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Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Review Article

Application of an evidence-based, out-patient treatment strategy for COVID-19: Multidisciplinary medical practice principles to prevent severe disease☆

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ABSTRACT

The COVID-19 pandemic has devastated individuals, families, and institutions throughout the world. Despite the breakneck speed of vaccine development, the human population remains at risk of further devastation. The decision to not become vaccinated, the protracted rollout of available vaccine, vaccine failure, mutational forms of the SARS virus, which may exhibit mounting resistance to our molecular strike at only one form of the viral family, and the rapid ability of the virus(es) to hitch a ride on our global transportation systems, means that we are will likely continue to confront an invisible, yet devastating foe. The enemy targets one of our human physiology's most important and vulnerable life-preserving body tissues, our broncho-alveolar gas exchange apparatus.

Notwithstanding the fear and the fury of this microbe's potential to raise existential questions across the entire spectrum of human endeavor, the application of an early treatment intervention initiative may represent a crucial tool in our defensive strategy. This strategy is driven by evidence-based medical practice principles, those not likely to become antiquated, given the molecular diversity and mutational evolution of this very clever *"world traveler"*.

☆ This paper, tables, figures and recommendations are meant to be followed in conjunction with the advice of a medical professional such as your Primary or Principal Care Provider. Although the recommendations are sound, there may be underlying reasons why a specific patient SHOULD NOT follow all of the recommendations. Please consult your Medical Provider for specific instructions and guidance.

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L-albuterol
Budesonide
Dexamethasone
Methotrexate

1. Introduction

Never before has the human family shared a more compelling and existential challenge from which to acknowledge our common plight, rather than our differences. Only through the establishment and mutual endorsement and enforcement of universal public health principles, collaborative research on a global scale, and universal preparedness to act decisively with early and strategically formulated interventions, can we hope to stay ahead of this most formidable foe [1,2].

Supported by long-established standards of care protocols, as well as randomized controlled trials aimed to either confirm or refute hypothesis-driven therapeutic questions on the efficacy of novel agents identified through innovations in discovery, we are on the brink of ushering in a literal Renaissance of modern medicine. The era's overarching goal shall be to establish the most sophisticated attempt to date, utilizing discrete knowledge of human heterogeneity, for the identification of effective treatments for even a single patient, the era of Precision CARE. Until then, we share herein a protocol for the early treatment of mild and moderate COVID-19, the purpose of which is to prevent the transition to severe disease.

1.1. Omission of an early treatment strategic initiative fueled the hospital crisis

The circumstances of the COVID-19 crisis created many formidably complex challenges in clinical trial design and execution. Nowhere has such complexity been more limiting than in the outpatient investigation of infected patients characterized as having mild to moderate disease, and who have been summarily sent home without education, counseling, monitoring recommendations, nor with any treatment intervention whatsoever. This in part is due to the overwhelming numbers of patients flooding our hospitals and point of care services, but also because our global healthcare system's most precious asset, our '*front-line-people' (composed of physicians, nurses, nurse practitioners, physician assistants, and their support staff across the spectrum of emergency and acute care medical services)*, are tired and have been completely overwhelmed. Further, 'our people' have not been equipped with a systematic, educational, and corresponding out-patient multidisciplinary treatment strategy for mild and moderate COVID-19, with the specific aim of preventing the transition to severe disease, an achivement of monumental significance for both those we serve, and for those with the unprecedented fiduciary responsibilities who do the 'serving'.

Notwithstanding the preeminent importance of the expanding global vaccine initiative, and achieving the highly anticipated goal of herd immunity, in the interim, we are recognizing disseminated and dangerously expanding spikes in new cases of COVID-19. Mid-April 2021 has the highest incident rates of the pandemic since the inception. This ominous observation, along with evidence of new cases emerging among vaccinated patients (as well as those who remain steadfast in their opposition to active immunization, at least via vaccination, a superior method of actively acquired immunity when compared to developing COVID-19 via infection with the SARS-CoV-2 etiologic agent) provides the most compelling justification to date to offer COVID-19 patients specific treatment recommendations at the time of diagnostic confirmation, or as early as possible, and irrespective of symptom magnitude.

Symptom severity has been demonstrated to poorly correlate (especially when considering individual patients, which is how we best provide CARE for them, individually, one at a time) with propensity to transition to severe disease. It is not uncommon to appreciate a mismatch between clinical semiology and the underlying histopathological burden of disease. This highly salient aspect of COVID-19 is not dissimilar to other conditions whereby the presence of a mild clinical disease phenotype does NOT militate against the simultaneous presence of occult disease activity. In fact, in a disease such as multiple sclerosis, a 'clinico-radiologic-paradox', provides instructive principles which underscore the powerful prognostic predictability for future severity of disability, contingent upon the dissemination and volumetric burden of central nervous system lesions, despite the absence of significant clinical correlation at the time of magnetic resonance imaging (MRI). Similarly, considerable and constitutively recalcitrant targeting, injury, and even obliteration of our bronchoalveolar gas-exchange apparatus, can progressively advance in a mildly affected COVID-19 patient (even in those completely asymptomatic), until a critical threshold of injury is exceeded such that the patient then exhibits the highly salient and most treatment refractory clinical characteristics, which are the cardinal hallmarks of severe COVID-19, the phase of this disease state which must be actively prevented in order to provide the best chance for optimizing recovery, limiting tissue and organ damage, thereby extending life and the quality of it.

Our 'front-line' healthcare alliance desperately need a carefully assembled, and coherently codified, multidisciplinary, remission-exacting treatment strategy to prevent transition to severe disease. Such a tool could serve to literally decouple the vast out-patient population of COVID-19 patients as the primary driving source for emergency and acute care service demands, which far exceeds the resources available, even within and across the most advanced, expansive, experienced and well-endowed healthcare systems and infrastructures in the world. Providing a pragmatic, evidence-based, and out-patient treatment strategy, predicated upon established medical practice principles, and commensurate with the realistic objectives, and the much needed confidence to advance our capabilities from those of community ascertainment, diagnostic confirmation, adoption of public health and home quarantine, to a bona fide disease-modifying strategy aimed at abolishing COVID-19, and neutralizing its pathoetiologic agent, the SARS-CoV-2 virus.

1.2. The telemedicine transformation: limitations and opportunities

The near cessation of outpatient clinic medicine, and the transformation to virtual telemedicine resulted in a critical disconnection between providers and patients, and the framework of systematic methods for translating clinical history and the performance of the directed examination into the corresponding formulation of diagnostic and treatment plans. Alternately, the rapid availability and adoption of the telemedicine platform did allow us to use a convenience sample of consecutive patients seeking our help with COVID-19 management. Disseminating information about their experience to family, friends, and

colleagues has led to a nearly geometric application of our current treatment protocol, outlined in this paper, to COVID-19 patients throughout the country and globally.

Our willingness to provide counsel and specific treatment recommendations, based upon established and evidence-based, medical practice principles, has compelled us to share information germane to already established standards of care. The number of lives potentially saved with this protocol, as well as those protected from the potential of residual deficits we now recognize to be plaguing many patients, "*the long-haulers syndrome*", grows as we target those who were designated as having mild to moderate disease or even asymptomatic individuals.

2. Outcome observations of early treatment intervention

At the time of the completion of this manuscript for submission, the lead author treated more than 125 patients with confirmed COVID-19 following the protocol described in this paper. In conjunction with estimates from colleagues, the number of patients treated with the enclosed protocol exceeds 1000. To date, of those who followed this protocol, we are unaware of a single COVID-19-related death, or of a single patient who has required pressure ventilation in an intensive care unit. Further, the vast majority of those treated with the regimen have exhibited a stereotypic defervescence of symptoms and a marked and durable recovery within 4–10 days with only an occasional patient reporting features suggestive of "long-hauler's" syndrome.

We must replicate our observations in the context of a rigorously controlled trial, with methodology aimed to also expose confounding influences that always accompany such investigations. Our observations from a convenience sample are not, however, irrelevant. This is especially true given that we base our recommendations upon evidence that supports the employment of pragmatic, effective, and timely treatment recommendations, just as we would for many other conditions. The regimen detailed herein crosses the domains of in-home monitoring, application of nutritional principles, pulmonary hygiene, as well as the intervention with therapeutic agents aimed at attenuating the inflammatory crisis in the lungs while seeking to maintain both ventilation and perfusion characteristics, the physiologic coupling of which defines our life-sustaining gas exchange apparatus.

2.1. Application of established medical practice principles

With the pandemic and its ultrarapid dissemination of infectivity throughout the world, our current submission is meant to be a contribution to the cause of reminding clinicians to *reach back into the toolbox* of their general medical training and *never forget that there are many such tools available to fulfill our first commitment* to each and every patient that we evaluate. The first commitment is to CARE, and CARE enough to employ strategies that were somehow passed over during the ongoing pandemic. Quite often, these strategies were opaquely overshadowed by the politicization of the world's medical response to this most unparalleled threat to the health and wellness of the human family, and as such, of all the nations of the world.

Having an early treatment protocol for all who test positive, irrespective of symptom magnitude, is smart medicine. Why? Symptoms do not necessarily reflect the underlying damage happening; a process we now know is constitutive, even in those asymptomatic. *Why care if you don't have symptoms?* The answer is simple; you can change tracks to more severe disease and still have morbidity and mortality, and most importantly, the damage already sustained may not appear relevant now, but may be relevant later, once critical thresholds in tissue damage and alveolar loss accumulates.

2.2. Life sustaining oxygen: supply:demand bioenergetics

What part of us does NOT need to utilize oxygen? Insufficient oxygen delivery compromises mechanisms in our physiology which aim to match the supply of energy currency with that of tissue and organ functional demands. Most crucially, the amounts of energy currency being made (i.e. adenosine triphosphate (ATP)) and its energy currency *colleagues*, flavin adenine dinucleotide (FAD), and nicotinamide adenine dinucleotide (NAD), all require oxygen to run the electron transport chain in our cellular mitochondria, and may become wholly inadequate to maintain the high efficiency state of the health, wellness, and quality of life that is inextricably coupled and dependent upon the integrity and high fidelity processes which characterize the biochemistry of human intermediary metabolism.

2.3. Consequences of delayed treatment intervention

If all who are infected are urgently treated, we not only attenuate the Prolific Activation of a Network Immune Inflammatory Crisis ('PANIC') Attack of inflammation, but also abort viral replication [2]. This halt in replication abolishes downstream tissue injury mechanisms at both ends of the COVID syndrome. These mechanisms include the parochial triggering of 'PANIC', where we can least recover from the inflammatory crisis, the broncho-alveolar gas exchange units of the most remote reaches of our lung anatomy and physiology. Additionally, the high-jacking of our alveolar epithelial molecular machinery for its own self-serving purposes causes an additional bystander effect that is the irreversible damage and obliteration of this most precious asset of gas exchange, which cannot be replaced.

The prevention, as well as the reversing of the high-jacking of our alveolar epithelial cell molecular machinery for purposes of the SARS-CoV-2 viral replication, represents another major goal of COVID-19 treatment. Halting replication itself reduces the inflammatory ignition switch that foments site activation of exuberant inflammation, while releasing factors (e.g. C3a and C5a; anaphylatoxins and chemotaxins) promote the redistribution of peripheral immune effector cells, recruiting them to the site of primary infection, the broncho-alveolar units. Upon the arrival of the peripheral immune effector cells to the primary site of infection, the bronco-alveolar units, the effector cells release free radicals, super oxides, and other injurious agents, which all serve to intensify and expand the injury cascades.

Less viral presence also means a reduced likelihood of viral segment integration within the alveolar epithelium (as so-called "syncytia"), with SPIKE protein 'dangled' into the alveolus, potentially generating antibody locally from our own B cells. This may sound like a good thing? It is not! *Such locally generated antibodies against SPIKE protein on the SARS-CoV-2 virus expressed upon our alveolar epithelium ignites the terminal complement cascade, specifically the C5-convertase*. This in turn promotes the assembly of proteins derivative of the C5, C6, C7, and C8 pathways to construct the terminal and most injurious effector mechanism of the entire complement system, the membrane attack complex (MAC).

In the case of COVID-19, MAC assembly upon our alveolar epithelium is then primed for the final "kill-shot". Specifically, the MAC architecture includes a centrally localized channel which facilitates the passage of the terminal complement protein C9 from the opening orientation directly toward the alveolar space. The MAC architecture serves as a direct line of sight for the bullet-like action of C9 upon reaching the terminus of the MAC adhered to the epithelial surface.

Upon its arrival, C9 then penetrates the alveolar cell membrane, inflicting an irreversible breach in the integrity of the cell's barrier and physiologic dividing line, crucial for maintaining innumerable processes, including those that sustain the life and viability of these cells. The "kill-shot" mechanism culminates in osmotic shock, completing what we now designate as complement-dependent cytotoxicity (CDC). What then follows is damage commensurate with the transition to severe disease and the heightened risk of alveolar obliteration.

2.4. Dividends of early/earliest treatment intervention for COVID-19

Now imagine if all patients were treated at the time of diagnosis, when COVID-19 is at its mildest to moderate stages, with interventions aimed at multiple mechanisms that when uncoupled, we have our best chance to protect the lung, monitor the disease process at home, and remain in touch with care providers in order to provide guidance, course changes, and always with the default of hospitalization should the condition warrant closer observation and/or intensification of the treatment plans.

This is a highly unusual paper. Why? Its *principal purpose is to underscore the prospects and possibilities of controlling the most dangerous aspects of the COVID-19 pandemic before it begins*. Imagine if the world recognized that by having the advents of public health practices, coupled with an effective out-patient treatment regimen, we could prevent hospitalizations and death, while our vaccination programs come to fruition and herd immunity is ultimately achieved.

We absolutely believe this can be achieved if enough of our medical community and patient population (essentially everyone) accepts the premise of the hypothesis that we put forth. However, we must be prepared for new variants, and to learn from the painful and cataclysmic lessons of the current pandemic. One glaring observational lesson is that the medical community became completely paralyzed by the increasing and inevitable onslaught of severe illness, ultimately exceeding our available resources.

One very painful outcome of this past year of the pandemic experience is that there has been almost a complete lack of management of those with mild and moderate disease, as well as those wholly asymptomatic. Unfortunately, it is during this initial time, the initial assessment where patients have been summarily told to 'go home and not return until you are more sick', that may represent a time when they are beyond our capability to nurse them back to health, or even to save their lives.

2.5. Specific aims of our paper and accompanying YouTube video

This paper is our attempt to focus precisely upon strategies that have successfully 'left-shifted' patients toward ultimate recovery, and away from the potential 'right-shifting' to severe disease, and the corresponding escalation in morbidity and mortality associated with it.

We begin by advancing a number of 'Imagine' statements, specifically focused upon the marked mitigation of this pandemic and its effects upon people, families, communities, and institutions. We then detail a specific, albeit not dogmatic, regimen which addresses a diversity of semiologic factors associated with COVID-19, and which can be remedied with the employment of established practice principles and their systematic implementation, given that all that we proscribe, devices, techniques, nutritional agents, and prescription medications, are all generic and widely available throughout the world [3–110].

This paper is intended to showcase our protocol in conjunction with medical illustrations to be utilized for purposes of organization, and for counseling each of our individual patients and their families. Similarly, we provide a highly detailed figure, along with a table of detailed legends such that the pathophysiologic underpinnings of COVID-19 can be parsed and individually addressed in terms of mitigating or even achieving the remission exacting effects of our proposed interventions [111–116].

This paper is accompanied by a video, published here (click on thumbnail) and on YouTube (https://thefrohmanfoundation.org/outpatient-covid-19-treatment-to-prevent-severe-disease/), that shall be released in synchrony with the publication of this manuscript. The multimedia architecture of the video is intended to inform, educate, counsel, inspire, and to build confidence both among those infected, as well as their family members, and their CARE provider alliances.

(Click here)

It is our hope that by bringing this real-world experience to light, it shall broadly illuminate for all to see, a systematic strategy capable of solving the complex riddle of the SARS-CoV-2 agent, and its clinical manifestations as COVID-19. We take a broader view of the inception of

the illness, exploit the vast toolbox of established medical, health, and wellness capabilities that can be wielded with predictable effects, including the ability to abort the infection, and thereby abolish the mechanisms responsible for the consequences of this infection.

2.6. Preparing for the future: avoid repeating the mistakes from the past

The reports of new mutations, in conjunction with spikes of the illness being disseminated throughout the world, suggest that this paper offers a timely plan to mitigate the illness and prevent the transition to severe disease.

This monitoring and treatment protocol recognizes CARE pathways addressing each of the early mechanisms and manifestations of this illness, while assembling a concerted attack directly upon the culprit, as well as applying a treatment strategy which finally is focused upon the most relevant constellation of treatable facets of this dangerous, complex, and clever microbial agent [3–116].

From the start, we have possessed the tools to 'checkmate' this challenger, despite it targeting of one of our body's most vulnerable and life-sustaining circuitries. Even at the most remote reaches of our lung physiology, employment of site-selective inhalational therapies, in conjunction with nutritional support measures, pulmonary hygiene, and respiratory muscle training, we can begin to provide a path forward by which to prevent symptom worsening and possibly prevent hospitalization, while learning lessons that shall prepare us for future challenges that shall no doubt be forthcoming.

Herein the time is right to now begin by asking you, the reader, to be open minded enough to consider the "IMAGINE" statements that follow; inspired by John Lennon's 1971 verse from his raison d'être.

IMAGINE

"You may say I'm a dreamer
But I'm not the only one
I hope someday you'll join us
And the world will be as one"

John Lennon, October 11, 1971

Imagine	If we could treat patients with COVID-19 at the beginning, when most only have mild to moderate disease, thereby preventing severe disease.
Imagine	If the treatment were based on evidenced-based medical principles and such a regimen were completely detailed right here for you, your family, and your healthcare provider.
Imagine	If, while you are waiting to get vaccinated, those already infected could receive a simple treatment regimen along with education on how to administer it as an out patient at home, and education on when to contact their medical provider or go to the emergency department.
Imagine	If this treatment were cheap, involved both over-the-counter therapies, and only a few prescriptions, and was administered over a 10-day course in most patients.
Imagine	If the vast majority utilizing such a regimen would never advance to severe COVID-19, would NOT require hospitalization, and as such, would completely avoid ventilatory support, and death.
Imagine	If the effectiveness of this treatment strategy produced similar protective effects across the age, gender, racial, and co-morbid condition demographic spectrum.
Imagine	*That we know the time to act and initiate treatment is at the time of COVID-19 diagnosis (pre-emption to avoid progression to severe disease)*, NOT wait for a favorable prognostic outcome that may never materialize, or until the patient is sufficiently sick to warrant hospitalization (a reactive and much more dangerous strategy). Such delay to act early may be too late to avoid progression to severe COVID-19.
Imagine	That we have provided the details of a protocol assembled by our team of colleagues, and have already observed nearly uniform capability to rescue over 1000 patients at the time when their infection is early in the course. A time that represents our best chance to mitigate suffering, and more importantly, to prevent progression to severe disease and its associated ramifications, including death.
Imagine	Now imagine if the entire world became aware of this early treatment regimen, and its ability to prevent progression to severe disease? This is NOT unimaginable. Rather, together we can do this; and do this NOW, and together we can lives.

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Author contributions

Elliot M Frohman: conception, critical revision of manuscript for intellectual content.

Nicole R. Villemarette-Pittman: conception, critical revision of manuscript for intellectual content.

Adriana Rodriguez: conception, critical revision of manuscript for intellectual content.

Robert Glanzman: conception, critical revision of manuscript for intellectual content.

Sarah Rugheimer: conception, critical revision of manuscript for intellectual content.

Oleg Komogortsev: conception, critical revision of manuscript for intellectual content.

Scott S Zamvil: conception, critical revision of the manuscript for intellectual content.

Roberto A. Cruz: conception, critical revision of manuscript for intellectual content.

Thomas C Varkey: conception, critical revision of manuscript for intellectual content.

Ashley Frohman: conception, critical revision of manuscript for intellectual content.

Audrey Frohman: conception, critical revision of manuscript for intellectual content.

Matthew S Parsons: conception, critical revision of manuscript for intellectual content.

Emily Heckmann Konkle: conception, critical revision of manuscript for intellectual content.

Teresa C Frohman: conception, critical revision of manuscript for intellectual content.

Author disclosures

Elliot Frohman: Has received speaker honoraria from Genzyme, Novartis, Janssen, Alexion and Acorda.

Nicole R. Villemarette-Pittman: Is the Managing Editor for the Journal of the Neurological Sciences.

Adriana Rodriguez: Has nothing to disclose.

Robert Glanzman: Is the Chief Medical Officer for Clene Nanomedicine.

Sarah Rugheimer: Has nothing to disclose.

Oleg Komogortsev: Has nothing to disclose.

Scott S Zamvil: Dr. Zamvil is Deputy Editor of *Neurology, Neuroimmunology and Neuroinflammation* and is an Associate Editor for *Frontiers in Immunology* and *Frontiers in Neurology*. He serves on the Advisory Committee for the American Congress on Treatment and Research in Multiple Sclerosis (ACTRIMS) and is a standing member of the research grant review committee for the National Multiple Sclerosis Society (NMSS). He has served on the Editorial Board of the *Journal of Clinical Investigation*, *The Journal of Immunology* and *The Journal of Neurological Sciences*, and has been a charter member of the grant review committee for the National Institutes of Health (NIH) Clinical Neuroimmunology and Brain Tumors (CNBT). He has served, or serves, as a consultant and received honoraria from Alexion, Biogen-Idec, EMD-Serono, Genzyme, Novartis, Roche/Genentech, and Teva Pharmaceuticals Inc., and has served on Data Safety Monitoring Boards for Lilly, BioMS, Teva and Opexa Therapeutics.

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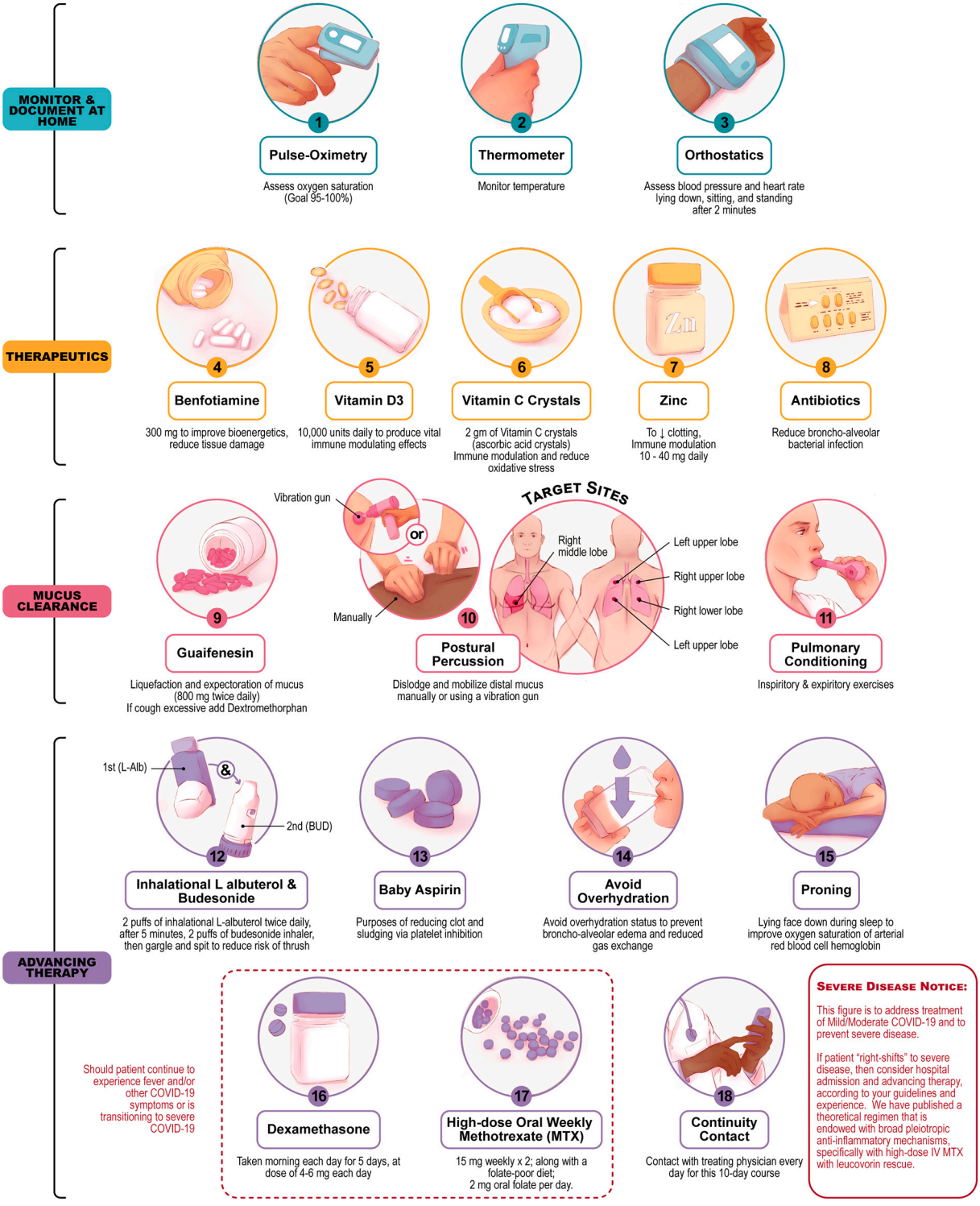
Treatment of Mild and Moderate COVID-19 To Prevent Severe Disease
10-Day Treatment Course



(caption on next page)

Fig. 1. All steps are taken for a total of 10 days.
[Numbers Correspond to those in Fig. 1]

Monitoring & Documenting at Home	
1. Pulse Oximetry	**Use a simple and inexpensive finger pulse-oximeter** to assess oxygen saturation status multiple times daily and record along with all other daily measures. This is especially key when patients experience the perception of "difficulty getting in enough air"' (a symptom likely implicating a reduced negative inspiratory force [NIF]). **Instructions from your care provider should be given as to *when* to notify them** (e.g. with oxygen saturations in the **low 90s** or a significant change over a defined period). [3-7]
2. Thermometer	Body temperature is a key indicator of both infection as well as ongoing inflammatory mechanisms not being adequately treated (e.g. release of cytokines, especially interleukin-1; IL-1) Monitor and document temperature twice daily; more frequently if you perceive changes, or instructed by your care provider**. If temperature exceeds 100.4˚ (F)/38˚ (C) and/or is rising, you should contact your care provider.** Instructions for use of fever reducers (ibuprofen, acetaminophen/paracetamol, etc.) will vary across countries and even across physicians in the same country. We generally provide instructions for the administration of these agents (dose and frequency) and in response to temperature parameters (e.g. 400-600 mg of ibuprofen daily to twice daily to attempt to lower and maintain a normal body temperature between certain parameters; such as an attempt to maintain body temperature below 100.4 °F/38°C).
3. Orthostatic Measures	Please assess blood pressure and heart rate lying supine (flat), sitting, and then standing (with 2-minute intervals between each) to assess for orthostatic changes (drop in systolic blood pressure of 10-20 mm Hg, with the corresponding escalation in heart rate, which may be secondary to orthostatic hypotension, often in response to dehydration). **Changes may trigger further input and instructions from your care provider concerning hydration, to maintain cardiac output.**

Therapeutics Nutrition & Antibiotics [8-12]	
4. Benfotiamine	We recommend 300 mg of Benfotiamine to improve bioenergetics and reduce tissue damage. [13-16]
5. Vitamin D3	We instruct our patients to take vitamin D_3 at 10,000 units daily, every day, as this vitamin at this dosage produces vital immune-modulating effects that are favorable in several conditions, now including COVID-19. [14-21]
6. Vitamin C	We suggest ingestions of 2 g of Vitamin C crystals daily (ascorbic acid crystals) or tablets/capsules, which provide a variety of benefits, including the reduction of oxidative stress associated with the Prolific Activation of a Network Immune Inflammatory Crisis ("PANIC"). [22]
7. Zinc	Zinc deficiency is associated with worse COVID-19 prognoses, perhaps related to the associated increase in clot formation and stasis in the para-alveolar pulmonary capillary network. Further, Zinc deficiency can contribute to insomnia, compromising sleep hygiene when it is needed most, in addition to diminished smell, taste, and libido, as well as reduced erectile function and orgasm. Adequate Zinc reduces infection risk, reduces oxidative stress, attenuates the release of inflammatory cytokines, and contributes to the induction and maintenance of sleep. This helps with clotting and immune modulation. We recommend rMetx zinc-silver solution (ZnAg); a clear liquid solution of the minerals, zinc (Zn) and silver (Ag), present in a deionized purified water suspension as dissolved ions, measured in parts per million (ppm, μg/mL). The dose of rMetx is 30 - 60 ml Q12 hours as needed. Recommended on an empty stomach and nothing by mouth for 20 min after. Alternatively, we recommend 10-40 mg of Zinc daily in the form of Zinc gluconate or Zinc picolinate. Avoid overdosing (beyond 50 mg daily), which can reduce copper absorption, leading to myelopathy, nausea, vomiting, tenesmus, diarrhea, and headaches. [23-25]
8. Antibiotics	We recommend a course of antibiotics (a "Z-Pak" of azithromycin vs 5 days of amoxicillin/clavulanate b.i.d. vs Bactrim DS b.i.d. for 5 days), as this would address any inspissated, deep pulmonary tree bacterial elements mixed with mucus, which could become a source of further immune stimulation (i.e. PANIC). [26-37]

Fig. 1. (*continued*).

Mucus Clearance & Pulmonary Hygiene	
9. Guaifenesin	**To promote liquification of mucus for subsequent mobilization out of the peripheral bronchopulmonary tree, we recommend using guaifenesin (available over the counter in most countries) twice daily at 1200 mg, extended-release formulation.** **If the cough is excessive or fatiguing, then guaifenesin + dextromethorphan** (the latter, a cough suppressant, can also attenuate adenosine mediated headaches) is indicated. **Thick mucus formation can become organized in the distal bronchioles and compromise local and then general ventilation characteristics, ultimately affecting gas-exchange at the alveoli apparatus**. [38-52]
10. Postural Percussion	**Mobilization (expectoration) of distal mucus** (in those with no cough, non-productive cough, and with productive cough) **by liquefying (following step 9, above). Follow by either manual postural percussion or use of a percussion vibratory instrument on the back**, to dislodge mucus in the upper and lower lobes (right and left), and apply similar percussion to the right middle lobe, also known as the lingular lobe. **This is key, as the right middle lobe is the one at greatest risk of consolidation and infection, along with atelectasis (a partial or complete collapse of the lung).** **Right middle lobe pulmonary hygiene (i.e. percussion and expectoration) is best achieved by having the patient raise their right arm and percuss from the front approximately under the breast between the 4th or 6th intercostal spaces**. [53-55]
11. Pulmonary Conditioning and 12. Respiratory Muscle Training	**Performance of pulmonary exercises promotes normalizing pulmonary functioning via improved conditioning**. 10-20 breaths of inspiration and expiration with ***The Breather*** (a respiratory muscle trainer which can be purchased online, as well as other devices such as incentive spirometry device), three times daily. Begin at setting #1; each day see if the patient can advance by one setting until arriving at the top setting (e.g. with the highest resistance to inspiration and expiration). [56-60]

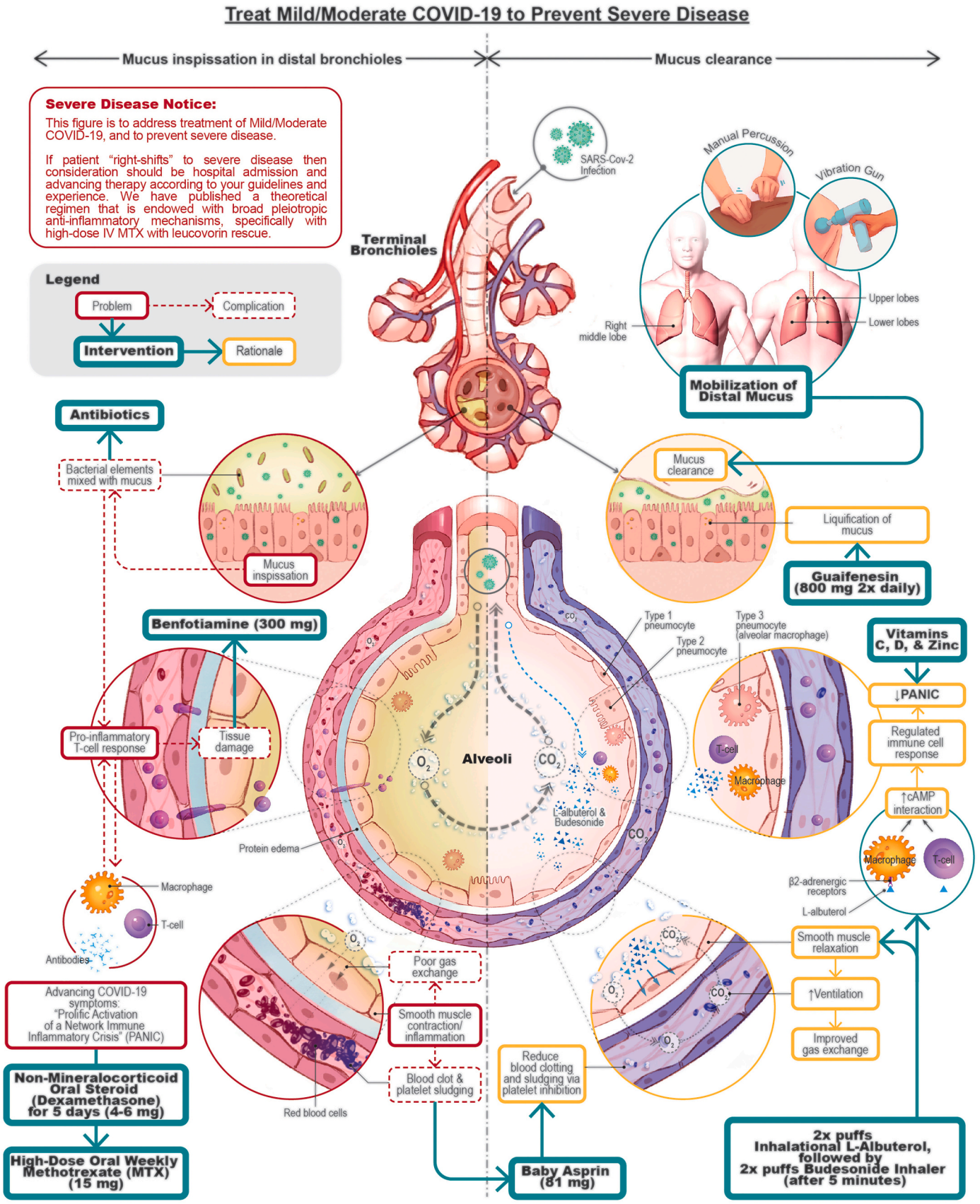
Fig. 1. (*continued*).

Advance Therapy # 1	
13. L-Albuterol & Budesonide	**We recommend inhalational L-albuterol** to **facilitate improved ventilation and delivery of medication to the distal bronchopulmonary tree**. L-albuterol has the active "R" isomer of the molecule and serves to relax bronchial smooth muscle, and is more lung selective than the racemic form (R & D isomers). Albuterol is a beta-2 adrenergic agonist and serves to relax bronchiole smooth muscle. Additionally, via its interaction with beta-receptors on lung mononuclear cells (especially macrophages, T- and B-lymphocytes), it promotes the escalation in intracellular cAMP, and thereby the transition of mononuclear cells from pro-inflammatory to modulated and even to a regulatory cell phenotype. This mitigates the "**P**rolific **A**ctivation of a **N**etwork **I**mmune **I**nflammatory **C**risis" (PANIC), the principal mechanisms of COVID-19 associated with tissue damage of the lungs. [61-65] **We recommend 2 puffs twice daily, along with 2 puffs of a budesonide inhaler (Pulmicort) administered 5 minutes after taking L-albuterol inhaler therapy, to provide some time for bronchial smooth muscle relaxation.** **Administration of L-albuterol improves ventilatory characteristics for the site-selective delivery of the inhalational steroid budesonide into the distal broncho-alveolar region of the most distal bronchopulmonary tree**. This subsequently acts to coordinate a constellation of steroid-mediated anti-inflammatory actions, also serving to mitigate the effects of COVID-19-associated inflammatory activity. After administration of the two inhalational puffs of L-albuterol, followed by the two puffs of budesonide, we recommend that the patient gargle with water x 2 and spit, to avoid the development of thrush. [66-67]
14. Baby Aspirin	Unless formal anticoagulation is indicated, (per guidelines contingent upon D-Dimer levels), **we recommend 1 baby aspirin daily (81 mg) for purposes of reducing clot and sludging via platelet inhibition** (unless aspirin in the patient is contraindicated). [68-77]
15. Avoid Overhydration	**Avoid overhydrating because increased protein-rich fluid can accumulate in the distal bronchopulmonary tree,** which can increase the distance between the alveolar epithelium and the pulmonary vascular capillary bed endothelium, thereby compromising the gas exchange apparatus (as demonstrated in the FACCT TRIAL). **If your patient is dehydrated (e.g. from diarrhea), then fluid reconstitution and potentially potassium repletion may need to be considered.** [78-82]
16. Proning	**Lie prone (positioned on your stomach) during sleep (or perhaps 2/3 of sleep time prone, the other 1/3 supine).** **This improves the oxygen saturation of arterial red blood cell hemoglobin** (as demonstrated in the PROSERVA TRIAL). [83-87]

Fig. 1. (*continued*).

Advance Therapy # 2	
17. Dexamethasone	Should the patient continue to experience fever and/or other COVID-19 symptoms despite the above regimen, we consider the addition of the oral steroid dexamethasone. If utilized, take Dexamethasone in the morning each day for 5 days, at a dose of 4-6 mg each day, generally with breakfast. Be mindful of the potential risk of steroid psychosis (euphoria, agitation, confusion, delusional thinking, obsessive compulsions, reduced inhibitions, risk-taking, etc. [88-91]
18. High Dose Oral Weekly Methotrexate	**IF TRANSITIONING INTO THE SEVERE VARIANT OF COVID-19, WE WOULD THEN CONSIDER THE ADDITION OF ORAL METHOTREXATE.** Methotrexate is considered a 'necessary' treatment by the World Health Organization (WHO) given its diversity of immune modulatory and anti-inflammatory actions [92-108]. 1. High-dose oral weekly Methotrexate (15 mg weekly x 2) 2. A folate poor diet (i.e. reduced vegetables, and instead emphasize meat and seafood for the duration of the 10-day regimen) 3. Daily Folate at 2 mg, starting 12 hours after the oral Methotrexate dose administration, to define precise folate intake.
18. Continuity of Care	Finally, we recommend that you contact your treating care provider every day during this 10-day course to assess your status.
19 Advancing to Hospital Admission	Several factors influence hospital admission including: 1. Persistent fever 2. Falling oxygen saturation, or not improving despite this regimen 3. Pulmonary fatigue not resolving 4. Evolution of progressive symptoms, such as those suggestive of stroke, heart attack, renal failure, persistent/worsening headache, behavioral change
20. Public Health "Matters" **"W-W-W"** **WEAR** A MASK **WALK/WAIT** AT LEAST 6-FEET APART FROM OTHERS WHEN OUTSIDE YOUR HOME OR IN PUBLIC OR ENCLOSED SPACES **WASH** YOUR HANDS OFTEN AND FOR AT LAST 20 SECONDS	Public health measures do NOT disappear because: a) you've been infected and recovered with or without treatment b) you have been vaccinated. We are still learning about these great additions to the war against COVID-19 and a vaccine alone is only part of the battle. Encourage your family, friends, and co-workers to follow suit by practicing social distancing, hygiene measures, and the use of facial covering (i.e. a mask) until the pandemic is over [109-110] c) you are outside of your home but others are not around. Coronavirus can survive on surfaces that we pick up with our hands, potentially transferring the COVID-19 agent to our mucus membranes (and then to the lungs), or to others. *Please continue to wash your hands frequently.* The risk of infection and serious consequences remain high even for younger populations. . We must *all* do our part to protect ourselves, and each other.

Fig. 1. (*continued*).



(caption on next page)

Fig. 2. Pathophysiology of severe COVID-19 from mild/moderate COVID-19 and the mechanistic treatment for its prevention.

General Architecture	Overall, this figure is dichotomized by characterizing the features of mild and moderate COVID-19 and the interventions that comprise our regimen to prevent progression to severe disease.
Legend **The color-encased boxes are utilized for purposes of:**	Defining a problem (RED box)
	Potential complications from the problem (DOTTED RED box)
	Proscribed intervention (GREEN box)
	Rationale for each intervention (ORANGE box)
Mucus Inspissation Potentially mixed with bacterial flora	To prevent the organization of complex inspissated mucus with bacterial flora in the distal bronchopulmonary tree, potentially serving to "endocast" the bronchoalveolar anatomy responsible for ventilation and perfusion characteristics germane to high-fidelity gas exchange.
Mucus Obstruction of the distal bronchopulmonary tree	The SARS-CoV-2 virus, which causes COVID-19, principally does so by targeting our most vulnerable lung anatomy, the bronchoalveolar terminals where high-fidelity gas exchange occurs, representing the entire body's supply of oxyhemoglobin and its delivery via cardiopulmonary physiology [2, 112]. To maintain such constant and uninterrupted gas exchange, both ventilation and pulmonary arterial perfusion must be commensurate with threshold states that guarantee the reliable delivery of oxygen to the pulmonary arterial capillary network, while the lung parenchyma simultaneously expels carbon dioxide by reverse expiratory flow, oscillating with the inspiration of fresh air whose composition is 21% O_2. Oxygenated pulmonary venous return to the left heart is then prepared to deliver cardiac output via the left ventricular systolic pump and its ejection fraction of blood in to and out of the aortic root. The mobilization of dangerous mucus organization in the distal bronchioles is achieved with a combination of: 1. Liquification via 800-1200mg of oral twice daily guaifenesin, 2. Excessive cough, which can be counteracted by the use of guaifenesin with dextromethorphan 3. Manual percussion of the upper and lower lung lobes from the back and anterior percussion of the right middle lobe, which can serve to mobilize and ultimately expectorate the mucus burden in the distal lung fields. 4. Percussion and mucus expectoration, which is more efficiently achieved by utilizing a vibratory "gun," making this part of pulmonary hygiene less cumbersome and exhausting for the assistant, partner, or family member. 5. Special attention given to the right middle lung lobe, approaching anteriorly (between the 4^{th}-6^{th} intercostal spaces, with the breast lifted in those with abundant breast tissue) Remember that the right middle lobe is most predisposed to the development of pneumonic consolidation (i.e. pneumonia and pneumonitis), as well as atelectasis (i.e. lobular collapse and its associated cessation of gas exchange, and higher infection risk).

The Prolific Activation of a Network Immune Inflammatory Crisis ("PANIC") results in complex supply/demand challenges to the bioenergetic system, a failure of which contributes to tissue destruction	Benfotiamine is an ultra-purified form of thiamine (vitamin B1), a crucial co-factor across several biochemical enzyme systems that are crucial for meeting the bioenergetic demands of cells. This is particularly challenging to those with highly stringent thresholds, beyond which supply/demand mismatch and can contribute to the failure of many crucial cellular physiologic mechanisms, including a failure in the efficiency of transition from anaerobic glycolytic to aerobic mechanisms of oxidative phosphorylation, which is required for producing the bioenergetic cellular currency (i.e. ATP). High-fidelity gas exchange providing the necessary oxygenation in order to drive the tricarboxylic acid (TCA) cycle, and Benfotiamine, a co-factor for pyruvate dehydrogenase, which along with alpha-lipoic acid and flavin adenine dinucleotide (FAD), catalyzes the incorporation of pyruvate into oxaloacetate, the first step of the TCA cycle.
Smooth Muscle Contraction can lead to poor ventilation and, thereby gas exchange, in addition to associated sludging and clotting	Aspirin therapy can serve to reduce sludging via platelet inhibition. Depending upon D-Dimer criteria, some patients may require formal anticoagulation. L-albuterol can promote smooth muscle relaxation, thereby improving ventilation at the bronchoalveolar gas exchange apparatus. Further, this agent acts as an agonist at the beta-2-adrenergic receptor on lung mononuclear cells (e.g. lymphocytes and macrophages) resulting in the escalation of intracellular cAMP, resulting in improved immune regulation and attenuation of a Prolific Activation of a Network-Immune Inflammatory Crisis (PANIC) [2, 116]. Budesonide is an inhalational steroid that promotes a constellation of anti-inflammatory mechanisms relevant to reducing PANIC and reconstitutes coordinated regulatory influences in the SARS-CoV-2 infected lung. Vitamins D_3, C, and Zinc all have favorable effects upon oxidative stress, immune regulation, and influence on clot formation reduction.
Recalcitrant Fever and other COVID-19 symptoms often reflect inadequate control over SARS-CoV-2 mediated COVID and its constellation of triggered inflammatory mechanisms; in essence, PANIC.	**STEP 1:** Administer the potent oral and non-mineralocorticoid steroid, dexamethasone, at 4-6 mg, taken in the morning with breakfast for 5 days (some use longer regimens). This can rapidly attenuate systemic mechanisms of PANIC, such as the elaboration of cytokine storms, most prominently with IL-1, which targets hypothalamic temperature regulatory networks, and IL-6, which can provoke the activation of several injurious inflammatory networks exceeding intra- and inter-network regulatory mechanisms. These mechanisms normally serve to mitigate bystander injury to host tissues wherein such paroxysmal bursts of irrationally exuberant inflammatory crises are fomented. **STEP 2:** Those who continue to exhibit recalcitrant fever or other features of ongoing immune activation, despite all measures employed above, may be candidates for advancing from dexamethasone to high dose oral methotrexate (we recommend 15 mg, taken once weekly).

Fig. 2. (*continued*).

	This "Necessary Drug", as designated by the World Health Organization (WHO), exerts broad pleiotropic mechanisms. These mechanisms include: • pharmacologic duality as both a folate analog, as well as folate antagonist, • cell cycle S-phase inhibitor, • inhibition of DNA and RNA base synthesis for both purines and pyrimidines, thereby exerting a powerful inhibition of viral replication (including that of SARS-CoV-2) • marked attenuation of cytokine release syndromes, • modulation of adenosine mediated anti-inflammatory mechanisms, • inhibition of NFκB, and • promotion of the production of tissue inhibitors of metalloproteinases [TIMPS], modulation of JAK/STAT signaling platforms, modulation of reactive oxygen species, and inhibition of the binding of HMGB1 to RAGE, or indirectly interfering with this interaction via inhibition of the cytokine production of TNF-α, IL-1, IL-6, and IL-8). [2]
Hospital Admission	There does come a time when the above interventions are not sufficient to avoid the "right-shifting" of the patient from mild/moderate COVID-19 into severe disease. Such circumstances necessitate hospital admission for: 1. Close observation 2. Augmentation of oxygen support (e.g. 1-4 L of O_2 by nasal cannula 3. Expanded investigations to ascertain the severity of metabolic and hematologic derangements (Ferritin, hsCRP, D-Dimer), presence of concomitant infection (including secondary pneumonia, if bacterial suspected prompting treatment with IV antibiotics), and CT assessment of the lung, to stage the severity and burden of injury to the lung parenchyma. Further, cardiac investigations are increasingly being performed given increasing evidence that COVID-19 can affect the heart, predisposing patients to markedly increased morbidity and mortality. To diagnostically and therapeutically address extra-pulmonary organ pathologies, such as brain imaging to assess for stroke, renal insufficiency or failure, and endocrine and neuroendocrine pathology. 4. Multidisciplinary management 5. Intensive care unit (ICU) management 6. Consideration of intensive interventions (e.g. plasma, high dose IV methotrexate with leucovorin rescue; monoclonal antibodies against IL-1, IL-6, etc) 7. Ventilator support

Fig. 2. (*continued*).

Future Directions	While much has been learned over the past year about the COVID-19 pandemic and the SARS-CoV-2 Coronavirus which causes it, we are increasingly recognizing that while the lung is the principal target of the disease, virtually any tissue or body organ can ultimately become a target of the disease process (either via direct viral targeting, or through secondary mechanisms whereby damage is produced by a compromise in the necessary, constant, and high fidelity delivery of life-sustaining oxygen-rich blood everywhere throughout the body. A crucial area of scientific inquiry shall address the rapidly expanding observation that subsequent to surviving COVID-19; even those with the mildest variants of this disorder, can be predisposed to the development of a post-COVID-19 syndrome; so-called "Long-Hauler's" syndrome [112-115]. Long-Hauler's syndrome is characterized by a constellation of recalcitrant symptoms, which can include chronic fatigue, alterations in cognitive capabilities, persistent breathing problems, exercise intolerance, as well as residual deficits in those who have suffered stroke, seizures, heart attack, kidney and liver derangements, as well as disturbances in the gastrointestinal tract [112-115]. We believe that the information underscored above, further support our contention about the role of early treatment intervention, as both a prevention and disease attenuation strategy. 'Time is tissue', and the earlier we can intervene to quench the exaggerated immune network inflammatory responses to the SARS-CoV-2 agent, the less likely our patients are to progressively advance to severe disease, and thereby manifest more severe morbidity, persistence of post-COVID-19 syndromes, and even death from this very serious infection [116].

Fig. 2. (*continued*).

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