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
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 centriflobular 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 normalities are seen in patients who recovered from COVID-19 [23]. They are associated with a poorer prognosis in patients with novel coronavirus pneumonia (NCP) [31]. 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 centriflobular 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 normalities are seen in patients who recovered from COVID-19 [23].

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-κB) 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-κBα [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, intermittent. No other associated prior symptoms relapsed from 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 nonsupplement, and no history of significant cardiac arrhythmias and/or QT prolongation on an electrocardiogram. He was seen again in January 2020 when his old Lyme symptoms remained at 95% or higher. He was 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 with a metallic taste, low-grade fevers (99.5–100.5 Fahrenheit), sweats (day and night occasionally interfering with sleep), body aches with flu-like 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 nonsupplement, and no history of significant cardiac arrhythmias and/or QT prolongation on an electrocardiogram.
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 250 mg 4 tablets QD treatment for her tick-borne illness, and had a dramatic improvement.

Glutathione at a dose of 2 g up to twice a day PRN for shortness of breath. To falling ill with COVID-19, the patient was healthy and eating a balanced diet with no notable health complaints. Free. As antibody tests were not readily available in NYC at the time of 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 receiving initial doses of GSH, the patient remained well and symptom free.

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 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.
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 intracellular 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 synthetase (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, curcumin 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-kappaB 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 Bruzzone 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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