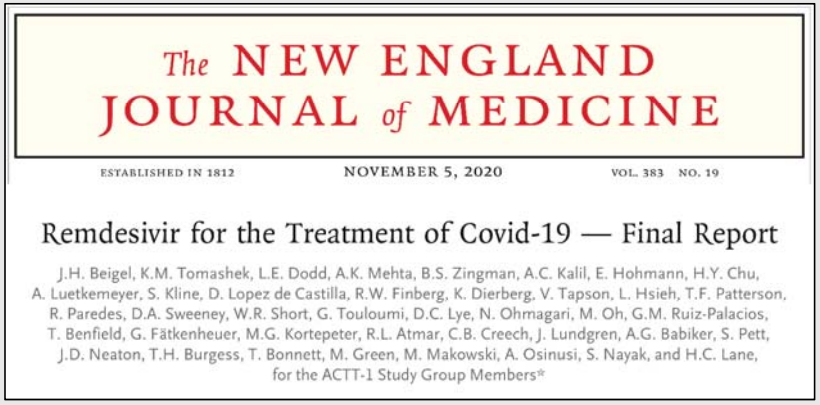
COVID: THERAPEUTICS

Ihab Dorotta, MD

Agenda: ABC

- A = Antiviral therapy/ARDS
- B = BLOOD CLOTS
- C = Cytokine storm or immune response

Antiviral therapy: Remdesivir early



The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 NOVEMBER 5, 2020 VOL. 383 NO. 19

Remdesivir for the Treatment of Covid-19 — Final Report

J.H. Beigel, K.M. Tomashek, L.E. Dodd, A.K. Mehta, B.S. Zingman, A.C. Kalil, E. Hohmann, H.Y. Chu, A. Luetkemeyer, S. Kline, D. Lopez de Castilla, R.W. Finberg, K. Dierberg, V. Tapson, L. Hsieh, T.F. Patterson, R. Paredes, D.A. Sweeney, W.R. Short, G. Touloumi, D.C. Lye, N. Ohmagari, M. Oh, G.M. Ruiz-Palacios, T. Benfield, G. Fätkenheuer, M.G. Kortepeter, R.L. Atmar, C.B. Creech, J. Lundgren, A.G. Babiker, S. Pett, J.D. Neaton, T.H. Burgess, T. Bonnett, M. Green, M. Makowski, A. Osinusi, S. Nayak, and H.C. Lane, for the ACTT-1 Study Group Members*

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Repurposed Antiviral Drugs for Covid-19 — Interim WHO Solidarity Trial Results

WHO Solidarity Trial Consortium*

50% faster time to recovery 15 days – 10 days
Lower progression to Mech. Ventilation

A: ARDS

- Awake proning only beneficial in some
- Saturation improves but the same number of patients will need intubation, MV and will die
- Time to intubation not associated with mortality
- No specific COVID ARDS data so old literature suggests:
  - Protective lung strategy
  - Intubated Proning
  - Paralysis
  - 60% survival.

B: Blood Clots. Anti thrombotic therapy: Anticoagulation

Patients with	28-day mortality: Treating with heparin, %	28-day mortality: Nontreating with heparin, %	Univariate analysis: Odds ratio (95% CI)	Univariate analysis: *P* value
SIC score ≥ 4 (n = 97)	40.0	64.2	0.372 (0.154-0.901)	.029
SIC score ≤ 4 (n = 352)	29.0	22.6	1.284 (0.700-2.358)	.419
D-dimer ≤ 1 ULN (n = 34)	33.3	9.7	4.667 (0.320-68.03)	.260
D-dimer > 1 ULN (n = 415)	30.2	32.7	0.934 (0.569-1.533)	.788
D-dimer > 2 ULN (n = 317)	32.1	36.9	0.810 (0.477-1.375)	.435
D-dimer > 3 ULN (n = 253)	31.1	42.5	0.611 (0.344-1.086)	.093
D-dimer > 4 ULN (n = 224)	33.3	44.5	0.623 (0.345-1.127)	.118
D-dimer > 5 ULN (n = 190)	34.9	48.8	0.563 (0.301-1.050)	.071
D-dimer > 6 ULN (n = 161)	32.8	52.4	0.442 (0.226-0.865)	.017
D-dimer > 8 ULN (n = 150)	33.3	54.8	0.412 (0.207-0.817)	.011

Abbreviation: ULN, upper limit of normal (0.5 μg/mL for D-dimer).

449 patients with COVID 19, d dimer level benefit. Significant at 6 x nl limits

ORIGINAL ARTICLE

Anticoagulant treatment is associated with decreased mortality in severe coronavirus disease 2019 patients with coagulopathy

Ning Tang[1] | Huan Bai[1] | Xing Chen[1] | Jiale Gong[1] | Dengju Li[2] | Ziyong Sun[1]

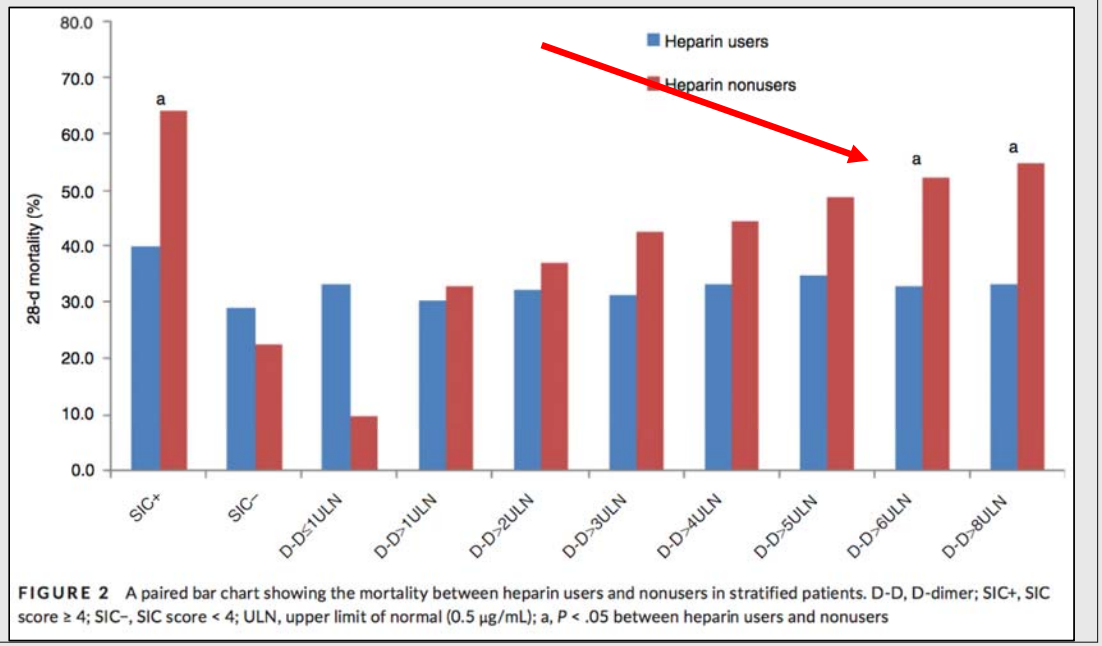


FIGURE 2 A paired bar chart showing the mortality between heparin users and nonusers in stratified patients. D-D, D-dimer; SIC+, SIC score ≥ 4; SIC−, SIC score < 4; ULN, upper limit of normal (0.5 μg/mL); a, *P* < .05 between heparin users and nonusers

B: Blood Clots. Anti thrombotic therapy: Anticoagulation

Journal of the American College of Cardiology
Volume 76, Issue 1, 7 July 2020, Pages 122-124

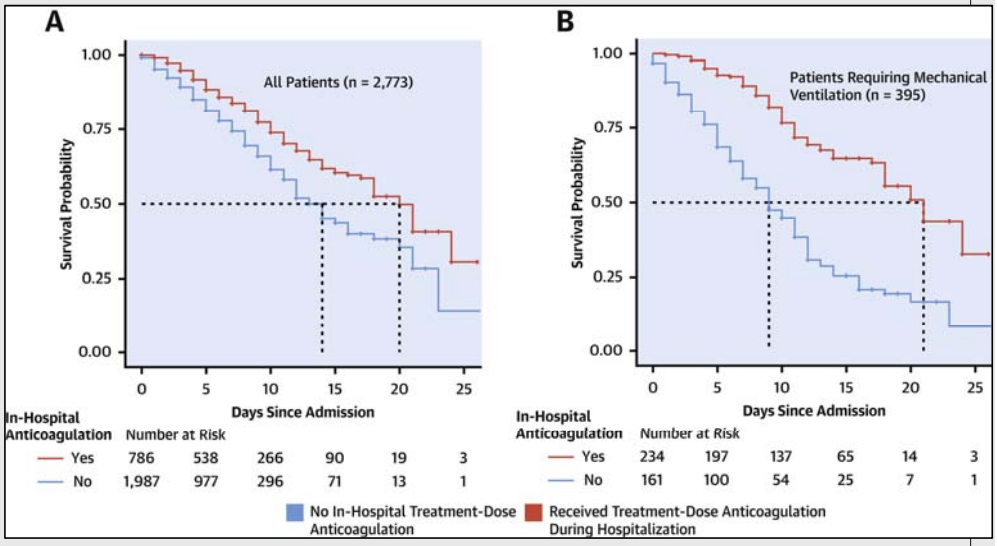
Letters

Association of Treatment Dose Anticoagulation With In-Hospital Survival Among Hospitalized Patients With COVID-19

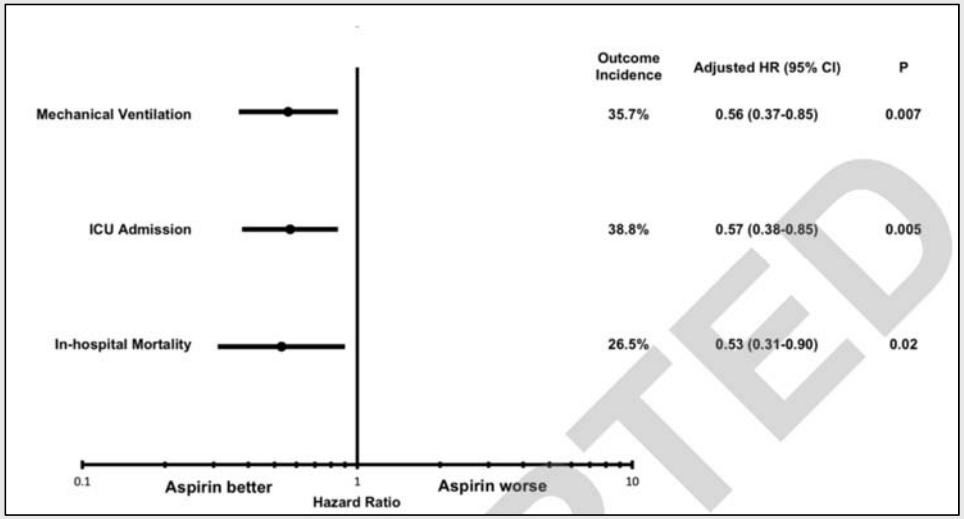
Ishan Paranjpe BS, Valentin Fuster MD, PhD, Anuradha Lala MD, Adam J. Russak MD, Benjamin S. Glicksberg PhD, Matthew A. Levin MD, Alexander W. Charney MD, PhD, Jagat Narula MD, PhD, Zahi A. Fayad PhD, Emilia Bagiella PhD, Shan Zhao MD, PhD, Girish N. Nadkarni MD, MPH

2773 patients, 786 receiving AC
Overall 22.5 vs 22.8% mortality
For MV patients 29.1 vs 62.7%

Association only

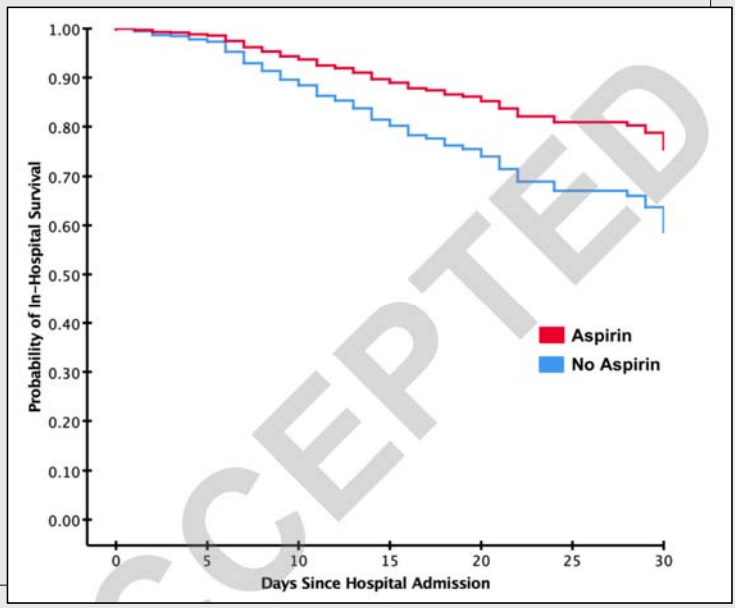


B: Blood clots. ASA



Aspirin Use is Associated with Decreased Mechanical Ventilation, ICU Admission, and In-Hospital Mortality in Hospitalized Patients with COVID-19

Chow, Jonathan H. MD; Khanna, Ashish K. MD[2,3]; Kethireddy, Shravan MD[4]; Yamane, David MD[5]; Levine, Andrea MD[6]; Jackson, Amanda M. MD, MAJ, MC, USA[7]; McCurdy, Michael T. MD[7]; Tabatabai, Ali MD[6,8]; Kumar, Gagan MD[4]; Park, Paul MD[9]; Benjenk, Ivy RN, MPH.[10]; Menaker, Jay MD[8,11]; Ahmed, Nayab MD[12]; Glidewell, Evan MD[13]; Presutto, Elizabeth MD[9]; Cain, Shannon M.D.[14]; Haridasa, Naeha B.S[10]; Field, Wesley MD[12]; Fowler, Jacob G. B.S.[13]; Trinh, Duy MD[9]; Johnson, Kathleen N. B.S.[13]; Kaur, Aman DO[12]; Lee, Amanda B.S.[9]; Sebastian, Kyle MD[13]; Ulrich, Allison MD[9]; Peña, Salvador MD, PhD[13]; Carpenter, Ross MD[9]; Sudhakar, Shruti MD[9]; Uppal, Pushpinder MD[9]; Fedeles, Benjamin T. MD, Capt., USAF, MC[9]; Sachs, Aaron MD[9]; Dahbour, Layth MD[9]; Teeter, William MD[8,15]; Tanaka, Kenichi MD[16]; Galvagno, Samuel M. DO, PhD[1,8]; Herr, Daniel L. MD[7]; Scalea, Thomas M. MD[8,11]; Mazzeffi, Michael A. MD, MPH[1,16]



- 412 patients. 24% received ASA
- Less MV 36 vs 48%
- Less ICU admissions 38 vs 51%
- After adjustment for 8 variables HR for mortality was 0.53

B: Blood clots

- Daily Aspirin might be helpful, less sick and less need for intubation
- DVT and PE common in COVID 19 patients
- DVT prophylaxis for all patients
- Full anticoagulation based on D-Dimer levels

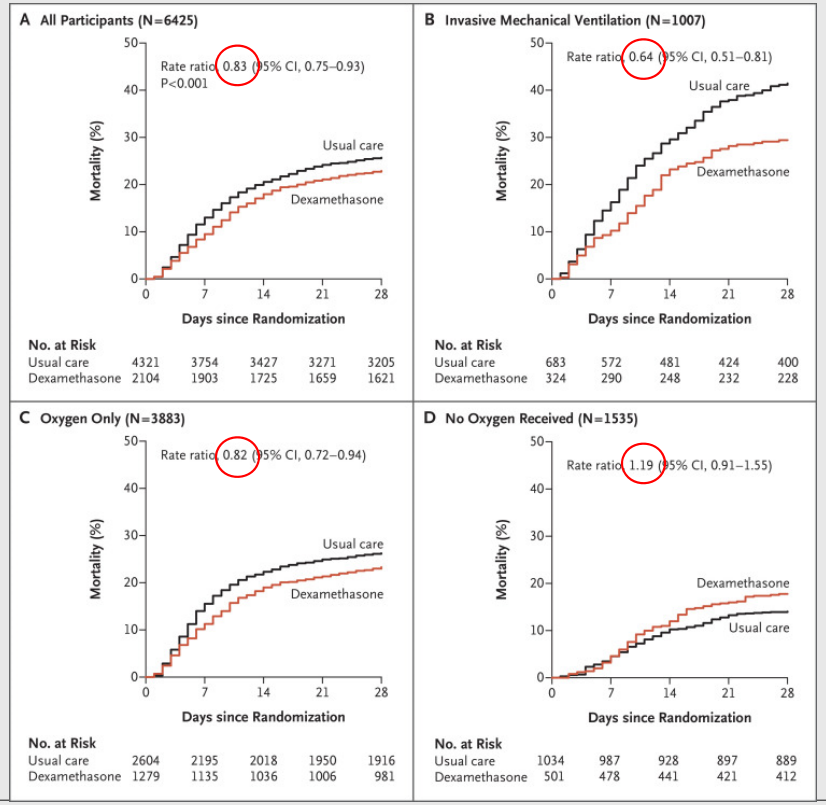
C: Cytokine storm.Dexamethasone: Recovery trial

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

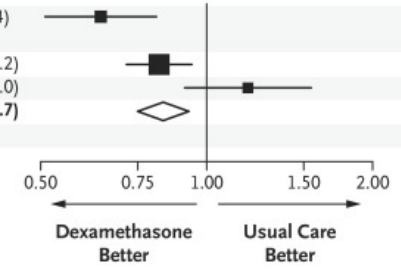
Dexamethasone in Hospitalized Patients with Covid-19 — Preliminary Report

The RECOVERY Collaborative Group*



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



C:Cytokine storm.Tocilizumab: Covacta

Roche provides an update on the phase III COVACTA trial of Actemra/RoActemra in hospitalised patients with severe COVID-19 associated pneumonia

- COVACTA trial did not meet its primary endpoint of improved clinical status in patients with COVID-19 associated pneumonia, or the key secondary endpoint of reduced patient mortality
- The study is the first global, randomised, double-blind, placebo-controlled phase III trial investigating Actemra/RoActemra in this setting
- Roche remains committed to continuing the Actemra/RoActemra clinical trial programme in COVID-19 to further explore Actemra/RoActemra in other treatment settings, including in combination with an antiviral

- 450 patients
- No difference in Mortality or need for oxygen therapy at 28 days
- Multiple phase III studies ongoing: REMDACTA, EMDACTA and MARIPOSA

Tocilizumab

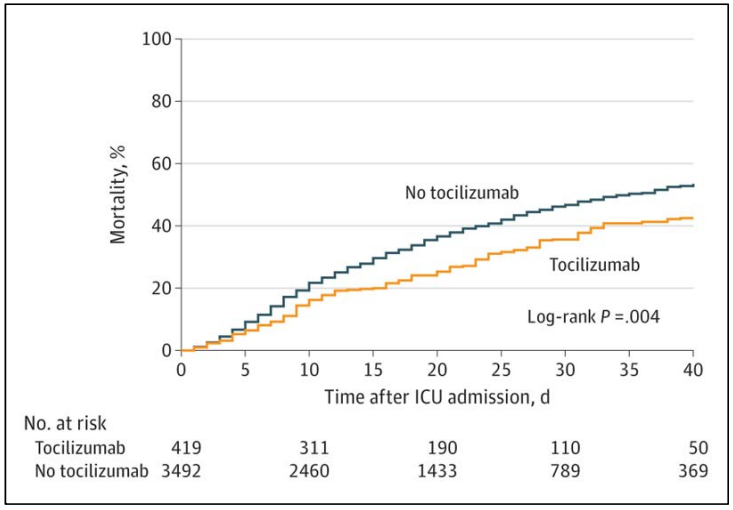
Original Investigation

October 20, 2020

Association Between Early Treatment With Tocilizumab and Mortality Among Critically Ill Patients With COVID-19

Shruti Gupta, MD, MPH[1]; Wei Wang, PhD[2]; Salim S. Hayek, MD[3]; et al

Source	No. of deaths / No. of patients (%) Tocilizumab	No tocilizumab	Adjusted HR (95% CI)	P value for interaction
Primary analysis	125/433 (28.9)	1419/3491 (40.6)	0.71 (0.56-0.92)	NA
Sensitivity analyses				
Without censoring at discharge	125/433 (28.9)	1419/3491 (40.6)	0.72 (0.56-0.93)	NA
Unweighted Cox model	125/433 (28.9)	1419/3491 (40.6)	0.75 (0.62-0.91)	NA
Nested target trial approach	125/433 (28.9)	1419/3491 (40.6)	0.64 (0.50-0.81)	NA
Exclusion of moribund patients[a]	119/426 (27.9)	1339/3392 (39.5)	0.71 (0.55-0.92)	NA
Adjustment for No. of ICU beds	125/433 (28.9)	1419/3491 (40.6)	0.71 (0.55-0.90)	NA
Subgroups				
Age, y				.40
<60	57/240 (23.8)	366/1425 (25.7)	0.80 (0.57-1.12)	
≥60	68/193 (35.2)	1053/2066 (51.0)	0.66 (0.49-0.89)	
Sex				.96
Male	88/299 (29.4)	925/2165 (42.7)	0.71 (0.52-0.97)	
Female	37/134 (27.6)	494/1326 (37.3)	0.72 (0.48-1.08)	
Time from symptom onset to ICU admission, d				.03
≤3	15/58 (25.9)	429/835 (51.4)	0.41 (0.23-0.74)	
>3	110/375 (29.3)	990/2656 (37.3)	0.85 (0.65-1.11)	
PaO_2:FiO_2 ratio on ICU admission				.14
≥200 Or not mechanically ventilated	48/188 (25.5)	581/1834 (31.7)	0.88 (0.58-1.35)	
<200 And mechanically ventilated	65/205 (31.7)	663/1322 (50.2)	0.59 (0.43-0.81)	
Vasopressor treatment on ICU admission				.60
No	68/254 (26.8)	769/2126 (36.2)	0.76 (0.53-1.07)	
Yes	57/179 (31.8)	650/1365 (47.6)	0.66 (0.47-0.93)	
Corticosteroid treatment on ICU admission				.83
No	91/352 (25.9)	1189/3051 (39.0)	0.71 (0.53-0.96)	
Yes	34/81 (42.0)	230/440 (52.3)	0.68 (0.46-0.99)	



4485 patients in 68 hospitals in the US.
27% vs 37 % favoring TOCI given in the ICU
Toci patients were younger and less sick
Toci arms also received more therapeutic agents

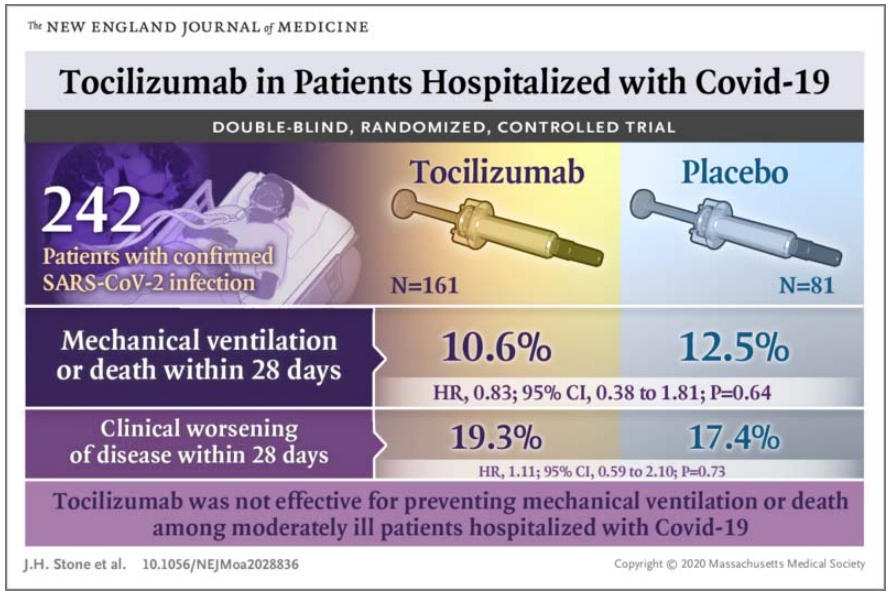
The NEW ENGLAND JOURNAL of MEDICINE

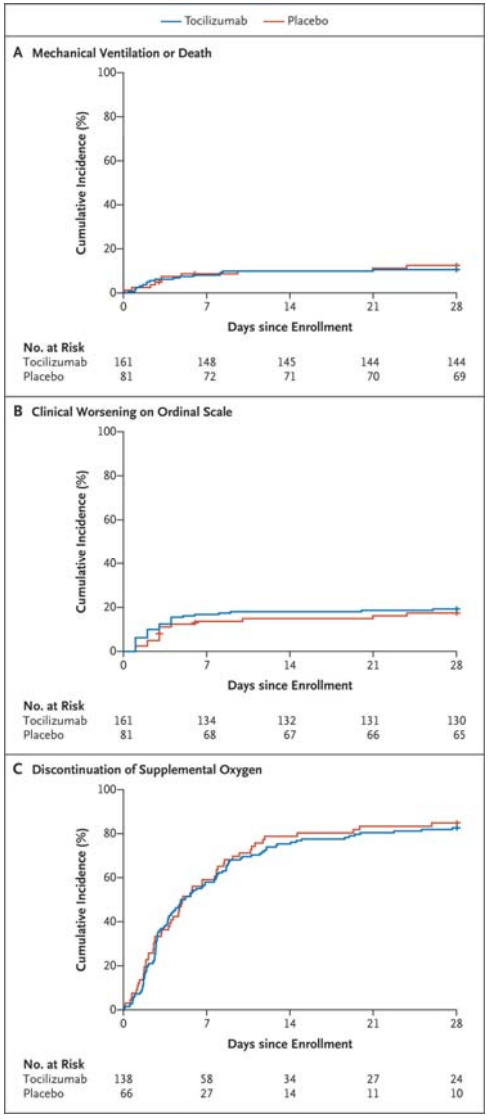
ORIGINAL ARTICLE

Efficacy of Tocilizumab in Patients Hospitalized with Covid-19

J.H. Stone, M.J. Frigault, N.J. Serling-Boyd, A.D. Fernandes, L. Harvey, A.S. Foulkes, N.K. Horick, B.C. Healy, R. Shah, A.M. Bensaci, A.E. Woolley, S. Nikiforow, N. Lin, M. Sagar, H. Schrager, D.S. Huckins, M. Axelrod, M.D. Pincus, J. Fleisher, C.A. Sacks, M. Dougan, C.M. North, Y.-D. Halvorsen, T.K. Thurber, Z. Dagher, A. Scherer, R.S. Wallwork, A.Y. Kim, S. Schoenfeld, P. Sen, T.G. Neilan, C.A. Perugino, S.H. Unizony, D.S. Collier, M.A. Matza, J.M. Yinh, K.A. Bowman, E. Meyerowitz, A. Zafar, Z.D. Drobni, M.B. Bolster, M. Kohler, K.M. D'Silva, J. Dau, M.M. Lockwood, C. Cubbison, B.N. Weber, and M.K. Mansour, for the BACC Bay Tocilizumab Trial Investigators*

EMPACTA Trial:
Randomized double blind placebo controlled





Monoclonal Antibodies: Bamlanivimab BLAZE trial

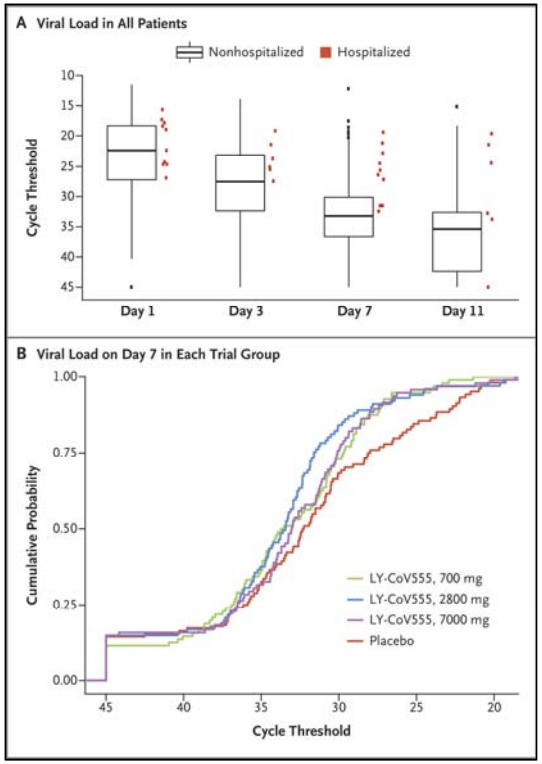


Table 3. Hospitalization.*

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 include this category.

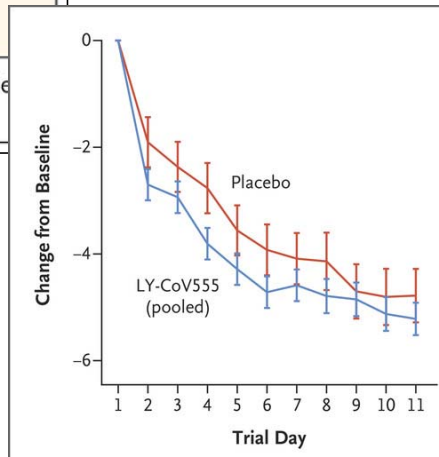
452 participants within 3 days of a positive text
ACTIV-3 trial for inpatient Bmab → NO BENEFIT

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

SARS-CoV-2 Neutralizing Antibody LY-CoV555 in Outpatients with Covid-19

Peter Chen, M.D., Ajay Nirula, M.D., Ph.D., Barry Heller, M.D., Robert L. Gottlieb, M.D., Ph.D., Joseph Boscia, M.D., Jason Morris, M.D., Gregory Huhn, M.D., M.P.H.T.M., Jose Cardona, M.D., Bharat Mocherla, M.D., Valentina Stosor, M.D., Imad Shawa, M.D., Andrew C. Adams, Ph.D., Jacob Van Naarden, B.S., Kenneth L. Custer, Ph.D., Lei Shen, Ph.D., Michael Durante, M.S., Gerard Oakley, M.D., Andrew E. Schade, M.D., Ph.D., Janelle Sabo, Pharm.D., Dipak R. Patel, M.D., Ph.D., Paul Klekotka, M.D., Ph.D., and Daniel M. Skovronsky, M.D., Ph.D., for the BLAZE-1 Investigators*



	Delta Value (95% CI)
Day 2	−0.79 (−1.35 to −0.24)
Day 3	−0.57 (−1.12 to −0.01)
Day 4	−1.04 (−1.60 to −0.49)
Day 5	−0.73 (−1.28 to −0.17)
Day 6	−0.79 (−1.35 to −0.23)
Day 7	−0.50 (−1.06 to 0.07)
Day 8	−0.65 (−1.28 to −0.02)
Day 9	−0.15 (−0.75 to 0.45)
Day 10	−0.32 (−0.94 to 0.29)
Day 11	−0.44 (−1.02 to 0.15)

FLCCC ALLIANCE

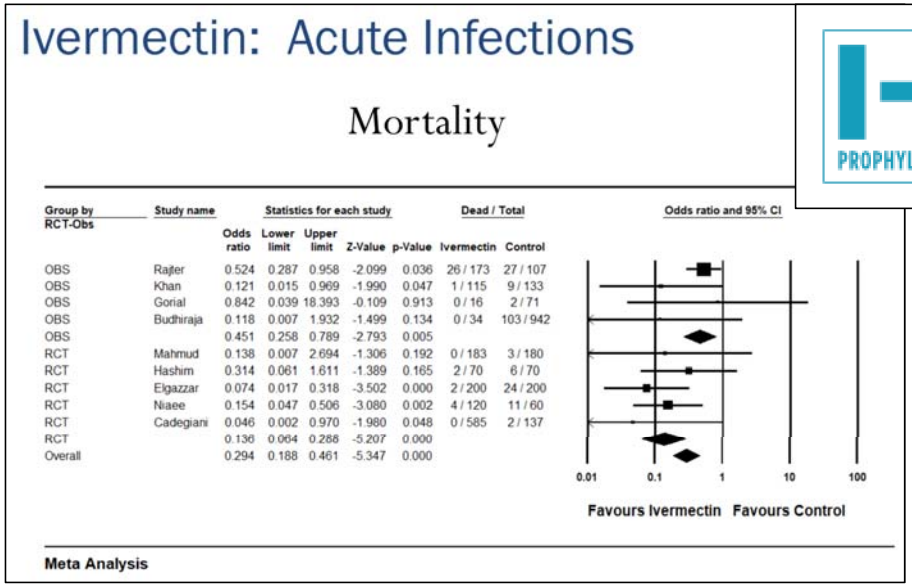
Front Line COVID-19 Critical Care Alliance
Prophylaxis & Treatment Protocols for COVID-19

ABOUT | I-MASK+ PROTOCOL | MATH+ PROTOCOL | MEDICAL EVIDENCE | NETWORK & SUPPORT | MEDIA

Front Line COVID-19 Critical Care Alliance

Ivermectin: Acute Infections

Mortality



I-MASK+
PROPHYLAXIS & EARLY OUTPATIENT TREATMENT PROTOCOL FOR COVID-19

MATH+
HOSPITAL TREATMENT PROTOCOL FOR COVID-19

- Presented to the NIH on January the 7th.

IVERMECTIN

- Multiple studies in outpatient and inpatient settings.
- not powered enough
- Many confounders not adjusted for.

- January 14th update:

The Panel has determined that there are insufficient data to recommend either for or against the use of ivermectin for the treatment of COVID-19. Results from adequately powered, well-designed, and well-conducted clinical trials are needed to provide further guidance on the role of ivermectin in the treatment of COVID-19.

C: Cytokine storm

- Steroids helpful for HFNC/MV patients, Harmful early
- Outpatient early treatment with monoclonal antibodies
- Unknown effect for immunomodulators (Toci and Anakinra) as of yet.

SO old principles still apply:

- Early decrease of **viral Load** Matters:
  - Monoclonal antibodies "Bmab" if you are outpatient
  - Remdesivir if you are inpatient and need Oxygen
  - NO BENEFIT if you are admitted on HFNC or Intubated.
- Mitigating the **immune response** late:
  - Steroids helpful Late, harmful early
  - Immunomodulators. No Benefit as of yet

What are others doing?

Clinical Guideline

COVID-19 Clinical Management

Last updated: January 5, 2021

Recommendation Summary

Click name to view the full section for that therapy for additional details and a summary of the available evidence.

✓ = use **recommended** O = may consider, no recommendation for or against X = use NOT recommended

Therapy	COVID-19 severity / Supplementary oxygen requirement: Outpatient – no supp. O_2	Inpatient – no supp. O_2	Low-flow O_2	High-flow O_2 or mechanical ventilation	Notes
Antivirals					
Remdesivir	X	X	O	X	Recommended course ≤ 5 days (d/c at discharge if < 5 days)
Hydroxychloroquine Interferon ± ribavirin Ivermectin Lopinavir/ritonavir	X	X	X	X	
Immunomodulators					
Dexamethasone	X	X	✓	✓	Recommended course ≤ 10 days (d/c at discharge if < 10 days)
Baricitinib Tocilizumab Other immunomodulators	X	X	X	X	
Antibody Therapy					
Monoclonal antibodies (incl. bamlanivimab or casirivimab + imdevimab)	O*	X	X	X	*see full AH Use Criteria
Convalescent plasma	X	X	X	X	
Miscellaneous					
Azithromycin; Colchicine; Fenofibrate; Nitazoxanide	X	X	X	X	
Thiamine; Vitamin C/D; Zinc	O	O	O	O	

Questions

- Remdesivir and steroids for pediatric and pregnant population
- If you do not have the test use the EWS.
- If antiviral medications are scarce focus on indicated steroids, anticoagulation and antibiotics +/- Ivermectin
- Vitamins, ASA as outpatients
- Resource allocation:
  - Proactive plan based on likelihood of survival
  - Age, SOFA scores, co-morbidities

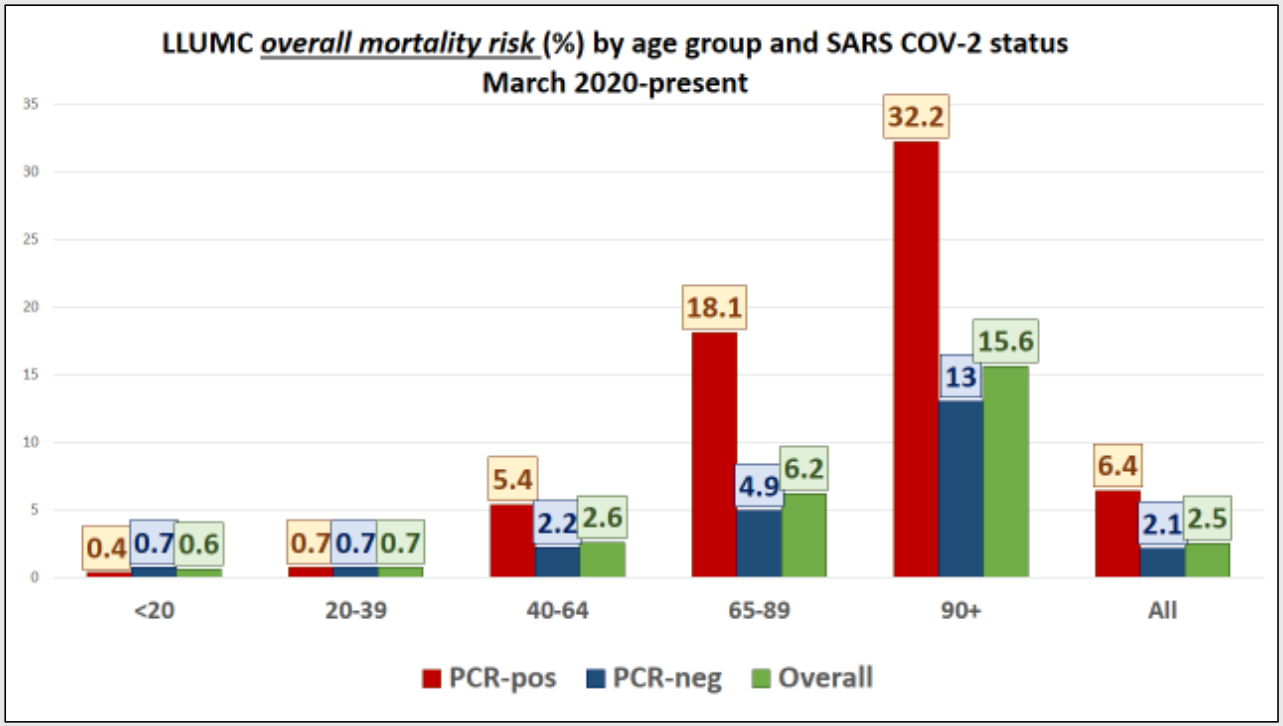
COVID-19 Early Warning Score (COVID-19 EWS)

Parameters	Assessment	Score
Signs of pneumonia on CT	Yes	5
History of close contact with COVID-19 confirmed patient	Yes	5
Fever	Yes	3
Age	≥ 44 years old	1
Sex	Male	1
Tmax[a]	≥ 37.8 ℃ (100 ℉)	1
Meaningful respiratory symptoms (including cough, expectoration, and dyspnea)	≥ 1 sympotom	1
NLR[b]	≥ 5.8	1
Highly suspected patient		≥ 10

*SARS-CoV-2 nucleicacid detection positive is the independent diagnostic indicator.
[a]Tmax: the highest body temperature from illness onset to first hospital admission
[b]NLR: neutrophil-to-lymphocyte ratio

Song CY et al. COVID-19 Early Warning Score: A multi-parameter screening tool to identify highly suspected patients. MedRxIV 2020; **doi:** https://doi.org/10.1101/2020.03.05.20031906

Loma Linda Mortality



Thank you