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Why an inexpensive anti-inflammatory drug used to treat severe respiratory failure and shown to decrease mortality and dependence on a ventilator goes unused in COVID-19 patients

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In this country and the industrialized world, ICUs are overwhelmed by the lack of ventilators for critically ill patients with COVID-19 pneumonia and acute respiratory distress syndrome (ARDS). Any intervention directed at decreasing dependence on ventilators and mortality in COVID-19 patients could have a significant impact on public health and national security.

Corticosteroids (CS) are powerful anti-inflammatory drugs commonly used to treat inflammatory lung diseases. They have been off-patent for greater than 30 years, and they are cheap and globally equitable. Randomized controlled trials have demonstrated safety and effectiveness in non-viral ARDS (7 days reduction in duration of mechanical ventilation; 35 % reduction in mortality), and large-scale observational studies have shown – after adjustment for confounders – a sizable reduction (approximately 50 %) in mortality in SARS-CoV (5,327 patients) and H1N1 influenza (2,141 patients). Recent publications from China also report improvement in oxygenation, resolution of pulmonary densities on computed tomography, and in one study, a reduction in mortality. Ongoing randomized trials in COVID-19 patients will provide valuable information to clinicians. However, those results are months away; what to do until then?

Today, many clinicians in the USA shy away from corticosteroid treatment solely based on the WHO recommendations that the use of this potent anti-inflammatory treatment be limited to subjects recruited in randomized trials. Overall the WHO offered a cursive summary of a few selected publications grossly under-representing

the available evidence, an approach appallingly inadequate for a critical recommendation that impacts so many lives. The evidence provided in the March 13 Interim Guidance was limited to a meta-analysis of 1,500 patients, and two observational studies involving 600 patients with H1N1, and 300 patients with MERS pneumonia. While these observational studies reported no reduction in mortality after adjustment for baseline confounders and time-dependent covariates, one reported a reduction in viral clearance. This latter finding was part of the justification for the categorical recommendation; yet, the study showed that if corticosteroid treatment was longer than 7 days, clearance was not affected. The WHO's review ignored new data from (i) ten RCTs in non-viral ARDS (1,093 patients) including a significant reduction in interleukin-6 blood levels, (ii) the four largest studies – totaling 9,149 patients with SARS-CoV or H1N1 influenza – reporting a reduction

in duration of mechanical ventilation and mortality, (iii) the early positive results from China with COVI-19 patients, and (iv) the experts' recommendations from the frontlines of China, Korea, and Italy. The WHO position, to categorically deny the most common anti-inflammatory treatment used in hospitals worldwide, has provided unique opportunities for the investigation of alternative approaches to curb inflammation. Pharmaceutical companies are rushing to promote their yet unproven interventions and succeed in making news and influencing the stock market. Their influence in more subtle ways also controls medical education amplifying favorable messages and under or misrepresenting what is not favorable. We argue that the WHO position is unjustifiable based on the totality of available evidence. We believe that there is no evidence-based support or ethical ground to categorically deny a widely prescribed anti-inflammatory treatment in a condition characterized by massive inflammation that rapidly destroys the vital organs and kills patients. Corticosteroids are part of the armamentarium that has been used by physicians for the last fifty years. Monitoring response to treatment with serial measurements of C-reactive protein levels can guide physicians in adjusting treatment to achieve optimal results. Guidelines on the most effective approach were provided in a recent Commentary (https://journals.lww.com/ccejournal/Fulltext/2020/04000/Rationale_for_Prolonged_Corticosteroid_Treatment.18.aspx).

A recent review (https://www.frontiersin.org/articles/10.3389/fendo.2020.00161/full) of the updated scientific literature on the central role played by corticosteroids and essential vitamins in resolution of critical illness provides the rationale for early co-interventions that include prolonged corticosteroid treatment in association with rapid correction of a severe deficiency of Vitamins C, B1, and D. Corticosteroids are essential drugs, unsung heroes, the hormones produced by the body under stress to protect and restore our body to normal function. In the 1980s, during the HIV epidemic, AIDS patients were dying from pneumocystis pneumonia. Following the observation that death was caused by lung inflammation in response to the pathogen and not by the pathogen itself, corticosteroid treatment was intro-

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duced, leading to a reduction in mortality. Strong patients' advocacy allowed for rapid, widespread implementation; lives were saved. In the COVID-19 pandemic, patients' advocacy organizations are missing. There is no pharmaco-economic interest promoting the use of an off-patent treatment and recommendations by some American medical organizations are based on an anemic review of the evidence and a biased interpretation of the data. As a result of the WHO's dogmatic recommendation, thousands of COVID-19 patients are still dying from massive inflammation while doctors are discouraged to use the most potent anti-inflammatory treatment presently available. Following the publication in Critical Care Explorations of a Commentary "Rationale for prolonged glucocorticoid treatment in COVID-19" physicians responded favorably on Facebook and with emails. A few comments on their experience are reproduced below.

FACEBOOK COMMENTS – APRIL 16, 2020 – www.facebook.com/FrontlineCovid19CriticalCare

"We floundered for two weeks. Lots of codes, intubations and death. Maybe 15 discharges. We started steroids and discharge 250 patients. Less intubations, less codes. And the ones that ended up on vent, not as serious.

CXR/CT Changes = steroids
Hypoxia on admission = steroids
Ambulatory hypoxia = steroids

Completely changed our trajectory.
Steroids are a game changer.

Hospitalist, SE Michigan – Our group is taking care of 700 plus COVID+ patients"

"I'm here in New Orleans and we've been using it for the last four weeks. We notice a great success once we started using steroids. Do not underestimate this study. This was a game changer in our hospital. We were able to free ventilators and get elderly patient out of the hospital without needing a ventilator. Patients that were obviously crashing quickly, who we had to have end of life talk with were able to walk out of the hospital. At no point did any of our patient worsen and because of steroids. These patients shed viruses 4 weeks later, With or without steroids. The virus doesn't kill anybody, it's the inflammation that does. Let the virus replicate however slow down the inflammation."

EMAIL FROM A PHYSICIAN IN MICHIGAN

We instituted early low dose short course methylprednisolone in our treatment algorithm for COVID19 pneumonia over a month ago and there is no looking back. Came across Dr. Meduri's metanalysis in Journal of Intensive care on glucocorticoid use in ARDS a couple of weeks ago. The paper made so much sense especially in the context of COVID19 related lung injury. His second manuscript in Critical Care Explorations is a commentary specific to COVID 19 ARDS. In addition to our own experience, we have collective anecdotal experience on early immunomodulation (methylprednisolone, Il-1, IL-6 inhibitors) from multiple centers across the U.S., Spain, India, publications from Wuhan (The Lancet 29th Feb Lianhan Shang among others), autopsy data. Curious now if the Recovery Trial rolled out by NHS with early dexamethasone would pan out to substantiate our experience and save lives and reduce ventilator use. Based on my experience it would be unethical to have a trial which does not have early immunomodulation as a standard of care for COVID19 related cytokine-chemokines lung injury-ARDS. If an effective oral/IV antiviral and or convalescent plasma with documented protective Neutralizing Ab titer (when begun in the first several days from onset) controls and aborts the viremia and hence the cytokine response and or agents like colchicine (contactless trial), Jak-2 inhibitors, prevent the inflammatory cascade from going on an overdrive we have to continue the early immunomodulation as a life-saving strategy.