Evolving COVID-19 clinical experience:

Promising hospital and at-home strategies based on emerging evidence, clinicians' reports and a unifying hypothesis

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Yes, there is an answer to COVID-19. It's cheap, available and doctors prescribe it every day, but medical culture (not science) keeps it from being widely used.

ABSTRACT

It appears likely SARS-CoV-2 compromises its host by suppressing the natural adrenal cortisol stress response to the viral challenge even more strongly than happens with typical influenza. COVID-19's "flu-like" symptoms (fever, exhaustion, headache, myalgia, etc.) compared to common flu are often more pronounced and prolonged, and it responds well to appropriately administered corticosteroids. That suggests that viral suppression/dysregulation of the adrenal response may be a key underlying factor in the disease process. It presents the possibility for a simple, inexpensive and universally available early at-home outpatient treatment that could spare large numbers worldwide from needing hospitalization and from more serious, potentially fatal complications.

[added 8/19/21] Study released November 2020 "Improvement of critically ill patients Covid 19 positive placed on glucocorticoids may suggest impairment of the adrenal function. Our objective was to evaluate baseline serum cortisol in covid+ patients. … Sixty-nine patients (86.3%) had baseline cortisol ≤413.79nmol/l … Conclusion: The absence of a marked rise of cortisol during COVID-19 suggests possible involvement of the hypothalamic-pituitary-adrenal axis in this infection."

Etoga N, Inna A, Guewo-Fokeng M, Dehayem M, Boli A, et al. Baseline Serum Total Cortisol During the Primary Corona Virus Infection in the Beginning of the Pandemic in Cameroon. Research Square *In Review* preprint. 2020 Nov 19. [Abstract/PDF]

EVIDENCE OF EFFICACY IN COVID AND RELATED ILLNESSES

When hydrocortisone first became available in the 1950s, doctors noted dramatic benefits in autoimmune disease, allergy, asthma, inflammatory disorders, etc. But they soon discovered that prolonged use at what now are known to be supraphysiological doses can cause serious complications.

Although it is always advised that corticosteroids be given in the smallest dosages that will produce benefit, the distinction between appropriate, *physiological* dosages and excessive, *supra*-physiological dosages in various clinical situations has not been well defined.

Instead, what remains is a pervasive reluctance to prescribe steroids[1] in situations where they might be appropriate and beneficial if used correctly. In COVID-19, this is a matter of life and death.

Before June 16, 2020 (the date the Oxford RECOVERY dexamethasone study was pre-released), health agencies and governing bodies (WHO, CDC, etc.) advised against steroids for COVID-19.

That advice was based on two major fallacies:

1. They failed to notice research that has shown corticosteroids given in more appropriate dosages and durations do not show the same complications (e.g., delayed viral clearance).

   "In univariable analyses, treatment with high-dose corticosteroids was associated with prolonged shedding … but treatment with low doses was not [associated with prolonged shedding]*."*[2]

2. They did not consider that most of the research on COVID-19, SARS1, MERS, H1N1, viral pneumonia, etc. simply looked at "steroids" without considering that some dosages may be therapeutic and some may be harmful, and these dosages will change depending on the severity of illness. Milder illness typically responds better to lower dosages; more severe illness requires higher dosages.

Hewing to the "safe" and familiar track, medical bodies, educators and commentators still fail to consider that a dosage beneficial to a gravely ill patient will overdose a patient who is not as sick. Overlooking important evidence, they continue to recommend against the use of *all* steroids in milder cases, regardless of dosage and length of treatment.

That conclusion fails to distinguish between *appropriate*, physiological, therapeutic dosages and *excessive*, supra-physiological, potentially harmful dosages.

During Flu Epidemics in 1976 & 1994-95, Dr. William McK. Jefferies (Professor of Endocrinology, Case Western Reserve Medical School/Cleveland Clinic and University of Virginia Medical School) tested the hypothesis that familiar "flu-like" symptoms may be caused by a transient viral suppression of adrenal cortisol response.[1, 3] He found:

1. *Low plasma cortisol in influenza patients (1976 study)*
2. *Low ACTH in influenza patients (1994-95 study)*
3. *Normal adrenal response in influenza patients to ACTH stimulation test, indicating intact adrenal function but suppression of HPA signal to produce cortisol*
4. *Swift resolution of symptoms and quick recovery when influenza patients were treated with appropriate dosages of hydrocortisone, with no evidence of increased risk of secondary bacterial infection or other complications.*

Symptoms of Acute Adrenal Insufficiency

COVID-19 and related febrile illnesses share many symptoms in common with adrenocortical insufficiency:

- *malaise*
- *fatigue (often extreme with COVID)*
- *anorexia*
- *myalgia*
- *headache*
- *diarrhea*
- *nausea*
- *fever*
- *chills*
- *sweating*
- *dehydration*

- *confusion*
- *hallucination (seen with some COVID patients)*
- *etc.*

Frontline clinical experience is driving treatment protocols to evolve

I. EVOLUTION OF INPATIENT HOSPITAL USE OF STEROIDS TO TREAT COVID-19

1. **March 13, 2020:** "… routine corticosteroids should be avoided"[4]

   — World Health Organization: *Clinical management of COVID-19 interim guidance*

2. **May 19:** "An early short course of methylprednisolone in patients with moderate to severe COVID-19 reduced escalation of care and improved clinical outcomes."[5]

   — *Clinical Infectious Diseases*: "Early Short Course Corticosteroids in Hospitalized Patients with COVID-19"

3. **June 16:** "WHO welcomes the initial clinical trial results … that show dexamethasone, a corticosteroid, can be lifesaving. … This is the first treatment to be shown to reduce mortality in patients with COVID-19 … ."[6]

   — World Health Organization press release

4. **June 16:** "The reasons [methylprednisolone works better than dexamethasone] are as follows:" [7, 8]

   "1) Methylprednisolone reaches higher concentrations in lung tissue,

   "2) Based on analysis of the inflammatory gene activation patterns induced by SARS-CoV-2, methylprednisolone gene suppression activity most closely matches it, suggesting a higher efficacy when used in Covid-19 than dexamethasone, and

   "3) The dose of dexamethasone in the RECOVERY trial was modest and likely insufficient for some of the more severe cases."

   — Marik PE, Kory P, Meduri GU, Varon J, Iglesias J et al.; Front Line Covid-19 Critical Care Alliance

5. **July 20:** "[M]ethylprednisolone [250 mg on day 1 followed by 80 mg on days 2–5], followed by tocilizumab if needed, may accelerate respiratory recovery, lower hospital mortality and reduce the likelihood of invasive mechanical ventilation in COVID-19-associated CSS."[9]

   Treated patients (n = 86) had 79% higher likelihood of reaching the primary outcome [≥2 stages of improvement on a 7-item WHO-endorsed scale], 65% less mortality and 71% less invasive mechanical ventilation.

   — *Annals of the Rheumatic diseases/British Medical Journals*: "Historically controlled comparison of glucocorticoids … versus supportive care only … Results of the CHIC study"

6. **July 30:** "The NIH COVID-19 Treatment Guidelines Panel recommends using dexamethasone 6 mg per day for up to 10 days for the treatment of COVID-19 in patients who are mechanically ventilated and in patients who require supplemental oxygen but who are not mechanically ventilated."[10]

   — US National Institutes of Health: *COVID-19 Treatment Guidelines: Corticosteroids.*

7. **August 5:** [Using the MATH+ methylprednisolone-based protocol] "The average hospital mortality at these two centers … was 5.1%, … more than a 75% absolute risk reduction in mortality compared to the average published hospital mortality of 22.9 % … ."[11]

   — Marik P, Kory P, Meduri GU, Varon J, Iglesias J; Front Line Covid-19 Critical Care Alliance: "Scientific Review of COVID-19 and MATH+"

TABLE 1

Comparison of methylprednisolone-based protocol (MATH+) outcomes with published hospital mortality in COVID-19[11]

>75% absolute risk reduction in mortality compared to average hospital mortality

Center	*Country*	*Number of Hospitalized patients*	*Data Collection End Dates*	*Hospital or 28-Day Mortality*	*Number of Hospitals*
Non-MATH+ Protocol	UK, USA, China	38,571	1/31/20 – 6/8/20	15.6% – 32.0%	461
MATH+ Protocol	USA	331	7/20/20	5.1%	2

MATH+ protocol centers *(mortality = 5.1%)*
United Memorial Medical Center; Houston, Texas, USA *(140 COVID patients)*
Sentara Norfolk General Hospital; Norfolk, Virginia, USA *(191 COVID patients)*

8. **September 2:** "We recommend systemic corticosteroids rather than no corticosteroids for the treatment of patients with severe and critical COVID-19 (strong recommendation, based on moderate certainty evidence)"

   "We suggest not to use corticosteroids in the treatment of patients with non-severe COVID-19 (***conditional*** recommendation, based on ***low certainty evidence***[my emphases])"[12]

   — World Health Organization: *Corticosteroids for COVID-19 Living guidance, 2 September 2020*

9. **September 2:** "Steroids is clearly the highest quality evidence with the greatest gain."[13]

   — Howard Bauchner, MD, Editor in Chief, *Journal of the American Medical Association*

II. OUTPATIENT AT-HOME USE OF STEROIDS TO TREAT COVID-19

10. **April 16, 2020:** "In particular, case 1 developed pneumonia from the time of admission, started LPV/r and escaped the acute phase of inflammation, but poor oxygenation continued, and loss of appetite was prolonged. She became physically weak, was in danger of acute exacerbation, and CT showed a worsening trend. [W]e received the information of the possible favorable anti-SARS-CoV-2 effect of ciclesonide and started the administration, resulting rapid improvement described here. This was an impressive case. Among former 3 pneumonia patients, 2 of them had required respiratory management beforehand; but after its introduction, these 3 cases were relieved of symptoms."[14]

    — *Journal of Infection and Chemotherapy*: "Therapeutic potential of ciclesonide inhalation for COVID-19 pneumonia: Report of three cases"

11. **May 21, 2020:** "I have been giving very low dose of steroid – Medrol pack [PO methylprednisolone, 21- 4mg tablets: 1 tab 6X on day 1, taper by 1 tab/day until done], to my patients, when they call me with early symptoms. … I so far have been successful on all cases [n = ~25+ through 8/18], with none requiring hospitalization."[15]

    — Thuy Tran, MD; Internal Medicine, UCLA Medical Center

12. **June 17:** "… a successful empirical treatment plan was put into place (budesonide 0.5mg nebulizer, twice daily, clarithromycin 500mg tab, twice daily for ten days, Zinc 50mg tab, twice daily, and aspirin 81mg tab, daily). … Some patients may require an increase in the budesonide dose due to chest tightness or shortness of breath. Nebulized budesonide 1mg every two hours has been effective for patients in those circumstances."[16]

    — Bartlett RP, Watkins A: "SARS-Cov-2 and the Case for Empirical Treatment"

13. **July 15:** "… with oral steroids I too have had excellent success, but I'm also using an inhaled steroid on my diabetic patients. I've followed hundreds of patients and only two have had to go to the hospital [both with serious underlying conditions]. But the great majority we've had success keeping them out of the hospital, keeping them fairly mildly or asymptomatic and getting them back to work."[17]

    — Ralph L. Abraham, MD [and US Congressman], Mangham, Louisiana

14. **August 10:** "[I had] a mild form of COVID, with a dry upper tracheal irritative cough, but none of the other lower respiratory and systemic features. Positive test in late July. Treated with PO steroid taper, inhaled steroids and IV vitamin C [etc.]. Felt back to normal by, and re-tested negative nine days after positive test. Back to work in ICU the next day."

    – private communication, an MD treating critically-ill COVID patients

    [This is characteristic of the reticence physicians have told me they and their colleagues have about discussing their experience publicly. There are MANY more clinicians than the few I've cited here who have been prescribing these protocols successfully.]

15. **August 19:** According to news reports, in late June and early July, Frio Regional (Texas) hospital's 25 beds started to fill up with COVID patients.[18]

    "Sometimes they would be there for six, seven days … and then all of a sudden they would just start going down. If we waited on double blind peer reviewed studies, we would have so many people dead. …

    "If I'm not adding a risk, it's worth seeing if there's a benefit. It's enough for me to know that [with nebulized budesonide] I'm not putting tubes in people's throats ..."

    — Andrea Malcolm, Certified Registered Nurse Anesthetist, the sole critical care provider at Frio Regional Hospital

    Most of the hospital's COVID patients have gone home and admissions for COVID have reportedly dropped off since doctors in the area began prescribing nebulized budesonide for at-home outpatient treatment.

[added 8/19/21] Study released November 2020 "Use of hydroxychloroquine (HCQ), prednisone or both significantly reduced hospitalization risk by 50–60%. Ivermectin, azithromycin and oseltamivir did not substantially reduce risk further. … Similar magnitudes of reduced risk with HCQ and prednisone use were seen for mortality risk, though were not significant because of

only 11 deaths among the 717 patients. No cardiac arrhythmias requiring medication termination were observed for any of the medications."

Fonseca S, Sousa A, Wolkoff A, Moreira M, Pinto B, et al. Risk of hospitalization for Covid-19 outpatients treated with various drug regimens in Brazil: Comparative analysis. *Travel Med Infect Dis*. 2020 Nov-Dec;38 [Abstract]

IIa. ONGOING CLINICAL TRIALS OF OUTPATENT USE OF STEROIDS TO TREAT COVID-19

Estimated Study Completion Dates

16. **~ December 31, 2020:** "A Trial of Ciclesonide in Adults With Mild COVID-19"[19]

    "According to In vitro studies, ciclesonide showed good antiviral activity against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Although some cases were reported for the clinical effectiveness of ciclesonide in the treatment of COVID-19, there is no clinical trial to evaluate the antiviral effect on the reduction of viral load in patients with COVID-19. In this study, we aimed to investigate whether ciclesonide alone or in combination with hydroxychloroquine could eradicate SARS-CoV-2 from respiratory tract earlier in patients with mild COVID-19."

17. **~ December 1, 2020 [RELEASED April 15, 2021, see below]:** "A Study of the Safety and Efficacy of Ciclesonide in the Treatment of Non-hospitalized COVID-19 Patients"[20]

[added 8/19/21] "We are disappointed the results were not more positive, although there was a trend toward earlier cough cessation in the ciclesonide group." —Michael Blaiss, MD

The study demonstrated a treatment difference between ciclesonide (70.6%) and placebo (63.5%) in the percentage of patients with an improved time to alleviation of COVID-19 related symptoms (cough, dyspnea, chills, feeling feverish, repeated shaking with chills, muscle pain, headache, sore throat, and new loss of taste or smell), which was not statistically significant, with a p-value of 0.5502.

Pharma Group press release

These are exactly the results that would be predicted if, as we assert, the systemic steroid effect is an important component of benefit in COVID-19. Ciclesonide, unlike budesonide, has near zero systemic effect. There was no benefit from inhaled ciclesonide for the systemic symptoms (chills, fever, muscle pain, headache, etc.) but there was a benefit locally in the lungs with the trend toward earlier cessation of cough.

18. **~ December 30, 2020 [RELEASED February 8, 2021, see below]:** "STerOids In COVID-19 Study (STOIC)"[21]

    "Early data from multiple studies in China, where the virus originated, show that severe cases of CoVID-19 are not as prevalent in patients with chronic lung diseases as expected. This data has been confirmed by the Italian physicians. The investigators think that the widespread use of inhaled corticosteroids reduces the risk of CoVID-19 pneumonia in patients with chronic lung disease. Early microbiological data also shows that these corticosteroids are effective at slowing down the rate of coronavirus replication on lung cells.

    "Inhaled corticosteroids are widely used to manage common lung conditions, such as asthma. This type of medicine is among the top 3 most common medication prescribed around the world. Their safety is well understood, and their potential side effects are mild and reversible."

[added 8/19/21] On February 8, 2021 Oxford released its "Steroids in COVID-19" (STOIC) randomized controlled trial of inhaled budesonide powder (Pulmicort) for treatment of early outpatient COVID. April 9, it was published in *The Lancet Respiratory Medicine*

Beginning an average 3 days after symptom onset, inhaled budesonide, 400 mcg/puff, 2 puffs bid was taken for a median duration of 7 (4 to 10.5) days. Urgent care visits, including emergency room evaluations and hospital admissions, were 91% lower compared to usual care (P = 0.004).

The trial was designed around a hoped-for 50% reduction in risk. However, because the actual result was a 91% reduction, the trial achieved statistical significance sooner than expected. On December 9, the study team requested an independent statistical monitoring committee review, on the basis of which the trial was concluded early. One of the reasons given was "ethical consideration of the primary outcome."

"We stopped early because, how could we ethically randomise participants to the non-budesonide arm knowing they had a 10-fold chance of needing hospitalisation? This, in addition to knowing that people recover faster in the budesonide arm, have lower fevers, report less congestive symptoms, etc." —Dan V. Nicolau Jr., MD PhD

Ramakrishnan S, Nicolau DV, Langford B, Mahdi M, Jeffers H, Mwasuku C, et al., Univ. of Oxford, Inhaled budesonide in the treatment of early COVID-19 (STOIC): a phase 2, open-label, randomised controlled trial. *Lancet Respir Med*. 2021 Apr 9. [Full Text]

The Oxford PRINCIPLE trial, released August 10, 2021, enrolled higher risk patients and began treatment on average 6 days after symptom onset. PRINCIPLE reported milder illness and 3 days reduction in recovery time but the observed reduction in hospitalization and death did not reach statistical significance. PRINCIPLE's treatment was begun later than STOIC using the same dosage. Better results would likely have been achieved if frequency and/or dosage had been increased as needed according to severity of illness and clinical response.

Yu L, Bafadhel M, Dorward J, Hayward G, Saville B, et al. Inhaled budesonide for COVID-19 in people at high risk of complications in the community in the UK (PRINCIPLE): a randomised, controlled, open-label, adaptive platform trial. *Lancet.*2021 Aug 10. [Full Text]

THREE LOW-DOSE STEROID OUTPATIENT PROTOCOLS WITH REPORTED EFFICACY AND SAFETY *(n = ~500+ patients, likely much higher but hard to assess because many clinicians worldwide are using these protocols and we don't have a way of communicating with most of them)*

Clinicians have reported success with these three protocols in influenza and COVID-19. With COVID, they are consistently reporting near-zero hospitalizations with fewer and milder complications compared to patients not treated with these protocols.

Typically these protocols are prescribed along with synergistic measures that may provide additional antiviral, antibacterial, anticoagulant, etc. benefit. Dosages and length of treatment may be adjusted according to patient response.

- ***HYDROCORTISONE*, 20mg by mouth four times daily before meals and at bedtime. Patients continued this dosage until they felt well, (efficacy reported in influenza; untested in COVID-19)**
- **Then decreased to 10 mg four times daily for two days, then 5 mg four times daily for two days, then stop.**

– William McK. Jefferies, MD; et al.

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Note that Dr. Jefferies found no increased incidence of bacterial infection with appropriate dosages of hydrocortisone to treat influenza.

- ***BUDESONIDE*, 0.5mg nebulizer, twice daily or metered-dose powder, 800 mcg twice daily.**
- **Some patients may require an increase in the budesonide dose due to chest tightness or shortness of breath. Nebulized budesonide 1mg every two hours has been effective for patients in those circumstances.**

– Richard P. Bartlett, MD; Alexandria Watkins, DNP; Ralph L. Abraham, MD; et al.

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- ***METHYLPREDNISOLONE*, oral 6-day taper (twenty-one 4mg tablets).**
- **Day 1: Six 4mg tablets in divided doses.**
- **Days 2 -6: Reduce each day by one tablet per day until used up.**

– Thuy Tran, MD; Ralph L. Abraham, MD; et al.

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ANSWERING THE CONCERNS

In this crisis providers must care for the patients they see every day. Between the time of this writing and December 30 while we wait for the trials, at the current rate half a million more will die.

That mortality must be weighed against concerns about possible risks using appropriately calibrated steroids in treating COVID patients, whether in hospitals or with milder out-patient cases at home:

1. Will appropriately low-dose steroids, either oral or inhaled, increase viral shedding and intensify the illness?[22]

   Based on the reported experience of doctors treating ~500-1,000 cases to date, this does not appear to be an issue.

   Studies suggest a viral inoculum dose-response relationship in which the initial inoculum dosage and early viral load are factors in transmission and severity of disease.[23] This underscores the importance of masks, social distancing, etc. to reduce exposure.

   However, front line clinical experience does not suggest it might be a rationale for withholding appropriately low-dose steroids in early COVID-19 patients. To date, there is no evidence the low dosages and/or short treatment courses clinicians are reporting to be effective increase the viral load or intensify/prolong the illness.

   The data show higher inoculum dosage is associated with more severe hyper-inflammatory reaction. This is consistent with viral suppression of the adrenal cortisol stress response needed to regulate inflammatory processes. More virus will distribute more of the protein sequences
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that trigger auto-immune interference with the ACTH/cortisol dynamics, leading to an inadequate/inappropriate cortisol stress response and runaway hyper-inflammation.

Although in some cases there can be direct damage from the virus, clinicians report they are not seeing this when the hyper-inflammatory reaction is managed with appropriately timed and dosed steroids. Although the mechanism isn't clear, it appears successfully addressing the hyper-inflammatory reaction may protect from both sources of harm, even without other anti-viral interventions.

2. Will appropriately low-dose steroids prolong the time of viral clearance?

Again, based on clinical experience, this does not appear to be an issue, both symptomatically in the fact that patients recover quickly, and based on the fact that test-positive COVID patients who have been treated with these protocols re-test negative soon after completing the course of treatment.

3. Will appropriately low-dose steroids increase the risk of secondary infections?

Some doctors have chosen to prescribe budesonide preferentially over ciclesonide, as research suggests a possibly lower risk of secondary infection with budesonide. Also, some are prescribing antibiotics (e.g., clarithromycin) for prophylaxis together with the steroids. In practice, both with inhaled and systemic oral low-dose steroids in COVID, secondary infection has not emerged as a problem in hands-on clinical experience.

4. Will the systemic effects of oral or IV steroids cause problems?

Again, this is a matter of appropriate dosage for the severity of the illness. When dosage and length of administration are appropriately matched to the severity of illness, issues with systemic effects (immune suppression, hyperglycemia, etc.) have not been reported.

In fact, the systemic effects of steroids appear beneficial in treating COVID, both in bringing the hyper-immune over-reaction back into balance and in providing hormonal and metabolic resources to address the challenge. Below I will explain why this may be especially significant in COVID and other illnesses that display "flu-like" symptoms. I will also explain the potential importance of low-dose systemic steroids in treating COVID "long-haulers."

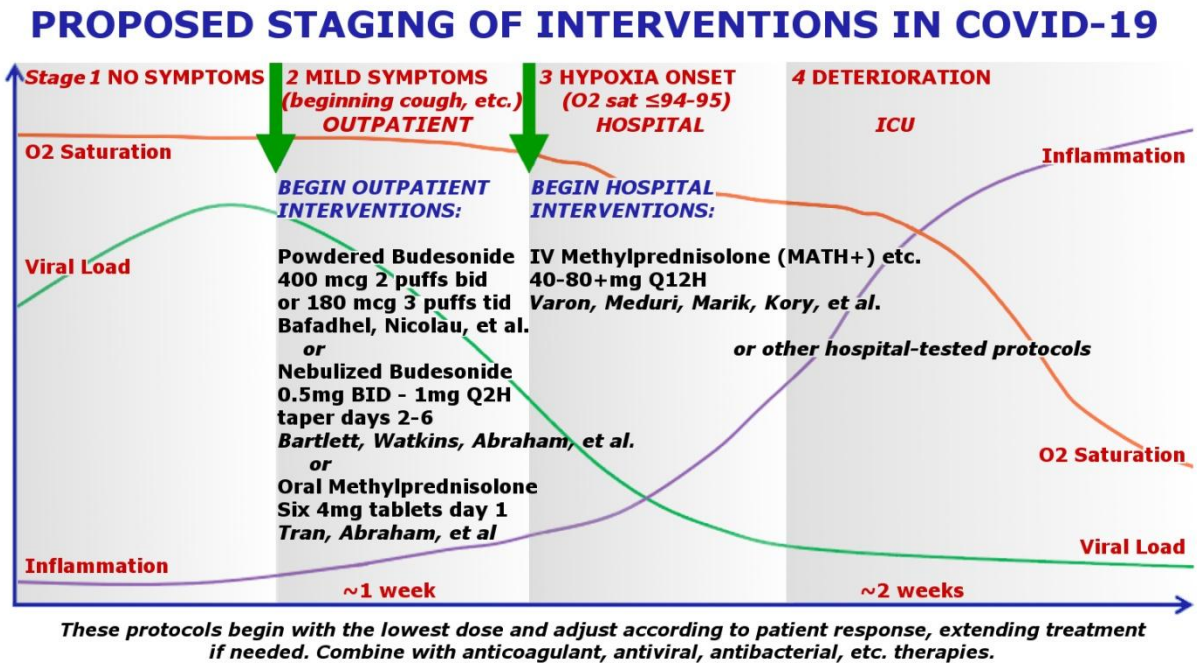
5. Will appropriately low-dose steroids cause problems with elevated blood sugar, especially in diabetic patients?

In hospitalized patients, blood sugar can be monitored and managed. Even hospitalized, critically-ill diabetic COVID patients receiving the MATH+ and similar appropriately dosed IV steroid-based protocols have done well. In at-home diabetic outpatients where precise management of blood sugar is less practical, it may be preferable to give inhaled, instead of oral, steroids.

6. Will use of nebulized, inhaled steroids increase the risk of transmission in hospitals?

In hospital settings, oral or IV protocols may be simpler to administer because they don't require negative-air-pressure isolation rooms to help mitigate potential aerosolized transmission from nebulized inhalation treatment. However, both inhaled and oral/IV protocols are being used successfully in hospitals.

FIGURE 1



WHY ARE STEROIDS SO IMPORTANT TO TREAT COVID-19?

So far, the ONLY medicines shown in published research to reduce COVID-19 mortality have been corticosteroids.

It is well-known that these steroids can help mitigate the hyper-inflammatory reaction, which is how COVID does much of its harm. But how does the reaction get out of control in the first place, and what does that have to do with glucocorticoids?

Many of the complications COVID-19 are not caused directly by the virus itself but by mechanisms the virus unleashes or disrupts that subsequently cause damage even as the virus itself diminishes.

MANY with SARS-CoV-2 develop only mild or no symptoms after becoming infected. On the flip side are the long-haulers (most of whom were never hospitalized) whose symptoms persist long after the initial infection has passed, even after there is no sign the virus itself is still in their bodies.

What decides who will become sick and who will not after getting infected? What decides who remains sick after the virus is gone? If much of the damage is not caused by the virus itself, what switch does it flip? Where is that Pandora's box the virus opens to unleash a runaway hyper-immune reaction?

The answer, it appears, is in the way SARS-CoV-2 and other viruses disrupt the body's normal adrenal cortisol stress response.

Adrenal insufficiency patients are routinely instructed to increase their hydrocortisone dosage at the onset of flu and other febrile illnesses. In the medical textbook, *Safe Uses of Cortisol* (3rd edition, 2004, Charles C. Thomas Publisher) Dr. William McK. Jefferies wrote of research he conducted during the influenza epidemic that swept through Ohio in March, 1976. At the time, Dr. Jefferies was Professor of Endocrinology at Case Western Reserve Medical School/Cleveland Clinic:

> *"When [chronic adrenal insufficiency] patients followed these instructions, symptoms of fever, generalized aching, acute malaise and anorexia often cleared within forty-eight hours. The*

dosage was then gradually tapered to their maintenance dosage over the next week, and no recurrence developed, nor were there evidences of complicating bacterial infections.

"The impressive improvement of these patients with steroid therapy, plus THE SIMILARITY BETWEEN SYMPTOMS OF ACUTE INFLUENZA AND ACUTE ADRENAL INSUFFICIENCY [my emphasis] led to a decision to study plasma cortisol levels in this disease. During the epidemic of influenza … plasma cortisol levels were obtained on patients [without previous underlying adrenal insufficiency] presenting in the acute stages of the illness. When these were found to be remarkably low, ACTH was administered to determine whether the low values were due to adrenal insufficiency. Normal responses to ACTH indicated that the adrenals were not at fault and that the defect lay in the pituitary or the hypothalamus. Furthermore, the administration of cortisol, 20 mg by mouth four times daily, resulted in dramatic improvement. …

"As a result of these findings, it was decided to treat patients with acute influenza in the same manner in which patients with chronic adrenal insufficiency were treated when they developed acute infections. Cortisol, 20mg by mouth four times daily before meals and at bedtime, was started. Patients were instructed to continue this dosage until they felt well, then decrease to 10 mg four times daily for two days, then 5 mg four times daily for two days, then stop. …

"Clinical responses were striking. WITHIN TWENTY-FOUR HOURS ALL PATIENTS FELT MUCH BETTER, AND WITHIN FORTY-EIGHT HOURS SYMPTOMS SUCH AS FEVER, MALAISE AND GENERALIZED ACHING HAD COMPLETELY SUBSIDED [my emphasis] and they felt quite well. The initial dosage of cortisol was decreased after forty-eight hours and discontinued after six days of therapy. No relapses or complications occurred."

[This is the same response primary care doctors are reporting when they prescribe inhaled or oral steroids in appropriate dosages and durations to COVID-19 patients.]

In the early 1990s I was office manager in a medical practice that consulted with Dr. Jefferies for guidance treating some of our patients. During that time, the physician I worked for came down with the flu. I visited his house and found him lying on the couch complaining of malaise with fever, sweating, headache, exhaustion.

I suggested we try Dr. Jefferies hydrocortisone influenza protocol and he agreed. His wife brought him 20 milligrams of Cortef and went back to the kitchen. Half an hour later, he called to his wife, "I'm starving. Feed me!" He sat up and ate enthusiastically, stating he felt much better. When he returned to the office, he prescribed the same protocol for a few of our patients, who reported, "That was the mildest flu I've ever had."

During the flu seasons of 1994 and 1995, Dr. Jefferies measured plasma ACTH and cortisol levels in young adults with influenza virus type A and in comparable healthy controls. He found ACTH levels in flu patients were skewed lower relative to their plasma cortisol levels compared to healthy controls, whose ACTH levels were higher.

The influenza patients' plasma cortisol was within the normal baseline range for *unstressed*, healthy subjects and did not show the expected two-fold or higher increase that would be seen with a normal adrenocortical stress response to the viral challenge.

"These findings suggest that influenza virus type A infection may have an inhibitory effect on the production or release of ACTH."

— Jefferies, et al. Low plasma levels of adrenocorticotropic hormone in patients with acute Influenza. *Clin Infect Dis*. 1998 Mar 1;26.

HOW DO VIRUSES LIKE SARS-COV-2 DISRUPT THE ADRENOCORTICAL STRESS RESPONSE?

> *" [There is evidence that an] immunoevasive strategy utilized by the SARS virus, like influenza, is to inhibit its host's corticosteroid stress response. This is accomplished by viral expression of amino acid sequences that are molecular mimics of the host's adrenocorticotropin hormone (ACTH).When the host produces antibodies against these viral antigens, the antibodies also bind to the host's own ACTH, which limits the host's stress response by interfering with ACTH's ability to stimulate the secretion of corticosteroids."*[24]

Some studies have also shown increased ACTH in some critical patients, which may be due to assays that detected autoantibody-bound ACTH; or free ACTH may have actually been elevated. Some studies have shown elevated plasma cortisol in some critical patients, and some data suggest glucocorticoid tissue/receptor resistance in some critical patients.[25]

All these seemingly contradictory findings may be caused by the same viral process, the end result of which is to derange and disable the body's natural adrenocortical stress response:

- Viral-induced autoantibodies binding to ACTH will deactivate it and cause a viral-induced hypocortisolism.
- If some of the autoantibodies produced in response to viral ACTH analogs bind less stably to endogenous ACTH compared to normal albumin-bound ACTH (which is likely, because there are fewer matching peptide residues on viral counterfeit ACTH than on endogenous ACTH), there may be a surging effect as some ACTH becomes unbound and biologically active again, triggering random, dysregulated production of excess cortisol.[26]
- Glucocorticoid receptor resistance may be caused both by viral-produced molecules blocking the GC receptors or by endogenous deactivation of the receptors in response to excessive circulating cortisol.

  In either case, despite seemingly high cortisol, a runaway hyper-immune reaction demonstrates functional hypocortisolism even in the presence of elevated plasma cortisol. For that reason, clinicians are advised to administer steroids based on inflammatory markers (e.g., CRP), etc. and not based on measures of plasma cortisol and ACTH.[27, 28]

WHAT THIS MEANS FOR COVID LONG-HAULERS

"Twenty-four (39.3%) [SARS-CoV-1] patients had evidence of hypocortisolism. The hypothalamic–pituitary–adrenal (HPA) axis dysfunction of the majority resolved within a year."[29]

— *Clinical Endocrinology*: Hypocortisolism in survivors of severe acute respiratory syndrome (SARS)

This almost certainly is also happening in long-hauler COVID-19 survivors. Providers report that repeating a course of corticosteroids (e.g., methylprednisolone dose pack) in such patients often clears the persistent exhaustion, brain fog, inflammatory symptoms (e.g., coughing, shortness of breath), fevers, diarrhea, etc., which are common not only in COVID long-haulers but also in acute adrenal insufficiency.

It bears consideration, however, whether such "burst-and-taper" is the best approach. Would it be better to provide longer-term, sub-replacement *physiological* dosages of corticosteroids, exactly as one would treating a patient with chronic adrenal insufficiency?

A logical longer-term regimen in such post-viral cases would be 15-20mg oral hydrocortisone per day in three or four divided doses (typically larger doses AM, smaller ones later to match the natural cycle), adjusted based on patient response. The importance of using these lower, physiological, *subreplacement* dosages of hydrocortisone is that it may help the adrenals recover.

Higher doses (especially if prolonged) that replace or exceed the body's normal cortisol cause the adrenals to stop producing. If the adrenals still retain at least some capacity for production, it is better to allow them to remain active.

That can be done by only replacing part of the needed cortisol with exogenous corticosteroid. Then the adrenals must make some cortisol, but without being pushed to their limit. In such cases, clinical experience [Jefferies, et al.] has seen that the adrenals often recover and the supplemental hydrocortisone can be tapered and eventually stopped.

To determine appropriate dosage, simply follow the clinical response. The patient can tell if the amount of hydrocortisone is not enough, about right, or too much. Too much will feel over-stimulating. Not enough will have little or no noticeable effect. The right amount will resolve or significantly improve the symptoms. This may change over time, typically with progressively smaller dosages needed as the adrenals recover.

The top 10 COVID-19 Long-Hauler symptoms *(n = 1,567)*

1. Fatigue (100%)
2. Muscle or body aches (66.8%)
3. Shortness of breath or difficulty breathing (65.1%)
4. Difficulty concentrating or focusing (59.0%)
5. Inability to exercise or be active (58.5%)
6. Headache (57.6%)
7. Difficulty sleeping (49.9%)
8. Anxiety (47.6%)
9. Memory problems (45.6%)
10. Dizziness (41.9%)

Also common:

-- Diarrhea (32.3%)
-- Night sweats (30.3%)
-- Fever/chills (28.1%)

— Natalie Lambert, PhD (Associate Research Professor of Medicine, Indiana University Medical School) & Survivor Corps[30]

INHALED VS. ORAL STEROIDS

Case reports of systemic COVID-19 symptoms (fever, malaise, headache, dizziness, myalgia etc.) resolving when inhaled steroids were given suggest the systemic effect of these medicines may be an important component of their benefit.

"On the average, [inhaled budesonide] doses ≥1.84 mg/day/70 kg adult (26.3 µg/kg/day) exhibited systemic effects on the 8 am serum cortisol level and blood eosinophil count equivalent to ≥15 mg of [oral prednisone] per day."[31]

Thus, the recommended starting dosage (0.5mg BID) of nebulized budesonide will be equivalent to about 6.4mg/day oral prednisolone, 8mg/day oral prednisone, or 32mg/day oral hydrocortisone.

That is a significant systemic effect, especially considering that the highest suggested inhaled budesonide dosages for COVID (up to 1mg budesonide Q2H) will have a systemic effect equivalent to about 77mg/day oral methylprednisolone).

TABLE 2

Equivalent Dosages of Inhaled Budesonide vs. Oral Corticosteroids[31]			
Inhaled Budesonide	***Oral Methylprednisolone***	***Oral Prednisone***	***Oral Hydrocortisone***
1mg/day	~6.4mg/day	~8mg/day	~32mg/day
4mg/day	~25.6mg/day	~32mg/day	~128mg/day
8mg/day	~51.2mg/day	~64mg/day	~256mg/day
12mg/day	~76.8mg/day	~96mg/day	~384mg/day

OTHER INTERVENTIONS

As potential new treatments emerge, one of the most promising appears to be vitamin D. Not actually a vitamin, it is a steroid hormone the body produces from cholesterol in response to sunlight. Vitamin D is similar in structure to hydrocortisone, testosterone, estrogen, etc.

September 17, 2020:

> *"SARS-CoV-2 positivity is strongly and inversely associated with circulating 25(OH)D levels"* (n=191,779)
>
> *"[T]hose who had a circulating level of 25(OH)D <20 ng/mL had a 54% higher positivity rate compared to those who had a blood level of 30–34 ng/mL. The risk of SARS-CoV-2 positivity continued to decline until the serum levels reached 55 ng/mL."*[32]

Vitamin D is cheap, it is widely-dispensed to protect vulnerable populations from deficiency disease, and its safety and pharmacokinetics are well researched. *Vitamin D deficiency/inadequacy is estimated to affect up to half the world population.*

These data suggest fifty or more million of the most at-risk people in the US and over two billion worldwide might be protected from infection if they started taking adequate vitamin D immediately.

NOTE: If dispensing of sufficient vitamin D to large numbers of people could be accomplished during the 2020-2021 flu season, we would likely see a reduction in the rate and severity not only of COVID-19, but also of influenza infections, including measurable reductions in mortality:

> *"A previous study found that each 4 ng/mL increase in circulating 25(OH)D levels was associated with a 7% decreased risk of seasonal infection, a decrement of approximately 1.75% per ng/mL* [33]. *This is remarkably similar to the 1.6% lower risk of SARS-CoV-2 positivity per ng/mL found in our adjusted multivariable model."*[32]

August 29, 2020:

> *"Of 50* [hospitalized] *patients treated with calcifediol* [calcidiol, 25-hydroxy vitamin D]*, one required admission to the ICU (2%), while of 26 untreated patients, 13 required admission (50%)… X2 Fischer test p < 0.001. …*
>
> *Of the patients treated with calcifediol, none died, and all were discharged, without complications.* [Of the 26] *patients not treated with calcifediol, … two* [15.4%] *died and* [24] *were discharged."*[34]
>
> — *Journal of Steroid Biochemistry and Molecular Biology*: Effect of Calcifediol Treatment and best Available Therapy versus best Available Therapy on Intensive Care Unit Admission and Mortality Among Patients Hospitalized for COVID-19: A Pilot Randomized Clinical study

These 76 hospitalized COVID-19 patients did not receive corticosteroids. The authors wrote:

> *"An interesting perspective … could be to evaluate calcifediol* [given together with] *dexamethasone or other corticoid … ."*

A protocol that includes both vitamin D and corticosteroids has already been tested. The MATH+ methylprednisolone-based protocol[35] that produced a >75% absolute risk reduction in COVID-19 hospital mortality compared to published hospital statistics includes 4,000 IU/day oral D3. [Marik, et al. "Scientific Review of COVID-19 and MATH+"]

September 28, 2020:

The MATH+ methylprednisolone-based protocol [35] was updated to include this recommendation:

> *"Vitamin D3 20 000 – 60 000u single oral dose. Calcifediol 200 -500 ug is an alternative. This should be followed by 20 000u D3 (or 200ug calcifediol) weekly until discharged from hospital. Calcifediol is more efficiently absorbed, achieves 1,25 OH vitamin D levels quicker and is three times more potent than vitamin D3."*
>
> — Marik P; Eastern Virginia Medical School. EVMS critical care COVID-19 management protocol. 2020 Mar. (updated frequently, current version Sep 28, 2020)

TABLE 3

Comparison of 25-hydroxy vitamin D etc. w/o corticosteroids[34] **vs. methylprednisolone + vitamin D3 etc. (MATH+) hospital protocols in COVID-19**[11]				
	Corticosteroid	***Vitamin D***	***ICU admissions***	***Deaths***
Methyl-prednisolone etc. study (n = 331)	IV methyl-prednisolone 40 – 80+ mg BID	Oral vitamin D3 4,000 IU/day	Not recorded	>75% absolute reduction compared to published hospital mortality
Calcifediol etc. study (n = 76)	None	Oral calcifediol (25-hydroxy vitamin D) 21,280 IU (532 mcg) on day one, then 10,640 (266 mcg) IU on days 3, then once weekly until released from hospital	1 in test group (n = 50) 2% 13 in control group (n = 26) 50% 94% reduction in ICU admissions (p = .001)	0 in test group (n = 50) 2 in control group (n = 26) Larger studies needed to assess significance

WHAT WILL HAPPEN WHEN YOU COMBINE THESE TWO PROTOCOLS?

Between these studies, two features differ in the administration of vitamin D:

1. Different forms of vitamin D given:
    a. D3 (cholecalciferol) given in methylprednisolone-based protocol study
    b. 25-hydroxy vitamin D (calcifediol) given in study w/o corticosteroids
2. Different dosages and schedules:
    a. 4,000 IU daily w/o loading dose given in methylprednisolone-based protocol study
    b. 21,280 IU (532 mcg) loading dose of 25-hydroxy vitamin D (equivalent to 42,560 - 127,680 IU of vitamin D3) followed by 10,640 IU (266 mcg) 25-hydroxy vitamin D on days 3 & 7, then weekly until released from hospital given in study w/o corticosteroids

That raises two questions:

1. ***Do the different forms of vitamin D used make a difference?*** (Yes.)

    The liver must convert vitamin D3 to 25-hydroxy vitamin D. With hospitalized, acute patients, it makes sense to use 25-hydroxy vitamin D, which is the more bio-available, faster acting form.

> *"Calcifediol given daily, weekly, or as a single bolus is about 2 - 3* [some say 3 - 6 [36]] *times more potent in increasing plasma 25(OH)D3 concentrations than vitamin D3. Plasma 25(OH)D3 concentrations of 30 ng/mL were reached more rapidly and reliably with calcifediol."*[37]
>
> — *Bone*: Pharmacokinetics of oral vitamin D3 and calcifediol

Calcifediol is more potent than vitamin D3. The loading dose used in the COVID-19 study (532 mcg or 21,280 IU) would be equivalent to 42,560 - 127,680 IU of vitamin D3.

(If kidney function is impaired, it will be necessary to give calcitriol, which is the end-product, active vitamin D form produced in the kidneys from calcifediol.)

2. ***Does a loading dose make a difference?*** (Again, yes.)

> *"Serum calcidiol rose promptly after cholecalciferol* [D3] *dosing* [single dose, 100,000 IU by mouth] *from a mean (±SD) baseline of 27.1 ± 7.7 ng/mL to a concentration maximum of 42.0 ± 9.1 ng/mL. Seven percent of the supplemented cohort failed to achieve 32.1 ng/mL at any time point. The highest achieved concentration in any subject was 64.2 ng/mL. The control group had a nonsignificant change from baseline of −0.72 ± 0.80 ng/mL during 4 mo."*[38]
>
> — *American Journal of Clinical Nutrition*: Pharmacokinetics of a single, large dose of cholecalciferol

In aggregate, about half the rise in serum 25-hydroxy vitamin D occurred in the first 24-48 hours, which is much faster than with daily, smaller doses. Blood levels in older subjects and heavier subjects tended to rise more slowly.

Loading or monthly higher-dose vitamin D3 has been investigated[39].

"Monthly supplementation of 100,000 IU vitamin D3 for a median of 3.3 years did not affect participant-reported adverse events."

—Clinical Nutrition: Monthly high-dose vitamin D3 supplementation and self-reported adverse events in a 4-year randomized controlled trial

One-time or weeks-apart doses from ~40,000 - ~100,000 IU have been found effective to raise serum 25-hydroxy vitamin D in populations susceptible to deficiency. However, with COVID-19 because levels need to be raised as quickly as possible, a loading dose of 100,000 IU of D3 or equivalent potency of calcifediol (e.g., ~500 mcg) seems prudent.

Vitamin D for COVID outpatients

Research suggests deficient or low blood levels of vitamin D (measured as serum 25-hydroxy vit. D) increases the risk of viral infections (including COVID-19 and their complications). Some clinicians suggest vitamin D3, 2,000 - 4,000 IU/day as a routine measure for prophylaxis and for support during the illness.

To safely raise as quickly as possible, blood levels of vitamin D in symptomatic, or in asymptomatic test-positive, COVID outpatients it is logical to use a single 100,000 IU loading dose and 2,000 - 4,000 IU/day thereafter for maintenance. Such dosages have been reported safe in patients who are without contraindications.

Oral calcifediol (25-hydroxy vitamin D) raises serum vitamin D more quickly than does oral D3 but calcifediol is fairly expensive and less likely to make a difference compared to vitamin D3 for milder,

outpatient cases unless there is liver impairment. (For hospitalized patients, if the more expensive calcifediol reduces the stay by a single day and/or protects from more serious complications, the net savings will surely be greater than the cost of the drug.)

CONCLUSIONS AND RECOMMENDATIONS

In a crisis where thousands die daily, we must look at the evidence we have, however preliminary. We must weigh that evidence against the risks of providing access to emerging treatments that may be helpful.

If the risks appear low enough relative to the potential harm of withholding treatment, providers must have latitude, based on their best judgment, to test for themselves and to share information about what is working.

These medicines are available worldwide. They are inexpensive, noncontroversial, and every physician is familiar with them in routine practice. At the suggested low dosages and/or short treatment durations, their safety record is well known.

Dr. Jefferies submitted his 1976 influenza study for publication but it was rejected by journals, "possibly because of the bad reputation of glucocorticoids in infections."[Jefferies WM. *Safe uses of cortisol*] In 1998, the journal *Clinical Infectious Diseases* published Dr. Jefferies' later study, "Low plasma levels of adrenocorticotropic hormone in patients with acute influenza."

According to WHO, worldwide influenza-related deaths number ~250,000 - 650,000 per year. In the forty or so years since Dr. Jefferies' research was first submitted for publication, as many as twenty-six *million* people have died from influenza and its complications.

So far in 2020, COVID has killed more than 1,000,000 people.

This paper makes the case for a group of related interventions that show potential to reverse this deadly pandemic.

However, for that to happen, the information must be made available to primary care and hospital clinicians quickly, so they can evaluate current, front line clinical experience on its own merit. As they apply that information in managing their own COVID cases, their experience will add to the knowledge base and advance the entire effort in this emergency. Again:

In this crisis providers must care for the patients they see every day. Between now and December 31 while we wait for the trials, at the current rate half a million more will die.

Although the death and morbidity from COVID-19 are horrific, a possible silver lining will be if we can learn some of the lessons this pandemic is offering to teach us.

If we *do* succeed in understanding how to treat this illness so we can keep patients out of hospitals and get them well quickly, we will have field-tested an approach that may also dramatically reduce the annual death rate from influenza and related illnesses. That, at least, would leave a legacy to help assure that those who have died of COVID-19 did not die in vain.

AUTHOR INFORMATION:

Jerry Freeman is a retired medical administrator with a background in journalism and public relations. The last seven months he's worked full time as an unpaid volunteer networking with providers, health administrators, medical educators and the public to identify and report what's working for clinicians on the front lines of the pandemic. Every few weeks, Mr. Freeman writes an email briefing that circulates to several thousand clinicians.

In 1993 Mr. Freeman was diagnosed with adrenal insufficiency and has taken hydrocortisone every day for the last 27 years. This has included bouts of influenza during which he followed the recommended regimen of increasing hydrocortisone intake to replicate a normal adrenal cortisol stress response to the viral challenge.

The author states he has no commercial or financial relationships that could be construed as potential conflicts of interest.

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