VCU Health Cardiology Grand Rounds

“Pharmacotherapy for COVID-19 pneumonia: a clinical translational update”

Antonio Abbate, MD, PhD

Educational Objectives:
Understand the challenges of conducting research during the COVID-19 pandemic
Understand the key pathophysiological therapeutic aspects of COVID-19 research
Review the preliminary results of COVID-19 research to date

Code for CME Credit

TEXT: 15186-15155

to 804-625-4041

*** DO NOT FORGET THE DASH IN CODE ***

Pharmacotherapy for COVID-19 pneumonia: a clinical translational update

Antonio Abbate, MD, PhD

'James C. Roberts Esq.' - Professor of Cardiology

Associate Director – *Wright* Center for Clinical and Translational Research

Medical Director – Clinical Research Unit

Virginia Commonwealth University

Department of Internal Medicine

Richmond, VA, USA

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VCU Pauley Heart Center

Virginia Commonwealth University

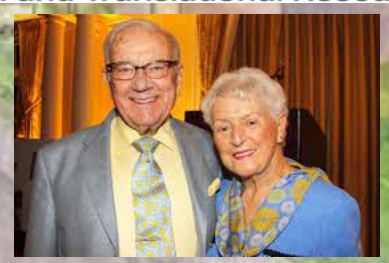
VCU

VIRGINIA COMMONWEALTH UNIVERSITY

C. Kenneth and Dianne Wright Center for Clinical and Translational Research

James C. Roberts, Esquire

… a man of great character and integrity, and yet completely approachable by the newest and youngest lawyer seeking encouragement or advice. He is a shining example of how lawyers can serve the community and their profession … VA State Bar May 17, 2007



Disclosures

Research support: Dr. Abbate has received research support from Janssen, Kiniksa, Novartis, Olatec, Regeneron, Serpin Pharma, Swedish Orphan Biovitrum

Consultant work: Dr. Abbate has served as a consultant to Astra Zeneca, Janssen, Kiniksa, Merck, Novartis, Olatec, Serpin Pharma, Swedish Orphan Biovitrum

Additional Disclosures

Clinical information for COVID-19 is rapidly evolving, please do not consider the date contained herein as necessarily up-to-date.

Statements presented herein are my own considerations NOT clinical recommendations.

Clinical recommendations for care of patients with suspected or confirmed COVID-19 are available through the VCU Health Department of Infectious of Disease as well as other national and international organizations such as the Center of Disease Control and World Health Organization, such recommendations are frequently revised and updated.

Additional Disclosures (2)

- Much of what I presenting today is the results of daily discussions within the COVID-19 Clinical Trial team, therefore special thanks to Benjamin Van Tassell, PharmD; Roshi Markley, MD; Melissa Sears, RN; Aldo Bonaventura, MD; Alessandra Vecchiè, MD; Yub Sedhai, MD; Jane Ho, PharmD; Virginia Mihalick, MS; George Wohlford, PharmD; Anna Priday, MS, and others, and to Michael Stevens, MD, from the Division of Infectious Disease.
- Dr. Abbate is also part of CCTR COVID-19 Clinical Trial Committee led by Dr. F. Gerard Moeller that reviewed, discussed, and triaged COVID-19 clinical trials.

Additional Disclosures (3)

- In March 2020, Dave Dixon, PharmD, and I led a review article published in the Journal of Cardiovascular Pharmacology, while much of the content is outdated, I owe the structure of this presentation to the initial discussions held with Dr. Dixon
- In April 2020, Michael Kontos, MD, and I presented on Cardiovascular Manifestations of COVID-19, and in May 2020, Dr. Kontos, with Dr. Dixon and Ajay Pillai, MD, presented at Hospital Medicine Grand Rounds – I have built on those presentations to provide an update for you today

CoVID-19

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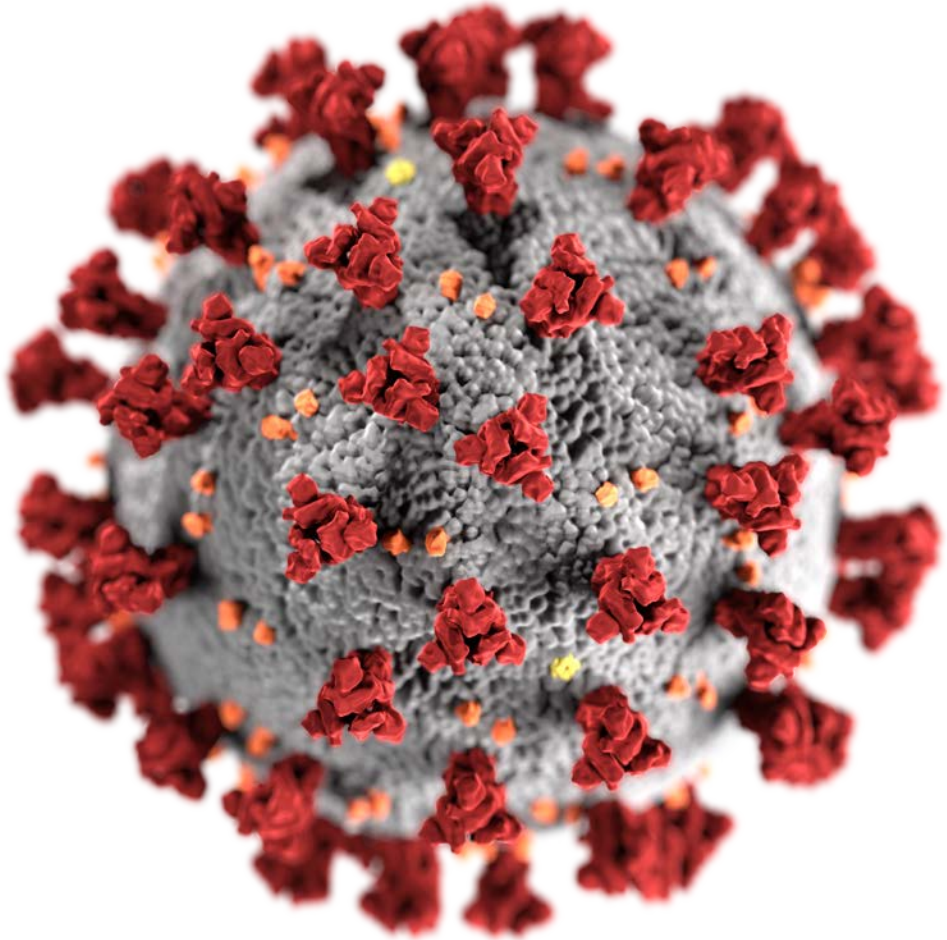

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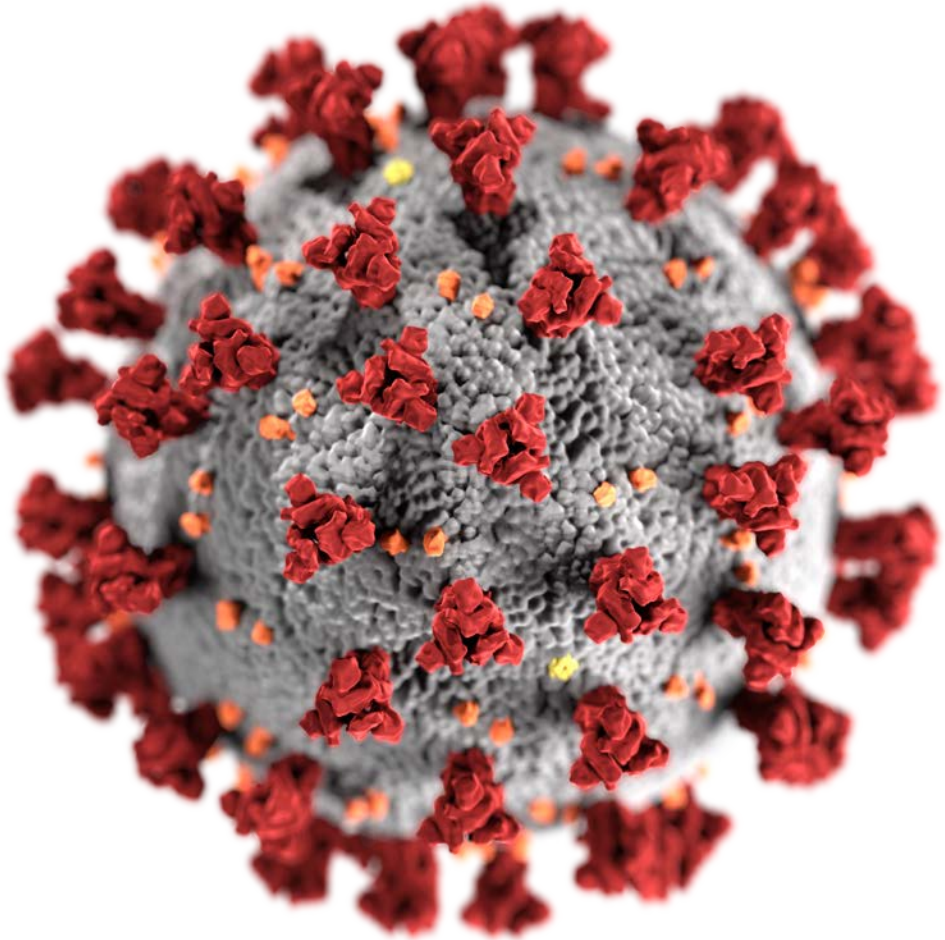

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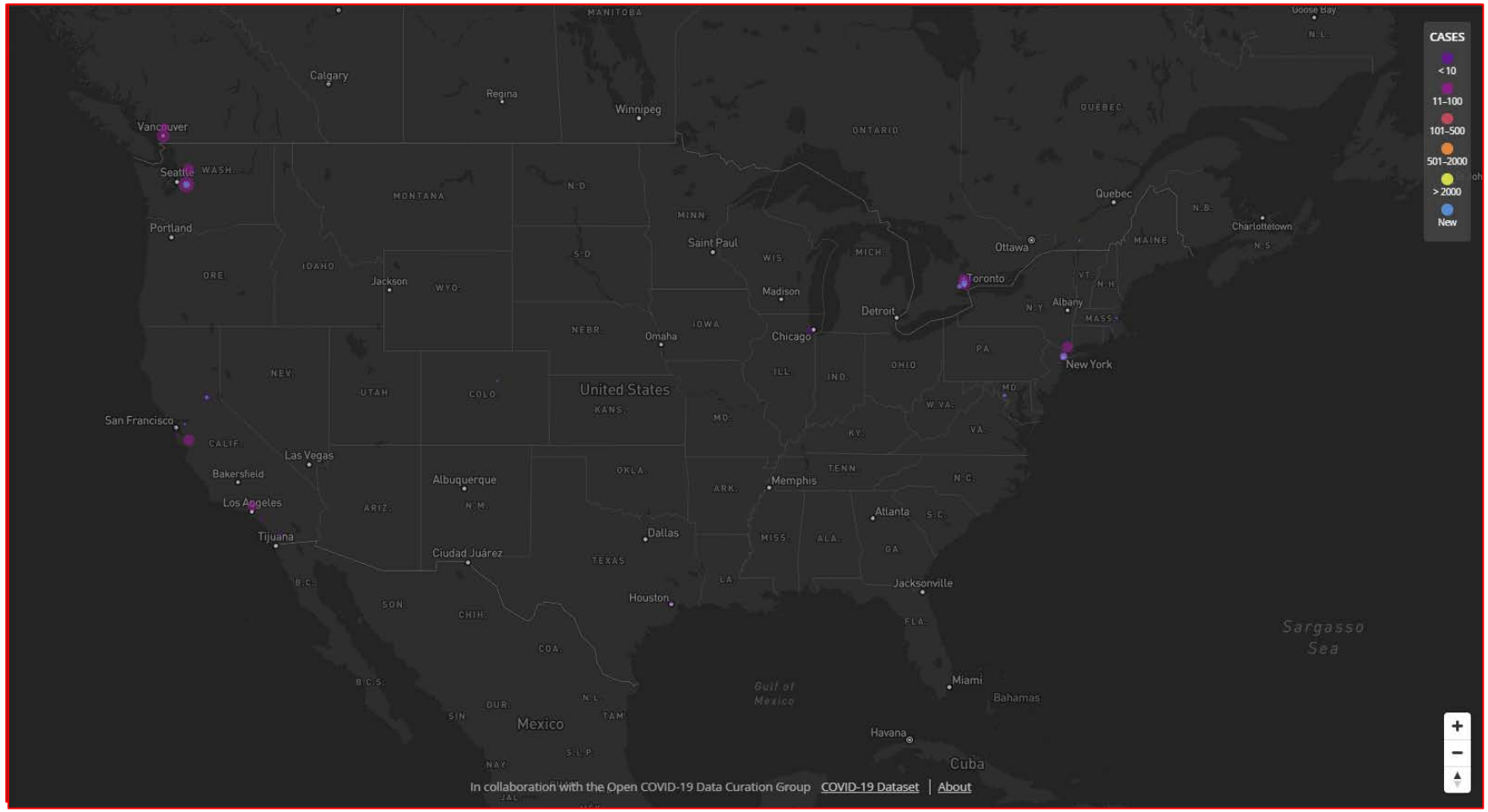
CoVID-19 | Impact of CoVID-19 in USA

- 1.5.20
- 3.5.20



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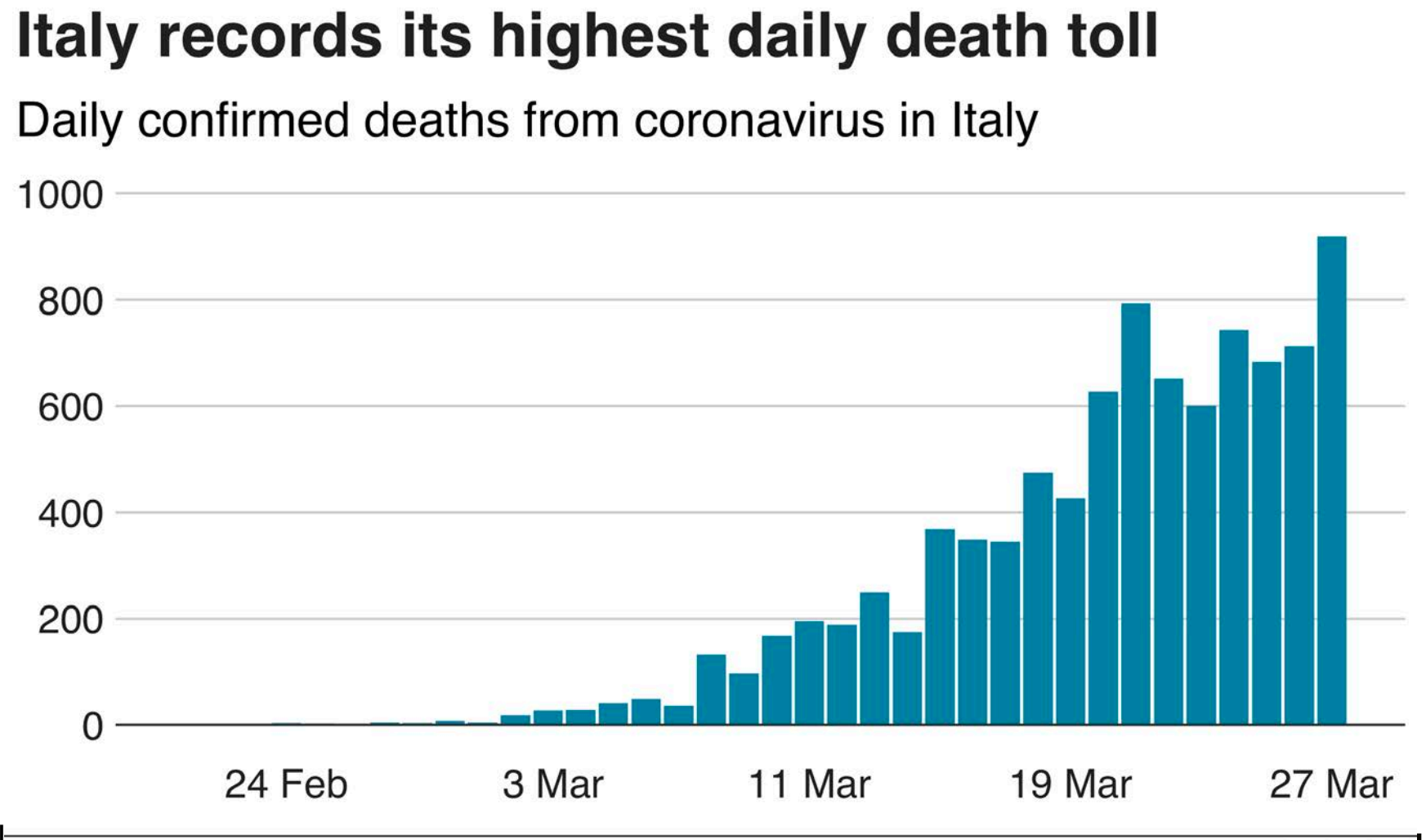
CoVID-19 | Impact of CoVID-19 in Italy



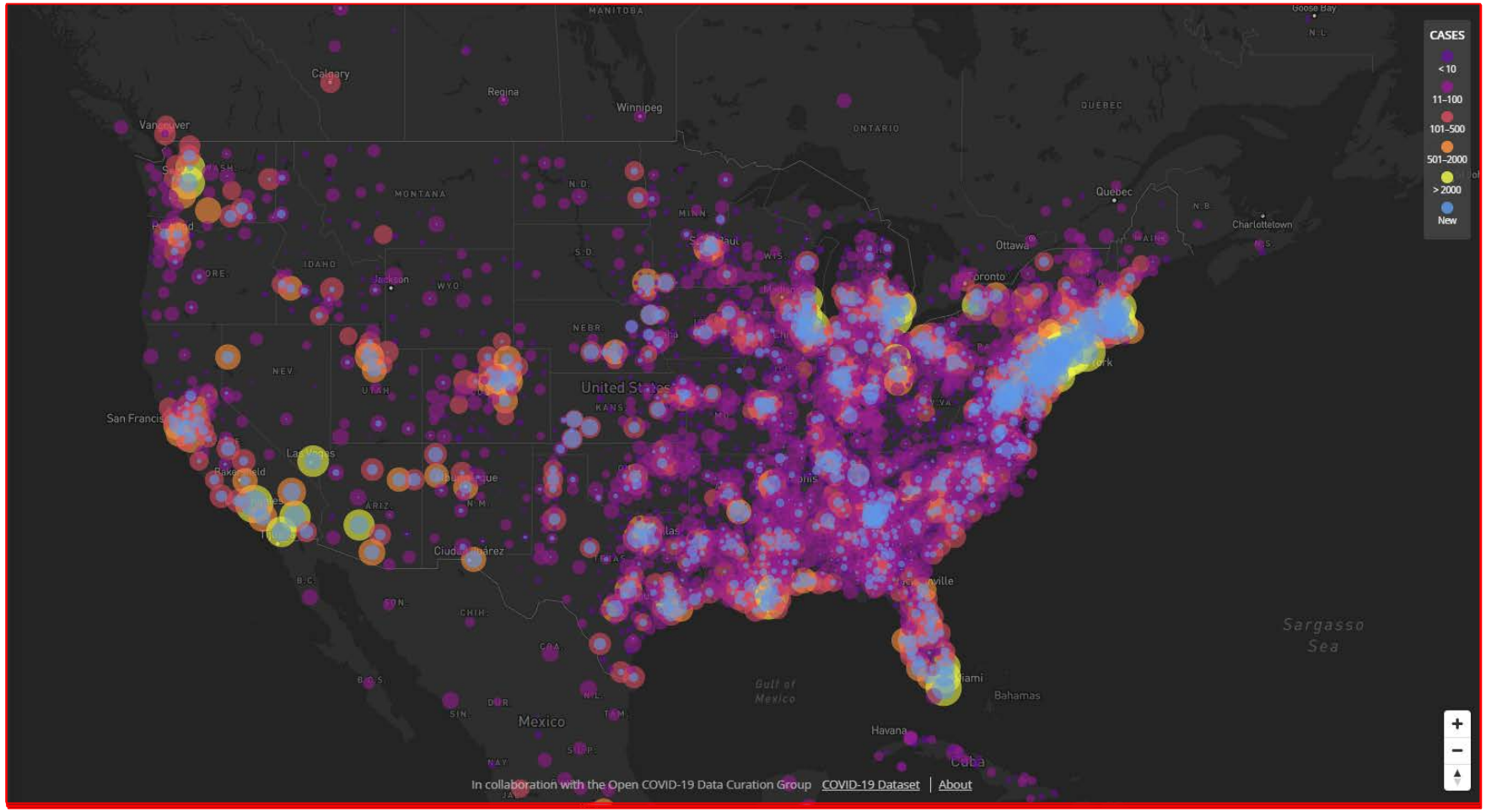
CoVID-19

Activating COVID-19 research at VCU Health

- Early March: realization that COVID-19 was about to hit USA
- Data from Italy showing a logarithmic rise in death toll
- VCU Health Infectious Disease team reviewing evidence for drugs :
  - Hydroxychloroquine? Widely available – but efficacious? Safe?
  - Lopinavir/Ritonavir? Widely available – but efficacious?
  - Remdesivir? Not available
- Urgent need to find access to better treatments
  - Fight against time

CoVID-19 | Impact of CoVID-19 in USA

- 1.5.20
- 3.5.20
- 3.20.20
- 4.5.20
- 4.23.20



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VCU Pauley Heart Center

CoVID-19 | Urgent need to find access to COVID-19 treatments

- Where to start? What challenges?
  - Time required to set up research studies
  - Challenges associated with conducting research during pandemic
  - Poor understanding of virus
  - Poor understanding of the disease
  - Rapidly evolving scenarios

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CoVID-19

Time required to set up a NEW clinical trial

• Average time to start up a new Industry clinical trial (where an IND has already been obtained)	120-180 days
• Average time to obtain a new IND for a drug already approved for another indication	30-60 days
• Average time to obtain a new IND for a drug NOT previously approved	90-120 days

Unacceptably long times

CoVID-19

CCTR COVID-19 Clinical Trial Committee

- Goal to gather and coordinate resource to support COVID-19 clinical trials: *all hand on deck* approach
  - Strong Collaborative Work between VCU and VCU Health Research Leadership (Mary Harmon & Lisa Ballance)
  - Dedicated staff 7 day/week from Office of Sponsored Program
  - Dedicated staff from Fiscal Administration
  - Dedicated IRB panel for COVID-19 research
  - Allocation of dedicated nursing staff for training and support
  - Selection of trials based on merit and creation of triaging protocol

CoVID-19

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CoVID-19

Selection of trials by the CCTR committee

High Impact Studies

- Strong rationale – specific to COVID-19 (clear pathophysiologic mechanism)
- Multi-center trials with coordination by a Clinical Research Organization
- Phase III clinical trials
- Drugs that are FDA approved and/or have a known safety/risk profile

Low Impact Studies

- Incomplete developed rationale (i.e. vague mechanisms)
- Single-center studies exploring a small number of patients
- Lack of coordination by a Clinical Research Organization
- Phase I-II clinical trials
- Drugs without unknown safety risk profile

CoVID-19

Time required to set up a NEW clinical trial

- Average time to start up a new Industry clinical trial (where an IND has already been obtained)
- Average time to obtain a new IND for a drug already approved for another indication
- Average time to obtain a new IND for a drug NOT previously approved

<7-14 days

Not needed as selecting industry studies with active INDs (for the most part)

Acceptable results – 2 studies up and running by end of March

CoVID-19

VIRGINIA'S NEWS LEADER

Richmond Times-Dispatch

$2.00 · MONDAY, APRIL 27, 2020 · NEWS 24/7 AT RICHMOND.COM · FINAL

Va. researchers ramp up clinical trials to try to find treatments for COVID-19

Dr. F. Gerard Moeller chairs the committee at Virginia Commonwealth University that reviews new clinical trials.

BY BRIDGET BALCH
Richmond Times-Dispatch

For the doctors treating the hundreds of patients who are hospitalized for COVID-19 in Virginia, there's no playbook.

The disease that has spread rapidly across the world — killing hundreds in the state and more than 200,000 worldwide — has no known treatment, so COVID-19 has presented a unique challenge to the doctors faced with saving lives against a mostly unknown enemy.

But in an effort to discover treatments, medical researchers in the state have dropped everything to ramp up experimental clinical trials that may be the patients' best hope of recovery.

When Dr. Antonio Abbate speaks with patients about the possibility of joining a clinical trial, he's used to standing next to the patients, holding their hands and looking into their eyes.

Joining a clinical trial means he or she is volunteering to receive an experimental treatment that has not been proven to be effective. Abbate, the medical director of the clinical research unit at VCU Medical Center, has to tell them about the possible benefits and risks.

But in the new reality where physical proximity means greater danger for health care workers and patients alike, he's had to get accustomed to having those conversations by video chat.

TREATMENTS, Page A11

VCU Childcare Co-op

Medical students offer to watch kids, pets of health care workers. Page A2

NO PLAYBOOK FOR DOCTORS TREATING PATIENTS

"We're not jumping steps; we're just working nights and weekends to make things happen. I am optimistic that we will have treatments within months."

Dr. Antonio Abbate, the medical director of the clinical research unit at VCU Medical Center

BOB BROWN/TIMES-DISPATCH

Dr. Antonio Abbate (left), Dr. Arun Sanyal and Dr. Marjolein de Wit stand outside VCU Medical Center at 11th and Clay streets in downtown Richmond. The three are leading the medical center's clinical trials to try to find treatments for COVID-19.

VCU Health

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CoVID-19 | Urgent need to find access to COVID-19 treatments

- Where to start? What challenges?
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CoVID-19 | Challenges associated with conducting research

Unprecedented challenges

- Physical barriers
  - Closed rooms (limited access)
  - PPE shortage
- Psychological challenges
  - Fear
  - Unknown
- Additional barriers
  - Language (Hispanic community)

CoVID-19 Challenges associated with conducting research

Solutions

- Teamwork
  - Primary team / consultants
  - Nurse leaders/educators (Joni Greer Alison Montpetit, CRU nurses)
- Technology
  - iPhone/iPad
  - Email
- Additional help
  - Translation service

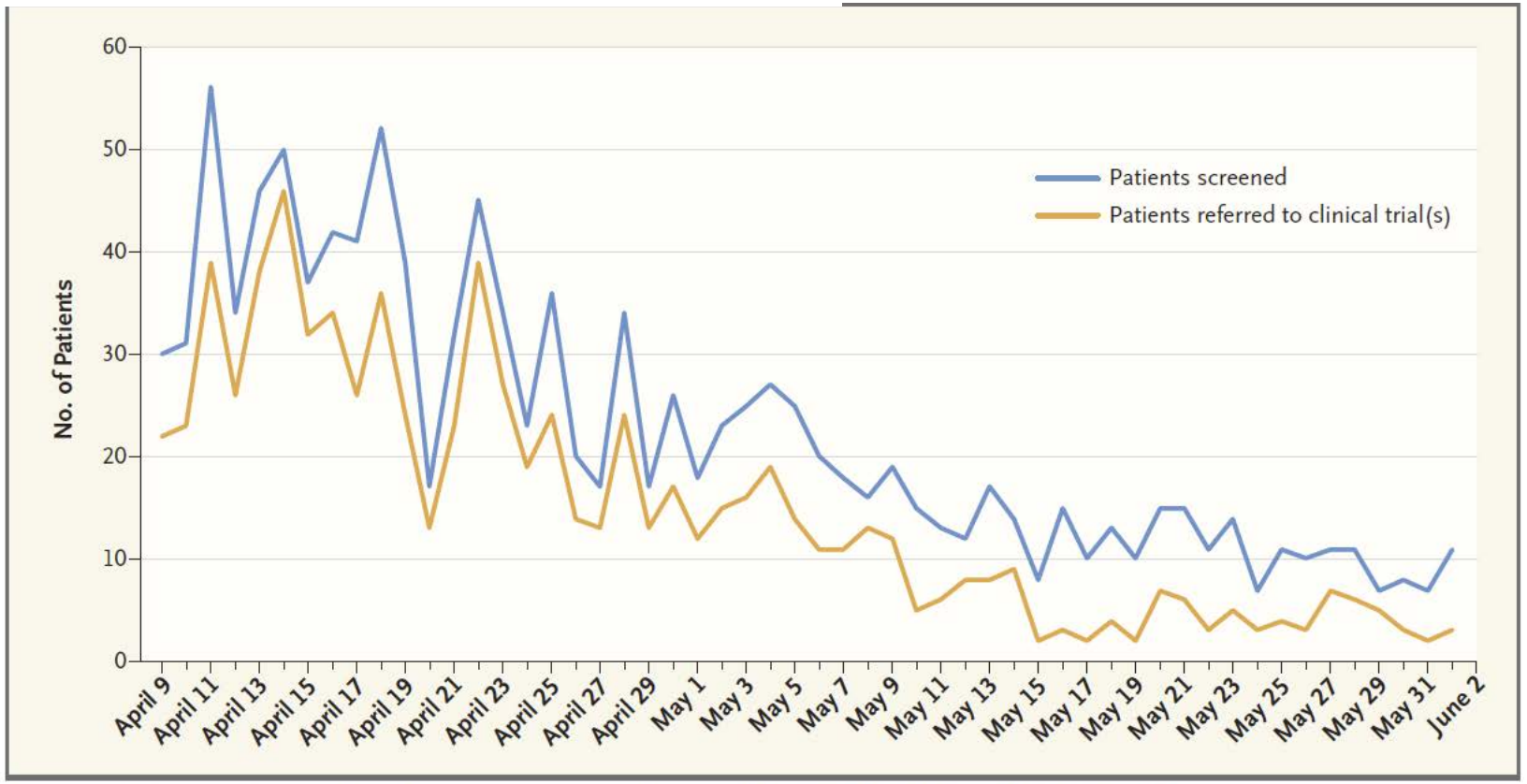
CoVID-19

Perspective

Improving Clinical Trial Enrollment — In the Covid-19 Era and Beyond

Crystal M. North, M.D., M.P.H., Michael L. Dougan, M.D., Ph.D., and Chana A. Sacks, M.D., M.P.H.

N Engl J Med 2020



Number of Patients Screened at Massachusetts General Hospital for Covid-19 Clinical Trials, April 9 to June 1, 2020.

CoVID-19 | Urgent need to find access to COVID-19 treatments

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CoVID-19

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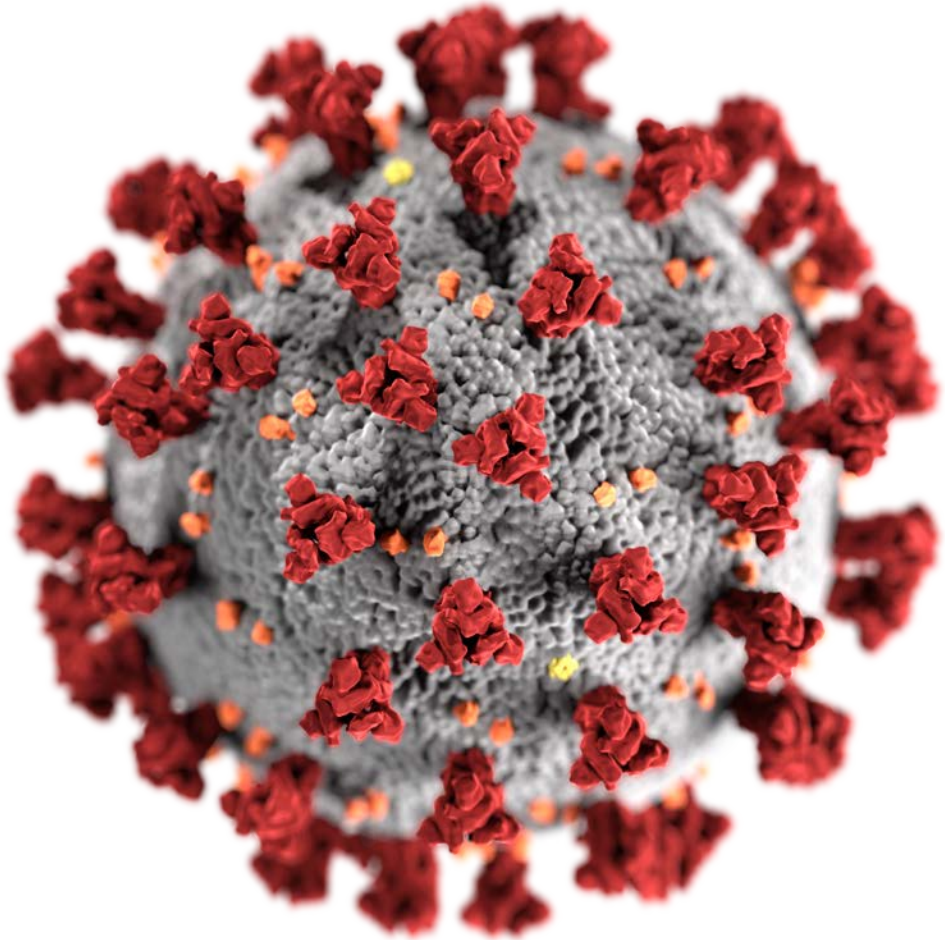

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CoVID-19 | SARS-CoV2: Structure & Cell Entry

- Positive-sense single-stranded RNA virus.
- Approximately 50-200nm in diameter.
- Initial reservoir likely the horseshoe bat.

- Gains entry via ACE2 receptor in concert with host's TMPRSS2 membrane protease.
- ACE2 expression: lymphocytes/dendritic cells, lung, GI smooth muscle, heart/vascular endothelium

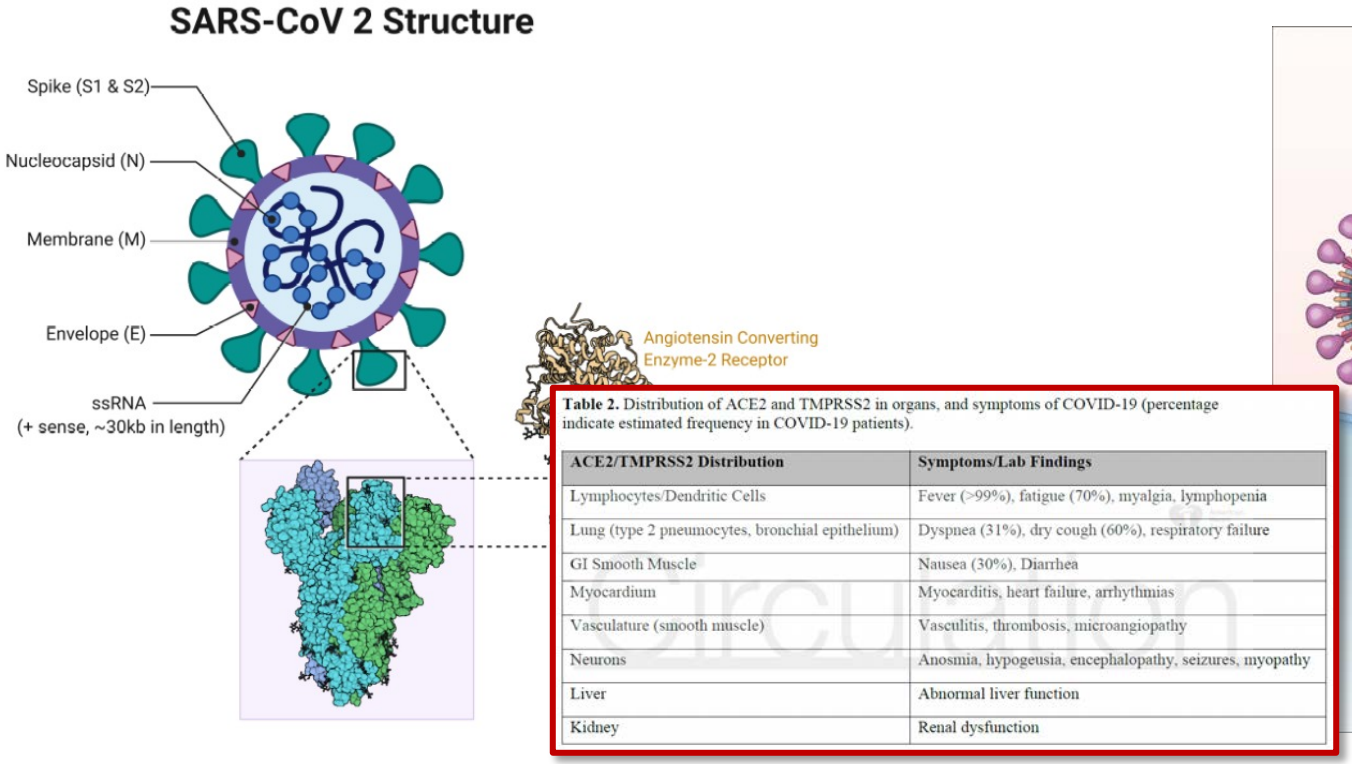
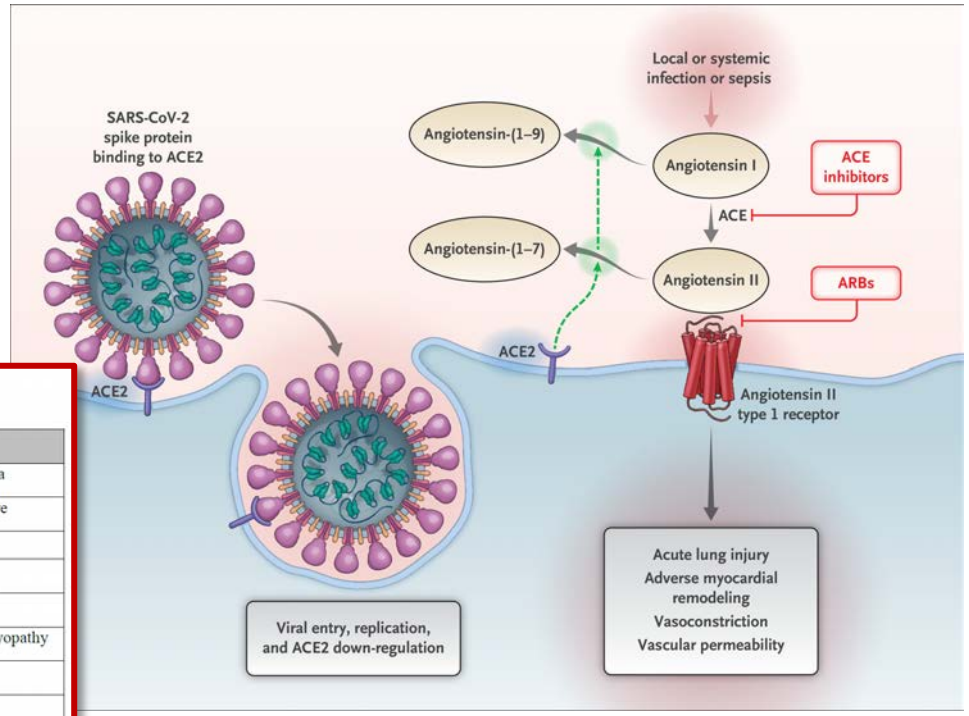


Table 2. Distribution of ACE2 and TMPRSS2 in organs, and symptoms of COVID-19 (percentage indicate estimated frequency in COVID-19 patients).

ACE2/TMPRSS2 Distribution	Symptoms/Lab Findings
Lymphocytes/Dendritic Cells	Fever (>99%), fatigue (70%), myalgia, lymphopenia
Lung (type 2 pneumocytes, bronchial epithelium)	Dyspnea (31%), dry cough (60%), respiratory failure
GI Smooth Muscle	Nausea (30%), Diarrhea
Myocardium	Myocarditis, heart failure, arrhythmias
Vasculature (smooth muscle)	Vasculitis, thrombosis, microangiopathy
Neurons	Anosmia, hypogeusia, encephalopathy, seizures, myopathy
Liver	Abnormal liver function
Kidney	Renal dysfunction



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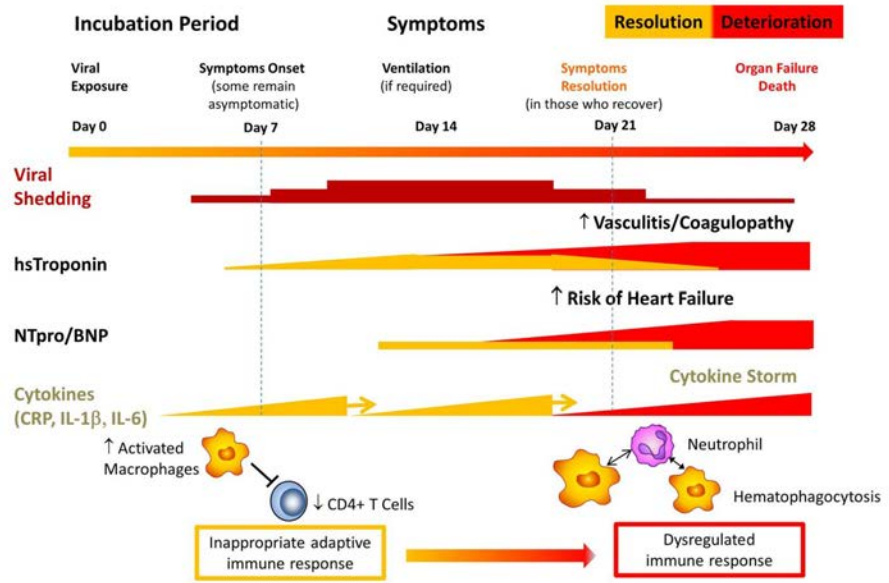
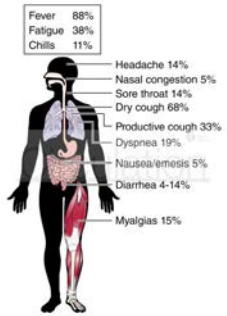
2. By Aditya Joshi - Own work, CC BY-SA 3.0, https://commons.wikimedia.org/w/index.php?curid=20131071
3. Image from: Vaduganathan M, et al. Renin–Angiotensin–Aldosterone System Inhibitors in Patients with Covid-19. NEJM. 3-30-20. DOI: 10.1056/NEJMsr2005760.

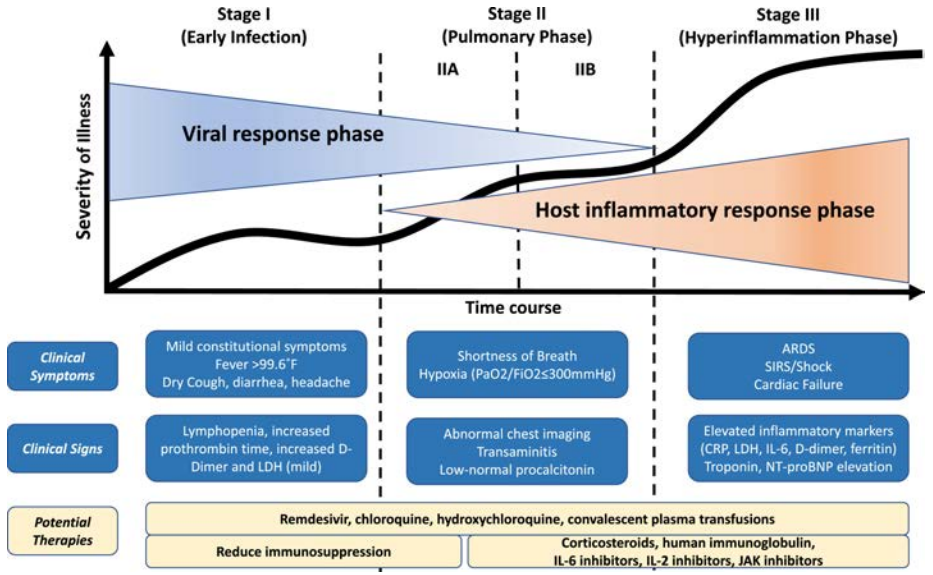
CoVID-19 | Clinical Characteristics & Immunopathology

- Spread predominantly via respiratory droplets, but can be aerosolized or detected in stool.
- Symptomatic and asymptomatic spread.
- Incubation time: 3-14 days, R0 2-4 (97.5% sx 11 days)
- Median viral shedding: 20 days
- Respiratory viral co-infection more common than initially thought: ~20%.



- **ILI:** Most common symptoms initially reported as fever (44-94%), cough (68-83%), anosmia (~70%)
- Severe: 14% (dyspnea, RR>30, SpO2 <93%, P/F ratio <300, >50% lung infiltrates within 24-48hrs)
- Critical: 5% (respiratory failure, septic shock, MOD)

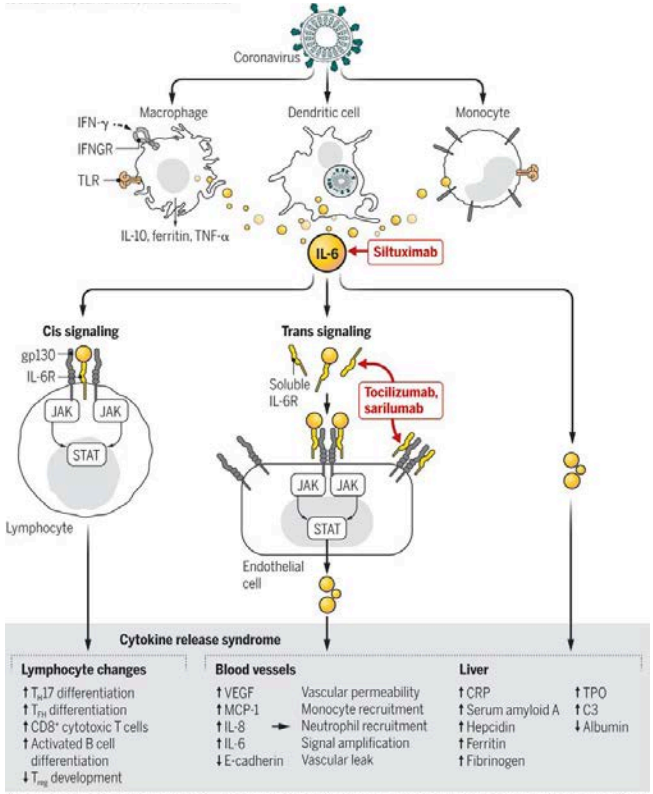




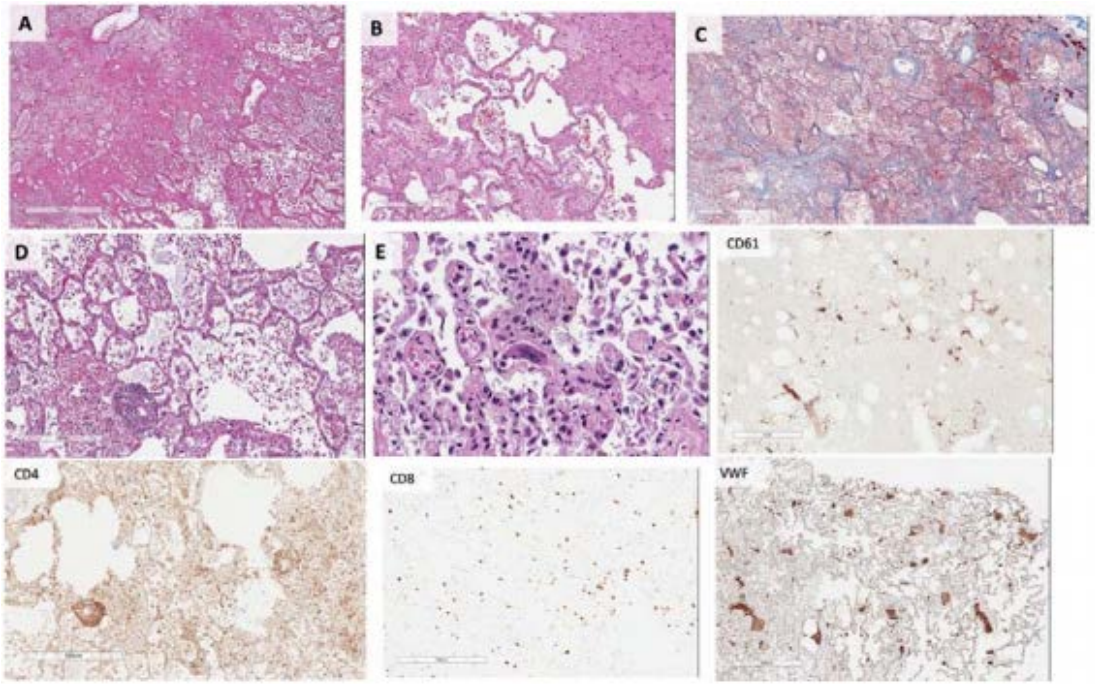
1. Clerkin et al. Coronavirus Disease 2019 and Cardiovascular Disease 10.1161/CIRCULATIONAHA.120.046941
2. Siddiqi HK, Mehra MR. COVID-19 Illness in Native and Immunosuppressed States: A Clinical-Therapeutic Staging Proposal. JHLT. 2020

CoVID-19 | Symptoms & Severity

- Lymphopenia, mild hepatocellular injury, elevated D-Dimer & inflammatory markers.
- Severe disease: associated w/ cytokine release syndrome. IL-6 elevation correlates with ARF, ARDS, and adverse outcomes.



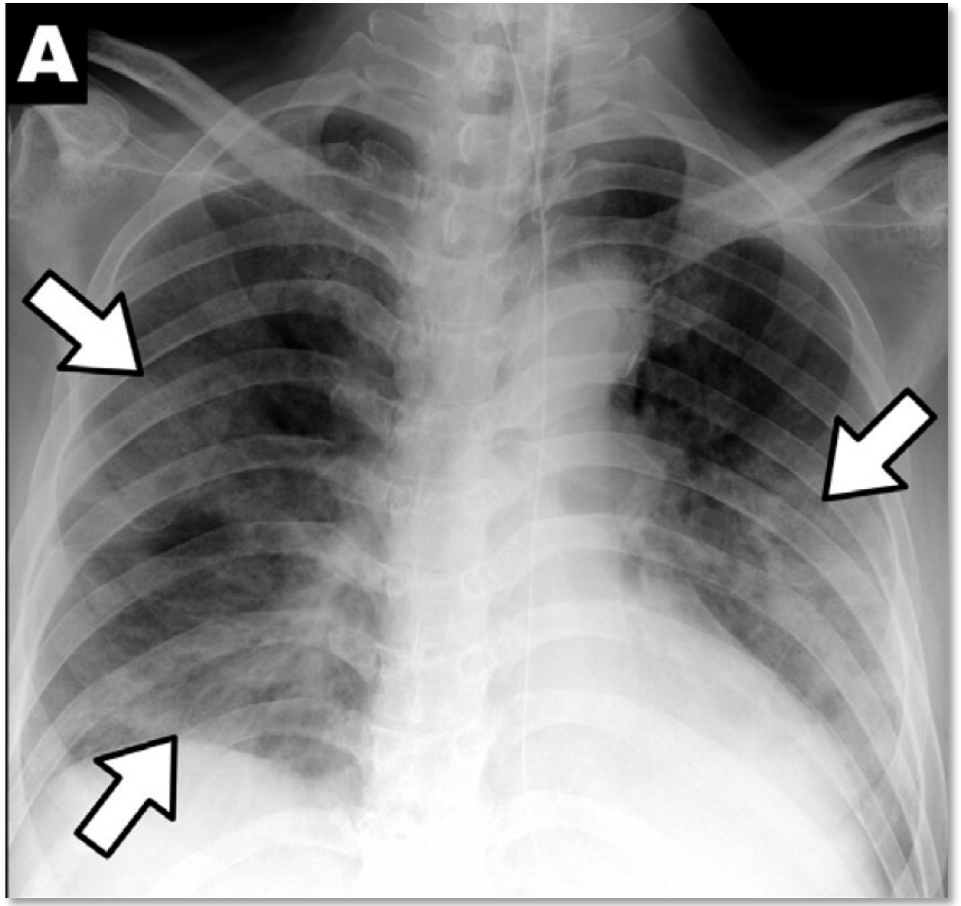
- Intensely inflammatory and pro-thrombotic: systemic increases in IL-6, IL-2, IL-7, granulocyte colony-stimulating factor, CXCL10, CCL2, TNF-alpha.
- Pathology: Diffuse alveolar damage, hyaline membrane & hemorrhage, fibrin thrombi/deposition, megakaryocytes



1. Moore JB, June CH. Cytokine Release Syndrome in severe COVID-19. Science. 10.1126/science.abb8925 (2020)
2. Fox et al. Pulmonary and Cardiac Pathology in Covid-19: The First Autopsy Series from New Orleans. medRxiv 2020.04.06.20050575; doi: https://doi.org/10.1101/2020.04.06.20050575

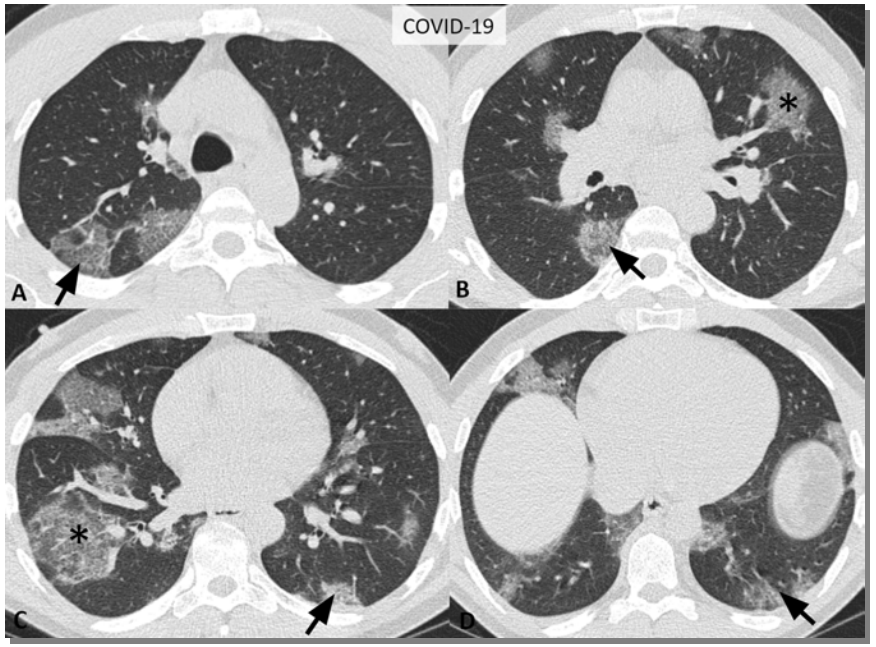
CoVID-19 | Chest Imaging: X-RAY

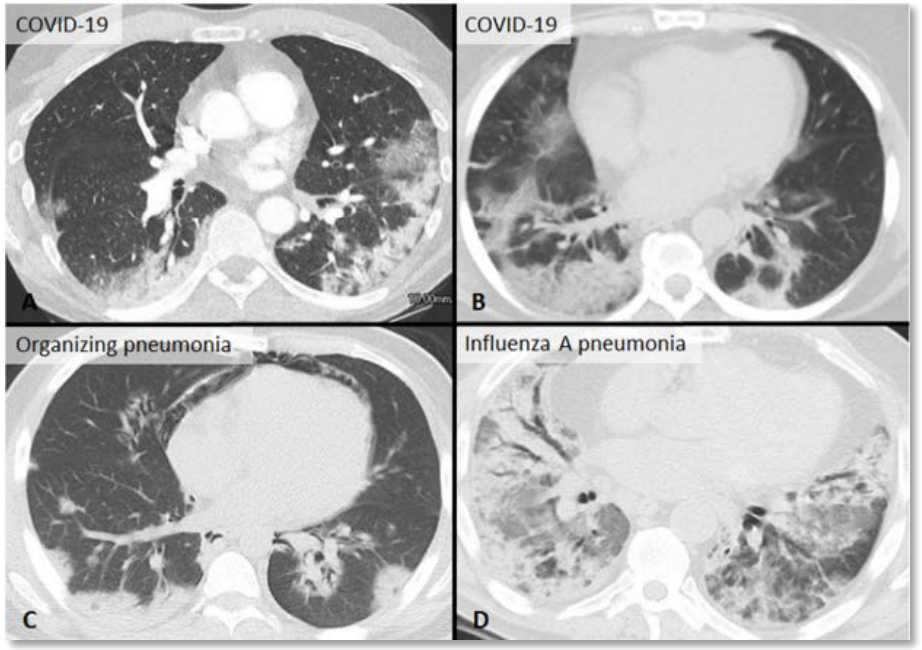
Characteristic	Number (% of 64 patients)
Number of normal baseline CXRs	20 (31%)
Number of abnormal baseline CXRs	44 (69%)
Number of patients with normal baseline CXRs later becoming abnormal	7 (11%)
Type of parenchymal opacity at baseline CXR	
Consolidation	30 (59%)
Ground glass opacities	21 (41%)
Distribution at baseline CXR	
Peripheral predominant	26 (51%)
Perihilar predominant	6 (12%)
Neither peripheral nor perihilar	19 (37%)
Right lung	10 (20%)
Left lung	9 (18%)
Bilateral lungs	32 (63%)
Upper zone predominant	0 (0%)
Lower zone predominant	32 (63%)
No zonal predominance	19 (37%)
Other features on baseline CXR	
Pleural effusion	2 (3%)
Pulmonary nodules	0 (0%)



CoVID-19 | Chest Imaging: Computed Tomography

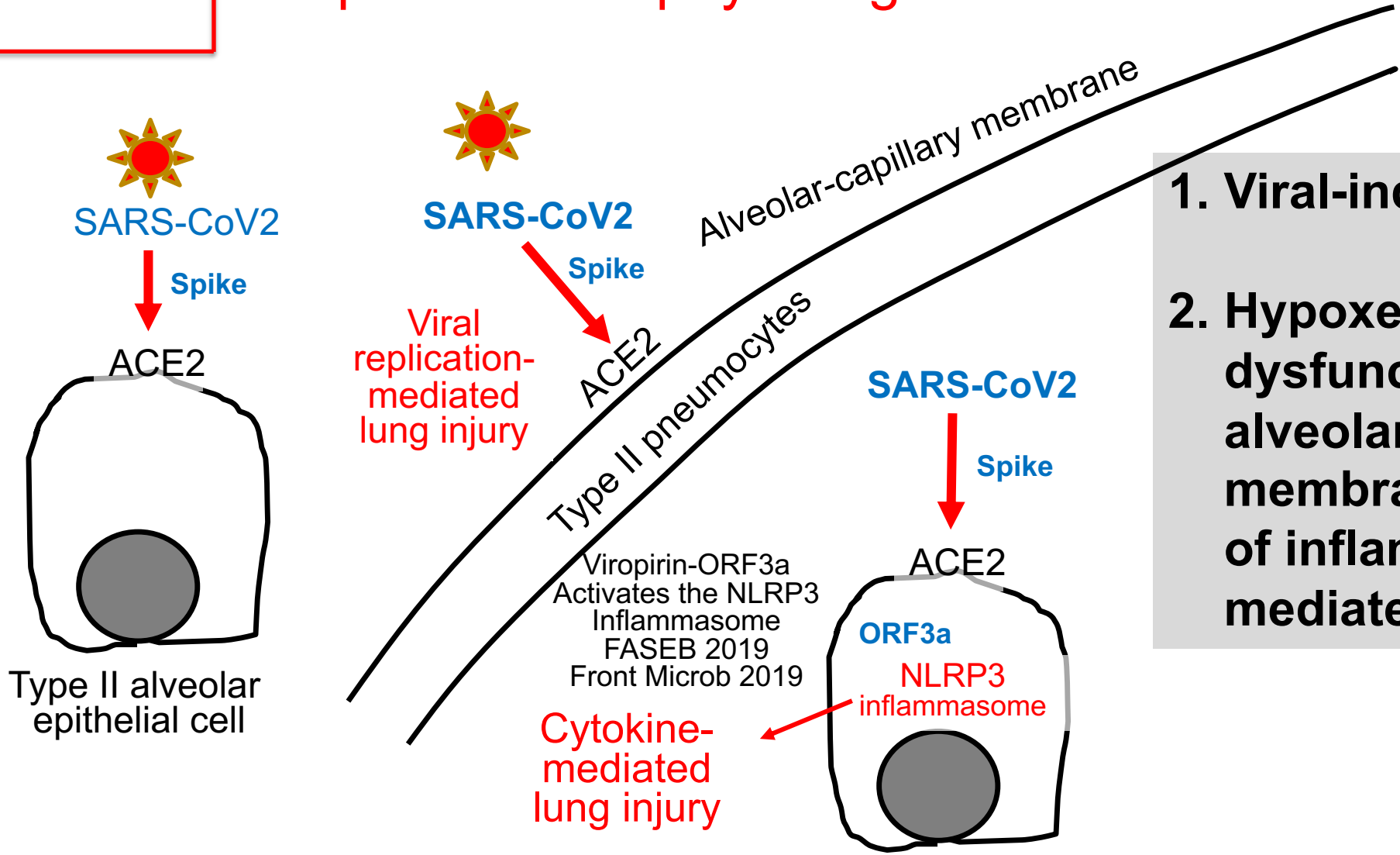
- Features: Ground glass opacities (GG) with or without consolidation in peripheral, posterior, and diffuse or lower lung zone distribution. GGO reported to have 'round' morphology or 'crazy paving' pattern.
- Lacks: perihilar pattern, bronchial wall thickening, mucoid impactions, nodules
- Sensitivity 60-98%. Positive predictive value of ~92%.





1. Simpson S. Radiological Society of North America Expert Consensus Statement on Reporting Chest CT Findings Related to COVID-19. Endorsed by the Society of Thoracic Radiology, the American College of Radiology, and RSNA.Published Online: March 25, 2020 https://doi.org/10.1148/ryct.2020200152
2. Correlation of Chest CT and RT-PCR Testing in Coronavirus Disease 2019 (COVID-19) in China: A Report of 1014 Cases Tao Ai, Zhenlu Yang, Hongyan Hou, Chenao Zhan, Chong Chen, Wenzhi Lv, Qian Tao, Ziyong Sun, and Liming Xia Radiology 0 0:0

CoVID-19 | Simplified Pathophysiologic Scheme of COVID-19



1. **Viral-induced injury**
2. **Hypoxemia a result of dysfunction of the alveolar-capillary membrane as a result of inflammation-mediated injury**

frontiers in Medicine

SYSTEMATIC REVIEW
published: 09 June 2020
doi: 10.3389/fmed.2020.00301

Immune-Inflammatory Parameters in COVID-19 Cases: A Systematic Review and Meta-Analysis

Xudong Feng†, Shuangshuang Li†, Qiang Sun†, Jiaqi Zhu, Bo Chen, Maoming Xiong* and Guodong Cao**

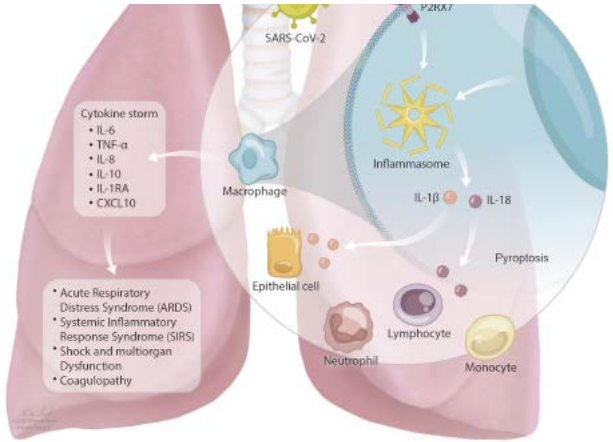
frontiers in Immunology

MINI REVIEW
published: 23 June 2020
doi: 10.3389/fimmu.2020.01518

Targeting the NLRP3 Inflammasome in Severe COVID-19

*Tracey L. Freeman and Talia H. Swartz**

Division of Infectious Diseases, Department of Medicine, Immunology Institute, Icahn School of Medicine at Mount Sinai, New York, NY, United States



RE 1 | The NLRP3 inflammasome mediates lung inflammation in SARS-CoV-2 infection. SARS-CoV-2 is inhaled into the airway and mediates activation of the

CardioRenal Medicine

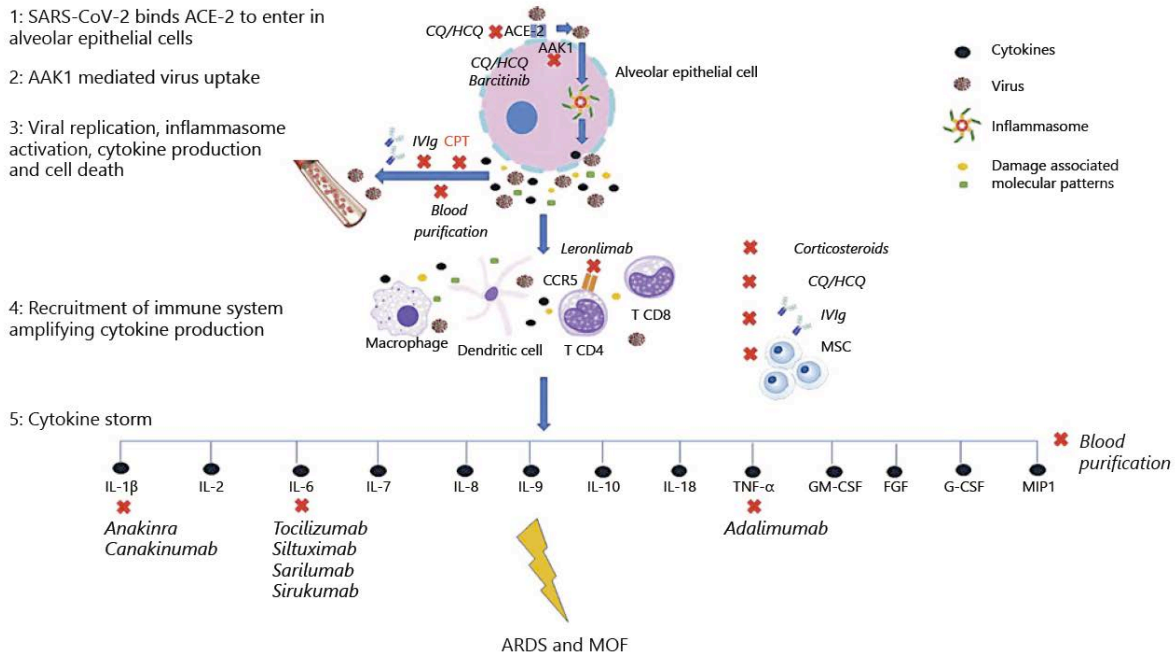
Cardiorenal Med
DOI: 10.1159/000509483
Received: May 14, 2020
Accepted: June 12, 2020
Published online: June 29, 2020

www.karger.com/crm

Review Article

Weathering the Cytokine Storm in COVID-19: Therapeutic Implications

Giulia Iannaccone[a] Roberto Scacciavillani[a] Marco Giuseppe Del Buono[a] Massimiliano Camilli[a] Claudio Ronco[b, c] Carl J. Lavie[d] Antonio Abbate[e] Filippo Crea[a, f] Massimo Massetti[a, f] Nadia Aspromonte[f]



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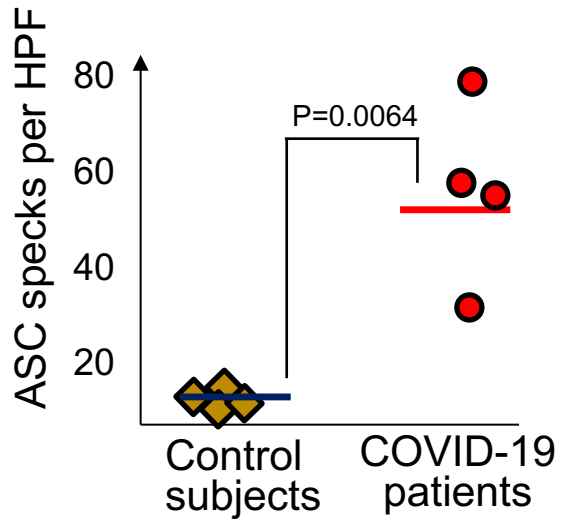
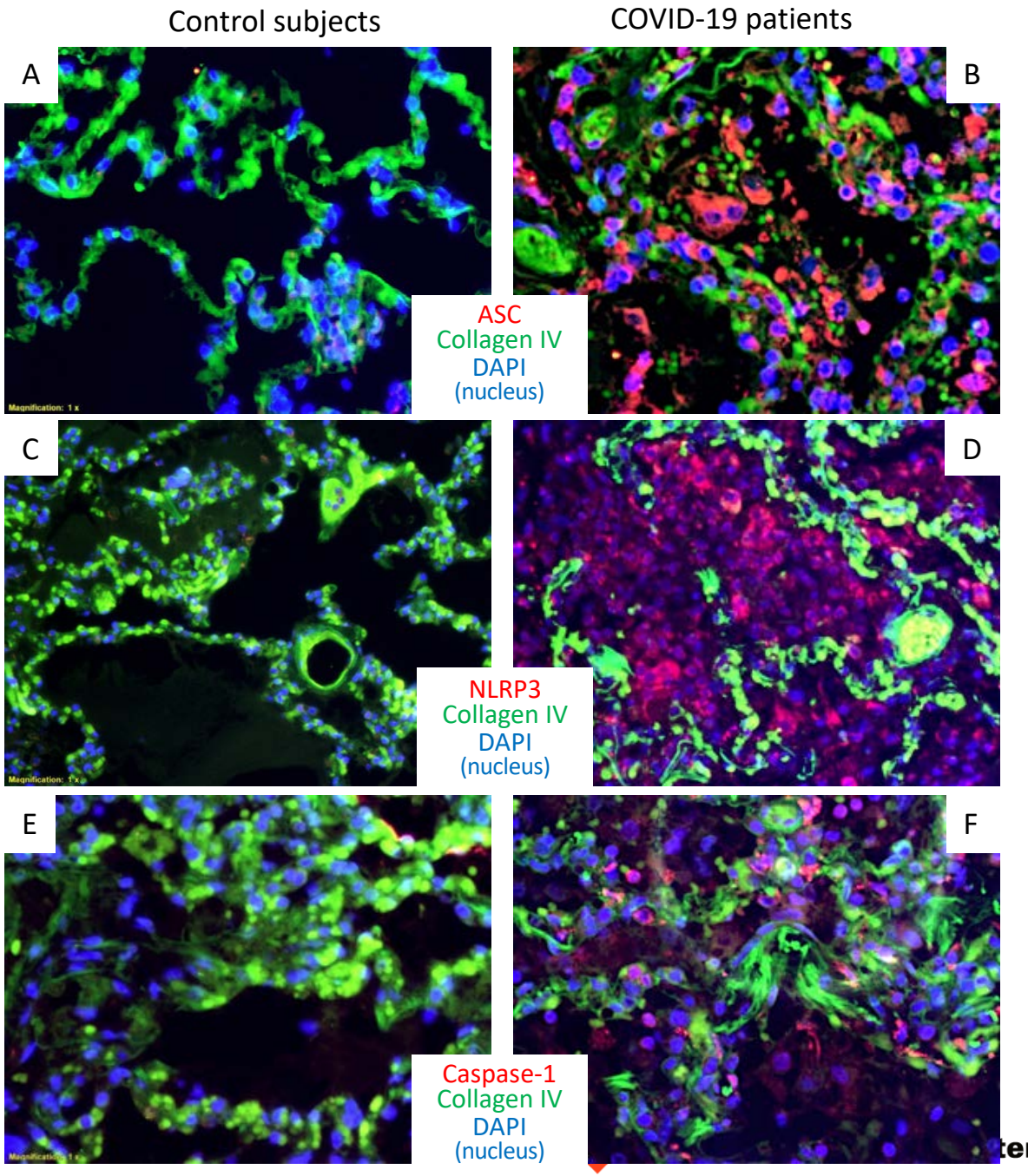
CoVID-19

Inflammasome in the lungs of fatal COVID-19

- Collaborative work with University of Trieste
- Laboratory of Dr. Stefano Toldo @ VCU Pauley Heart Center





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Unpublished data

CoVID-19 | 1st study open at VCU – Remdesivir to target SARS-CoV2

- Remdesivir had been already developed by Gilead for SARS, MERS and Ebola
- Remdesivir became immediately available as part of a compassionate use program
- An initial clinical trial from China was halted prematurely due to inability to enroll patients, showing no benefits
- Two additional trials were completed in the USA one led by NIH/NIAID and one by Gilead

Remdesivir is a a prodrug of an adenosine analogue that functions as an inhibitor of the inhibitor of the viral RNA-dependent, RNA polymerase for SARS-CoV2

CoVID-19 | Remdesivir clinical trials

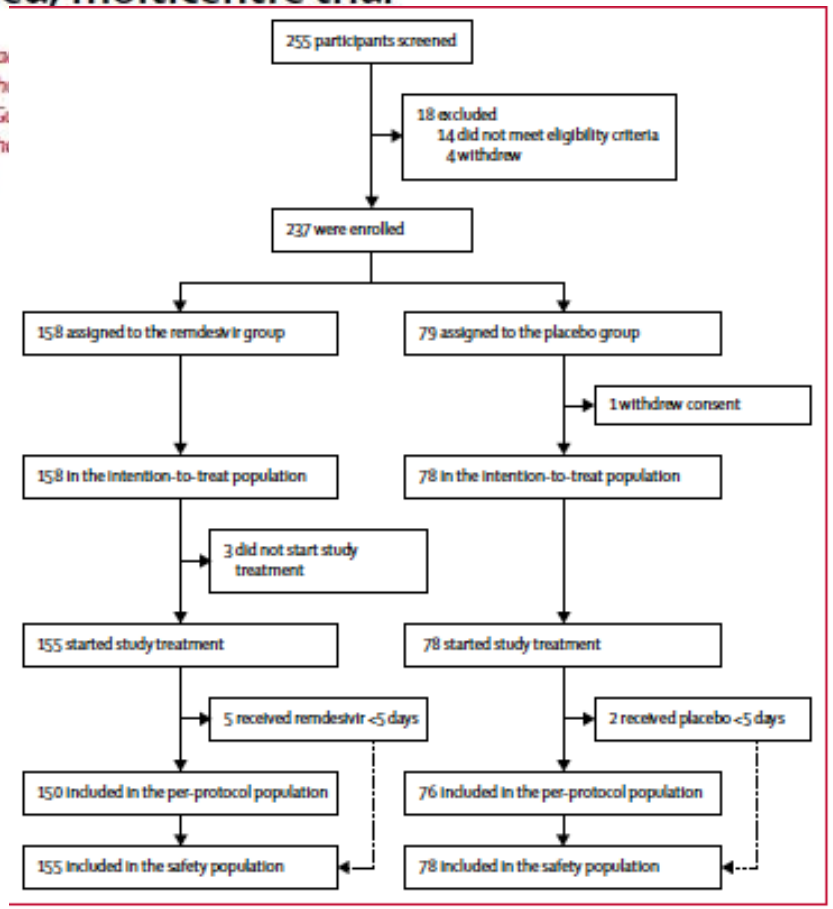
Remdesivir in adults with severe COVID-19: a randomised, double-blind, placebo-controlled, multicentre trial

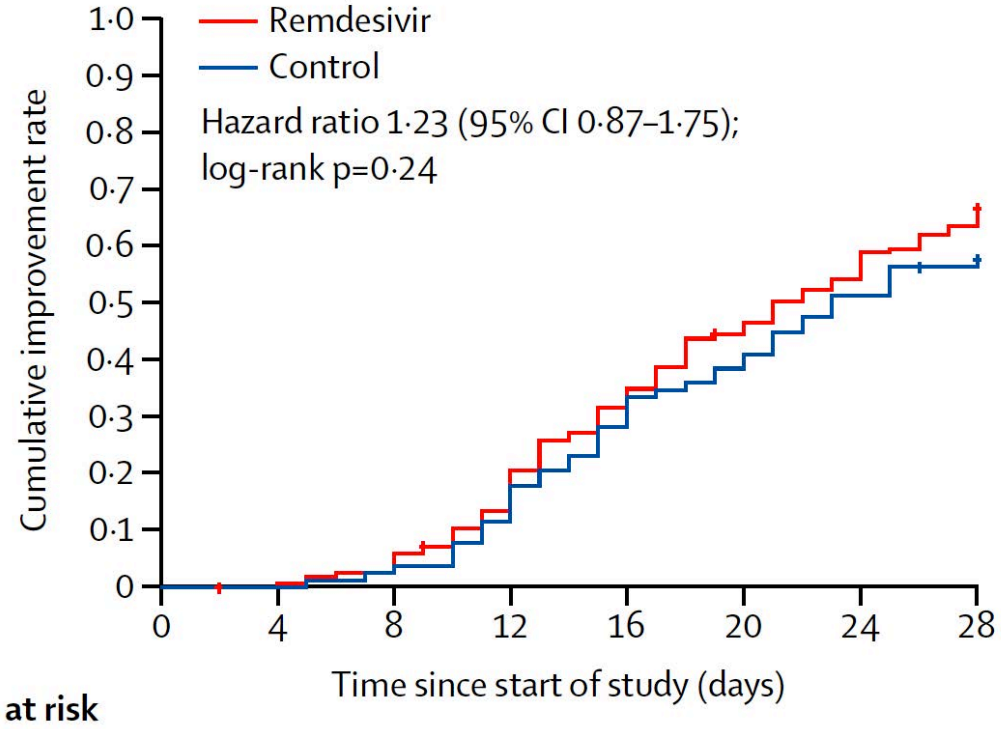
Yeming Wang*, Dingyu Zhang*, Guanhua Du*, Ronghui Du*, Jianping Zha
Yi Hu*, Guangwei Luo*, Ke Wang, Yang Lu, Huadong Li, Shuzhen Wang, Sh
Xin Tang, Xianzhi Ye, Yingchun Ye, Bing Liu, Jie Yang, Wen Yin, Aili Wang, G
Yi Zhang, Lianjun Cao, Tingting Guo, Yan Wan, Hong Qin, Yushen Jiang, Th

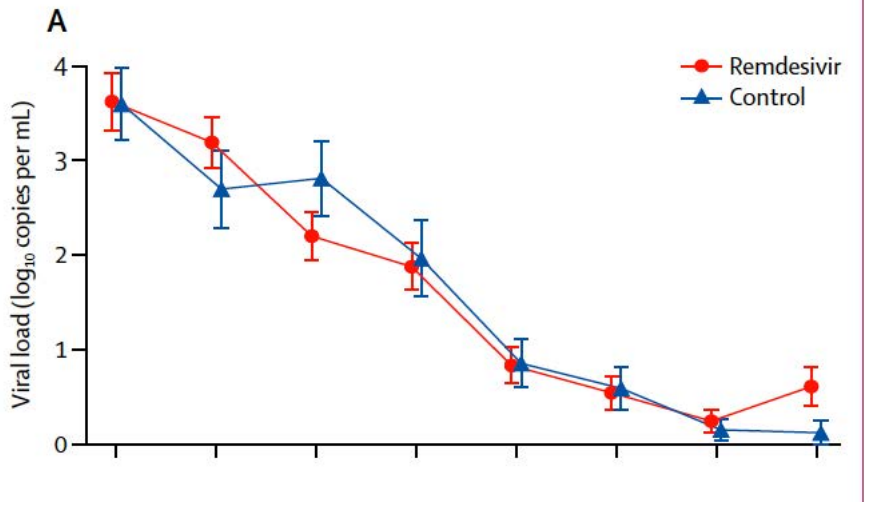
Lancet 2020

China

Primary endpoint:
2 point reduction







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CoVID-19 | Remdesivir cli

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Remdesivir for the Treatment of Covid-19 — Preliminary Report

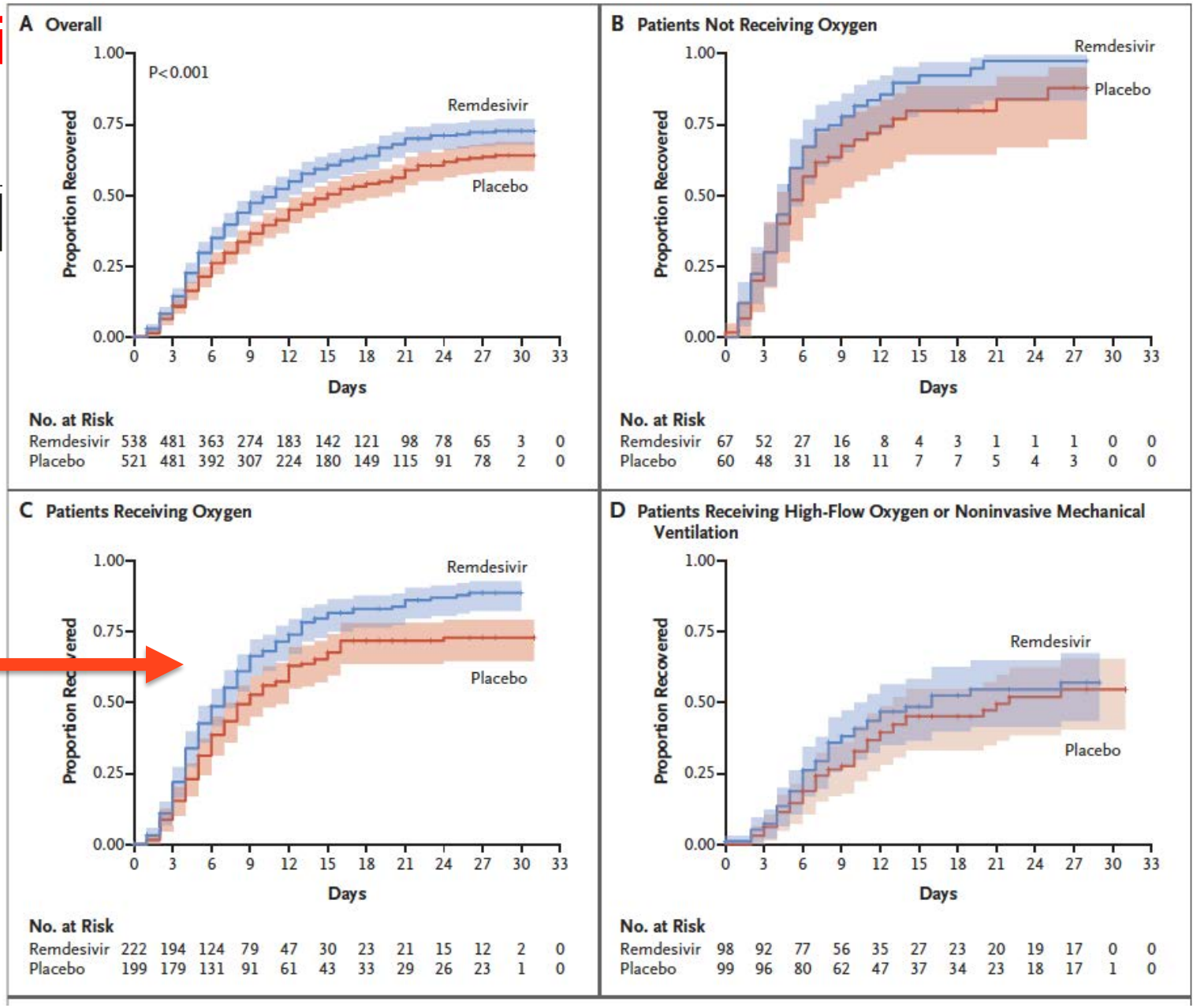
J.H. Beigel, K.M. Tomashek, L.E. Dodd, A.K. Mehta, B.S. Zingman, A.C. Kalil, E. Hohmann, H.Y. Chu, A. Luetkemeyer, S. Kline, D. Lopez de Castilla, R.W. Finberg, K. Dierberg, V. Tapson, L. Hsieh, T.F. Patterson, R. Paredes,

NEJM 2020

USA, Europe, Asia

Primary endpoint:
Time to recovery

Greatest benefit
In patients on
suppl O2 not
through HFNC,
NIV or IV



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CoVID-19 | Remdesivir clinical trials

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Remdesivir for 5 or 10 Days in Patients with Severe Covid-19

Jason D. Goldman, M.D., M.P.H., David C.B. Lye, M.B., B.S., David S. Hui, M.D., Kristen M. Marks, M.D., Raffaele Bruno, M.D., Rocio Montejano, M.D., Christoph D. Spinner, M.D., Massimo Galli, M.D., Mi-Young Ahn, M.D.,

NEJM 2020

402 patients
USA, Europe, Asia

Primary endpoint:
Clinical status on day 14

Some benefit of continuing to 10 days if you remained critically ill after 5 days

CONCLUSIONS

In patients with severe Covid-19 not requiring mechanical ventilation, our trial did not show a significant difference between a 5-day course and a 10-day course of remdesivir. With no placebo control, however, the magnitude of benefit cannot be determined.

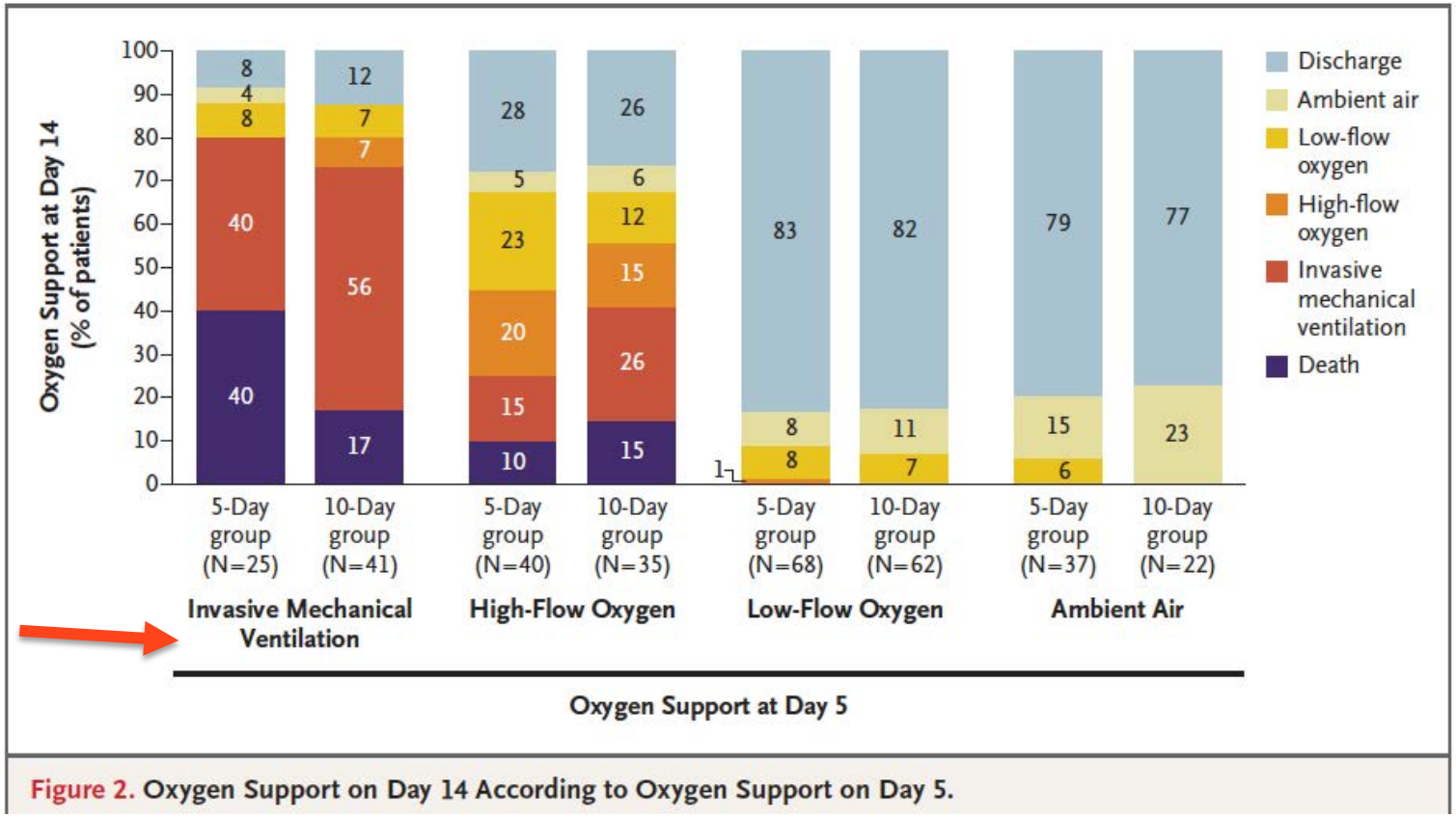

Figure 2. Oxygen Support on Day 14 According to Oxygen Support on Day 5.

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CoVID-19

May 1 - FDA announces EUA for Remdesivir

FACT SHEET FOR HEALTH CARE PROVIDERS EMERGENCY USE AUTHORIZATION (EUA) OF REMDESIVIR (GS-5734™)

The U.S. Food and Drug Administration (FDA) has issued an Emergency Use Authorization (EUA) to permit the emergency use of the unapproved product remdesivir for treatment of suspected or laboratory confirmed coronavirus disease 2019 (COVID-19) in adults and pediatric patients hospitalized with severe disease. Severe disease is defined as patients with an oxygen saturation (SpO2) ≤94% on room air or requiring supplemental oxygen or requiring mechanical ventilation or requiring extracorporeal membrane oxygenation (ECMO).

July 24 – NIH COVID-19 Guidelines

Recommendation for Prioritizing Limited Supplies of Remdesivir

- **Because remdesivir supplies are limited, the Panel recommends that remdesivir be prioritized for use in hospitalized patients with COVID-19 who require supplemental oxygen but who are not on high-flow oxygen, noninvasive ventilation, mechanical ventilation, or extracorporeal membrane oxygenation (ECMO) (BI).**

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CoVID-19

Another anti-viral study was completed at VCU Health ORCHID trial with Hydroxychloroquine

- Small studies had suggested a benefit of hydroxychloroquine in COVID-19
- Widespread off-label use occurred all over the world, including at VCU Health
- There was a need for randomized clinical trials
- The ORCHID Trial was a NIH sponsored trial

Hydroxychloroquine is an anti-inflammatory drug with anti-viral activity in vitro against SARS-CoV2.

CoVID-19

RECOVERY
Randomised Evaluation of COVID-19 Therapy

No clinical benefit from use of hydroxychloroquine in hospitalised patients with COVID-19

5 June 2020

'A total of 1542 patients were randomised to hydroxychloroquine and compared with 3132 patients randomised to usual care alone. There was no significant difference in the primary endpoint of 28-day mortality (25.7% hydroxychloroquine vs. 23.5% usual care; hazard ratio 1.11 [95% confidence interval 0.98-1.26]; p=0.10). There was also no evidence of beneficial effects on hospital stay duration or other outcomes.

'These data convincingly rule out any meaningful mortality benefit of hydroxychloroquine in patients hospitalised with COVID-19. Full results will be made available as soon as possible.

CoVID-19 | ORCHID Trial – NIH sponsored - Hydroxychloroquine

Unpublished

Interim analysis 470 pts

USA

Hospitalized patients

Media Advisory Saturday, June 20, 2020

NIH halts clinical trial of hydroxychloroquine

Study shows treatment does no harm, but provides no benefit

What

A clinical trial to evaluate the safety and effectiveness of hydroxychloroquine for the treatment of adults hospitalized with coronavirus disease 2019 (COVID-19) has been stopped by the National Institutes of Health. A data and safety monitoring board (DSMB) met late Friday and determined that while there was no harm, the study drug was very unlikely to be beneficial to hospitalized patients with COVID-19. After its fourth interim analysis the DSMB, which regularly monitors the trial, recommended to the National Heart, Lung, and Blood Institute (NHLBI), part of NIH, to stop the study. NHLBI halted the trial immediately.

The Outcomes Related to COVID-19 treated with hydroxychloroquine among In-patients with symptomatic Disease study, or ORCHID Study, was being conducted by the Prevention and Early Treatment of Acute Lung Injury (PETAL) Clinical Trials Network of NHLBI. The data from this study indicate that this drug provided no additional benefit compared to placebo control for the treatment of COVID-19 in hospitalized patients.

CoVID-19 | Another Hydroxychloroquine trial

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Hydroxychloroquine with or without Azithromycin in Mild-to-Moderate Covid-19

A.B. Cavalcanti, F.G. Zampieri, R.G. Rosa, L.C.P. Azevedo, V.C. Veiga, A. Avezum, L.P. Damiani, A. Marcadenti, L. Kawano-Dourado, T. Lisboa, D.L.M. Junqueira, P.G.M. de Barros e Silva, L. Tramujas, E.O. Abreu-Silva, L.N. Laranjeira, A.T. Soares, L.S. Echenique, A.J. Pereira, F.G.R. Freitas, O.C.E. Gebara, V.C.S. Dantas, R.H.M. Furtado, E.P. Milan, N.A. Golin, F.F. Cardoso, I.S. Maia, C.R. Hoffmann Filho, A.P.M. Kormann, R.B. Amazonas, M.F. Bocchi de Oliveira, A. Serpa-Neto, M. Falavigna, R.D. Lopes, F.R. Machado, and O. Berwanger, for the Coalition Covid-19 Brazil I Investigators*

CONCLUSIONS

Among patients hospitalized with mild-to-moderate Covid-19, the use of hydroxychloroquine, alone or with azithromycin, did not improve clinical status at 15 days as compared with standard care. (Funded by the Coalition Covid-19 Brazil and EMS Pharma; ClinicalTrials.gov number, NCT04322123.)

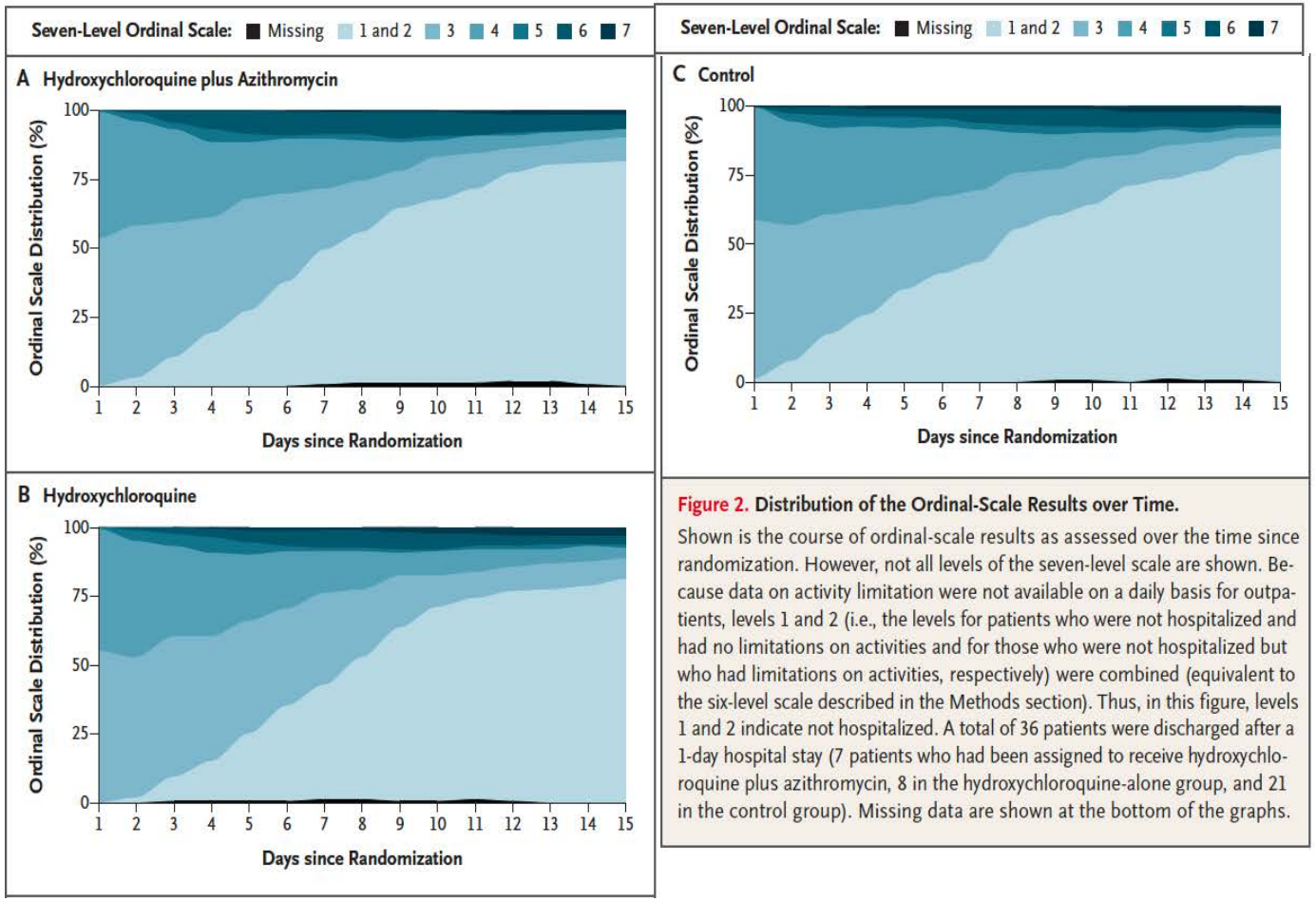

Figure 2. Distribution of the Ordinal-Scale Results over Time.

Shown is the course of ordinal-scale results as assessed over the time since randomization. However, not all levels of the seven-level scale are shown. Because data on activity limitation were not available on a daily basis for outpatients, levels 1 and 2 (i.e., the levels for patients who were not hospitalized and had no limitations on activities and for those who were not hospitalized but who had limitations on activities, respectively) were combined (equivalent to the six-level scale described in the Methods section). Thus, in this figure, levels 1 and 2 indicate not hospitalized. A total of 36 patients were discharged after a 1-day hospital stay (7 patients who had been assigned to receive hydroxychloroquine plus azithromycin, 8 in the hydroxychloroquine-alone group, and 21 in the control group). Missing data are shown at the bottom of the graphs.

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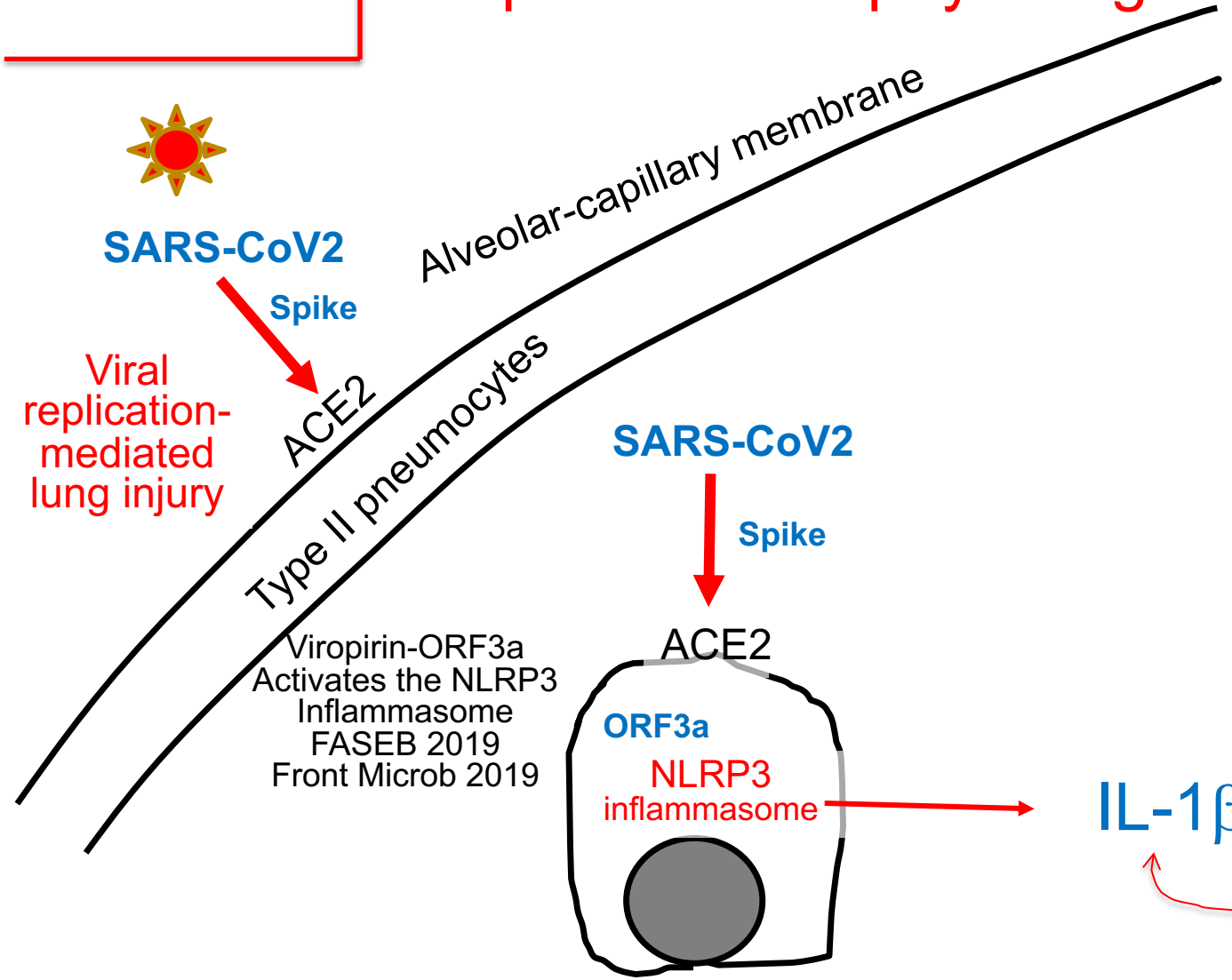
Simplified Pathophysiologic Scheme of COVID-19



1. **Viral-induced injury**
2. **Hypoxemia a result of dysfunction of the alveolar-capillary membrane as a result of inflammation-mediated injury**

TOCILIZUMAB
SARILUMAB

IL-1β → *NF-kB* → IL-6 → Other mediators → *NF-kB* → Cytokine-mediated lung injury

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CoVID-19

IL-6 as a therapeutic target in COVID-19

- Elevated IL-6 levels in patients with severe and critical COVID-19
- Worse prognosis in patients with higher IL-6 levels
- Initial report of ‘promising’ results in 21 patients treated with Tocilizumab, an IL-6 receptor blocker, in China
- Tocilizumab already approved for Cytokine Release Syndrome
- Anecdotal ‘dramatic’ responses in patients treated with Tocilizumab appear from Italy first then from all over the world
- Tocilizumab becomes part of standard of care for critical COVID-19 in many institutions around the world, including VCU Health, in March
- Several case-control studies suggest a beneficial effect

CoVID-19 | Tocilizumab: case-control reports from Italy

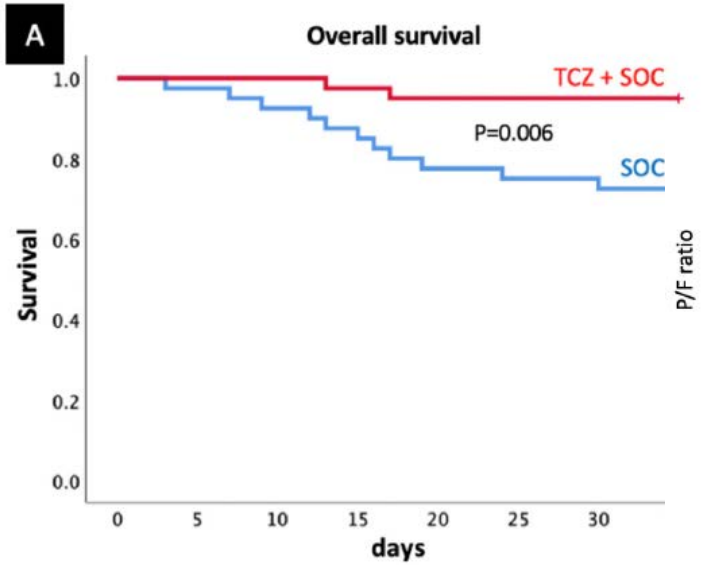
Ann Rheum Dis 2020

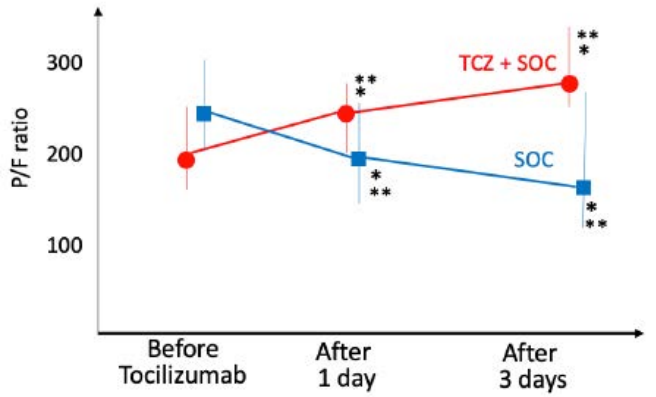
Interleukin-6 receptor blockade with subcutaneous tocilizumab in severe COVID-19 pneumonia and hyperinflammation: a case–control study

Nicola Potere,[1,2] Marcello Di Nisio,[3,4] Donatella Cibelli,[5] Rosa Scurti,[6] Antonella Frattari,[7] Ettore Porreca,[1] Antonio Abbate,[2] Giustino Parruti [5]

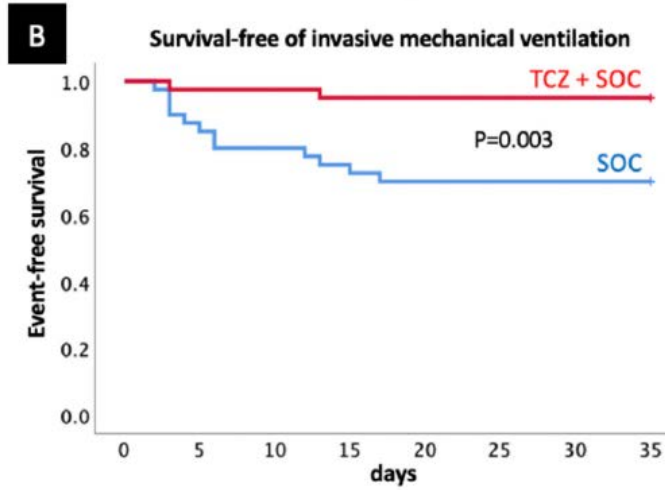
[1]Department of Medical, Oral and Biotechnological Sciences, "G D'Annunzio" University, Chieti, Italy
[2]VCU Pauley Heart Center, Virginia Commonwealth University, Richmond, Virginia, USA
[3]Department of Medicine and Ageing Sciences, "G' D'Annunzio" University, Chieti-Pescara, Italy
[4]Department of Vascular Medicine, Amsterdam Medical Center, Amsterdam, The Netherlands
[5]Infectious Diseases Unit, Pescara General Hospital, Pescara, Italy
[6]Geriatric Medicine Unit, Pescara General Hospital, Pescara, Italy
[7]Intensive Care Unit, Pescara General Hospital, Pescara, Italy

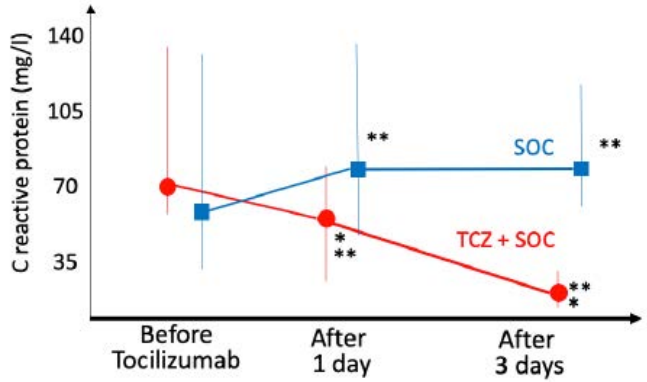
40 patients treated with Tocilizumab s.c. and 40 matched controls





* P<0.005 for within-group analysis





* P<0.001 for within-group analysis
** P<0.001 for between-groups analysis

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Tocilizumab: case-control reports from Italy

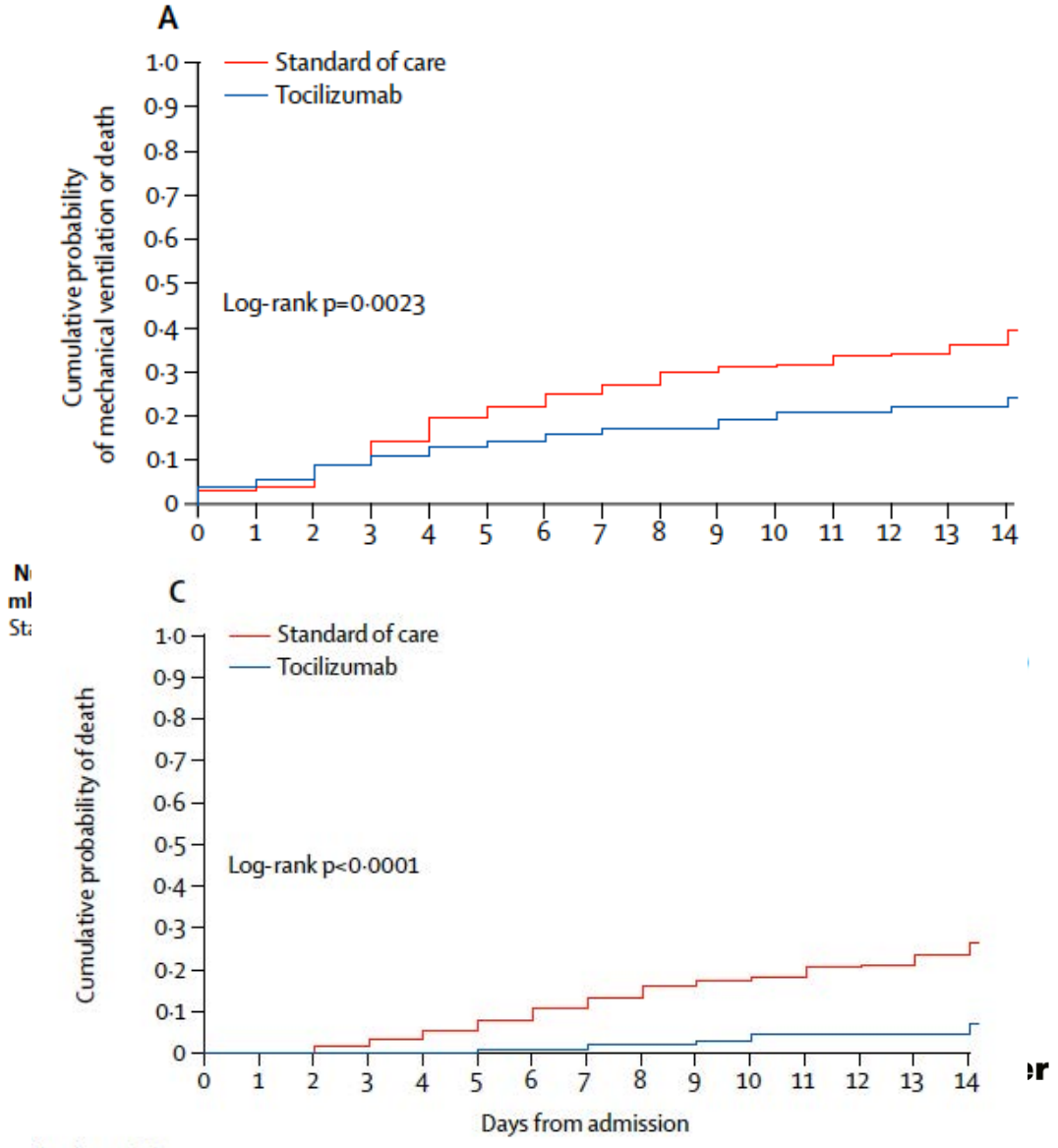
Tocilizumab in patients with severe COVID-19: a retrospective cohort study

Giovanni Guaraldi, Marianna Meschiari*, Alessandro Cozzi-Lepri, Jovana Milic, Roberto Tonelli, Marianna Menozzi, Erica Franceschini, Gianluca Cuomo, Gabriella Orlando, Vanni Borghi, Antonella Santoro, Margherita Di Gaetano, Cinzia Puzzolante, Federica Carli, Andrea Bedini, Luca Corradi, Riccardo Fantini, Ivana Castaniere, Luca Tabbì, Massimo Girardis, Sara Tedeschi, Maddalena Giannella, Michele Bartoletti, Renato Pascale, Giovanni Dolci, Lucio Brugioni, Antonello Pietrangelo, Andrea Cossarizza, Federico Pea, Enrico Clini, Carlo Salvarani, Marco Massari, Pier Luigi Viale, Cristina Mussini*

Summary

Lancet Rheumatology 2020

179 patients treated with Tocilizumab i.v. or s.c.
365 matched controls



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Tocilizumab: case-control reports from Italy

Contents lists available at ScienceDirect

Autoimmunity Reviews

journal homepage: www.elsevier.com/locate/autrev

Tocilizumab for the treatment of severe COVID-19 pneumonia with hyperinflammatory syndrome and acute respiratory failure: A single center study of 100 patients in Brescia, Italy

European Journal of Internal Medicine 76 (2020) 43–49

Contents lists available at ScienceDirect

European Journal of Internal Medicine

journal homepage: www.elsevier.com/locate/ejim

Original article

Efficacy and safety of tocilizumab in severe COVID-19 patients: a single-centre retrospective cohort study

Title: Improved survival outcome in SARs-CoV-2 (COVID-19) Acute Respiratory Distress Syndrome patients with Tocilizumab administration

Pre-Print NJ experience

Authors:

Nafisa Wadud[2], Naim Ahmed[2], Mannu Shergil[2], Maida Khan[2], Murali Krishna[3], Aamir Gilani[3], Samer El Zarif[3], Jodi Galaydick[3], Karthika Linga[3], Shravan Koor[3], Julia Galea[4], Lauren Stuczynski[4], Maria B Osundele[4]

Clinical and Experimental Rheumatology 2020; 38: 00-00

BRIEF PAPER

Pilot prospective open, single-arm multicentre study on off-label use of tocilizumab in patients with severe COVID-19

S. Sciascia[1,2], F. Aprà[2], A. Baffa[1,2], S. Baldovino[1,2], D. Boaro[2], R. Boero[2], S. Bonora[2], A. Calcagno[2], I. Cecchi[1,2], G. Cinnirella[2], M. Converso[2], M. Cozzi[1,2],

ABSTRACT

Objective. *No agent has yet been proven to be effective for the treatment of patients with severe COVID-19.*

Methods. *We conducted a pilot prospective open, single-arm multicentre study on off-label use of tocilizumab (TCZ) involving 63 hospitalised adult patients (56 males, age 62.6±12.5) with severe COVID-19. Clinical and laboratory parameters were prospectively collected at baseline, day 1, 2, 7 and 14. No moderate-to-severe adverse events*

tool for tampering the cytokine storms in critically ill patients (4).

Methods

We conducted a prospective open, single-arm multicentre study on the off-label use of TCZ in hospitalised adult patients with confirmed severe COVID-19 infection. Inclusion criteria were the following: a) polymerase chain reaction-confirmed COVID-19 infection; b) pulmonary involvement, assessed either by oxygen saturation

AND MANY MORE

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CoVID-19

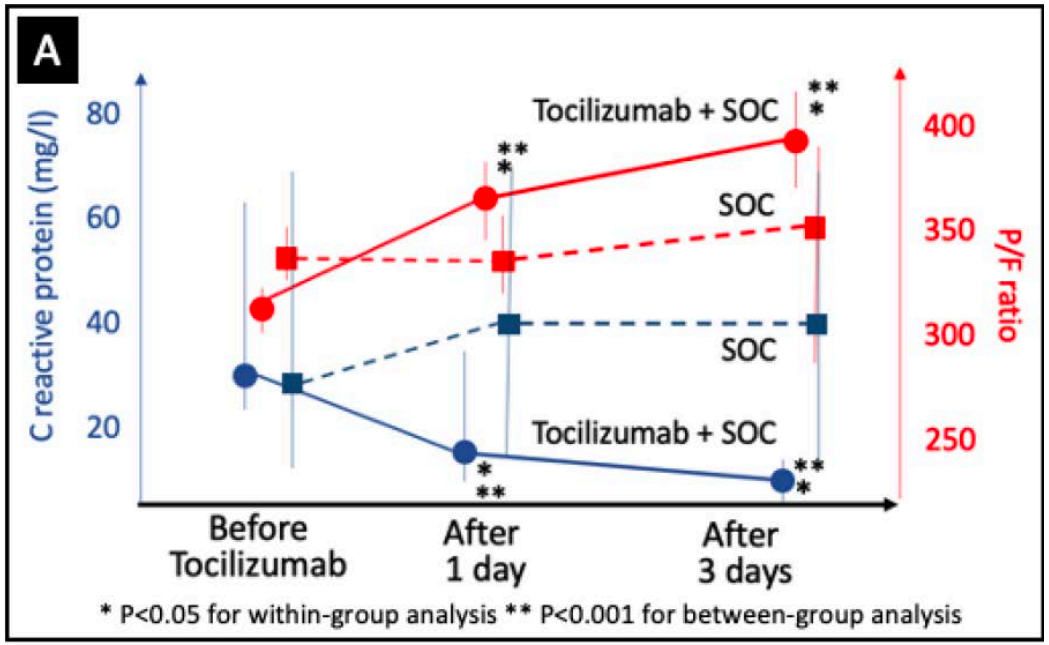
Low-Dose Subcutaneous Tocilizumab to Prevent Disease Progression in Patients with Moderate COVID-19 Pneumonia and Hyperinflammation

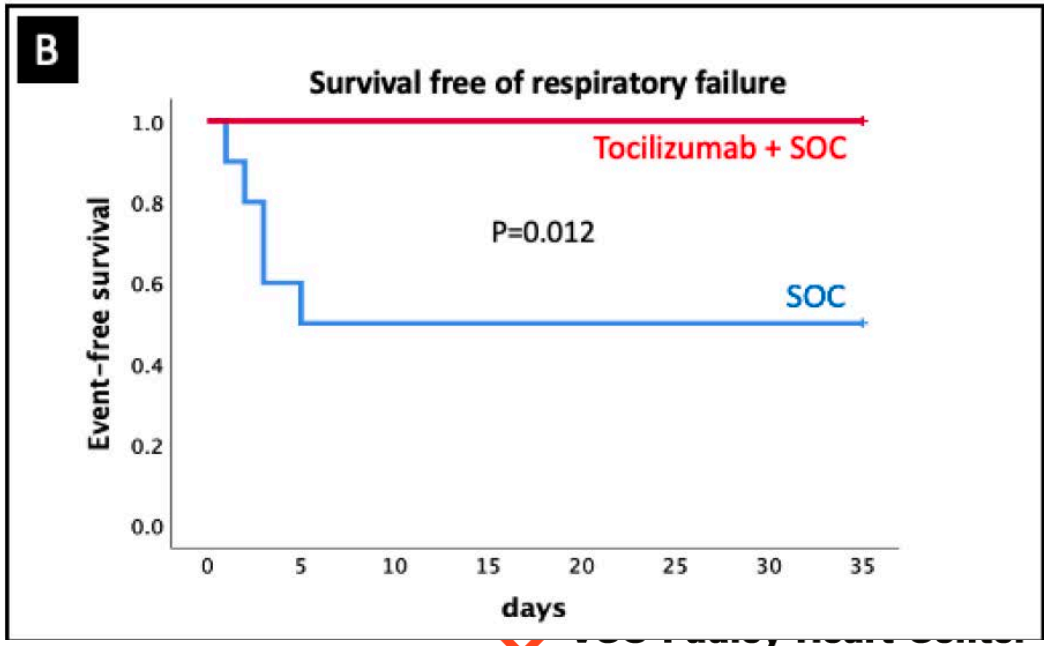
Authors:

Nicola Potere[1,2], Marcello Di Nisio[3,4], Giulia Rizzo[1], Matteo La Vella[1], Ennio Polilli[5], Adriana Agostinone[6], Antonella Spacone[7], Silvio Di Carlo[7], Alberto Costantini[8], Antonio Abbate[2], Ettore Porreca[1], Giustino Parruti[6]

10 patients with moderate COVID-19 pneumonia (not hypoxic or on supplemental O2) treated with Tocilizumab s.c. and 10 matched controls

Int J Infect Dis 2020 – in press





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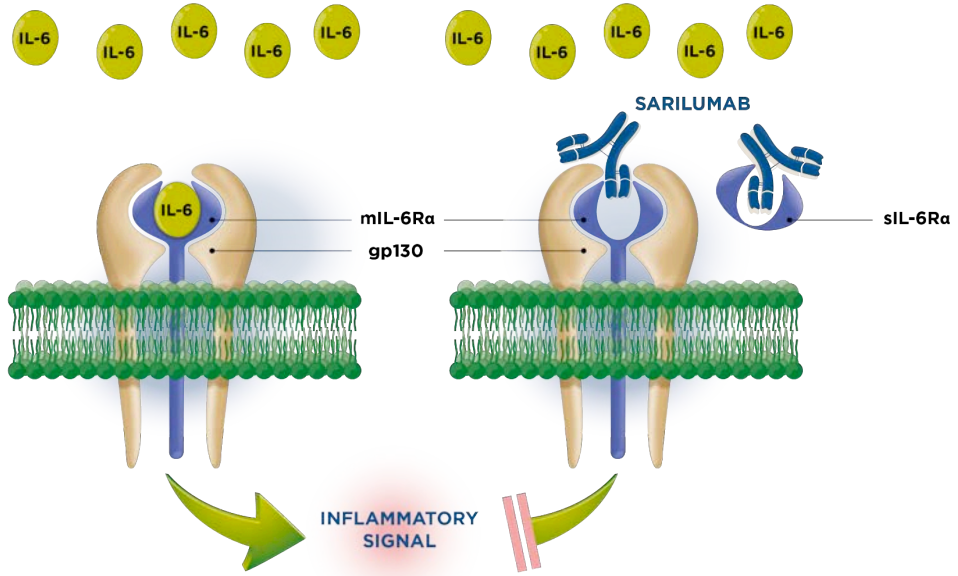
CoVID-19 REGENERON CLINICAL TRIAL OF SARILUMAB

- Sarilumab (Kevzara) an IL-6R blocker (Regeneron)
- Sarilumab also is approved for Rheumatoid Arthritis
- Regeneron initiated an adaptive phase II-III clinical trial of Sarilumab in patients with COVID-19 across a wide range of severity of illness
  - Severe COVID-19 (hypoxemic on suppl O2 via NC)
  - Critical COVID-19 (on HFNC, NIV or IV)
  - Multi-organ failure COVID-19 (shock or need for RRT)
  - COVID-19 with immunodepression (any stage)



CoVID-19

REGENERON CLINICAL TRIAL OF SARILUMAB

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

April 27, 2020

TARRYTOWN, N.Y. and PARIS, April 27, 2020 /PRNewswire/ --

Independent Data Monitoring Committee recommended continuing ongoing Phase 3 trial only in the more advanced "critical" group with Kevzara higher-dose versus placebo and discontinuing less advanced "severe" group

Phase 3 trial will be amended to enroll only "critical" patients

Phase 3 trial will also be amended to discontinue lower-dose Kevzara (200 mg); all new patients to receive either higher-dose Kevzara (400 mg) or placebo

No new safety findings were observed for Kevzara use in COVID-19 patients

CoVID-19

REGENERON CLINICAL TRIAL OF SARILUMAB

	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 ³2 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%)

April 27, 2020
Press Release

VCU Health

VCU Pauley Heart Center

CoVID-19

REGENERON CLINICAL TRIAL OF SARILUMAB

Cohort not on a ventilator	Placebo	Sarilumab	
		200 mg	400 mg
Severe patient stratum – Phase 3			
	(n=60)	(n=110)	(n=106)
Died or "On a ventilator"	8 (13%)	15 (14%)	16 (15%)
Died	5 (8%)	7 (6%)	9 (8%)
On a ventilator	3 (5%)	8 (7%)	7 (7%)
Clinical improvement (Achieved ≥2 point improvement on 7-point scale)[1]	37 (62%)	62 (56%)	64 (60%)
Off oxygenation	39 (65%)	66 (60%)	71 (67%)
Discharged	38 (63%)	63 (57%)	66 (62%)

Note: Data cut-off date of 22 April 2020

CoVID-19

REGENERON CLINICAL TRIAL OF SARILUMAB

REGENERON

Press Release

Regeneron and Sanofi Provide Update on Kevzara® (sarilumab) Phase 3 U.S. Trial in COVID-19 Patients

Tarrytown, N.Y. and Paris, July 2, 2020 – Regeneron Pharmaceuticals, Inc. (NASDAQ: **REGN**) and Sanofi today announced that the U.S. Phase 3 trial of Kevzara® (sarilumab) 400 mg in COVID-19 patients requiring mechanical ventilation did not meet its primary and key secondary endpoints when Kevzara was added to best supportive care compared to best supportive care alone (placebo).

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CoVID-19

Media & Investor Release

Roche

July 29, 2020

450 patients
COVID-19 pneumonia
w/ hypoxemia

COVACTA Phase III clinical trial

Summary of Key COVACTA Clinical and Safety Findings

- Primary endpoint not met: The difference in clinical status between Actemra/RoActemra and placebo in patients assessed using a 7-category ordinal scale at week four was not statistically significant (p=0.36; odds ratio [95% CI] = 1.19 [0.81, 1.76], a statistically significant odds ratio greater than 1 would have favoured Actemra/RoActemra).
- There was no difference between Actemra/RoActemra and placebo in the percentage of patients that died by week four (Actemra/RoActemra = 19.7% and placebo = 19.4% with a difference [95% CI] of 0.3% [-7.6%, 8.2%], p=0.9410)
- Time to hospital discharge or 'ready to discharge' was shorter in patients treated with Actemra/RoActemra than in those treated with placebo. The median time to discharge or 'ready to discharge' for Actemra/RoActemra was 20 days and for placebo was 28 days (median time [95% CI]: Actemra/RoActemra = 20.0 [17.0, 27.0]; placebo = 28.0 [20.0, NE], p=0.0370). However, the difference cannot be considered statistically significant as the primary endpoint was not met.
- The difference in ventilator-free days between Actemra/RoActemra and placebo was not statistically significant (median of 22 days for Actemra/RoActemra and 16.5 days with placebo, difference in medians [95% CI] = 5.5 [-2.8, 13.0], p=0.3202).
- At week four, rates of infections were 38.3% and 40.6% in the Actemra/RoActemra and placebo arms, respectively, and the rates of serious infections were 21.0% and 25.9% in the Actemra/RoActemra and placebo arms, respectively. The COVACTA study did not identify any new safety signals for Actemra/RoActemra.

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CoVID-19

OTHER TOCILIZUMAB CLINICAL TRIALS

Tocilizumab improves significantly clinical outcomes of patients with moderate or severe COVID-19 pneumonia

Publié le 27/04/2020.

LES COORDONNÉES DU SERVICE PRESSE

A total of 129 patients were randomized: 65 to standard of care + tocilizumab and 64 to standard of care alone. A significantly lower proportion of patients reached the primary outcome in the tocilizumab arm. Results of this study will be submitted for publication in a peer-reviewed journal.

HEALTH NEWS

JUNE 17, 2020 / 4:54 PM / A MONTH AGO

Roche rheumatoid arthritis drug fails to help COVID-19 patients in Italian study

Emilio Parodi, Carl O'Donnell

(Reuters) - Roche's rheumatoid arthritis drug Actemra failed to help patients with early-stage COVID-19 pneumonia in an Italian study, the latest instance in which an anti-inflammatory drug has fallen through in a coronavirus trial.

Actemra did not reduce severe respiratory symptoms, intensive care visits, or death any better than standard treatments, the Italian Medicines Agency (Aifa), Italy's drugs regulator which authorized the study, said in a statement on Wednesday.

The trial, which enrolled 126 patients, about a third of the intended number, was stopped early after an interim analysis raised doubts about the anti-inflammatory medicine's effectiveness.

In the Recovery clinical trial protocol, there is a second randomisation for patients who are critically unwell to receive tocilizumab or no treatment and if required a second dose of tociliziumab to be given at the discretion of the treating physician within a window of 12 to 24 hours after the first dose.

Many other trials ongoing worldwide

VCU Pauley Heart Center

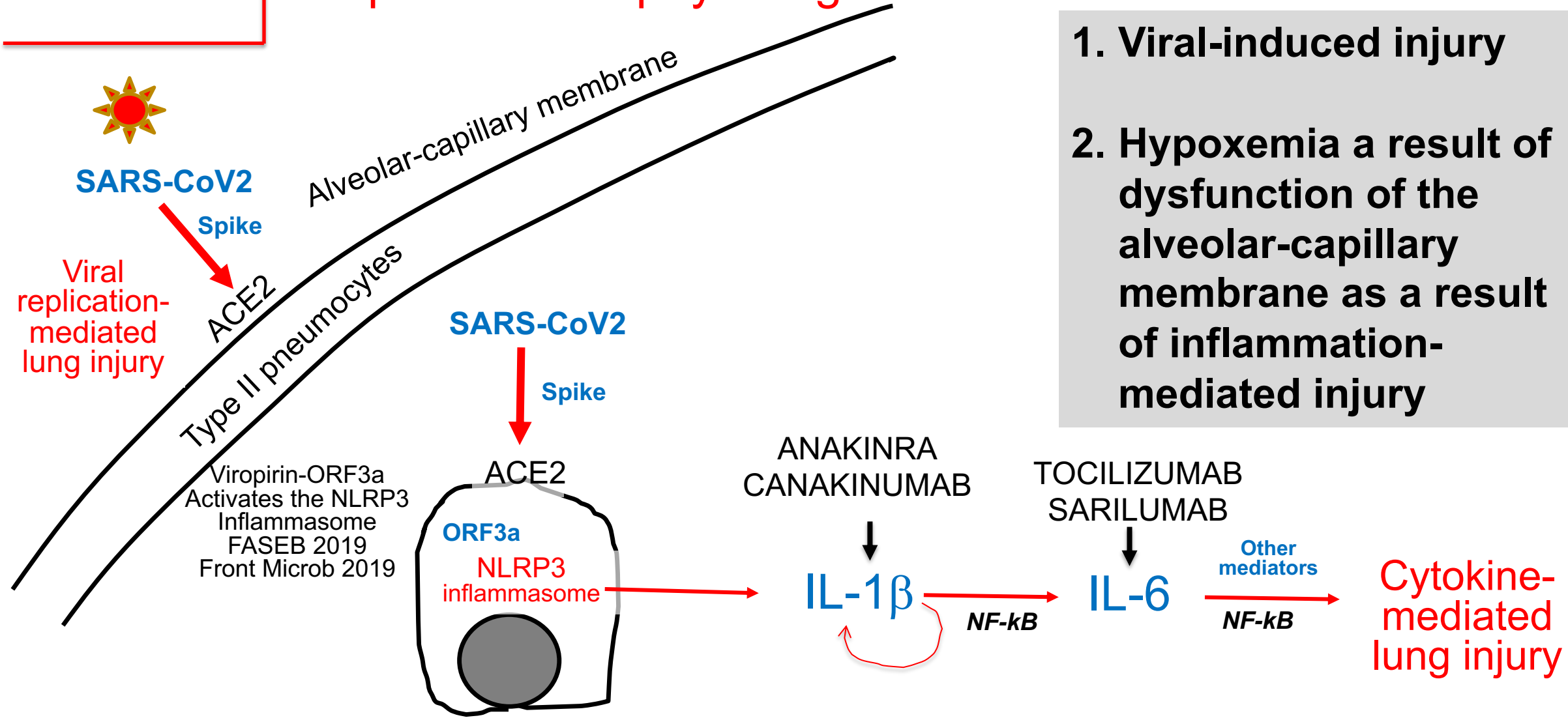
CoVID-19 | Use of IL-6R blockers - summary

- Elevated (and rising) levels of CRP and IL-6 associated with worse outcomes
- Several case-control studies suggestive of a benefit of IL-6R tocilizumab
- Lack of benefit with Sarilumab in Regeneron clinical trial
- Inconsistent/minor benefits in Tocilizumab clinical trials

Reasons? Biases of retrospective studies? Small sample size – insufficient power of RCTs? Inappropriate study design? Changing profile of background therapies? Off-label use? Wrong biology?

CoVID-19

Simplified Pathophysiologic Scheme of COVID-19



1. **Viral-induced injury**
2. **Hypoxemia a result of dysfunction of the alveolar-capillary membrane as a result of inflammation-mediated injury**

CoVID-19

IL-1 as a therapeutic target in COVID-19

- IL-1 is also known as fever molecule and is an upstream mediator
- IL-6 and CRP are surrogates for IL-1 levels
- Worse prognosis in patients with higher IL-1 levels
- Several case control studies suggest a beneficial effect
- Several randomized controlled trials are ongoing

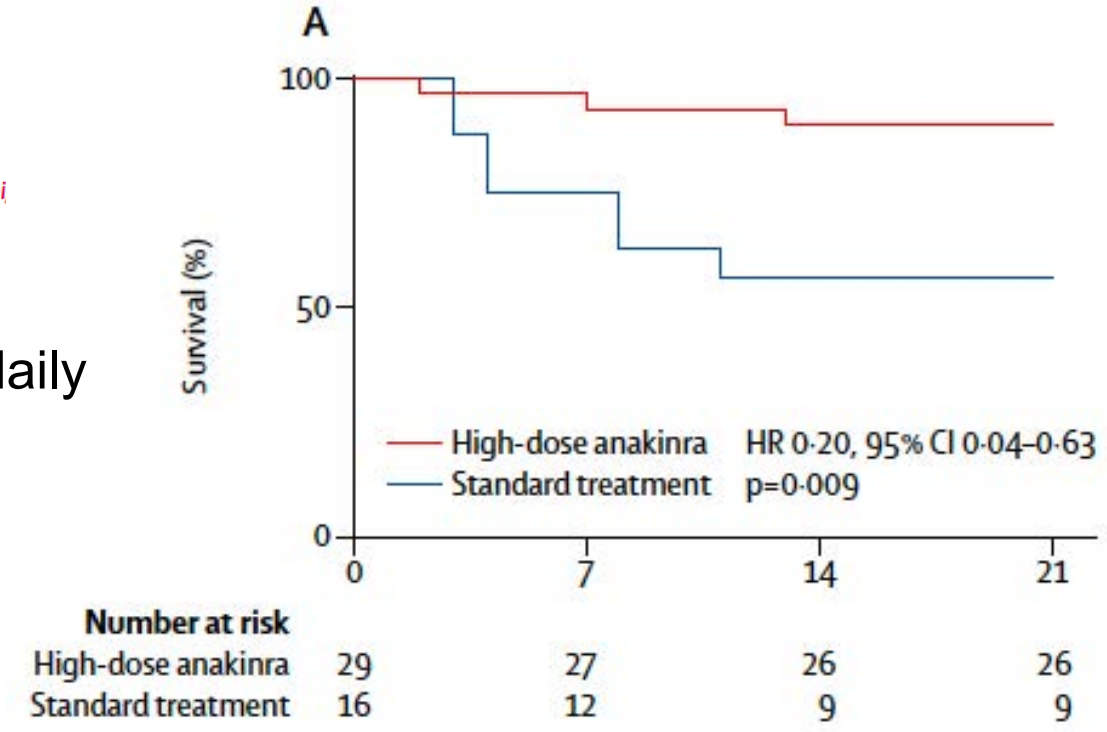
CoVID-19

Anakinra case-control studies in COVID-19

Interleukin-1 blockade with high-dose anakinra in patients with COVID-19, acute respiratory distress syndrome, and hyperinflammation: a retrospective cohort study

Giulio Cavalli, Giacomo De Luca, Corrado Campochiaro, Emanuel Della-Torre, Marco Ripa, Diana Canetti, Chiara Oltolini, Barbara Castiglioni, Chiara Tassan Din, Nicola Boffini, Alessandro Tomelleri, Nicola Farina, Annalisa Ruggeri, Patrizia Rovere-Querini, Giuseppe Di Lucca, Sabina Martinenghi, Raffaella Scotti, Moreno Tresoldi, Fabio Ciceri, Giovanni Landoni, Alberto Zangrillo, Paolo Scarpellini, Lorenzo Dagna

29 patients treated with high-dose anakinra 10 mg/kg IV daily and 16 matched controls



OTHER CASE SERIES PUBLISHED

VCU Health

VCU Pauley Heart Center

CoVID-19

Anakinra case-control studies in COVID-19

Anakinra for severe forms of COVID-19: a cohort study

Thomas Huet, Hélène Beaussier, Olivier Voisin, Stéphane Jouveshomme, Gaëlle Dauriat, Isabelle Lazareth, Emmanuelle Sacco, Jean-Marc Naccache, Yvonnick Bézie, Sophie Laplanche, Alice Le Berre, Jérôme Le Pavec, Sergio Salmeron, Joseph Emmerich, Jean-Jacques Mourad, Gilles Chatellier, Gilles Hayem

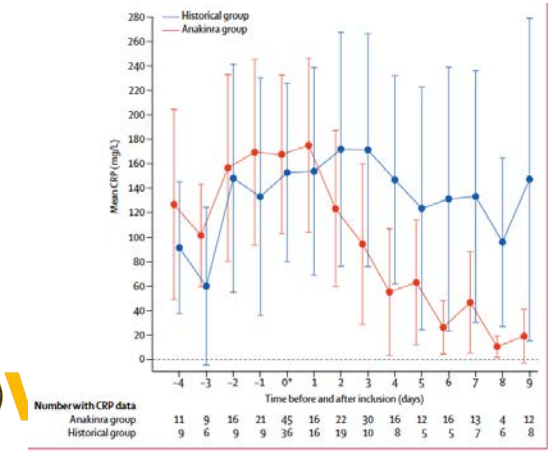
Ana-COVID study

52 patients treated with anakinra

100 mg x2/day for 3 days

then 1/day for 7 days

and 44 matched controls



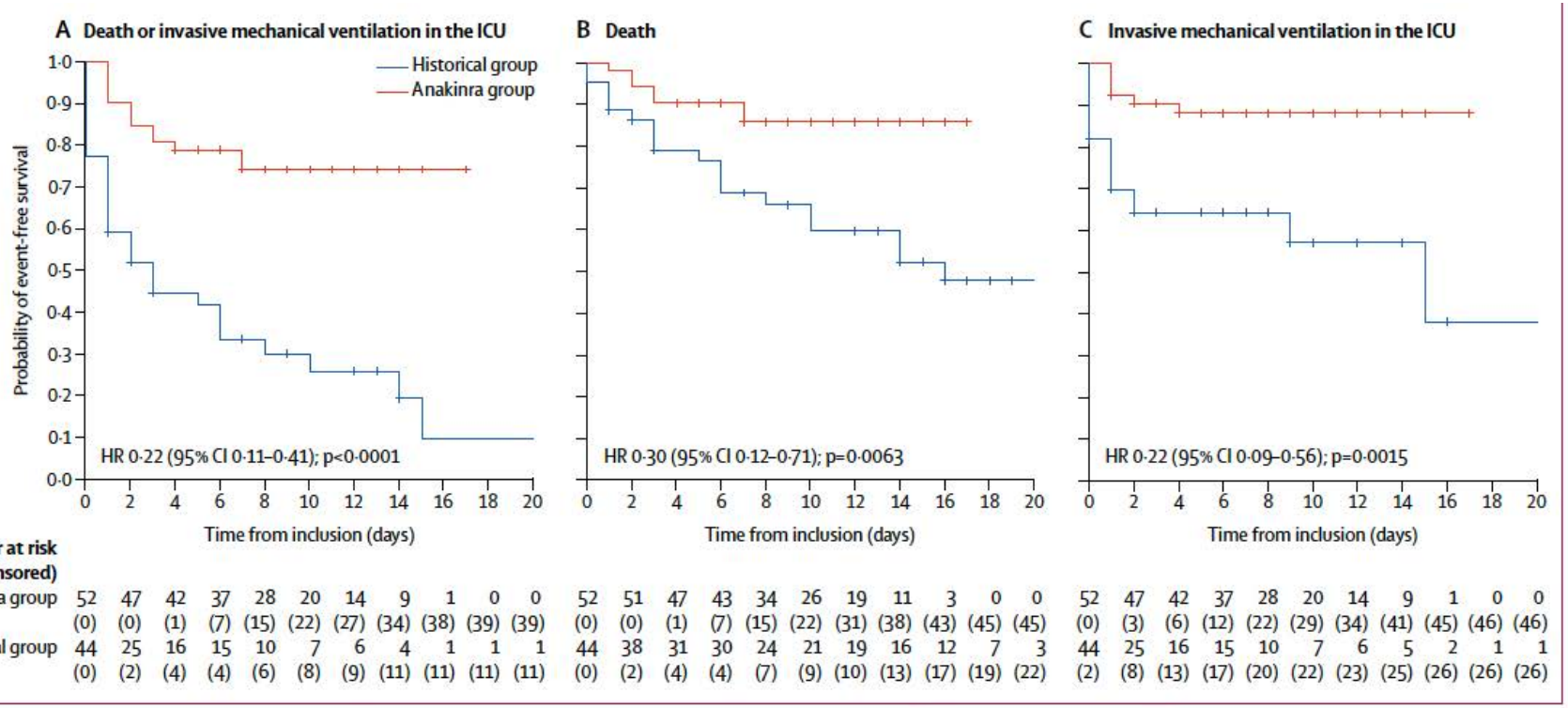


Figure 1: Kaplan-Meier cumulative estimates of probability of death or invasive mechanical ventilation in the ICU (A), death (B) and invasive mechanical ventilation in the ICU (C) in the anakinra group compared with the historical group

HR=hazard ratio. ICU=intensive care unit.

CoVID-19 | Anakinra cas—control study in severe COVID-19

Early IL-1 receptor blockade in severe inflammatory respiratory failure complicating COVID-19

Raphaël Cauchois[a,1], Marie Koubi[a,1], David Delarbre[b], Cécile Manet[c], Julien Carvelli[d], Valery Benjamin Blasco[e], Rodolphe Jean[a], Louis Fouche[f], Charleric Bornet[g], Vanessa Pauly[h], Karin Mazodier[a], Vincent Pestre[c], Pierre-André Jarrot[a], Charles A. Dinarello[i,2], and Gilles Kaplanski[a,2]

[a]Division of Clinical Immunology, Aix-Marseille Université, Assistance Publique-Hôpitaux de Marseille, 13005 Marseille, France; [b]Division of Internal Medicine, L'hôpital d'Instruction des Armées Sainte Anne, 83000 Toulon, France; [c]Division of Internal Medicine, Centre Hospitalier Henri Duffaut, 84 Avignon, France; [d]Réanimation des Urgences, Assistance Publique-Hôpitaux de Marseille, 13005 Marseille, France; [e]Réanimation Polyvalente des Pathologies du Foie, Assistance Publique-Hôpitaux de Marseille, 13005 Marseille, France; [f]Réanimation des Brûlés, Assistance Publique-Hôpitaux de Marseille, 13005 Marseille, France; [g]Pharmacy, Assistance Publique-Hôpitaux de Marseille, 13005 Marseille, France; [h]Department of Medical Informat Assistance Publique-Hôpitaux de Marseille, 13005 Marseille, France; and [i]Department of Medicine, University of Colorado, Aurora, CO 80045

PNAS 2020

Marseille's experience

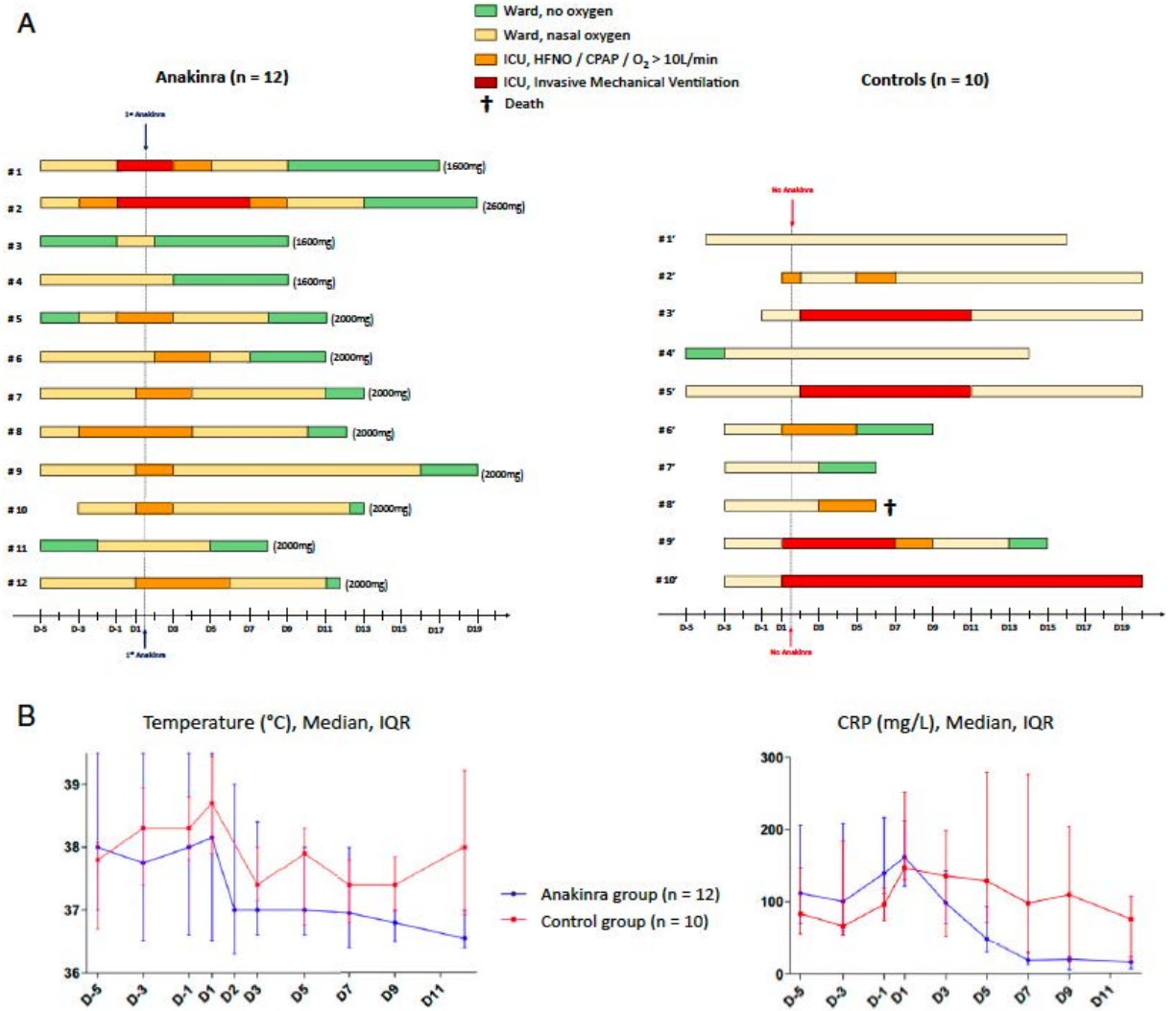


Fig. 1. (*A*) Daily disposition of the 12 patients treated with anakinra and the 10 control patients treated with standard of care only; the total dose of anakinra for each patient is indicated in parentheses. (*B*) Body temperatures (degrees Celsius), and CRP (milligrams per liter) evolution over time, in patients who received anakinra or in controls. IQR, interquartile range.

VCU Health

CoVID-19

Canakinumab case-control study in COVID-19

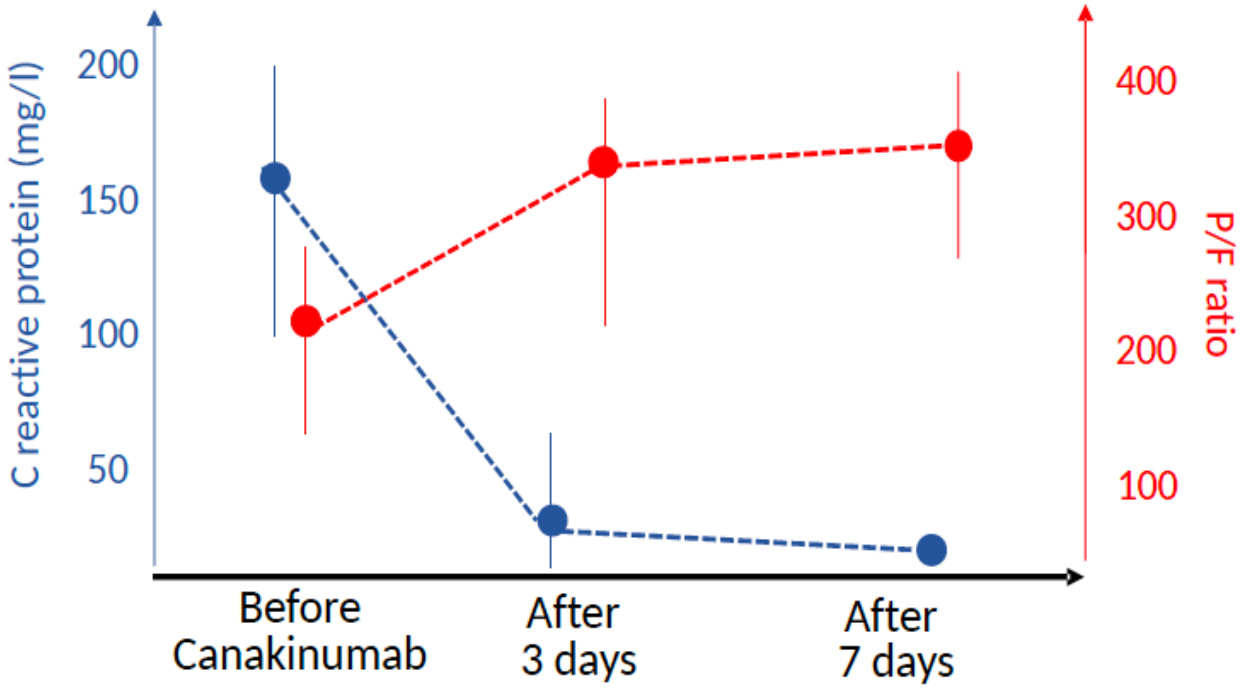
Canakinumab is an IL-1beta targeted antibody

Canakinumab in a subgroup of patients with COVID-19

*Claudio Ucciferri, Antonio Auricchio, Marta Di Nicola, Nicola Potere, Antonio Abbate, Francesco Cipollon Jacopo Vecchiet, *Katia Falasca*
k.falasca@unich.it

Lancet Rheum 2020

10 patients severe COVID-19
on suppl O2 via NC
with elevated CRP
10 matched controls



Anakinra and Canakinumab – our old friends in Cardiology

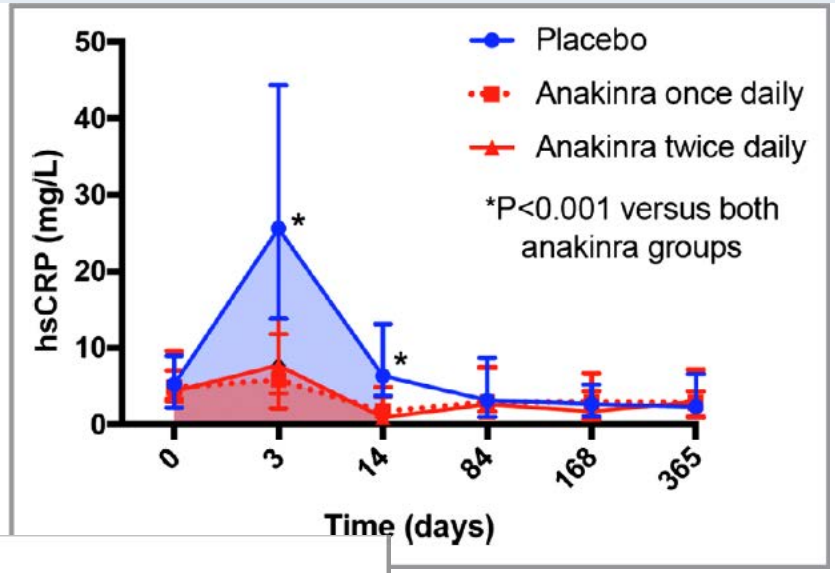
ORIGINAL RESEARCH

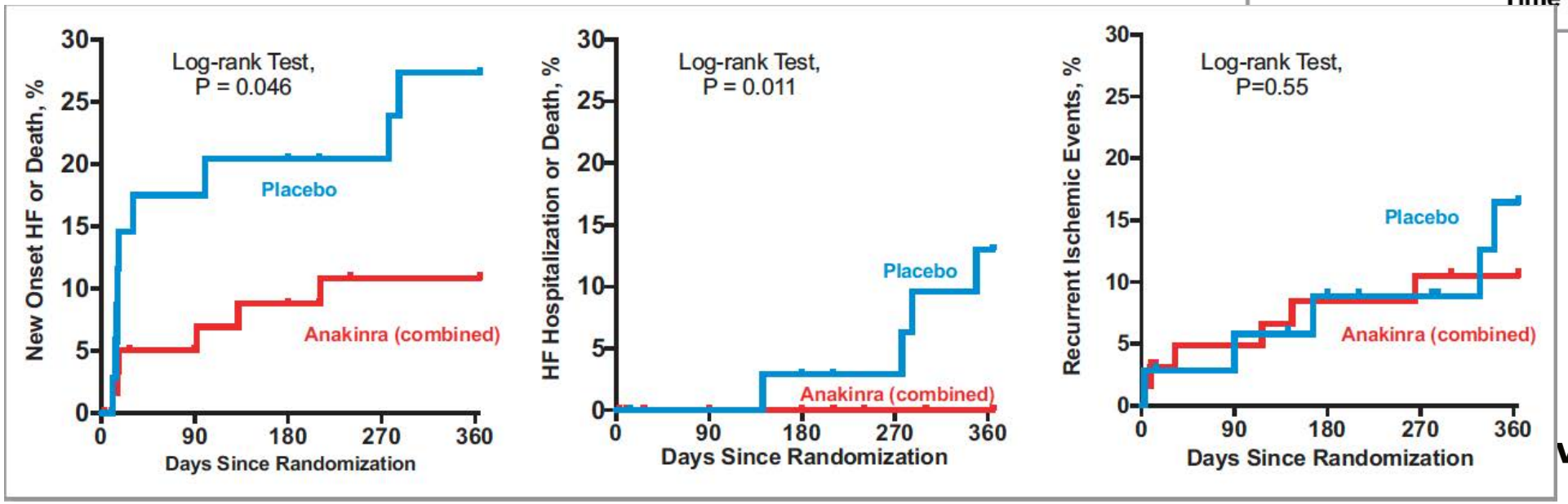
VCUART3 study w/ Anakinra

American Heart Association.

Interleukin-1 Blockade Inhibits the Acute Inflammatory Response in Patients With ST-Segment–Elevation Myocardial Infarction

Antonio Abbate, MD, PhD; Cory R. Trankle, MD; Leo F. Buckley, PharmD; Michael J. Lipinski, MD, PhD; Darryn Appleton, MD; Dinesh Kadariya, MD; Justin M. Canada, PhD; Salvatore Carbone, PhD; Charlotte S. Roberts, NP; Nayef Abouzaki, MD; Ryan Melchior, DO; Sanah Christopher, MD; Jeremy Turlington, MD; George Mueller, DO; James Garnett, MD; Christopher Thomas, MD; Roshanak Markley, MD; George F. Wohlford, PharmD; Laura Puckett, RN; Horacio Medina de Chazal, MD; Juan G. Chiabrando, MD; Edoardo Bressi, MD; Marco Giuseppe Del Buono, MD; Aaron Schatz, MD; Chau Vo, MD; Dave L. Dixon, PharmD; Giuseppe G. Biondi-Zoccai, MD, MStat; Michael C. Kontos, MD; Benjamin W. Van Tassell, PharmD





J Am Heart Assoc 2020

VCU Pauley Heart Center

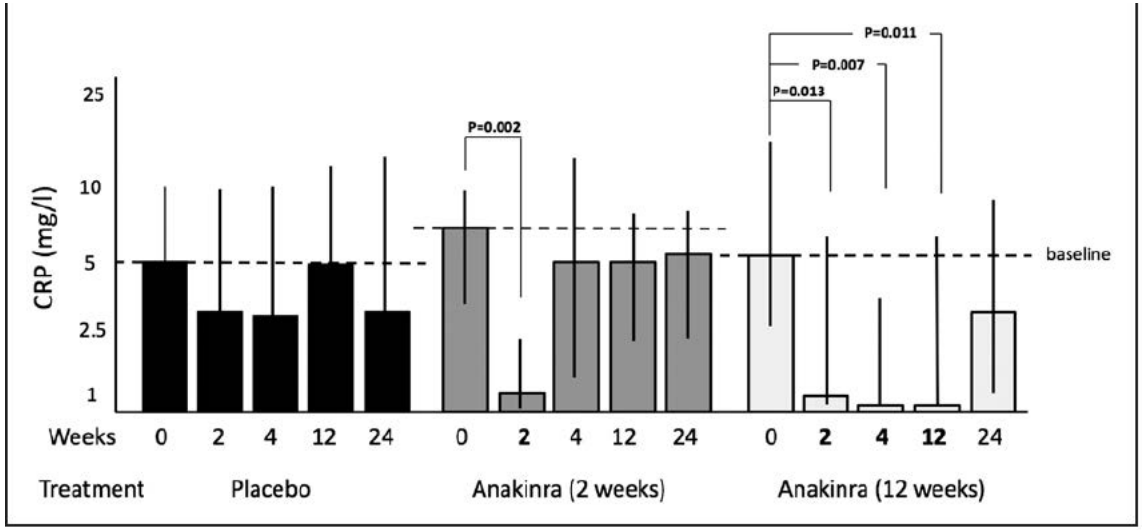
Anakinra and Canakinumab – our old friends in Cardiology

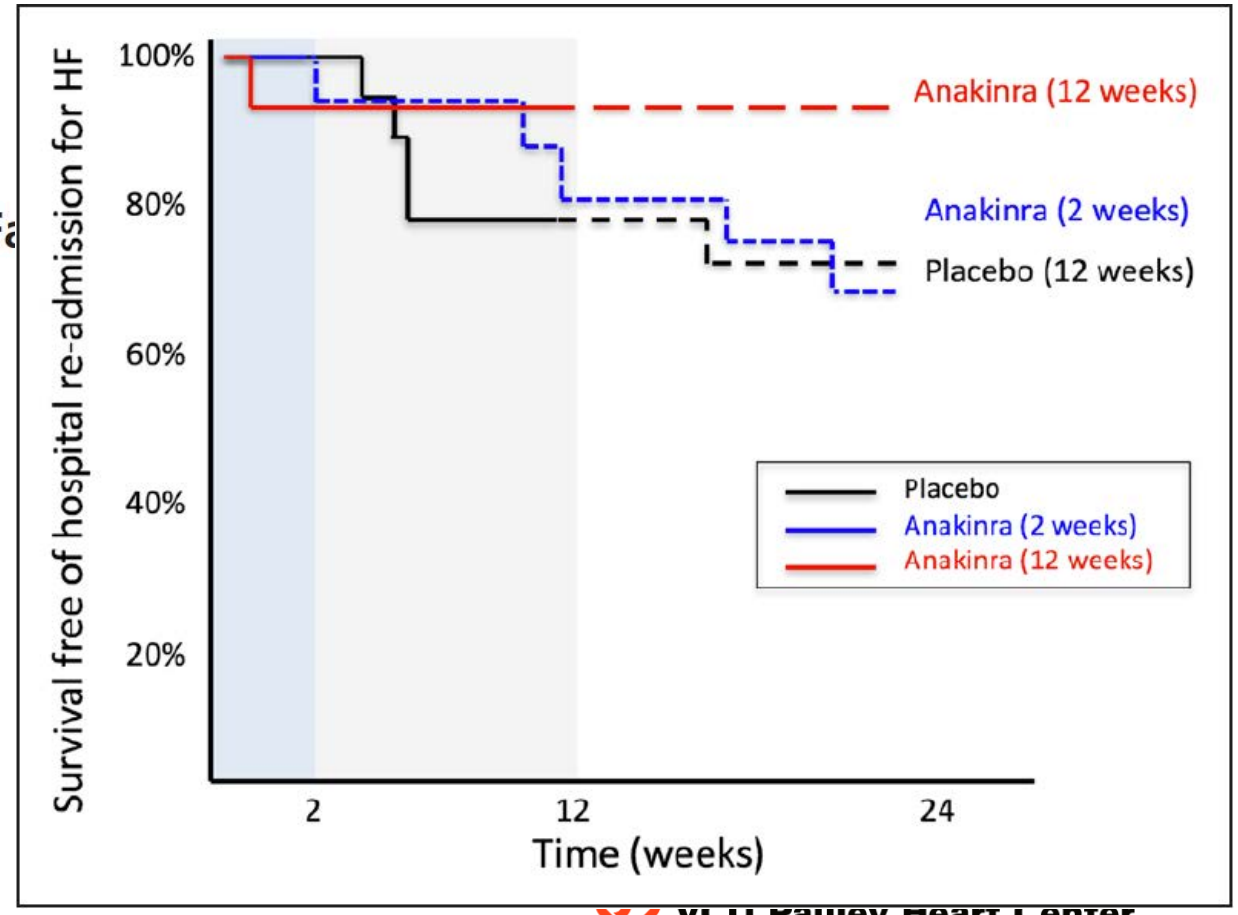
ORIGINAL ARTICLE REDHART study w/ Anakinra

Circ HF 2017

Interleukin-1 Blockade in Recently Decompensated Systolic Heart Failure

Results From REDHART (Recently Decompensated Heart Fa
Anakinra Response Trial)





VCU Health

VCU Pauley Heart Center

Anakinra and Canakinumab – our old friends in Cardiology

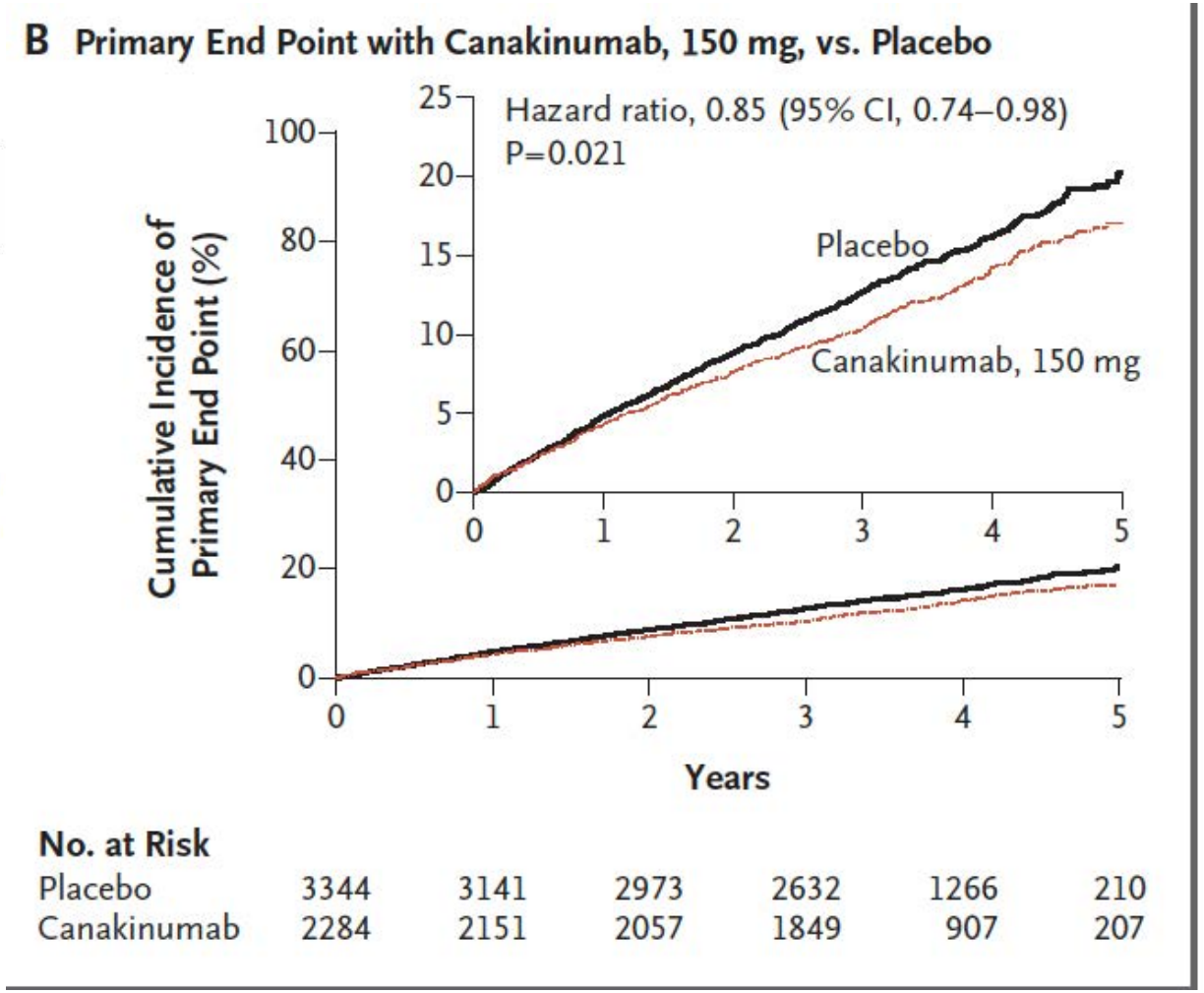
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Antiinflammatory Therapy with Canakinumab for Atherosclerotic Disease

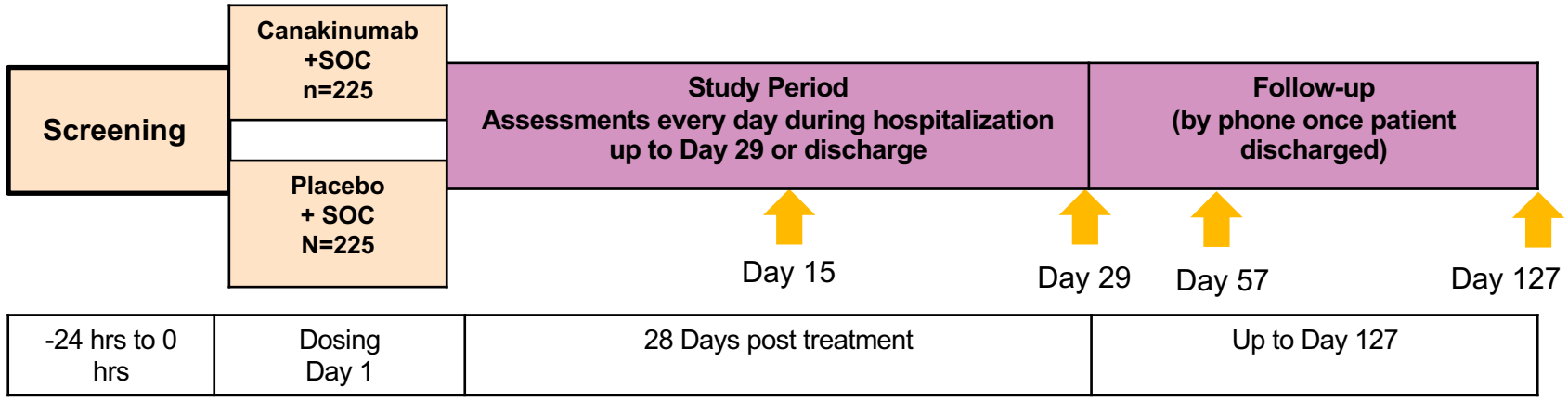
P.M. Ridker, B.M. Everett, T. Thuren, J.G. MacFadyen, W.H. Chang, C. Ballantyne, F. Fonseca, J. Nicolau, W. Koenig, S.D. Anker, J.J.P. Kastelein, J.H. Cornel, P. Pais, D. Pella, J. Genest, R. Cifkova, A. Lorenzatti, T. Forster, Z. Kobalava, L. Vida-Simiti, M. Flather, H. Shimokawa, H. Ogawa, M. Dellborg, P.R.F. Rossi, R.P.T. Troquay, P. Libby, and R.J. Glynn, for the CANTOS Trial Group*

N Engl J Med 2017



CoVID-19 | CAN-COVID: Canakinumab in severe COVID-19

Study Design



Once a patient is discharged, follow-up to be conducted by phone; patient will not need to return to the site for in-person visits.

VCU is #1 enrolling site, 47 patients enrolled as of 7/29/2020

88% enrollment completed

No safety concerns observed

CoVID-19 | Urgent need to find access to COVID-19 treatments

- Where to start? What challenges?
  - Poor understanding of virus
  - Poor understanding of the disease
  - Time required to set up research studies
  - Challenges associated with conducting research during pandemic
  - Rapidly evolving scenarios

CoVID-19

Dexamethasone UK RECOVERY Trial

- Rationale: inflammatory biomarkers predict worse outcomes
- Beneficial effects in other pulmonary infections and critical illnesses
- However concerns about viral clearance
- Chinese guidelines recommended glucocorticoids for severe/critical forms of COVID-19 pneumonia, WHO recommended against it

CoVID-19 | Steroids in severe pulmonary disease

N Engl J Med 1990

A CONTROLLED TRIAL OF EARLY ADJUNCTIVE TREATMENT WITH CORTICOSTEROIDS FOR *PNEUMOCYSTIS CARINII* PNEUMONIA IN THE ACQUIRED IMMUNODEFICIENCY SYNDROME

Samuel A. Bozzette, M.D., Fred R. Sattler, M.D., Joseph Chiu, M.D., Albert W. Wu, M.D., Daniel Gluckstein, M.D., Carol Kemper, M.D., Angie Bartok, M.P.H., Jeannie Niosi, B.S., Ian Abramson, Ph.D., Jeanine Coffman, R.N., Claire Hughlett, R.N., Ronaldo Loya, P.A., Brett Cassens, M.D., Bisher Akil, M.D., Tze-Chiang Meng, M.D., C. Thomas Boylen, M.D., Donald Nielsen, M.D., Douglas D. Richman, M.D., Jeremiah G. Tilles, M.D., John Leedom, M.D., J. Allen McCutchan, M.D., and the California Collaborative Treatment Group*

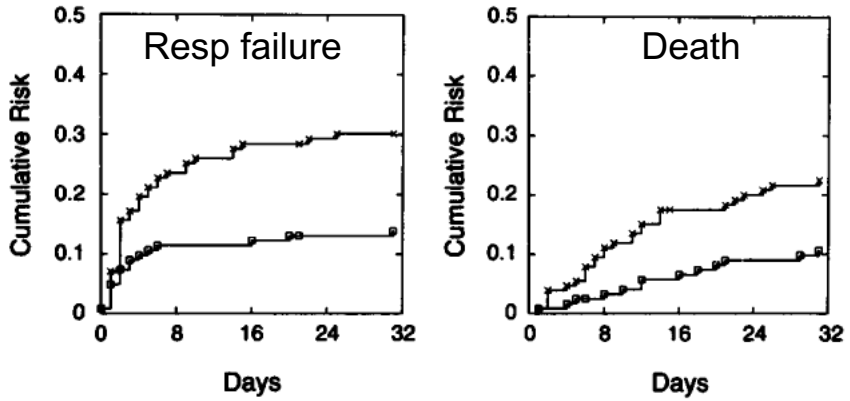


Figure 1. Cumulative Risk of an Unfavorable Outcome over a Period of 31 Days.

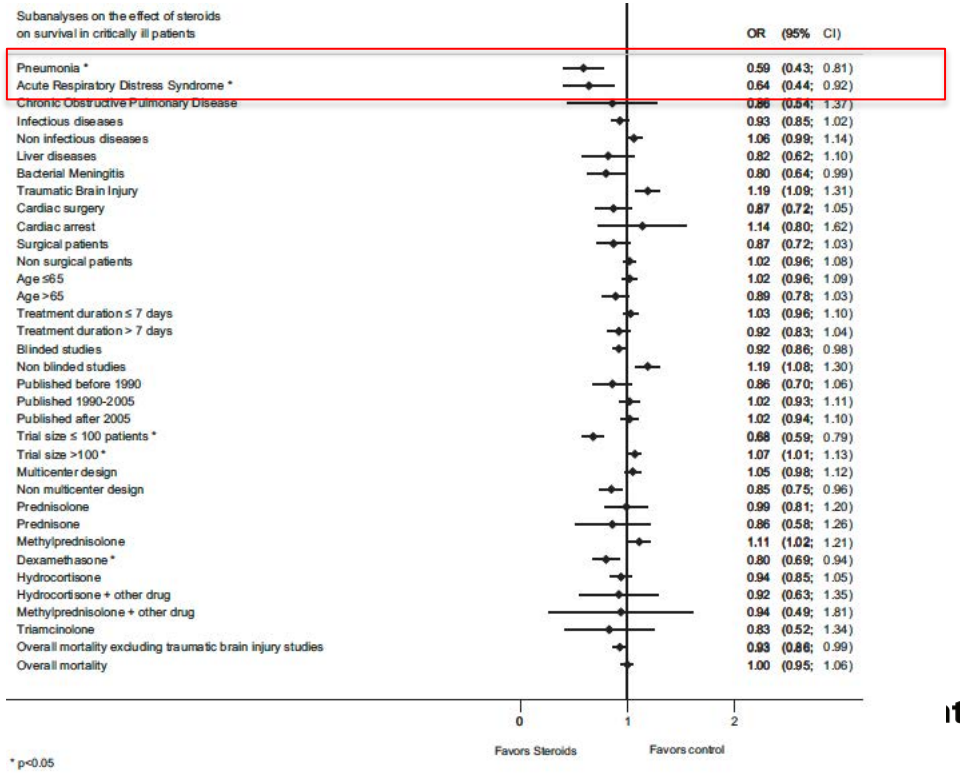
The risk of respiratory failure (left panel) was 0.14 in the corticosteroid group (□) and 0.30 in the standard-treatment group (×) (P = 0.004). The risks of death (right panel) were 0.11 and 0.23, respectively (P = 0.009).

Journal of Cardiothoracic and Vascular Anesthesia

journal homepage: www.jcvaonline.com

Original Article

Steroids and Survival in Critically Ill Adult Patients: A Meta-analysis of 135 Randomized Trials

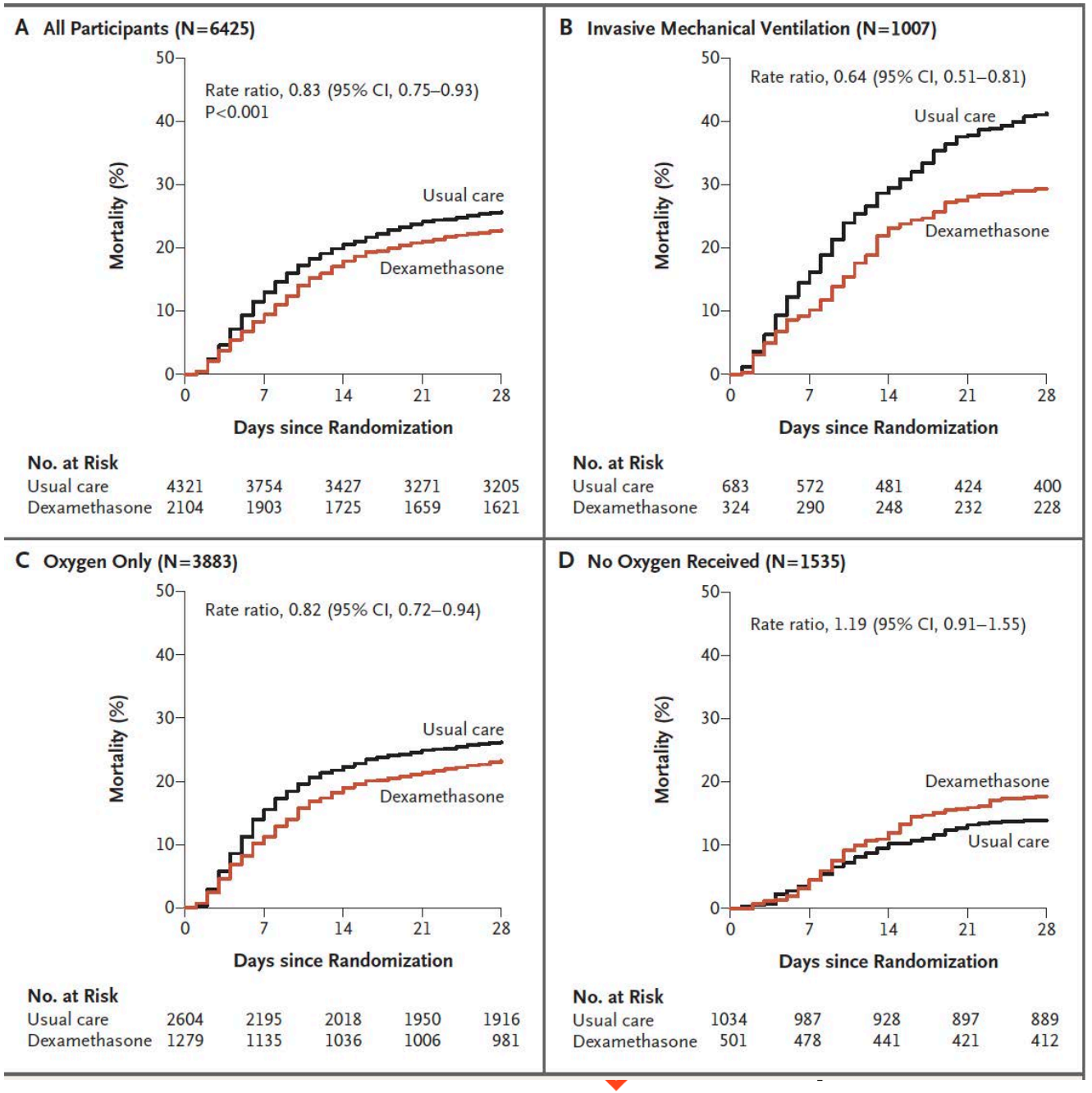


CoVID-19

Dexamethasone UK RECOVERY Trial

- Open label study
- >150 centers
- 6,425 patients randomized 2:1 to placebo or dexamethasone
- Placebo part of a common randomization platform

- PRESS RELEASE on June 16, 2020
- Local and global guidelines changed the same day



VCU Health

CoVID-19 | Retrospective analysis: Corticosteroid Use in NY

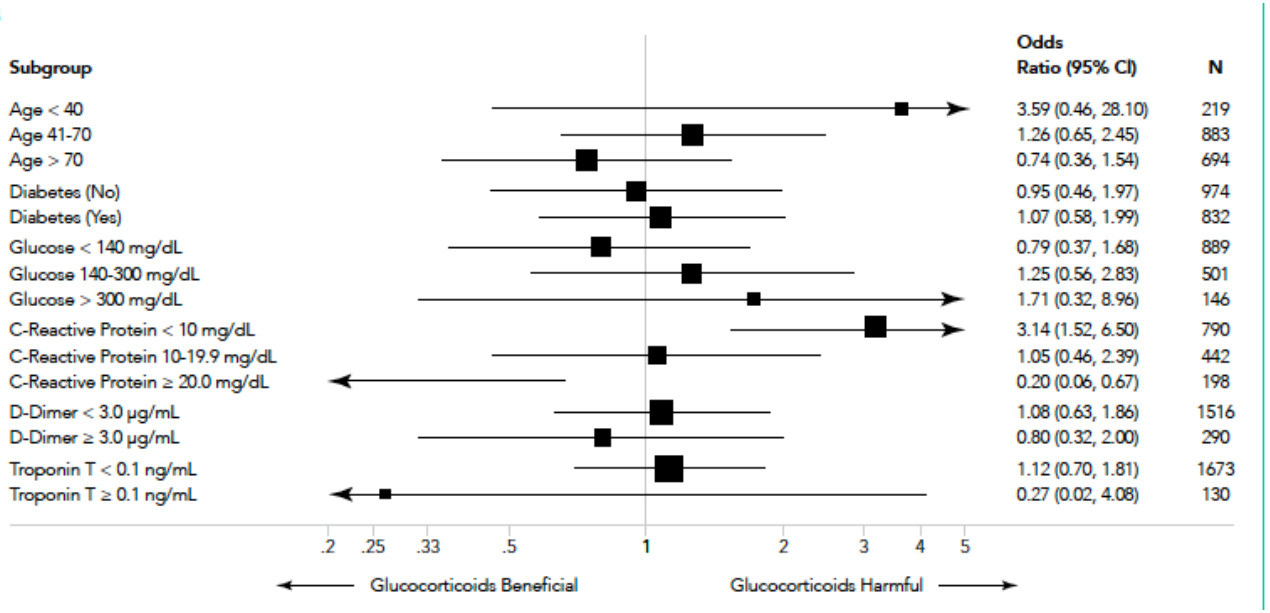
Effect of Systemic Glucocorticoids on Mortality or Mechanical Ventilation in Patients With COVID-19

Marla J Keller, MD[1]*, Elizabeth A Kitsis, MD, MBE[2], Shitij Arora, MD[3], Jen-Ting Chen, MD, MS[4], Shivani Agarwal, MD, MPH[5], Michael J Ross, MD[6], Yaron Tomer, MD[5], William Southern, MD, MS[3]

[1]Division of Infectious Diseases, Department of Medicine, Montefiore Medical Center and Albert Einstein College of Medicine, Bronx, New York; [2]Division of Rheumatology, Department of Medicine, Montefiore Medical Center and Albert Einstein College of Medicine, Bronx, New York; [3]Division of Hospital Medicine, Department of Medicine, Montefiore Medical Center and Albert Einstein College of Medicine, Bronx, New York; [4]Division of Critical Care Medicine, Department of Medicine, Montefiore Medical Center and Albert Einstein College of Medicine, Bronx, New York; [5]Division of Endocrinology, Department of Medicine, Montefiore Medical Center and Albert Einstein College of Medicine, Bronx, New York; [6]Division of Nephrology, Department of Medicine, Montefiore Medical Center and Albert Einstein College of Medicine, Bronx, New York.

The efficacy of glucocorticoids in COVID-19 is unclear. This study was designed to determine whether systemic glucocorticoid treatment in COVID-19 patients is associated with reduced mortality or mechanical ventilation. This observational study included 1,806 hospitalized COVID-19 patients; 140 were treated with glucocorticoids within 48 hours of admission. Early use of glucocorticoids was not associated with mortality or mechanical ventilation. However, glucocorticoid treatment of patients with initial C-reactive protein (CRP) ≥20 mg/dL was associated with significantly reduced risk of mortality or mechanical ventilation (odds ratio, 0.23; 95% CI, 0.08-0.70), while glucocorticoid treatment of patients with CRP <10 mg/dL was associated with significantly increased risk of mortality or mechanical ventilation (OR, 2.64; 95% CI, 1.39-5.03). Whether glucocorticoid treatment is associated with changes in mortality or mechanical ventilation in patients with high or low CRP needs study in prospective, randomized clinical trials. *Journal of Hospital Medicine* 2020;15:489-493. © 2020 Society of Hospital Medicine

B



- 1,806 cases
- 140 treated with corticosteroids

J Hospital Med 2020

TABLE 2B. **Mortality or Mechanical Ventilation by CRP Value**

CRP Subgroup	OR (95% CI)	aOR* (95% CI)
0-9.9 mg/dL (n = 807)	2.64 (1.39-5.03)	3.14 (1.52-6.50)
10-19.9 mg/dL (n = 442)	1.03 (0.47-2.23)	1.05 (0.46-2.39)
≥20 mg/dL (n = 198)	0.23 (0.08-0.70)	0.20 (0.06-0.67)

*Parsimonious model adjusted for body mass index, chronic obstructive pulmonary disease, asthma, rheumatologic disease, previous glucocorticoid use, ferritin, and procalcitonin.
Abbreviations: aOR, adjusted odds ratio; CI, confidence interval; CRP, C-reactive protein; OR, odds ratio.

VCU Health

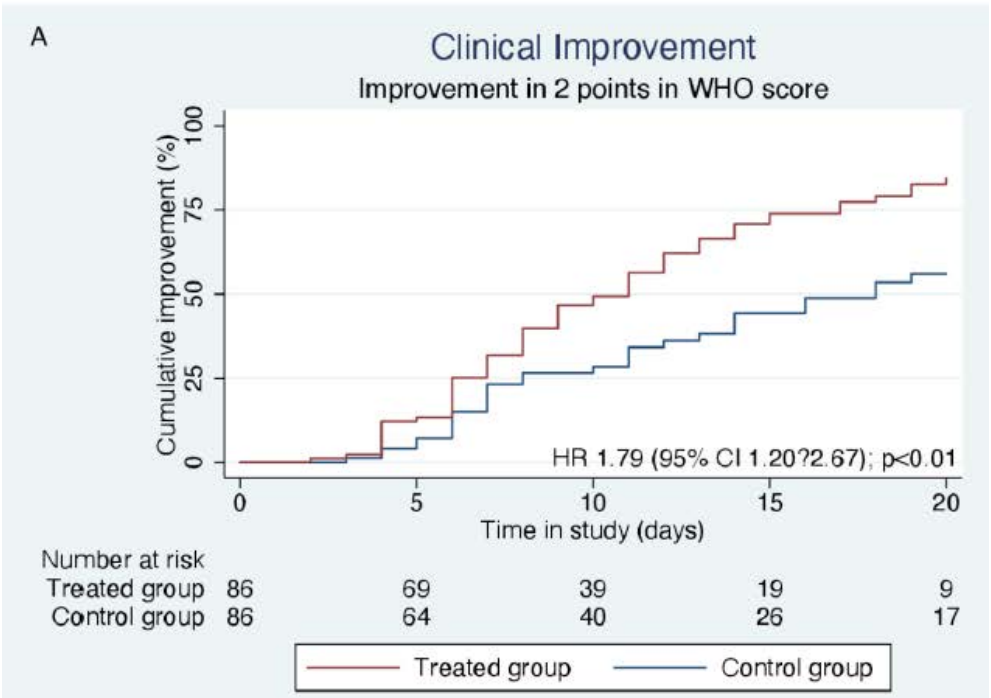
CoVID-19

What about IL-6R / dexamethasone interaction?

Historically controlled comparison of glucocorticoids with or without tocilizumab versus supportive care only in patients with COVID-19-associated cytokine storm syndrome: results of the CHIC study

Sofia Ramiro [1,2] Rémy L M Mostard,[3] César Magro-Checa,[1] Christel M P van Dongen,[1] Tom Dormans,[4] Jacqueline Buijs,[5] Michiel Gronenschild,[3] Martijn D de Kruif,[3] Eric H J van Haren,[3] Tom van Kraaij,[3] Mathie P G Leers,[6] Ralph Peeters,[1] Dennis R Wong,[7] Robert B M Landewé [1,8]

Ann Rheum Dis 2020



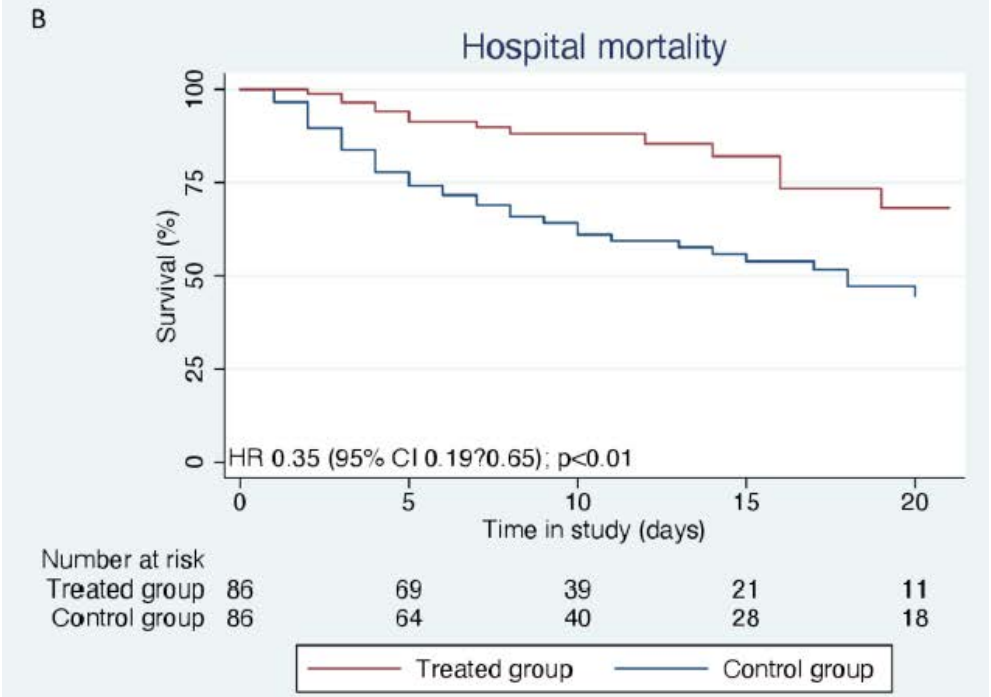


Figure 1 Clinical improvement and hospital mortality. Plots show clinical improvement (A) defined as a 2-point improvement in the 7-point WHO score and (B) hospital mortality in patients with COVID-19-associated cytokine release syndrome stratified for treatment (treated vs control group).

VCU Health

CoVID-19 | Convalescent plasma from donors

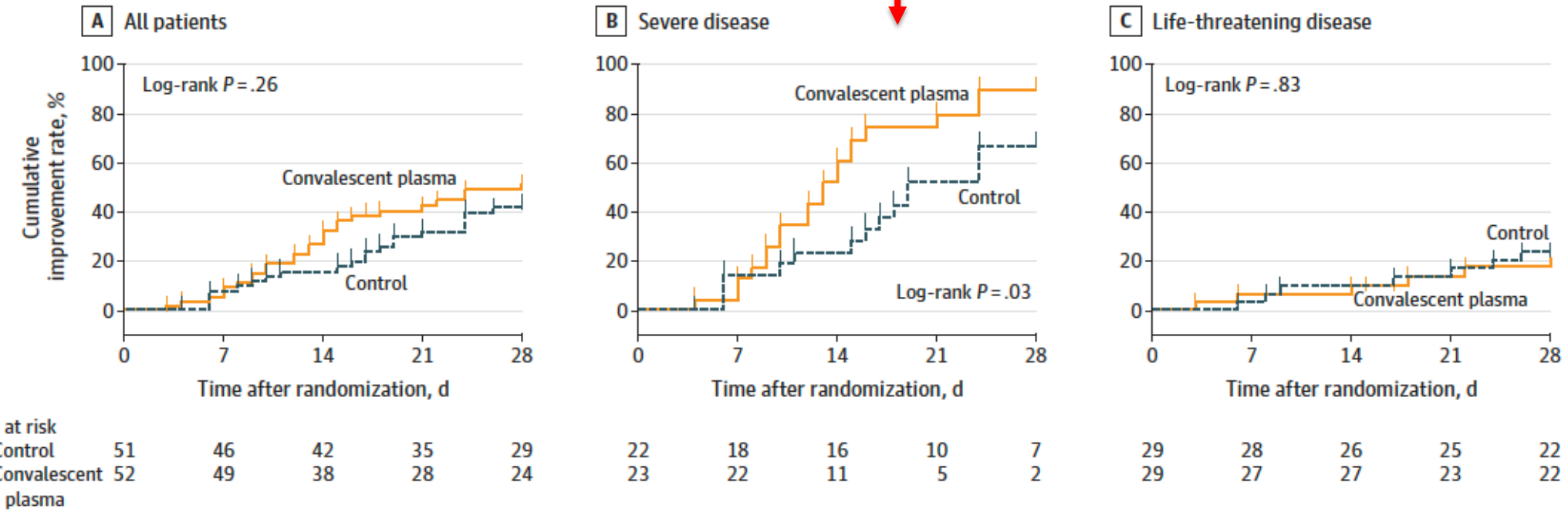
JAMA | Original Investigation

Effect of Convalescent Plasma Therapy on Time to Clinical Improvement in Patients With Severe and Life-threatening COVID-19
A Randomized Clinical Trial

Ling Li, MD, PhD; Wei Zhang, MD
Lili Ren, PhD; Qing Wei, MD; Hen
Yong Guo, PhD; Xiaoxiong Wu, M
Yu Liu, PhD; Haixia Xu, MD; E. De
Jianwei Wang, PhD; Yanyun Wu,

Most benefit seems to be in severe disease (<7 days from onset)

Figure 2. Time to Clinical Improvement in Patients With COVID-19



No. at risk															
Control	51	46	42	35	29	22	18	16	10	7	29	28	26	25	22
Convalescent plasma	52	49	38	28	24	23	22	11	5	2	29	27	27	23	22

VCU Health

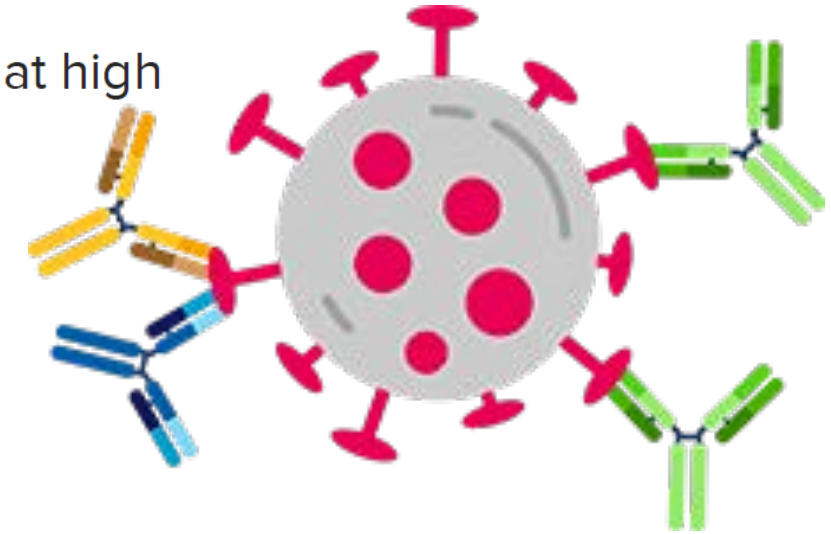
VCU Pauley Heart Center

CoVID-19 | Novel antiviral strategy – targeted antibodies

BIOPHARMA

Regeneron starts two trials of two-antibody antiviral cocktail for Covid-19

The company plans to test REGN-COV2 - consisting of the SARS-CoV-2-specific antibodies REGN10933 and REGN10987 - in four populations, including infected patients and uninfected people at high risk of infection.



Currently open at VCU for infected patients

Another study for exposed patient without symptoms will start soon

CoVID-19

Colchicine for moderate COVID-19 pneumonia

JAMA Network | Open

Original Investigation | Infectious Diseases

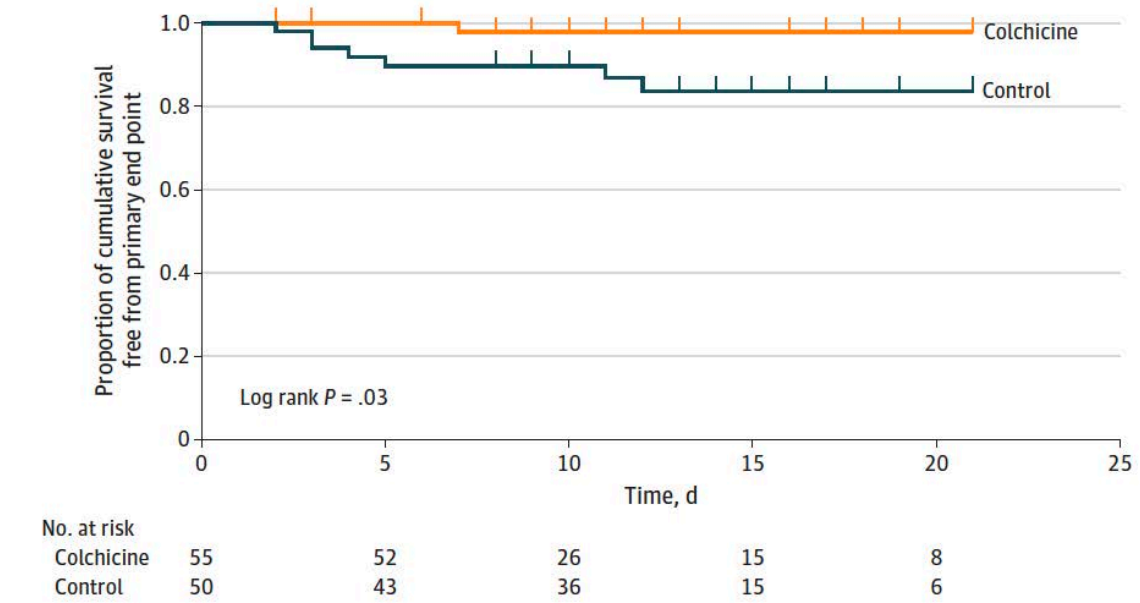
Effect of Colchicine vs Standard Care on Cardiac and Inflammatory Biomarkers and Clinical Outcomes in Patients Hospitalized With Coronavirus Disease 2019

The GRECCO-19 Randomized Clinical Trial

Spyridon G. Deftereos, MD, PhD; Georgios Giannopoulos, MD, PhD; Dimitrios A. Vrachatis, MD, MSc, PhD; Gerasimos D. Siasos, MD, MSc, PhD; Panagiotis Gargalianos, MD, PhD; Simeon Metallidis, MD, PhD; George Sianos, MD, PhD; Stefanos Baltagiannis, MD, MSc; Periklis Panagopoulos Konstantinos Dolianitis, MD, MSc; Efthalia Randou, MD; Konstantinos Syrigos, MD, PhD; Anastasia Kotanidou, MD, PhD; Nikolaos G. Koulouris, Haralampos Milionis, MD, PhD; Nikolaos Sipsas, MD, PhD; Charalampos Gogos, MD, PhD; George Tsoukalas, MD, PhD; Christoforos D. Olympios Eleftheria Tsagalou, MD, PhD; Ilias Migdalis, MD, PhD; Styliani Gerakari, MD; Christos Angelidis, MD; Dimitrios Alexopoulos, MD, PhD; Pericles D George Hahalis, MD, PhD; Ioannis Kanonidis, MD, PhD; Demosthenes Katritsis, MD, PhD; Theofilos Kolettis, MD, PhD; Antonios S. Manolis, MD, Lampros Michalis, MD, PhD; Katerina K. Naka, MD, PhD; Vlasios N. Pyrgakis, MD, PhD; Konstantinos P. Toutouzas, MD, PhD; Filippos Triposkiadi Konstantinos Tsioufis, MD, PhD; Emmanouil Vavouranakis, MD, PhD; Luis Martinèz-Dolz, MD, PhD; Bernhard Reimers, MD; Giulio G. Stefanini, Michael Cleman, MD, PhD; John Goudevenos, MD, PhD; Sotirios Tsiodras, MD, PhD; Dimitrios Tousoulis, MD, PhD; Efstathios Iliodromitis, MD, P Roxana Mehran, MD, PhD; George Dangas, MD, PhD; Christodoulos Stefanadis, MD, PhD; on behalf of the GRECCO-19 investigators

Event: NIV or IV or death

Figure 2. Kaplan-Meier Curves for Survival From the Primary Clinical End Point



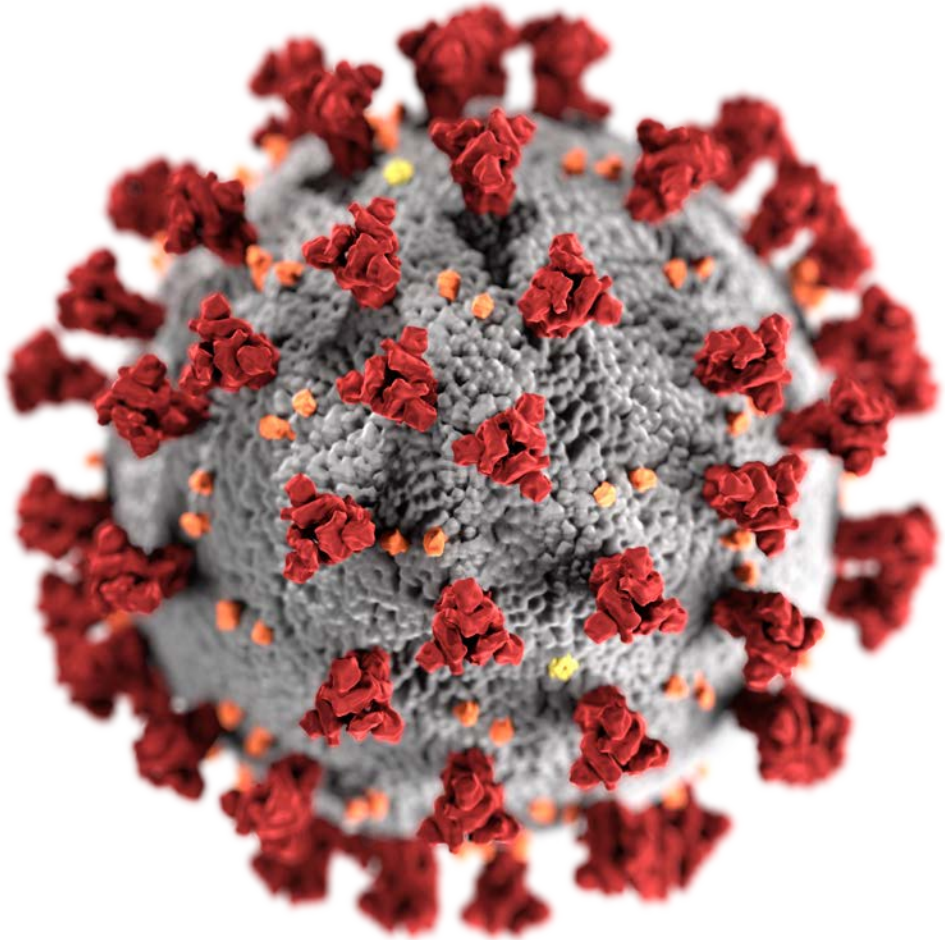
VCU Health

VCU Pauley Heart Center

CoVID-19

Learning Objectives

1. Understand the challenges of conducting research during the COVID-19 pandemic
2. Understand the key pathophysiological therapeutic aspects of COVID-19 research
3. Review the preliminary results of COVID-19 research to date



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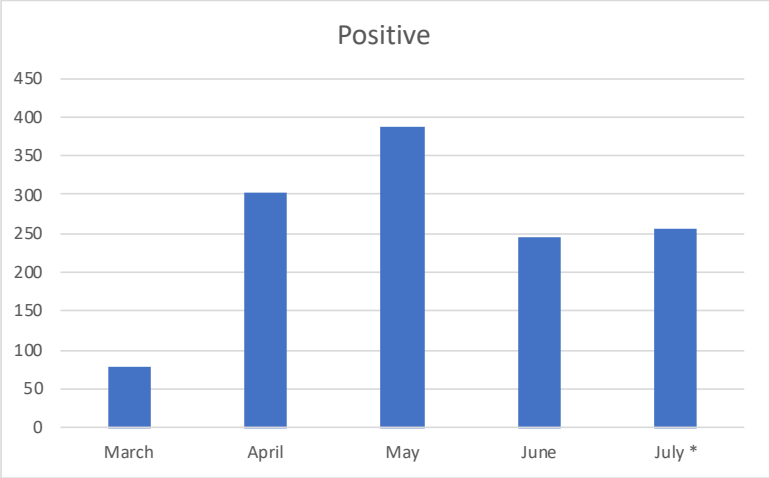
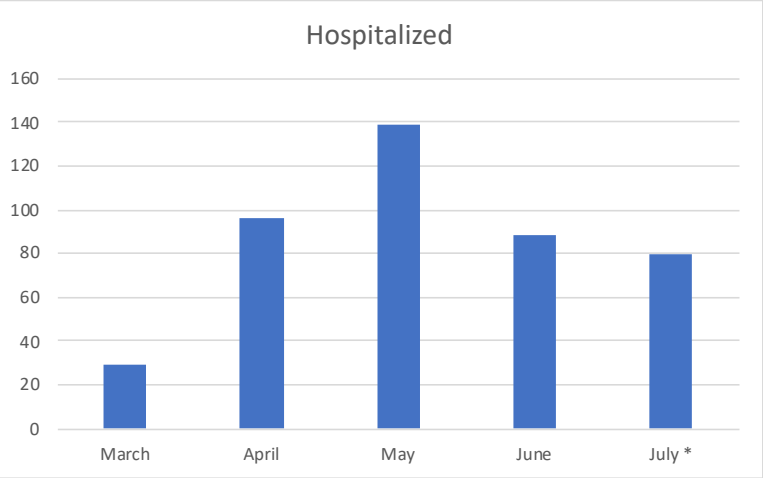
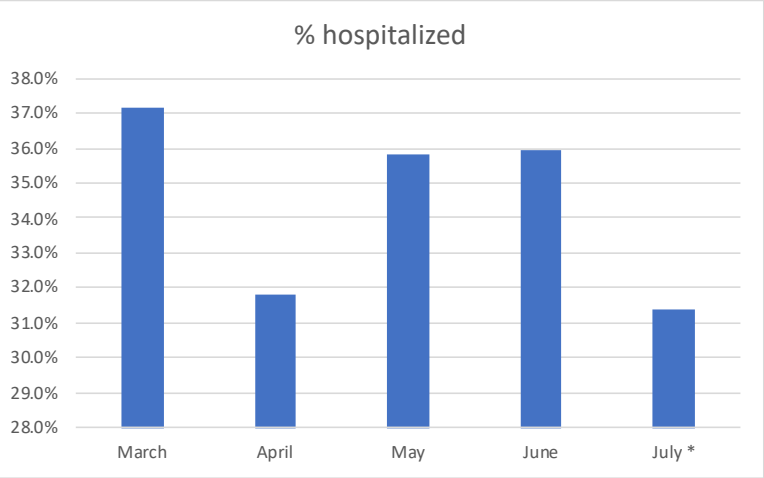
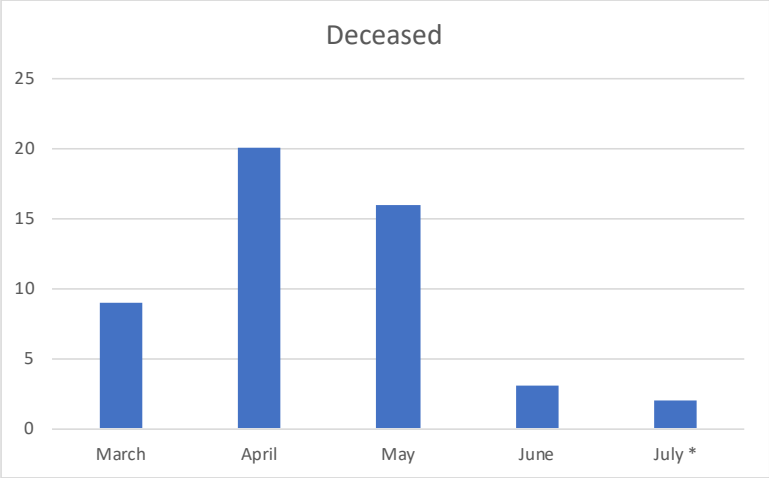
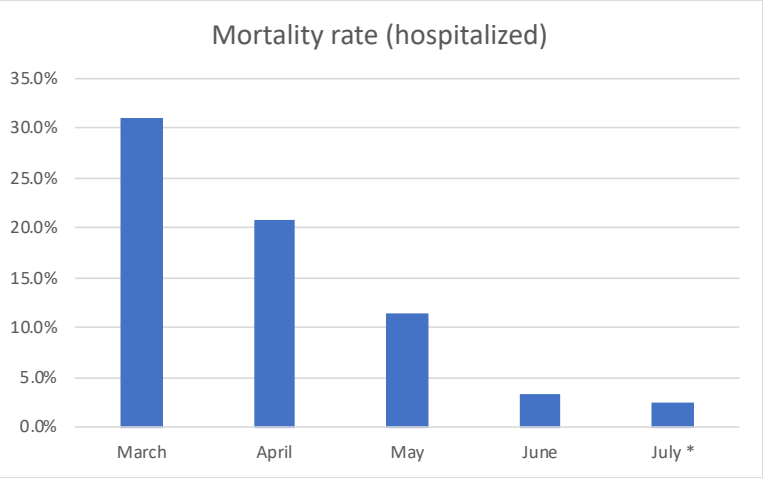
CoVID-19 Unadjusted Event rates at VCU Health up to July 24, 2020

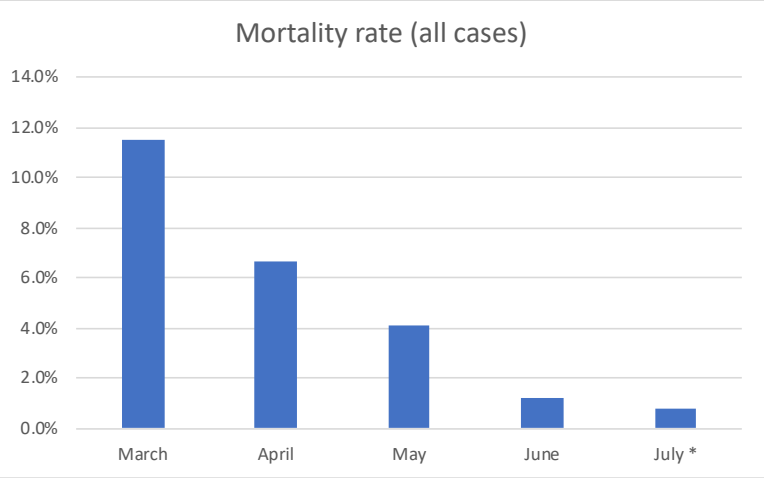












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MANY FACTORS COME IN TO PLAY!!!!!!

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CoVID-19

Review of the preliminary results of COVID-19 trials

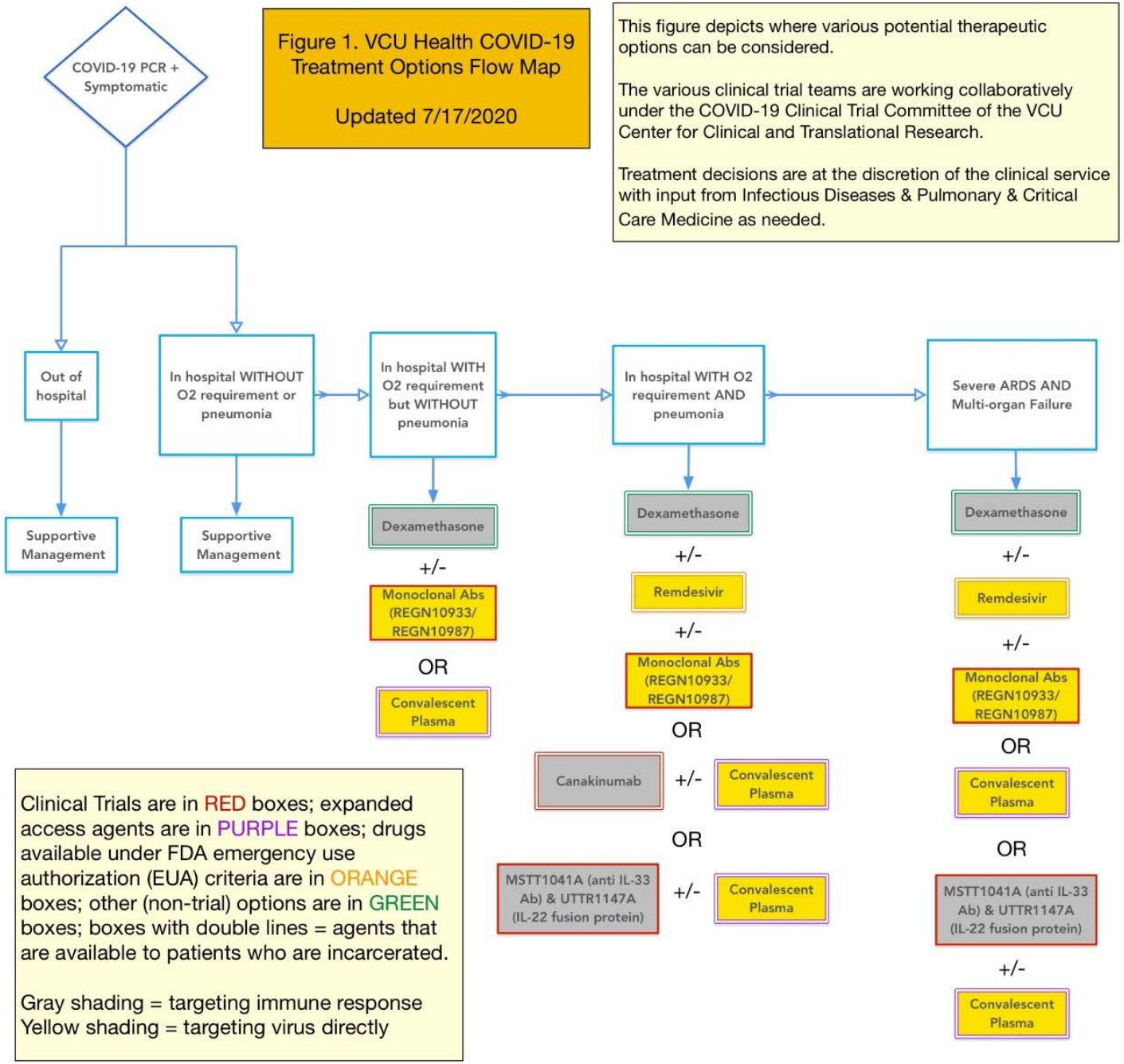
Evidence from randomized trials is limited

- Preliminary data show that **Remdesivir** (for 5-10 days IV) improves outcomes in patients with severe (or critical) COVID-19 pneumonia, early initiation preferred, most effective in reducing disease duration
- Preliminary data show that **Dexamethasone** (6 mg daily for up to 10 days) reduces mortality in patients with severe or critical COVID-19, with no benefit in patients with early, mild or moderate disease
- Preliminary data on convalescent plasma suggest a potential benefit in patients with severe COVID-19
- Insufficient data to recommend IL-6R or IL-1 blockers – at present the use as salvage therapy may be considered for selected critical cases of cytokine release syndrome failing standard treatment

CoVID-19

Treatment algorithm at VCU

Updated frequently



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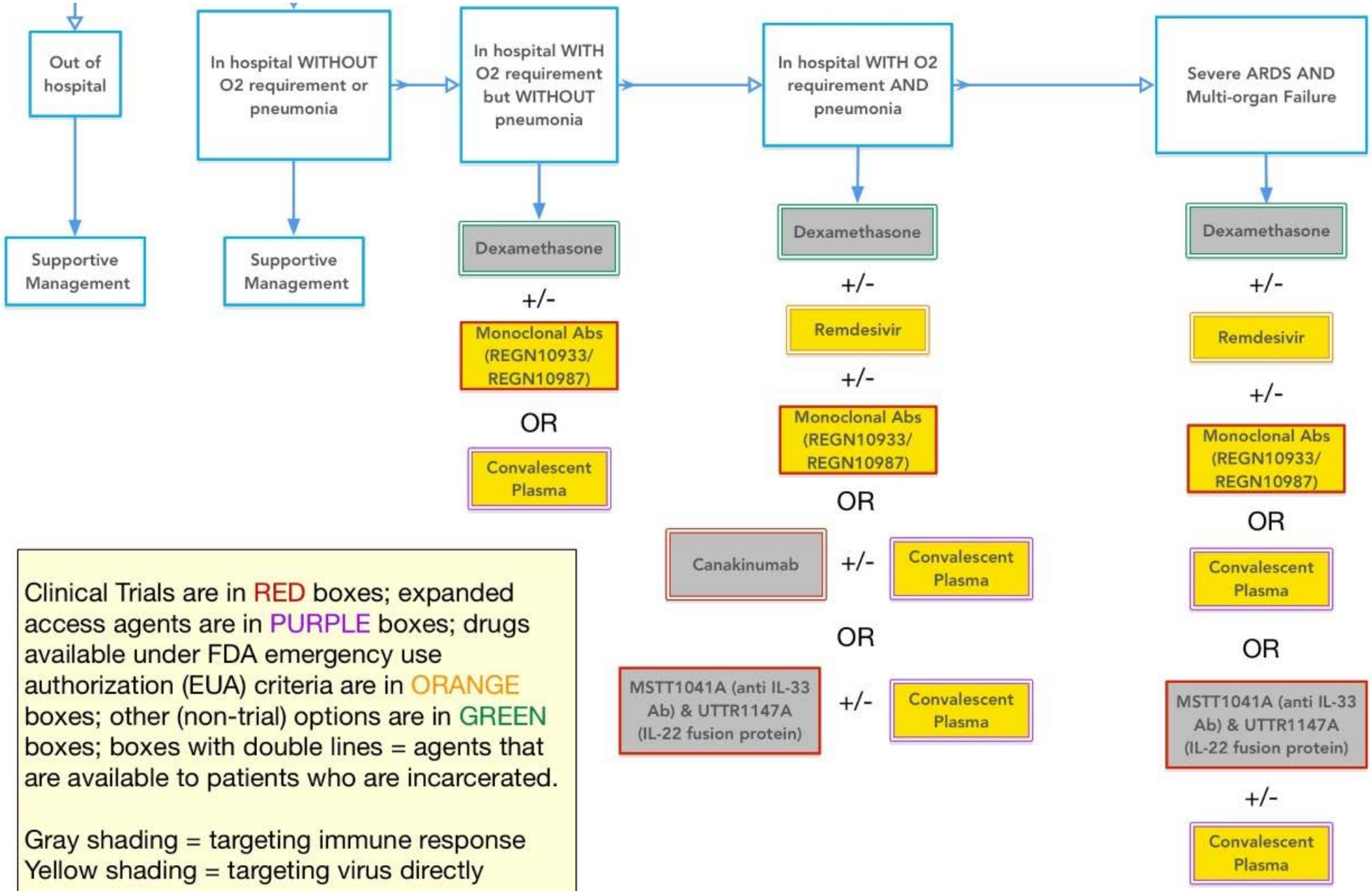

Clinical Trials are in RED boxes; expanded access agents are in PURPLE boxes; drugs available under FDA emergency use authorization (EUA) criteria are in ORANGE boxes; other (non-trial) options are in GREEN boxes; boxes with double lines = agents that are available to patients who are incarcerated.

Gray shading = targeting immune response
Yellow shading = targeting virus directly

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CoVID-19

Conclusions

- ✓ Learned a lot about the virus and the disease
- ✓ Better at detecting and diagnosing disease
- ✓ Have a rapid system in place to evaluate and initiate clinical trials at VCUHealth
- ✓ Remdesivir and Dexamethasone show efficacy in patients with severe and critical COVID-19

- ✕ Need better prevention and treatments for early stage disease to prevent severe illness
- ✕ Need more data on patient-centered outcomes (i.e. symptoms resolution etc..)
- ✕ Need additional treatments for critical disease to further reduce mortality

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Thank you for your attention

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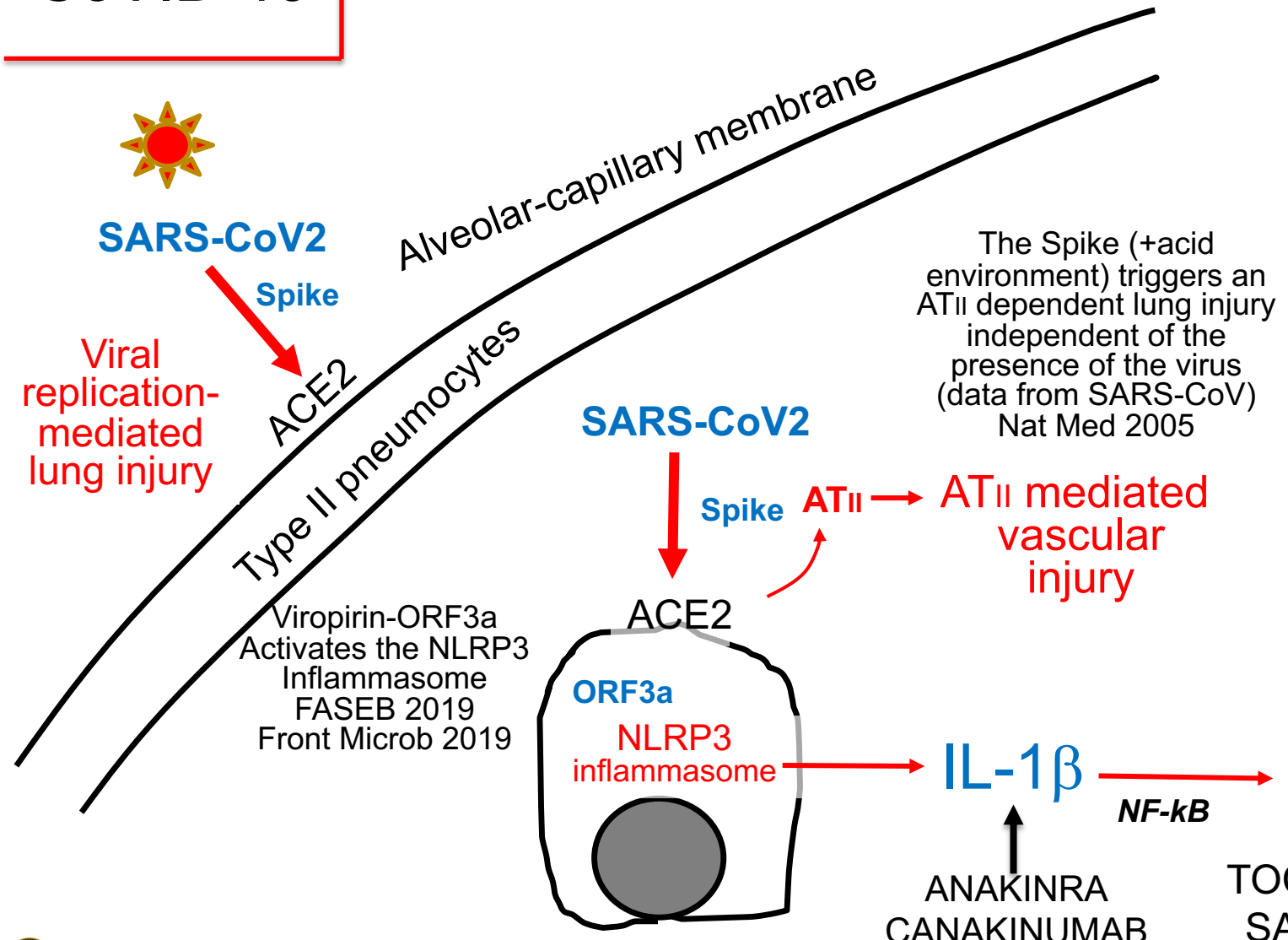
CoVID-19

BACK-UP SLIDE

CoVID-19

Simplified Pathophysiologic Scheme of COVID-19



The Spike (+acid environment) triggers an ATII dependent lung injury independent of the presence of the virus (data from SARS-CoV) Nat Med 2005

Viropirin-ORF3a Activates the NLRP3 Inflammasome FASEB 2019 Front Microb 2019

1. **Viral-induced injury**
2. **Hypoxemia a result of dysfunction of the alveolar-capillary membrane as a result of inflammation-mediated injury**
3. **Angiotensin-mediated vascular and thrombotic effects**

VCUH Type II pneumocyte(s) or neutrophils

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