0.80-1.80]
ACTT: no O_2	3/75 (4.1)	3/63 (4.8)	-0.3	1.5	0.82 [0.10-6.61]
ACTT: low-flow O_2	9/232 (4.0)	25/203 (12.7)	-8.0	6.7	0.30 [0.11-0.81]
ACTT: hi-flow O_2 or non-invasive ventilation	19/95 (21.2)	20/98 (20.4)	0.2	9.6	1.02 [0.44-2.34]
ACTT: invasive ventilation	28/131 (21.9)	29/154 (19.3)	1.7	14.3	1.13 [0.57-2.23]
Wuhan: low-flow O_2	11/129 (8.5)	(7/68) x2† (10.3)	-0.8	3.7	0.81 [0.21-3.07]
Wuhan: hi-flow O2 or ventilation	11/29 (37.9)	(3/10) x2† (30.0)	0.6	1.8	1.40 [0.20-9.52]
SIMPLE: no O_2	5/384 (1.3)	(4/200) x2† (2.0)	-0.9	2.0	0.64 [0.10-3.94]
Subtotals					
Lower risk groups (with no ventilation)	231/3309 (7.0)	282/3277 (8.6)	-27.6	121.6	0.80 [0.63-1.01]
Higher risk groups	156/509 (30.6)	126/505 (25.0)	10.1	66.5	1.16 [0.85-1.60]
Total	**387/3818 (10.1)**	**408/3782 (10.8)**	**-17.5**	**188.2**	**0.91 [0.79-1.05]**
					2p = 0.20



■/□ 99% or ◇ 95% confidence interval (CI), K-M Kaplan-Meier.

* Log-rank O-E for Solidarity, O-E from 2x2 tables for Wuhan and SIMPLE, and w.log$_e$HR for ACTT strata (with the weight w being the inverse of the variance of log$_e$HR, which is got from the HR's CI). RR is got by taking log$_e$RR to be (O-E)/V with Normal variance 1/V. Subtotals or totals of (O-E) and of V yield inverse-variance-weighted averages of the log$_e$RR values.

† For balance, controls in the 2:1 studies count twice in the control totals and subtotals.

Limitations

- No placebo (needed to prevent treatment assessment bias)
- No double-blinding (needed to prevent information bias, treatment assessment bias, adherence bias, follow up bias)
- No data monitoring (needed for the appropriate trial conduct and patient safety)
- No diagnostic confirmation of infection (needed to ensure patients have equal proportion of confirmed diagnosis between both arms)
- No timing of symptoms duration before treatment initiation (needed to ensure the intervention is given at equal times of the natural course of the disease)
- Unknown supportive care provided
- Patients were required to stay in the hospital for a fixed 10-day course of remdesivir even if they were well to go home? – if confirmed, would always be biased against the drug
- Implementation and study drug distribution were plagued by delivery failures and disorganization, which compromised the proper conduct of the trial.

Dexamethasone

- Corticosteroid which was first made in 1957 by Philip Showalter Hench and approved in 1961
  - Listed as one of WHO's Essential Medicines
  - In 2017, was the 321st most prescribed medication in US (over 1 million)

- Prior to 2020, mainly used to treat inflammatory, anaphylaxis, and autoimmune conditions

- Initial study out of Spain showed methylprednisolone had beneficial effect in severe COVID-19 pneumonia decreasing composite score of ICU admission, non-invasive ventilation, or death

Corral L, et al. GLUCOCOVID: a controlled trial of methylprednisolone in adults hospitalized with COVID-19 pneumonia. June 18, 2020. (https://www.medrxiv.org/content/10.1101/2020.06.17.20133579v1).

Recovery Trial

- Studied hospitalized patients at 176 sites in UK
- Randomized to PO or IV Dexamethasone for up to 10 days vs placebo
- Primary Outcome: 28 day mortality
  - Secondary: Time until discharge, need for mechanical ventilation if not initially on ventilator, duration of ventilation, need for HD, and major cardiac arrhythmia

Patient Characteristics

Table 1. Characteristics of the Patients at Baseline, According to Treatment Assignment and Level of Respiratory Support.*

Characteristic	Treatment Assignment		Respiratory Support Received at Randomization		
	Dexamethasone (N=2104)	Usual Care (N=4321)	No Receipt of Oxygen (N=1535)	Oxygen Only (N=3883)	Invasive Mechanical Ventilation (N=1007)
Age†					
Mean — yr	66.9±15.4	65.8±15.8	69.4±17.5	66.7±15.3	59.1±11.4
Distribution — no. (%)					
<70 yr	1141 (54)	2504 (58)	659 (43)	2148 (55)	838 (83)
70 to 79 yr	469 (22)	859 (20)	338 (22)	837 (22)	153 (15)
≥80 yr	494 (23)	958 (22)	538 (35)	898 (23)	16 (2)
Sex — no. (%)					
Male	1338 (64)	2749 (64)	891 (58)	2462 (63)	734 (73)
Female‡	766 (36)	1572 (36)	644 (42)	1421 (37)	273 (27)
Median no. of days since symptom onset (IQR)§	8 (5–13)	9 (5–13)	6 (3–10)	9 (5–12)	13 (8–18)
Median no. of days since hospitalization (IQR)	2 (1–5)	2 (1–5)	2 (1–6)	2 (1–4)	5 (3–9)
Respiratory support received — no. (%)					
No oxygen	501 (24)	1034 (24)	1535 (100)	NA	NA
Oxygen only	1279 (61)	2604 (60)	NA	3883 (100)	NA
Invasive mechanical ventilation	324 (15)	683 (16)	NA	NA	1007 (100)
Previous coexisting disease					
Any	1174 (56)	2417 (56)	911 (59)	2175 (56)	505 (50)
Diabetes	521 (25)	1025 (24)	342 (22)	950 (24)	254 (25)
Heart disease	586 (28)	1171 (27)	519 (34)	1074 (28)	164 (16)
Chronic lung disease	415 (20)	931 (22)	351 (23)	883 (23)	112 (11)
Tuberculosis	6 (<1)	19 (<1)	8 (1)	11 (<1)	6 (1)
HIV infection	12 (1)	20 (<1)	5 (<1)	21 (1)	6 (1)
Severe liver disease¶	37 (2)	82 (2)	32 (2)	72 (2)	15 (1)
Severe kidney impairment‖	166 (8)	358 (8)	119 (8)	253 (7)	152 (15)
SARS-CoV-2 test result					
Positive	1850 (88)	3848 (89)	1333 (87)	3416 (88)	949 (94)
Negative	247 (12)	453 (10)	193 (13)	452 (12)	55 (5)
Test result not yet known	7 (<1)	20 (<1)	9 (1)	15 (<1)	3 (<1)

Results

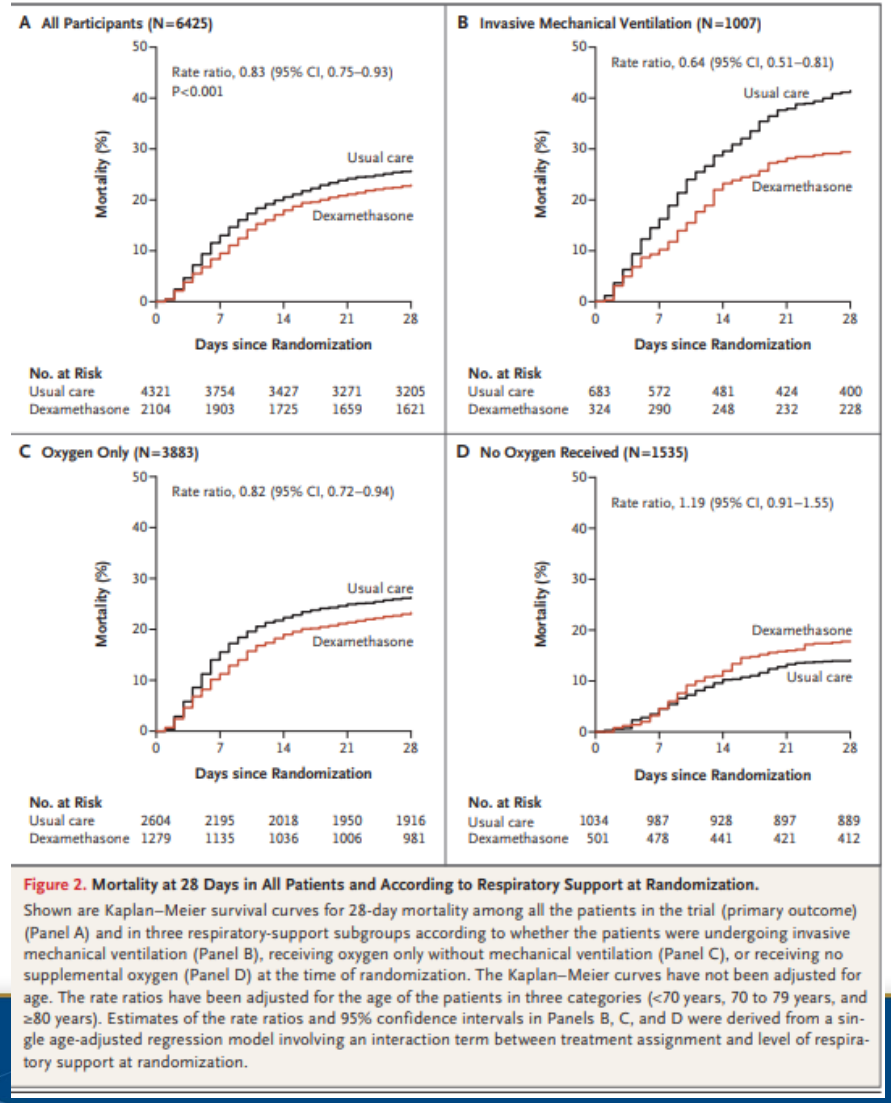


Figure 2. Mortality at 28 Days in All Patients and According to Respiratory Support at Randomization.

Shown are Kaplan–Meier survival curves for 28-day mortality among all the patients in the trial (primary outcome) (Panel A) and in three respiratory-support subgroups according to whether the patients were undergoing invasive mechanical ventilation (Panel B), receiving oxygen only without mechanical ventilation (Panel C), or receiving no supplemental oxygen (Panel D) at the time of randomization. The Kaplan–Meier curves have not been adjusted for age. The rate ratios have been adjusted for the age of the patients in three categories (<70 years, 70 to 79 years, and ≥80 years). Estimates of the rate ratios and 95% confidence intervals in Panels B, C, and D were derived from a single age-adjusted regression model involving an interaction term between treatment assignment and level of respiratory support at randomization.

Respiratory Support at Randomization	Dexamethasone	Usual Care	Rate Ratio (95% CI)
	no. of events/total no. (%)		
Invasive mechanical ventilation	95/324 (29.3)	283/683 (41.4)	0.64 (0.51–0.81)
Oxygen only	298/1279 (23.3)	682/2604 (26.2)	0.82 (0.72–0.94)
No oxygen received	89/501 (17.8)	145/1034 (14.0)	1.19 (0.91–1.55)
All Patients	**482/2104 (22.9)**	**1110/4321 (25.7)**	**0.83 (0.75–0.93)**
			P<0.001

Chi-square trend across three categories: 11.5

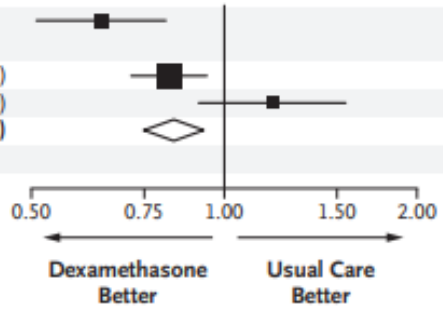


Figure 3. Effect of Dexamethasone on 28-Day Mortality, According to Respiratory Support at Randomization.

Shown are subgroup-specific rate ratios for all the patients and for those who were receiving no oxygen, receiving oxygen only, or undergoing invasive mechanical ventilation at the time of randomization. Rate ratios are plotted as squares, with the size of each square proportional to the amount of statistical information that was available; the horizontal lines represent 95% confidence intervals.

JAMA | Original Investigation | CARING FOR THE CRITICALLY ILL PATIENT

Effect of Dexamethasone on Days Alive and Ventilator-Free in Patients With Moderate or Severe Acute Respiratory Distress Syndrome and COVID-19
The CoDEX Randomized Clinical Trial

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- Multi-center, randomized, open-label study in ICU in Brazil
- Moderate to severe ARDS patients included from April-June 2020
- Patients received 20mg daily x 5 days followed by 10mg daily x 5 days or until ICU discharge
- Outcome of days alive and ventilator free at Day 28

Results

Table 2. Study Outcomes

Outcomes	Mean (95% CI)		Effect statistic	Between-group effect			
				Adjusted[a]		Unadjusted	
	Dexamethasone (n = 151)	Standard care (n = 148)		Estimate (95% CI)	*P* value	Estimate (95% CI)	*P* value
Primary outcome							
Days alive and ventilator free at 28 d							
Mean (95% CI)	6.6 (5.0 to 8.2)	4.0 (2.9 to 5.4)	MD	2.26 (0.2 to 4.38)[b]	.04	2.55 (0.46 to 4.6)	.02
Median (IQR)	0 (0 to 17)	0 (0 to 3)					
Secondary outcomes							
6-Point ordinal scale at day 15, median (IQR)[c]	5 (3 to 6)	5 (5 to 6)	OR	0.66 (0.43 to 1.03)	.07	0.62 (0.41 to 0.94)	.03
28-Day results							
All-cause mortality No. (%)	85 (56.3)	91 (61.5)	HR	0.97 (0.72 to 1.31)	.85	0.86 (0.64 to 1.15)	.31
ICU free, d	2.1 (1.0 to 4.5)	2.0 (0.8 to 4.2)	MD	0.28 (−0.49 to 1.02)	.50	0.14 (−0.92 to 1.27)	.78
MV duration, d	12.5 (11.2 to 13.8)	13.9 (12.7 to 15.1)	MD	−1.54 (−3.24 to 0.12)	.11	−1.46 (−3.10 to 0.57)	.18
SOFA score[d]							
48 h	8.1 (7.6 to 8.6)	8.4 (7.8 to 8.9)	MD	−0.11 (−0.86 to 0.63)	.76	−0.24 (−1 to 0.51)	.53
No. of patients	151	147					
72 h	7.7 (7.2 to 8.3)	8.3 (7.8 to 8.9)	MD	−0.38 (−1.13 to 0.37)	.32	−0.6 (−1.37 to 0.16)	.12
No. of patients	145	144					
7 d	6.1 (5.5 to 6.7)	7.5 (6.9 to 8.1)	MD	−1.16 (−1.94 to −0.38)	.004	−1.38 (−2.21 to −0.55)	.001
No. of patients	127	120					

Summary of Steroid Use

Table 1. Characteristics of Included Trials

	DEXA-COVID 19	CoDEX	RECOVERY	CAPE COVID	COVID STEROID	REMAP-CAP	Steroids-SARI[a]
ClinicalTrials.gov identifier	NCT04325061	NCT04327401	NCT04381936	NCT02517489	NCT04348305	NCT02735707	NCT04244591
Planned sample size	200	350	NA	290	1000	NA[b]	80
Eligibility criteria	• Intubation • Mechanical ventilation • Moderate to severe ARDS per Berlin criteria[9] • Confirmed COVID-19	• Intubation • Mechanical ventilation • Moderate to severe ARDS per Berlin criteria[9] • Onset of ARDS <48 h before randomization • Probable or confirmed COVID-19	Criteria[c] used for this meta-analysis: Intubation Suspected or confirmed COVID-19	• Minimal severity • Admitted to ICU or intermediate care unit • Oxygen (≥6 L/min) • Probable or confirmed COVID-19	• Oxygen (≥10 L/min) • Confirmed COVID-19	• Admitted to ICU receiving high-flow nasal oxygen with FIO_2 ≥0.4 at ≥30 L/min, noninvasive or invasive ventilatory support, or receiving vasopressors • Probable or confirmed COVID-19	• Admitted to ICU with PaO_2:FIO_2 <200 mm Hg on positive pressure ventilation (invasive or noninvasive) or high-flow nasal canulae >45 L/min • Confirmed COVID-19
Corticosteroid							
Drug name	Dexamethasone	Dexamethasone	Dexamethasone	Hydrocortisone	Hydrocortisone	Hydrocortisone	Methylprednisolone
Dosage and administration	20 mg/d intravenously × 5 d and then 10 mg/d intravenously × 5 d	20 mg/d intravenously × 5 d and then 10 mg/d intravenously × 5 d	6 mg/d orally or intravenously	Continuous intravenous infusion × 8 d or 14 d (200 mg/d × 4 d or 7 d; 100 mg/d × 2 d or 4 d; 50 mg/d × 2 d or 3 d)	200 mg/d intravenously × 7 d (continuous or bolus dosing every 6 h)	50 mg intravenously every 6 h × 7 d[d]	40 mg intravenously every 12 h × 5 d
Dose classification	High	High	Low	Low	Low	Low	High
Control intervention	Usual care	Usual care	Usual care	Placebo	Placebo	Usual care	Usual care
Primary outcome	60-d mortality	Ventilator-free days	28-d mortality	21-d treatment failure (death or persistent requirement for mechanical ventilation or high-flow oxygen therapy)	Days alive without life support at 28 d	Composite of hospital mortality and ICU organ support-free days to 21 d	Lower lung injury score at 7 d and 14 d
Mortality outcome, d	28	28	28	21	28	28	30
Serious adverse event definitions	• Secondary infections of pneumonia, sepsis, or other similar • Pulmonary embolism	• Mortality • Infections • Insulin use	• Cause-specific mortality • Ventilation • Dialysis • Cardiac arrhythmia (in a subset) • Other that were believed to be related to study treatment	• Any • Excluded some listed in protocol • Excluded expected adverse events related to the patient's disease or comorbidity	• New episodes of septic shock (Sepsis-3 criteria) • Invasive fungal infection • Clinically important gastrointestinal bleeding • Anaphylaxis	• Per ICH good clinical practice guidelines (events not already captured as a trial end point; eg, mortality) • When the event may reasonably have occurred because of study participation	• Secondary bacterial infections • Barotrauma • Severe hyperglycemia • Gastrointestinal bleeding requiring transfusion • Acquired weakness
Location	Spain	Brazil	UK	France	Denmark	Australia, Canada, European Union, New Zealand, UK, US	China

Abbreviations: ARDS, acute respiratory distress syndrome; CAPE COVID, Community-Acquired Pneumonia: Evaluation of Corticosteroids in Coronavirus Disease; CoDEX, COVID-19 Dexamethasone; COVID-19, coronavirus disease 2019; COVID STEROID, Hydrocortisone for COVID-19 and Severe Hypoxia; DEXA-COVID 19, Efficacy of Dexamethasone Treatment for Patients With ARDS Caused by COVID-19; FIO_2, fraction of inspired oxygen; ICU, intensive care unit; NA, not applicable; RECOVERY, Randomized Evaluation of COVID-19 Therapy; REMAP-CAP, Randomized, Embedded, Multifactorial Adaptive Platform Trial for Community-Acquired Pneumonia; Sepsis-3, Third International Consensus Definitions for Sepsis and Septic Shock; Steroids-SARI, Glucocorticoid Therapy for COVID-19 Critically Ill Patients With Severe Acute Respiratory Failure.

[a] Trial did not specify whether adverse events were serious or nonserious.

[b] No sample size was specified at the start of the trial.

[c] The RECOVERY trial also recruited hospitalized patients with suspected or confirmed COVID-19 who were not receiving invasive mechanical ventilation at randomization.

[d] Too few patients were randomized to the high-dose group to permit separate analyses.

Mortality was main outcome in most studies!

Association Between Administration of Systemic Corticosteroids and Mortality Among Critically Ill Patients With COVID-19 A Meta-analysis. JAMA 2020

Summary of Steroid Use

Table 2. Characteristics of Patients Included in the Prospective Meta-analysis

	DEXA-COVID 19		CoDEX		RECOVERY		CAPE COVID		COVID STEROID		REMAP-CAP[a]		Steroids-SARI[b]	
	Steroid	No steroid	Steroid	No steroid	Steroid	No steroid	Steroid	No steroid	Steroid	No steroid	Steroid	No steroid	Steroid	No steroid
Patients randomized by June 9, 2020	7	12	128	128	324	683	76	73	15	14	105	92	24	23
Age, median (IQR), y	62 (48-68)	60 (52-69)	62 (50-70)	64 (57-73)	59 (52-66)	60 (52-68)	63 (52-71)	66 (54-73)	57 (52-75)	62 (55-71)	59 (53-68)	62 (50-72)	67 (61-74)	62 (54-68)
Female sex, No. (%)	3 (42.9)	3 (25)	47 (36.7)	44 (34.4)	91 (28.1)	182 (26.6)	22 (28.9)	23 (31.5)	2 (13.3)	4 (28.6)	30 (28.6)	25 (27.2)	7 (29)	5 (22)
PCR-confirmed SARS-CoV-2 infection, No. (%)	7 (100)	12 (100)	120 (93.8)	122 (95.3)	301 (92.9)	647 (94.7)	72 (94.7)	72 (98.6)	15 (100)	14 (100)	80 (76.2)	75 (81.5)	24 (100)	23 (100)
Treatments at randomization, No. (%)														
Mechanical ventilation	7 (100)	12 (100)	128 (100)	128 (100)	324 (100)	683 (100)	62 (81.6)	59 (80.8)	7 (46.7)	8 (57.1)	68 (64.8)	49 (53.3)	13 (54)	14 (61)
Vasoactive	3 (42.9)	7 (58.3)	83 (65.4)	88 (68.8)	Not recorded	Not recorded	18 (23.7)	13 (17.8)	5 (33.3)	5 (35.7)	46 (43.8)	27 (29.3)	14 (58)	18 (78)
Any antiviral[c]	6 (86)	10 (83)	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	24 (100)	23 (100)
Remdesivir	Not recorded	Not recorded	0	0	1 (0.3)	0	1 (1.3)	0	0	4 (28.6)	1 (1.0)	0	Not recorded	Not recorded
Lopinavir or ritonavir	Not recorded	Not recorded	0	1 (0.8)	0	0	8 (10.5)	9 (12.3)	0	0	0	2 (2.2)	Not recorded	Not recorded
Favipravir	Not recorded	Not recorded	0	0	0	0	0	0	0	0	0	0	Not recorded	Not recorded
Hydroxychloroquine	7 (100)	12 (100)	30 (23.4)	22 (17.2)	0	0	29 (38.2)	32 (43.8)	1 (6.7)	0	5 (4.8)	2 (2.2)	0	0
Azithromycin	0	0	83 (64.8)	81 (63.3)	59 (18.2)	81 (11.9)	19 (25.0)	24 (32.9)	Not recorded	Not recorded	9 (8.6)	6 (6.5)	Not recorded	Not recorded
Convalescent plasma	0	0	Not recorded	Not recorded	0	0	0	0	0	2 (14.3)	0	0	Not recorded	Not recorded

Abbreviations: CAPE COVID, Community-Acquired Pneumonia: Evaluation of Corticosteroids in Coronavirus Disease; CoDEX, COVID-19 Dexamethasone; COVID STEROID, Hydrocortisone for COVID-19 and Severe Hypoxia; DEXA-COVID 19, Efficacy of Dexamethasone Treatment for Patients With ARDS Caused by COVID-19; IQR, interquartile range; NA, not applicable; PCR, polymerase chain reaction; RECOVERY, Randomized Evaluation of COVID-19 Therapy; REMAP-CAP, Randomized, Embedded, Multifactorial Adaptive Platform Trial for Community-Acquired Pneumonia; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; Steroids-SARI, Glucocorticoid Therapy for COVID-19 Critically Ill Patients With Severe Acute Respiratory Failure.

[a] Missing substantial data on antiviral use.

[b] Missing data on PCR results.

[c] Some of the trials did not provide information on individual antiviral drugs, which is indicated by "not recorded." The trials with NA is this row provided data on individual antiviral drugs in the rows below.

Summary of Steroid Use

Figure 2. Association Between Corticosteroids and 28-Day All-Cause Mortality in Each Trial, Overall, and According to Corticosteroid Drug

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) $P = .31$ for heterogeneity; $I^2 = 15.6\%$			222/678	425/1025	0.66 (0.53-0.82)	100.0
Overall (random effects[a])			222/678	425/1025	0.70 (0.48-1.01)	

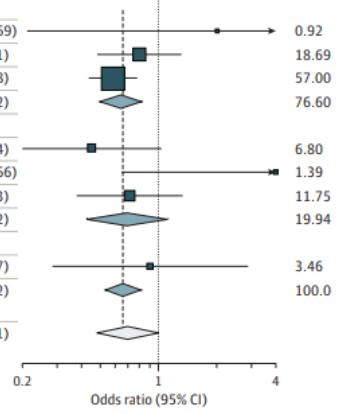
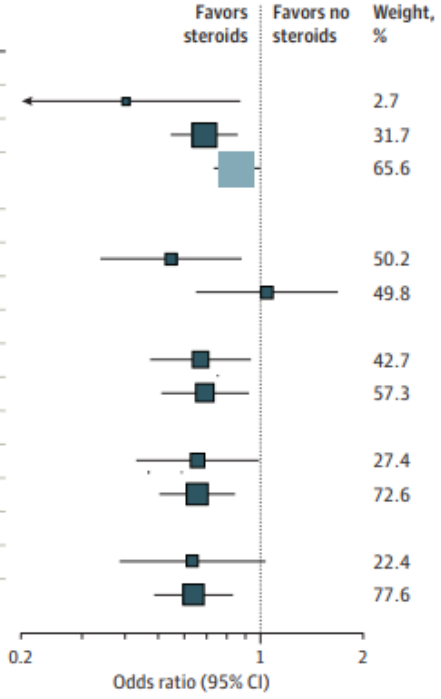


Figure 3. Association Between Corticosteroids and 28-Day All-Cause Mortality Within Subgroups Defined by Patient Characteristics at the Time of Randomization

Subgroup	No. of deaths/total No. of patients: Steroids	No. of deaths/total No. of patients: No steroids	Odds ratio (95% CI)	Weight, %
Invasive mechanical ventilation (IMV)				
No ($I^2 = 0\%$)	14/70	28/74	0.41 (0.19-0.88)	2.7
Yes ($I^2 = 44.1\%$)	208/608	397/951	0.69 (0.55-0.86)	31.7
Oxygen treatment without IMV (RECOVERY)	298/1279	682/2604	0.86 (0.73-1.00)	65.6
Taking vasoactive medication				
No ($I^2 = 0\%$)	51/184	68/184	0.55 (0.34-0.88)	50.2
Yes ($I^2 = 0\%$)	76/169	74/158	1.05 (0.65-1.69)	49.8
Age, y				
≤60 ($I^2 = 0\%$)	72/338	141/483	0.67 (0.48-0.94)	42.7
>60 ($I^2 = 49.7\%$)	150/339	284/541	0.69 (0.51-0.93)	57.3
Sex				
Female ($I^2 = 0\%$)	60/202	106/286	0.66 (0.43-0.99)	27.4
Male ($I^2 = 14.7\%$)	162/476	319/739	0.66 (0.51-0.84)	72.6
Symptomatic, d				
≤7 ($I^2 = 69.1\%$)	51/130	99/211	0.63 (0.39-1.04)	22.4
>7 ($I^2 = 0\%$)	139/418	293/693	0.64 (0.49-0.83)	77.6



Dexamethasone Take Home Points

- Only drug to show mortality benefit thus far

But…

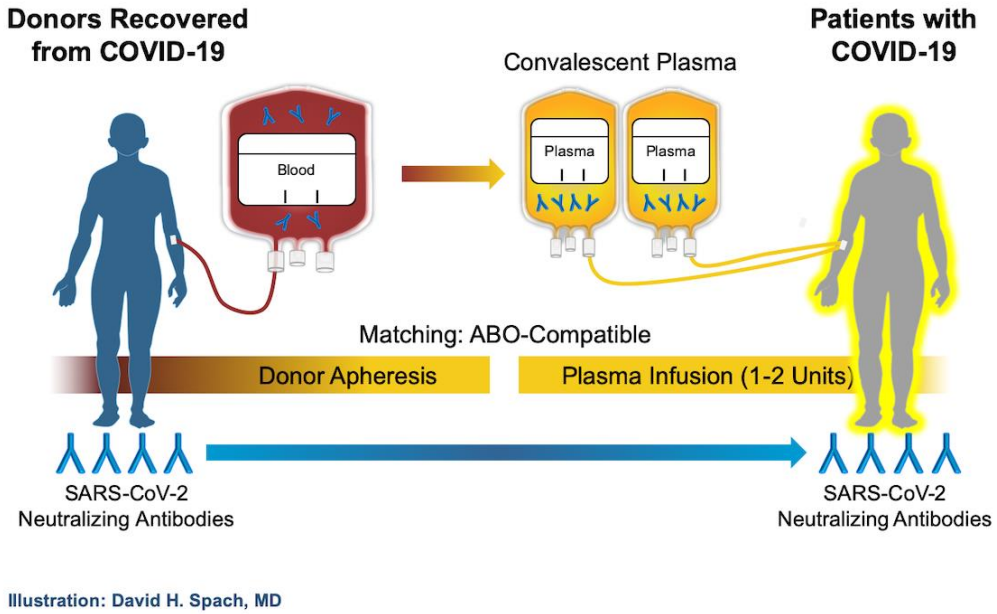
- Recovery and CoDEX had high baseline mortality rates

Convalescent Plasma (CVP)

- Initially studied in early infections due to diphtheria and tetanus

- To date no certainty that CVP offers benefit to hospitalized patients in recent Cochrane Review
  - Included 2 RCTs, 8 controlled non-randomized studies and, and 9 non-controlled, non-randomized studies
  - Included ~36k patients

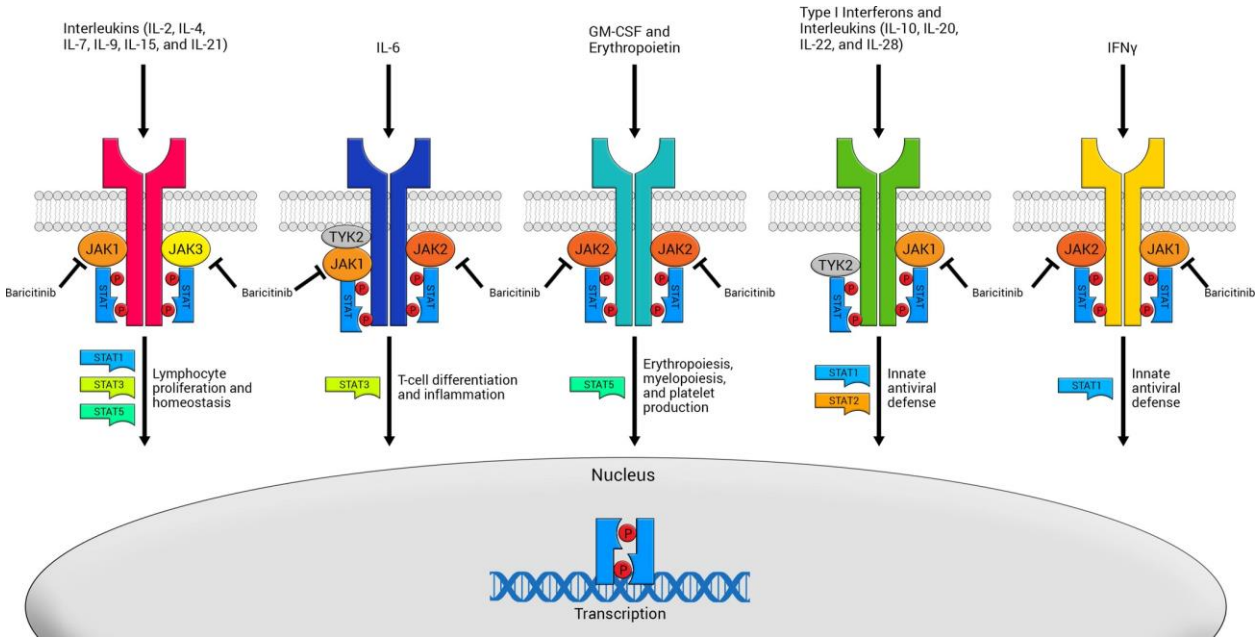
- Possible side effects seen a week after infusion
  - 146 serious adverse events at 4 hours vs 1136 within 7 days



Chai KL, et al. Convalescent plasma or hyperimmune immunoglobulin for people with COVID-19: a living systematic review. Cochrane Database of Systematic Reviews 2020, Issue 10. Art. No.: CD013600. DOI: 10.1002/14651858.CD013600.pub3.

Baricitinib

- Inhibitor of janus kinase (JAK)
  - Specifically JAK1 and JAK2
- In 2018, FDA approved Baricitinib for RA who had inadequate response to one or more TNF-antagonists
- In Nov 2020, FDA issued emergency use authorization of baricitinib in combination with remdesivir for patients receiving supplemental oxygen, invasive mechanical ventilation, or ECMO



Baricitinib

- Currently 9 studies registered in clinical trials site in US, UK, Spain, Denmark, Canada, and Italy

- Off-label use first reported in Italy in March 2020 in combination with lopinavir/ritonavir
  - Only 12 patients in each group
  - 7 (58%) in Baricitinib arm recovered to discharge by 2 weeks. None in control arm

- ACTT-2: NIH sponsored adaptive trial comparing remdesivir +/- baricitinib

ACTT-2 NIH Trial

- 1033 patients were followed for 29 days
  - 515 received Baricitinib + Remdesivir; 518 received Remdesivir + placebo
- Time to recovery was primary end point
  - Hospital discharge or no longer receiving supplemental oxygen or ongoing medical care

- Median time was 7 days in B+R vs 8 days in R+P
- Lower odds of death or intubation by Day 29
- Higher odds of clinical improvement by Day 15

Safety Concerns

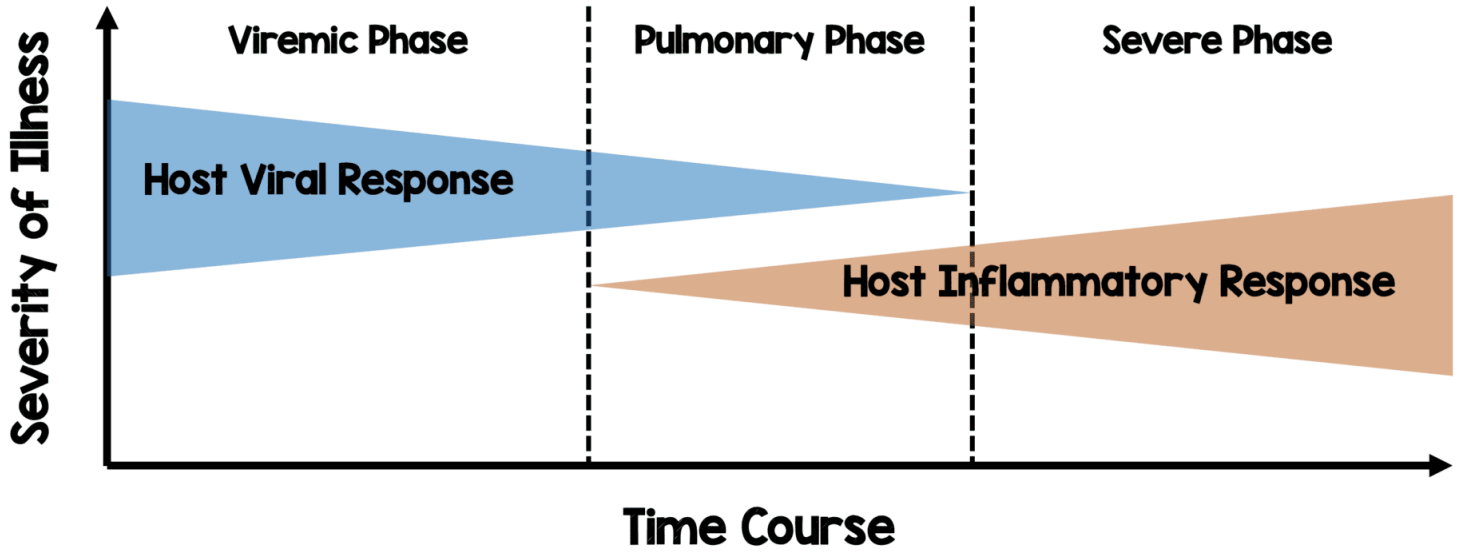
- Monitor CBC with diff + CMP

- Risk of lymphopenia, neutropenia, elevation in liver enzymes
- Risk of thrombosis and opportunistic infections also reported

URMC Patient Data(as of 12/2)

- 27 patients placed on Baricitinib as of 12/6
- 3 patients approved but never received dose
  - 2 refusals, 1 intubated before starting
- 6 live discharges
  - Range of therapy: 3-7
- 1 death
- 2 serious adverse events
  - 1 ALC < 100
  - 1 AKI

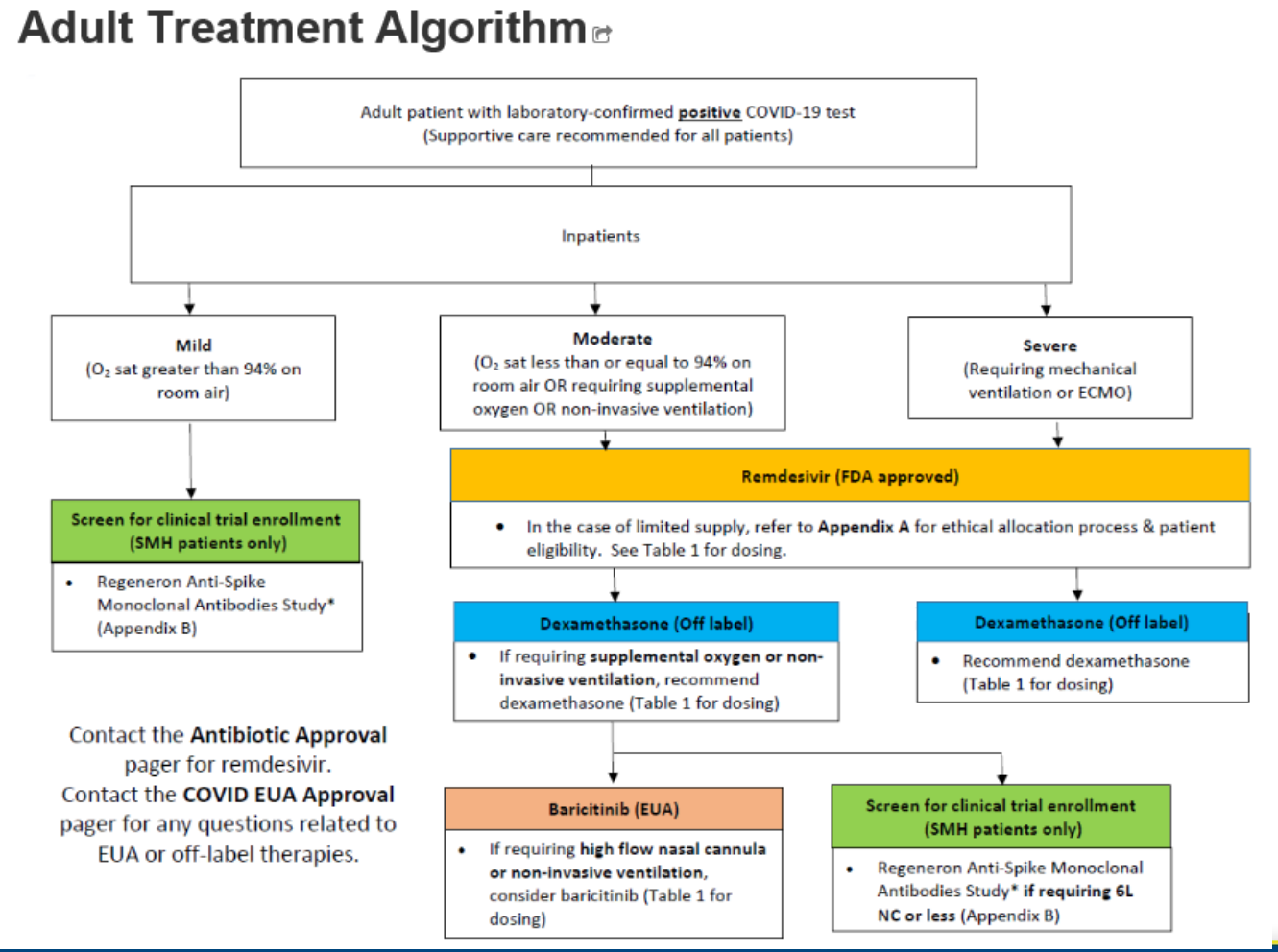
COVID-19: Clinical Therapeutic Staging



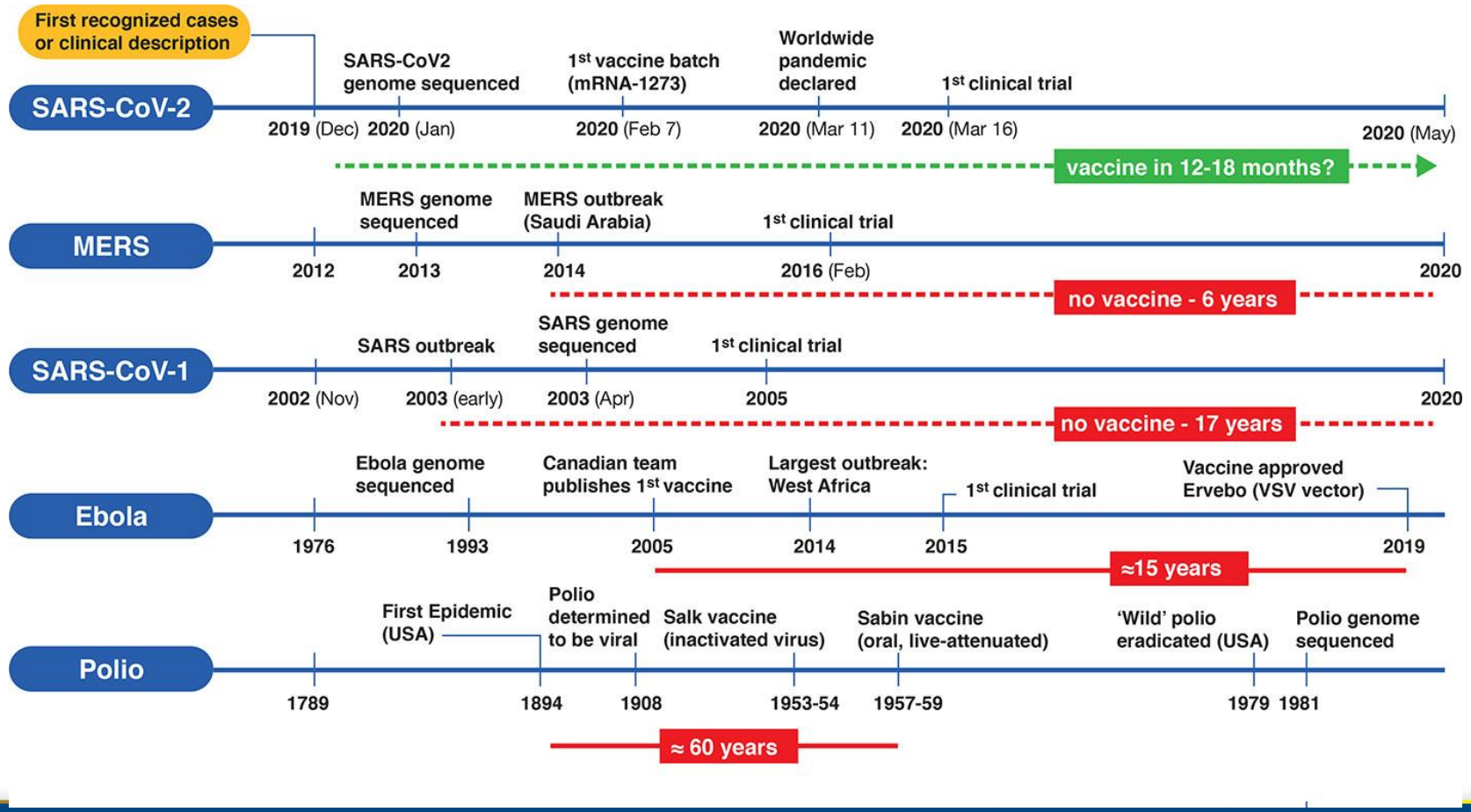
Antivirals	Antivirals, Corticosteroids, Anticoagulation, Convalescent Plasma	Corticosteroids, Anticoagulation, IL-6 Inhibitors, JAK Inhibitors
Reduce duration of symptoms, minimize contagiousness, & potentially reduce progression of disease	Anti-inflammatory therapy	Anti-inflammatory and immunomodulatory therapy

Rebel EM. Covid-19 Disease Progression. Emergency Medicine Blog

URMC COVID Treatment Guidelines



The Future



Funk CD, et al. Front. Pharmcol. 19 June 2020

Summary

- Conducting studies during a pandemic is difficult
- Be wary of pre-print study results
- No “miracle” drug has been found but Remdesivir and Dexamethasone (possibly Baricitinib) do offer benefit
- Basic public health measures such as hand washing, social distancing, and masking remain our best treatment

Questions?