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SARS-CoV-2 Treatment Regimen Based Upon the

Fleming Inflammation & Cardiovascular Disease Theory.

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Corresponding Author:	Richard M Fleming, PhD, MD, JD FHHI-OI-Camelot Studio City, CA UNITED STATES
Corresponding Author Secondary Information:	
Corresponding Author's Institution:	FHHI-OI-Camelot
Corresponding Author's Secondary Institution:	
First Author:	Richard M Fleming, PhD, MD, JD
First Author Secondary Information:	
Order of Authors:	Richard M Fleming, PhD, MD, JD
	Matthew R Fleming, BS, BA, NRP
Order of Authors Secondary Information:	
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SARS-CoV-2 Treatment Regimen Based Upon the Fleming Inflammation & Cardiovascular Disease Theory.

[1]Richard M Fleming, PhD, MD, JD (ORCID # 0000-0001-9964-1518)

[1]Matthew R Fleming, BS, NRP (ORCID # 0000-0002-9974-0468)

[1]FHHI-OI-Camelot Foundation Los Angeles, CA, USA

Running title: Treating SARS-CoV-2 with Fleming Inflammation Theory

Address all correspondence to:
Richard M. Fleming, PhD, MD, JD
Los Angeles, CA, USA
DrRichardMFleming@gmail.com

Key words: SARS-CoV-2; CoVid-19; FMTVDM; Fleming Inflammation and Cardiovascular Disease Theory; InflammoThrombotic Response (ITR); FMTVDM; Cytotoxic Immune Response; Adaptive Humoral Antibody Response; NCT04349410

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[1]Richard M Fleming, PhD, MD, JD (ORCID # 0000-0001-9964-1518)

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Address all correspondence to:
Richard M. Fleming, PhD, MD, JD
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Key Points:

- The majority of deaths following SARS-CoV-2 infections are the result of people dying with SARS-CoV-2 due to the InflammoThrombotic responses (ITR) to the viral infection.
- Awareness of the ITR following SARS-CoV-2 infection in the immunologically naïve and patients with comorbidities, and treatment directed to that ITR is critical to the care and management of SARS-CoV-2 patients.

Abstract

This paper discusses the importance of addressing, measuring and treating the infectious, inflammatory and thrombotic tissue effect resulting from the body's immunologic response to SARS-CoV-2 using methods previously detailed in the medical literature, in an effort to reduce SARS-CoV-2 morbidity and mortality.

Successful treatment of SARS-CoV-2 requires addressing each of the four stages of the viral infection including oxygenation, acute cytotoxic immune response, adaptive humoral-antibody response, and viral cellular attachment and replication. Information obtained from the National Clinical Trial NCT04349410 has proven the need to treat each of these four factors. A paper detailing the NCT04349410 results is currently being submitted for publication and confirms this paper.

Introduction –Understanding and Measuring the Effect of SARS-CoV-2.

In 2019 SARS-CoV-2 validated the Fleming Inflammation and Cardiovascular Disease Theory confirming the role that viruses, including SARS-CoV-2, and other factors play in the InflammoThrombotic disease process responsible for the deaths of more than a million people worldwide. These deaths are the result of the immunologic InflammoThrombotic Response (ITR) to the virus and the unrestrained over activation of the immune system. This paper looks at critical information needed by clinicians and researchers alike, as they diagnose and treat SARS-CoV-2 patients.

In 1994 the Fleming Inflammation and Cardiovascular Disease Theory was initially presented [1,2] at the American Heart Association (AHA) meetings in an effort to explain the continued increase in heart and other blood vessel diseases despite improvements in lipid

management. The Fleming Theory established 12-fundamental factors responsible for inflammatory and vascular diseases including infections [3,4]. The initial presentation was followed by subsequent AHA presentations and publication of the Theory in a Cardiology Textbook [5] in 1999. Further research demonstrated the effectiveness of treating bacterial infections [6] and reversing coronary artery disease (CAD) and the ITR process using this Theory. Portions of this work were discussed in 2004 on 20/20 [7].

Measurement of changes in tissue caused by the SARS-CoV-2 viral infection and the resulting ITR within pulmonary tissue is made possible using the Fleming Method for Tissue and Vascular Differentiation and Metabolism (FMTVDM) [8].

FMTVDM quantitatively calibrates nuclear imaging cameras and then enhances regional metabolic and blood flow differences to measure changes in tissue – in this instance the lungs – resulting from the altered regional blood flow and metabolic reaction to the virus and subsequent ITR. FMTVDM [Figure 1] provides an objective measurement of the severity of the infection and when performed serially can measure the exact effect of treatment. These serial FMTVDM measurements make it possible to rapidly adjust treatment based upon a measured response of the virus to treatment in each individual; saving time, money, resources and lives.

ASKING THE WRONG QUESTIONS.

The emphasis on mass PCR testing has some limitations. PCR testing does not tell the clinician what's happening at the tissue level; the information so critical to understanding how extensive the infection and immune response to the infection are. Similarly, antibody testing cannot answer the question regarding how long an individual will be immune to SARS-CoV-2 infection.

The PCR test that looks for evidence of viral particles in the nose or throat, does not tell you if there is an active infection and it certainly doesn't tell you what the treatment should be. The PCR test is a research tool meant to amplify minimal antigens to a greater level for detection. No doubt, the PCR antigen and antibody testing could roughly help us to know how many people have been potentially infected and who may be protected from future infections.

We also need to ask a very fundamental question. When in the history of mankind have we pancultured everyone in the population for anything - including a viral infection? In other words, when we see increasing rates of spread of SARS-CoV-2, are we to conclude this is a problem or are we to conclude that this is what viruses normally do?

ASKING THE RIGHT QUESTIONS.

People with inflammatory diseases including obesity, heart disease, cancer, hypertension, diabetes, et cetera, as well as people who have naïve immune systems including the young and people with diabetes or immune deficiency diseases, are at increased risk of complications and death due to the failure of their immune systems to maintain homeostatic control and balance under states of increased immune response – including viral infections.

The treatment of patients infected with SARS-CoV-2, particularly the individuals with comorbidities, requires that physicians pay close attention to each of the four components of the SARS-CoV-2 infection and ITR – viz. viral infection and replication, oxygenation, acute cytotoxic immune response, and adaptive humoral antibody response. Table 1 shows each of these components along with multiple potential treatments and their mechanisms of action. It is important that treatment be driven by objective measureable outcomes such as FMTVDM and not merely the presence or absence of viral antigens or antibodies.

Early Intervention and Treatment During the Viral Attachment and Replication Phase.

Early intervention is not the equivalent of merely PCR testing. Early intervention requires medical treatment of those who are symptomatic, and who are suspected of having been infected. Treatment must be initiated during the early stages of viral replication while waiting for test results. This has been the medical practice of treating infections for the last century if not longer.

Early intervention can minimize the ITR by reducing viral replication and in those with comorbidities the subsequent over activation of the immune system.

Potential treatments available in this early pre-hospital stage are shown in Table 1 and Figure 2 and focus on the use of medications that inhibit the attachment of SARS-CoV-2 to cells and the ability of the virus to replicate within cells. The current list of such drug candidates includes *inter alia* hydroxychloroquine, primaquine, zinc, azithromycin, doxycycline, clindamycin, remdesivir and interferon α-2β.

The rapid initiation of these treatments can dramatically reduce the potentially devastating ITR to SARS-CoV-2 worsening patient comorbidities, including myocardial infarction, thrombosis leading to cerebrovascular (CVA) strokes, pulmonary emboli (PE), peripheral thrombosis (DVT), acute respiratory distress syndrome (ARDS) and death.

OXYGENATION AND THE EARLY INNATE CYTOTOXIC IMMUNE Phases.

Successful treatment of SARS-CoV-2 requires careful attention to the patient's oxygen status and the immunologic response associated with the innate T-cell cytotoxic phagocytosis and presentation of viral antigens resulting in the release of interleukins, cytokines and initiation of the ITR [5].

Oxygen (O_2) is not the primary determinant of the patient's respiratory rate. Hydrogen ions are, and these ions are primarily determined by the patient's carbon dioxide (CO_2) level. It is CO_2 not O_2 that determines the correct ventilator settings in these patients including tidal volumes (V_T) and back up respiratory rate.

These settings are substantially different for patients with SARS-CoV-2 whose inflammatory pulmonary edema results in Acute Respiratory Distress Syndrome (ARDS), respiratory failure and the need for intubation. An ARDS complicated by both the inflammatory edema and potential for ITR thrombosis of pulmonary blood vessels further compromising the patient's oxygen status [9]. Failure to recognize and treat this ITR to SARS-CoV-2 has arguably resulted in hundreds of thousands of deaths [10].

Progression of disease resulting in hospitalization does not mean the initial treatments have failed or should be abandoned. In fact, absent FMTVDM, there is no true method for measuring the actual treatment effect of these drugs. If FMTVDM shows improvement with prior treatments or stabilization with treatment, physicians should seriously consider continuation of current treatment; with the addition of new treatment if no improvement is measured. If however FMTVDM shows progression of disease in the face of current treatment, alternative treatment should be considered [11].

Treatment of failing oxygenation should be addressed either by prone positioning, supplemental oxygenation, or reduced ventilator tidal volume. The use of specific bronchodilators [11] should also be employed to improve oxygen and carbon dioxide exchange. If the only problem is oxygenation and not cardiac function, patients may also be treated using vein-to-vein (V-V) extracorporeal membrane oxygenation (ECMO); alternatively if there is cardiac compromise, one can consider using vein-to-artery (V-A) ECMO.

Having addressed the oxygenation factor, attention also needs to be paid to the innate acute T-cell cytotoxic immune response. In this early stage of SARS-CoV-2 treatment, the immune system is phagocytosing the virus while simultaneously releasing cytokines, interleukins, interferons, and other chemical mediators – all with the expressed purpose of eradicating the virus. However, the unrestrained ITR can and does result in other tissue damage and consequences [10].

The goal of medical treatment is to minimize viral replication while simultaneously minimizing the damage resulting from the release of interleukins (e.g. IL-6) and other InflammoThrombotic mediators that will ultimately produce systemic InflammoThrombotic damage elsewhere in the body – particularly among the immune naïve and those with comorbid InflammoThrombotic health problems.

Treatment during this still relatively early stage (Table 1; Figure 2) of the disease includes – if not already started – immune support including Folate, Vitamins C, B6, B12 and D3. In addition to these and other vitamins and minerals detailed in NCT04349410 [11], this is the time to begin treatment with IL-6 receptor antagonists e.g. Tocilizumab and/or other agents that can reduce or inhibit the release and effect of IL-6; including Interferon α-2β and Methylprednisolone – remembering that the administration of steroids will shift the immune response away from T helper 1 cells promoting cytotoxic response by CD8 suppressor/cytotoxic cells, towards T helper 2 cells promoting humoral antibody response, which through the Fc component of the antibodies produced can promote further thrombotic activity via the complement cascade as shown in Figure 1. It must also be remembered that excessive administration of steroids can shut down the immune response, thus providing no protection

against viral infection, replication and allowing potential further activation of the ITR to the SARS-CoV-2 infection.

Treating The Late Adaptive Humoral Immune Response.

While one of the presumptive desired responses to any viral infection is the production of host antibodies following the interaction between T-cells and B-cells resulting in both the production of antibodies by plasma cells and memory B-cells for any future infections, it must be remembered that this late adaptive humoral immune response only occurs with the continued release of cytokines, interleukins and the InflammoThrombotic process.

Patient treatment during this progressed stage of the disease – essentially within the first week of hospitalization – must continue to focus on balancing the ITR to the virus. Failure to be familiar with the ITR [5,7,8] including the correct management of patients on ventilators can easily result in poor measureable outcomes [8] including death.

Treatment of SARS-CoV-2 means finding the homeostatic balance – control of the virus without causing extensive harm to the patient. Journalists, lawyers, judges, insurance companies, and politicians do not treat patients – physicians do. Every SARS-CoV-2 patient's ITR must be looked at from the perspective of each individual patient's immune response – is it too much or too little for that patient? Treatment must be individualized, focused [3,11] and based upon what is happening to that specific patient.

It is during this period of time the physician must – presuming it has not already been initiated – treat the patient for possible tissue thrombosis and blood clotting. This includes CVAs, MI's, renal damage, PEs, DVTs, et cetera. Clearly any one of these ITR consequences

will further complicate the patient's clinical course and care, resulting in undesirable complications and death [12].

Treatment during this stage of the disease continues to rely upon tailoring medications shown in Table 1 and Figure 2, and when possible focusing on the patient's actual measured treatment response (FMTVDM). One potential treatment option should be relegated to this later phase of the ITR using passive humoral antibody treatment from convalescent plasma remembering that the administration of plasma with fibrinogen includes potential thrombotic concerns and transfusion reaction problems. It must also be remembered that convalescent plasma can only provide passive immunity. Once an antibody is used to bind to a viral antigen – it is forever used.

THE FLEMING CORONA VIRUS DISEASE (COVID) TREATMENT PROTOCOL BASED UPON THE HYPER-INFLAMMOTHROMBOTIC RESPONSE (HYPER-ITR) TO SARS-CoV-2.

It should now be obvious after hundreds of thousands of deaths that the morbidity and mortality associated with SARS-CoV-2 is the result of the body's hyper-ITR to SARS-CoV-2 viral infection [1,5] occurring in two major groups of individuals: (a) those who are immune naïve including the young, diabetic and those with immune deficiency syndromes, and (b) those with a variety of comorbid conditions including *inter alia* obesity, heart disease, cancer, hypertension, cerebrovascular disease, the elderly, and those with diabetes.

Treatment of this hyper-ITR to SARS-CoV-2 therefore requires careful attention to the consequences of this ITR [2]. Addressing each of these four fundamental issues: (1) viral infection and replication, (2) oxygenation, (3) innate cytotoxic immune response, and (4) adaptive humoral immune response, and addressing them in a timely manner is critical to

treatment success or failure. Failure to do so – as we have repeatedly seen – can easily result in morbidity and death.

As the incidence of SARS-CoV-2 infections continue to increase and hospitals continue to admit these patients for treatment, we offer this proposed treatment guideline [Table 1; Figure 2] and information for consideration and use by others [5, 20].

ADDRESSING SARS-COV-2 VULNERABILITY; UNDERLYING CHRONIC INFLAMMATORY DISEASES.

Let us look at a final problem that SARS-CoV-2 has made blatantly apparent; the vulnerability that occurs when the diet and lifestyles currently promulgated produce comorbidities that increase our susceptibility to hyper-inflammatory scenarios whereby the very immune system evolved to save lives now predisposes people with comorbidities to develop a hyper-ITR response; now associated with so many deaths.

The spread of SARS-CoV-2 has literally shaken the world; psychologically, emotionally, physically and economically. Responding to the primal fears of our ancestors, societies shut down and "sheltered in place" as if some invisible enemy would simply pass by if we stayed quiet long enough.

Such an approach did not result in the enemy simply passing by. Despite the devastating consequences of sheltering in place for months on end, the virus – like all viruses – did not go away. Viruses simply do not merely go away because we want them to. Fear and misinformation have also remained.

The much talked about curve was flattened providing more than adequate time for treatment to focus on the ITR to the virus. However, treatment of patients with SARS-CoV-2 did

not focus on treating the ITR despite this knowledge having been disseminated more than a quarter of a century earlier [1-9].

While the immune naïve and those with immune deficiency syndromes have little they can do to correct their status – absent waiting for development of their immune systems– there is much that could have been done to eliminate to prevalence of the comorbid InflammoThrombotic states that have plagued modern society.

We have repeatedly emphasized the role that dietary and lifestyle factors play in exposing so many to the InflammoThrombotic consequence of heart disease, cancer, diabetes, obesity, hypertension, advanced age, et cetera [5, 13-16], and the need to address these practices.

We now know that these people have been placed in extremely vulnerable situations when exposed to viruses like SARS-CoV-2 or other pro-InflammoThrombotic circumstances and absent correcting the underlying cause of these diseases, they will continue to be so exposed [3,17,18].

The introduction of SARS-CoV-2 has ushered in an era of human awareness of the spread of viruses and their potential harm [19] to everyone with these InflammoThrombotic diseases [1-5]. The need to address the underlying health problems associated with these comorbid diseases and the need to accurately measure treatment responses [8,20] have never been greater.

Failure to address the InflammoThrombotic effect of these diseases and failure to measure the effect of SARS-CoV-2 treatment(s) [8] has resulted in hundreds of thousands of people dying. The question is where does humanity go from here? Do we continue on our current trajectory or do we embrace the paradigm shift before us? Do we treat people based upon the

pathogenesis of the ITR and measure the treatment outcomes, or do we continue to ignore the information before us and hope the virus will pass us by?

CONCLUSION

The year 2020 ushered in SARS-CoV-2 reminding us of the vulnerability of people with underlying InflammoThrombotic diseases and those with naïve immune systems. Their commonality being impaired immune homeostasis resulting either from an inadequately developed immune system or an already over activated immune response resulting from diseases associated with modern civilization.

The medical caveat of treat the underlying cause of the disease and not just the symptoms should have resulted in far fewer deaths than we have seen. However, the consequences of an overwhelmed medical system couple with lack of understanding of the underlying pathogenesis of the resulting ITR to SARS-CoV-2 provided by the Fleming Inflammation and Cardiovascular Disease Theory [5], the FMTVDM measurement [20] of the severity and treatment response, and failure to address ventilator settings in these patients resulted in a significant uncontrolled pandemic with hundreds of thousands of deaths.

This paper highlights that information for the reader providing a treatment regimen focused on these principles and Theory.

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REFERENCES

1. Fleming RM., Fleming DM, Gaede R. Improving the Accuracy of Reading Percent Diameter Stenosis from Coronary Arteriograms: A Training Program. The Council on Arteriosclerosis for the 67th Scientific Sessions of the AHA. November 1994:101.
2. Fleming RM. Arteriosclerosis as Defined by Quantitative Coronary Arteriography. The Council on Arteriosclerosis for the 67th Scientific Sessions of the AHA. November 1994:102.
3. https://fmtvdm.wixsite.com/fhhi-omnific/inflammation-heart-disease
4. Fleming RM. Stop Inflammation Now! ~~with Tom Monte.~~ Published by Putnam Books and Avery Books. December 2003. ISBN: 0399151117
5. Fleming RM. Chapter 64. The Pathogenesis of Vascular Disease. Textbook of Angiology. John C. Chang Editor, Springer-Verlag New York, NY. 1999, pp. 787-798. doi:10.1007/978-1-4612-1190-7_64.
6. Fleming RM. The Fleming Unified Theory of Vascular Disease: A Link Between Atherosclerosis, Inflammation, and Bacterially Aggravated Atherosclerosis (BAA). Angiol 2000; 51: 87-89.
7. "Hidden Heart Disease. Could a simple, inexpensive test save your life?" 20/20 - ABC Network with Barbara Walters and Dr. Timothy Johnson 16 April 2004. https://www.youtube.com/watch?v=Hvb_Ced7KyA&t=22s
8. The Fleming Method for Tissue and Vascular Differentiation and Metabolism (FMTVDM) using same state single or sequential quantification comparisons. Patent Number 9566037. Issued 02/14/2017. https://patents.google.com/patent/US9566037B2/en
9. Fleming RM. Unmasking CoVid Currently submitted for publication 2020.
10. Why Surviving the Virus Might Come Down to Which Hospital Admits You. Written by Brian M Rosenthal, Joseph Goldstein, Sharon Otterman and Sheri Fink. https://www.nytimes.com/2020/07/01/nyregion/Coronavirus-hospitals.html
11. The Fleming [FMTVDM] Directed CoVid-19 Treatment Protocol (FMTVDM). https://clinicaltrials.gov/ct2/show/NCT04349410
12. https://www.foxnews.com/entertainment/nick-cordero-coronavirus-death- broadway-star-amanda-kloots

13.Fleming RM. Stop Inflammation Now! with Tom Monte. Published by Putnam Books and Avery Books. December 2003. ISBN: 0399151117

14.Fleming RM. Chapter 29. Atherosclerosis: Understanding the relationship between coronary artery disease and stenosis flow reserve. Textbook of Angiology. John C. Chang Editor, Springer-Verlag, New York, NY. 1999. pp. 381-387.

15.Fleming RM, Fleming MR. The Impact of Low Carb – KETO Diets on CAD. Why more Research is needed. J Cardiovasc Med Cardiol 2020;7(2):110-121. DOI:10.17352/2455-2976.000124. https://www.peertechz.com/articles/JCMC-7- 224.php

16.Fleming RM, Fleming MR, Chaudhuri TK, Harrington GM. Cardiovascular Outcomes of Diet Counseling. Edel J Biomed Res Rev. 2019;1(1):20-29. http://edelweisspublications.com/articles/48/531/cardiovascular-outcomes-diet-counseling

17. https://www.youtube.com/watch?v=mGyEvutNkvs&t=1s

18. https://fmtvdm.wixsite.com/fhhi-omnific/covid-inflammothrombotic-response

19. Fleming RM, Boyd L, Forster M. Reversing Heart Disease in the New Millennium - The Fleming Unified Theory, Angiology 2000;51(10):617-629.

20. Fleming RM, Fleming MR, Dooley WC, Chaudhuri TK. Invited Editorial. The Importance of Differentiating Between Qualitative, Semi-Quantitative and Quantitative Imaging – Close Only Counts in Horseshoes. Eur J Nucl Med Mol Imaging. 2020;47(4):753-755. DOI:10.1007/s00259-019-04668-y. Published online 17 January 2020 https://link.springer.com/article/10.1007/s00259-019- 04668-y https://rdcu.be/b22Dd

TABLES

Table 1. Proven and proposed SARS-CoV-2 treatments based upon mechanism of action.

Treatment	Viral Attachment and Replication	Innate T-cell Cytotoxic Response	Oxygenation and ARDS**	Adaptive Humoral (Antibody) Response.
1,25-Dihydroxycholecalciferol (Vit. D3)		Improved immune response.		Improved immune response.
Ascorbic Acid (Vit. C)		Improved immune response.		Ascorbic Acid (Vit. C)
Atrovent			β-2 bronchodilator to increase airway diameter and reduce bronchial secretions without the increase in heart rate and potential QTc prolongation associated with β-1 agonists.	
Azithromycin	Inhibition of viral protein translation.			
Clindamycin	Potential inhibitor of viral attachment by inhibiting Transmembrane protease serine 2 (TMPRSS2).			
Clindamycin	Inhibition of viral protein translation.	Inhibits cytokine release decreasing tissue necrosis factor – alpha (TNF-α) and IL-1β (Interleukin-1 beta).		Inhibits cytokine release decreasing tissue necrosis factor – alpha (TNF-α) and IL-1β (Interleukin-1 beta).
Convalescent Plasma				Provides passive immunity reducing potential ITR although the increased fibrinogen levels associated with plasma transfusions may increase thrombus formation.
Cyanocobalamin (Vit. B12)		Improved immune response and reduction of inflammatory homocysteine.		Improved immune response and reduction of inflammatory homocysteine.
Doxycycline	Inhibition of viral protein translation.			
Folate (Vit. B9)		Improved immune response and reduction of inflammatory homocysteine.		Improved immune response and reduction of inflammatory homocysteine.
Hydroxychloroquine	Inhibits viral RNA replication.	Inhibits toll-like receptor 7 (TLR7) to reduce inflammatory response.		Inhibits glycoprotein IIb/IIIa thereby interfering with thrombus formation.
Hydroxychloroquine	Inhibits viral attachment at ACE2 receptor site.	Reduces the production of pro-inflammatory cytokines.		
Hydroxychloroquine	Enhances entry of zinc through			

	zinc ionophore.			
Hydroxychloroquine	Increases cytosol pH to reduce removal of viral envelope required for replication.	Increases cellular pH decreasing major histocompatability complex (MHC) viral antigen presentation to b-cells thereby decreasing release of inflammatory cytokines.		
Hydroxychloroquine	Enhances production of Type I Interferons.			
Interferon a-2b	Interferes with viral replication.	Reduction of IL-6 levels.		Reduction of IL-6 levels.
Losartan***			Potential to decrease ARDS.	
Magnesium		Improved immune response and reduction of QTc prolongation potential.		Improved immune response and reduction of QTc prolongation potential.
Methylprednisolone		Reduces IL-6 levels.	Stimulates β-2 receptors improving airway flow.	Reduces IL-6 levels.
Methylprednisolone			Decreases endothelial leakage producing ARDS.	
Oxygen (supplemental) other than ventilator.* [Prone positioning, BiPAP, V-V ECMO, V-A ECMO, NC, Venti Mask.]			Reduced inflammatory stretching of alveoli and subsequent worsening of ARDS.	
Primaquine	Inhibits entry of Virulent Newcastle Disease (VND) virus.			
Primaquine	Inhibits viral RNA replication and protein translation.			
Pyridoxine (Vit. B6)		Improved immune response and reduction of inflammatory homocysteine.		Improved immune response and reduction of inflammatory homocysteine.
Remdesivir	Interferes with formation of mRNA via RdRP.****			
Tocilizumab		Blocks IL-6 receptors reducing ITR.		Blocks IL-6 receptors reducing ITR.
Zinc	May reduce ACE2 receptor activity.	Improved immune response.		Improved immune response.
Zinc	Interferes with RdRP and polyprotein transcription.			

* BiPAP = Bilevel Positive Airway Pressure, V-V is vein to vein, V-A is vein to artery, ECMO = extracorporeal membrane oxygenation, NC = nasal cannula, and Venti = Venturi.

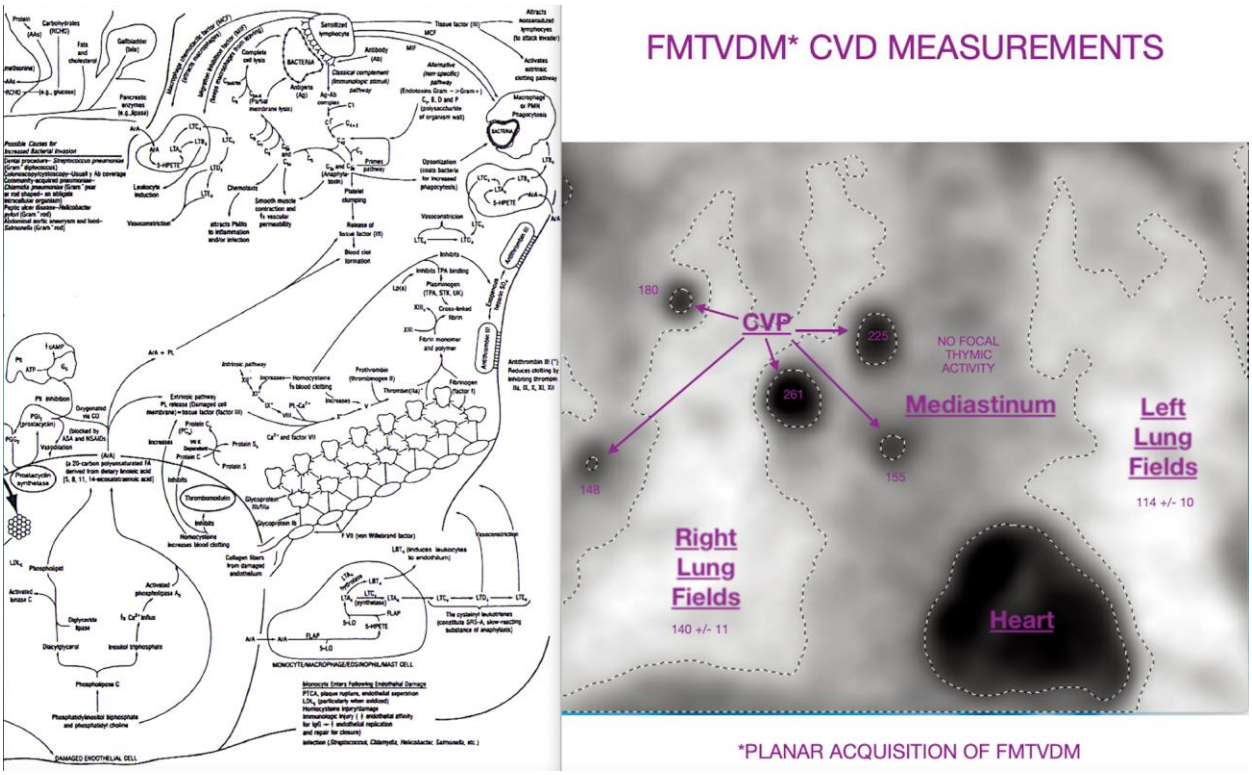
** Acute Respiratory Distress Syndrome.

*** Originally included in study design with prior pre-clinical studies in animals suggesting a possible mechanism of action inhibiting ARDS with H5N1 virus. Excluded from study after IRB review and consideration of concerns for angiotensin-converting-enzyme (ACE) inhibitors and angiotensin II receptor blockers (ARBs). Included in this table for completeness.

**** RdRP = RNA dependent RNA polymerase.

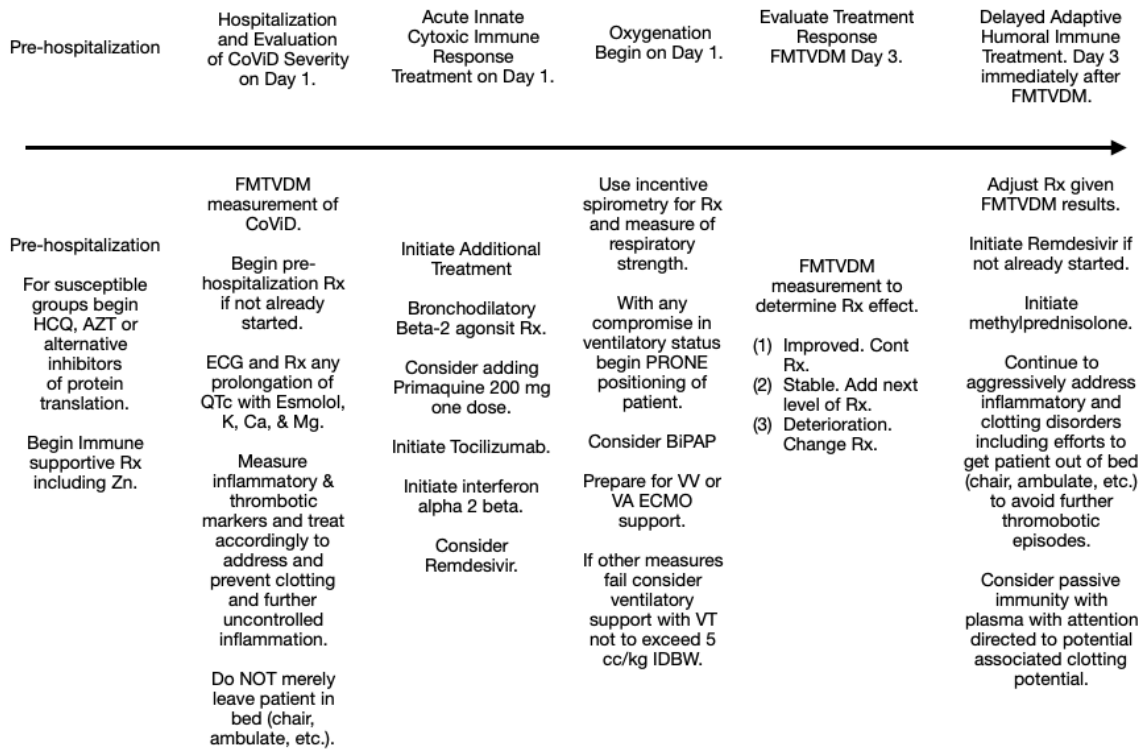
FIGURES

Figure 1. Inflammothrombotic interactions between infection, inflammation, interleukins, cytokines and the blood-clotting complement cascade. FMTVDM tissue measurement of the viral and InflammoThrombotic Response (ITR).



Legend: The left half of the figure [5] shows the interactions between infectious agents, the complement clotting cascade, cytokines, interleukins, and glycoprotein IIb/IIIa as they worsen already existing InflammoThrombotic coronary artery (vascular) disease in addition to other inflammatory diseases including *inter alia* obesity, cerebrovascular (CVA) disease, diabetes, cancer, advanced age, and hypertension. The right half of the figure [8] shows FMTVDM measurement of regional differences in blood flow and metabolism at the tissue level resulting from SARS-CoV-2 and the associated ITR [FMTVDM U.S. patent # 9566037; NCT04349410] making it possible to measure both the severity of SARS-CoV-2 as well as treatment success or failure.

Figure 2. Proposed serial treatment for SARS-CoV-2 based upon the stage of infection and immune response.



Legend: Incorporation of a systematic treatment of SARS-CoV-2 based upon the extent of immunologic response. Initial treatment needs to focus on reduction of viral stimulation of immune cytotoxic response by decreasing viral infection and replication, as well as reducing further ITR by minimizing ARDS and damaging interleukin and cytokine release.

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