The Pathophysiology of the Disease: The Rationale for Apheresis

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Forbes

Feb 19, 2017, 12:40am EST

Bill Gates Warns Of Epidemic That Could Kill Over 30 Million People

Bruce Y. Lee Senior Contributor
Health
I am a writer, journalist, professor, systems modeler, computational and digital health expert, avocado-eater, and entrepreneur, not always in that order.

idea to listen. Yesterday, at the Munich Security Conference in Germany, the man who tops the *Forbes* richest person in the world list and is co-chair of the Bill and Melinda Gates Foundation said:

> Whether it occurs by a quirk of nature or at the hand of a terrorist, epidemiologists say a fast-moving airborne pathogen could kill more than 30 million people in less than a year. And they say there is a reasonable probability the world will experience such an outbreak in the next 10 to 15 years.

Notice that this was at a security conference and not a health meeting.

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https://www.forbes.com/sites/brucelee/2017/02/19/bill-gates-warns-of-epidemic-that-will-kill-over-30-million-people/?sh=22c7ef63282f

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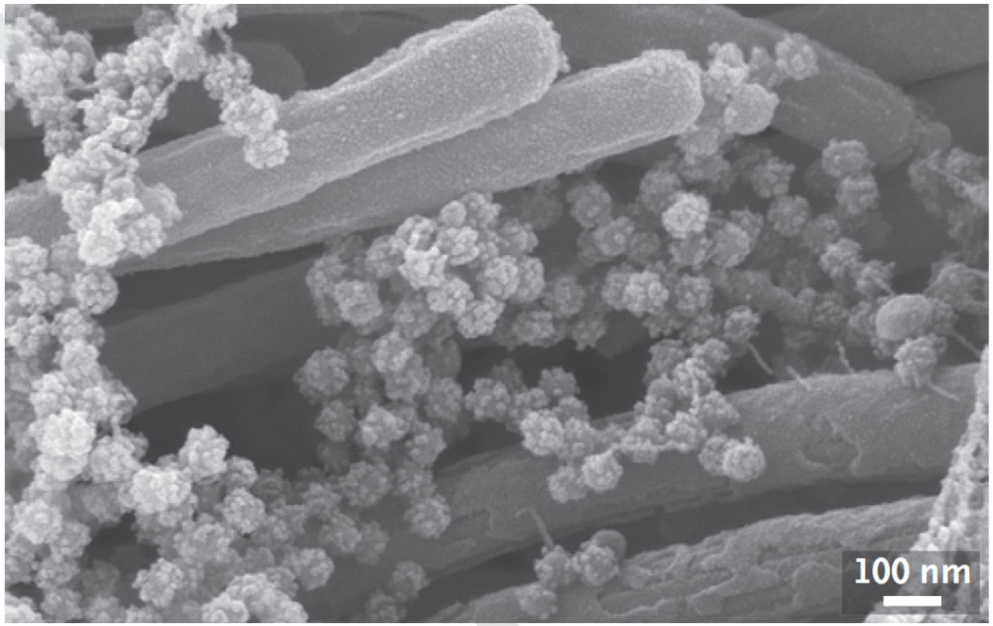
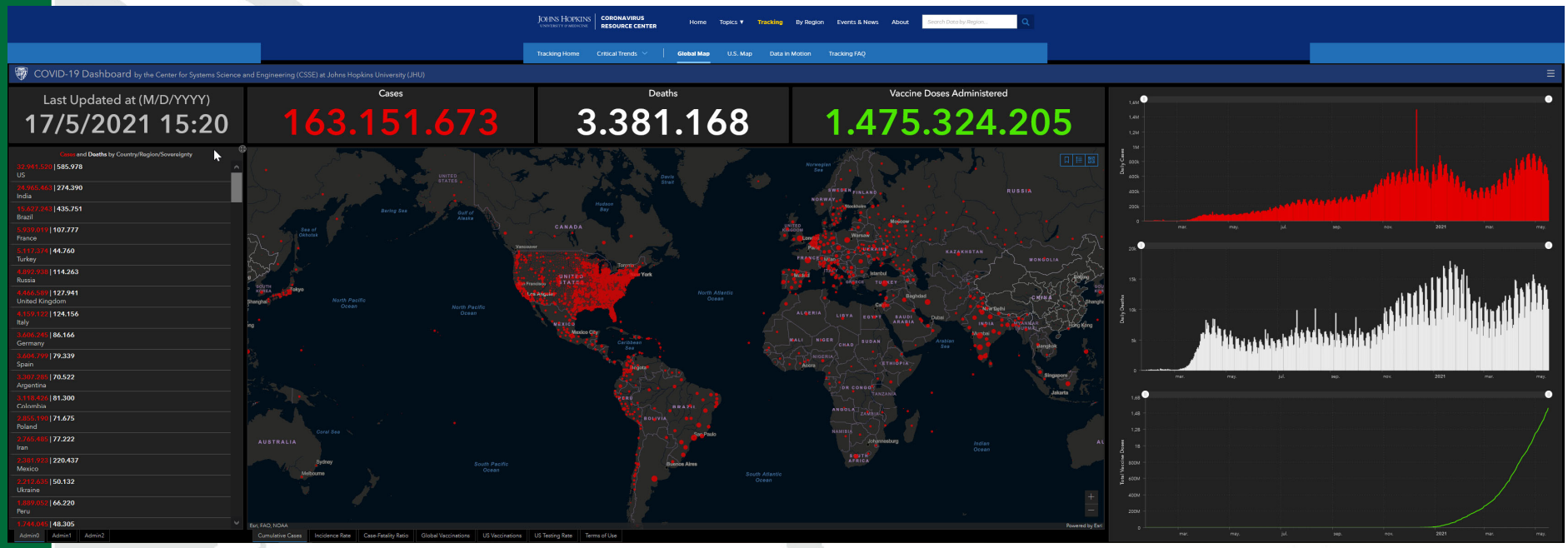
SARS-CoV-2

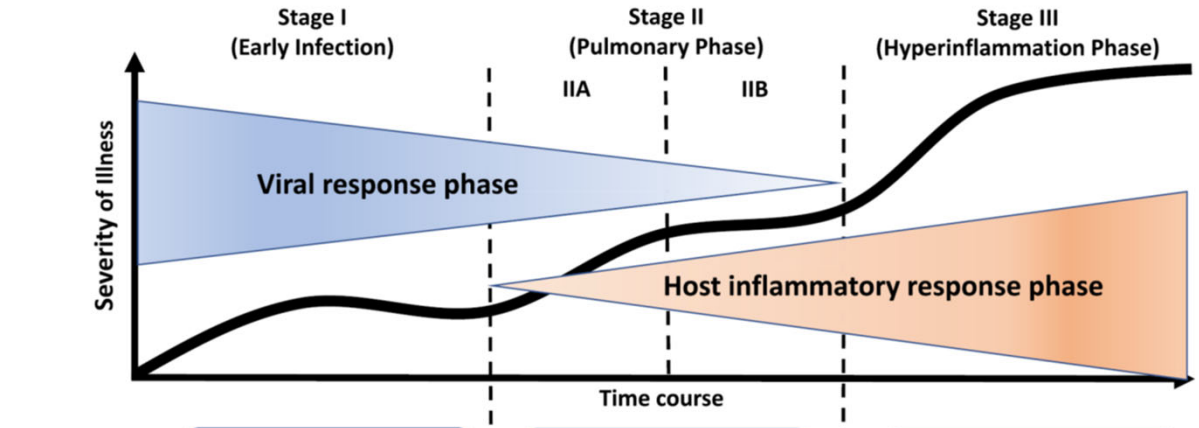


Ehre C. N Eng J Med 2020; 383: 969



https://coronavirus.jhu.edu/map.html

Classification of COVID-19 disease states



	Stage I (Early Infection)	Stage II (Pulmonary Phase)	Stage III (Hyperinflammation Phase)
Clinical Symptoms	Mild constitutional symptoms Fever >99.6°F 37,5°C Dry Cough	Shortness of Breath without (IIA) and with Hypoxia (IIB) (PaO2/FiO2≤300mmHg)	ARDS SIRS/Shock Cardiac Failure
Clinical Signs	Lymphopenia	Abnormal chest imaging Transaminitis Low-normal procalcitonin	Elevated inflammatory markers (CRP, LDH, IL-6, D-dimer, ferritin) Troponin, NT-proBNP elevation

5% of cases
Fatality 50%

Siddiqi HK et al. J Heart Lung Transplant. 2020; 39:405-7

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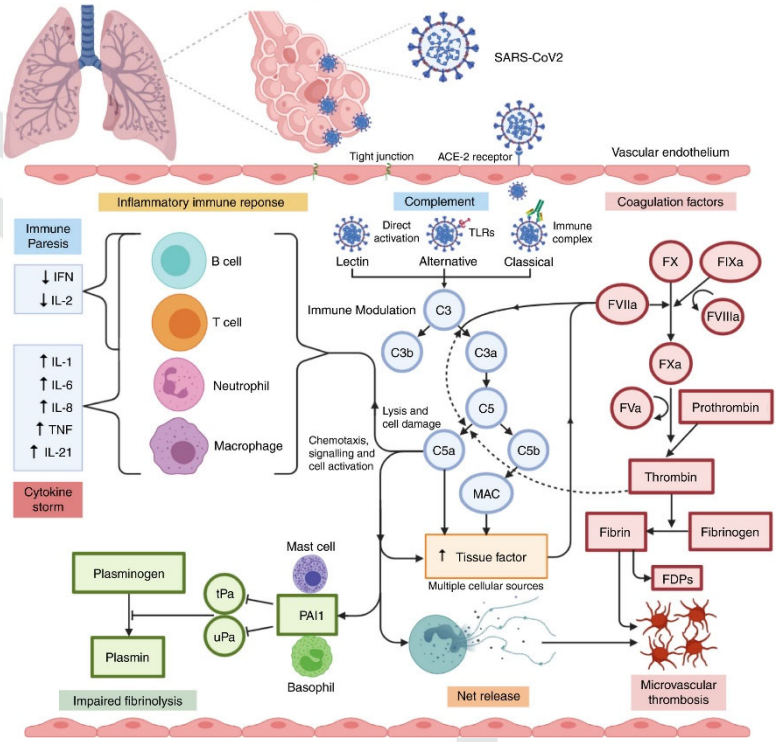
COVID-19: A collision of complement, coagulation and inflammatory pathways



Chauhan AJ. J Thromb Haemost 2020;18:2110-7

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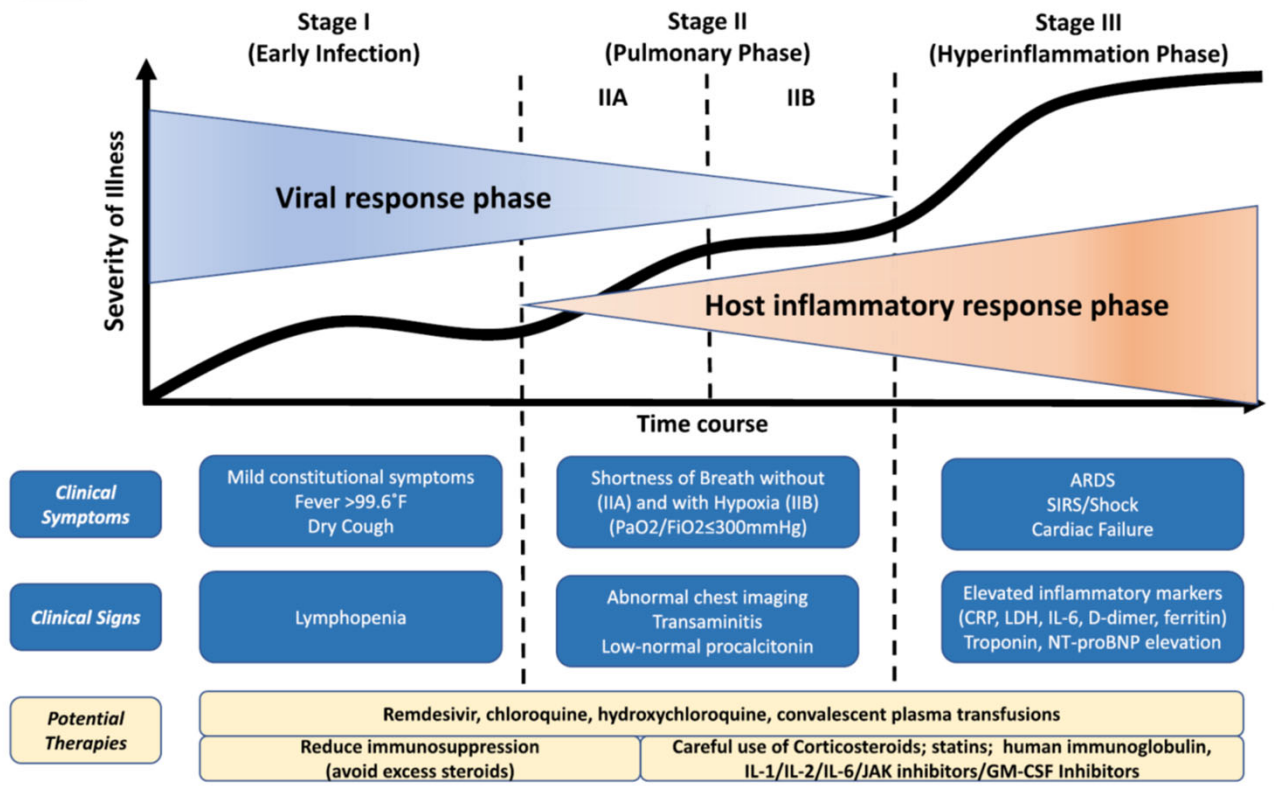
Classification of COVID-19 disease states



Siddiqi HK et al. J Heart Lung Transplant. 2020; 39:405-7

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*

CONCLUSIONS

Our data show that remdesivir was superior to placebo in shortening the time to recovery in adults who were hospitalized with Covid-19 and had evidence of lower respiratory tract infection. (Funded by the National Institute of Allergy and Infectious Diseases and others; ACTT-1 ClinicalTrials.gov number, NCT04280705.)

countries since that time. However, given high mortality despite the use of remdesivir, it is clear that treatment with an antiviral drug alone is not likely to be sufficient for all patients. Current strategies are evaluating remdesivir in combination with modifiers of the immune response (e.g., the Janus kinase [JAK] inhibitor baricitinib in ACTT-2, and interferon beta-1a in ACTT-3). A

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Beigel HK, et al. N Eng J Med 2020;383:1813-26

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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*

METHODS

We performed a randomized, double-blind, placebo-controlled trial involving patients with confirmed severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, hyperinflammatory states, and at least two of the following signs: fever (body temperature >38°C), pulmonary infiltrates, or the need for supplemental oxygen in order to maintain an oxygen saturation greater than 92%. Patients were randomly assigned in a 2:1 ratio to receive standard care plus a single dose of either tocilizumab (8 mg per kilogram of body weight) or placebo. The primary outcome was intubation or death, assessed in a time-to-event analysis. The secondary efficacy outcomes were clinical worsening and discontinuation of supplemental oxygen among patients who had been receiving it at baseline, both assessed in time-to-event analyses.

RESULTS

We enrolled 243 patients; 141 (58%) were men, and 102 (42%) were women. The median age was 59.8 years (range, 21.7 to 85.4), and 45% of the patients were Hispanic or Latino. The hazard ratio for intubation or death in the tocilizumab group as compared with the placebo group was 0.83 (95% confidence interval [CI], 0.38 to 1.81; P=0.64), and the hazard ratio for disease worsening was 1.11 (95% CI, 0.59 to 2.10; P=0.73). At 14 days, 18.0% of the patients in the tocilizumab group and 14.9% of the patients in the placebo group had had worsening of disease. The median time to discontinuation of supplemental oxygen was 5.0 days (95% CI, 3.8 to 7.6) in the tocilizumab group and 4.9 days (95% CI, 3.8 to 7.8) in the placebo group (P=0.69). At 14 days, 24.6% of the patients in the tocilizumab group and 21.2% of the patients in the placebo group were still receiving supplemental oxygen. Patients who received tocilizumab had fewer serious infections than patients who received placebo.

CONCLUSIONS

Tocilizumab was not effective for preventing intubation or death in moderately ill hospitalized patients with Covid-19. Some benefit or harm cannot be ruled out, however, because the confidence intervals for efficacy comparisons were wide. (Funded by Genentech; ClinicalTrials.gov number, NCT04356937.)

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Tocilizumab in Hospitalized Patients with Severe Covid-19 Pneumonia

I.O. Rosas, N. Bräu, M. Waters, R.C. Go, B.D. Hunter, S. Bhagani, D. Skiest, M.S. Aziz, N. Cooper, I.S. Douglas, S. Savic, T. Youngstein, L. Del Sorbo, A. Cubillo Gracian, D.J. De La Zerda, A. Ustianowski, M. Bao, S. Dimonaco, E. Graham, B. Matharu, H. Spotswood, L. Tsai, and A. Malhotra

BACKGROUND

Coronavirus disease 2019 (Covid-19) is associated with immune dysregulation and hyperinflammation, including elevated interleukin-6 levels. The use of tocilizumab, a monoclonal antibody against the interleukin-6 receptor, has resulted in better outcomes in patients with severe Covid-19 pneumonia in case reports and retrospective observational cohort studies. Data are needed from randomized, placebo-controlled trials.

METHODS

In this phase 3 trial, we randomly assigned patients who were hospitalized with severe Covid-19 pneumonia in a 2:1 ratio receive a single intravenous infusion of tocilizumab (at a dose of 8 mg per kilogram of body weight) or placebo. Approximately one quarter of the participants received a second dose of tocilizumab or placebo 8 to 24 hours after the first dose. The primary outcome was clinical status at day 28 on an ordinal scale ranging from 1 (discharged or ready for discharge) to 7 (death) in the modified intention-to-treat population, which included all the patients who had received at least one dose of tocilizumab or placebo.

RESULTS

Of the 452 patients who underwent randomization, 438 (294 in the tocilizumab group and 144 in the placebo group) were included in the primary and secondary analyses. The median value for clinical status on the ordinal scale at day 28 was 1.0 (95% confidence interval [CI], 1.0 to 1.0) in the tocilizumab group and 2.0 (non-ICU hospitalization without supplemental oxygen) (95% CI, 1.0 to 4.0) in the placebo group (between-group difference, –1.0; 95% CI, –2.5 to 0; P=0.31 by the van Elteren test). In the safety population, serious adverse events occurred in 103 of 295 patients (34.9%) in the tocilizumab group and in 55 of 143 patients (38.5%) in the placebo group. Mortality at day 28 was 19.7% in the tocilizumab group and 19.4% in the placebo group (weighted difference, 0.3 percentage points; 95% CI, –7.6 to 8.2; nominal P=0.94).

CONCLUSIONS

In this randomized trial involving hospitalized patients with severe Covid-19 pneumonia, the use of tocilizumab did not result in significantly better clinical status or lower mortality than placebo at 28 days. (Funded by F. Hoffmann–La Roche and the Department of Health and Human Services; COVACTA ClinicalTrials.gov number, NCT04320615.)

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 FEBRUARY 25, 2021 VOL. 384 NO. 8

Dexamethasone in Hospitalized Patients with Covid-19

The RECOVERY Collaborative Group*

METHODS

In this controlled, open-label trial comparing a range of possible treatments in patients who were hospitalized with Covid-19, we randomly assigned patients to receive oral or intravenous dexamethasone (at a dose of 6 mg once daily) for up to 10 days or to receive usual care alone. The primary outcome was 28-day mortality. Here, we report the preliminary results of this comparison.

RESULTS

A total of 2104 patients were assigned to receive dexamethasone and 4321 to receive usual care. Overall, 482 patients (22.9%) in the dexamethasone group and 1110 patients (25.7%) in the usual care group died within 28 days after randomization (age-adjusted rate ratio, 0.83; 95% confidence interval [CI], 0.75 to 0.93; P<0.001). The proportional and absolute between-group differences in mortality varied considerably according to the level of respiratory support that the patients were receiving at the time of randomization. In the dexamethasone group, the incidence of death was lower than that in the usual care group among patients receiving invasive mechanical ventilation (29.3% vs. 41.4%; rate ratio, 0.64; 95% CI, 0.51 to 0.81) and among those receiving oxygen without invasive mechanical ventilation (23.3% vs. 26.2%; rate ratio, 0.82; 95% CI, 0.72 to 0.94) but not among those who were receiving no respiratory support at randomization (17.8% vs. 14.0%; rate ratio, 1.19; 95% CI, 0.91 to 1.55).

CONCLUSIONS

In patients hospitalized with Covid-19, the use of dexamethasone resulted in lower 28-day mortality among those who were receiving either invasive mechanical ventilation or oxygen alone at randomization but not among those receiving no respiratory support. (Funded by the Medical Research Council and National Institute for Health Research and others; RECOVERY ClinicalTrials.gov number, NCT04381936; ISRCTN number, 50189673.)

RECOVERY Collaborative Group. N Engl J Med 2021;384:693-704.

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Potential Roles of Plasma Exchange in Severe COVID-19

- Fast removal of inflammatory mediators

- Other reasons for plasma exchange…..

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Science

RESEARCH ARTICLES

Cite as: P. Bastard *et al.*, *Science*
10.1126/science.abd4585 (2020).

Auto-antibodies against type I IFNs in patients with life-threatening COVID-19

Interindividual clinical variability in the course of SARS-CoV-2 infection is immense. We report that at least 101 of 987 patients with life-threatening COVID-19 pneumonia had neutralizing IgG auto-Abs against IFN-ω (13 patients), the 13 types of IFN-α (36), or both (52), at the onset of critical disease; a few also had auto-Abs against the other three type I IFNs. The auto-Abs neutralize the ability of the corresponding type I IFNs to block SARS-CoV-2 infection in vitro. These auto-Abs were not found in 663 individuals with asymptomatic or mild SARS-CoV-2 infection and were present in only 4 of 1,227 healthy individuals. Patients with auto-Abs were aged 25 to 87 years and 95 were men. A B cell auto-immune phenocopy of inborn errors of type I IFN immunity underlies life-threatening COVID-19 pneumonia in at least 2.6% of women and 12.5% of men.

Second, this unexpected finding paves the way for therapeutic intervention, including plasmapheresis, monoclonal Abs depleting plasmablasts, and the specific inhibition of type I IFN-reactive B cells (*30*). Finally, in this patient group, early treatment with IFN-α is unlikely to be

Science Translational Medicine

RESEARCH ARTICLES

Cite as: Y. Zuo *et al.*, *Sci. Transl. Med.* 10.1126/scitranslmed.abd3876 (2020).

CORONAVIRUS

Prothrombotic autoantibodies in serum from patients hospitalized with COVID-19

Yu Zuo[1], Shanea K. Estes[1], Ramadan A. Ali[1], Alex A. Gandhi[1], Srilakshmi Yalavarthi[1], Hui Shi[1,2], Gautam Sule[1], Kelsey Gockman[1], Jacqueline A. Madison[1], Melanie Zuo[3], Vinita Yadav[4], Jintao Wang[5], Wrenn Woodard[6], Sean P. Lezak[6], Njira L. Lugogo[7], Stephanie A. Smith[8], James H. Morrissey[8], Yogendra Kanthi[4,5‡], and Jason S. Knight[1‡]

Patients with COVID-19 are at high risk for thrombotic arterial and venous occlusions. Lung histopathology often reveals fibrin-based occlusions in the small blood vessels of patients who succumb to the disease. Antiphospholipid syndrome is an acquired and potentially life-threatening thrombophilia in which patients develop pathogenic autoantibodies targeting phospholipids and phospholipid-binding proteins (aPL antibodies). Case series have recently detected aPL antibodies in patients with COVID-19. Here, we measured eight types of aPL antibodies in serum samples from 172 patients hospitalized with COVID-19. These aPL antibodies included anticardiolipin IgG, IgM and IgA; anti-β2 glycoprotein I IgG, IgM, and IgA; and anti-phosphatidylserine/ prothrombin (aPS/PT) IgG and IgM. We detected aPS/PT IgG in 24% of serum samples, anticardiolipin IgM in 23% of samples, and aPS/PT IgM in 18% of samples. Antiphospholipid autoantibodies were present in 52% of serum samples using the manufacturer's threshold and in 30% using a more stringent cutoff (≥40 ELISA-specific units). Higher titers of aPL antibodies were associated with neutrophil hyperactivity including the release of neutrophil extracellular traps (NETs), higher platelet counts, more severe respiratory disease, and lower clinical estimated glomerular filtration rate. Similar to IgG from patients with antiphospholipid syndrome, IgG fractions isolated from COVID-19 patients promoted NET release from neutrophils isolated from healthy individuals. Furthermore, injection of IgG purified from COVID-19 patient serum into mice accelerated venous thrombosis in two mouse models. These findings suggest that half of patients hospitalized with COVID-19 become at least transiently positive for aPL antibodies and that these autoantibodies are potentially pathogenic.

SCIENCE TRANSLATIONAL MEDICINE | RESEARCH ARTICLE

CIRRHOSIS

Albumin internalizes and inhibits endosomal TLR signaling in leukocytes from patients with decompensated cirrhosis

Mireia Casulleras[1,2], Roger Flores-Costa[2], Marta Duran-Güell[1,2], José Alcaraz-Quiles[2], Silvia Sanz[2]*, Esther Titos[2,3], Cristina López-Vicario[1,2], Javier Fernández[1,4], Raquel Horrillo[5], Montserrat Costa[5], Pierre de la Grange[6], Richard Moreau[1,7], Vicente Arroyo[1], Joan Clària[1,2,3†]

Human serum albumin (HSA) is an emerging treatment for preventing excessive systemic inflammation and organ failure(s) in patients with acutely decompensated (AD) cirrhosis. Here, we investigated the molecular mechanisms underlying the immunomodulatory properties of HSA. Administration of HSA to patients with AD cirrhosis with elevated circulating bacterial DNA rich in unmethylated cytosine-phosphate-guanine dideoxynucleotide motifs (CpG-DNA) was associated with reduced plasma cytokine concentrations. In isolated leukocytes, HSA abolished CpG-DNA–induced cytokine expression and release independently of its oncotic and scavenging properties. Similar anti-inflammatory effects were observed with recombinant human albumin. HSA exerted widespread changes on the immune cell transcriptome, specifically in genes related to cytokines and type I interferon responses. Our data revealed that HSA was taken up by leukocytes and internalized in vesicles positively stained with early endosome antigen 1 and colocalized with CpG-DNA in endosomes, where the latter binds to Toll-like receptor 9 (TLR9), its cognate receptor. Furthermore, HSA also inhibited polyinosinic:polycytidylic acid– and lipopolysaccharide-induced interferon regulatory factor 3 phosphorylation and TIR domain–containing adapter-inducing interferon-β–mediated responses, which are exclusive of endosomal TLR3 and TLR4 signaling, respectively. The immunomodulatory actions of HSA did not compromise leukocyte defensive mechanisms such as phagocytosis, efferocytosis, and intracellular reactive oxygen species production. The in vitro immunomodulatory effects of HSA were confirmed in vivo in analbuminemic humanized neonatal Fc receptor transgenic mice. These findings indicate that HSA internalizes in immune cells and modulates their responses through interaction with endosomal TLR signaling, thus providing a mechanism for the benefits of HSA infusions in patients with cirrhosis.

Potential Roles of Plasma Exchange in Severe COVID-19

- Fast removal of inflammatory mediators
- Removal of pathogenic autoantibodies
- Potential anti-inflammatory effect of albumin

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Plasma Exchange: An Effective Rescue Therapy in Critically Ill Patients With Coronavirus Disease 2019 Infection

Javier Fernandez, PhD[1,2]; Jordi Gratacos-Ginès, MD[1]; Pol Olivas, MD[1]; Montserrat Costa, BS[1]; Susana Nieto, BS[1]; Dolors Mateo, BS[3]; María Belén Sánchez, BSc[4]; Ferran Aguilar, MSC[2]; Octavi Bassegoda, MD[1]; Pablo Ruiz, PhD[1]; Berta Caballol, MD[1]; Anna Pocurull, MD[1]; Joan Llach, MD[1]; María Jesús Mustieles, BS[3]; Joan Cid, PhD[3]; Enric Reverter, PhD[1]; Nestor David Toapanta, MD[1]; María Hernández-Tejero, MD[1]; José Antonio Martínez, PhD[5]; Joan Claria, PhD[2,4]; Carlos Fernández, MD[6]; José Mensa, PhD[5]; Vicente Arroyo, PhD[2]; Pedro Castro, PhD[7]; Miquel Lozano, PhD[3]; for the Covid Clinic Critical Care (CCCC) Group

Fernandez J, *et al* Crit Care Med 2020; 48: e1350-e1355

Clinical Findings at ICU Admission

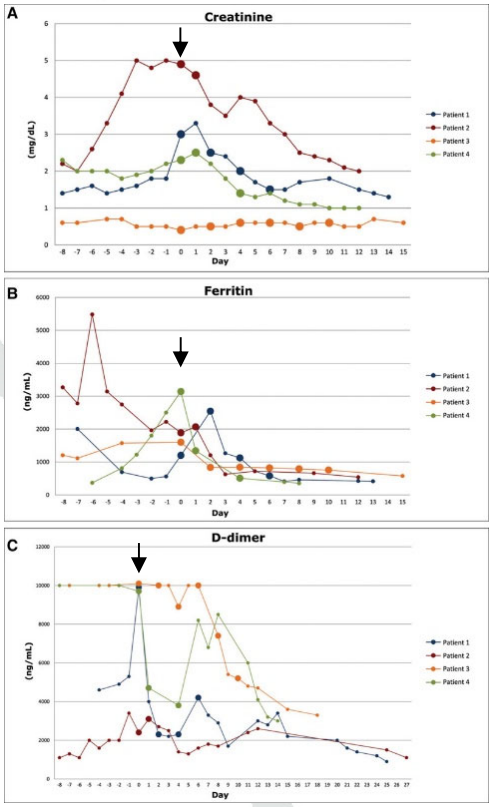
	Patient 1	Patient 2	Patient 3	Patient 4
Age, years	49	59	56	64
Sex	Male	Male	Male	Male
Comorbidities	Type 2 DM, hypertension, obesity	Type 2 DM, hypertension, CPOD	Hypertension, obesity	Type 2 DM, hypertension, LC
Days from illness onset to ICU admission	9	10	4	6
Complications	ARDS, AKI, shock	ARDS, AKI, shock	ARDS, AKI, shock, PE	ARDS, AKI, shock
Organ support	IMV, VP	IMV, VP	VP	IMV, VP
Treatments:	Antiviral, antibiotic, corticosteroids, tocilizumab	Antiviral, antibiotic, corticosteroids, anakinra	Antiviral, antibiotic, corticosteroids,	Antiviral, antibiotic, corticosteroids,

DM: diabetes mellitus. CPOD: chronic pulmonary obstructive disease. LC: liver cirrhosis. ARDS: acute respiratory distress syndrome. AKI: acute kidney injury. PE: pulmonary embolism. IMV: invasive mechanical ventilation. VP: vasopressors

PE Treatment and Clinical Outcome

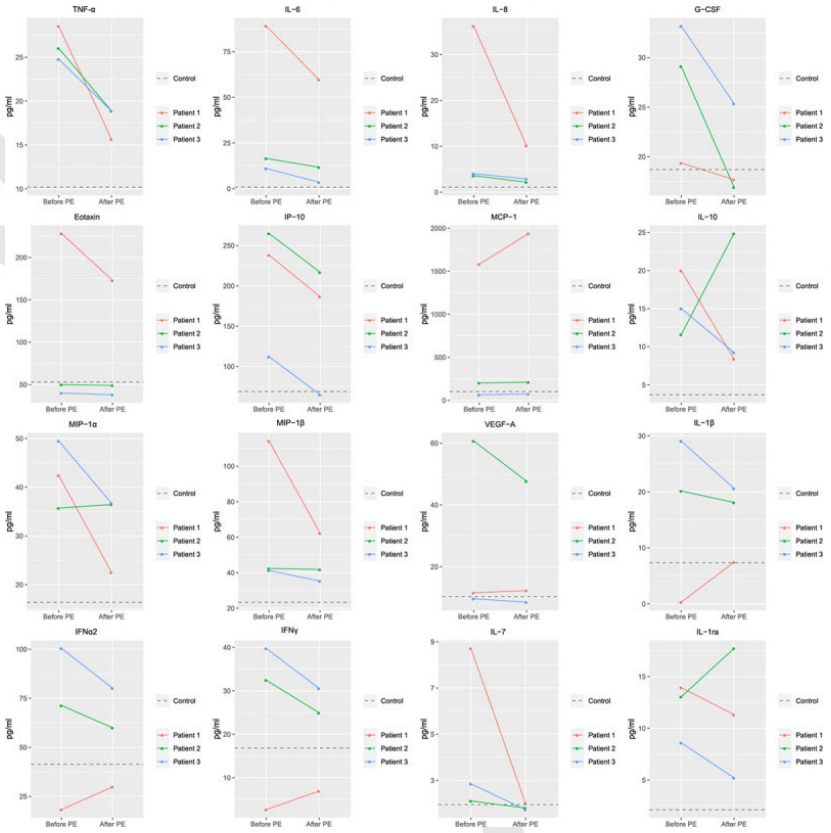
	Patient 1	Patient 2	Patient 3	Patient 4
Days from ICU admission to PE	9	8	15	26
Indication	Multiorgan failure	Multiorgan failure	Catastrophic antiphospholipid synd.	Multiorgan failure
Number of PE	4	2	6	3
ICU discharge (days)	Yes (38)	Yes (31)	Yes (20)	No (death 95)
Hospital discharge (days)	Yes (51)	Yes (40)	Yes (33)	No (death 95)

Effect of Plasma Exchange on Serum Levels of Creatinine, Ferritin and D-dimer



Fernandez J, *et al* Crit Care Med 2020; 48: e1350-e1355

Effect of Plasma Exchange on Plasma levels of Cytokines and Chemokines



Fernandez J, *et al* Crit Care Med. Published online ahead of print. 2020 Aug 24:

REP-COVID Clinical Trial

- Multicenter randomized, controlled, open labelled clinical trial.
- Patients with COVID-19 requiring ventilatory support (invasive and noninvasive)
- Standard medical therapy with or without PE
- Centers:
  - Hospital Clínic, Barcelona
  - Hospital Josep Trueta, Girona
  - Hospital Mútua de Terrassa
  - Hospital Ramón y Cajal, Madrid
  - Hospital Virgen del Rocío, Sevilla
- To include 120 patients, 60 in each arm

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REP-COVID Clinical Trial

- Inclusion criteria:
  - Age 18-79 years
  - COVID-19 confirmed by PCR in nasopharyngeal swab, sputum or broncoaspirate
  - Respiratory support (mechanical ventilation or noninvasive (high flow nasal cannula oxygen)
  - Informed consent

- Exclusion criteria:
  - > 10 days of respiratory support
  - Refractory shock
  - Severe liver, kidney, pulmonary or cardiac chronic disease

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REP-COVID Clinical Trial

- Primary outcome:
  - 28-day all cause mortality
- Secondary outcomes:
  - Time of ventilatory, vasopressor and renal support
  - ICU admittance
  - Degree Organ failure (SOFA and APACHE scores) days 1 thorugh 7
  - Serum inflammatory markers
  - Coagulation profile
  - Safety: adverse events

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REP-COVID Clinical Trial

- PE of 1.2 – 1.5 plasma volumes using 5% albumin as replacement fluid:
  - If Quick index< 50%: 2/3 albumin + 1/3 FFP
- 4 sessions: days 1, 2, 4, 6
- After each PE session 100 mg/kg of IVIG

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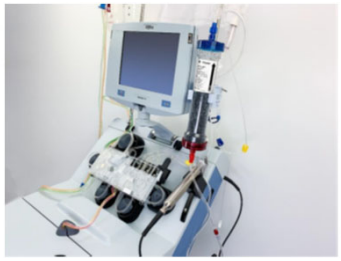
Extracorporeal Adsorption Columns

- Plasma adsorption:
  - D2000, Marker Therapeutics AG[1],



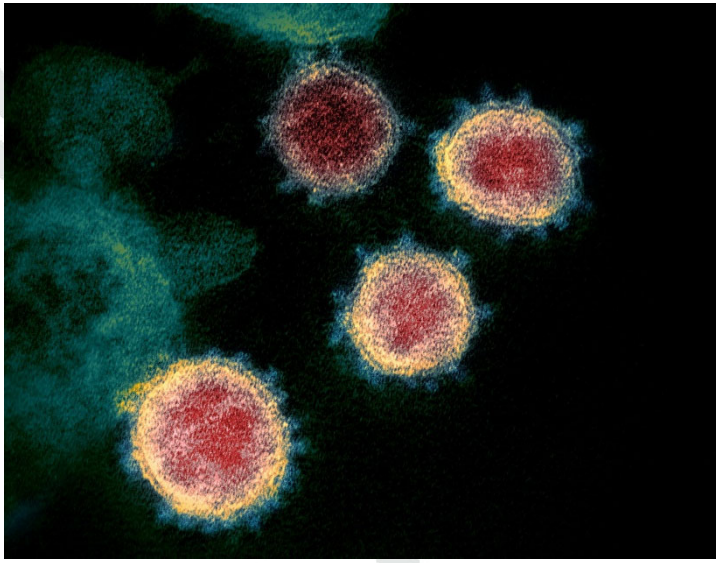
- Blood adsorption:
  - CytoSorb®, CytoSorbents[1]

1. FDA, Emergency Use Authorization 10 April 2020

Conclusions

- SARS-CoV-2 pandemic has provoked a huge impact on the heath care systems around the world
- The treatment of patients with severe COVID-19 has been a real race against time and has varied significantly as the results of comparative randomized clinical trials have become available.
- Anti-inflammatory drugs are the only drugs that have so far demonstrated a mortality-reducing effect in randomized controlled clinical trials.
- Plasma exchange could perhaps be effective in the group of critically ill patients

SARS-CoV-2 Transmission Electron Microscope Image



NIAID's Rocky Mountain Laboratories (RML) in Hamilton, MT, USA
https://www.flickr.com/photos/niaid/49534865371/

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