A RCT of NAC, Glutathione and Nutraceuticals Compared to Ivermectin in COVID-19. Stopping Ongoing Progression of Illness: The STOP COVID Trial
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Richard I. Horowitz, MD
Medical director, Hudson Valley Healing Arts Center
Board certified internal medicine
Member HHS Tick-borne Disease Working Group 2017-2019
Co-chair HHS Other Tick-borne Diseases and Co-infections subcommittee 2017-2019
Member, HHS Babesia and Other Tick-borne Pathogens 2019-2020

A hypothetical three-part prevention, diagnostic, and treatment approach based on an up-to-date scientific literature review for COVID-19 was published by Horowitz et al. in 2020.[1] The primary hypothesis behind designing an effective prevention and treatment approach was based on the medical literature showing that infection, immune dysfunction, and inflammation (3 I's) cause severe symptoms/clinical manifestations in COVID-19. Pathogenicity of COVID-19 has been linked in some patients to "Cytokine Storm Syndrome" (CSS) with "Acute Respiratory Distress Syndrome" (ARDS), which is the primary cause of death, along with fulminant myocarditis and multiorgan dysfunction. This results from an uncontrolled systemic inflammatory response with an increase in large amounts of pro-inflammatory cytokines (IFN-α, IFN-γ, IL-1β, IL-6, IL-12, IL-18, IL-33, TNF-α, TGFβ, etc.) & chemokines (CXCL9, CXCL10, etc.) by immune effector cells. [2] [3] Recent scientific research has determined that not all patients who succumb to COVID-19 have evidence of a cytokine storm however, and the etiology underlying severe manifestations is still being investigated.[4]

One hypothesis that urgently needs to be investigated in the pathogenesis of COVID-19 and severe manifestations including ARDS is glutathione deficiency. Endogenous deficiency of glutathione is considered by some authors to be a likely cause of serious manifestations and death in COVID-19 patients. [5] Glutathione (GSH) is the body's primary antioxidant and has been shown to be deficient in viral, bacterial pneumonia & ARDS. [6] Based on the evidence attesting to the ability of glutathione (GSH) to inhibit viral replication and decrease levels of IL-6 in human immunodeficiency virus (HIV) and tuberculosis (TB) patients, as well as beneficial effects of GSH on other pulmonary diseases processes, the use of liposomal GSH has been hypothesized to be beneficial in COVID-19 patients. [7] No clinical studies on COVID patients have been performed to date however to prove the hypothesis.

Dr Horowitz has over a 20-year experience using glutathione in thousands of patients with Lyme disease, where glutathione helps lower inflammatory cytokines produced during Herxheimer reactions. [8] These are similar inflammatory cytokines seen in COVID-19,[3] which is the basis for the Horowitz COVID protocol. The use of glutathione for COVID-19 has also been validated in a small pilot trial of 40 patients with COVID in his clinical practice, where patients reported a rapid improvement in symptoms following administration of oral glutathione, glutathione precursors (N-acetylcysteine), nutraceuticals (alpha lipoic acid, zinc, beta glucan) as well as ivermectin. No patients to date have required hospitalization. Two of those cases were published by Horowitz and Freeman in the Journal of Respiratory Case Reports in April 2020, which showed benefit using GSH for COVID-19 pneumonia, relieving dyspnea and associated symptoms, i.e., fatigue, myalgias, headaches.[9] Since that time, the glutathione article by

Horowitz et al. has been cited by 51 authors as a potential treatment for COVID-19 (https://scholar.google.com/scholar?rlz=1C1EJFC_enUS894US894&um=1&ie=UTF-8&lr&cites=9901749048605479286) without the benefit of proving the hypothesis via a RCT.

The scientific reasoning behind a glutathione trial, is that the primary roles of glutathione (GSH) in the body include antioxidant/anti-inflammatory activity by neutralizing potentially dangerous molecules (Reactive oxygen species [ROS], Reactive nitrogen species [RNS]), xenobiotics, and metals; regulating cell processes of metabolism, proliferation, differentiation, and apoptosis; and regulating our immune response, since the concentration of GSH and its oxidized form, glutathione disulfide (GSSG), mainly determines the redox state of the cell, which plays a direct role in viral pathogenesis [10] [11] [12] The positive effects of N-acetylcysteine (a precursor of glutathione), oral glutathione (GSH) and a novel sublingual form of GSH on oxidative stress markers have been demonstrated in a randomized, controlled comparative crossover study. [13] Glutathione, NAC and alpha lipoic acid all have the ability to block NFKappaB, a switch inside the nucleus which increases oxidative stress and inflammatory cytokine production, which accounts in part for its anti-inflammatory and antiviral activity. [14] [15] [16] [17] [18] [19] Many studies have shown that NF-kappaB plays an important role in the pathogenesis of lung diseases, including a role in COVID-19. [20] Published research has shown that COVID-19 activation of transcription factor NF-kappa B (NF-κB) in macrophages found in the lung, liver, kidney, central nervous system, gastrointestinal system and cardiovascular system leads to production of inflammatory cytokines IL-1, IL-2, IL-6, IL-12, TNF-α, LT-α, LT-β, GM-CSF, and a wide variety of chemokines, which in the elderly and in patients with underlying risk factors such as metabolic syndrome makes this population susceptible to COVID-19 and its worst complications, including higher mortality". [21] This is especially relevant in the elderly, where low blood glutathione levels have been found in healthy aging adults, and the incidence of low blood GSH in the older subjects increased significantly, particularly in the 60- to 79-year-old group.[22] This would potentially explain why the elderly are at higher risk for COVID-19 and why glutathione supplementation and GSH precursors which block NF-κB may be of benefit. Glutathione deficiency would leave individuals susceptible to high levels of ROS and oxidative stress, damaging lung tissue and causing multisystemic dysfunction.

Apart from lowering inflammation by blocking NF-κB and affecting the redox state of the cell, GSH also has direct anti-viral activity. [23] [24] [25] Glutathione has been shown to fine-tune the innate immune response toward antiviral pathways in a macrophage cell line independently of its antioxidant properties, [25] and has been shown to inhibit viruses including herpes simplex virus type 1, HIV, and influenza virus. [26] [27] [28]. Loss of glutathione, with associated oxidative stress and decreased intracellular pH have been shown to be sequential steps in viral infection, [29] and some of the antiviral activity of GSH is through a process known as glutathionylation. [30] Glutathionylation is the formation of mixed disulfides between protein cysteines and (GSH) cysteines. Microbial proteins undergo glutathionylation with modification of their functions, and viruses alter the intracellular redox state to pro-oxidant conditions, which is an alteration that contributes to viral pathogenesis. N- Acetyl-L-cysteine (NAC) is a precursor of reduced glutathione (GSH) and both NAC and GSH have disulfide bonds, [31] which may also account in part for their anti-viral effect, as thiols have been shown to block the angiotensin-converting enzyme (ACE) 2 receptor, thereby hampering penetration of SARS-CoV-2 into cells.[32] This is in addition to NAC's mucolytic effects, [33] indirect and direct anti-inflammatory effects, and helping

to regenerate glutathione in the body. [34] The efficacy of oral long-term N-acetylcysteine in chronic bronchopulmonary disease has previously been established in a meta-analysis of published double-blind, placebo-controlled clinical trials, and found to prevent acute exacerbations of chronic bronchitis, thus possibly decreasing morbidity and associated health care costs.[35]

In order to effectively address increased reactive oxygen species (ROS) and inflammation during COVID, postulated to be one of the primary mechanisms responsible for increased morbidity and mortality, we will also be adding alpha lipoic acid (ALA) to NAC and glutathione. Alpha lipoic acid has similarly been shown to block NF-kappaB inside the nucleus. [18] [36] [37]. Since NF-κB plays a key role in the orchestration of the multifaceted inflammatory response, in the pro-inflammatory phase and later in the resolution of inflammation when anti-inflammatory genes are expressed (ARE) [19] it is potentially a key biochemical pathway in COVID pathogenesis. NF-B regulates the expression of a large number of genes involved in inflammation and is considered to be the master regulator of the inflammatory response. [38] Activation of NF-kappaB has also been found to be required for transcription of the genes that increase the pro-inflammatory mediators associated with ARDS.[39] No clinical trials to date have used NAC, GSH and ALA in the treatment of ARDS, and effective treatments for ARDS are lacking. A clinical trial of these nutraceuticals is therefore essential in the quest to find more effective treatments.

Despite considerable advances in our knowledge regarding the pathophysiology of ARDS, insights into the biologic mechanisms of lung injury and repair, and advances in supportive care, particularly ventilatory management, there remains no effective pharmacological therapy for this syndrome.[40]Although dexamethasone has been found to be helpful in certain severe cases of COVID, [41] certain authors caution against its immunosuppressive properties. This is due to dexamethasone's ability to inhibit the protective function of T cells, while blocking B cells from making antibodies, potentially leading to increased plasma viral load that will persist after a patient survives SARS. Moreover, dexamethasone would block macrophages from clearing secondary, nosocomial, infections. Hence, dexamethasone may be useful for the short-term in severe, intubated, COVID-19 patients, but could be outright dangerous during recovery since the virus will not only persist, but the body will be prevented from generating protective antibodies".[42] For that reason, a pilot study of NAC, ALA, and high dose IV glutathione will be performed in the ICU setting with critically ill patients who may be on ventilators, to determine the protocols efficacy in resolving ARDS, improving oxygenation and the ability to wean.

Glutathione (GSH) is the main antioxidant agent in mammalians, and it is the most important antioxidant defense in the lungs as it not only augments innate and adaptive immunity and lowers inflammation, but confers protection against microbial and viral infections. [43] Multiple pulmonary diseases including asthma, chemically induced edema, and Idiopathic Pulmonary Fibrosis (IPF) have improved with glutathione administration. [43] Patients with IPF have a 4-fold lower GSH concentration in the epithelial lining fluid of the normal lower respiratory tract, and the administration of the GSH precursor NAC restores GSH levels. [44] Normal alveolar epithelial lining contains high levels of glutathione [45] which may be lowered by oxidative stress and infection.

Another biochemical pathway which will be addressing in our RCT is the Nrf2 pathway. Nrf2 regulates the oxidative stress response in cells and helps lower inflammation. [46] When oxidative stress is present, a molecule in the cytoplasm, KEAP-1 is released and goes into the nucleus to stimulate antioxidant response element genes (ARE). The redox-sensitive signaling system Keap1/Nrf2/ARE plays a key role in the maintenance of cellular homeostasis under stress, especially inflammatory and pro-apoptotic conditions, which is why it is being considered in our trial as a pharmacological target.[47] Thereby, sulfhydryl (SH) group donors, activators of Nrf2 and NF-κB inhibitors, through their regulator molecules (KEAP-1 and IκB, respectively), are potential therapeutic options for SARS-CoV-2 infection. In the STOP COVID RCT, the antioxidant curcumin will be used as our Nrf2 activator. Curcumin has been published to have a broad range of immunomodulatory effects, and effectively lower inflammation via activation of Nrf2,[48] [49] [16] which along with NAC, ALA and GSH, provide a logical basis for their use in COVID. Curcumin may have an added benefit, as it has been evaluated as a potential inhibitor of the COVID-19 Main Protease (Mpro).[50]

The other nutritional supplements that will be evaluated in the STOP COVID trial, taken along with high dose NAC (1200 mg BID) alpha lipoic acid, liposomal glutathione (2000 mg TID) and curcumin, are zinc and 3,6 Beta glucan. Zinc-deficiency has been shown to increase susceptibility to pathogens, whereas after zinc supplementation, there is a lower incidence of infections and decreased TNF-α & oxidative stress markers. [51] [52] Zinc also inhibits induction of TNF-α and IL-1β mRNA in mononuclear cells (MNCs), provides protection against TNF-α–induced nuclear factor–κβ activation in mononuclear cells, and macrophages are adversely affected by zinc deficiency, leading to dysregulated intracellular killing and cytokine production.[53] [54] As zinc is also essential to preserve natural tissue barriers such as the respiratory epithelium, preventing pathogen entry, for a balanced function of the immune system and the redox system, zinc deficiency is felt by some authors as one of the factors predisposing individuals to infection and detrimental progression of COVID-19.[55] In one recent study, a significant number of COVID-19 patients were zinc deficient, developed more complications, and zinc deficiency was associated with a prolonged hospital stay and increased mortality.[56] We will therefore measure not only serum zinc, but RBC zinc in our RCT, as prior studies by Horowitz et al. have shown that many serum minerals including zinc, copper and magnesium have significant intracellular concentrations. [57]

The last nutraceutical to be included in MedPax-1 is Beta glucan. Since certain COVID patients have been shown to have worse outcomes due to immune deficiency and lymphopenia, [58] and Beta glucan has been shown to have immunostimulatory effects, [59] helping to raise numbers of T cells and NK cells [60] [61] it will be included in the STOP COVID trial.

All of the above referenced supplements will be in MedPax-1 from Xymogen at the following dosages:

COVID Study Medpax #1:

Zinc Glycinate – 20 mg, 1capsule in each am/pm packet (20 mg BID)
NAC 600 mg – 2 capsules in each am/pm packet (1200 mg BID)
Alamax CR *(alpha lipoic acid-controlled release) - 1 tablet in each am/pm packet (alpha lipoic acid, 600 mg BID)
Curcuplex 95 - 1 capsule of curcumin is in each am/pm packet (500 mg BID)

Immunotix 250 mg (3,6 Beta glucan): 1capsule in each am/pm packet (250 mg BID).
In one arm of the study, each MedPax-1 will be taken twice a day, along with liposomal GSH from Wellness Pharmacy, at a dose of 8 capsules, 250 mg each (2000 mg) three times a day. The liposomal glutathione can be taken at the same time as each MedPax, with breakfast (7-8 am) and dinner (7-8 pm), with the third dose of liposomal glutathione taken mid-day (2 pm).

MedPax #2: this will be used in the other arm of our trial, along with ivermectin, dosed at 0.2 mg/kg, once a day. Each packet of MedPax-2 contains 3 Active Nutrients (multivitamin) without copper or Fe, along with magnesium (OptiMag) 125 mg, and 5-MTHF (methyl-tetra-hydrofolate). None of these have significant anti-inflammatory effects, and we will be able to compare

Considering the rapid spread worldwide and elevated morbidity and mortality rates of COVID-19 despite the use of FDA approved therapies including remdesivir, [62]dexamethasone, [63 64 65] and monoclonal antibodies, [66] a RCT of glutathione and anti-inflammatory nutraceuticals needs to be urgently performed, based on their known biological properties. The use of ivermectin as an adjunctive anti-viral strategy also needs to be examined, based on its pharmaceutical properties and multiple peer-reviewed studies showing potential benefit for COVID-19. [67 68 69 70 71(p19) 72 73(p19)] Of 54 ivermectin trials on clinicaltrials.gov,[74] just three are based in the United States, none of them federally funded. Outpacing the U.S. are Egypt, with 10 trials; India, eight; Spain, five; and Argentina, four. Like the U.S., Brazil, Bangladesh, and Mexico list three studies each. A generic pill used against parasites with anti-viral activity apparently holds little interest for investors, pharmaceutical companies, or government funders. Yet a RCT using a generic, oral treatment with a drug that has a long safety record and multiple published studies for COVID-19 is urgently needed, especially with a recent study published in Chest, showing lower mortality rates in COVID-19. [75] In that study, ivermectin treatment was associated with lower mortality during treatment of COVID-19, especially in patients with severe pulmonary involvement, but a randomized controlled trial is needed to confirm these findings.

The proposed RCT will involve approximately 175 patients, in three arms of a study. One group of 100 patients will be evaluated in the outpatient setting. The emergency department at UCI sees approximately 50 patients per day, and 13% of those patients according to UCI have been testing positive for COVID (i.e., 8 patients per day). We may therefore be able to enroll 100 patients within a four-week time frame in the outpatient setting, as the numbers of COVID cases are again beginning to spike in the United States, however, full enrollment in the study for all arms is expected to take approximately 8 weeks, since not all patients will consent to be part of the

trial. The details of the three arms of the study and primary and secondary objectives are listed below:

The powered study for the Horowitz COVID protocol will evaluate the following parameters:

1. **Primary Objective: Stopping Progression of Illness:** This will involve evaluating avoidance of admission to the hospital in arm 1, and prevention of disease progression in arms 2 (preventing admission to the ICU) and arm 3 (preventing the need for ventilator support or improving vital signs/respiratory parameters on ventilators and ability to wean).
2. **Secondary Objectives: Evaluate symptom response with validated screening tools**, **including time to clinical recovery.** Symptom response will be evaluated by several questionnaires.

A. **The SF-36** (Medical Outcomes Trust, Boston, MA) is a multipurpose, short-form health survey with 36 questions. It yields an eight-scale profile of scores as well as physical and mental health summary measures. It is a generic measure, as opposed to one that targets a specific age, disease, or treatment group. Accordingly, the SF-36 has been useful in comparing general and specific populations, comparing the relative burden of diseases, differentiating the health benefits produced by a wide range of different treatments, and screening individual patients. (Ware, J. E., Jr. (1999). SF-36 Health Survey. In M. E. Maruish (Ed.), The use of psychological testing for treatment planning and outcomes assessment (p. 1227–1246). Lawrence Erlbaum Associates Publishers).

B. **COVID Severity of Symptoms Questionnaire:** This will evaluate the initial severity of symptoms (Table 1) and how symptom severity changes over time with treatment (Table 2). Secondary Endpoints: All causes mortality, Frequency of respiratory progression (defined as SPO2≤ 94% on room air or PaO2/FiO2 <300mmHg and requirement for supplemental oxygen or more advanced ventilator support), time to defervescence (in those with fever at enrolment), frequency of requirement for supplemental oxygen or non-invasive ventilation, frequency of requirement for mechanical ventilation, frequency of serious adverse events as per DAIDS table grade of severity.

C. **COVID Time to Clinical recovery (TTCR).** See Table 3. These measures are based on a recent NIH trial (https://pubmed.ncbi.nlm.nih.gov/33081849/ and defined as the time (in hours/days) from initiation of the study treatment protocol (glutathione or ivermectin) until there is normalization of fever, respiratory rate, oxygen saturation, and alleviation of cough, sustained for at least 72 hours, as well as time to normalize associated symptoms (headache, fatigue, sore throat, diarrhea, etc.). (2) Time to SARS-CoV-2 RT-PCR negative in upper respiratory tract specimen, time to laboratory recovery of each organ involvement. Initial outcomes are monitored for 28 days from the time of enrollment into the study OR until the patient is discharged or death whichever is longer. Time to becoming PCR negative will be measured in the inpatient setting as per UCI standard of care. In Arm 1, in the outpatient setting, RT-PCR can be measured on days 14 and 28 when repeat laboratory testing is done (see above).

The three arms of the study are listed below:

Arm 1: As there is no standard of care for treating COVID in the outpatient setting, the study design will be to randomize outpatients to one of two protocols. Either a COVID MedPak-1 (Xymogen) taken twice a day X 14 days, which contains in total: NAC 1200 mg BID, alpha lipoic acid (ALA) 600 mg BID, zinc 20 mg BID, curcumin 500 mg BID, and 3,6 Beta glucan 250 mg BID. This will be taken for 14 days along with liposomal glutathione (250 mg/capsules, Wellness Pharmacy) 8 capsules three times a day (2000 mg TID) for 10 days. The NAC, ALA, and glutathione block NFKappa B, the curcumin stimulates Nrf2 pathways, and zinc along with Beta glucan supports a healthy immune response (see medical references below). The other randomized arm of the trial will receive a COVID MedPak-2 (Xymogen) which will contain a multivitamin, minerals (magnesium) and B vitamin (methyl-folate) supplements, while being given ivermectin 0.2 mg/kg once a day X 14 days.

Dosing of ivermectin will be determined by taking the body weight in lbs., dividing by 2.2 (to measure kilograms) and multiplying by 0.2 mg to determine the total dose taken once a day. Since ivermectin comes in 3 mg tablets and is scored, the dose will be rounded up to the nearest ½ tablet or full tablet, as illustrated by the following chart:

Weight lbs.	Weight Kg	Dose Ivermectin
100	45.45	9.09 mg PO QD (round up to 3 ½ pills, at 3 mg/each, 10.5 mg)
110	50	10 mg PO QD (round up to 3 ½ pills once a day, 10.5 mg)
120	54.54	10.9 mg PO QD (round to 4 pills once a day, 12 mg)
130	59.09	11.8 mg PO QD (round up to 4 pills once a day, 12 mg)
140	63.6	12.72 mg PO QD (round up to 4 ½ pills QD, 13.5 mg)
150	68.18	13.6 mg PO QD (round up to 5 pills QD, 15 mg)
160	72.72	14.54 mg PO QD (round up to 5 pills QD, 15 mg)
170	77.27	15.45 mg PO QD (round up to 51/2 pills QD, 16.5 mg)

To cut the pills: a pill cutter can be provided. Alternatively, putting the tablet on a hard surface and pushing down on both sides of the scored tablet with both thumbs causes the tablet break in half.

In Arm 1, oxygen saturations will be measured with a pulse oximeter given to each study participant, and temperature/fevers and blood pressure/pulse will be measured with a digital thermometer and BP cuff, also provided at the time of enrollment. Respiratory rate will only be measured in arms 2 + 3, in the inpatient setting.

Study Calendar: Labs that will be drawn at time 0, day 14 and day 28 for each participant in all arms of the study will include a UCI panel with a CBC and lymphocyte count, CD8 T cell count, NK cell count (number/function) CMP (electrolytes, LFT's, BUN/creatinine), LDH, hs-CRP, ferritin, procalcitonin, D-dimer, fibrinogen, CPK, ESR, IL-6, serum zinc and RBC zinc levels, serum copper and RBC copper levels, serum magnesium and RBC magnesium levels, and a serum glutathione level. Men should also have a testosterone level drawn. A basic cytokine panel which checks levels of TNF-alpha, interferon-ß (IFN-ß), Interferon gamma, IL-1Beta, IL-2, IL-6, IL-8, IL-10 and IL-17 will also be drawn on day 1, day 14 and day 28 to evaluate the effect of each treatment arm on cytokine levels.

An initial pulse oximetry will be recorded, and ABG will be done if oxygen saturations are less than 90% (as per UCI protocol). An initial CXR will be done at the time of enrollment in all groups who have tested positive for COVID-19 and will be repeated as per UCI protocols in the inpatient setting. A repeat CXR in the outpatient group will only be done if COVID pneumonia is present, if there is clinical deterioration (increased cough, shortness of breath) or if oxygen saturations drop below 90%. Any patient with a CXR suggestive of COVID pneumonia with a

positive procalcitonin, will receive doxycycline 100 mg BID and zinc 40 mg/day as per early clinical published research, [69] or as per ID protocols at UCI. Probiotics including a broad spectrum acidophilus and *saccharomyces boulardii* will be prescribed BID if patients are on antibiotics to prevent antibiotic associated diarrhea. [76] [77]

Outpatient testing: Patients in Arm 1 will be sent home with their own pulse oximeters, blood pressure cuffs and thermometers, instructing them to check in by phone and video chat when needed with a clinical coordinator (9 am – 5 pm PST). Temperature, pulse oximetry and blood pressure will be checked twice a day (i.e., 8 am, 8 pm), and recorded in a patient diary provided at enrollment. (Kranthi Sitammagari, MD et al. Insights From Rapid Deployment of a "Virtual Hospital" as Standard Care During the COVID-19 Pandemic. Annals of Int Med. 11 Nov 2020. https://www.acpjournals.org/doi/10.7326/M20-4076)

Arm 2 of the study will be the same treatment design but will involve 50 in patients on the medical ward, who will be randomized to one of two treatment arms, crossing over to the other arm of the study after 14 days. The powered study will evaluate progression to the ICU. Subgroup analysis will evaluate symptom relief, time to clinical recovery (TTCR) and the above secondary endpoints. All patients will receive the Horowitz COVID protocol listed above along with the standard of care from UCI (if eligible, i.e., remdesivir, dexamethasone, monoclonal antibodies).

Arm 3 of the study will be a pilot study in the ICU. This will not be randomized, and all patients will receive both the COVID MedPack-1 (NAC, ALA, curcumin, zinc, beta glucan) with IV glutathione 2000 mg TID as well as ivermectin, 0,2 mg/kg. Prior RCT's of ivermectin showed COVID patients on ventilators had lower mortality rates. No one to date has evaluated the efficacy of glutathione in ARDS. Since glutathione deficiency has been identified in viral, bacterial pneumonia and ARDS, the goal will be to add this treatment protocol to the standard of care at UCI and evaluate whether we can improve morbidity and mortality and the ability to wean more quickly off the ventilator. Secondary endpoints listed from structured NIH trials will be included. There will not be enough patients to properly power the study, so this will be a pilot study to evaluate the feasibility of doing a larger RCT through the NIH. We will follow CXR's, measure oxygen saturations, vital signs, peak pressures, ability to wean, Apache scores, evidence of DVT/PE's (standard of care at UCI) as well as inflammatory markers validated for COVID outcomes listed above i.e., (LDH, hs-CRP, D-dimers, cytopenias, ferritin…), and depending on cost, follow inflammatory cytokines before and after treatment with glutathione and ivermectin. In a recently published study 24% of patients died with COVID (Mudd, P. et al. Distinct inflammatory profiles distinguish COVID-19 from influenza with limited contributions from cytokine storm DOI: 10.1126/sciadv.abe3024). Serum glutathione levels should therefore be checked before and after treatment in all three treatment arms to evaluate changes in blood levels, which will be correlated with clinical response.

Once each group has finished 14 days of their protocol (arms 1 + 2), they will be crossed-over to the other treatment arm. This will allow us to evaluate the effect of blocking inflammation and supporting glutathione production in the body in one arm, vs simply giving an anti-viral medication (ivermectin) without anti-inflammatory support during the first 14 days of being diagnosed with COVID. The study schema listed below outlines the three arms of the study.

Study Calendar: Apart from standardized lab testing for all groups on day 0 (beginning of the trial), and days 14 and 28 (listed above), all patients will fill out validated screening questionnaires at time 0 (testing positive in the outpatient setting or testing positive and being

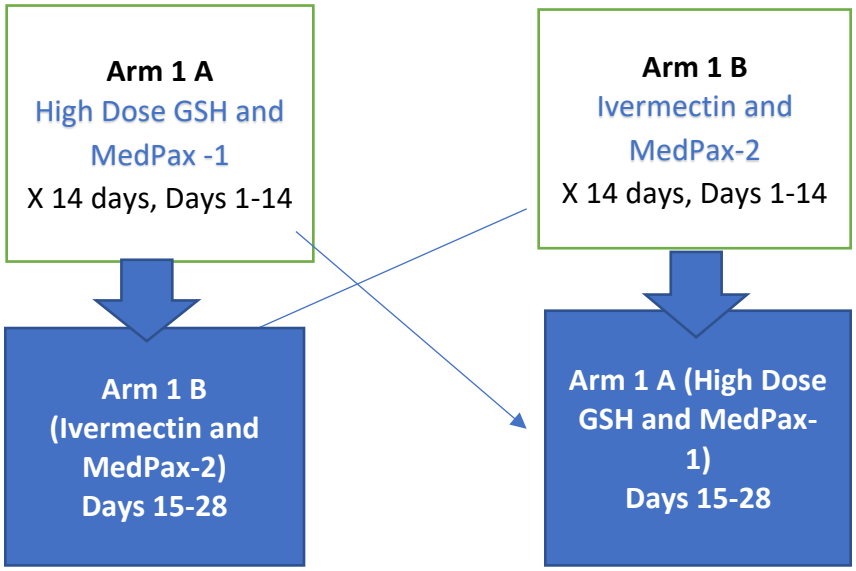
admitted to the medical ward), and then again on days 3, 7, 14, 18, 21 and 28, which will include questions on active symptoms and time to clinical recovery. This will include the SF-36, and Questionnaires 1, 2, 3 (Table 1, 2, 3). A follow-up questionnaire will be administered one-month post trial, and three months post trial, to evaluate long term sequelae (i.e. progression of illness to COVID longhauler status).

Randomization: The randomization will be done using a secured central computer-based randomization using a secure website using a central, computer-based randomization program in a ratio of 1:1.

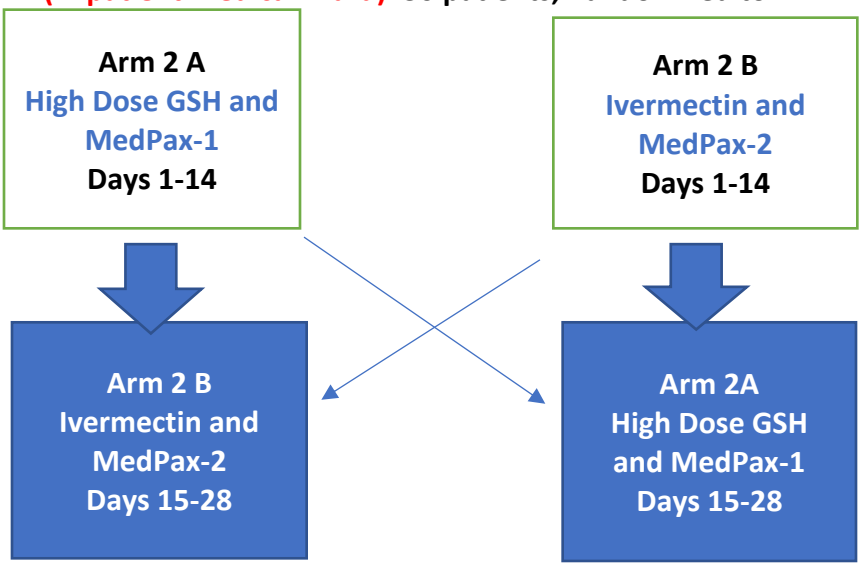
Diagrammatic Outline of Three Arms of The Horowitz Glutathione/Ivermectin Study Protocol for COVID-19. Figure 1

Arm 1 (Outpatient Setting) 100 Patients, Randomized to Arm A or Arm B

Arm 1 A will cross over to Arm 1 B after 14 days, Arm 1 B will cross over to Arm 1 A after 14 days



Arm 2 (In patient Medical Ward): 50 patients, Randomized to Arm 2 A and 2 B



Arm 3, In patient, ICU: **Nonrandomized. All patients will receive IV GSH 2000 mg IV TID X 10 days, MedPax-1, Ivermectin 0.2 mg/kg PO QD (as per dosing chart above)**

Inclusion Criteria: Patients greater than 18 years old, with positive COVID testing (AB, RT PCR) and mild-severe symptoms (see Table 1 for COVID symptom list)
Exclusion Criteria: history of a severe sulfa sensitivity (i.e., anaphylaxis, Stevens Johnson Syndrome), allergy to meat products and/or gelatin (alpha gal allergy) and/or a history of an allergy or intolerance to ivermectin
Since glutathione is made in the liver phase II pathways, oral GSH does not usually cause severe reactions, even in those who have a mild-moderate sulfa sensitivity. Zyrtec (cetirizine) 10 mg PO QD and Famotidine 20 mg PO QD (H1 and H2 blockade) can be administered during the trial to those who have a history of mild- moderate sulfa sensitivity to minimize the possibility of any reactions. IV glutathione may cause mild allergic reactions in those with multiple chemical sensitivity and severe allergies to Bactrim (sulfamethoxazole/trimethoprim), but since these patients will be in the ICU setting, with close monitoring (and probable administration of dexamethasone), only a history of Stevens Johnson Syndrome would be an absolute contra-indication to IV GSH.
Potential Side Effects: no significant adverse side effects from the nutritional supplements or ivermectin are expected in the trial based on years of experience prescribing this protocol for other indications. Rarely, individuals with significant reactive hypoglycemia may experience an increase in blood sugar swings with alpha lipoic acid 600 mg BID. Participants should be informed that if they have type I or type II diabetes, or a history or reactive hypoglycemia, that strict adherence to a diabetic diet, i.e., Mediterranean/Paleo type diet (40% healthy protein/30% healthy fats [olive oil, avocado], 30% complex carbohydrates) is necessary to avoid increased blood sugar swings, and should adjust diabetic medication accordingly, as per their HCP.

Xymogen will be labeling the MedPax as '1 and 2', as these will be printed on each of the packets/boxes. We can also use a sticker to label the patient number on the packet or box. Xymogen will be contacted immediately once we have a start date so they can begin production. After the patient is randomized to MedPax 1 or 2, they will receive a typed instruction sheet on how to take the supplements (with meals, but one hour away from antibiotics to avoid any minerals interfering with absorption); The liposomal glutathione pills are to be taken one at a time with a sip of water, until reaching the dose of 8 capsules (2000 mg); A compliance sheet can be provided to make sure patients do not miss any doses (check marks/signatures can be placed on the sheet after each time they take their medication/supplements), as illustrated below (dates are appx, patients will fill in the start date):

MedPax 1: Glutathione and Nutraceuticals: 14-day Compliance Checklist

Date	Morning Dose	Mid-day Dose	Evening Dose
Day 1, December 14			
December 15			
December 16			
December 17			
December 18			
December 19			
December 20			
December 21			

December 22			
December 23			
December 24			
December 25			
December 26			
December 27			
Move to Med Pax 2			

MedPax 2: Ivemectin and Nutraceuticals: 14-day Compliance Checklist

Date	Ivermectin	Morning Dose	Evening Dose
Day 1, December 28			
December 29			
December 30			
December 31			
January 1			
January 2			
January 3			
January 4			
January 5			
January 6			
January 7			
January 8			
January 9			
January 10, End			

Patients will submit their completed compliance sheets online, as well as fill out the validated symptom questionnaires and submit them online in a HIPPA compliant fashion (unless an app is available through UCI). A patient coordinator for the study will be available to answer questions between 9 am and 5 pm, and an emergency line will be also be provided for the study participants.

The primary goal of the first arm of the randomized clinical study with a cross-over design will be to evaluate whether the glutathione protocol and/or ivermectin arms of the study prevent admission to the hospital. The second arm of the study, which will involve 50 in patients on the medical wards with COVID-19, will be to evaluate the efficacy of the protocol in preventing progression to the ICU. All patients will also be evaluated using the secondary endpoints listed above.
Validated symptom questionnaires evaluating fatigue (SF-36), as well as common ENT and respiratory symptoms along with psychological manifestations (Int J Environ Res Public Health, see below) will be used to follow treatment response, along with the standard of care practiced at the UCI. We added the following 3 symptoms to the ENT questionnaire, which are part of the COVID symptom complex, but not included in the initial version of the ENT questionnaire: chills, vomiting, brain fog/memory problems.
The initial intake: This should contain chief complaints, Past Medical History (PMH), medications, supplements, allergies/intolerances, Review of Systems (ROS) as per UCI protocol.
Risk factors listed in the scientific literature should also be included in the initial intake:

Advanced age (≥ 65), male gender, low T, race (African-American, Hispanic, Native American), ? type O blood (if known) with CCL-2 SNPs, obesity, smoking history, as well as a PMH: HTN, DM, CV and respiratory disease (asthma, emphysema), Hemorrhagic or ischemic strokes, immunosuppression, cancer, chronic kidney and liver disease & secondary infections; children however are also at risk with MIS (Multi-inflammatory Syndrome).

Rating Severity of Symptoms: when asking patients to rate the overall severity of their symptoms and change from their last report, scoring for each question will allow for both improvement and worsening. The initial questionnaire will determine the severity of symptoms at the beginning of the trial. Follow up questionnaires will evaluate the severity of symptoms since the last report: (0 [no change], + 1 [mild improvement], + 2 [moderate improvement], + 3 [significant improvement], +4 [symptom resolved]. - 1 [mild worsening], + 2 [moderate worsening], + 3 [significant worsening].

Table 1: Initial COVID Symptom Questionnaire, Day of Enrollment, w/ FU days 14 and 28 Horowitz, R.I. (modified from Int J Environ Res Public Health)

A follow-up questionnaire can be administered **one-month post trial, and three months post trial**, to evaluate long term sequelae (i.e., progression to status of COVID longhauler)

COVID Symptom	None (not applicable)	Mild	Moderate	Severe
Fever		99.9 F or below	100 degrees-101.9 F.	Greater than 102 degrees F
Chills				
Shortness of Breath				
Cough				
Sputum (expectorate)				
Sore throat				
Loss of sense of smell (anosmia)				
Loss of sense of taste (dysgeusia)				
Nasal congestion				
Eye irritation (conjunctivitis)				
Fatigue (exhaustion)				
Muscle pain				
Nausea				
Vomiting				
Diarrhea				
Headache				
Brain fog/Cognitive Difficulties				
Anxiety				
Depression				

Distressed				

Table 2: COVID Symptom Questionnaire, Change in Severity of Symptoms Over Time Day 3, 7, 14, 18, 21, 28. Horowitz, R.I.

COVID Symptom	None N/A	No Change	+1 Mild Improv	+2 Mod Improv	+3 Signif Improv	+4 Resolved	-1 Mildly Worse	-2 Mod Worse	-3 Signif Worse
Fever									
Chills									
Shortness Of Breath									
Cough									
Sputum expectorate									
Sore Throat									
Loss of Sense of Smell									
Loss of Sense of Taste									
Nasal Congestion									
Eye Irritation (conjunctivitis)									
Fatigue (exhaustion)									
Muscle Pain									
Nausea									
Vomiting									
Diarrhea									
Headache									
Brain Fog Cognitive Diff's									
Anxiety									
Depression									
Distressed									

Rating Time to Clinical Recovery: Starting on day one of your treatment, if symptoms have improved or worsened, please rate the time it took for symptoms to change since your last treatment: (0 [no change], +1 [improved within 24 hours], + 2 [improved within 48 hours], +3

[symptom resolved]; - 1 [worsened within 24 hours], -2 [worsened within 48 hours], - 3 [required admission to the hospital or ICU]

Compared to the last time you filled out the COVID symptom questionnaire (please review your prior questionnaire to ensure accuracy and avoid recall bias)

Table 3: Time to Clinical Recovery: Evaluation of Symptoms Day 3, 7, 14, 18, 21, 28 Horowitz, R.I. (based on a recent NIH trial (https://pubmed.ncbi.nlm.nih.gov/33081849/)

COVID Symptom	None (N/A)	No Change	+1 Improved In 24 hrs	+2 Improved In 48 hrs	+3 Symptom Resolved	-1 Worsened In 24 hrs	-2 Worsened In 48 hrs	Required Hospital/ ICU Admission
Fever								
Chills								
Shortness of Breath								
Cough								
Sputum								
Sore throat								
Loss of Sense of Smell								
Loss of Sense of Taste								
Nasal Congestion								
Eye Irritation								
Fatigue (Exhaustion)								
Muscle pain								
Nausea								
Vomiting								
Diarrhea								
Headache								
Brain Fog Cognitive Difficulties								
Anxiety								
Depression								
Distressed								

https://www.phenxtoolkit.org/toolkit_content/PDF/MGH_CTSM_Symptoms.pdf

Symptoms can be collected via a secure online questionnaire vs app. A follow-up questionnaire can be administered one-month post trial, and three months post trial, to evaluate long term sequelae and the development of COVID longhauler status. According to a recent JAMA article, accumulating evidence is showing morbidity beyond the initial infection (Datta SD, Talwar A, Lee JT. A Proposed Framework and Timeline of the Spectrum of Disease Due to SARS-CoV-2 Infection: Illness Beyond Acute Infection and Public Health Implications. JAMA. Published online November 18, 2020. doi:10.1001/jama.2020.22717). We can capture data post glutathione and ivermectin to evaluate residual symptoms and whether a post-acute hyperinflammatory illness and late inflammatory sequalae exist.

"Although much of the response to the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic has focused on acute coronavirus disease 2019 (COVID-19) illness, accumulating evidence demonstrates morbidity beyond acute SARS-CoV-2 infection.1-4 At least 2 other periods of illness appear to be temporally associated with SARS-CoV-2 infection: a rare postacute hyperinflammatory illness and late inflammatory and virological sequelae. These 3 illness periods not only define the temporal course of SARS-CoV-2 infection at the population level but also capture distinct phases of host-viral interaction. A theoretical framework describing illness periods of SARS-CoV-2 infection (including clinical presentations and timing of onset), their pathophysiological underpinnings, and associated key laboratory findings may contribute to a more inclusive and ordered understanding of the natural history of SARS-CoV-2 infection and enhance research efforts. Within the proposed framework, a patient may experience any combination of these illnesses or may have asymptomatic infection without illness"
The initial validated ENT questionnaire is listed below for reference.

PMC full text: Int J Environ Res Public Health. 2020 Jul; 17(14): 5218.

Published online 2020 Jul 20. doi: 10.3390/ijerph17145218

Severe complications of COVID published in the medical literature 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, pneumothorax, liver dysfunction & acute kidney injury. [78] [79] These potential complications will be monitored by the onsite investigator (Dr Alpesh Amin) for both outpatient and inpatients, and recorded at discharge from the hospital. See Table 4.

Table 4: Severe Complications of COVID-19: Clinical Evaluation

Patient #	**Symptom**	Yes/ No	Out patient	Inpatient Med Ward (Y/N)	ICU (Y/ N)	Progression Of Illness Y/N	Death Y/N
	NCP (pneumonia)						
	ARDS/						

	Resp Failure						
	Cardiac injury						
	Pneumothorax						
	Liver Dysfunction						
	Kidney Injury						

Laboratory markers which will be followed during the STOP COVID RCT are based on a medical literature review of the most common complications reported.

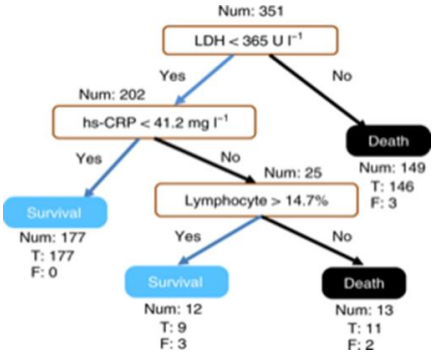
Table 5: Procedures/Laboratory Evaluation

Procedure	Patient #	Day 0	Day 14	Day 28	Follow up > 28 d
FiO2					
Oxygen sat					
Vital Signs					
CBC + lymph ct					
Chemistries (LFT's, lytes, BUN, 16reate, IgM, IgG					
LDH					
hs-CRP					
Ferritin					
Procalcitonin					
D-dimer					
Fibrinogen					
CPK/troponin					
ESR					
Serum Zinc					
RBC Zinc					
Serum Copper					
RBC Copper					
Serum Mag++					
RBC Mag++					
Serum glutathione level					
Serum Testosterone lev					
Cytokine Panel (TNF-alpha, interferon-B [IFN-B], interferon gamma, IL-1Beta, IL-2, IL-6, IL-8, IL-10, IL-17)					
Influenza A,B, RSV, parainfluenza					

Flow Cytometry					
CXR					
CTA/VQ scan					

The laboratory markers of inflammation before, after, and during the trial to stratify risk and outcome, are based on establishment of published host risk scores, [80] hospitalization rates and characteristics of patients hospitalized with COVID-19, [81] clinical course and risk factors for mortality of adult inpatients with COVID-19, [82] Apache II scores, [83] as well as an interpretable mortality prediction model for COVID-19 patients (see figure 1 below). [58] As there is a direct correlation between the lower level of serum testosterone, inflammatory cytokines, disease severity, and poor clinical outcomes among male patients with COVID, [84] we will also follow testosterone levels over time.

Figure 1: From 'Yan, L., et al. An Interpretable mortality prediction model for COVID 19 patients. Nature Machine Intelligence. https://doi.org/10.1038/s42256-020-0180-7



Other complications of COVID-19 include secondary Hemophagocytic Lymphohistiocytosis (sHLH), also known as Macrophage Activation Syndrome (MAS). This is a hyperinflammatory syndrome characterized by a fulminant and fatal hypercytokinemia with multiorgan failure. It is seen in approximately 4% of cases triggered by viral infections and/or sepsis.[85 86 87]
Cardinal features of sHLH/MAS include unremitting fever, cytopenia's, low or absent natural killer (NK) cell activity, hepatosplenomegaly (HSM), hepatobiliary dysfunction (HBD), coagulopathy, increased ferritin levels (≥500), fasting triglycerides ≥265 mg/dl with fibrinogen levels ≤150 mg/dl. These markers along with CD4/CD8 counts and Apache scores (inpatient) will therefore be included in data collection for the RCT, as they can be associated with pulmonary involvement with ARDS (Ground glass opacities [GGO], crazy paving pattern, ill-defined consolidation), which can occur in up to 50% of pts, and in those with fatal complications of COVID-19. [85 88] especially since eighty one percent of critically ill COVID-19 patients develop life-threatening ARDS and hypoxemic respiratory failure. [89]
Therefore, the laboratory markers of inflammation listed above (apart from measuring inflammatory cytokines/chemokines) and previously mentioned levels of HS-CRP, LDH and cytopenias with CD4/CD8 counts, will be included in the study along with D-dimers, ferritin levels, and fibrinogen to evaluate changes in critical lab values over time with treatment. As influenza A, B, or respiratory viruses (RSV, parainfluenza) could affect outcomes, and require anti-viral therapies, [90] these will also be followed.

The etiology of ARDS lung injury include neutrophil & platelet-dependent damage to the endothelial and epithelial barriers of the lung, frequently caused by pneumonia. [91] Neutrophils become activated and increase toxic mediators including reactive oxygen species (ROS), proinflammatory cytokines (TNF-α, IL-6, IL-8) & procoagulant molecules. [92] The synergistic interaction with platelets increases the damage, and procoagulant effects with coagulopathy, leading to pulmonary emboli (PE's) in susceptible individuals.[93 94 95 96]

The three arms of the treatment protocol will therefore be based on the above scientific review. As previously stated, no harm is to be expected in giving NAC, ALA, glutathione, zinc, beta glucan or a multivitamin. The same applies to ivermectin, which has a long safety profile. The only rare potential side effect that would normally be seen with alpha lipoic acid at a dose of 600 mg BID (in 3 patients in 30 years in Dr Horowitz's practice) could be an increase in reactive hypoglycemia. Therefore, a low carbohydrate diet, with healthy protein and fats, and small frequent meals, could be considered as a dietary recommendation for the COVID-19 trial through UCI to help prevent reactive hypoglycemia. If patients are ruled out for reactive hypoglycemia, severe sulfa sensitivity, intolerance to ivermectin or any nutritional supplement, and/or multiple chemical sensitivity, no expected harm should be seen.

For ICU patients in the non-randomized arm (Arm 3), Dr Horowitz has used IV GSH among hundreds of patients during the past 30 years. It has been very well tolerated and the worst allergic case seen in two patients was a mild rash and slight wheezing, which subsequently resolved within a half-hour with Benadryl. Since glutathione could potentially be lifesaving in ARDS, based on prior peer-reviewed literature showing GSH deficiencies in viral pneumonia and ARDS, anyone with a history of a significant sulfa sensitivity should receive an H1 blocker (Benadryl 25 mg) and H2 blocker (famotidine 40 mg) in advance of administration of IV glutathione. The only contraindication to IV glutathione would be anyone with a history of Stevens-Johnson syndrome post administration of sulfamethoxazole/trimethoprim (Bactrim) as stated above.

Patients in the ICU on ventilators, would receive IV glutathione 2000 mg TID, although it can be administered via oral administration via G-tube. This would not be preferable since absorption rates may vary in chronically ill patients. IV GSH is compounded at 200 mg/ml, so a 10 ml dose, mixed with equal amounts of 0.9% NS, is administered via slow push or piggyback. This would be given three times a day for 10 days (following oxygen saturations, CXR's and respiratory parameters during the trial), along with ivermectin 0,2 mg/kg PO QD, and MedPack-1. This treatment would be administered with standard of care at UCI. The goal will be to evaluate in this pilot trial whether IV glutathione, ivermectin and NAC, ALA, zinc, curcumin, and Beta glucan given with dexamethasone/remdesivir (standard of care) can improve outcomes, with faster weaning off the ventilator, while decreasing morbidity and mortality. Any patients with COVID pneumonia in the ICU, and/or those with a high procalcitonin level (a potential marker for pneumonia) should also receive not only ivermectin, but also doxycycline and zinc, as per prior published literature. Evidence of overlapping viral pneumonia should also be evaluated, Infectious disease physicians can determine the best antibiotic and/or anti-viral protocol in the ICU.

If the trial succeeds, it would be important to eventually evaluate the Horowitz COVID protocol in nursing homes and/or prisons, and in the elderly and those with significant risk factors (Hispanic, African American, Native American, male, underlying inflammatory conditions or immunosuppression), to protect the most vulnerable of our population. If The STOP COVID RCT shows positive effects in the short term, for prevention of ongoing illness, and positive effects in the long term (i.e., preventing COVID longhauler status), it would allow us to safely open schools and the economy and lower the high associated morbidity and mortality rates seen to date with COVID. Congressman Chris Smith and the head of HHS, Alex Azar, are supporting the study, and I have been told that they would fast track a larger clinical trial through the NIH once our results are tabulated and published.

Thank you for the opportunity to help find a more effective treatment for COVID-19. Please let me know if any other information is required before engaging in the RCT.

Sincerely,

Dr Richard Horowitz
Medical director, Hudson Valley Healing Arts Center
Board certified internal medicine
Member HHS Tick-borne Disease Working Group 2017-2019
Co-chair HHS Other Tick-borne Diseases and Co-infections subcommittee 2017-2019
Member, HHS Babesia and Other Tick-borne Pathogens 2019-2020

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