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PERSPECTIVE

MATH+ protocol for the treatment of SARS-CoV-2 infection: the scientific rationale

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ABSTRACT

Introduction: COVID-19 disease progresses through a number of distinct phases. The management of each phase is unique and specific. The pulmonary phase of COVID-19 is characterized by an organizing pneumonia with profound immune dysregulation, activation of clotting, and a severe microvascular injury culminating in severe hypoxemia. The core treatment strategy to manage the pulmonary phase includes the combination of methylprednisolone, ascorbic acid, thiamine, and heparin (MATH+ protocol). The rationale for the MATH+ protocol is reviewed in this paper.

Areas covered: We provide an overview on the pathophysiological changes occurring in patients with COVID-19 respiratory failure and a treatment strategy to reverse these changes thereby preventing progressive lung injury and death.

Expert opinion: While there is no single 'Silver Bullet' to cure COVID-19, we believe that the severely disturbed pathological processes leading to respiratory failure in patients with COVID-19 organizing pneumonia will respond to the combination of Methylprednisone, Ascorbic acid, Thiamine, and full anticoagulation with Heparin (MATH+ protocol).We believe that it is no longer ethically acceptable to limit management to 'supportive care' alone, in the face of effective, safe, and inexpensive medications that can effectively treat this disease and thereby reduce the risk of complications and death.

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COVID-19; methylprednisolone; ascorbic acid; heparin

1. Introduction

We are in the midst of a severe pandemic caused by the novel coronaviruses SARS-CoV-2. The virus has infected millions of individuals on all five continents of the Earth and claimed hundreds of thousands of lives. As there is no specific therapy for SARS-CoV-2, almost all professional organizations including the World Health Organization (WHO) have recommended a supportive treatment approach to patients with severe COVID-19 disease [1–3]. We argue that a number of repurposed commonly available and inexpensive medications when used in combination (MATH+ protocol) has the potential to significantly reduce the morbidity and mortality from COVID-19 disease. This paper will briefly review the rationale for using MATH+ to treat the pulmonary phase of COVID-19 disease.

One needs a good understanding of the pathophysiology of a disease to effectively treat the disease. In the middle of this pandemic, understanding the mechanisms of SARS-CoV-2-induced disease is critical in formulating a treatment strategy and ethically more sound than demanding and waiting for randomized placebo-controlled clinical trials to be completed. Furthermore, it is important to appreciate that while COVID-19 is a remarkably heterogeneous disease, patients infected with SARS-CoV-2 progress through a number of phases (or stages) and that the treatment of COVID-19 is highly specific to each phase of the disease, as illustrated in Figure 1. Clinically, the immune response induced by SARS-CoV-2 infection is two phased. During the incubation and early symptomatic stages, a specific adaptive immune response is generated which eliminates the virus and prevents disease progression to pulmonary stages. SARS-CoV-2 has a marked predilection to spread to the lower respiratory tract, in part related to the high expression of ACE-2 receptors on type II pneumocytes. The pulmonary phase is characterized by a fall in viral replication and viral load but with a marked increase in production of pro-inflammatory cytokines and progression of the ground-glass infiltrates. SARS-CoV ssRNA's have powerful immunostimulatory activities which induce high levels of the pro-inflammatory cytokines tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6), and IL-12 via toll-like receptor-7 (TLR7) and TLR8 engagement (the 'cytokine storm') [4–6]. It should be noted that while increasing the expression of inflammatory cytokines and chemokines this highly pathogenic virus downregulates the expression of type-1 interferons, the host's primary antiviral defense mechanism [5]. Low innate antiviral defenses and high pro-inflammatory mediators contribute to ongoing and progressive lung injury. In a highly detailed analysis of tissues from 11 autopsies, one group found that the presence of SARS-CoV-2 RNA and protein had little correlation with the inflammation and organ dysfunction, supporting the observations that virus-

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Article highlights

- Patients infected with SARS-CoV-2 progress through a number of phases with the treatment of COVID-19 being highly specific for each phase of the disease.
- The pulmonary phase of COVID-19 is characterized by the development of an organizing pneumonia, severe pro-inflammatory state, and activation of clotting with macro- and microvascular thrombosis and hypoxemia.
- Supportive treatment alone is no longer acceptable during the pulmonary phase of COVID-19.
- Patients who have progressed to the pulmonary phase of COVID-19 are likely to benefit from treatment with the core components of the MATH protocol, consisting of methylprednisolone, ascorbic acid, thiamine, and full anticoagulation with heparin.
- The core components of the MATH protocol are safe, reasonably inexpensive, and readily available.
- We postulate that the addition of melatonin, famotidine, vitamin D, elemental zinc, magnesium, and atorvastatin (MATH +) will potentiate the efficacy of the core MATH components.

independent immunopathology is the primary mechanism underlying fatal Covid-19 [7]. This supports the concept that it is the host's response to the SARS-CoV-2 virus, rather the virus itself that is killing the host. The role of specific anti-viral therapies in the pulmonary phase of COVID-19 would therefore appear to be limited.

In addition to generating a profound hyper-inflammatory state, SARS-CoV-2 activates the coagulation system resulting in an intense pro-coagulant state. Activation of clotting is likely multifactorial, however, damage to the endothelium with clotting activation likely plays an important role. Furthermore, cleavage of the spike protein of the SARS coronavirus by protease factor Xa was associated with activation and release of factor Xa [8]. Yuriditsky et al. demonstrated that in excess of 70% of patients with COVID-19 disease have hypercoagulable thromboelastography (TEG) profiles [9].

An understanding of the pulmonary stages of COVID-19 leads to the unambiguous and irrefutable conclusion that three related pathophysiologic processes are driving the disease process and that all three of these derangements must be treated in order to reduce the mortality and morbidity of this deadly disease. These include i) an organizing pneumonia with a dysregulated immune system with the overproduction of pro-inflammatory mediators and a severe microvascular injury, ii) a hypercoagulable state with systemic micro- and macro-vascular disease that potentiates the microvascular injury, iii) with both these processes leading to severe ventilation/perfusion mismatching leading to severe hypoxemia. The core components of the MATH+ treatment protocol target all three major pathophysiologic processes with readily available, inexpensive, and safe FDA approved interventions (see Figure 2). The medications that make up the core components of the MATH+ protocol are listed below, followed by a brief review of these medications as they apply specifically to COVID-19.

2. Core components of MATH

The core components of the MATH+ protocol include a corticosteroid (methylprednisolone), ascorbic acid (vitamin C), thiamine, anticoagulation with heparin (enoxaparin), and supplemental oxygen.

(1) ***M**ethylprednisolone* 80 mg loading dose, followed by 40 mg q 12 hourly for at least 7 days and until transferred out of ICU. In patients with an increasing C-reactive protein (CRP) or worsening clinical status increase the dose to 80 mg q 12 hourly (and then 120 mg if required), then titrate down as appropriate.

(2) ***A**scorbic acid (Vitamin C)* 3 g IV q 6 hourly for at least 7 days or until transferred out of ICU. Note caution with point-of-care (POC) glucose testing (see below).

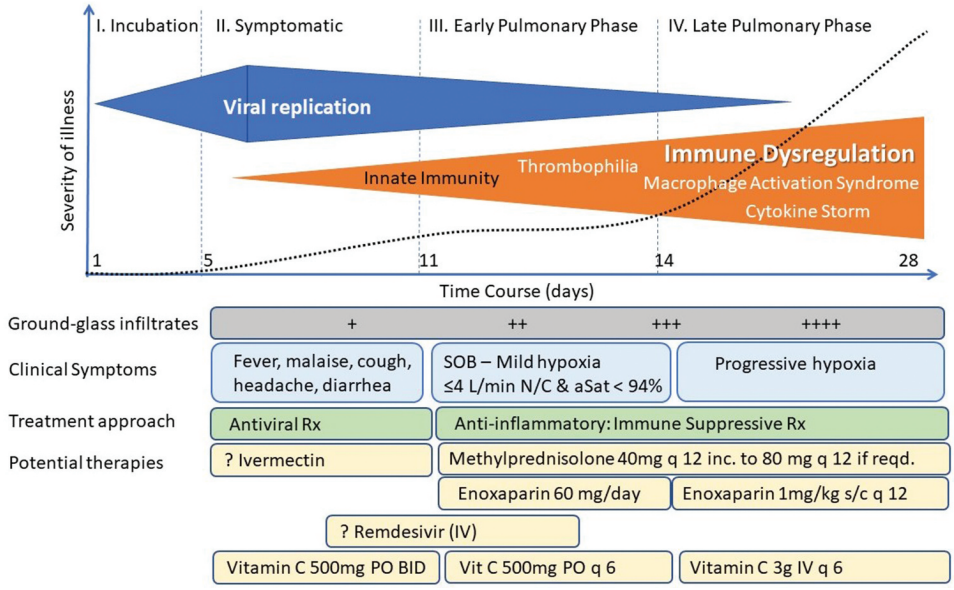

Figure 1. Typical course and stages of COVID-19 disease.

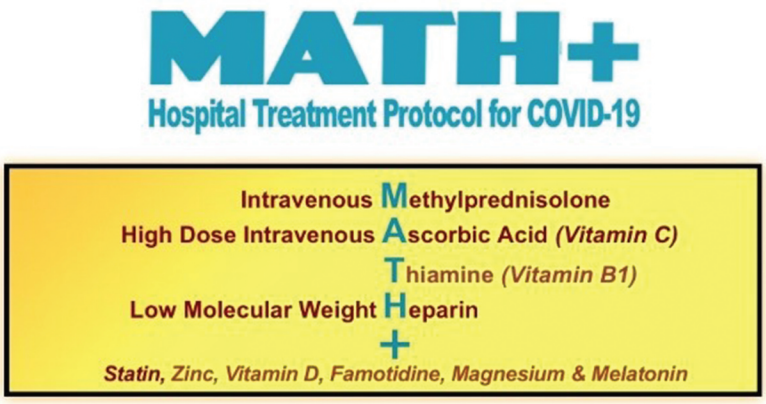

Figure 2. Outline of the MATH+ protocol.

(3) ***T**hiamine* 200 mg IV q 12 hourly for at least 7 days or until transferred out of ICU.
(4) *Heparin*: Unless contraindicated we suggest FULL anticoagulation (on admission to the ICU) with enoxaparin, i.e. 1 mg kg s/c q 12 hourly (dose adjust with CrCl < 30 ml/min). Unfractionated heparin is suggested with CrCl < 15 ml/min. Monitor anti-Xa activity in at risk patients (see below)
(5) Supplemental oxygen with high flow nasal canula with proning (cooperative repositioning) and epoprostenol as required. Intubation should be avoided if at all possible.

3. Methylprednisolone

Methylprednisolone is a potent synthetic glucocorticoid. Like all glucocorticoids, its effect is mediated by binding to the intracellular glucocorticoid receptor which then mediates the drugs genomic and non-genomic effects. The classic mechanism by which glucocorticoids suppress immune function is the activation or repression of multiple genes. This process involves several steps and the typical onset of action is four to 24 hours. The primary anti-inflammatory action of glucocorticoids is to repress a large number of pro-inflammatory genes which encode cytokines, chemokines, inflammatory enzymes, cell adhesion molecules coagulation factors and receptors. In addition, glucocorticoids inhibit a wide variety of processes that contribute to or are part of inflammation including edema formation, fibrin deposition, capillary dilation, leukocyte extravasation, and phagocytosis. Glucocorticoid receptor-mediated repression of the transcriptional activity of NF-κB and AP-1 plays a major role in mediating the anti-inflammatory actions of glucocorticoids.

Glucocorticoids effectively reverse the transcriptional activation of pro-inflammatory genes caused by SARS-CoV-2 thereby dampening the cytokine storm and associated tissue injury [10]. The unequivocal benefit of methylprednisolone in improving respiratory function, ventilator dependency, and mortality has been demonstrated in a number of observational studies [11–14]. It should be appreciated that there has been (until recently) enormous resistance on the use of glucocorticoids to treat COVID-19 organizing pneumonia. The systematic failure of critical care systems and intensivists around the world to adopt corticosteroid therapy resulted from the published recommendations against corticosteroids use by the World Health Organization (as recently as 27 May 2020) [1,15], and then perpetuated by the Centers for Disease Control and Prevention (CDC), the National Institute of Health (NIH), the American Thoracic Society (ATS), the Infectious Disease Society of America (IDSA) and the Society of Critical Care Medicine (SCCM) amongst others [2,16,17]. This flawed recommendation was based on erroneous and biased data interpretation which suggested that glucocorticoids would increase viral shedding and increase the risk of death in patients with COVID-19 [18–20]. It should however be noted that when glucocorticoids are used in the pulmonary phase (and not in the viral replicative phase) they do not appear to increase viral shedding nor impair protective immunity [12,21].

The results of the Randomized Evaluation of COVID-19 Therapy (RECOVERY) trial reversed the narrative with regards to the use of glucocorticoids in COVID-19 (results made available 16 June 2020) [22]. The RECOVERY trial randomized 2104 patients to receive dexamethasone (6 mg daily for up to 10 days); these patients were compared with 4321 patients concurrently allocated to usual care. Overall, 21.6% patient's allocated dexamethasone and 24.6% patients allocated usual care died within 28 days (rate ratio 0.83; 95% CI 0.74 to 0.92; P < 0.001). The mortality reduction was most marked in those patients receiving mechanical ventilation (29.0% vs. 40.7%, RR 0.65; 95% CI 0.51 to 0.82; p < 0.001). It should be noted that there was a trend to a worse outcome in those patients without respiratory failure who received dexamethasone (RR 1.22; 95% CI 0.93–1.61, NS); these findings are similar to studies from prior viral pandemics, where mortality was dramatically reduced in patients with moderate to severe disease while those with mild disease fared worse [23,24]. The results of the RECOVERY trial are consistent with the MATH+ protocol, in which we recommend the use of glucocorticoids only in patients with respiratory failure. Notwithstanding

the very important and impressive results of the RECOVERY study, we strongly believe that the investigators used the wrong glucocorticoid in the wrong dose.

Methylprednisolone is the glucocorticoid of choice for the pulmonary phase of COVID-19. This is based on pharmacokinetic data (better lung penetration) [25], genomic data specific for SARS-CoV-2 [10], and a long track record of successful use in inflammatory lung diseases. Furthermore, the dose of dexamethasone used in the RECOVERY study was very low (6 mg–30 mg methylprednisolone). An adequate initial loading bolus of glucocorticoid is necessary to achieve prompt elevation in plasma levels to approach maximal saturation of the glucocorticoid receptors (approximately 80 mg of methylprednisolone equivalent) in the cytoplasm and on the cell membrane for genomic and non-genomic actions [26]. This should be followed by a dose of at least 80 mg/day of methylprednisolone (best given in to divided doses) for adequate anti-inflammatory effects. In addition, the dose should be up-titrated according to clinical response and inflammatory biomarkers (namely CRP). No two patients are the same and treatment must be individualized according to each patient's response to therapy. Genomic data specific to SARS-CoV -2 demonstrates that methylprednisone is far superior to dexamethasone in reversing the alterations in gene expression of almost all of the known inflammatory mediators [10]. This finding supports the concept that different glucocorticoids have differential binding capacity to the seven isoforms of the glucocorticoid receptor, thereby mediating different genomic and non-genomic effects [27,28]. Our data (hospital mortality of 6.1%) as well as that of other groups [12] support the concept that methylprednisolone used in the correct dose for an adequate period of time will result in a greater mortality reduction than that seen in the RECOVERY trial. It is however important to stress that glucocorticoids are contraindicated in asymptomatic patients as well as during the early symptomatic phase; this drug is only indicated in patients requiring supplemental oxygen and those requiring mechanical ventilation [22].

4. Ascorbic acid

Ascorbic acid is a pleiotropic stress hormone (deficient in humans) that has important anti-inflammatory, immunomodulating, anti-oxidant, anti-thrombotic and antiviral properties [29–33]. Importantly, and with specific reference to COVID-19, ascorbic acid plays a critical role in downregulating the cytokine storm, in protecting the endothelium from oxidant injury [34,35], and as well as playing an essential role in tissue repair. Ascorbic acid enhances and potentiates the anti-inflammatory and endothelial cytoprotective effects of glucocorticoids [36]. Furthermore it should be noted that SARS-CoV -2 downregulates the expression of type-1 interferons (the hosts primary anti-viral defence mechanism) [5], while ascorbic acid upregulates these critically important host defense proteins [32]. The cumulative experience of the "Front Line Covid-19 Critical Care Alliance" (see https://flccc.net//) strongly supports the concept that ascorbic acid acts synergistically with glucocorticoids to reverse the cytokine storm and improve pulmonary function thereby dramatically reducing ventilator dependency and mortality from COVID-19. It should be noted that in patients receiving intravenous vitamin C, the Accu-Chek™ point-of-care (POC) blood glucose monitor will result in spuriously high blood glucose values [37,38]. Therefore, laboratory confirmation of blood glucose levels is recommended. There are no known contraindications to the use of "moderate dose" ascorbic acid, however the drug should be used with caution in patients with known hyper-oxalosis. Furthermore, our dosing strategy appears to be safe in patients with glucose-6-phosphate deficiency [39].

5. Thiamine

Thiamine is a water-soluble vitamin absorbed through thiamine transporter proteins in the proximal gastrointestinal tract. It exists in multiple forms through the addition of one or more phosphate groups [40]. The human adult can store around 30 mg of thiamine; these stores become rapidly depleted with decreased intake and metabolic stress; consequently, thiamine deficiency is common in critically ill patients [41–44]. Thiamine deficiency is particularly common in hospitalized elderly patients, those patients at greatest risk of developing COVID-19 [44–46]. In addition, functional thiamine deficiency is very common in patients with chronic renal failure [47]. Thiamine is the precursor of thiamine pyrophosphate (TPP), the essential coenzyme of several decarboxylases required for glucose metabolism, the Krebs cycle, the generation of ATP, the pentose-phosphate pathway, and the production of NADPH [40]. Thiamine being a co-factor of pentose-phosphate pathways, produce NADP during glutathione cycling, which, decreases reactive oxygen species, decreases microvascular dysfunction, decreases cellular apoptosis and improves endothelial dysfunction [48,49]. In addition, thiamine has anti-inflammatory effects and anti-oxidative effects, suppressing the oxidative stress-induced activation of NF-kB [48,50]. It is important to note that magnesium in an essential co-factor for TPP activity [51,52]. We suggest that the addition of thiamine to methylprednisolone, ascorbic acid and heparin will act synergistically to restore microvascular function in patients with COVID-19. In addition, thiamine is essential for cellular energy production and together with ascorbic acid and glucocorticoids may limit delirium in critically ill COVID-19 patients [53]. While the optimal dosing strategy of thiamine is unclear, based on the work of Donnino et al we suggest a dose of 200 mg IV 12 hourly for 7 day [43], followed by oral thiamine supplementation. There are no known contraindications to the use of intravenous thiamine. However, anaphylaxis is an extremely rare complication following intravenous thiamine administration [54,55].

6. Therapeutic anticoagulation in critically ill patients

As noted above, SARS-CoV-2 induces a profound procoagulant state that causes both macro- (deep venous thrombosis, pulmonary emboli, strokes) and microvascular thrombosis that contributes to the disease burden of COVID-19. Multiple studies have demonstrated that despite pharmacologic deep venous thrombosis prophylactic regimens, hospitalized patients, particularly those in the ICU with COVID-19 disease,

have an inordinately high incidence of deep vein thrombosis and other thrombotic complications [56–58]. Therapeutic dose anticoagulation (unless contraindicated) is therefore suggested in all patients with COVID-19 admitted to the ICU. Indeed, Paranjpe and colleagues demonstrated that in mechanically ventilated patients with COVID-19 full systemic anticoagulation reduced the hospital mortality from 62.7% to 29.1% ($p< 0.001$). Furthermore, in this study, multivariate modeling demonstrated that longer duration of anticoagulation was associated with a reduced risk of mortality (HR of 0.86 per day, 95% CI 0.82–0.89, $p<0.001$). In addition, in vitro studies demonstrate that heparin inhibits SARS-CoV-2 replication [59,60]. Due to the ease of administration and greater anti-Xa activity we prefer low molecular weight heparin (LMWH) to unfractionated heparin (UFH). Heparin resistance appears to be quite common in patients with COVID-19 [61]. Furthermore, due to augmented renal clearance COVID-19 patients may have reduced anti-Xa activity despite standard dosages of LMWH [62]. We therefore recommend monitoring anti-Xa activity in underweight and obese patients, those with chronic renal dysfunction and in those patients with an increasing D-dimer, aiming for an anti-Xa activity of 0.6–1.1 IU.ml. Multiple drug-drug interactions as well as metabolic alterations induced by acute disease cause unpredictable and unstable anticoagulant effects with the direct acting oral anticoagulants (DOAC's) which should therefore be avoided [63]. It should be appreciated that the combination of glucocorticoids, aspirin and heparin increase the risk of bleeding. Heparin should be avoided in patients with a recent major bleeding episode.

7. MATH +

While methylprednisolone, ascorbic acid, thiamine and heparin form the core treatment elements of the MATH protocol, we suggest the addition of the following medications to complement this protocol (MATH+): melatonin 6–12 mg at night, famotidine 40 mg daily (20 mg in renal impairment), vitamin D 2000–4000 u PO daily, elemental zinc (50–75 mg daily), magnesium supplementation and atorvastatin 80 mg/daily. The benefits of famotidine, melatonin and statins have been demonstrated in patients with COVID-19, and although the incremental benefit of these to MATH+ are unknown, all 6 medications are safe, cheap, readily available and are supported by sound scientific reasoning and experimental data [64–71].

8. Conclusions

COVID-19 disease progresses through a number of phases, each with a unique treatment approach. There is no 'silver bullet' to cure COVID-19. The pulmonary phase of COVID-19 is a treatable disease; it is inappropriate to limit therapy to 'supportive care' alone. The MATH + protocol consists of multiple drugs that have synergistic and overlapping biological effects that are safe, cheap, and readily available and are likely to significantly reduce the morbidly and mortality of this disease. It is likely that the MATH + protocol will be refined and evolve over time as new therapeutic agents are demonstrated to improve the outcome of this devastating disease.

9. Expert opinion

Based on an expert collaborative review of the increasing and rapidly emerging reports from China, Italy, and the US during the first surges of COVID-19 outbreaks along with our collective clinical experiences treating such patients, we formulated a combination therapy protocol designed to counteract the severely disturbed pathological processes leading to respiratory failure and death in patients with COVID-19. We believe that based on our knowledge of the existing medical literature together with our collective decades long clinical expertise in treating severe infections that the combination of **M**ethylprednisone, **A**scorbic acid, **T**hiamine and full anticoagulation with **H**eparin along with other co-interventions (MATH+ protocol) can effectively address the hyperinflammatory and hypercoagulable processes leading to the multiorgan dysfunction of COVID-19 which, when treated with supportive-care-only approaches caused the near-collapse of critical care systems in multiple cities and regions across the world.

Glucocorticoid therapy, a mainstay of the MATH+ protocol, has now been validated with the recent RECOVERY trial which reported a significant mortality reduction in COVID-19 patients requiring supplemental oxygen or mechanical ventilation. A surprising aspect of this result is that the intervention consisted of a glucocorticoid thought inferior in efficacy to methylprednisolone and at a dose far lower than previously determined optimal in ARDS and SARS. The likely superior performance of methylprednisolone is based not only on the average effects measured in prior trials of glucocorticoids in ARDS but also on the data supporting methylprednisolone from the large, positive trials in the SARS and H1N1 pandemics. This suggests that the choice of glucocorticoid may have a major impact on clinical outcome and that comparative trials are required to resolve this issue. Furthermore, various dosing regimens and durations of glucocorticoid therapy should be studied. In addition, the role of high 'pulse-dose' glucocorticoids in patients with the COVID-19 associated severe acute fibrosing organizing pneumonia (AFOP) needs to be evaluated. Due to the expense and limited availability, specific cytokine blocking agents such as tocilizumab and anakinra were not included in the MATH+ protocol. The role of these agents, preferably in combination with glucocorticoids should be studied.

The critical need for anti-coagulation, another major component of MATH+, is gaining support and validation through emerging studies showing a strong association of treatment dose anti-coagulation with improved survival in COVID-19 patients. However, additional studies are required to determine the optimal approach to anticoagulation is various subgroups of patients with COVID-19. The 'COVID-19 associated hyperviscosity syndrome' may explain the development of thrombotic complications in patients despite treatment dose anticoagulation. Given that hyperviscosity may be due to increased plasma proteins such as fibrinogen, the role of therapeutic plasma exchange in this syndrome needs to be explored.

Studies supporting the benefit of the other components of MATH+ including melatonin, statins, vitamin D, and zinc have recently been published. In this era of 'big data,' the role of these agents as well as that of vitamin C and thiamine needs to be further studied. These medications may be particularly beneficial as prophylaxis or in the early symptomatic phase of COVID-19. We are hopeful that randomized, controlled clinical trials will be performed to evaluate these inexpensive, readily available, and safe drugs for these indications.

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Declaration of interest

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Reviewer disclosures

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