An

evidence-based review to assist empirical management of SARS-COVID-19 induced “bilateral interstitial SARS-COVID-19 pneumonia” by using intravenous Ascorbic Acid June 23, 2020

IN SUPPORT OF DEDICATED SELFLESS MEDICAL PERSONNEL ALL OVER THE WORLD. HUMANITY OWES THEM!

Receiving sad news from all over the world, witnessing humanity overwhelming by an invisible enemy with no weapon to destroy it. Media pictures made me look around the treatment options offered currently.
I collected research results in immediate response to COVID-19 imposed “Bilateral interstitial pneumonia” management. In response to SARS- COVID-19 there are many ongoing empirical clinical trials with antimalarial, atazanavir and hydroxychloroquine (YNHHS Treatment Algorithm for Hospitalized Patients with Non–Severe* COVID-19. Updated 3/24/20 and 04/04/20) and many further MONOCLONALL ANTIBODIES such as remdesivir. After reviewing some of them the only one caught my attention is the first clinical trial for COVID-19 treatment Trial # NCT 04280705, I saw a deficiency in the established arms for these important studies. Missing :

1. Monitoring serum level of Ascorbic Acid (Vitamin C) by SARS-COVID-19 infected now immunocompromised patients is necessary, as
2. Monitoring CRP level, Lymphocyte count, and cytokine monitoring daily may provide information about the efficacy of the medications, and patients' improvement or deterioration, which are implemented.

Based on scientific research and clinical data, I suggest that patients infected with COVID-19 of the following categories below might receive the most benefits from the combination treatment of Ascorbic Acid and remdesivir and similar, as well as hydroxychloroquine… in the current clinical studies initiated in the USA.

Clinical Trial # NCT 04280705. Study ID 20-0006.

1- hospitalized, on an invasive mechanical ventilator or Extracorporeal membranous Oxygenation (ECMO),

2- hospitalized, on non-invasive mechanical ventilation or high flow oxygen devices,

3. hospitalized, requiring supplemental oxygen,

4. hospitalized, requiring supplemental oxygen, requiring ongoing medical care for COVID-19 related otherwise.

A critical look into the protocol and arms selected in the current clinical trial for SARS-COVID-19 # NCT 04280705. Study ID 20-0006, shows it is missing two important factors in the monitoring daily outcome of the result in patients receiving remdesivir treatment:

1. CRP (C-Reactive Protein) as an indicator of inflammation and infection, in order to determine the oxidative burden for the patient. Daily laboratory evaluation of IgM and IgG level, and cytokines,

2. Daily serum level of ascorbic acid concentration in patients under immunologic distress by COVID-19 and monoclonal antibody remdesivir administration.

Vitamin C(Ascorbic Acid) deficiency observed in all patients at any level of viral infection.

Human body is incapable of synthesizing vitamin C, this condition might complicate established therapeutic paradigms, independent what antiviral empiric chemistry being used in the study. Again, because **humans cannot synthesize vitamin C.** On the other hand, previous studies showed that "it is possible that vitamin C oxidizing to DHA before it is transported into the cells. Alternatively, other antioxidants such as glutathione (GSH) or DTT were unable to elicit the same effects. (1) It has been reasoned that the effects of vitamin C may be mediated by TET proteins and because TET proteins are the only known enzymes that oxidize 5-methylcytosine (5mC) to 5-hydroxymethylcytosine (5hmC). And vitamin C acts as a cofactor for TET proteins (2).

TET Proteins and their various mechanisms of coordinating transcription and splicing are being characterized, and some may be gene-specific (3).

Oncologic studies show that targeting the cancer DNA methylome by combining low-dose 5-aza-CdR and vitamin C stimulates the expression of ERVs, the induction of a cell-autonomous immune activation response, and increased apoptosis of cancer cells. The lack of vitamin C in a patient's plasma might cause a poor response to DNMT treatment in some patients. **Vitamin C deficiency has been seen previously in patients with multiple types of cancer, and viral infections.** including hematological malignancies. The biologic role of TET proteins is beyond the scope of this review but is discussed elsewhere e.g. (3) The TET Family of Proteins: Functions and Roles in Disease. J Mol Cell Biol. 2009 Dec; 1(2): 82–92.

It is known that patients under immunologic stressors are profoundly depleted of their level of vitamin C. The motivation for using intravenous infusions of vitamin C (IVC) to treat viral illnesses comes, in part, from observations that virally infected patients exhibit vitamin C deficiency (4).

This knowledge, in turn, suggests that clinical management of viral infections may benefit from supplementation. Improved recovery of subjects with viral infection upon supplementation with pharmacologic doses of vitamin C has been observed clinically (5).

In this critical time and narrow options left a highlighted in very detail analyzing effects of Ascorbate on native immune cells is out of the scope of my rapid action. By the introduction of IV-Ascorbic Acid to the Antiviral treatment in SARS-Covid-19 induced "bilateral interstitial pneumonia" daily may upregulate the effect of remdesivir and other antiviral therapeutics currently used. The presence of Ascorbic Acid may up-regulate TET proteins which are also

involved in a wide range of other processes, including repressing RNAP III transcription, DNA repair and RNA transport in the cell.

Widespread DNA methylation remodeling has been reported at genes and cell-specific enhancers with known T-cell function during human $CD4^+$ T differentiation [147,148], and TET2 was reported to be the critical DNA demethylase involved in the differentiation of T_H1 and T_H17 cells, leading to activation of effector cytokine gene expression [148]. TET2 has also been shown to regulate $CD8^+$ T-cell fate, particularly information of memory $CD8^+$ T cells [149].
Prolonged antigen stimulation in peptide immunotherapy is associated with demethylation of conserved regions of PD-1 promoter, possibly via TET, leading to sustained PD-1 expression in $CD4^+$ effector T cells [150].
Profound demethylation of histone H3K27 is observed after activation in $CD4^+$ T cells and corresponds to pathways crucial to T-cell function, including T-cell activation and the regulation of the JAK/STAT pathways [151,152]. Deletion of the histone demethylase JMJD3 was found to regulate gene expression resulting in T_H2 and T_H17 differentiation and inhibiting T_H1 and Treg cell differentiation via altered methylation status of H3K27 and/or H3K4 [153,154 (6)

Serum level of Ascorbic Acid:

The therapeutic serum level of Ascorbic Acid in the situation of a critical cytokine storm should be high enough without a doubt. A serum concentration by 10 μM-11.7 μM is representing a critically low level. This level is below the therapeutic peak plasma level of 20 mM (350-400 mg/dL). However, in very severe cases IV Plasma levels up to 780 mg/dL have been observed without toxicity. If high doses are not tolerated in achieving therapeutic range, lower dosage still augments the biological benefits of IV vitamin C (7).

Intracellular ascorbate concentrations in circulating lymphocytes, monocytes and neutrophils have been reported to be ~3.5, ~3 and ~1.5 mM, respectively, when plasma levels are at least 50 μM, reflecting the status in healthy individuals consuming ≥100 mg ascorbate daily [8,31]

However, when plasma levels fall below 50 μM, immune cell ascorbate content decreases, with intracellular concentrations at ~1.5, 1.2 and 0.5 mM in lymphocytes, monocytes, and neutrophils, respectively, when plasma levels are ≤20 μM [8,31]. However, when plasma levels fall below 50 μM, immune cell ascorbate content decreases, with intracellular concentrations at ~1.5, 1.2 and 0.5 mM in lymphocytes, monocytes, and neutrophils, respectively, when plasma levels are ≤20 μM [8,31] (8).

The potential effect of IV vitamin C therapy is studied in the reduction of serum pro-inflammatory cytokines IL-1α, IFN-^{Y}, IL-8, TNF- α and exotoxin even after 50-gram/24hr ascorbic infusion (9).

Ascorbic Acid metabolized to its active dehydroascorbic acid (DHA,) the oxidized form of vitamin C, acting as a cofactor for TET proteins. The selectivity of each protein plays a significant role in the induction of a cell-autonomous immune activation response and increased apoptosis of aggressor cells. Therefore, depletion of vitamin C during the period of immunological distress may downregulate the biologic-therapeutic efficacy of any medication such as antiviral monoclonal Antibodies used for the original standard treatment.

Thus, our review of data suggests that correction of vitamin C deficiency in patients with immunological stressors such as cancers and or disseminated viral infections such as SARS

COVID-19 may improve responses to epigenetic synergistic therapy with intravenous Ascorbic Acid.

Baseline screening laboratory recommended for:

1- hospitalized, on an invasive mechanical ventilator or Extracorporeal membranous Oxygenation (ECMO),

2- hospitalized, on non-invasive mechanical ventilation or high flow oxygen devices,

3. hospitalized, requiring supplemental oxygen,

4. hospitalized, requiring supplemental oxygen, requiring ongoing medical care for COVID-19 related otherwise, if Ascorbic Acid implemented are:

- Complete metabolic panel
- CBC
- Virus-specific IgM and IgG (daily)
- Lymphocyte count (daily)
- G6PDH must be normal (possible hemolysis if high)
- Complete urine analysis
- Vitamin C serum level (daily)
- CRP (daily).

Based on the critical time of worldwide SARS- COVID-19 fatal epidemic, I have been encouraged as a research and clinical physician to share my experiences and knowledge with the medical community in charge of current clinical trials and hospital physicians at the forefront of the patient care. My goal is to bring the Synergistic effect of Vitamin C to the attention of clinical health care providers. There is no shortage of Vitamin C and compounding pharmacies able to manufacture it rapidly in needed quantities in a Cure no Harm meaning.

Thank you for your attention.

Respectfully,

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References:

1- Ma Y, et al. (2014) High-dose parenteral ascorbate enhanced chemosensitivity of ovarian cancer and reduced toxicity of chemotherapy. Sci Transl Med 6(222):222ra18.

2- Minmin Liu, Hitoshi Ohtani, Wanding Zhou, Andreas Due Ørskov, Jessica Charlet, Yang W. Zhang, Hui Shen, Stephen B. Baylin, Gangning Liang, Kirsten Grønbæk, and Peter A. Jones: Vitamin C increases viral mimicry induced by 5-aza-2′-deoxycytidine, PNAS September 13, 2016, 113 (37) 10238-10244; first published August 29, 2016.

3- Adelene Y. Tan, James L. Manley; The TET Family of Proteins: Functions and Roles in Disease Journal of Molecular Cell Biology, Volume 1, Issue 2, December 2009, Pages 82–92, https://doi.org/10.1093/jmcb/mjp025.

4- Mayland, C., Bennett, M. & Allan, K., 2005. Vitamin C deficiency in cancer patients. Palliat Med, Volume 19, pp. 17-20. McCormick, W., 1959. Cancer: a collagen disease, secondary to nutrition deficiency. Arch. Pediatr., Volume 76, pp. 166-171. Mikirova, N., Casciari, J. & Riordan, N., 2012. Ascorbate inhibition of angiogenesis in aortic rings ex vivo and subcutaneous Matrigel plugs in vivo. J Angiogenesis Res, Volume 2, pp. 2-6.

5- 1- Mikirova, N., Casciari, J. & Riordan, N., 2012. Ascorbate inhibition of angiogenesis in aortic rings ex vivo and subcutaneous Matrigel plugs in vivo. J Angiogenesis Res, Volume 2, pp. 2-6. 2- Mikirova, N., Casciari, J., Taylor, P. & Rogers, A., 2012. Effect of high-dose intravenous vitamin C on inflammation in cancer patients. J Trans Med, Volume 10, pp. 189-99. 3- Mikirova, N., Ichim, T. & Riordan, N., 2008. Anti-angiogenic effect of high doses of ascorbic acid. J Transl Med, Volume 6, p. 50. 4-Mikirova, N., Rogers, A., Casciari, J. & Taylor, P., 2012. Effects of high dose intravenous ascorbic acid on the level of inflammation in patients with rheumatoid arthritis. Mod Res Inflamm, Volume 1, pp. 26-32)

6- Vitamin C and immune cell function in inflammation and cancer: Abel Ang, Juliet M. Pullar; Margaret J. Currie; Margreet C.M. Vissers. *Biochem Soc Trans* (2018) 46 (5): 1147–1159.

7- Riordanclinic.org/research-study/vitamin-c-research-ivc-protocol.

8- Vitamin C and immune cell function in inflammation and cancer: Abel Ang, Juliet M. Pullar; Margaret J. Currie; Margreet C.M. Vissers. *Biochem Soc Trans* (2018) 46 (5): 1147–1159.

9- Mikirova, et al.,2012.

Our approach to SARS-COVID 19 infected and symptomatic patients:

I. We do not wait until patients tests by Nasal Swab (CPR) returned in days positive or negative. Since many people tested negative, however they were positive and vice versa. The symptomatic patients receiving treatment no matter what is their test results. No compromise allowed. For prevention we recommend 1000mg Vitamin C twice per day, and Zinc sulfate or any type of zinc formula daily. Use of Mask and Social Distancing are imperative rule.

II. Quarantine from the first hour we have been notified of patient exposure or symptoms.

III. Start our medication regimen based on results from international medical communities :

- **Vitamin C 1000 mg twice a day**
- **Zinc Sulfate 220 mg twice a day**
- **Azithromycin 500 mg twice a day(Check for presence of QT- heart condition)**
- **Hydroxychloroquine 200 mg twice a day, all for 5 days, and Aspirin 81 mg daily for prevention of Pulmonary Emboli/other vascular inflammation.**
- **If person positive but no symptoms; take: Vitamin C 1000mg twice /day, zinc Sulfate 220mg twice/day, and Aspirin 81 mg per day and follow quarantine rules.**

We follow up daily by phone calls (24/7 availibity) to assure our patients are doing well or need more attention for hospitalization or other relief. Many patients live alone and nobody ask about their condition. Two weeks quarantine will be followed automatically.

We understand that the SARS-COVID 19 Virus affects different organs in different ways. The goal is safety and health of patients approaching us for help. We are sharp and consequent in our respect of the life. Science decides for life not politics. Virus came from scientific sources and need to be defeated by science.

Any comment appreciated in order to make our community stronger together. Thank you.

Sincerely,

Faro Ted Owiesy, M.D

Corona Doctors Medical Clinics, Inc.