Statistical evidence from case series data in support of early outpatient COVID-19 treatment protocols

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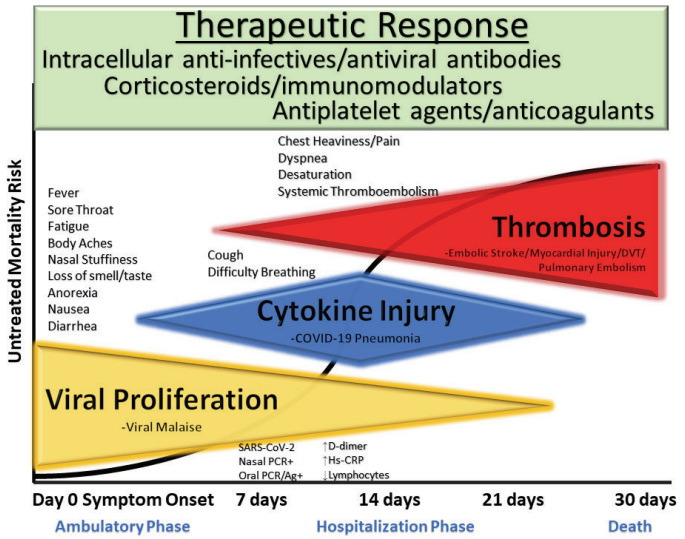
Publications

- Our paper
  1. E. Gkioulekas, P.A. McCullough, V. Zelenko: "Statistical analysis methods applied to early outpatient COVID-19 treatment case series data", *COVID* **2(8)** (2022), 1139-1182
- Zelenko protocol
  1. M. Scholz, R. Derwand, V. Zelenko. "COVID-19 outpatients - early risk-stratified treatment with zinc plus low dose hydroxychloroquine and azithromycin: a retrospective case series study", *International Journal of Antimicrobial Agents* **56** (2020), 106214
- McCullough protocol and Procter's study
  1. P.A. McCullough, P.E. Alexander, R. Armstrong, *et al.* "Multifaceted highly targeted sequential multidrug treatment of early ambulatory high-risk SARS-CoV-2 infection (COVID-19)", *Reviews in Cardiovascular Medicine* **21 (4)** (2020), 517-530
  2. B.C. Procter, C. Ross, V. Pickard, E. Smith, C. Hanson, P.A. McCullough. "Clinical outcomes after early ambulatory multidrug therapy for high-risk SARS-CoV-2 (COVID-19) infection", *Reviews in Cardiovascular Medicine* **21 (4)** (2020), 611-614
  3. B.C. Procter, C. Ross, V. Pickard, E. Smith, C. Hanson, P.A. McCullough, "Early Ambulatory Multidrug Therapy Reduces Hospitalization and Death in High-Risk Patients with SARS-CoV-2 (COVID-19)", *International Journal of Innovative Research in Medical Science* **6** (2021), 219-221
- Raoult study
  1. M. Million, J-C. Lagier, H. Tissot-DuPont, *et al.* "Early Treatment with Hydroxychloroquine and Azithromycin in 10,429 COVID-19 Outpatients: A Monocentric Retrospective Cohort Study", *Reviews in Cardiovascular Medicine* **22** (2021), 1063-1072

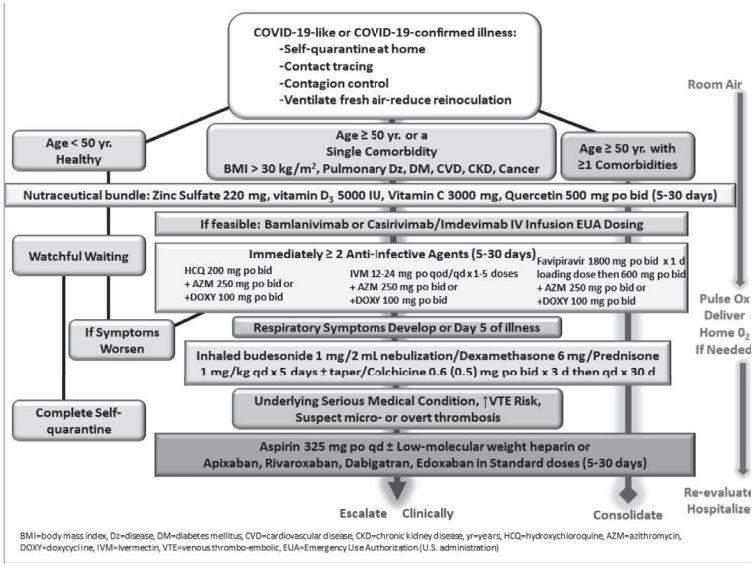
Early treatment – The Zelenko protocol

- The goal of early treatment of COVID-19 is to **prevent hospitalization and death.**
- Dr. Zelenko announced his treatment protocol on March 23 2020
  - **Risk stratify** patients as high risk vs low risk. High risk includes:
    1. Patients older than 60
    2. Patients that are immunocompromised or have comorbidities
    3. Patients not satisfying previous criteria that develop shortness of breath
  - **Treat** high risk patients with triple drug therapy: HCQ, Azithromycin, Zinc.
  - **Supportive care** and close monitoring of low risk patients.
- Zelenko incrementally improved his treatment protocol as follows:
  - Quercetin protocol for low-risk patients to reduce severity of symptoms
  - Dexamethasone and nebulized budesonide introduced at the beginning of May 2020.
  - Eliquis (blood thinner) introduced at the end of May 2020 and beginning of June 2020.
  - Ivermectin was used after October 2020.
- McCullough protocol
  - Similar risk stratification criteria
  - Age threshold for high-risk patients reduced to age ≥ 50
  - Sequenced multidrug treatment protocol that consists of:
    1. Nutraceutical bundle: for both low and high risk patients
    2. Antiviral agents: minimize or stop viral replication
    3. Immunomodulators to relieve inflammatory, hyper-dysregulated florid pneumonia
    4. Blood thinners: to prevent blood clots caused by the the spike protein part of dead viral particles.

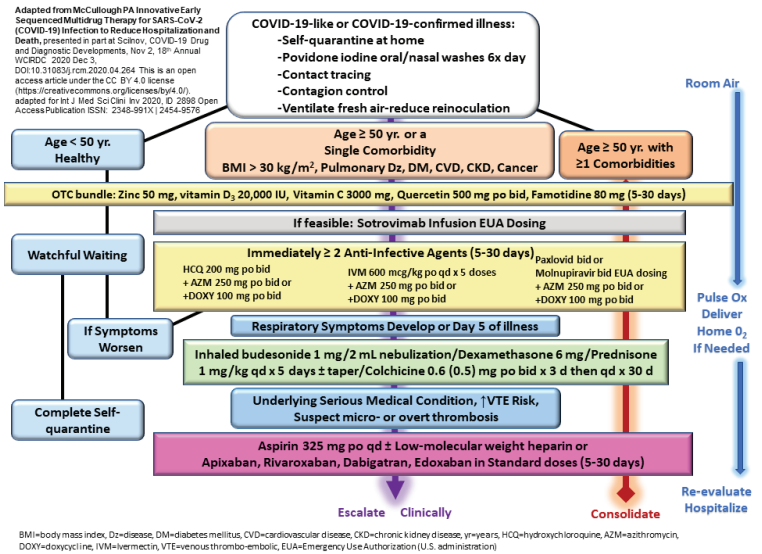
Peter McCullough's protocol. I. Rationale



Peter McCullough's protocol. II. 2020 version



Peter McCullough's protocol. III. 2022 version



What about evidence?

- No randomized control trials of the complete Zelenko or McCullough protocols.
  - There are contrived RCT studies testing one medication at a time, or incorrect dosages, or low-risk patient cohorts, or soft endpoints, or applying pre-hospital treatments to hospitalized patients.
  - There are no plans to conduct a proper RCT in the future.
  - The available observational studies can be sufficiently convincing to the extent that conducting an RCT is no longer ethical.
- Our approach:
  - With prior knowledge of acceptable safety, we only need to distinguish between **neutral** vs **positive** effect.
  - Contrast the treatment effect on mortality and hospitalization rates observed in case series against prior knowledge of **conservative lower bounds** of mortality and hospitalization rates without treatment on high-risk patients.
  - Preponderance of evidence threshold: Sufficient for emergency adoption.
  - Clear and convincing threshold: sufficient confidence that the treatment does have an effect and that it cannot be overturned by random selection bias. Clearly not ethical to conduct an RCT. Sufficient to adopt as community standard of care.
- Under article 37 of the 2013 Helsinki declaration:
  - *"In the treatment of an individual patient, where proven interventions do not exist or other known interventions have been ineffective, the physician, after seeking expert advice, with informed consent from the patient or a legally authorised representative, may use an unproven intervention if in the physician's judgement it offers hope of saving life, re-establishing health or alleviating suffering. This intervention should subsequently be made the object of research, designed to evaluate its safety and efficacy. In all cases, new information must be recorded and, where appropriate, made publicly available."*

Hospitalization risk without early treatment

- Early estimate of 10% to 18% hospitalization risk for patients older than 60
  - R. Verity and L.C. Okell and I. Dorigatti and P. Winskill and C. Whittaker and N. Imai and G. Cuomo-Dannenburg and H. Thompson and P.G.T. Walker and H. Fu and A. Dighe and J.T. Griffin and M. Baguelin and S. Bhatia and A. Boonyasiri and A. Cori and Z. Cucunuba and R. FitzJohn and K. Gaythorpe and W. Green and A. Hamlet and W. Hinsley and D. Laydon and G. Nedjati-Gilani and S. Riley and S. van Elsland and E. Volz and H. Wang and Y. Wang and X. Xi and C.A. Donnelly and A.C. Ghani and N.M. Ferguson. *Lancet Infect Dis* **20** (2020), 669-677
- Derwand-Scholz-Zelenko study – 15.4% hospitalization rate
  - M. Scholz, R. Derwand, V. Zelenko. *International Journal of Antimicrobial Agents* **56** (2020), 106214
- Cleveland study – 21% hospitalization rate
  - L. Jehi, X. Ji, A. Milinovich, S. Erzurum, A. Merlino, S. Gordon, J.B. Young, M.W. Kattan. *PLoS ONE* **15(8)** (2020), e0237419.
- Mass General Brigham study – 27% hospitalization rate
  - H. Dashti, E.C. Roche, D.W. Bates, S. Mora, and O. Demler. *Scientific Reports* **11** (2021), 4945
- CDC symptomatic hospitalization rate data from 02/2020 to 09/2021
  - age $\geq 50 \implies$ 13.79% (95% CI : 10.67% – 17.85%)
  - age $\geq 65 \implies$ 22.09% (96% CI : 17.09% – 28.52%)
- Without early treatment: **10%-25% risk of hospitalization for low+high risk demographic.**

Mortality risk without early treatment by age bracket. I

- R. Verity and L.C. Okell and I. Dorigatti and P. Winskill and C. Whittaker and N. Imai and G. Cuomo-Dannenburg and H. Thompson and P.G.T. Walker and H. Fu and A. Dighe and J.T. Griffin and M. Baguelin and S. Bhatia and A. Boonyasiri and A. Cori and Z. Cucunuba and R. FitzJohn and K. Gaythorpe and W. Green and A. Hamlet and W. Hinsley and D. Laydon and G. Nedjati-Gilani and S. Riley and S. van Elsland and E. Volz and H. Wang and Y. Wang and X. Xi and C.A. Donnelly and A.C. Ghani and N.M. Ferguson. *Lancet Infect Dis* **20** (2020), 669-677
  - Published in March 30, 2020. CFR based on data from China as of February 11, 2020.
  - From Table 1, the crude case fatality rates *in the absence of early treatment* are:

Age	Deaths	Cases	CFR
10-19	0	416	0%
20-29	7	3619	0.193%
30-39	18	7600	0.237%
40-49	38	8571	0.4%
50-59	130	10008	**1.3%**
60-69	309	8583	**3.6%**
70-79	312	3918	**7.96%**
$\geq$ 80	208	1408	**14.8%**
$\geq$ 60	829	13909	**5.96%**

Mortality risk without early treatment by age bracket. II

- Graziano Onder, Giovanni Rezza, Silvio Brusaferro. *JAMA* **323** (2020), 1775-1776
  - Published on March 23, 2020. Data as of March 17, 2020.
  - The mortality rates *in the absence of early treatment* in Italy, as a function of age bracket, are consistent with the mortality rates in China

Age	Italy CFR	China CFR
0-9	0%	0%
10-19	0%	0.2%
20-29	0%	0.2%
30-39	0.3%	0.2%
40-49	0.4%	0.4%
50-59	1.0%	1.3%
60-69	3.5%	3.6%
70-79	12.8%	8.0%
$\geq$ 80	20.2%	14.8%

- CDC symptomatic mortality rate data from 02/2020 to 09/2021
  - age $\geq 50 \implies 2.26\%$ (96% CI : $1.94\% - 2.61\%$)
  - age $\geq 65 \implies 4.79\%$ (95% CI : $4.11\% - 5.52\%$)
- Without early treatment: **Mortality rate risk for high-risk demographic due to age ranges from 3.5% to 20%.**

Mortality risk without early treatment from comorbidities

- N. Barda, D. Riesel, A. Akriv, J. Levy, U. Finkel, G. Yona, D. Greenfeld, S. Sheiba, J. Somer, E. Bachmat, G.N. Rothblum, U. Shalit, D. Netzer, R. Balicer, Noa Dagan. *Nature Communications* **11** (2020), 4439
- Epidemiology Group of Emergency Response Mechanism of New Coronavirus Pneumonia, Chinese Center for Disease Control and Prevention. *Chinese Journal of Epidemiology* **41** (2020), 145-151.
  - Case fatality rate based on early-stage analysis of COVID-19 outbreak in China in the period up to February 11, 2020 vs similar statistics from Israel published on September 7, 2020.

Comorbidity	Deaths	Cases	China CFR	Deaths	Cases	Israel CFR
Cardiovascular disease	92	873	10.5%	87	518	16.7%
Diabetes	80	1102	7.3%	71	531	13%
Respiratory disease	32	511	6.3%	23	361	6%
Hypertension	161	2683	6%	102	744	13.7%
Cancer	6	107	5.6%	37	264	10%

- Without early treatment: **Mortality rate risk for high-risk demographic due to comorbidities ranges from 5% to 15%.**

Mortality risk without early treatment from obesity and shortness of breath

- Previous papers do not provide a mortality rate risk due to obesity and shortness of breath.
- S.N.S. Fonseca, A. de Queiroz Sousa, A.G. Wolkoff, M.S. Moreira, B.C. Pinto, C.F.V. Takeda, E. Rebouas, A.P.V. Abdon, A.L.A. Nascimento, H.A. Risch. *Travel Medicine and Infectious Disease* **38** (2020), 101906
  - Comparison of mortality risk factors using multivariate regression analysis
  - Both obesity and dyspnea are more dangerous than heart disease.
- T.N. Poly, M.M. Islam, H.C. Yang, M.C. Lin, W-S Jian, M-H Hsu and Y-C Jack Li. *Frontiers in Medicine* **8** (2021), 620044.
  - Obesity presents more dangerous mortality risk than diabetes and heart disease
  - Obesity mortality risk increases with increasing BMI
- Shortness of breath indicates that:
  - Disease has progressed to hyperinflammatory stage and will lead to oxygen desaturation and hospitalization
  - Once hospitalized, probability of death exceeds 5% (Coracle study and Houston Methodist hospital study).
- Without early treatment: **Mortality rate risk due to obesity and dyspnea $\geq 5\%$.**
- So: **What happens *with* early treatment?**

Case series evidence

- Zelenko case series
  - M. Scholz; R. Derwand; V. Zelenko. *International Journal of Antimicrobial Agents* **56** (2020), 106214
  - E. Gkioulekas, P.A. McCullough, V. Zelenko. *COVID* **2(8)** (2022), 1139-1182
  - DSZ study – 141 high risk patients (age $\geq$ 60) – lab confirmed only – Zelenko protocol
  - DSZ control – 377 low and high-risk patients – supportive care
  - Zelenko 04/28/2020 – treated 405 high risk patients (age $\geq$ 60) – Zelenko protocol
  - Zelenko 06/14/2020 – treated 800 high risk patients (age $\geq$ 60) – enhanced Zelenko protocol
- Procter case series
  - B.C. Procter, C. Ross, V. Pickard, E. Smith, C. Hanson, P.A. McCullough. *Reviews in Cardiovascular Medicine* **21 (4)** (2020), 611-614
  - B.C. Procter, C. Ross, V. Pickard, E. Smith, C. Hanson, P.A. McCullough. *International Journal of Innovative Research in Medical Science* **6** (2021), 219-221
  - Procter I 09/2020 – treated 320 high risk patients (age $\geq$ 50) – McCullough protocol
  - Procter II 12/2020 – treated 869 high risk patients (age $\geq$ 50) – McCullough protocol
- Raoult study
  - M. Million, J-C. Lagier, H. Tissot-DuPont, *et al. Reviews in Cardiovascular Medicine* **22** (2021), 1063-1072
  - age $\geq$ 60 until 12/2020 – treated – 1495 high risk patients – McCullough protocol
  - age $\geq$ 60 until 12/2020 – control – 520 high-risk patients – incomplete protocol
- Israeli study
  - N. Barda, D. Riesel, A. Akriv, *et al. Nature Communications* **11** (2020), 4439
  - Israeli control – 4179 low and high-risk patients – supportive care

Summary of high risk patient case series

Study	Total	High-risk	Hospitalizations	Deaths
Case series data from Zelenko, Procter, Raoult studies				
DSZ study	335	141	4 (2.8%)	1 (0.7%)
Zelenko 04/2020	1450	405	6 (1.4%)	2 (0.4%)
Zelenko 06/2020	2200	800	12 (1.5%)	2 (0.25%)
Procter I	922	320	6 (1.8%)	1 (0.3%)
Procter II	?	869	20 (2.3%)	2 (0.2%)
Raoult	10429	1495	106 (7.0%)	5 (0.3%)
Control group data from Zelenko, Raoult, Israeli studies				
DSZ control	377	$<$ 377	58 ($>$15%)	13 ($>$3.4%)
Israeli control	4179	$<$ 4179	N/A	143 ($>$3.4%)
Raoult control	2114	520	38 (7.3%)	11 (2%)

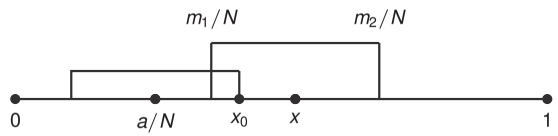
- Consistent high-risk mortality rates between Zelenko, Procter, and Raoult
- Consistent mortality rates between Zelenko control group (without demographic data) and Israeli control group (with demographic data; low+high risk)
- Raoult encouraged short hospitalization in his institution for close monitoring
- In the US, doctors tried to prevent hospitalizations due to poor NIH standard of care.
- Raoult control group did not receive the complete protocol (duration, medications).

Methodology: Analysis of case series. I.

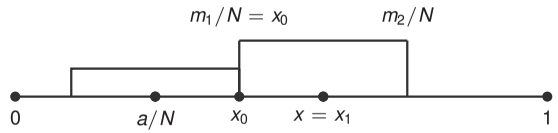
- **Notation**

N	Number of treated patients
a	Treated patients with negative outcome
x	Population-level negative outcome probability without treatment
$[m_1, m_2]$	Expected number of negative outcomes, without treatment, for a randomly selected sample of N patients
x_0	Efficacy threshold
x_1	Random selection bias threshold

- **Preponderance of the evidence**

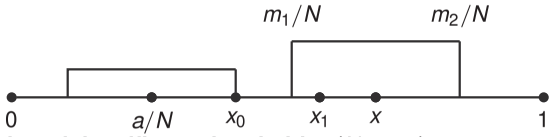


- **Crossover to clear and convincing**



Methodology: Analysis of case series. II.

- **Clear and convincing**



- **Evaluation of the efficacy threshold** $x_0(N, a, p_0)$
  - Choose the smallest value of x_0 that satisfies

$$x_0(N, a, p_0) < x \leq 1 \Longrightarrow p(N, a, x) < p_0$$

with $p(N, a, x)$ given by

$$p(N, a, x) = \sum_{n=0}^{N} \mathrm{pr}(N, n|x) H(\mathrm{pr}(N, a|x) - \mathrm{pr}(N, n|x))$$

$$\mathrm{pr}(N, a|x) = \binom{N}{a} x^a (1-x)^{N-a} \text{ and } H(x) = \begin{cases} 1, & \text{if } x \geq 0 \\ 0, & \text{if } x < 0 \end{cases}$$

- **Evaluation of random selection bias threshold** $x_1(N, x_0, p_0)$
  - Choose the smallest value of x_1 that satisfies

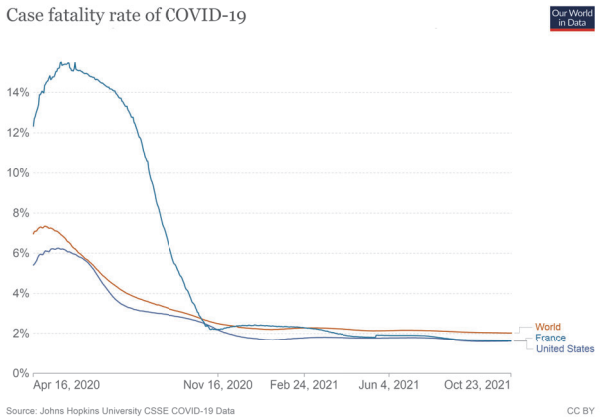
$$x_1(N, x_0, p_0) < x \leq 1 \Longrightarrow p(N, \lceil x_0 N \rceil, x) < p_0$$

Efficacy thresholds for mortality and hospitalization rates

Study	95% threshold	99% threshold	99.9% threshold
Mortality rate efficacy threshold (random selection bias threshold)			
DSZ study	3.8% (9.2%)	5.3% (12.8%)	7.0% (14.6%)
Zelenko 04/2020	1.8% (4.0%)	2.4% (5.2%)	2.9% (6.9%)
Zelenko 06/2020	1.0% (2.0%)	1.2% (2.7%)	1.6% (3.7%)
Procter I	1.7% (4.1%)	2.3% (5.8%)	3.1% (7.8%)
Procter II	0.84% (1.82%)	1.08% (2.46%)	1.4% (3.37%)
Raoult	0.79% (1.40%)	0.96% (1.87%)	1.18% (2.46%)
Hospitalization rate efficacy thresholds (random selection bias threshold)			
DSZ study	7.0% (12.7%)	8.8% (17.5%)	10.6% (21.5%)
Zelenko 04/2020	3.2% (5.4%)	3.9% (7.2%)	4.7% (9.5%)
Zelenko 06/2020	2.7% (4.2%)	3.0% (5.0%)	3.5% (6.4%)
Procter I	4.1% (7.3%)	4.9% (9.1%)	5.9% (11.6%)
Procter II	3.6% (5.2%)	4.0% (6.1%)	4.5% (7.5%)

- These are all case series with ***high-risk patients***
  - High-risk patient hospitalization rate $\geq$ 10%
  - High-risk patient (age $\geq$ 60) mortality rate $\geq$ 3.5%
  - High-risk patient (age $\geq$ 50) mortality rate $\geq$ 2.26%
- Mortality rate reduction
  - Preponderance of evidence: Zelenko 04/2020, Procter I
  - Clear and convincing: Zelenko 06/2020, Procter II, Raoult
- Hospitalization rate reduction
  - Preponderance of evidence: DSZ study
  - Clear and convincing: Zelenko 04/2020, Zelenko 06/2020, Procter I, Procter II

Compare with Case Fatality Rate in US and France



- US CFR ranged from 2% to 6% in 2020 and converged to 1.7% in 2021
- France CFR ranged from 2% to 16% in 2020 and also converged to 1.7% in 2021
- CFR exceeds efficacy thresholds for: Zelenko 06/2020, Procter II, Raoult
- CFR exceeds random selection bias threshold for: Raoult

Concluding thoughts

- Because:
  1. Signal of benefit for early treatment is very strong;
  2. Early treatment uses repurposed drugs with known excellent safety record;
  3. The alternative is to do nothing;

  it is possible to establish the existence of efficacy by comparing case series of high risk patients against previously observed mortality/hospitalization risks without treatment.
- From a given treatment case series, we derive two thresholds on population-level probability of adverse outcome without treatment: one for establishing efficacy by the *preponderance of evidence* and one for establishing efficacy by the *clear and convincing* evidentiary standard
- Omitted: Bayesian framework. Resilience of evidence against systemic selection bias tolerance.
- This approach proves existence of efficacy but does not precisely calculate efficacy.
- However, the decision to deploy early treatment is Boolean: yes or no
- *Preponderence of evidence* in support of using the original Zelenko early treatment protocol was available by April 29, 2020. Crossover to *clear and convincing* by June 2020.
- Early treatment has been and still is suppressed by public health officials.
  1. S.J. Hatfill. *Journal of the American Physicians and Surgeons* **26** (2021), 74-76
  2. L. Mucchielli. *Journal of Sociology* **56** (2020), 736-744
  3. E. Gkioulekas, M. Rendell, H. Risch, R.B. Stricker. *Journal of the American Physicians and Surgeons* **27 (3)** (2022), 65-68
- The methodology should be used only on treatment protocols based on repurposed medications with acceptable safety.
- For the authorization and approval of new medications or new vaccines, RCTs should be used to balance risks and benefits.

Thank you!