DeVos Cardiovascular Research Program

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SPECTRUM HEALTH | Van Andel Institute

DEVELOP

DeVos Cardiovascular Research Program's **E**mergency **L**etter **o**n the **P**andemia

Scientific Stream Update On COVID19

(This information is not officially sanctioned by any authorities and does not represent a complete summary, just a summary of part of the information flow)

Published 8 am Every Weekday 10 am on the weekends

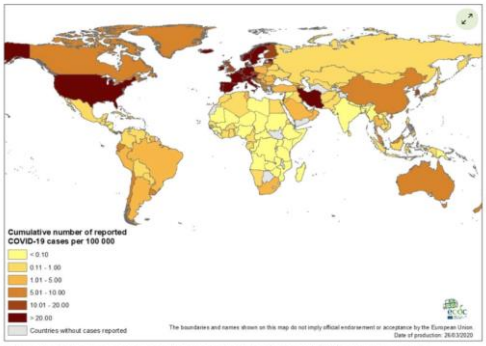
March 27 2020

Introduction

US is well into the disease development. Now the country with the most cases in the world. The continuous spread in the more tropical areas of the US gives little hope for the disease to be "shut down", rather it will be slowing down, over the summer.
https://coronavirus.jhu.edu/map.html.

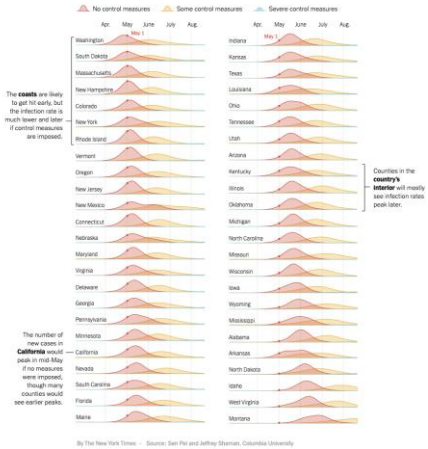
US is in the strata with the highest prevalence >20/100,000.

Geographic distribution of cumulative number of reported COVID-19 cases per 100 000 population, worldwide, as of 26 March 2020



Geographic distribution of cumulative number of reported COVID-19 cases per 100 000 population, worldwide

Source: https://www.ecdc.europa.eu/en/geographical-distribution-2019-ncov-cases



From NYT's database for COVID cases, the following simulation has been done about the time of the peak, by state.

Comments:

- For Michigan that would be peaking at the end of May if we had a full outbreak.
- For Michigan a modulated spread, by e.g. stay-home order we would see a less intense but more prolonged development which might peak in July instead.

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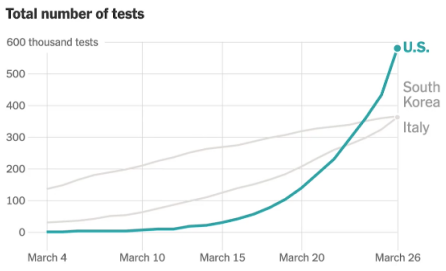
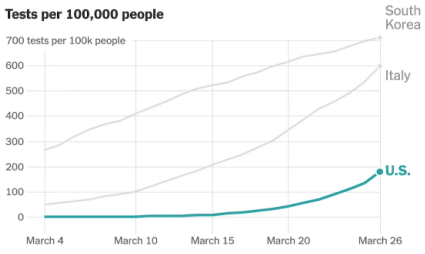
Testing is taking up but is still too lo



The pace of testing in the United States has seen a meteoric rise in the past week. But the country still lags in tests relative to its population, despite having the world's most reported coronavirus cases. Weiyi Cai

Testing has been criticized, it has been far too insufficient. Now US has taken the most tests but is still when normalized to the population more the number of tests is lagging.

Source: New York Times



The pace of testing in the United States has seen a meteoric rise in the past week. But the country still lags in tests relative to its population, despite having the world's most reported coronavirus cases. Weiyi Cai

Source: New York Times

To remember; the number of COVID-19^{+} is the denominator in the Case-fatality-rate (CFR). Thus if you fo not test you get a lower case rate and then a higher CFR. Countries who had an extensive testing like Germany and South Korea, do have the lowest CFR. It is pure mathematics but also by being more ambitious in testing it could having more aggressive strategy in isolation and treatment.

It is probably, to a lesser extent also confounded by the fact that a m,ore aggressive strategy towards screening also copuld be accompanied towards a more aggressive strategy towards the disease in treatment and social distancing. E.g. Germany has done more testing than Italy early on and the mathematics give a lower CFR than Italy 0.2% vs 7.2%. However, the overwhelming of Italy's healthcare can also be seen in the higher mortality in the highest age groups compared to China[1]; When there is no more ventilators then the oldest age group tend to be less prone to get treatment.

Table. Case-Fatality Rate by Age Group in Italy and China[a]

	Italy as of March 17, 2020		China as of February 11, 2020	
	No. of deaths (% of total)	Case-fatality rate, %[b]	No. of deaths (% of total)	Case-fatality rate, %[b]
All	1625 (100)	7.2	1023 (100)	2.3
Age groups, y				
0-9	0	0	0	0
10-19	0	0	1 (0.1)	0.2
20-29	0	0	7 (0.7)	0.2
30-39	4 (0.3)	0.3	18 (1.8)	0.2
40-49	10 (0.6)	0.4	38 (3.7)	0.4
50-59	43 (2.7)	1.0	130 (12.7)	1.3
60-69	139 (8.6)	3.5	309 (30.2)	3.6
70-79	578 (35.6)	12.8	312 (30.5)	8.0
≥80	850 (52.3)	20.2	208 (20.3)	14.8

[a] Data from China are from Chinese Center for Disease Control and Prevention.[4] Age was not available for 1 patient.

[b] Case-fatality rate calculated as number of deaths/number of cases.

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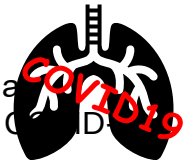
SCIENCE REPORTS IN THE FLOW



SARS-CoV-2 and the Liver – Not a primary concern [2]

- 452 patients defined as "severe COVID-19", of which 42 were identified a having chronic liver disease. (Includes data from 7 previously published C D 19 studies)
- Elevated LFTs and bilirubin have been identified in COVID-19 patients and may be more common in severe COVID-19
- Hypothesis of causes of elevated LFTs
    - PEEP>hepatic congestion by increased RA pressure and impaired venous return
        - Argument against: LFTs were elevated prior to ventilation
    - Drug induced liver injury
        - Argument against: LFTs were elevated prior to significant medication use
    - Creatinine kinase, LDH, and myoglobin may also be elevated and thus LFTs may be collateral change related to myositis. *seen in severe influenza
- **Only 1 post-mortem liver biopsy** completed: microvesicular steatosis (also found in sepsis)
- In severe COVID-19, there may be activation of fibrinolytic pathways, low platelets, high neutrophil to lymphocyte ratio, and elevated ferritin
    - These are all non-specific markers of inflammation
- **42 patients with chronic liver disease**
- **Mortality was 0-2% compared to 0-62% in other patients identified to have most severe COVID-19 disease**
- The liver may be collateral damage caused by the dysregulated immune response and cytotoxic T cell activation.
- **Conclusion**: **It is unlikely that COVID-19 causes direct liver injury through viral hepatitis. The risks of COVID-19 in patients with chronic liver disease and cirrhosis is due to poor immune function at baseline. Covid-19-induced hepatic damage may be a "clinical distraction."**
- **Comments:** More to be said in later studies; LFT derangement seen was mild and not presented in all studies. Later presentation have not shown worsening of LFT. The chronic liver disease was not defined. The study reselts are derived from small samples. Post-mortem results from only one patients. The "severe COVID-19"definition was heterogenous and unclear between studies.
- *Review by Dr Kathrine Kelly Schuette*

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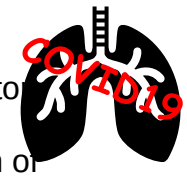
Mouse data suggest thatCytokine Storm In COVID-19 Patients by TH17 cells/IL17 could potentially be inhibitesd by the use of Fedratinib [3]



- Backkground:
  - Fedratinib, a specific inhibitor of JAK2 (a specific JAK2 inhibitor which is FDA approved for treatment of myeloproliferative neoplasms), resulted in decreased relative mRNA expression of pro-inflammatory cytokines (IL-17 and IL-22) in vitro when compared to control ($p < 0.05$).
  - The symptoms resulting from ARDS are associated with a cytokine storm (elevated serum levels of various interleukins, interferon and tumor necrosis factor-alpha, etc). The sickest patients, those in the ICU, appeared to have the highest levels of these cytokines.
  - T-helper 17 cells (TH17)produce several different cytokines themselves, including IL-17 which has broad pro-inflammatory effects, and induces other cytokines that cause systemic inflammatory symptoms like fever. IL-17 is one of the cytokines noted to be elevated in COvID-19 patients. IL-17 is associated with autoimmune and inflammatory diseases.
- The study:
  - Study performed in vitro using mouse TH17 cells. Total of 2 experiments with 3 tests in each group.
- Comments/Critique/Take home:
  - Possible benefit on cytokine stoirm of Fedratinib.
  - Focuses on blunting the pathological response, rather than symptomatic treatments.
  - Concern the applicability for human in vivo studies. Unknown whether decreasing production of specific interleukins would have clinical significance. Limited sample size.

- *Reviewed by Dr Meredith Busman*

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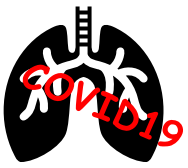
Strategy document for ECMOservice in COVID-19 patients[4]:



- Optimize the Ventilator settings/treatment to reduce the need for ECMO since the availability is very limited.

Therapy	Implementation
High-flow nasal oxygen	Might prevent or delay the need for intubation
Tidal volume	Use 6 mL/kg per predicted bodyweight (can reduce to 4 mL/kg per predicted bodyweight)
Plateau airway pressure	Maintain at <30 cm H_20 if possible
Positive end-expiratory pressure	Consider moderate to high levels if needed
Recruitment manoeuvres	Little value
Neuromuscular blockade	For ventilator dyssynchrony, increased airway pressure, hypoxaemia
Prone positioning	For worsening hypoxaemia, PaO_2:FiO_2 <100–150 mm Hg
Inhaled NO	Use 5–20 ppm
Fluid management	Aim for negative fluid balance of 0·5–1·0 L per day
Renal replacement therapy	For oliguric renal failure, acid-base management, negative fluid balance
Antibiotics	For secondary bacterial infections
Glucocorticoids	Not recommended
Extracorporeal membrane oxygenation	Use EOLIA trial criteria[3]

Figure: Therapeutic options for severe acute respiratory distress syndrome related to coronavirus disease 2019
ppm=parts per million.

- As pointed out in the March 25 Newsletter the recommendation is to use the <u>settings of the ventilator while being on ECMO</u> as was done in the EOLIA and CESAR trials. These were not testing these settings against other settings or strategies on ventilator while being on ERCMO rather these trials were controlled against ventilator treatment only. But this is the best we have currently.
    - EOLIA [5]
        - Plateau pressure of ≤24 cm H2O
        - Positive end-expiratory pressure of at least 10 cm H_2O
        - Respiratory rate of 10–30 breaths per min
    - CESAR [6]
        - Peak inspiratory pressure 20–25 cm H_2O
        - Positive end-expiratory pressure 10 cm H_2O
        - Respiratory rate of 10 breaths per min)
- *Reviewed By Drs Disha Geriani, Candace Smith-King*

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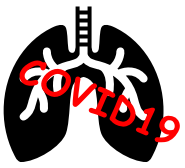
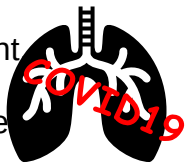
INVESTIGATIONAL TREATMENTS AVAILABLE IN US (Not a complete list (More to follow):



- Hydrochloroquinone
  - Based on *in vitro* results and a small n= study in Italy
  - NCT04318444: Hydroxychloroquine Post Exposure Prophylaxis for Coronavirus Disease (COVID-19)
  - Not Yet Recruiting
  - Incl Crit: Household contact of index case:
  - Sponsor: Colombia Univ, NY
  - Site: Columbia University Irving Medical Center
    New York, New York, United States, 10032
  - Contact: Elizabeth Oelsner, MD, MPH 212-305-9056
    eco7@cumc.columbia.edu
- PUL-042
  - Based on that ACE2 the rec for SARS-CoV-2 if given as a rh protein would bind free virus in the respiratory airways (by inhalation) before it binds to cells
  - NCT04313023: Hydroxychloroquine Post Exposure Prophylaxis for Coronavirus Disease (COVID-19)
  - Not Yet Recruiting
  - Incl Crit:
    1. Subjects must have documented exposure to COVID-19 and have a documented negative test for the virus within 72 hours of the administration of study drug
    2. Subjects must be free of clinical symptoms (fever, cough, shortness of breath) of a potential COVID-19 infection
    3. Subjects must be under quarantine in a controlled facility or hospital (home quarantine is not sufficient)
    4. Spirometry (forced expiratory volume in one second [FEV1] and forced vital capacity [FVC]) ,@•70% of predicted value
    5. If female, must be either post-menopausal (one year or greater without menses), surgically sterile, or, for female subjects of child-bearing potential who are capable of conception must be: practicing two effective methods of birth control (acceptable methods include intrauterine device, spermicide, barrier, male partner surgical sterilization, and hormonal contraception) during the study and through 30

days after completion of the study. Abstinence is not classified as an effective method of birth control.
6. If female, must not be pregnant, plan to become pregnant or nurse a child during the study and through 30 days after completion of the study. A pregnancy test must be negative at the Screening Visit, prior to dosing on Day 1.
7. If male, must be surgically sterile or willing to practice two effective methods of birth control (acceptable methods include barrier, spermicide, or female partner surgical sterilization) during the study and through 30 days after completion of the study. Abstinence is not classified as an effective method of birth control.
8. Ability to understand and give informed consent.



- NB Not for already infected
- Sponsor: Pulmotect
- Site: None
- Contact: Colin Broom, MD 713-579-9226
  clinicaltrials@pulmotect.com
- Contact: Brenton Scott, Ph D 713-579-9226
  clincaltrials@pulmotect.com

- **Losartan**
  - NCT04312009: Losartan for Patients With COVID-19 Requiring Hospitalization. Based on that ACE2 the rec for SARS-CoV-2
  - Not Yet Recruiting
  - Incl Criteria:
    - Presumptive positive laboratory test for SARS-CoV-2 or upper respiratory infection with recent exposure to laboratory-proven SARS-CoV-2-infected person
    - Negative influenza and respiratory virus panelNew or worsening hypoxia (SpO2 <95%) compared to baseline or increasing oxygen requirement
  - NB: Pat has to be naïve to ARB.
  - Sponsor: Univ of Minnesota
  - Site: United States, Minnesota
    Hennepin County Medical Center
  - Minneapolis, Minnesota, United States, 55415 Contact: Christopher Tignanelli, MD 612-625-7911 ctignane@umn.edu
  - Contact: Michael Puskarich, MD, MS 612-626-6911
    mike-em@umn.edu

- **Eculizumab (Soliris)**
  - NCT04288713: Eculizumab (Soliris) in Covid-19 Infected Patients (SOLID-C19)
  - Based on that COVID19 wiould elicit a too active immune response. It is a C5 inhibitor.
  - Not Yet Recruiting
  - Incl Criteria:
    - COVID-19 positive
  - NB: Pat can't be intubated
  - Sponsor: Hudson Medical
  - Site: United States, Minnesota
    Hennepin County Medical Center
  - Contact: Thomas C Pitts, M.D. 6465967386
    Drpitts@hudsonmedical.com

- **CDF24Fc**
  - NCT04317040: CD24Fc as a Non-antiviral Immunomodulator in COVID-19 Treatment (SAC-COVID)
  - Based on CD24Fc is a biological immunomodulator in Phase II/III clinical trial stage. CD24Fc comprises the nonpolymorphic regions of CD24 attached to the Fc region of human IgG1. It has been shown that CD24 is an innate checkpoint against the inflammatory response to tissue injuries or danger-associated molecular patterns (DAMPs).
  - Not Yet Recruiting
  - Incl Criteria:
    - Should be at least 18 years of age,
    - Male or female,
    - Diagnosed with COVID-19 and confirmed SARS-coV-2 viral infection.
    - Able to sign the consent form.
    - Severe COVID-19 (Appendix A), or NIAID 7-point ordinal score 3 to 4 (requiring non-invasive ventilation or oxygen, a SpO2 </= 94% or tachypnea (respiratory rate >/= 24 breaths/min), Appendix B).
    - The absolute lymphocyte count is ≤ 0.8 × 10^9 / L (8x10^5 / mL, 800 / mm3).
    - NB: Not in ARDS.

- Sponsor: Onco Immune Inc
- Site: Institute of Human Virology, University of Maryland Baltimore, Maryland, United States, 21201
- Contact: Pan Zheng, MD, PhD (202) 7516823
  pzheng@oncoimmune.com
- Contact: Martin Devenport, PhD (410) 2070582
  mdevenport@oncoimmune.com

- **Aviptadil**
  - NCT04311697: Intravenous Aviptadil for COVID-19 Associated Acute Respiratory Distress (COVID-AIV)
  - Is a synthetic version of Vasoactive Intestinal Polypeptide (VIP) Based on. That VIP antagonizes IL6 and TNFa effects. Is currently being studied in Sarcoidosis and Pulmonary Fibrosis
  - Not Yet Recruiting
  - Incl Criteria:
    - ARDS associated with COVID-19 infection
    - Medical necessity for endotracheal intubation and mechanical ventilation
    - Physician determination that patient is on maximal conventional medical therapy
    - NB: Not in organ failure. Sponsor: Onco Immune Inc
  - Site: Institute of Human Virology, University of Maryland Baltimore, Maryland, United States, 21201

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- **Investigational COVID-19 Convalescent Plasma - Emergency INDs Background**
  - Historically there are experiences with convalesacent plasma in the first SARS epidemic. One report claimed difference in the start of treatment, earlier in the ones that had a mild disease to those who had more severe [7]. Convalescent plasma therapy has been used to treat patients with Machupo virus (Bolivian hemorrhagic fever) [8], Junin virus (Argentinian hemorrhagic fever) [9], Lassa fever[10] Ebola virus[11], West Nile encephalitis [12].
  - Previous studies:
    1. <u>The Hongkong experience in a study on previous SARS epidemic n=80</u>
       - Incl criteria:
       - Patients with SARS according ot CDC
       - Patients whose condition continued to deteriorate, as defined by
       - SaO2<90% on 0.5
       - FiO2,
       - Treatment were then given 200–400 ml (4–5 ml/kg) of ABOcompatible convalescent plasma at the discretion of the attending clinicians and according to convalescent plasma availability.
       - Patients were given cefotaxime, cefotaxime and levofloxacin (or clarithromycin) on the day of admission to cover community-acquired pneumonia. If fever persisted, ribavirin (administered as 1200 mg p.o. t.i.d. or i.v. 400 mg q8h) and prednisolone (0.5–1 mg/kg) were started on day 3. This setting the convalescent plasma was given.
       - Comments:
         - This study wasn't controlled just comparing the course of the disease as mild or severe
         - The selection of the criteria for disease were most likely done post-hoc

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Table 1 Comparison of clinical characteristics of patients with SARS according to outcome

Characteristic	Good outcome[a]	Poor outcome[b]	*P* value	Logistic regression *P* value
No. of patients	33	47		
Age	37.9±12.5	50.2±15.1	<0.001	0.009
Admission LDH (IU/l)	268.6±117.6	334±183.7	0.08	0.014
Mean day of plasma infusion[c]	11.7±2.3	16.0±6.0	<0.001	0.012
Mean plasma volume	253.6±99.9	297.23±141.4	0.11	0.174
PCR positive and seronegative for SARS[d]	20	10	<0.001	0.006

[a]Discharged by day 22 from symptom onset
[b]Death before day 22 or late discharge
[c]Calculated from day of symptom onset
[d]Status at time plasma was given

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2. Another study on the first SARS epidemic compared stereoid vs convalescent serum [13]. Convalescent plasma showed a better survival than steroids:

- Incl Criteria: clinical and radiographic deterioration despi… ribavirin and three doses (500 mg each) of pulsed methylprednisolone
- Excl criteria: Patients who had received intravenous immunoglobulin, pentaglobulin, protease inhibitors or fewer than three doses of methylprednisolone were excluded.

Table 1. Clinical demographics of patients in the plasma-treated and steroid-treated groups

	Plasma group[a]	Steroid group[b]	p
No. of patients	19	21	
Age (years)	38.7 ± 12.39	47.9 ± 19.60	0.087
Admission LDH (IU/L)	256.1 ± 90.75	247.7 ± 94.58	0.7
Co-morbidities[c]	1 (DM, old TB)	1 SLE, 2 DM with old TB, 4 hypertension, 1 atrial fibrillation	0.05

[a]Three doses of methylprednisolone, followed by convalescent plasma.
[b]Four or more doses of methylprednisolone.
[c]Two patients were hepatitis B carriers (one in each group), but without clinical evidence of cirrhosis; they were not considered as having co-morbidities.
DM, diabetes mellitus; LDH, lactate dehydrogenase; SLE, systemic lupus erythematosus; TB, tuberculosis.

Table 2. Comparison of treatment outcome between patients in the plasma-treated and steroid-treated groups

	Plasma group[a]	Steroid group[b]	p
Discharge rate by day 22 following onset of illness	73.4% (n = 14)	19% (n = 4)	0.001
Discharge rate by day 22 after adjustment for co-morbidities	77.8% (14/18)	23% (3/13)	0.004
Death rate	0%	23.8% (n = 5)	0.049

[a]Three doses of methylprednisolone, followed by convalescent plasma.
[b]Four or more doses of methylprednisolone.

- Comments:
- Only 40 patients
- Five deaths only

These studies form the basis for the FDA opening to use convalescent plasma to treat COVID-19 patients. NB Approval needed per patient.

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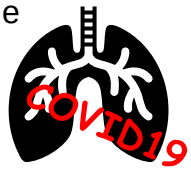
FDA approves the use of Convalescent Serum on COVID patients



- COVID-19 convalescent plasma can be used under a single patient emergency IND, give an iunformed consent, if following is true:
- COVID-19 convalescent plasma must only be collected from recovered individuals if they are eligible to donate blood (21 CFR 630.10, 21 CFR 630.15). Required testing must be performed (21 CFR 610.40) and the donation must be found suitable (21 CFR 630.30).
- Prior diagnosis of COVID-19 documented by a laboratory test
- Complete resolution of symptoms at least 14 days prior to donation
- Female donors negative for HLA antibodies or male donors
- Negative results for COVID-19 either from one or more nasopharyngeal swab specimens or by a molecular diagnostic test from blood. A partial list of available tests can be accessed at https://www.fda.gov/medical-devices/emergency-situations-medical-devices/emergency-use-authorizations.
- Defined SARS-CoV-2 neutralizing antibody titers, if testing can be conducted (e.g., optimally greater than 1:320)
- The container label of COVID-19 convalescent plasma units must include the following statement, "Caution: New Drug--Limited by Federal (or United States) law to investigational use." (21 CFR 312.6 (a))
  - Eligible patients for use under expanded access provisions:
- Must have laboratory confirmed COVID-19
- Must have severe or immediately life-threatening COVID-19

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- Severe disease is defined as:
  - dyspnea
  - respiratory frequency: 30/min,
  - blood oxygen saturation ,â§ 93%,
  - partial pressure of arterial oxygen to fraction of inspired oxygen ratio < 300, and/or
  - lung infiltrates > 50% within 24 to 48 hours
- Life-threatening disease is defined as:
  - respiratory failure,
  - septic shock, and/or ultiple organ failure

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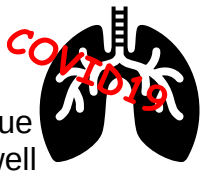
To start the treatment see https://www.fda.gov/vaccines-blood-biologics/investigational-new-drug-ind-or-device-exemption-ide-process-cber/investigational-covid-19-convalescent-plasma-emergency-inds



Comments: There is support from previous experiences to believe in the value of such treatment. By nature the format of these studies are not completely well randomized, blinded or of larger size.

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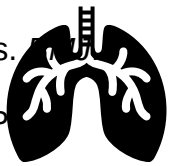

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