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At the request of the Journal Editor and the Publisher, the following article has been retracted.

Kory P, Meduri GU, Iglesias J, Varon J, & Marik PE. Clinical and Scientific Rationale for the "MATH+" Hospital Treatment Protocol for COVID-19. *J Intensive Care Med*. 2021:36;135-156. 10.1177/0885066620973585

The article has been retracted after the journal received notice from Sentara Norfolk General Hospital in Norfolk, Virginia ("Sentara") raising concerns about the accuracy of COVID-19 hospital mortality data reported in the article pertaining to Sentara. Sentara's notice included the following statements:

'The data from Sentara Norfolk General Hospital were presented in Table 2, which lists in-hospital or 28-day mortality rates at the 2 MATH+ centers as compared to 10 published single-center and multicenter reports. The mortality rate among 191 patients at Sentara Norfolk General Hospital as of July 20, 2020 was reported as 6.1%, as compared to mortality rates reported in the literature ranging from 15.6% to 32%. The authors state that these data "provide supportive clinical evidence for the physiologic rationale and efficacy of the MATH+ treatment protocol."'

'The data from Sentara Norfolk General Hospital that [are] reported in this paper are inaccurate. The paper briefly states the methods as: "Available hospital outcome data for COVID-19 patients treated at these 2 hospitals as of July 20,2020 are provided in Table 2 including comparison to the published hospital mortality rates from multiple COVID-19 publications across the United States and the world."'

'We have conducted a careful review of our data for patients with COVID-19 from March 22, 2020 to July 20, 2020, which shows that among the 191 patients referenced in Table 2 that the mortality rate was 10.5%, rather than 6.1%. In addition, of those 191 patients, only 73 patients (38.2%) received at least 1 of the 4 MATH+ therapies, and their mortality rate was 24.7%. Only 25 of 191 patients (13.1%) received all 4 MATH+ therapies, and their mortality rate was 28%.'

'Apparently […] census and mortality counts from hospital reports [were used] to calculate a mortality rate, but in so doing counted some patients in the denominator but not in the numerator because they died after July 20, 2020, the reported end date of the study. This would be an incorrect calculation of a hospital mortality rate, but might explain the incorrect number of 6.1% in Table 2. Using this incorrect mortality rate to compare with the published reports and claim a "75% absolute risk reduction" is thus an incorrect conclusion regardless of which mortality rate is used.'

Given the above concerns that are material to the article's findings, the article has been retracted.

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RETRACTED Clinical and Scientific Rationale for the "MATH+" Hospital Treatment Protocol for COVID-19

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Abstract

In December 2019, COVID-19, a severe respiratory illness caused by the new coronavirus SARS-CoV-2 (COVID-19) emerged in Wuhan, China. The greatest impact that COVID-19 had was on intensive care units (ICUs), given that approximately 20% of hospitalized cases developed acute respiratory failure (ARF) requiring ICU admission. Based on the assumption that COVID-19 represented a viral pneumonia and no anti-coronaviral therapy existed, nearly all national and international health care societies' recommended "supportive care only" avoiding other therapies outside of randomized controlled trials, with a specific prohibition against the use of corticosteroids in treatment. However, early studies of COVID-19-associated ARF reported inexplicably high mortality rates, with frequent prolonged durations of mechanical ventilation (MV), even from centers expert in such supportive care strategies. These reports led the authors to form a clinical expert panel called the Front-Line COVID-19 Critical Care Alliance (www.flccc.net). The panel collaboratively reviewed the emerging clinical, radiographic, and pathological reports of COVID-19 while initiating multiple discussions among a wide clinical network of front-line clinical ICU experts from initial outbreak areas in China, Italy, and New York. Based on the shared early impressions of "*what was working and what wasn't working,*" the increasing medical journal publications and the rapidly accumulating personal clinical experiences with COVID-19 patients, a treatment protocol was created for the hospitalized patients based on the core therapies of methylprednisolone, ascorbic acid, thiamine, heparin and co-interventions (MATH+). This manuscript reviews the scientific and clinical rationale behind MATH+ based on published in-vitro, pre-clinical, and clinical data in support of each medicine, with a special emphasis of studies supporting their use in the treatment of patients with viral syndromes and COVID-19 specifically. The review concludes with a comparison of published multi-national mortality data with MATH+ center outcomes.

Keywords

lung infection, respiratory failure, thrombin, breathlessness

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Introduction

In December 2019, an illness characterized by pneumonia associated with the new coronavirus SARS-CoV-2 (COVID-19) emerged in Wuhan, China. By March 11, 2020, the World Health Organization (WHO) had characterized the novel coronavirus outbreak as a pandemic, with confirmed cases in 213 countries. The greatest impact this malady had was on intensive care units (ICUs), given approximately 20% of hospitalized cases developed acute respiratory failure (ARF) requiring ICU admission.[1,2]

Since COVID-19 was initially defined as a primary viral syndrome and no validated anti-coronavirus therapy existed, nearly all national and international health care societies advocated a primary focus on supportive care with avoidance of other therapies outside of randomized controlled trials, and with specific recommendations to avoid the use of corticosteroids.[3-5]

The pervasive belief among world health care societies that corticosteroids were harmful in COVID-19 respiratory illness was surprising for several reasons. First, as will be detailed in this manuscript, contrary to the WHO and CDC's interpretation

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of prior pandemic data, a review of the same data by a group including one of the authors (G.U.M) was both published and publicized by the Society for Critical Care Medicine in early April 2020 which concluded that the largest and most well-controlled studies from the SARS, MERS, and H1N1 pandemics found that the mortality of patients with moderate to severe illness was significantly reduced when treated with corticosteroids.[6] Second, reports from the "front-line" clinicians in Italy and New York reported on rapidly observable, positive impacts when corticosteroids were used in treatment. Further, an expert panel of U.S radiologists had published a tragically little-noticed review of the early CT scans from Wuhan, China in March of 2020, where they concluded that the "most common pattern of lung injury in COVID-19 is of an organizing pneumonia" (OP), a condition accurately identifiable by CT scan and whose first-line therapy is corticosteroids. The presence of OP likely explains both the seemingly baffling clinical presentation of early COVID-19 respiratory disease as well as the efficacy of corticosteroids as evidenced in a recent review by one of the authors (PK).[7,8]

However, in that period prior to the now-widespread use of corticosteroids, multiple early studies of COVID-19-associated ARF reported inexplicably high mortality rates, with frequent prolonged durations of mechanical ventilation (MV), even from centers expert in such supportive care strategies.[9] These reports led many physicians, including the authors of this manuscript, to question the widely recommended supportive care-only approach, and to review the evidence behind therapies that could counteract the well-recognized syndrome of severe hypoxemia, hyper-inflammation, and hypercoagulability, with the rationale that interventions targeted at these pathophysiologies could decrease dependence on mechanical ventilators and mortality in COVID-19 patients, and thus, have an immediate significant global impact on this public health emergency.[9,10]

As a group of clinical researchers in critical care with over a 100-year collective front-line, bedside ICU experience in the treatment of severe infections and acute respiratory distress syndrome (ARDS), the authors formed a clinical expert panel which we called the Front-Line COVID-19 Critical Care Alliance (www.flccc.net). The panel collaboratively reviewed the emerging clinical, radiographic, and pathological reports of COVID-19 while initiating multiple discussions among a wide clinical network of front-line clinical ICU experts from the initial outbreak areas in China, Italy, and New York. Based on the shared early impressions of "*what was working and what wasn't working*," the increasing medical journal publications and the rapidly accumulating personal clinical experiences with COVID-19 patients, a treatment protocol was created for hospitalized patients, adapted from a protocol created by one of the authors (P.E.M) at their home institution. The protocol consisted of the 4 "core" therapies of methylprednisolone, ascorbic acid, thiamine, heparin and a number of co-interventions and thus was called "MATH+" (Table 1). The core medicines were all highly familiar, low-cost, FDA-approved medications with known therapeutic mechanisms, well-established safety profiles and multiple clinical trials showing benefit in similar disease models such as ARDS. The additional co-interventions were also supported by either promising early clinical data, strong scientific rationale, and/or a pre-existing clinical evidence base for similar critical care conditions as those in COVID-19. Since the development of MATH+ early in the pandemic, the treatment efficacy of the majority of the protocol components (corticosteroids, ascorbic acid, heparin, statins, Vitamin D, melatonin) have now been either validated in subsequent randomized controlled trials or more strongly supported with large observational data sets.[11-16]

Many centers similarly attempted to develop "treatment guidelines" for COVID-19, and although they primarily emphasized supportive respiratory care techniques, many also included approaches either quickly retracted as obviously harmful, such as "early intubation" or therapeutic agents and interventions whose mechanisms of action held only theoretical anti-SARS-CoV-2 activity.[17-21]

To study the efficacy of the proposed MATH+ protocol against COVID-19, a collective decision was made to do so via the formation of a patient registry to measure and compare the outcomes of patients treated with MATH+, not only against the prevailing "supportive-care only" strategy, but also against other novel proposed treatment approaches employed throughout the country and world.[17-19]

The authors were troubled by editorials published in major peer-reviewed medical journals which argued that all treatments used in a "novel" disease were "experimental" and thus use should be restricted to only within randomized controlled trials (RCT).[22] "Experimental" therapies, best defined as those with either no clinical evidence to support or near nil clinical familiarity with use in similar disease states, were indeed adopted and widely used, particularly in the early weeks of the pandemic when drugs such as hydroxychloroquine, remdesivir, lopinavir/ritonavir and tocilizumab were employed. However, these agents stand in marked contrast to the core MATH+ therapies of which there was extensive clinical experience and expertise amongst the authors along with published clinical evidence showing positive outcomes when used in the treatment of patients with similar diseases and conditions. In some instances, several were already incorporated into standard ICU treatment protocols for conditions such as severe pneumonia, ARDS, and sepsis in their institutions. Each element of MATH+ has been extensively studied in critical illness, almost all sufficiently so that meta-analyses have been published on their use and indications, thus none could be viewed as an "experimental therapy," given they are considered more in-line with "standard" or "supportive care" for many critical illness states.

Although the authors place immense value and importance on the need for well-conducted observational and/or randomized controlled trials, in such a novel disease syndrome, it must be recognized that not all institutions possess the necessary experience, resources, or infrastructure to design and conduct such trials, especially during a pandemic. Further, the group decided against a randomized, placebo-controlled trial

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Table 1. MATH+ Hospital Treatment Protocol for COVID-19 (www.flccc.net).

Medication	Indication/Initiation	Recommended dosing	Titration/Duration
Methylprednisolone	A. Mild hypoxemia: requires O_2 via NC to maintain saturation > 92%	40 mg IV bolus then 20 mg IV twice daily	A1. Once off O_2, then taper with 20 mg daily x 3 days then 10 mg daily x 3 days, monitor CRP response. A2. If FiO_2, or CRP increase move to B.
	B. Moderate–severe hypoxemia (High Flow O_2, NIPPV, IMV)	COVID-19 Respiratory Failure protocol (see Figure 2) Preferred: 80 mg IV bolus, followed by 80 mg / 240 ml normal saline IV infusion at 10 ml/hr Alternate: 40 mg IV twice daily	B1. Once off IMV, NPPV, or High flow O_2, decrease to 20 mg twice daily. Once off O_2, then taper with 20 mg/day for 3 days then 10 mg/day for 3 days. B2. If no improvement in oxygenation in 2–4 days, double dose to 160 mg/daily. B3. If no improvement and increase in CRP/Ferritin, move to "Pulse Dose" below.
	C. Refractory Illness/ Cytokine Storm	"Pulse" dose with 125 mg IV every 6–8 hours	Continue for 3 days then decrease to 80 mg IV/daily dose above (B). If still no response or CRP/Ferritin high/rising, consider "Salvage Therapy" below
Ascorbic Acid	O_2 < 4 L on hospital ward	500–1000 mg oral every 6 hours	Until discharge
	O_2 > 4 L or in ICU	1.5–3 g intravenously every 6 hours	Sooner of 7 days or discharge from ICU, then switch to oral dose above
Thiamine	ICU patients	200 mg IV twice daily	Sooner of 7 days or discharge from ICU
Heparin (LMWH)	Hospital ward patients on $\leq$ 4 L O_2	0.5 mg/kg twice daily. Monitor anti-Xa, target 0.2–0.5 IU/ml	Until discharge then start DOAC at half dose for 4 weeks
	ICU patients or > 4 L O_2	1 mg/kg twice daily (monitor anti-Xa levels, target 0.6–1.1 IU/ml)	Later of: discharge from ICU or off oxygen, then decrease to hospital ward dosing above
Vitamin D	Hospital ward patients on $\leq$ 4 L O_2	Calcifediol preferred: 0.532 mg PO day 1, then 0.266 mg PO day 3 and 7 and weekly thereafter Cholecalciferol: 10,000 IU/day PO or 60,000 IU day 1, 30,000 IU days 3 and 7 and then weekly	Until discharge from ICU
	ICU patients or on > 4 L O_2	Cholecalciferol 480,000 IU (30 ml) PO on admission, then check Vitamin D level on day 5, if < 20 ng/ml, 90,000 PO IU/day for 5 days	Until discharge from ICU
Atorvastatin	ICU Patients	80 mg PO daily	Until discharge
Melatonin	Hospitalized patients	6–12 mg PO at night	Until discharge
Zinc	Hospitalized patients	75–100 mg PO daily	Until discharge
Famotidine	Hospitalized Patients	40–80 PO mg twice daily	Until discharge
Therapeutic Plasma Exchange	Patients refractory to pulse dose steroids	5 sessions, every other day	Completion of 5 exchanges

Legend: CRP = C-Reactive Protein, DOAC = direct oral anti-coagulant, ICU = Intensive Care Unit, IMV = Invasive Mechanical Ventilation, IU = International units, IV = intravenous, NIPPV = Non-Invasive Positive Pressure Ventilation, O_2 = oxygen, PO (per os) = oral administration.

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design given that such trials require investigators to possess "clinical equipoise," which is the belief by the investigator that neither intervention in the control or experimental group is "better." With respect to each of the individual "core" therapies of MATH+, all authors felt the therapies either superior to any placebo or possessed evidence of minimal risk and cost compared to potential benefit such that use was favored, with these judgements based on not only the rapidly accumulated evidence and insight into COVID-19 but also from our collective knowledge, research, and experience with each of the component medications in critical illness and other severe infections.

Conversely, the authors believe it is within the immense power and resources of large research institutions to conduct such trials where clinical equipoise exists. A powerful example of such an accomplishment is the RECOVERY trial conducted

by researchers at Oxford University.[11] Specifically, the design and execution of the RECOVERY trial depended on investigators with clinical equipoise around the use of corticosteroids in the treatment of a severe coronavirus syndrome. The MATH+ authors did not possess such equipoise, as we held a collective belief as to the critical importance of corticosteroid therapy in COVID-19, as evidenced above.[6,8,23]

Thus, it came as no surprise to the authors that the RECOVERY trial was stopped early due to excess deaths in a control group consisting of over 4000 patients treated with placebo. A conservative estimate of avoidable death in the placebo group if they had instead received corticosteroids is that over 200 lives would have been saved; 109 in patients requiring oxygen and 84 in those on mechanical ventilation.[11]

The scientific and clinical rationale supporting the MATH+ treatment protocol will be reviewed in the following sections through a review of the published in-vitro, pre-clinical, and clinical data in support of each medicine, with a special emphasis on studies involving the treatment of viral syndromes and COVID-19 specifically. The review will conclude with a report on the preliminary outcomes data from the 2 hospitals that adopted the MATH+ protocol in the treatment of COVID-19 patients.

Methylprednisolone and COVID-19

Methylprednisolone was chosen based on the following criteria: (i) evidence of corticosteroid responsive disease, (ii) results of relevant clinical studies, many from prior viral pandemics including more than 10,000 patients, and (iii) pharmacological characteristics.

Similar to ARDS, patients with severe COVID-19 have a significant reduction in glucocorticoid receptor expression in bronchoalveolar lavage fluid myeloid cells that negatively related to lung neutrophilic inflammation, NETosis, and disease severity.[24,25] The dysregulated inflammation and coagulation observed in COVID-19 (see Pathophysiology) is also similar to that of multifactorial ARDS where ample evidence has demonstrated the ability of prolonged corticosteroid treatment (CST) to downregulate – systemic and pulmonary—inflammation-coagulation-fibroproliferation and accelerate disease resolution.[24,26] Additionally, the computed tomography findings of ground-glass opacities and the histological findings of organizing pneumonia, hyaline membranes, inflammatory exudates, and acute fibrinous and organizing pneumonia are all compatible with CST-responsive inflammatory lung disease.[8,27,28]

Relevant clinical studies at the time of the creation of MATH+ included randomized controlled trials (RCTs) in adult patients with non-viral ARDS, large-scale observational studies in patients with SARS-CoV (n = 7008), H1N1 (n = 2141), influenza, and early results from multiple COVID-19 observational studies.[29-35] In non-viral ARDS, aggregate data from 10 RCTs (n = 1093) showed that CST was associated with a sizable increase by day 28 in MV-free days (WMD 6.18 days, 95% CI 3.45 days to 8.90 days), ICU-free days (WMD 8.12 days, 95% CI 3.87 days to 12.37 days) and a reduction in hospital mortality (RR 0.67, CI 0.52-0.870) with the greatest impact observed with methylprednisolone treatment.[6,32,36] Importantly, the survival benefit observed during hospitalization persisted after hospital discharge with follow-up observations extending up to 1 year.[6] Except for transient hyperglycemia (mostly within the 36 hours following an initial bolus), CST was not associated with increased risk for neuromuscular weakness, gastrointestinal bleeding, or nosocomial infections (RR 0.83 (95% CI 0.67 to 1.02).

The evidence of benefit in viral pneumonia (SARS, H1N1) relies on large-scale studies (n = 9149) which included adjustment for confounders and analysis of CST variables (type, timing, dose, and duration) on the outcome.[31,32] These studies reported a significant reduction in mortality with dosage and duration of CST similar to the one recommended by the Corticosteroid Guideline Task Force of the Society of Critical Care Medicine (SCCM) and the European Society of Intensive Care Medicine (ESICM) (Figure 1).[6,37] In the largest SARS-CoV study, after adjustment for possible confounders, methylprednisolone 80mg/day was safe and decreased the risk for death by 63% (HR 0.37, 95% CI: 0.24-0.56).[31] In the H1N1 study, subgroup analysis among patients with PaO_2: FiO_2 <300 mm Hg (535 vs. 462), low-to-moderate-dose CST (methylprednisolone 25-150 mg/day) significantly reduced both 30-day mortality (aHR 0.49 [95% CI 0.32-0.77]) and 60-day mortality (aHR 0.51 [95% CI 0.33-0.78]) despite having a higher rate of nosocomial infections.[32]

Methylprednisolone, for its greater penetration in lung tissue, longer residence time, and greater inhibitory activity of transcription factor nuclear factor-kB (driver of lung inflammation) is the most frequently used intravenous corticosteroid for the treatment of severe acute inflammatory lung diseases.[38-40] The initial daily dose of 1 mg/Kg of ideal body weight (approximately 80 mg) was the one shown to be associated with the highest mortality reduction in RCTs of non-viral ARDS and large observational studies in SARS-CoV and H1N1 pneumonia.[6,31,32] A recent study that matched the expression changes induced by SARS-CoV2 in human lung tissue tissues and A549 lung cell line against the expression changes triggered by 5,694 FDA-approved drugs, found methylprednisolone to be the drug with the greatest potential to revert the changes induced by COVID-19, while other closely related corticosteroids, such as dexamethasone or prednisone, were not.[41]

The risk for decreased viral clearance with CST is overstated and the most frequently quoted article by Arabi et al., in patients that received greater than 7 days CST there was a strong trend toward lower 90-day mortality [aOR 0.51, 95% confidence interval (CI) 0.26-1.00; p = 0.05] and no impact on viral clearance [aOR 0.94, 95% confidence interval (CI) 0.36-2.47; p = 0.90].[42] Contrary to the widespread, unfounded fears of delayed viral clearance which unfortunately influenced the multiple national and international society recommendations against use of CST in COVID-19, the reality is that there is no evidence linking delayed viral clearance to worsened

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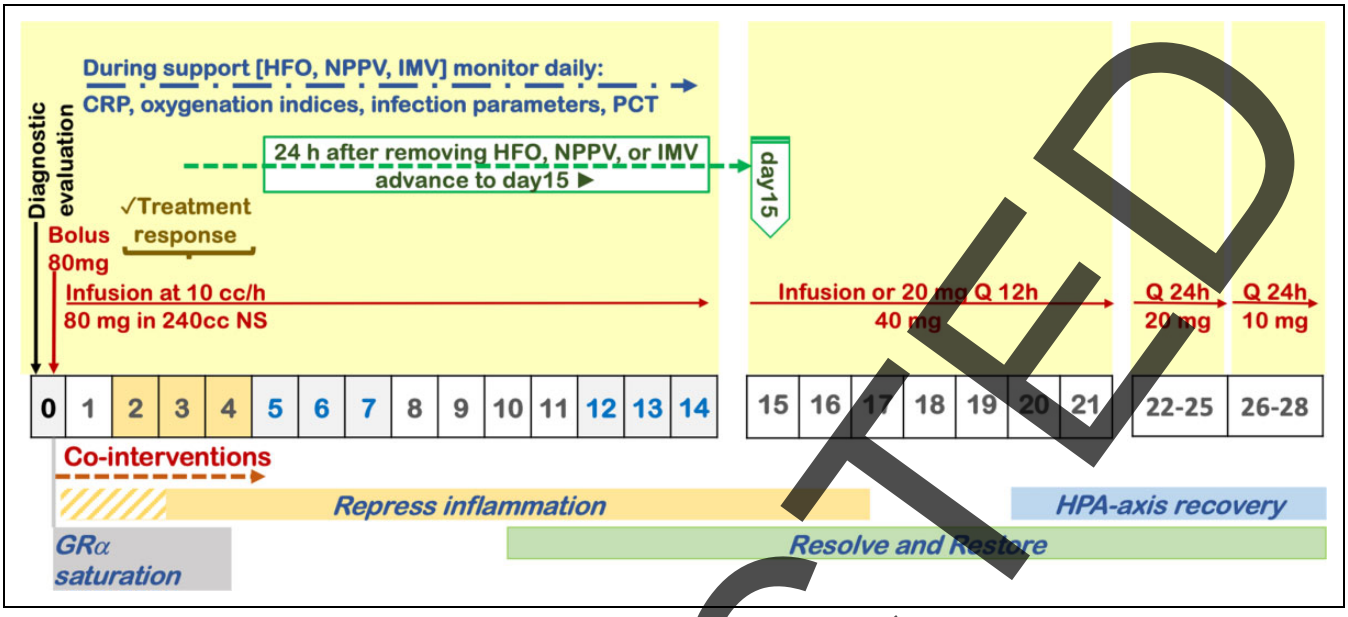

Figure 1. Protocol for prolonged corticosteroid treatment recommended by the corticosteroid guideline task force of the society of critical care medicine (SCCM) and the European society of intensive care medicine (ESICM).

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outcomes in critically ill COVID-19 patients, and further, it is unlikely that it would have a greater negative impact than the hosts own "cytokine storm."[26]

Subsequent to the introduction of the MATH+ protocol, even more definitive support for CST was provided by a large randomized trial along with prospective observational studies. The RECOVERY trial investigated dexamethasone (6 mg once daily for up to 10 days) in a randomized, controlled, open-label, adaptive, platform trial with a primary outcome of 28-day mortality.[11] The RCT studied 2104 patients randomly allocated to receive dexamethasone compared to 4321 patients concurrently allocated to usual care. CST was associated with a significant reduction in mortality (21.6% vs. 24.6%) with an age adjusted rate ratio [RR] 0.83; 95% confidence interval [CI] 0.74 to 0.92; P < 0.001). Dexamethasone reduced deaths by one-third in the subgroup of patients receiving invasive mechanical ventilation (29.0% vs. 40.7%, RR 0.65 [95% CI 0.51 to 0.82]; p < 0.001), by one-fifth in patients receiving oxygen without invasive mechanical ventilation (21.5% vs. 25.0%, RR 0.80 [95% CI 0.70 to 0.92]; p = 0.002), but did not reduce mortality in patients not receiving respiratory support at randomization (17.0% vs.13.2%, RR 1.22 [95% CI 0.93 to 1.61]; p = 0.14). However, it should be noted that dexamethasone is the corticosteroid associated with greater suppression of the adrenal gland. Notably, the RECOVERY RCT utilized a small dose of dexamethasone and did not incorporate tapering to prevent rebound inflammation.

An Italian multicenter, prospective observational study explored the association between exposure to prolonged CST (a pre-designed protocol: methylprednisolone 80 mg for 9 days followed by tapering based on improvement in predefined laboratory parameters) and the need for ICU referral, intubation or death within 28 days (composite primary endpoint) in patients (83 on CST vs. 90 matched control) with severe COVID-19 pneumonia admitted to Italian respiratory high-dependency units.[43] The composite primary endpoint was met by 19 vs. 40 [adjusted hazard ratio (HR) 0.41; 95% confidence interval (CI): 0.24-0.72]. Transfer to ICU and need for invasive MV was necessary in 15 vs. 27 (p = 0.07) and 14 vs. 26 (p = 0.10), respectively. By day 28, the MP group had fewer deaths (6 vs. 21, adjusted HR = 0.29; 95% CI: 0.12-0.73) and more days off invasive MV (24.0 ± 9.0 vs. 17.5 ± 12.8; p = 0.001). Study treatment was associated with rapid improvement in PaO_2: FiO_2 and CRP levels without affecting lymphocyte count. The complication rate was similar for the 2 groups (p = 0.84). No difference was observed in viral shedding, determined as the number of days between hospital referral and the first negative nasopharyngeal swab.

A Spanish semi-randomized study investigated methylprednisolone (3 days each, 80 mg and 40 mg, respectively) in 85 COVID-19 (56 CST, 29 control) hypoxemic patients; the primary composite outcome similar to the Italian study.[44] CST was associated with reduced risk of the composite endpoint in the intention-to-treat, age-stratified analysis (combined risk ratio—RR—0.55 [95% CI 0.33-0.91]; p = 0.024).

The Henry Ford COVID-19 Management Task Force conducted a single pre-test, single post-test quasi-experiment in a multi-center health system in Michigan.[34] They investigated 213 patients with confirmed moderate to severe COVID admitted over a 2 weeks period; the first week 81 patients received standard of care (SOC), the second week 132 patients also received SOC and early initiation of CST (methylprednisolone 0.5 to 1 mg/kg/day for 3 days, and longer duration if they required MV). In the first week, half of the patients in the SOC group received CST but with a later initiation. The primary composite outcome was similar to the Italian study, and was

reached by fewer patients in the CST group (34.9% vs. 54.3%, $p = 0.005$).[43] This treatment effect was observed within each individual component of the composite endpoint. Significant reduction in median hospital length of stay was also observed in the early corticosteroid group (8 vs. 5 days, $p < 0.001$). Hospital length of stay was decreased by 3 days ($p < 0.001$).[34]

In the aftermath of the RECOVERY trial, a total of 6 additional RCTs investigating corticosteroid treatment in patients with severe COVID-19 were published. An updated meta-analysis requested by the WHO included patients randomized to receive systemic dexamethasone, hydrocortisone, or methylprednisolone (678 patients) or to receive usual care or placebo (1025 patients).[45] Data on mortality found little inconsistency between the trial results ($I2 = 15.6\%$) and the summary OR was 0.70 (95%CI, 0.48-1.01; $P = .053$) based on the random-effects meta-analysis. They reported 222 deaths among patients randomized to corticosteroids (32.7%) and 425 deaths (42.5%) among patients randomized to usual care or placebo (summary OR, 0.66 [95%CI, 0.53-0.82]; $P < .001$). As a result of these findings, the WHO updated their "Corticosteroids for COVID-19: Living Guidance" document recommending "systemic corticosteroids rather than no corticosteroids for the treatment of patients with severe and critical COVID-19 (strong recommendation, based on moderate certainty evidence)."[46]

Ascorbic Acid (AA) and COVID-19

Approximately 15% of patients with Covid-19 infection progress to a respiratory illness, which in its early phase is consistent with OP, and if either not treated or insufficiently treated with corticosteroids progresses to a more severe pneumonitis, with about 5-10% requiring mechanical ventilation which then further injures the lung and causes ARDS often coincident with a cytokine storm characterized by vasoplegia, hypercoagulability and multiorgan failure.[10,24,26] Ascorbic acid (AA) is the most potent and important anti-oxidant in mammals with pleiotropic modes of action targeting multiple molecules and biological pathways involved in inflammatory states such as sepsis, ARDS, trauma, and burns.[47-49]

A significant body of preclinical and clinical evidence in septic shock and other types of stress responses demonstrate that intravenous AA can attenuate many of the life threatening complications of a dysregulated immune system during Covid-19 infection.[49,26,50] In contrast to influenza and other respiratory viruses, there is a blunted antiviral response with low interferon production and increase in pro-inflammatory cytokines. In a minority of patients, cytokine storm ensues with overwhelming production of pro-inflammatory cytokines and reactive oxygen species leading to progressive organ failure.[24,26,51-53]

The innate immune and adaptive response provides an essential role in the antiviral response and is mediated by the release of type I interferon α/β by macrophages, lymphocytes and infected immune cells.[51,54] Several experiments employing H1N1 infected knockout mice unable to synthesize AA found that administration of AA increases interferon production, restores expression of genes necessary for production of interferons and decreases proinflammatory gene expression with a subsequent decrease in the release of proinflammatory cytokines.[54,55] AA is thus an essential factor in the anti-viral immune response during the early phase of virus infection through the production of type I IFNs.[54]

Ascorbic acid is also a cofactor for the production of endogenous catecholamines and corticosteroid synthesis.[25-38] Given that humans, due to an evolutionary mutation, are almost unique among all mammals in their inability to synthesize AA, in states of stress plasma AA levels are rapidly and markedly decreased as opposed to other mammals such as goats that immediately begin to produce many grams of AA in stressed or infected states.[49,56,57] AA reverses ROS induced oxidant stress impairment of glucocorticoid receptor function.[58,59] Thus, AA is synergistic with endogenous and exogenous corticosteroids in reversal of shock.[49,60] In clinical studies AA given with or without steroids results in decreases in vasopressor requirement and reversal of shock.[49,57,59,60] AA antioxidative and ROS scavenging properties may counteract cytokine, chemokine and inflammatory cell mediated excessive production of reactive oxygen species which are known to cause decreased vascular tone and endothelial injury.[58,59]

In animal models, intravenous ascorbic acid was shown to improve arteriolar responsiveness to vasoconstrictors and decrease microvascular permeability.[57,61] The hemodynamic effects of AA have been demonstrated in septic shock, trauma, and burns where administration of ascorbic acid reduced vasopressor and volume resuscitation requirement.[47,49,62,63]

Marik et al, in a propensity adjusted study of patients with sepsis, administered intravenous AA, hydrocortisone, and thiamine in patients with severe sepsis and found a significant survival benefit.[47] CITRIS-ALI, the largest double blind placebo controlled trial of high dose AA in ARDS patients found that both mortality and decreased ICU length of stay were significantly reduced in the treatment arm.[64] The reasons for the lack of immediate adoption of this therapy in ARDS can only be explained by the fact that the original primary outcome analysis failed to account for all the early excess deaths in the control group, where no severity of illness (SOFA) score was assigned to the patients who died. A subsequent letter to the editor by a group of prominent scientists demanded an analysis accounting for these early deaths. The study authors complied and found that the primary outcome of SOFA score to be statistically significantly decreased at 96 hours along with the mortality in the treated group.[65] Thus, CITRIS-ALI, although inexplicably portrayed as a negative trial, was instead profoundly positive in terms of both its primary outcome and important secondary outcomes.

Two large meta-analyses involving critically ill patients demonstrated intravenous vitamin C administration showed no adverse reactions, reduced the need for fluids and vasopressor support and reduced the length of time on mechanical ventilators.[50,66]

Most importantly, a prospective, randomized, double-blind, placebo-controlled trial of high-dose intravenous AA in

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COVID-19 respiratory failure was conducted at 3 hospitals in Hubei, China where the intervention group were treated with 12 g of IV AA every 12 hours for 7 days.[15] The trial was stopped early due to control of the epidemic, thus only 56 patients were included. Although the primary endpoint of invasive mechanical ventilation free days was not significant 26.0 vs 22.0 ($p = .57$), significant improvements in oxygenation and reductions in IL-6 were found in the intervention group over the 7 days and a reduction in 28 day mortality was observed, although the difference was not statistically significant (22.2% vs. 37.9% $p = .31$). In the sub-group of patients with SOFA scores ≥ 3, the differences in ICU and hospital mortality were statistically significant while the 28-day mortality approached, but did not reach statistical significance. (21.7% vs. 52.4%, $p = .06$).

In summary, intravenous AA was included based on the pleiotropic effects on important physiologic functions, its properties as powerful antioxidant/ROS scavenger, and reversal of ROS induced oxidant stress impairment of glucocorticoid receptor function, its impact on outcomes in the treatment of both COVID respiratory failure and non-COVID ARDS as well as other hyperinflammatory conditions along with an impeccable safety profile and low cost.

Thiamine and COVID-19

Thiamine is a water-soluble vitamin passively absorbed in the small intestine. After ingestion, free thiamine is converted to the active form thiamine pyrophosphate (TPP), commonly known as vitamin B1, by thiamine pyrophosphokinase. The majority of TPP in the body is found in erythrocytes and accounts for approximately 80% of the body's total storage.[67] TPP is a key co-factor for pyruvate dehydrogenase, the gatekeeper for entry into the Krebs Cycle, without which pyruvate would be converted to lactate as opposed to acetyl-coenzyme A.[67]

Multiple other non-cofactor roles of thiamine exist within the immune system, gene regulation, oxidative stress response, cholinergic activity, chloride channel function, and neurotransmission.[67] In experimental rheumatoid arthritis, thiamine increased the ability of corticosteroids to suppress production of TNF-α and IL-6.[68]

The human adult can store around 30 mg of thiamine in muscle tissue, liver and kidneys, however, these stores can become depleted in as little as 18 days after the cessation of thiamine intake.[67] A thiamine deficiency syndrome, beriberi, bears a number of similarities to sepsis, including peripheral vasodilation, cardiac dysfunction, and elevated lactate levels.[49] In critical illness, the prevalence of thiamine deficiency is in 10-20% upon admission and can increase up to 71% during ICU stay, suggesting rapid depletion of this vitamin.[69,70] Based on limited data, no association was detected between thiamine levels, markers of oxidative stress and mortality.[70,71]

In one study, a significant negative correlation was reported between thiamine and lactic acid levels in patients with sepsis without liver dysfunction.[69] In a pilot randomized controlled trial (RCT) of patients with septic shock ($n = 88$), the administration of thiamine (200 mg twice a day for 7 days) reduced lactate levels and improved mortality over time in a pre-defined subgroup of patients with thiamine deficiency (35% of cohort).[72] In a retrospective, single-center, matched cohort study, administration of thiamine within 24 hours of septic shock ($n = 123$) was associated with improved likelihood of lactate clearance and a reduction in 28-day mortality.[73] In a randomized study of patient undergoing gastrointestinal surgery, thiamine administration (200 mg/ daily for 3 days) was associated with significant reduction in post-operative delirium.[74]

It should be noted that the increased secretion of IL-17 by TH17 cells contributes to the proinflammatory cytokine storm characteristic of COVID-19.[75] In an ex-vivo study, Vatsalya et al demonstrated that 200 mg thiamine/day decreased TH17 cell activation.[76]

Given these promising results and favorable safety profile, the MATH+ protocol included thiamine supplementation as part of the combination therapy in critically ill COVID-19 patients.

Anticoagulation and COVID-19

From the earliest clinical experiences caring for COVID-19 patients, physician reports of excess clotting emerged from China and Italy.[77-79] Infections are recognized activators of inflammatory and coagulation responses as part of the host defense, and in COVID-19, although patients present with prominent elevation of D-dimer and fibrin/fibrinogen degradation products as is typically seen in traditional disseminated intravascular coagulation DIC, either little or no abnormalities in prothrombin time (PT), partial thromboplastin time (PTT), and platelet counts are seen initially.[77] The term COVID-19 Associated Coagulopathy (CAC) was created to describe these abnormalities in tests although typical impaired clotting that results in increased bleeding is not observed.[77] Conversely, nearly all published clinical reports describe CAC as a "hypercoagulable" condition.

Thromboelastography (TEG) has best elucidated the hypercoagulable nature of CAC given its ability to assess both the pro-thrombotic and hypocoagulable dynamics of whole blood as it forms clot under conditions of low shear stress. A group including one of the authors (PK) recently published a case series of TEG studies from the first wave of COVID-19 patients encountered which consistently revealed hypercoagulability with rapid and large amplitudes of clot formation with little to no fibrinolytic activity present.[80,81] These early insights, along with the large amount of subsequent investigations reviewed below, served as an initial basis for the more aggressive anti-coagulation regimen incorporated within MATH+.

Given that investigations into CAC found severe hypercoagulability, it is unsurprising that the majority of published data report a higher than previously reported frequency of clotting in critically ill COVID-19 patients despite receiving thromboprophylaxis. Helms et al.[82] from France reported an incidence

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of 16.7% of VTE (mainly pulmonary embolism) in their COVID-19 respiratory failure patients; an incidence 6-fold higher than a matched population of non-COVID ARDS patients treated a year prior. Equally alarming, 96.6% of patients on continuous renal replacement therapy developed circuit clotting. In 2 studies from Holland the incidence of VTE in ICU patients was up to one third by day 7 and greater than 50% after day 14.[72,79]

In a lower extremity ultrasound screening study of an ICU population with 2/3 on systemic anticoagulation (AC) and 1/3 on thromboprophylaxis, VTE was found in 69% of the patients, with a 100% incidence in those on prophylaxis and 56% in patients on AC.[83] The VTE rates reported in the above ICU populations of COVID-19 patients are magnitudes higher than the approximate 8% rate of VTE reported in previous studies of non-COVID-19 ICU patients receiving thromboprophylaxis.[84]

In contrast to COVID-19 ICU patients, the rates of VTE in COVID-19 hospitalized ward patients have been lower. Middeldorp reported a cumulative 9.2% incidence of VTE, similar to pre-COVID-19 incidences in non-ICU patients, however another study found a cumulative incidence of 27% with 4% arterial thrombosis resulting in a composite incidence of 29%.[85,86] However, not all studies of hospital ward patients found such high incidences, for instance Lodigiani et al[87] reported a 6.6% incidence in this population while Cattaneo et al found that in a population of 388 COVID-19 patients, 64 of whom underwent screening leg ultrasound, no patient developed VTE.[88]

In regard to PE incidences alone, a recent systematic review of PE prevalence in COVID-19 analyzed 52 studies which included 20,523 patients and reported a markedly increased pooled prevalence of 9% in non-ICU patients and 19% among ICU patients.[89]

In addition to the markedly elevated incidence of "macrovascular" thrombosis, autopsies have also revealed extensive microvascular thromboses, with one report finding severe endothelial injury associated with the presence of intracellular virus and disrupted cell membranes and widespread thrombosis with microangiopathy.[90] Another found that alveolar capillary microthrombi were 9 times as prevalent in COVID-19 patients than patients with influenza ($p < 0.001$).[91] Microvascular thrombosis is also a prominent feature in multiple organs, in some cases despite full anticoagulation and regardless of timing of the disease course, suggesting that it plays an early role in causing illness.[92] A recent autopsy series found that in 17 of 25 examined lungs, intravascular fibrin thrombi were found within medium sized arteries or arterioles while in 23 of the 25, platelet aggregates and/or thrombi were found in medium sized arteries, arterioles and capillaries.[93] Even more worrisome were the brain findings where a widespread presence of microthrombi and acute infarction was observed in 6 of 20 cases. In 2 of the cases with clinical infarction there was global anoxic brain injury. Further, in a recent systematic review examining the incidence of stroke in COVID-19, the proportion of COVID-19 patients with stroke (1.8%, 95%CI 0.9-3.7%) was 8x higher than that reported among hospitalized patients with influenza (0.2%).[94] More concerning was the suggestion that these estimates were almost certainly a gross underestimate due to; 1) missed stroke diagnoses in those not extubated and who died, 2) the restrictions on and therefore lack of autopsies, and 3) the well-recognized drop in the number of patients with acute cerebrovascular symptoms seeking medical attention in the COVID-19 era.

Given such high and devastating incidences of macro and micro-vascular thrombosis in multiple organs among COVID-19 patients, a major clinical question is whether anti-coagulant therapy can improve the outcomes of COVID-19 patients. Tang first reported on 449 patients with "severe" COVID-19 and found that low-molecular weight heparin (LMWH), the majority of the time in prophylactic doses, was associated with a large mortality benefit in the sub-group of patients meeting sepsis-induced coagulopathy score ≥ 4 (40.0% vs 64.2%, $P = 0.029$), or D-dimer > 6 fold of upper limit of normal (32.8% vs 52.4%, $P = 0.017$).[95] A large study from Mt. Sinai in New York City on 2,777 patients reported a mortality of 29.1% in those treated with therapeutic AC compared to 62.7% who did not receive treatment dose.[96] Another study found that among 49 mechanically ventilated patients, 33% were diagnosed with PE and that the use of high intensity thromboprophylaxis was associated with a lower occurrence of PE (2/18; 11%) than a standard regimen (11/22; 50%—OR 0.13 [0.02-0.69]; p = .02).[97]

A retrospective study of 468 hospitalized patients also found that the initial use of high intensity thromboprophylaxis was associated with improved 30 day mortality (adjusted RR 0.26; 95% CI,.0.07-0.97; p = .04) without a significant increase of bleeding.[98] The now largest cohort study of 4,389 patients found that both prophylactic and therapeutic anticoagulation were associated with an absolute decrease of in-hospital mortality and intubation by almost 50% and 30% respectively.[99] Among the sub-group of patients (n = 1860) initiated on AC within 48 hours of admission, therapeutic AC was associated with lower in-hospital mortality than prophylactic AC, although the difference was not statistically significant (aHR 0.86; 95% CI 0.73-1.02; p = .08). Interestingly, rates of major bleeding were similar on therapeutic AC (27/900, 3.0%) as compared to patients on prophylactic AC (33/1959, 1.7%) and no AC (29/1530, 1.9%). Jonmarker et al compared the outcomes of COVID-19 ICU patients treated with standard, intermediate, and full dose anti-coagulation.[100] They found that mortality was lower in high dose (13.5%) vs medium dose (25.0%) and low dose thromboprophylaxis (38.8%) groups, p = 0.02.

The first RCT comparing therapeutic AC to standard thromboprophylaxis in COVID-19 ICU patients on mechanical ventilation (HESACOVID) was recently published, and although small, reported statistically significant improvements in oxygenation, liberation from mechanical ventilation (hazard ratio: 4.0 [95% CI 1.035–15.053], p = 0.031), and ventilator-free days (15 days [IQR 6–16] versus 0 days [IQR 0–11], p = 0.028) in patients treated with therapeutic doses of AC.[101]

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Although it is encouraging that the initial MATH+ protocol-recommended treatment dose AC for COVID-19 ICU patients has now been strongly associated with improved survival, what is worrisome are the multiple reports of "coagulation failure" in which severe thrombotic complications occurred in COVID-19 patients despite therapeutic AC.[83,85,102] A possible explanation for this phenomena was provided by Maier et al, where they used capillary viscometry in 15 severely ill COVID-19 ICU patients, almost all in ARDS, and found that all patients had a blood viscosity exceeding 95% of normal, a condition they termed "COVID-19 associated hyperviscosity."[103] The 4 patients with the highest viscosity all suffered thrombotic complications despite the majority of patients having been on either systemic AC or intermediate dose prophylaxis. Given that hyperviscosity is thought due to increased plasma proteins such as fibrinogen or immunoglobulin which then damage endothelium, this suggests that therapeutic plasma exchange (TPE) may play a role.[104] The growing body of evidence strongly supporting the role of TPE in COVID-19 is reviewed below in the section "Salvage Therapy."

To the best of our knowledge, no major national or international medical society to date has recommended therapeutic AC be administered as standard practice in any sub-group of COVID-19 patients. Many have instead recommended standard thromboprophylaxis for all hospitalized patients with COVID-19 while also avoiding a recommendation for even high-intensity thromboprophylaxis. This therapeutic conservatism is puzzling, given that, *based on the best available evidence to date*, the incidence and risks of the now well-described severe hypercoagulability appear to far outweigh the risks of even a slightly more aggressive anticoagulation regimen, based on the large magnitude of survival associated with therapy and the paucity of reports of significantly increased bleeding complications.[95,96] Thus we believe that, in hospitalized patients, an aggressive thromboprophylaxis regimen is warranted while in critically ill patients, therapeutic dose AC be administered unless specifically contra-indicated.

The "intermediate" dose thromboprophylaxis we recommend in hospital ward patients is based on pharmacokinetic and anti-Xa level monitoring studies and suggest use of weight-based prophylaxis with 0.5 mg/kg twice daily of low-molecular weight heparin (LMWH).[105]

In ICU patients, we recommend treatment dose AC be provided using 1mg/kg LMWH twice daily. Further, we recommend monitoring of Anti-Xa levels aiming for an anti-Xa activity of 0.6-1.1 IU/ml due to reports that heparin resistance appears to be common in COVID-19.[106] In addition, due to augmented renal clearance, COVID-19 patients may have reduced anti-Xa activity despite standard dosages of LMWH.[107]

Melatonin and COVID-19

Melatonin (*N*-acetyl-5-methoxytryptamine) is synthesized from tryptophan in the pineal gland and in the mitochondria of almost all cells in the body.[108] Melatonin is released from the pineal gland into the systemic circulation, achieving plasma concentration between 80 and 120 pg/mL at night and 10–20 pg/mL during the day. Melatonin binds to 2 receptor subtypes: MT1 and MT2.[109] The melatonin receptors are G-protein coupled receptors (GPCRs) which both activate and inhibit a constellation of intracellular signaling pathways.

In addition to its role in regulating the circadian rhythm, melatonin is a potent antioxidant and immune regulator that controls both the innate and adaptive immune response[108,110] The anti-oxidative effect of melatonin cooperates with its anti-inflammatory actions by up-regulating anti-oxidative enzymes (e.g. superoxide dismutase), down-regulating pro-oxidative enzymes (e.g. nitric oxide synthase), and by interacting directly with free radicals, functioning as free radical scavenger.[108,111] Melatonin plays an important role in protecting the mitochondria from oxidative injury, thereby playing a critical role in maintaining energy production.[108] Melatonin has significant anti-inflammatory, anti-apoptotic properties, anti NF-κB activation and has been demonstrated to reduce pro-inflammatory cytokines levels.[112-115]

Melatonin levels falls off dramatically after age 40; these are also the patients at highest risk of developing COVID-19 and from dying from the disease.[116,117]

SARS-CoV-2 induced endothelial dysfunction is initiated by increases in the phosphorylation levels of JAK2 and STAT3, producing increased amounts of reactive oxygen species.[118] These changes can be reversed by administration of melatonin by abating the production of superoxide anion, hydrogen peroxide and peroxynitrite.[112] The clinical utility of melatonin in COVID-19 was first demonstrated in a large prospective registry created to identify risk factors for the development of a positive SARS-CoV-2 test.[16] Researchers found that the most potentially impactful intervention to lower risk of testing positive were if patients were taking melatonin, paroxetine, or carvedilol, all medications that had been previously identified in drug-repurposing studies to have specific activity and potential benefit against SARS-CoV-2.[16,115]

Oral melatonin use by humans is exceedingly safe, with only minor side effects such as headache and drowsiness. The lethal dose 50 (LD 50) of melatonin is reported to be infinity; i.e. it is impossible to administer a large enough dose of melatonin to kill an animal. It should be noted that there is marked variability in first-pass hepatic metabolism, resulting in marked unpredictability in serum levels.[116] Furthermore, the optimal dose of melatonin in "healthy individuals" and those with inflammatory disorders is unknown. For patients with COVID-19 we suggest a dose of between 6-12 mg, taken at night.[112] However, a dose of up to 400 mg has been suggested.[114]

Zinc and COVID-19

Zinc likely has an important role in the prophylaxis of COVID-19, in the treatment of the early symptomatic phase, and in limiting the immune dysregulation and associated cytokine

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storm in the pulmonary phase.[119] Zinc is a nutritionally fundamental trace element and is the second most abundant trace metal in the human body after iron. Since zinc does not have a major storage depot in the body, zinc deficiency is easily and rapidly produced. It should be recognized that the same dietary factors leading to deficiency of zinc frequently result in the deficiency of other micronutrients. Zinc plays an important role in the host's anti-viral (and antibacterial) immune response. In addition, zinc is directly viricidal. Zinc is a component of over 1000 transcription factors, including DNA binding proteins and is required in over 300 metalloenzymes. Zinc plays a central role in cellular differentiation and proliferation, and its deficiency causes impaired immune response, increased susceptibility to infections and impaired wound healing.[120,121] Zinc is necessary for optimal functioning of both innate and adaptive immunity. Zinc status strongly affects T- and B-lymphocyte function and antibody formation.[120] Impaired immune function due to inadequate zinc status may be the most common cause of secondary immunodeficiency in humans. Zinc deficiency is an important public health problem affecting 2 billion people worldwide, including a considerable proportion of the Western population.[120,121-123] Zinc levels are reported to be very low in critically ill patients, particularly those with sepsis and acute respiratory failure.[124-126] Low zinc levels have been reported to be associated with recurrent infections and increased hospital mortality.[127] In addition, zinc deficiency has been demonstrated to potentiate ventilator induced lung injury.[128]

Previous studies have demonstrated the benefit of zinc supplementation in viral infections, most notably upper respiratory tract infections. Meta-analyses of RCTS have demonstrated that Zinc lozenges at a dose of $\geq$ 75mg/day (elemental zinc) administered within 24 hours of onset of symptoms and taken for at least 5 days significantly reduced the duration of common cold symptoms, school absence and the use of antibiotic.[129,130] Trials of low dose zinc lozenges (<75 mg/day zinc) found no effect on the duration of colds. However, when combined with vitamin C, low dose zinc was reported to reduce the duration of symptoms of the common cold.[123] When used prophylactically for at least 5 months zinc lozenges at a dose $\geq$ 75mg/day reduced the risk of developing a common cold. Zinc supplementation of nursing home elderly patients was reported to reduce the incidence of pneumonia.[131] Adverse events of Zinc lozenges include a bad taste and increased incidence of nausea.

Te Velthuis and colleagues demonstrated that zinc together with the zinc ionophore pyrithione inhibited the activity of the SARS-Co-V RNA dependent RNA polymerase blocking viral replication in a cell culture.[132] It should be noted that both hydroxychloroquine and the plant phytochemical quercetin are Zinc ionophores.[133,134] However, the role of zinc with or without the addition of zinc ionophores in the treatment of COVID-19 remains speculative.[135]

Vitamin D and COVID-19

Vitamin D is obtained via the diet or produced in the skin by UVB light. Aside from its known role in calcium metabolism and bone health it also has important roles in the immune system including support of endothelial barriers, and innate and adaptive immunity.[136] The innate immune system in COVID-19 produces both pro-inflammatory and anti-inflammatory cytokines while vitamin D reduces the production of pro-inflammatory Th1 cytokines such as tumor necrosis factor α and interferon γ and increase the expression of anti-inflammatory cytokines by macrophages.[137-139]

Given it's important roles in immune function, many have hypothesized that vitamin D deficiency increases susceptibility to infections and that supplementation may improve outcomes, particularly in COVID-19.[140,141] Data supportive of the theory that deficiency leads to infections largely rest on the fact that seasonal influenza infections generally peak in conjunction with times of the year when 25(OH)D concentrations are lowest.[142] Further, the onset of the epidemic and higher case load in countries during the winter season also raises the possible association with low vitamin D status.[143] Rhodes et al[144] first identified this link by comparing the mortality of COVID-19 in relation to country latitude and found that, even after adjusting for age, there was a 4.4% increase in mortality for each degree latitude north of 28 degrees. Further, ethnic minorities in both the United States and the United Kingdom have high rates of Vitamin D deficiency, potentially explaining why the mortality rates in these populations are much higher. Recently, strong evidence supporting a prophylactic role of Vitamin D supplementation in COVID-19 comes from a large observational analysis of de-identified tests from a national laboratory which included over 190,000 patients from all 50 states. They analyzed SARS-CoV-2 test results among patients with a Vitamin D level drawn at some point in the previous 12 months. The SARS-CoV-2 positive test rates among 3 Vitamin D range levels were as follows: 12.5% if "deficient" (<20 ng/ml), 8.1% if "adequate" (30-34ng/ml), and 5.9% if the level was above 55ng/ml.[145]

Given the strong associations of Vitamin D deficiency with higher rates of viral infections, multiple studies have tested whether vitamin D supplementation can reduce this risk. Although studies have conflicted in their findings, a recent meta-analysis from 2018 found that regular supplementation with vitamin D decreased the risk of acute respiratory tract infections, with the most profound effects in patients with severe vitamin D deficiency.[146]

The risk of Vitamin D insufficiency and the benefits of pre-illness supplementation were most recently highlighted in a Iranian study of 235 patients with Vitamin D levels measured on admission.[147] They found that of the patients with severe COVID-19, 67.2% had vitamin D insufficiency. Further, the mortality rates of patients over 40 with and without sufficient Vitamin D was 9.7% vs. 20%, suggesting that vitamin D serves an important role in modulating the immune response.

In the ICU, vitamin D deficiency is common and levels decrease rapidly after admission.[148,149] Further, deficiency has strong negative correlations with outcomes, namely higher mortality.[150,151] Multiple, initial studies of Vitamin D supplementation in critically ill populations were conducted and

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included in a 2017 meta-analysis that found a statistically significant effect in reducing mortality.[152,153] However, more recently, the results of a large, prospective, multi-national, double blind, placebo controlled trial (VIOLET) on the effects of cholecalciferol supplementation in Vitamin D deficient critically ill patients was published.[154] The study results, surprisingly, were profoundly negative in that no benefits were found of giving a large single dose supplement given around the time of admission into the ICU. Further, no benefits were found in any individual sub-group, even among those with more severe illness or with more severe deficiency.

Although the findings of the VIOLET trial strongly suggest that Vitamin D supplementation alone has no benefit as an intervention in the critically ill, our inclusion of Vitamin D in COVID-19 treatment, aside from the evidence suggesting the possibility of a more potent therapeutic role in both viral syndromes and COVID-19 (likely few patients with viral syndromes were included in the VIOLET study), is largely based on the therapeutic enhancement of corticosteroid effect when co-administered with Vitamin D, similar to the synergistic effects of corticosteroids with Vitamin C.[155] Investigators have demonstrated that Vitamin D up-regulates glucocorticoid receptors which leads to increased T-cell apoptosis while it can also enhance the corticosteroid effect on and suppression of cytokine production in peripheral blood cell monocytes.[156-158]

Recently, in a pilot RCT of Vitamin D therapy in hospitalized COVID-19 patients using calcifediol, the direct precursor to the active form of Vitamin D in the serum, patients were treated on the day of admission with an oral dose of 0.532 mg (roughly equivalent in potency to a dose of 68,000 IU of Vitamin D_3), then they gave half the dose on day 3, day 7, and weekly thereafter. They found that of the 50 patients treated with calcifediol, one required admission to the ICU (2%) while of 26 untreated patients, 13 required admission to the ICU (50%), $p < .001$, OR 0.02 [0.002-0.17].[14] None of the treated patients died while 2 control group patients died. The authors concluded that calcifediol seems to reduce the severity of the disease, but larger trials will be required to provide a more definitive answer.

Thus, available data suggest that high-dose vitamin D supplementation is beneficial not only in the prevention of viral infections but also in COVID-19 and in improving the effects of corticosteroid therapy.

Although the impact of supplementation varies by deficiency status as well as severity of illness, vitamin D supplementation is safe: one meta-analysis of healthy patients found no adverse events, while in the critically ill, mild hypercalcemia was the most common adverse effect.[146,159]

Serum levels greater than 50 nmol/L (20ng/mL) are thought sufficient for protection against acute respiratory tract infections.[146] It should be noted that the predominant form of supplementation in North America is Vitamin D2 (ergocalciferol) and in Europe it is Vitamin D3 (cholecalciferol), although the dosing is the same. One report found that "doses up to 10,000 IU/day is safe, although well above what is needed" and that "only 1,000-2,000 IU may be needed to obtain optimal effects on bone and immunity."[160] Thus to reduce the risk of infection, one expert recommended that people at risk of COVID-19 consider taking 10,000 IU/day of vitamin D3 for a few weeks to rapidly raise 25(OH)D concentrations, followed by 5000 IU/d. The goal should be to raise 25(OH)D concentrations above 40–60 ng/mL (100–150 nmol/L).[160]

In the critically ill, the doses used from published RCT's ranged from 200,000-600,000 IU of Vitamin D3, generally in a single enteral dose.[152,161,162] Based on the Castillo et al trial of calcifediol in COVID-19, in hospitalized patients, we recommend either the same doses of calcifediol be used or the equivalent doses with cholecalciferol. In the ICU, we favor a single large dose of 480,000 IU (30 ml) similar to the prior ICU trials above (Table 1). The Vitamin D level should then be rechecked on day 5, if <20 ng/ml, a supplemental dose of 96,000 IU/day for 5 days should be given.

Statin Therapy and Covid-19

Statins are medicines that lower lipid levels but also have multiple anti-inflammatory actions. Over a decade of observational studies, both matched and non-matched showed largely consistent benefits in patients with sepsis and/or ARDS.[163] Multiple randomized controlled trials were then conducted using various statins and doses, however, in a well-conducted meta-analysis of RCT's in sepsis involving 2628 patients, no difference in mortality between groups was found.[164] Similarly, in ARDS trials, a meta-analysis from 2016 found no difference in important outcomes.[165] However, in an editorial that reviewed the outcomes from the STATInS and HARP-2 trials, they found that an alteration of just 3 events would have yielded statistically significant results in favor of statin use based on mortality outcomes.[166-168] This low "fragility index" suggests that benefits in subgroups exist but are then "lost" in the heterogenous populations that are often included in RCT's of critical illness syndromes such as ARDS and sepsis. This hypothesis was seemingly validated by a secondary analysis of the HARP-2 trial in which the authors split patients into 2 phenotypes of ARDS, a "hyperinflammatory" and "hypoinflammatory" type.[169] The hyperinflammatory group had higher values of sTNFr-1 and IL-6, lower platelet counts, more vasopressor use, fewer ventilator free days and much higher 28-day mortality. When the hyperinflammatory phenotype received simvastatin 80 mg, a large and statistically significant reduction in mortality was found. Further, in COVID-19, 2 retrospective studies have demonstrated a strong association of statin use with survival. In a large study of 13,981 patients in China, among which 1,219 received statins, the all-cause mortality was almost halved in the statin treated patients (HR = .58, (95% CI, 0.43-0.80, p = .001).[13] In a smaller study in the US, one group found that among a group of 88 patients, 55% of whom died, atorvastatin use was associated with a 73% lower risk of progression to death (aHR 0.38 (95% CI 0.18-0.77, p = .008).[170] Thus, given the frequent hyperinflammation and elevated levels of IL-6 in COVID-19 respiratory failure, it appears reasonable to employ statin therapy. Atorvastatin is favored

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due to its more favorable drug-interaction profile and a higher dose of 80 mg should be used, similar to the HARP-2 trial.

Famotidine and COVID-19

Famotidine, a histamine-2 receptor antagonist (H2RA), although commonly used to suppress acid production in the stomach, is also known to have in-vitro properties which not only inhibit viral replication such as in HIV but also exert stimulatory effects on almost all immune cells of the innate and adaptive immune system.[171] It can also prevent H2 R cytokine inhibition and prevent inhibition by histamine on Th-1 cytokine release.[172,173]

H2RA's have proven effective in the past against other viruses. Cimetidine, and less so famotidine exhibited reduced viral infection with HIV in vitro, increased the clearance of warts caused by human papilloma virus, and appeared effective in improving the symptoms associated with chronic Epstein-Barr virus infection.[174-176] In fact, ranitidine bismuth citrate effectively inhibited the nucleoside triphosphate hydrolase and DNA unwinding activities of the SARS coronavirus helicase and dramatically reduced its replication levels in infected cells.[177]

Given prior evidence of anti-viral, and in particular anti-SARS-CoV and immune system effects, Freedberg et al performed a retrospective cohort study using propensity score matching in COVID-19 patients at a single medical center. The treatment group all received famotidine within 24 hours of admission. 1620 patients were included with 81 having received famotidine. They found that the use of famotidine was associated with a large reduced risk for death or intubation (adjusted hazard ratio (aHR) 0.42, 95% CI 0.21-0.85) and also with reduced risk for death alone (aHR 0.30, 95% CI 0.11-0.80).[178] An interesting associated finding was that in patients on proton pump inhibitors, no reduced risk for any patient outcomes was observed. Although an observational study, propensity score matching was performed between groups, and a large difference in intubation and death was observed. Although such a study should be strictly be considered as hypothesis generating only with the need for an RCT to optimally validate, in the interim, given the biologic plausibility, prior efficacy against other viruses along with a well-known safety profile, low cost, high availability and potentially large associated reduction in mortality, use of famotidine in the treatment of COVID-19 appears reasonable. Doses used in the Freedberg study were 10 mg in 17%, 20 mg in 47%, and 40 mg in 35% with a median of 5.8 days of use.[178]

Management of Respiratory Failure

Although a comprehensive review of the optimal support of oxygenation and ventilation in COVID-19 respiratory failure is beyond the scope of this manuscript, several key physiologic insights should be recognized.

Early publications quickly highlighted the puzzling discordance between the degree of hypoxemia and modest work of breathing observed in COVID-19 patients, describing it as "silent hypoxemia" and such patients as "happy hypoxemics."[179,180] Similarly, soon after mechanical ventilation was instituted, unexpectedly high degrees of lung compliance in conjunction with severe hypoxemia was deemed a new "L" phenotype. Although reasons for lack of dyspnea are multiple, the largest contributors are; 1) early COVID-19 is an "organizing pneumonia" representing a cellular infiltration into the alveoli and ducts rather than alveolar fluid accumulation/edema as in classic ARDS making the lung "dry and light" versus "heavy and fluid-filled" and thus leads to less energy work to inflate and counter-act de-recruitment, 2) the as yet unexplained, paradoxical hyperperfusion of the foci of organizing pneumonia suggesting a failure of typical hypoxic pulmonary vasoconstriction and causing disproportionate hypoxemia (Figure 2), and 3) the likely early and extensive micro and/or macrovascular clotting not detected on routine imaging studies.[8,181,182]

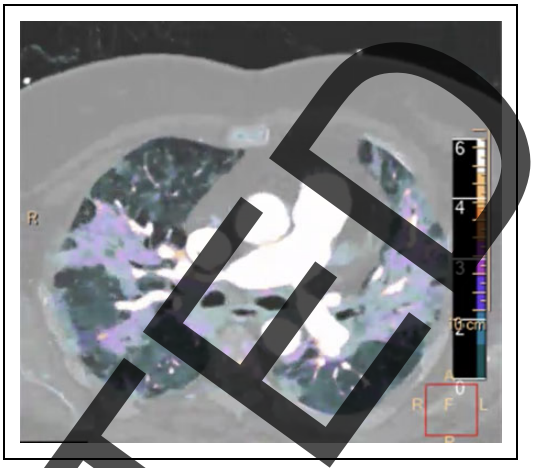

Figure 2. Spectral CT image with contrast in a COVID-19 patient. Markedly increased iodine uptake is seen (color scale on right of image), indicating increased perfusion to the ground glass opacities.

These differences from "traditional ARDS" were unfortunately both widely minimized and overlooked as evidenced by frequent recommendations for "early intubation" in what was an unfounded fear of the mechanically well-tolerated hypoxemia. Such approaches likely contributed to not only the unacceptably high mortality first reported but also the widespread shortages of ventilators, ICU beds, ventilators, nurses and medications in some of the earliest hard-hit areas. Such approaches curiously departed from the long held therapeutic principle of instituting mechanical ventilation, "neither too early, nor too late," with decisions to intubate resting upon an assessment of the patients work of breathing WOB) and their ability to sustain that work rather than solely on a presumed necessary level of oxygen saturation. When WOB is felt excessive or unsustainable despite non-invasive modes, then and only then should initiation of invasive mechanical support be pursued. Our recommended strategy for COVID-19 respiratory failure is

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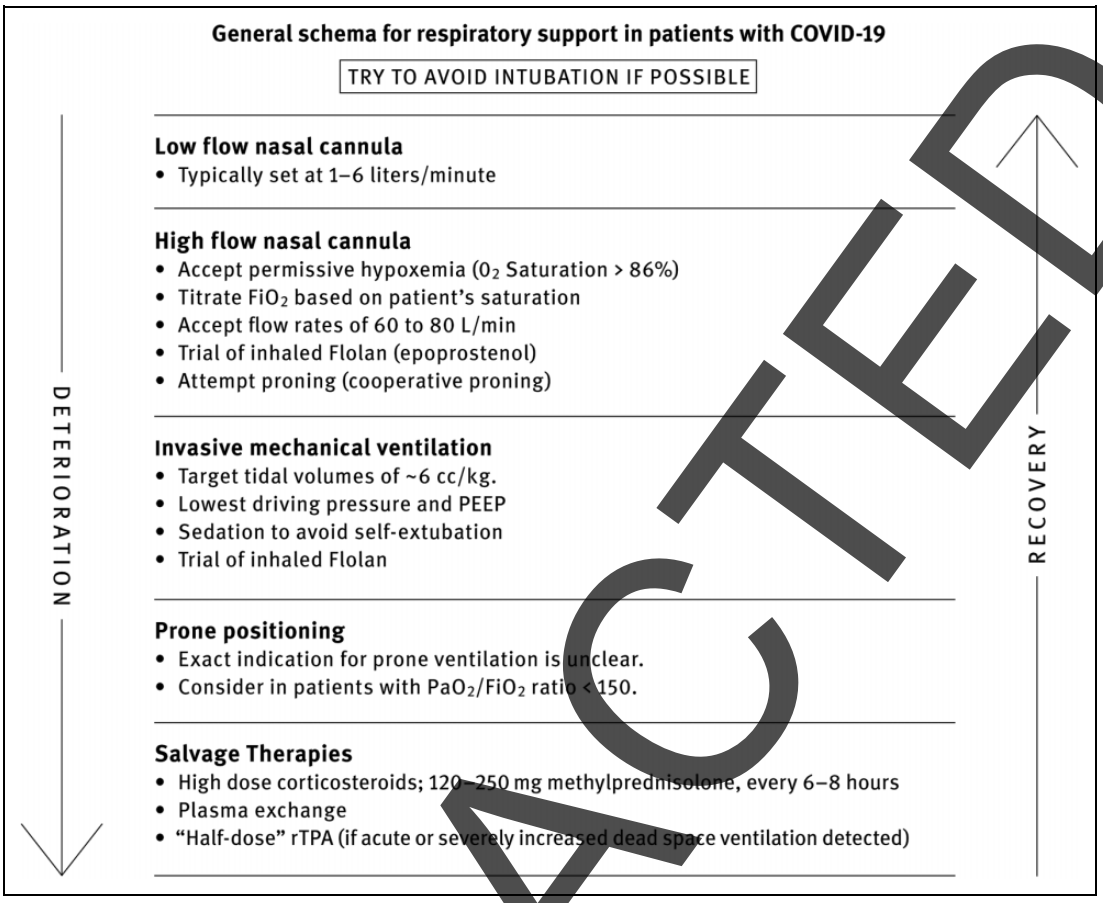

Figure 3. Therapeutic Approach to Hypoxemia and Respiratory Failure in COVID-19.

illustrated in Figure 3. With similar approaches, many centers quickly learned that adopting a such a primary focus on the support of oxygenation using non-invasive means and methods (self-proning) led to less need for ventilators and ICU beds with improved outcomes.

Salvage Therapy

It has become increasingly recognized that the pathophysiologic mechanisms leading to hospitalization in COVID-19 occur in phases (Figure 4) and are largely driven by the systemic host response phase rather than the cytopathic viral replicative phase.[183] Since the host response is now understood as a complex interaction of inflammation, endotheliopathy, cytokine storm, and hypercoagulability, some have argued that therapeutic plasma exchange could offer unique benefits by removing cytokines, stabilizing endothelial membranes, and reversing the hypercoagulable state.[184]

In several of the authors clinical experiences, they have encountered a subset of patients who have failed to respond physiologically to the combined therapies that make up the MATH+ protocol, largely thought secondary to advanced disease at the time of presentation or extensive co-morbidity. In the first such cases, therapeutic plasma exchange (TPE) was trialed with temporally associated physiologic improvements observed which then led to both extubation and discharge. In 2 of the authors experiences (PEM, PK), at the time of this writing, they encountered a total of 16 patients that demonstrated little physiologic improvement despite being treated with high-dose MATH+ protocol who were then empirically treated with TPE. 13 of the 16 were extubated and discharged while 3 failed to respond and later died. Increasing publications of case series and case reports from centers across the world have now described the efficacy of TPE in over 60 COVID-19 patients that did not respond to initial therapies, with the majority having been treated with corticosteroids.[185-195] Nearly all describe similar positive physiologic and clinical responses temporally associated with initiation or completion of TPE. Further, 3 retrospective, observational cohort studies including a total of 74 patients treated with plasmapheresis have reported dramatic differences in both extubation and survival.[104,196,197] The largest, a study from Pakistan of 45 COVID-19 patients treated with plasmapheresis compared to 45 propensity matched controls, reported that the mortality in the plasmapheresis treated group was 8.9% vs 38.5% in controls, HR 0.21, 95% CI 0.09-0.53, log rank .002.[197] Khamis et al in Oman published on 31

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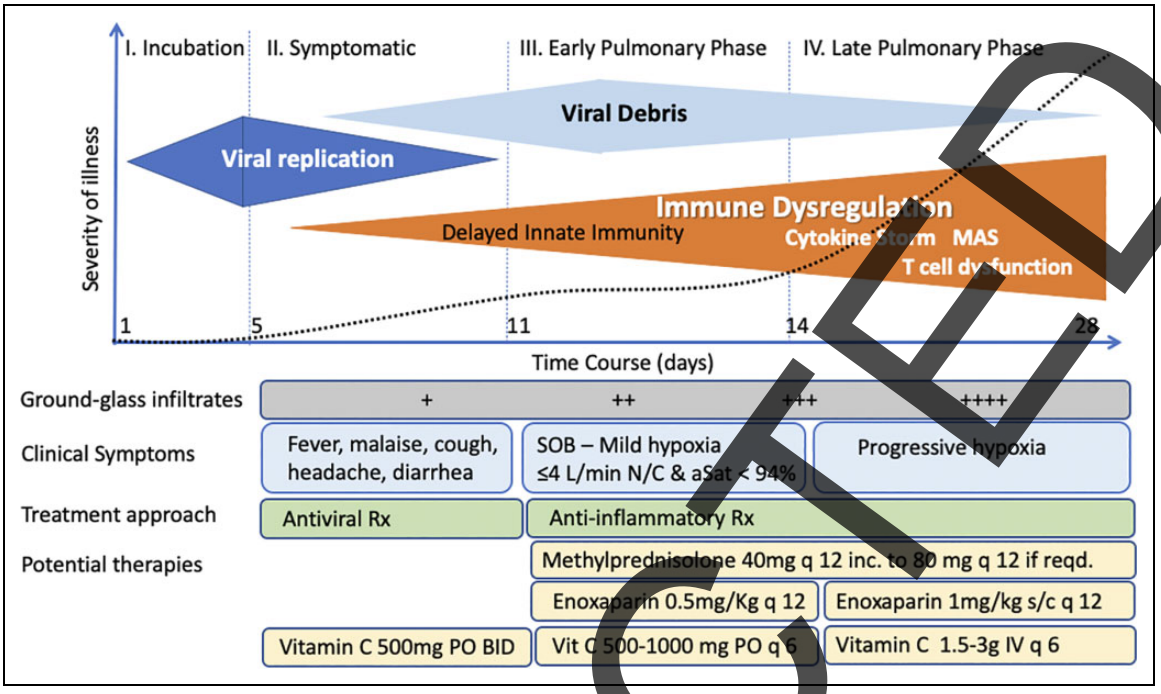

Figure 4. Phases of COVID-19 Illness.

Table 2. Comparison of MATH+ Center Outcomes With Published Hospital Mortality in COVID-19.

Author		Country	Number of hospitalized patients	Data collection end date	Hospital or 28 day mortality (%)	Number of hospitals
Docherty [a]		UK	20,133	4-19-20	26.0	208
Richardson [b]		USA	2,634	4-1-20	21.0	12
Horby [c]		UK	6,425	6-8-20	22.9	176
Rosenberg [d]		USA	1,438	4-24-20	20.3	25
Arshad [e]		USA	2,541	5-2-20	18.1	6
Myers [f]		USA	377	3-31-20	15.6	21
Mikami [g]		USA	3,708	4-17-20	21.7	8
Vizcaychipi [h]		UK	923	4-22-20	32.0	2
Zhou [i]		China	191	1-31-20	28.3	2
Wu [j]		China	201	2-13-20	26.4	1
MATH+ hospitals	(A)	USA	140	7-20-20	4.4*	2
	(B)		191		6.1*	

Legend: (A) United Memorial Medical Center, Houston, TX; (B) Sentara Norfolk General Hospital, Norfolk, Virginia.
*Data obtained from Hospital Chief Medical Officer.

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COVID-19 patients in moderate to severe respiratory failure where 11 of the more severely ill patients received TPE with a slightly higher proportion of the TPE group also receiving tocilizumab compared to controls.[104] They reported both large improvements in extubation rates (73% vs. 20%, p = .018) and mortality (0% vs 35%, p = .03).

Although these studies are strongly suggestive of a role for TPE in the management of COVID-19 patients unresponsive to now standard therapies such as corticosteroids, both prospective and/or randomized studies should be done to better establish the indications, duration, and efficacy of TPE.

MATH+ Protocol Hospital Mortality Outcomes and COVID-19

The MATH+ protocol (Table 1) reviewed above has been implemented in the treatment of COVID-19 patients at 2 hospitals in the United States; United Memorial Hospital in Houston, Texas (J.V) and Norfolk General Hospital in Norfolk, Virginia (P.E.M). MATH+ was systematically provided upon admission to the hospital at United Memorial while at Norfolk General, the protocol was administered upon admission to the ICU. Available hospital outcome data for COVID-19 patients treated at these 2 hospitals as of July 20, 2020 are provided in

Table 2, including comparison to the published hospital mortality rates from multiple COVID-19 publications across the United States and world. The average hospital mortality at these 2 centers in over 300 patients treated is 5.1%, which represents more than a 75% absolute risk reduction in mortality compared to the average published hospital mortality of 22.9% among COVID-19 patients. Although this is a limited comparison due to a lack of data regarding severity of illness and treatments provided, the low reported mortality at the 2 centers within a considerable sample size of patients provide supportive clinical evidence for the physiologic rationale and efficacy of the MATH+ treatment protocol. One limitation with this comparison is that the comparative studies were all published before the RECOVERY trial identified the mortality improvements with corticosteroid use, and thus, with more widespread use of corticosteroids the reported mortality from other centers may decrease over time. However, it should be noted that in the RECOVERY trial, even in the patients who benefited from corticosteroids such as those on oxygen or who required mechanical ventilation, the 28-day mortality rates were still between 20%-30% respectively, while the patients who were not on oxygen had mortality rates between 10-20% depending on whether corticosteroids were used, all higher than the centers using the MATH+ protocol.

Conclusion

In conclusion, the varied pathophysiologic mechanisms identified in COVID-19 likely require multiple therapeutic agents working in concert to counteract the diverse, deleterious consequences of this aberrant immune response. It is exceedingly unlikely that a "magic bullet" will be found, or even a medicine which would be effective at multiple stages of the disease. The Math+ treatment protocol instead offers an inexpensive combination of medicines with a well-known safety profile based on strong physiologic rationale and an increasing clinical evidence base which potentially offers a life-saving approach to the management of COVID-19 patients.

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