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Efficacy of glutathione therapy in relieving dyspnea associated with COVID-19 pneumonia: A report of 2 cases

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Case report

Efficacy of glutathione therapy in relieving dyspnea associated with COVID-19 pneumonia: A report of 2 cases

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ABSTRACT

Purpose: Infection with COVID-19 potentially can result in severe outcomes and death from "cytokine storm syndrome", resulting in novel coronavirus pneumonia (NCP) with severe dyspnea, acute respiratory distress syndrome (ARDS), fulminant myocarditis and multiorgan dysfunction with or without disseminated intravascular coagulation. No published treatment to date has been shown to adequately control the inflammation and respiratory symptoms associated with COVID-19, apart from oxygen therapy and assisted ventilation. We evaluated the effects of using high dose oral and/or IV glutathione in the treatment of 2 patients with dyspnea secondary to COVID-19 pneumonia.

Methods: Two patients living in New York City (NYC) with a history of Lyme and tick-borne co-infections experienced a cough and dyspnea and demonstrated radiological findings consistent with novel coronavirus pneumonia (NCP). A trial of 2 g of PO or IV glutathione was used in both patients and improved their dyspnea within 1 h of use. Repeated use of both 2000 mg of PO and IV glutathione was effective in further relieving respiratory symptoms.

Conclusion: Oral and IV glutathione, glutathione precursors (N-acetyl-cysteine) and alpha lipoic acid may represent a novel treatment approach for blocking NF-κB and addressing "cytokine storm syndrome" and respiratory distress in patients with COVID-19 pneumonia.

1. Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) first identified in Wuhan, China is responsible for the coronavirus disease outbreak of 2019 (COVID-19), now declared a pandemic by the World Health Organization (WHO) as of March of 2020 [1]. Among the CoV's known to cause human disease, the three most highly pathogenic of the group include the SARS coronavirus (SARS-CoV now named SARS-CoV-1) [2], the Middle East respiratory syndrome (MERS) coronavirus (MERS-CoV) [3] and SARS-CoV-2, the agent of COVID-19, identified in patients with severe pneumonia in Wuhan, China [4]. Early prodromal symptoms of infection with COVID-19 include anosmia, hyposmia and dysgeusia [5] followed days later by fever (91.7%), cough (75.0%) and shortness of breath, fatigue (75.0%) and gastrointestinal symptoms including diarrhea (39.6%) [6]. A sore throat, headache, myalgias and rarely conjunctivitis has also been reported [7] as well as episodes of confusion [8]. This is similar to the clinical picture of MERS, where a fever, chills, cough, sore throat, wheezing, shortness of breath, myalgia, chest pain, gastro-intestinal symptoms (diarrhea, vomiting, and abdominal pain) and confusion may result [9].

Although exposure to COVID-19 is asymptomatic or mild in most affected of younger age, those at highest risk for fulminant disease have been identified as having certain risk factors. These factors include advanced age and a smoking history [10], male gender [11], race (African-American) [12], as well as prior medical problems including hypertension, cardiac disease, obesity, hemorrhagic or ischemic stroke, underlying respiratory illness (asthma, emphysema), cancer, immunosuppression, secondary infections as well as chronic kidney and liver disease [13–15]. 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 [16]. As of April 11, 2020, almost 1.7 million people worldwide have been infected [17] with global mortality rates over time leveling off to a higher rate of 5.7% converging with current WHO estimates [18]. These statistics reveal that we may have

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Alphabetical list of abbreviations

ARDS	Acute respiratory distress syndrome
ANA	Antinuclear antibodies
CoVs	Coronaviruses
CT	Computerized tomography
DHEA	Dehydroepiandrosterone
GSH	Glutathione
GGO	Ground glass opacities
IgM and IgG	Immunoglobulin M, immunoglobulin G
IFA	Immunofluorescent antibody
ICU	Intensive care unit
IL-1β	interleukin 1 beta
IL-6	interleukin 6
IL-8	interleukin 8
LD	Lyme disease
MERS-Cov	MERS coronavirus
NAC	N-acetyl-cysteine
NCP	novel coronavirus pneumonia
NF-kappaB (NF-κB)	nuclear factor-kappaB
NYC	New York City
NS	Nutritional support
PCR	Polymerase chain reaction
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
TNF-α	Tumor Necrosis Factor alpha
WHO	World Health Organization

underestimated the potential threat of COVID-19, and that rapid, effective testing strategies and treatments are essential, especially among those with severe respiratory complications and acute respiratory distress syndrome (ARDS).

Among the sickest patients and most common reasons for admission to the intensive care unit (ICU) during the initial outbreak of COVID-19 in the Seattle area were hypoxemic respiratory failure leading to mechanical ventilation, hypotension requiring vasopressor treatment, or both [19]. Mortality among these critically ill patients was high. The ICU mortality rate among those who required non-invasive ventilation in one case series in China was 79% and among those who required invasive mechanical ventilation was 86% [15]. The fundamental pathophysiology of infection with COVID-19 potentially resulting in such critical outcomes is "cytokine storm syndrome" with ARDS and fulminate myocarditis [20] with multiorgan dysfunction [7] acute kidney injury, liver dysfunction, and pneumothorax [21]. A hyperinflammatory syndrome known as secondary hemophagocytic lymphohistiocytosis (sHLH) or macrophage activation syndrome (MAS) can also result from fulminant and fatal hypercytokinemia [22]. Pulmonary involvement in patients with HLH/MAS revealed that 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]. Similar radiological abnormalities are 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 [24]. Chest radiographs and imaging results of patients with MERS Cov also have also shown features that resemble the findings of organizing pneumonia, which are different however from SARS, which show more of a fibrocellular intra-alveolar organization with a bronchiolitis obliterans organizing pneumonia-like pattern [9].

Despite differences in initial presentation, ARDS has been reported to be the main cause of death in COVID-19 [15], resulting from an uncontrolled systemic inflammatory response releasing large amounts of pro-inflammatory cytokines as well as chemokines by immune effector cells [25]. This is similar to the pathophysiology seen with SARS, i.e., immune cell injury–based damage with widespread organ involvement [26], with unbalanced cytokine and chemokine profiles [27,28]. Addressing the immune based lung pathology seen in COVID-19, similar to that seen in ARDS, might help to decrease morbidity and mortality.

ARDS is caused by lung inflammation and increased alveolar endothelial and epithelial permeabilities [29] leading to a protein-rich pulmonary edema that causes severe hypoxemia and impaired carbon dioxide excretion [30]. The lung injury is non-cardiogenic in nature and caused primarily by neutrophil-dependent and platelet-dependent damage to the endothelial and epithelial barriers of the lung, frequently caused by pneumonia [30]. A procoagulant effect with coagulopathy and anti-phospholipid antibodies has also recently been reported in patients with COVID-19 [31], associated with a poorer prognosis in patients with novel coronavirus pneumonia (NCP) [32]. Supportive measures in the management of ARDS have included attention to fluid balance, restrictive transfusion strategies, and minimization of sedatives and neuromuscular blocking agents, along with inhaled bronchodilators which have been shown to confer short term improvement without proven effect on survival [33].

Release of pro-inflammatory cytokines, such as Tumor Necrosis Factor alpha (TNF-α), interleukin 1 beta (IL-1β), interleukin 6 (IL-6), and interleukin 8 (IL-8) which in turn recruit components of the innate immune system have been shown to be associated with ARDS [34,35]. Neutrophils are recruited to the lungs by these cytokines, which then become activated and release toxic mediators [36], leading to extensive free radical production and reactive oxygen species which overwhelms endogenous anti-oxidants resulting in oxidative cell damage to lung tissue [37]. Pharmacological therapies that have been tried to date include nitric oxide, inhaled prostacycline, vasoconstrictors and anti-inflammatory agents including corticosteroids. Corticosteroids, however, have been shown to have no benefit and even cause harm [33].

Activation of nuclear factor-kappaB (NF-kappaB) has been shown to be required for transcription of the genes for many of the pro-inflammatory mediators associated with ARDS [38] where NF-κB plays a key role in the orchestration of the multifaceted inflammatory response. This is both in the pro-inflammatory phase and later in the regulation of the resolution of inflammation when anti-inflammatory genes are expressed [39]. Antioxidant therapies including N-acetyl-cysteine (NAC) [40], alpha lipoic acid (ALA) [41,42] and glutathione (GSH) have all been reported to regulate NF-κB signaling [43] and downregulate NF-kappaB [44]. To date there are no clinical trials using either precursors of glutathione (NAC) or PO/IV glutathione for COVID-19 dyspnea, pneumonia or ARDS.

Prior published, controlled clinical trials with NAC demonstrated that patients with ARDS have depressed plasma and red cell glutathione concentrations. These levels are substantially increased by therapy with intravenous NAC with measurable clinical responses to treatment regarding increased oxygen delivery, improved lung compliance and resolution of pulmonary edema [45]. The alveolar epithelial lining fluid of patients with ARDS has also been shown to be deficient in total GSH compared to normal subjects, where reactive oxygen species may play a key role in the pathogenesis of the acute lung injury with ARDS [46]. Since patients with ARDS are subjected to an increased burden of oxidants in the alveolar fluid, principally released by recruited neutrophils, this deficiency of GSH may predispose these patients to enhanced lung cell injury. Glutathione is one of the body's master antioxidants which has been shown to play an important role in antioxidant defense, nutrient metabolism, and regulation of cellular events, including cytokine production and immune response [47]. We therefore performed a trial of glutathione precursors, i.e. NAC, antioxidants (alpha lipoic acid,

Vitamin C) along with 2-g doses of PO and/or IV glutathione in 2 patients suffering from dyspnea associated with COVID-19 pneumonia who were previously on antibiotic treatment for COVID-19 pneumonia with mixed results.

2. Material and methods

A screening questionnaire for COVID-19 was used to track daily symptoms. The initial COVID-19 screening questionnaire and follow-up form included the following symptoms that were tracked during the course of illness: loss of sense of smell and/or taste; sore throat; fever, sweats, chills; cough (and whether it was dry or productive with associated shortness of breath); pulse oximetry readings if available, measured both without and with oxygen via nasal cannula; diarrhea; nasal congestion, sneezing, rhinorrhea; conjunctivitis; headaches; myalgias and/or arthralgias; and memory or concentration problems.

2.1. Participants

A 54-year-old white male and 48-year-old white female contacted our office after testing positive for COVID-19 by either antibody testing (patient 1) or with radiology exams (chest x-ray, CT scan) consistent with COVID-19 pneumonia (patients 1 and 2). Both patients had a history of Lyme disease (LD) and associated tickborne co-infections. Patient 1 had a history of persistent LD symptoms with a history of co-infections (anaplasma, babesia) with positive autoimmune markers after a short course of treatment in prior years, consistent with an underlying chronic inflammatory response. The second patient had a history of LD and *Bartonella henselae*, with prior exposure to *Rickettsia rickettsii, and Rickettsia typhi* when she began treatment. Neither patient needed to be excluded from the prescribed combination therapy based on their medical history, as there was no allergy or intolerance to any medication or supplement, and no history of significant cardiac arrhythmias and/or QT prolongation on an electrocardiogram.

2.2. Case studies

Case history 1: The patient is a 53-year-old white male with a past medical history (PMH) significant for Lyme disease (positive IgM Western blot), anaplasmosis, babesiosis, prior exposure to Epstein-Barr virus, human herpesvirus 6 and cytomegalovirus, with a history of intestinal parasites. Exposure risk for tick-borne infections included frequent travel to highly Lyme endemic areas on Long Island. PMH also included frequently elevated mercury levels in the blood, hypothyroidism, hypoglycemia, adrenal fatigue, low testosterone, low vitamin D, irritable bowel syndrome, and chronic insomnia. Significant autoimmune/inflammatory markers included a history of positive antinuclear antibodies (ANA) ranging between 1:40 and 1:320, positive rheumatoid factors (103, normal range less than 6) with a negative cyclic citrullinated peptide, and positive IgG anticardiolipin antibodies. All other autoimmune markers were negative including negative single-stranded DNA, double-stranded DNA, Sjogren's and Smith antibodies. After several months of treatment with antibiotics during the time period of 2011–2012, the patient remained in relatively good health. He was never completely symptom free from his tick-borne infections but was able to work at a high intensity job in the financial industry and did not require follow-up with our medical practice until 8 years later. Western blots showed old exposure to *Borrelia burgdorferi* with evidence of several Lyme specific bands.

He was seen again in January 2020 when his old Lyme symptoms began to relapse with moderate fatigue, insomnia (only sleeping 6 hours per night), occasional migratory pain in the muscles and joints, including low back, shoulders, ankles and feet, along with mild tremors and mild cognitive dysfunction. The patient stated that he was feeling approximately 85% of his normal functioning and repeat labs were performed. His Lyme C6 ELISA was negative, IgM and IgG immunoblot were negative with a negative PCR for *Borrelia burgdorferi*, along with negative Babesia testing and negative testing for other tickborne co-infections. Rheumatoid factor (IgM) was initially elevated at 154, ANA was positive at 1:320 (reference range less than 1:40) with a normal high-sensitivity CRP and normal ferritin level. All other autoimmune markers were negative. Mercury level in the blood was elevated at 15.3 (normal range less than 10 μg/L), and Lead level was 1 in the blood (normal range 0–4 μg/dL). A complete blood count and comprehensive metabolic profile were within normal limits, as were immunoglobulin levels (IGA, IgM and IgG) and mineral levels (iodine, zinc, copper, magnesium). Hormone precursors were low, with low levels of pregnenolone (15, normal range 22–237 ng/DL), low levels of unconjugated Dehydroepiandrosterone (DHEA) (87, normal range 147–1760 ng/deciliter), low total testosterone levels (232, reference range 250–1100 ng/deciliter) and a low normal level of cortisol in the blood (8.4 μg/deciliter, range between 4 and 22).

On 3/20/2020, the patient called the emergency line of our medical office with symptoms that included anosmia, dysgeusia with a metallic taste, low-grade fevers (99.5–100.5 Fahrenheit), sweats (day and night occasionally interfering with sleep), body aches with flulike symptoms, low back pain, a dry cough with labored breathing, scratchy throat, severe headache, brain fog and diarrhea. Symptoms started one week prior and when testing returned positive for COVID-19, he had a computerized tomography (CT) scan in the emergency room showing a left lower lobe pneumonia. We started him immediately on hydroxychloroquine as a loading dose of 400 mg BID × 2 days, followed by 200 mg TID × 8 days, nitazoxanide 500 mg PO BID, and Zithromax 250 mg BID × 10 days. He had also been using an albuterol inhaler that he received from the hospital emergency room several days prior, 2 pumps 4 × per day, without significant benefit in relieving his respiratory symptoms, along with acetaminophen 500 mg Q 4 hours. He was instructed to begin the above antibiotic regimen, along with immune and nutritional support (NS). This included several different probiotics, including acidophilus, lactobacillus, bifidobacterium and *Saccharomyces boulardii*, along with zinc 40 mg per day, Vitamin C up to 2 g, 3 × per day, 3, 6 beta glucan 1000 mg per day, curcumin 1 g twice a day, sulforaphane glucosinolate 100 mg twice a day, NAC 600 mg twice a day, alpha lipoic acid 600 mg twice a day, and glutathione 2, 500 mg capsules twice a day, to be increased to 2 g taken all at once prn for acute respiratory distress. He was also instructed to alkalize his body with sodium bicarbonate and/or fresh squeezed lemons and limes as needed while using glutathione, and to order a pulse oximetry at home to measure his oxygen saturation.

Day 11 postexposure, 4 days into the antibiotic regimen (day 4 of nitazoxanide) the patient began to clinically improve, although he still complained of anosmia, dysgeusia, poor appetite, a cough, significant shortness of breath, debilitating fatigue and several episodes of diarrhea per day with dehydration. Pulse oximetry's remained at 95% or higher. A trial of 2 g of oral glutathione was tried for the moderate shortness of breath, which significantly improved his dyspnea within 1 h. A home nursing service was subsequently hired to administer IV fluids, as the patient became increasingly dehydrated secondary to significant night sweats and diarrhea with difficulty keeping down fluids. Two grams of IV glutathione was subsequently administered with 1 L of 0.9% normal saline, along with PO Pedialyte for electrolyte replacement. Oxygen via nasal cannula, up to 3 L per minute for several hours per day was used PRN for dyspnea. Pulse oximetry increased from 94 to 95%–98% while on a nasal cannula with some relief of symptoms. IV fluids with 2 g of glutathione administered over 1 h improved his sense of well-being and quickly improved his dyspnea each time it was administered daily.

By day 17 (day 24 post exposure), his cough had resolved with no further dyspnea and body aches and headaches were also significantly improved. The only symptom that occasionally returned were night sweats with "air hunger" and a very mild, lingering cough which was intermittent. No other associated prior symptoms relapsed from COVID-19. After a detailed discussion, the patient reported that the present

symptoms were more suggestive of a reactivation of babesiosis he had experienced years prior. Since there were no associated fevers, worsening cough, or significant dyspnea, and laboratory testing was presently unavailable, the patient was placed atovaquone/proguanil 100/250 mg 4 tablets QD × 3 days, followed by 2 PO BID, along with oral glutathione at a dose of 2 g up to twice a day PRN for shortness of breath. The patient continued to improve on this protocol.

Case history 2: The patient is a 48-year-old, G4P4 female with a 15 pack-year smoking history; a history of three consecutive C-sections; psoriasis; and a history of Lyme disease and associated tick-borne infections (*Bartonella henselae*, *Rickettsia rickettsii*, *Rickettsia typhi*) which were diagnosed November 2016. Over the past three years, she received treatment for her tick-borne illness, and had a dramatic improvement. She had been symptom-free and off treatment for the past year, and prior to falling ill with COVID-19, the patient was healthy and eating a balanced diet with no notable health complaints.

On Sunday, March 22, 2020, the patient woke up with 103°F, severe dyspnea at rest that worsened with exertion, dry cough, chest tightness, nausea, dizziness, diarrhea, severe fatigue, body pains, weakness, shallow breathing, and anosmia. The patient was taken to the emergency room, where they performed a chest x-ray which showed "hazy opacities and peribronchial thickening in the left mid and lower lung field concerning for pneumonia, possible atypical". The patient was not tested for COVID-19 in the ER at the time of the X-ray due to the unavailability of testing in NYC. She was given a loading dose of 500 mg of azithromycin in the emergency room and discharged with a diagnosis of "Suspected 2019 Novel Coronavirus Infection and Atypical Pneumonia".

On Monday, March 23, 2020, the patient was started on a combination therapy of azithromycin 250 mg PO q12h, and a loading dose of hydroxychloroquine 400 mg PO q12h, followed by maintenance doses of hydroxychloroquine 200 mg TID × 9 days. Two days later, amoxicillin/clavulanate 875-125 mg PO q12h was added for extended coverage of the pneumonia as her dyspnea persisted. During antibiotic therapy from March 23rd to March 30th, the patient experienced gradual improvement but still complained of lingering symptoms of diarrhea and respiratory symptoms including a cough, dyspnea at rest that worsened with exertion, shallow breathing, inability to take a deep breath, and chest tightness.

On March 31, reduced, liposomal glutathione was added to her antibiotic regimen along with 50 mg of zinc and 1-g TID of Vitamin C. The patient was given 2000 mg of L-glutathione PO all at once with 2 Alka seltzer gold, along with alpha lipoic acid 600 mg, and N-acetylcysteine 1200 mg. The patient saw immediate improvement described as "being able to breath better and having more energy" within an hour of use. After administration of the glutathione, the cough resolved and she was able to sleep through the night for the first time since the onset of illness, despite having been on her antibiotic regimen for several days. She was also able to take a deep breath for the first time. The following morning after administration of 2000 mg of PO glutathione for a second time, the patient was able to ambulate, perform activities of daily living, and shower without pre-syncopal episodes arising from dyspnea. This was the first time she could perform activities of daily living since the onset of her illness. The following day, additional doses of glutathione were given, one time at a lower dose of 500 mg PO, which did not have the same therapeutic effects as the higher dose of 2000 mg of GSH. All doses of glutathione administered to the patient were liposomal doses; and were subsequently administered at 2,000 mg PO due to superior efficacy. Since that time, 5 days after receiving initial doses of GSH, the patient remained well and symptom free. As antibody tests were not readily available in NYC at the time of presentation, the patient was only able to receive a PCR test for COVID-19 two weeks after initiation of symptoms when she was asymptomatic, which was PCR negative.

3. Discussion

Several key clinical symptoms suggested a high likelihood of exposure to COVID-19 in our patients, including the constellation of early prodromal symptoms of anosmia, hyposmia, and dysgeusia, along with a fever, sore throat, cough and shortness of breath. Apart from neurodegenerative diseases, the three major causes of a loss of smell are trauma, rhinosinusitis/nasal polyps, and viral infections [48]. Olfactory and gustatory dysfunctions have now been reported as a clinical presentation of mild-to-moderate forms of the coronavirus disease (COVID-19) [49].

COVID-19 risk factors include those with immunosuppression and underlying infections [13,15]. Patients with active Lyme disease can be immunosuppressed with immunoglobulin and subclass deficiencies [50] as well as potentially having multiple sources of inflammation driving the inflammatory process [51]. This needs to be considered in the list of risk factors potentially complicating treatment outcomes. For example, patient one was also diagnosed with elevated levels of mercury before contracting COVID-19, known to increase free radical/oxidative stress [52]. Glutathione and alpha lipoic acid have both been shown to be important in mitigation of mercury toxicity and regulation of heavy metals [53]. He also had symptoms consistent with active Lyme disease with migratory pain and multiple positive inflammatory markers (positive ANA, rheumatoid factors). Migratory pain is one of the hallmark symptoms of an active infection with *Borrelia burgdorferi* once other differential diagnostic possibilities have been ruled out [54]. He was ruled out for rheumatoid arthritis with a negative cyclic citrullinated peptide, and lupus erythematosus with negative double-stranded DNA and Smith antibodies, another potential source of migratory pain [54].

Patients who suffer from Lyme disease and relapsing fever borreliosis oftentimes experience Herxheimer reactions once antibiotics are initiated [55] which has been shown to be due to the pro-inflammatory cytokines TNF-α, IL-6, and IL-8 [56]. These are some of the same cytokines expressed during viral infection with COVID-19 [24]. Glutathione and alkalizing the body to decrease acidic byproducts has been shown to be helpful in decreasing symptomatology in this population of patients [57]. Glutathione metabolism has also been discovered to be the most important target of *B. burgdorferi* infection, and this pathway is essential for cytokine production, likely through glutathionylation [58]. Glutathione and GSH precursors (NAC) with antioxidants that help regenerate GSH (alpha lipoic acid) have been an effective mainstay of treating cytokine storms and Herxheimer reactions in our tick-borne population for decades [59,60]. Both patients took glutathione for the first time on day ten/eleven, during the peak stage of their illness. According to recent published research [61], patients without severe respiratory distress during the disease course have lung abnormalities on chest CT of greatest severity approximately 10 days after the initial onset of symptoms. Both patients therefore had significant benefit with high-dose oral glutathione relieving their dyspnea during the peak stage of their illness.

Our patients were also given zinc, 40–50 mg per day, and Vitamin C 1–2 g TID. Zinc is known to play a central role in the immune system, and zinc-deficient persons experience increased susceptibility to a variety of pathogens [62]. Zinc is crucial for normal development and function of cells mediating nonspecific immunity such as neutrophils and natural killer cells [62] and after zinc supplementation, the incidence of infections, generation of tumor necrosis factor alpha and oxidative stress markers has been shown to be significantly lower in the zinc-supplemented than in the placebo group. Zinc supplementation in healthy human subjects also reduced the concentrations of the oxidative stress–related byproducts in the plasma; inhibited the ex vivo induction of TNF-α and IL-1β mRNA in mononuclear cells (MNCs) [63]; and provided protection against TNF-α–induced nuclear factor–κβ activation in isolated mononuclear cells [64]. Macrophages are adversely affected by zinc deficiency, which can dysregulate intracellular killing, and cytokine production [63].

We also used Vitamin C, another major free radical scavenger with

alpha lipoic acid and NAC. In the immune system, the major role of Vitamin C appears to be as an antioxidant, protecting host cells against oxidative stress caused by infections [65], especially infections affecting the lungs [65,66]. Other effects of Vitamin C include increased functioning of phagocytes, proliferation of T-lymphocytes and production of interferon, while decreasing the replication of viruses [67]. Alpha lipoic was administered simultaneously with Vitamin C, which apart from being an antioxidant and inhibiting airway inflammation [41], increases GSH through release from oxidized glutathione, increasing GSH synthesis, while activating the transcription factor Nrf2, and lowering expression of NF-kappa B [68]. Finally, NAC, a precursor of glutathione, was given at PO doses ranging from 1200 to 2400 mg/day, as it has been shown to lower the inflammatory response in patients with community acquired pneumonia in a randomized controlled trial [69] while increasing intracellular GSH and improving acute respiratory distress syndrome [70].

Glutathione is abundant in most cells, but is the most abundant antioxidant in the airway epithelial lining fluid, and acts as a vital intra- and extracellular antioxidant protecting against oxidative stress, helping to decrease pro-inflammatory processes in the lungs [71]. It has a rapid turnover and is quickly replenished by: (1) *de novo* synthesis by sequential action of two enzymes. The first, GCS (gamma-glutamyl-cysteine synthesase (ligase) is rate limiting and normally functions at substantially less than its maximum capacity because of feedback inhibition by GSH, while responding rapidly to GSH requirements [47]. In addition, GSH synthesis increases dramatically with oxidative stress through increase GCS transcription via Nrf2, providing there is adequate availability of cysteine, the rate limiting substrate [70]. Our patients took two Nrf2 activators, curcurmin and sulforaphane glucosinolate. Nrf2 suppresses macrophage inflammatory response by blocking proinflammatory cytokine transcription [72], and both curcumin and sulforaphane are potent Nrf2 activators that have been shown to decrease a broad range of inflammatory cytokines including IL-6 [73], helping to lower inflammation [74,75].

Elderly patients have been shown to have an increased risk from exposure to COVID-19 [13]. GCS activity decreases with age and from reduced recycling of reduced GSH from GSSG. With an adequate supply of cysteine, cells can have a large reserve capacity to increase GSH production and counter oxidative stress [47]. It is therefore possible that by administering large doses of NAC and glutathione, along with zinc, Vitamin C and Nrf2 activators, we lowered oxidative stress and inflammatory cytokine production, resulting in a rapid improvement in dyspnea and clinical symptomatology. A limitation of our study, apart from the small sample size however, is that we were unable to do laboratory testing in our patients, including checking oxidative stress markers (lipid peroxides) as well as inflammatory markers (CRP, ferritin, D-dimer) and LDH which might demonstrate a change post GSH administration [76–78]. A randomized, controlled trial of GSH, glutathione precursors with inflammatory/oxidative stress markers should be done in the future to fully elucidate the effects of blocking NF-kappaB, and to determine the effect of GSH and antioxidants on the clinical course of COVID-19 pneumonia and ARDS.

4. Conclusion

Activation of nuclear factor-kappaB (NF-kappaB) has been shown to be required for transcription of the genes for many of the pro-inflammatory mediators associated with ARDS. An intact inflammatory response, in which NF-κB plays a major role, is also required for appropriate host defense against viruses [79] and in the later stages of bacterial pneumonia [80]. In preclinical models of sepsis and acute lung injury, associated with rapid and large increases in pro-inflammatory cytokines and other mediators, suppression of NF-κB activation has been shown to result in improved survival [81,82]. NAC, alpha-lipoic acid and GSH all inhibit TNF-α-induced NF-kappaB activation. Oral and IV glutathione as well as glutathione precursors (N-acetyl-cysteine, alpha-lipoic acid) may, therefore, represent a novel treatment approach for blocking NFKappaB and addressing "cytokine storm syndrome" and respiratory distress in patients suffering with COVID 19 pneumonia. Zinc, vitamin C and NRF 2 activators may also be helpful in decreasing the inflammatory response and lowering cytokine production. Randomized controlled trials should be performed to evaluate the efficacy of these novel therapies in the treatment of patients with COVID-19 pneumonia and ARDS.

Disclaimer

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

Declaration of competing interest

The authors, Richard I Horowitz, Phyllis R Freeman, and James Bruzzese declare no conflict of interest. The funders had no role in the design of the study; in the collection, analyses, or interpretation of data; in the writing of the manuscript, and in the decision to publish the results.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.rmcr.2020.101063.

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