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Three novel prevention, diagnostic, and treatment options for COVID-19 urgently necessitating controlled randomized trials

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ABSTRACT

Purpose: Asymptomatic or minimally symptomatic infection with COVID-19 can result in silent transmission to large numbers of individuals, resulting in expansion of the pandemic with a global increase in morbidity and mortality. New ways of screening the general population for COVID-19 are urgently needed along with novel effective prevention and treatment strategies.

Hypothesis: A hypothetical three-part prevention, diagnostic, and treatment approach based on an up-to-date scientific literature review for COVID-19 is proposed. Regarding diagnosis, a validated screening questionnaire and digital app for COVID-19 could help identify individuals who are at risk of transmitting the disease, as well as those at highest risk for poor clinical outcomes. Global implementation and online tracking of vital signs and scored questionnaires that are statistically validated would help health authorities properly allocate essential health care resources to test and isolate those at highest risk for transmission and poor outcomes.

Second, regarding prevention, no validated protocols except for physical distancing, hand washing, and isolation exist, and recently ivermectin has been published to have anti-viral properties against COVID-19. A randomized trial of ivermectin, and/or nutraceuticals that have been published to support immune function including glutathione, vitamin C, zinc, and immunomodulatory supplements (3,6 Beta glucan) could be beneficial in preventing transmission or lessening symptomatology but requires statistical validation.

Third, concerning treatment, COVID-19 induced inflammation and "cytokine storm syndrome" with hemophagocytic lymphohistiocytosis (HLH)/Macrophage Activation Syndrome (MAS) have resulted in extreme morbidity and mortality in those with certain comorbidities, secondary to "acute respiratory distress syndrome" (ARDS) and multiorgan dysfunction with disseminated intravascular coagulation (DIC). Deficiency in red blood cell, serum and alveolar glutathione has been published in the medical literature for ARDS, as well as viral and bacterial pneumonias, resulting from increased levels of free radical/oxidative stress. A randomized controlled trial of blocking NF-κB and cytokine formation using glutathione precursors (*N*-acetyl-cysteine [NAC] and alpha lipoic acid) and PO/IV glutathione with associated anti-viral effects should be performed, along with an evaluation of Nrf2 activators (curcumin, sulforaphane glucosinolate) which have been scientifically proven to lower inflammation. Since high mortality rates from sepsis induced DIC due to COVID-19 infection has also been associated with thrombotic events and elevated levels of D-dimer, randomized controlled trials of using anticoagulant therapy with heparin is urgently required. This is especially important in patients on ventilators who have met certain sepsis induced coagulopathy (SIC) criteria. The use of acetazolamide with or without sildenafil also needs to be explored with or without heparin, since increased oxygen delivery to vital organs through prevention of thrombosis/pulmonary emboli along with carbonic anhydrase inhibition may help increase oxygenation and prevent adverse clinical outcomes.

Conclusion and Implications: A three-part prevention, diagnostic, and treatment plan is proposed for addressing the severe complications of COVID-19. Digital monitoring of symptoms to clinically diagnose early exposure and

Abbreviations: ARDS, acute respiratory distress syndrome; CRP, C-reactive protein; CXCL9, CXCL10, chemokines; CoVs, coronaviruses; CT, computerized tomography; DIC, disseminated intravascular coagulation; GSH, gluthathione; GGO, ground glass opacities; ICU, intensive care unit; IL-1β, interleukin 1 beta; IL-6, interleukin 6; IL-7, Interleukin 7; IL-8, interleukin 8; IL-10, interleukin 10; IL-12, interleukin 12; IL-18, interleukin 18; IL-33, interleukin 33; LDH, lactic dehydrogenase; LD, Lyme disease; MAS, macrophage activation syndrome; MERS-Cov, MERS coronavirus; NAC, *N*-acetyl-cysteine; NCP, novel coronavirus pneumonia; NS, nutritional support; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; TGFβ, transforming growth factor beta; TNF-α, tumor necrosis factor alpha; WHO, World Health Organization

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response to treatment; prevention with ivermectin as well as nutritional therapies that support a healthy immune response; treatment with anti-inflammatory therapies that block NF-κB and activate Nrf2 pathways, as well as novel therapies that address COVID-19 pneumonia and ARDS with DIC including anticoagulation and/or novel respiratory therapies with or without acetazolamide and sildenafil. These three broad-based interventions urgently need to be subjected to randomized, controlled trials.

Introduction

Coronaviruses are a large family of enveloped, positive-strand RNA viruses that cause a substantial number of upper respiratory tract infections (URI's) in children and adults [1] and severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is responsible for the coronavirus disease pandemic of 2019 (COVID-19) [2]. The disease may result in a broad range of clinical manifestations, ranging from asymptomatic infection to multiorgan dysfunction with severe ARDS and respiratory failure with death [3]. Those at highest risk for adverse outcomes includes advanced age, male gender [4], race (African-American) [5], obesity [6], smoking history [7], and prior medical histories including hypertension, diabetes, cardiovascular and respiratory disease (asthma, emphysema) [5], hemorrhagic or ischemic strokes, immunosuppression, cancer, chronic kidney and liver disease as well as those with secondary infections [8,9].

More than 100,000 people have died worldwide in the COVID-19 pandemic as of April 10, 2020 according to recent data from Johns Hopkins University [10], and one month later the morbidity and mortality figures were many times higher [11] with global mortality rates over time leveling off to a higher rate of 5.7% converging with current WHO estimates [12]. Finding practical solutions for reducing transmission and mitigating the high morbidity and mortality rates from COVID 19 is urgently needed.

Early prodromal symptoms can include hyposmia, anosmia and dysguesia [13] followed by a fever, sore throat, cough, chest tightness and shortness of breath [14]. Other symptoms may include a conjunctivitis, headaches and myalgias [15] as well as gastrointestinal symptoms of nausea, vomiting, abdominal discomfort, and diarrhea [16]. Rarely a productive cough and hemoptysis may result [9]. Severe complications include Novel Coronavirus Pneumonia (NCP) with or without acute respiratory distress syndrome (ARDS) and respiratory failure, organ function damage with cardiac injury and fulminate myocarditis [17], acute kidney injury, liver dysfunction, and pneumothorax [18].

ARDS, is however, the main cause of death in COVID-19 [9] and the fundamental pathophysiology underlying many of the above complications is "cytokine storm syndrome" [19]. This results from an uncontrolled systemic inflammatory response releasing large amounts of pro-inflammatory cytokines (IFN-α, IFN-γ, IL-1β, IL-6, IL-12, IL-18, IL-33, TNF-α, TGFβ, etc.) as well as chemokines (CXCL9, CXCL10, etc.) by immune effector cells [20]. Secondary hemophagocytic lymphohistiocytosis (sHLH), also known as macrophage activation syndrome (MAS), can similarly result [19]. This is a hyperinflammatory syndrome characterized by a fulminant and fatal hypercytokinemia with multiorgan failure, previously noted in approximately 4% of cases triggered by viral infections [21] and/or sepsis [22]. Cardinal features of sHLH/MAS include unremitting fever, cytopenias, low or absent natural killer (NK) cell activity, hepatosplenomegaly, hepatobiliary dysfunction (HBD), coagulopathy, high ferritin levels ($\geq$500 ng/ml), elevated C-reactive protein (CRP) and Lactate Dehydrogenase (LDH) levels, fasting triglycerides $\geq$265 mg/dl with fibrinogen levels $\leq$150 mg/dl; as well pulmonary involvement with ARDS which can occur in up to 50% of patients [19,23,94]. This same constellation of symptoms and laboratory abnormalities can be seen in those with fatal complications from COVID-19 [19].

Macrophage activating syndrome (MAS) has been previously reported in autoimmune disorders and infections which are primarily of viral origin. Pathogenesis is associated with increased activation of macrophages and NK cells [24], where an autocrine loop of interleukin (IL)-1β over-secretion leads to cytokine storm of IL-6, IL-18, ferritin, and interferon-gamma [22]; High ferritin levels have been proposed to be the diagnostic hallmark of MAS, and ferritin measurements within the first 24 h can be used as a diagnostic biomarker of MAS [25,26]. Among the cytokines produced, Interleukin-18 also has been shown to diagnostically distinguish and pathogenically promote human and murine macrophage activation syndrome [27]. Among pulmonary involvement in patients with HLH/MAS, dyspnea and cough were the most common symptoms at the onset of the disease, and radiographs revealed interstitial infiltrates with centrilobular nodules, ill-defined consolidation, or localized ground-glass opacities [23]. These are some of the same radiological abnormalities seen in patients who recovered from COVID-19 pneumonia, where initial lung findings on chest CT revealed small subpleural ground glass opacities (GGO) that grew larger with crazy-paving pattern and consolidation up to two weeks after disease onset, eventually being absorbed resulting in extensive GGO and subpleural parenchymal bands [28].

The sickest patients admitted to the intensive care units (ICUs) in the United States with COVID-19 pneumonia have been those with ARDS, hypoxemic respiratory failure leading to mechanical ventilation, and/or hypotension requiring vasopressor treatment [29]. The mortality rates of patients on ventilators has been extremely high [29], and compared with non-ICU patients, one recent Chinese study showed that ICU patients all presented with pneumonia, had higher plasma levels of cytokines including TNFα, IL-2, IL-7, IL-10 and shared common complications including acute cardiac injury, secondary infections and ARDS [9].

The pathophysiology underlying critical cases of viral pneumonia is often severe ARDS [30]. ARDS is caused by lung inflammation and increased alveolar endothelial and epithelial permeabilities [30] resulting in a protein-rich pulmonary edema with severe hypoxemia and impaired carbon dioxide excretion [31]. The lung injury is primarily due to neutrophil-dependent and platelet-dependent damage to the endothelial and epithelial barriers of the lung, frequently caused by pneumonia [31] Neutrophils can become activated, leading to the release of toxic mediators including reactive oxygen species (ROS), proinflammatory cytokines and procoagulant molecules [31], where further synergistic interaction with platelets increase damage to the lungs [32]. A procoagulant effect with coagulopathy and anti-phospholipid antibodies has recently been reported in patients with Covid-19 [33], and these abnormal coagulation parameters have been shown to be associated with a poorer prognosis in patients with novel coronavirus pneumonia (NCP) [34]. It is therefore imperative to find ways to decrease free radical oxidative stress (ROS), high levels of inflammatory cytokines and procoagulant pathways triggered by COVID-19 if we are to impact the high morbidity and mortality rates associated with the disease process.

Lack of adequate antioxidant protection in the setting of high levels of ROS may therefore play an important role in damaging the lungs. Prior published reports have shown that the alveolar epithelial lining fluid of patients with ARDS is deficient in total glutathione (GSH) compared to normal subjects, and glutathione is one of the master antioxidants in the body [35]. GSH measured in unconcentrated bronchoalveolar lavage (BAL) fluid in those with ARDS also showed that there was a deficiency in patients with ARDS compared to normal subjects. In this setting, reactive oxygen species such as hydrogen peroxide may

play a key role in the pathogenesis of the acute lung injury with ARDS [35].

The hypothesis/theory

Based on the above clinical and biochemical abnormalities post viral exposure to COVID-19, and high levels of infectivity, morbidity and mortality, we propose a novel three-part prevention, diagnostic, and treatment plan to help flatten the curve and improve clinical outcomes. Digital monitoring of symptoms to clinically diagnose early exposure and response to treatment; a controlled, randomized trial of therapies that prevent infection, support immunity and a healthy inflammatory response; as well as an evaluation of different physiological and respiratory therapies to address the high mortality rates associated with complications of COVID-19 induced DIC and ARDS.

Evaluation of the hypothesis/idea

1. Diagnosis: to date, physical isolation (including those who test positive for exposure), distancing, as well as handwashing have been mandated on a population-wide basis to prevent the spread of disease. There are several key clinical symptoms which would however suggest a high likelihood of exposure necessitating immediate isolation. This would include the constellation of early prodromal symptoms of anosmia, hyposmia, and dysgeusia, along with a fever, sore throat, cough and shortness of breath. There are very few diseases that cause a sudden loss or decreased sense of smell and/or taste. According to the medical literature, approximately 5% of people exhibit functional anosmia primarily caused by senescence[36], where 25% of people above the age of 50 have an impaired sense of smell [37,38]. Olfactory health can be a measure of the number of medications taken [39], and also directly reflect the overall health of a person, where lowered olfactory abilities seem to be negatively associated with life expectancy and an increased risk of death [40]. This is primarily due to those patients with neurodegenerative diseases, especially Parkinson's, Alzheimer's disease or Lewy body dementia, who have olfactory loss early on in the course of their disorder, allowing a tentative diagnosis years prior to the arising of motor or cognitive disturbances [41].

Apart from neurodegenerative diseases, the three major causes of a loss of smell are trauma, rhinosinusitis/nasal polyps, and viral infections [41]. Although the prevalence rates of acute rhinosinusitis with symptoms of nasal obstruction/congestion or nasal discharge (anterior/posterior nasal drip) and facial pain/pressure can range from 6 to 15% and between 2.7 and 8% in Western and Asian populations respectively [42], olfactory dysfunction linked to COVID-19 infection seems particular as it is not usually associated with rhinorrhea [43] which is part of the symptom complex of acute rhinosinusitis. Clinical studies from Asia did initially report rhinorrhea along with primary symptoms of a fever, sore throat, cough, dyspnea, sputum production, myalgia, arthralgia, headache, and diarrhea [44,45], but among a recent case series of 357 COVID-19 patients in Europe, up to 85.6% had olfactory dysfunction and 88% of patients reported gustatory dysfunction related to the infection which was not associated with rhinorrhea [43]. There was also a significant association between both disorders of anosmia and dysgeusia ($p < 0.001$). Using olfactory and gustatory questionnaires based on the smell and taste component of the National Health and Nutrition Examination Survey, and the short version of the Questionnaire of Olfactory Disorders-Negative Statements (sQOD-NS) can therefore be useful as an initial screening tool [43] especially when it is linked to a questionnaire evaluating the most prevalent symptoms of COVID-19. The likelihood of exposure to COVID-19 when there is a sudden change in smell and taste during the present pandemic is of high probability, especially when other risk factors and medical diseases have been ruled out.

Regarding the sudden loss or decreased sensation of taste, infectious diseases including upper respiratory viral infection, oral cavity infection, or viral hepatitis, frequently develop taste abnormalities [46], which have been shown to due to inflammation. For example, autoimmune diseases, e.g. Sjögren's syndrome and systemic lupus erythematosus (SLE), are known to affect taste function and are associated with the elevated levels of inflammatory cytokines interleukin (IL)-6 and interferon (IFN)-γ.[47,48] These are some of the same inflammatory cytokines seen in COVID-19 infection [20], and the strong association between inflammation and taste disorders suggests that the new, sudden onset of this symptom in the setting of a viral pandemic would again imply coronavirus exposure where inflammation is playing a role in the pathogenesis of taste dysfunction. Immediate isolation at first onset of these symptoms, even if otherwise asymptomatic, could help flatten the cure and decrease widespread exposure. When these symptoms are considered in the setting of the constellation of fevers, sore throat, cough and or shortness of breath, with or without fatigue, headaches, myalgias and/or diarrhea, then the new onset of anosmia, hyposmia, and/or dysgeusia would help clinically to confirm exposure with a high likelihood of probability.

These symptoms could be collected via an online questionnaire or digital app, as assessing clinical symptoms is a hallmark of medical diagnostic strategy. Previous research has demonstrated that self-reported symptoms can be reliable predictors of health outcomes, and poorer self-rated health is associated with elevated inflammatory markers among older adults [49] such as C-reactive protein and IL-6, the same inflammatory markers found in COVID-19. There is a long history of using validated self-report questionnaires for detecting/diagnosing medical and mental health conditions and quality of life issues in medicine, including but not limited to establishing a diagnosis of anxiety and clinical depression, gastrointestinal disorders including gastroesophageal reflux disease and dysphagia, peripheral artery disease, cancer care delivery, Lyme disease etc. [50–53].

Recently, an app was developed for clinical use by Israeli researchers, and has been instituted as a screening tool in Canada for COVID-19 [54]. This app has the capability to monitor peoples' vital signs when they look on their smartphone screens and "triage nurses can check vital signs (heart rate, respiratory rate, and the blood's oxygen saturation) without touching patients; the condition of certain hospitalized patients can be monitored from their beds; and the vital signs of patients at home can be checked remotely" [54]. Similarly, Adaptive Biotechnologies Corp. and Microsoft have recently collaborated on mapping the immune system's response to COVID-19, using machine learning capabilities to sift through data on the body's T-cell receptor sequences, which get generated in response to antigens in the blood, which can then refine a "map" of those sequences by "matching trillions of T cells to the diseases they recognize" [55]. By combining validated screening questionnaires, apps and machine learning, we can identify early exposure and monitor vital signs from a distance. If some of the newer experimental protocols for COVID-19 infection involve the use of hydroxychloroquine and azithromycin, which have recently been published to be of potential benefit [56], but also potential harm [95] monitoring of cardiac arrythmias and can also be done digitally at home via KardiaMobile, a FDA-cleared, clinical grade personal EKG monitor [57]. This would be important in those with cardiac risk factors since those on chloroquine or hydroxychloroquine with or without a macrolide had an increased risk of de-novo ventricular arrhythmias [95] and electrocardiograms can subsequently be stored on a smart phone and emailed to the physician for review.

2. Prevention: Prevention practices that need to be scientifically evaluated are the use of daily or pulse therapy ivermectin (once or twice a week), which has been shown to have anti-viral effects against COVID-19 in vitro [58] as well as nutraceuticals including zinc, vitamin C, Beta-glucan and GSH. Zinc-deficiency can lead to an increased susceptibility to a variety of pathogens [59], and zinc supplementation in healthy human subjects has been shown to lower oxidative stress related byproducts [60], inhibit induction of TNF alpha and interleukin 1 beta [61], protect against TNF-α–induced nuclear factor–κβ activation

in isolated mononuclear cells [61] and regulate intracellular killing and cytokine production by macrophages [61]. In the immune system, the major role of vitamin C appears to be as an antioxidant, protecting the lungs and host cells against oxidative stress caused by infections [62] as well as helping to increase phagocyte function, the proliferation of T-lymphocytes and the production of interferon, while decreasing the replication of viruses [66,64]. In one study, vitamin C was shown to shorten the length of the stay in the ICU and decrease the duration of mechanical ventilation for critically ill patients on respirators [65]. Finally, Beta-glucans have been extensively published in the medical literature as having significant immunomodulatory properties [66] and double blind, placebo controlled trials have shown benefit in decreasing the severity of upper respiratory tract infections and lowering monocyte chemotactic protein-1 [70,68]. Finally, the ability of GSH to help prevent viral infections needs to be studied, as GSH has been shown to have anti-viral properties and gene mapping for innate immunity and antiviral activity require GSH for their induction [96,108,110]. For that reason, controlled clinical trials of ivermectin, with or without nutraceuticals including zinc, vitamin C and Beta glucans are needed to evaluate their effects for both prevention and diminishing the severity of clinical symptomatology post exposure. This is critically important since development of a safe and effective vaccine may be months to years away, and effective antiviral approaches could help flatten the curve and prevent infection. Randomized controlled trials of ivermectin, with or without the nutraceuticals zinc, vitamin C, Beta-glucans and GSH could be done in association with screening questionnaires/app's, to potentially detect early symptoms, monitor the clinical course from a distance without using precious hospital resources and upload treatment data to the cloud for large data computing, expediting results.

3. Treatment: no randomized, controlled trials have been reported to date to evaluate the efficacy of antiviral therapies in the treatment of COVID-19. Chloroquine phosphate has shown apparent efficacy in treatment of COVID-19 associated pneumonia in clinical studies in China [69], but hydroxychloroquine was found to be more potent than chloroquine in vitro [70], and has less potential side effects [70]. An initial non-randomized small study done in France by Raoult et al showed benefit using hydroxychloroquine and azithromycin [56] but a recent large observational study showed no survival benefit and increased risk of arrhythmias and death using chloroquine, hydroxychloroquine and/or a macrolide [98]. Other potential treatments being considered are ivermectin [58], nitazoxanide [71], remdesivir [72], triple combination interferon beta-1b, lopinavir–ritonavir, and ribavirin [97], as well as repurposed drugs and nutritional supplements including but not limited to melatonin, mercaptopurine, and sirolimus [73]. An international, multicenter observational case-controlled study in 1,408 patients with COVID-19 (half of whom received ivermectin) demonstrated a lower in-hospital mortality (1.4%) in the treatment group, versus an 8.5% mortality in the non-treatment group) [98]. Since none of these except remdesivir have yet undergone randomized, placebo-controlled clinical trials [99], and no FDA treatments for COVID-19 are yet available, collecting data via an app and online questionnaire in those patients who have used these drug combinations and nutraceuticals 'off label' could be useful in directing clinical research.

Treatments for "cytokine storm syndrome" and macrophage activation syndrome

Inflammation and "cytokine storm syndrome" with hemophagocytic lymphohistiocytosis (HLH)/Macrophage Activation Syndrome (MAS) can lead to extreme morbidity and mortality. This is especially the case in those with certain comorbidities, including ARDS and multiorgan dysfunction with disseminated intravascular coagulation (DIC). ARDS is however the main cause of death in COVID-19 [9] and the fundamental pathophysiology underlying many of the above complications is "cytokine storm syndrome" [77,19]. Control of cytokine production and unbridled inflammation which damages lung tissue and essential organs secondary to high levels of free radical/oxidative stress is essential.

There are several potential mechanisms which can be helpful for lowering inflammation and need to be studied, apart from the effect of antiviral agents (hydroxychloroquine, chloroquine, remdesivir, nitazoxanide, ivermectin) and nutritional support (zinc, vitamin C, 3,6 beta glucan) previously described. Deficiency in red blood cell, serum and alveolar glutathione has been published in ARDS, viral and bacterial pneumonias, resulting from increased levels of free radical/oxidative stress [35,75]. Oxidative stress can trigger several biochemical pathways including NF-κB, which is a primary target for modulating inflammatory responses [76]. The transcription factor NF-κB regulates multiple aspects of innate and adaptive immune functions, is a pivotal mediator of inflammatory responses, induces the expression of various pro-inflammatory genes, including those encoding cytokines and chemokines, and also participates in inflammasome regulation [77]. In addition, NF-κB plays a critical role in regulating the survival, activation and differentiation of innate immune cells and inflammatory T cells needed to fight viral infections [77]. The pro-inflammatory function of NF-κB has also been extensively studied in macrophages, which are on the front line of an immune response against infections [78], involved in MAS. Prospective randomized, controlled studies are therefore needed to evaluate the role of NF-κB blockade in order to protect against the effects of COVID-19. Inhibitors to block NF-κB signaling include N-acetylcysteine (NAC) [79], alpha lipoic acid [80], as well as antioxidants like glutathione [81]. *N*-acetylcysteine and alpha lipoic acid can help increase production and regeneration of glutathione [82,83], and deficiency in red blood cell, serum and alveolar glutathione has been found in ARDS [35], as well as viral and bacterial pneumonias [84], resulting from increased levels of free radical/oxidative stress [85]. Another advantage of GSH is that it has antiviral properties due in part to its ability to enhance the functional activity of NK cells and T cells [2,106,107], support anti-viral activity of macrophages [108] as well as form disulfide bonds, potentially decreasing binding of the virus to the ACE2 receptors on the cell surface [109–111]. Data also suggests that exogenous GSH can inhibit the replication of viruses like HSV-1 by interfering with very late stages of the virus life cycle [100]. A randomized controlled trial of blocking NF-κB and cytokine formation using glutathione precursors (*N*-acetyl-cysteine [NAC] and alpha lipoic acid) as well as PO/IV glutathione with associated anti-viral effects should be performed, along with an evaluation of Nrf2 activators (curcumin, sulforaphane glucosinolate) which have been scientifically proven to lower inflammation [86,87]. The efficacy of glutathione therapy in rapidly relieving dyspnea associated with COVID-19 pneumonia was recently reported by Horowitz and Freeman in a peer-reviewed journal [101]. Since the Nrf2 pathway plays a pivotal role in inflammation [88] as does the NF-κB pathway and deficiencies in glutathione, these should be explored as part of a multifaceted approach to find effective treatments for COVID-19. This would be especially important in the most vulnerable populations including the elderly in nursing homes, and those with established risk factors for COVID-19.

Treatment for sepsis induced DIC and respiratory failure

High mortality rates from COVID-19 infection has been associated with abnormal coagulation parameters, thrombotic events and elevated levels of D-dimer with sepsis induced DIC [33,34]. Randomized controlled trials of using anticoagulant therapy with heparin is urgently required, especially in patients on ventilators who have met certain sepsis induced coagulopathy (SIC) criteria, since anticoagulation treatment has been published to decrease mortality from COVID-19 [92,102,103]. Anticoagulation has previously been shown to increase survival among patients with ARDS secondary to influenza virus A H1N1, and high D-dimer levels greater than 2 times normal can predict the risk of venous thromboembolism in the hospital [106,105].The use

of acetazolamide also needs to be explored with or without heparin, since increased oxygen delivery to vital organs via carbonic anhydrase inhibition may help improve hypoxia [90], along with the drug's ability to reverse metabolic alkalosis and facilitate weaning from mechanical ventilation. Although acetazolamide can improve arterial oxygen saturation (SaO2) by increasing ventilation, it is associated with an increased work and cost of breathing. Sildenafil could therefore also be used with acetazolamide to increase SaO2 possibly through a reduction in pulmonary hypertension and interstitial edema, helping to improve ventilation–perfusion matching [91].

Consequences of the hypothesis/conclusion and implications

Exposure to COVID-19 has high case fatality rates across countries worldwide [92]. Prevention is especially important since the US Center for Disease Control and Prevention (CDC) has estimated that hundreds of thousands of deaths will occur worldwide [93], with the WHO estimating a global mortality rate greater than 5% [12]. Innovative solutions that have a low risk and high potential yield therefore require scientific validation. A three-part prevention, diagnostic and treatment plan is proposed for addressing the severe complications of COVID-19. Digital monitoring of symptoms with a validated symptom questionnaire to clinically diagnose early exposure and response to treatment; prevention with daily or pulse dose ivermectin as well as other medications and nutritional therapies that support a healthy immune response; treatment with anti-inflammatory therapies that block NF-κB and activate Nrf2 pathways, as well as novel therapies that address COVID-19 pneumonia and ARDS with DIC, including anticoagulation with or without acetazolamide and sildenafil for those requiring respiratory support. These three hypothetical broad-based clinical interventions have been published in the medical literature to be of potential benefit in those with viral pneumonia and ARDS, with limited data available on their effects on COVID-19. We believe that it is urgent that these hypotheses be tested in a series of randomized, controlled trials to evaluate their ability to flatten the curve and decrease the presently high levels of morbidity and mortality associated with COVID-19.

Disclaimer

The views expressed are those of Dr. Richard Horowitz, and do not represent the views of the Tick-Borne Disease Working Group, HHS the United States.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

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