High Dose Ascorbic Acid Infusion for the Treatment of Severe 2019-nCoV Viral Pneumonia

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Summary:

The new coronavirus (2019-nCoV) and its pulmonary and systemic complications have caused worldwide concern and emergency. There is a lack of effective targeted antiviral drugs, and symptomatic supportive treatment is the only therapeutic approach for severe acute respiratory infection (SARI).

Ascorbic acid (AA) is an essential nutrient with important and diverse physiological effects. Moreover, at high doses (7,500 and over mg/day), especially when producing high micromolar or milimolar concentrations it has been shown to exhibit pharmacological properties. Among its many actions, it plays a role in reducing inflammation (a precipitating factor in SARI), supporting various aspects of the immune system and has a direct antiviral effect.

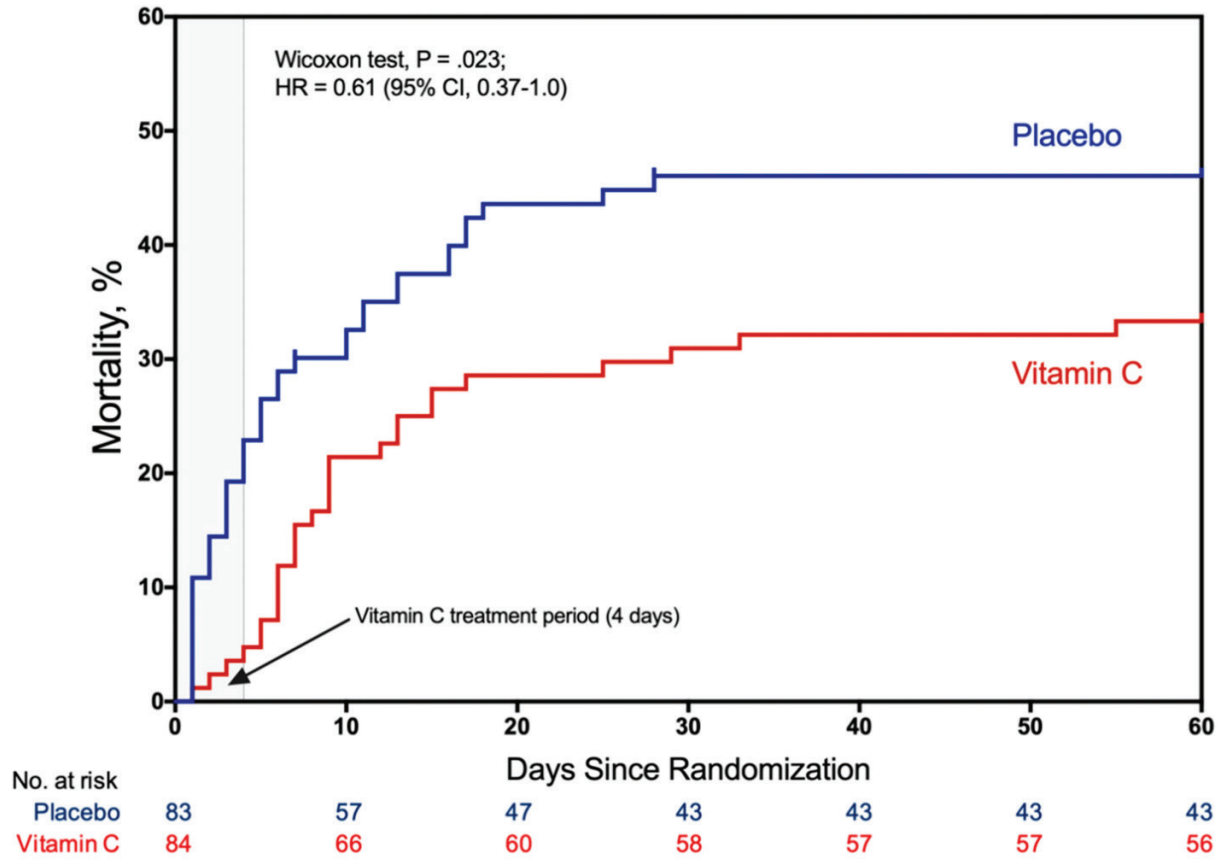
A number of studies describe an array of mechanisms by which ascorbic acid enhances the function of leukocytes including chemokinesis and chemotaxis properties, phagocytosis[2], production of lysosomal enzymes[3], generation of reactive oxygen species[4], and microbial killing[5], up-regulation of antibody response[6] and increased interferon[7]. These effects, as well as enhanced neutrophil chemotactic capacity[8,9], have also been documented in humans ingesting gram doses of vitamin C.

In addition, studies have shown clinical benefits which include lowering and reducing the risk of infection[10,11]. Studies in animal models have demonstrated that parenteral ascorbate improves sepsis and sepsis-induced multiple organ dysfunction syndrome via preventing of cellular immunosuppression[12]. Studies in septic mice suggest that increased survival occurs by activation of Nrf2/HO-1 signals[13].

In-vitro observations with pharmacologic concentrations (milimolar range) suggest a direct antiviral effect of ascorbate[14] consistent with clinical observations of patients with Epstein-Barr viral (EBV) infection. There was a significant reduction of the EBV antibodies upon pharmacologic intravenous ascorbate therapy[15]. Moreover, intravenous ascorbic acid has demonstrated clinical benefits in different viral infections[16,17,18,19].

Sepsis is a systemic response of an infection that results in an overwhelming production of reactive oxygen species (ROS) with widespread injury to multiple tissues, cells and organelles leading to progressive organ failure. The severe immune reaction in which the body releases too many cytokines into the blood too quickly produces an uncontrolled burst of damaging ROS is known as the cytokine storm and represents an important complication of covid-19 infection[20]. In summary, over 500 peer reviewed experimental and clinical studies have been published, clearly demonstrating the biologic credibility and biological and pharmacologic mechanisms of vitamin C alone or combined with other agents in the management of sepsis and other inflammatory disorders[21,22]. Based on these concepts, the most comprehensive randomized study using intravenous ascorbic acid in 167 patients with severe acute respiratory failure demonstrated at day 4 and forward significant reduction in mortality in the ascorbic acid group when compared to control group ($p = 0.023$)[23]. (See figure 1)

Figure 1. Patients with Sepsis and Severe Acute Respiratory Failure



Fowler et al (23) also gave patients 50mg/kg total body weight of ascorbic acid intravenously every 6 hours which amounted to a range of 3,500–5,000 mg every 6 hours for a total of 14,000–20,000 mg every 24 hours (Personal communication) with no unexpected treatment-related side effects.

Most vertebrates respond to a physiological stress such as sepsis with a dramatic increase in the synthesis of ascorbate by converting glucose by means of the enzyme l-gulono-g-lactone oxidase (GLO). When sufficient ascorbate is present, it helps: control excess inflammation, support leukocyte function, inhibit microbial pathogen growth and neutralize harmful ROS. However, since humans lack the GLO enzyme, we are not able to synthesize ascorbate and must acquire nutritional or pharmacologic doses according to the particular physiologic demands at hand.

Some recent studies suggest that the use of ascorbic acid as part of a protective protocol against sars-covid-2 can reduce mortality in patients hospitalized in intensive care units with sepsis. This ascorbic acid protocol can significantly reduce mortality from sepsis[24], reduce ICU stay length[25] and significantly reduce the time to resolution of shock[26]. The use of ascorbic acid injections also improved the ventricular function (EF) 72 hours after surgery and reduced the length of ICU stay in patients undergoing coronary artery bypass surgery[27].

The use of ascorbic acid as an effective antiviral has been documented as early as 1949 when Frederick R. Klenner, MD, documented the ability of vitamin C to reliably cure many different acute infectious diseases and to reliably neutralize any toxin treated, when sufficiently dosed and administered for a long enough period of time[28] including the cure of 60 out of 60 (100%) patients with polio within 4 days of ascorbic acid administration intramuscularly and orally[29]. He also reported the cure of advanced polio and its associated flaccid paralysis with ascorbic acid in 1951[30].

A paper by Marcial-Vega et al reported on the efficacy and safety of the use of intravenous 25–50 grams of ascorbic acid in the treatment of 56 patients with Chikungunya. These patients reported clinical improvements with no reported side effects. This protocol showed that the use of intravenous hydrogen peroxide and ascorbic acid is safe and strongly associated with a more than 71% post-infusion reduction of pain in patients affected with Chikungunya virus related arthralgia[31].

These results are consistent with previous in-vitro research which has shown that ascorbic acid inactivates the polio[32], herpes[33], vaccinia[34,35], tobacco mosaic[36], bacteriophage[37,38,39,40], entero[41], influenza[42] and rabies[43] viruses.

They are also consistent with previous clinical research showing ascorbic acid can resolve polio[9,10,11,44,45], its associated flaccid paralysis[10], acute hepatitis[46,47,48], viral encephalitis[49,50,51,52], measles[53], mumps[54], Herpes[55], influenza[56] and rabies in guinea pigs[57]. Also consistent with human case reports of influenza[18], mononucleosis[58], Chikungunya[59] and Zika[60] in which intravenous vitamin C was utilized successfully as therapy.

Recently there is some global movement leaning toward including ascorbic acid as part of the modalities used for the management of pulmonary failure due to the corona virus. One of these is a randomized protocol recently approved by the National Institutes of Health using 12 grams of intravenous ascorbic acid for severe infected 2019-nCov pneumonia. This research is led by Dr. ZhiYong Peng, Zhongnan Hospital in Wuhan, China[61].

More recently another clinical study using 10 grams of IVAA for hospitalized patients with COVID-19 started in Italy. This study lead by Salvatore Corrao, MD, from the University of Palermo started on March 13, 2020[62].

The Shanghai Expert Consensus on Covid-19 Treatment organized by the Shanghai Medical Association has included ascorbic acid as a treatment modality for Cov-2019 virus associated pneumonia[63].

An International Pulmonologist's Consensus Group has stated that a moderate dose of IV vitamin C could be considered (e.g., 1.5 grams IV q6 ascorbic acid plus 200 mg thiamine IV q12) for treatment of this disease and they consider this dose to be safe[64].

On a presentation given to us by Dr. Enqian Mao, chief of Emergency Medicine Department at Ruijin Hospital, Shanghai, affiliated with the Joatong University School of Medicine and a member of the Senior Expert Team at the Shanghai Public Health Center and co-author of the Shanghai Guidelines for the Treatment of Covid-19 infection, an official document endorsed by the Shanghai Medical Association and the Shanghai city government he stated[65]:

- In the year 2020, out of the 358 CoVid19 patients, 50 patients were treated with intravenous ascorbic acid (IVAA)
- Dose was 10–20 gm infused over 24 hours
- A patient that continued to deteriorate received an increased dose of 50 gm of ascorbic acid infused over a period of 4 hours and started responding during the infusion. This patient had a complete recovery and was eventually discharged.
- All patients receiving IVAA improved and there was zero mortality
- No side effects
- Patients who received IVAA had average 5 days shorter stay (from 30 to 25 days) than untreated patients

Given the track record of safety of intravenous ascorbic acid[66] and the diversity of favorable actions of ascorbate in the management of viral infections on sepsis and the effects on diminishing inflammatory complications in the scientific and clinical literature, we propose the evaluation of high dose intravenous ascorbic acid infusions as a therapeutic intervention in patients with severe acute respiratory infection from Covid-19. We propose this study to evaluate the clinical safety and efficacy of high dose intravenous vitamin C in the clinical management of severe acute respiratory infection from Covid-19.

Ascorbic Acid concentrations

Ascorbic acid, in addition to being a co-factor required for many physiological functions, in its reduced has a high electron-donating power and easily conversion back to the active reduced form. This gives that molecule the great ability to neutralize excess damaging oxidized reactive molecules. Ascorbate concentrations in body fluids and tissues are regulated through interactions of intestinal absorption, cellular transport, and excretion.

The amount of vitamin C needed to prevent scurvy is very small and generally believed to be easily obtained in nearly all Western diets. However, large cohort studies in US and Canada during the 21st century showed that the prevalence of low plasma vitamin C concentrations are as high as 22% to 33%, with 7% to 14% of them showing scorbutogenic deficiency[67,68]. **Scurvy** can be defined as a state of where signs or symptoms related **to deficient** ascorbate in the body associated with plasma ascorbate levels below 1.5 mg/L (0.0085 mM)[69] or below 1.9 mg/L [0.011 mM (11 µM)][70]. Marginal ascorbate hypovitaminosis or low plasma levels is a state que reserves are minimal and can easily develop scurvy upon a significant physiological stress and are characterized by ascorbate concentrations below 23 µmol/L[71,72]. Adequate levels to support health, depending on the criteria, is either anything above 23 µmol/L[70], or more specifically as recommended by a group European Countries about 50 µmol/L that compensates for metabolic losses[73,74]. Consumption of 5 to 9 servings of fruits and vegetables daily, or a 200 mg ascorbate supplement has been estimated to produce steady-state ascorbate plasma concentrations of 70–80 µmol/L[75]. Vigorous Oral vit C q 3 g 6 x d, peak values do not exceed 220 µmol/L[76]. Only when the ascorbic acid is given intravenously in high gram doses a supra-physiological, milimolar concentration is achieved with pharmacologic properties[77,78]. It has been documented that pharmacological concentrations of ascorbic acid in the milimolar range have antiviral properties against influenza virus in a dose dependent manner[79].

Ascorbate Plasma Levels	
Scorbutogenic deficiency	<1.5 mg/L (<8.5 µM)[69] <1.9 mg/L[70]
Low plasma level Sub-clinical vitamin C insufficiency (Nonspecific Sx; i.e., fatigue, irritability depression)	1.5–5 mg/L (28–8.5 µM)[70] <4 mg/L (23 µmol/L)[71]
Adequate plasma level (oral) 5 to 9 servings of fruits and vegetables or 200 mg supplement daily	> 5 mg/L (28–8.5 µM)[70] >23–50 µmol/L[72] achieve SS 70–80 µmol/L
Low Pharmacologic (oral) Oral 2.5 g qid to 3 g 6 x d	50–220 µmol/L micromolar
Mod-High Pharmacologic 10–50 gm intravenous dose	5000–13,400 µmol/L (5–13.4 mM) milimolar[76]

Ascorbic acid plasma Concentrations Analytical assay:
Blood samples for ascorbate quantification will be measured using HPLC with coulorimetric electrochemical detector. This method has been shown to accurately quantify ascorbate

in human plasma samples. The lower limit of ascorbate detection is typically 20 nM. Alternatively, the method that uses blood sugar meters could be adopted.

Study Design and Methodology

Study type:	Interventional, phase I-II pilot clinical trial
Estimated enrollment:	TBD # participants
Allocation:	Randomized
Masking:	Triple (participant, care provider and outcome assessor)
Treatment/Experimental group:	There are two randomizations. The first one is done immediately after a presumptive diagnosis of Covid-19 associated pneumonia and will involve:

Randomization 1
Oral Ascorbate or Placebo on patients with Presumptive CoVid-19 Pneumonia

1. A treated group receiving 28 mg/kg every 30 minutes (rounded to the nearest 500 mg unit dose) from a presumptive diagnosis of Covid-19 pneumonia.

   This can be accomplished by using ascorbate acid in fine crystals in 3–4 ounces water and having the patient drink the solution while the patient is awake until bowel tolerance (development of loose stool).

   Sick patients tolerate more ascorbic acid by mouth before diarrhea was produced. Dr. Carthcart reported that at least 80 percent of adult patients will tolerate 10 to 15 grams of ascorbic acid per day without having diarrhea when given dissolved in water in divided doses. In the case of very toxic diseases, doses may have to be taken every half hour. Short delays in taking these doses may prolong the disease[80].

   Absorption and distribution of ascorbate into the diseased tissues occur presumably because of increased ascorbate metabolism. Therefore, in order to supply the metabolic demand, this frequent dosing is designed to provide an adequate amount at an adequate rate[67].

2. Oral placebo group. This can be accomplished by using 5 mL of lemon concentrate diluting in 3–4 ounces water and having the patient drink the solution every hour while the patient is awake.

Oral bioavailability will be assessed by measuring blood concentration before starting oral intake and four samples after stating oral dosing at time: C_0 = pre-dose, C_1 = 1 hr, C_2 = 2 hr, C_3 = 4 hr, and C_4 = 8 hr.

Randomization 2
Patients enrolled in the Study with confirmed CoVid-19 Pneumonia

After the second randomization, both control and treated groups will receive **standard medical support care** which includes:

Severe Disease (14%)

- Respiratory rate > 30/min
- SPo2- <93%
- PaO2/FiO2 <300
- Lung infiltrates >50% within 24–48 hours
- Critically ill (5%)
- Respiratory failure (need of mechanical ventilation)
- Septic shock
- MODS
- No drug of choice
- Oxygen support
- Oxygen saturation to be maintained above 90%
- Conservative fluid management
- Give empirical antibiotics (As per institution based CAP guidelines) / anti-viral (Oseltamivir)
- High dependency / ICU care when needed

- **Control Group** **Conventional Treatment (CT)**
- **Experimental Group** **CT + Intravenous Ascorbate**

Patients that agree to participate and fulfill the eligibility and enrolled intravenous study will go on to the second randomization after a confirmed diagnosis of Covid-19 infection by nasal/oral cavity PCR.

Study group
In addition to the standard treatment for the patient, the **study group** will also receive intravenous ascorbic acid as described next. A dose of 50 mg/kg body weight of ascorbic acid in 50–100 cc lactated ringer's (or Sterile water or NSS) for injection IV Q6h for 7 days minimum. After 7 days of intravenous ascorbate, the treatment will be evaluated and patients will continue treatment until achieving clinical endpoints. Patients will remain in intravenous ascorbate if:

Criteria for intravenous ascorbate

1. Still in ICU
2. Below 90% oxygen saturation
3. Abnormal temperature (36.1–37.2°C)
4. Positive cultures (for bacterial or fungi)
5. Unstable blood pressures (3 or more measurements varying 10% or more)
6. Elevated white blood cell counts

In patients failing to respond and who are able to tolerate further fluids, a dose escalation to 100–200 mg/kg iv Q6 will be initiated and continued until the patient no longer maintains the intravenous ascorbate criteria.

Control group
In addition to the standard treatment for the patient, the **control group** will also receive 50 cc volume of lactated ringer iv Q6h for 7 days.

Statistical Analysis Plan:

Percentages, measures of central tendency and dispersion measures will used to summarize the distribution of variables, as appropriate. Graphs will be used to best visualize the distributions. The intervention and control groups will be compared in terms of baseline characteristics, to evaluate the effect of randomization, using chi-square test (for categorical variables) and two-sample t-test or Mann-Whitney test (for continuous variables), depending on the normality of the distribution (based on the results of Shapiro-Wilk normality test).

Primary (28-days mortality, ventilation free days, and ICU length of stay) and secondary (hospital stay, resolution of symptoms, and change of duration of positive swabs) outcomes of the study will be compared between experimental and the standard of care (control) groups. Binary variables of mortality and resolution of symptoms (yes/no) will be assessed through Chi-square test and logistic regression models to evaluate the magnitude of the association. Also, Kaplan Meier analysis will be performed to estimate the survival over time. The association between survival time of patients and the ascorbic acid infusion intervention will be evaluated using the Cox proportional hazard models (if proportional odds assumption is met).

All continuous outcomes will be compared between the ascorbic acid infusion intervention and the standard of care group using two-sample t-test; if normality assumption is not met, transformation of variables and non-parametric tests (Mann-Whitney test) will be considered. In addition, generalized linear regression models (GLM) will be performed to estimate the difference in outcome, along with their 95% confidence intervals, in patients with ascorbic acid infusion intervention as compared to those receiving the standard of care.

Interim analysis on the main outcomes will be conducted once the number of participants reaches 40% of the estimated sample size. Interim analysis results will be used to verify and fine-tune the planned sample size, as well as decide on early termination of the study based on evidence of intervention benefit.

Stata v16 (College Station, Texas 77845 USA) will be used to analyze all the study data. Significance level will be set at 0.05 for all statistical tests.

Ascorbic acid Plasma levels and pharmacokinetics (PK) assessment

Table 1. Timetable for dosing and blood sampling. * means vital signs taken.		
Time post-dose (hrs)	**Dose Number**	**Clock Time**
Day 1		
-	first	Before infusion*
0	first	After infusion, at 9:00 am*
6	first	3:00 pm; before next infusion*
Day 2		
6	fourth	Before infusion*
0	fifth	After infusion, at 9:00 am*
1	fifth	10:00 am
2	fifth	11:00 am
4	fifth	1:00 pm
6	fifth	3:00 pm; before next infusion*
Day 3		
0	ninth	30 min. after infusion, at 9:00 am*
Day 4		
0	13th	30 min. after infusion, at 9:00 am*
Day 6		
0	21st	30 min. after infusion, at 9:00 am*

1. Oral dosing study phase — A blood samples before and after ascorbate dosing will be collected in order to ascertain baseline and post dosing plasma concentrations of ascorbic acid.

2. Intravenous study phase — Blood samples will be taken to determine the concentrations achieved and study the possible correlation to efficacy and also if possible determine pharmacokinetic parameters of ascorbic acid in this population.

***PK Experiment (IV administration)*:** Vitamin C will be diluted with sufficient sterile water (or 50–100 cc lactated ringer's) to produce an intravenous fluid osmolality of less than 1,200 mOsm (500–1,000 mOsm), which is well tolerated by most subjects. The infusion rate (R0) will range from 0.4 to 0.6 g/min, which is well tolerated by most patients. Thirty minutes before administration, an intravenous angiocatheter will be placed for blood sampling. Individuals will be administered intravenously multiple repeated doses of 50–100 mg/kg each of Vitamin C, every 6 hrs, at the forearm region by intermittent short-term (10–15 min) IV infusions. Repeat this scheme during a minimum of 7 days. The intravenous vitamin C administration as well as blood samples collection for the study will be performed by nursing staff under supervision of the physicians of the study. Calculations were performed by using standard procedures based on early reported pharmacokinetic parameters[75,81,82].

Serial blood samples (5 ml at each time point; 12 points x 5 ml = 60 ml total within six days) will be taken under slight anesthesia from the catheter (counter-arm of the administration point), at the following times: First dose input (day 1, three points): pre-infusion; at the end of infusion and just before next input (day 1, at 03:00pm); fourth and fifth dose inputs (day 2, six points): before infusion, at the end of infusion and 1, 2, 4, and 6 hrs post-dose; ninth, 13th and 21st dose inputs (day 3, 4 and 6, one point each): 30 min. after infusions. All blood samples will be collected in EDTA purple top containers, and centrifuged at 4°C for 10 minutes at 1000 x g within 30 minutes of collection. Then, they will be separated into fractions and stored frozen until assay. Likewise, a fraction from the last blood sample taken (at 96 hrs after the third dose) will be used to determine serum creatinine (SCr, mg%) and BUN in each subject. The purpose of these assays is to rule out the occurrence of azotemia and to test renal function after completing the dosing scheme. Table 1 shows the time schedule for dosing and blood sampling. In addition, 12-hour urine will be collected from time to first dose (day 0) up to 144 hrs post-dose (day 6). The volume of urine (mL) will be determined for each collected sample and a portion will then be used for oxalate, uric acid assays and excreted ascorbate and dehydroascorbate (DHA) quantification. An acidic preservative (30 ml, HCL 6N) will be added to each container for urine collection during the last two 12-hour intervals to measure oxalate levels.

The traditional standard “single two-stage” (STS) method will be followed for obtaining both individual and average population PK data of vitamin C at high intravenous (IV) and oral doses. Additionally, the relationship between the PK parameters and subject characteristics (e.g., age, weight, gender, and degree of renal function) will be determined by categorization and regression analysis. The corresponding average population pharmacokinetic parameters (typical value) and variance (±S.D.) will be calculated from individual estimates following the STS method. Individual observations from each subject will be modeled separately to obtain average PK parameters. Covariates will be explored, but subjects with more or few observations will be weighed equal. Thus, average values will not be influenced by extreme observations. Uncertainty in individual parameter estimates is ignored, but each subject’s covariate and pharmacokinetic parameter will be correlated to explain between-subject variability (BSV). For PK purposes, no less than three subjects need to be enrolled in each dosage level to accomplish the proposed goals. Ideally, five to six subjects will suffice for each dosage levels to be tested.

Data analysis will be performed using a combined linear–log linear trapezoidal rule approach by following a non-compartmental analysis (NCA) in WinNonlin (Phoenix® WinNonlin® 7.0 software, Certara, NC, USA). PK parameters using the moments of the curve will be determined (e.g., area under curve, AUC; mean resident time, MRT). A time zero value will be considered for extrapolation purposes. The linear trapezoidal rule will be used up to peak level, after which the logarithmic trapezoidal rule will be applied. Lambda z is a first-order rate constant associated with the terminal (log linear) segment of the curve. It will be estimated by linear regression of the terminal data points. The largest adjusted regression will be selected in order to estimate lambda z, with one caveat: if the adjustments do not improve, but are rather within .0001 of the largest value, the regression with larger number of points will be used.

Primary Outcome Measures

1. 28 days mortality [Time Frame: on the day 28 after enrollment] whether the patient survives
2. Ventilation free days
3. ICU length of stay [Time Frame: on the day 28 after enrollment] days of the patients staying in the ICU

Secondary outcome measures

1. Hospital stay [Time Frame: 72 hours]
2. Ascorbic acid plasma concentration for correlation to outcomes
3. Pharmacokinetic parameters of ascorbic acid in study population
4. Symptoms [Time Frame: 72 hours] Resolution of symptoms (Fever, Cough, Shortness of breath or difficulty breathing)
5. Positive swab [Time Frame: 72 hours] Change of duration of positive swab (nasopharynx and throat)
6. Tomography imaging [Time Frame: 72 hours] Resolution of tomography imaging (example, patches located in the sub-pleural regions of the lung)
7. Demand for first aid measurements [Time Frame: on the day 28 after enrollment] the rate of CPR
8. Vasopressor days [Time Frame: on the day 28 after enrollment] days of using vasopressors
9. Respiratory indexes [Time Frame: on the day 10 and 28 after enrollment] P O2/Fi O2 which reflects patients' respiratory function
10. Ventilator parameters [Time Frame: on the day 10 and 28 after enrollment] ECMO or ventilator
11. APACHE II scores [Time Frame: on the day 10 after enrollment] Acute Physiology and Chronic Health Evaluation
12. SOFA scores [Time Frame: on the day 10 after enrollment] Sepsis-related Organ Failure Assessment
13. PCR levels [Time Frame: 72 hours]
14. Reduction of PCR levels > 50% in comparison with PCR levels at the admission, within 72 hours after the administration
15. Lactate clearance [Time Frame: 72 hours] Change of the lactate clearance

Eligibility Criteria

Inclusion Criteria:

1. ≥ 21 years old
2. Diagnosed as serious or critical SARI (according to the 4th version of Diagnosis and Clinical management of CoVi-19 infected pneumonia); Being treated in the ER, Hospital or ICU

3. Positive swab test of SARS-CoVi-19 and/or positive CoVi-19 antibodies
4. Patients hospitalized with a diagnosis of COVID-19 based on positive RT-PCR of nasal, oropharyngeal, or BAL specimen with hypoxemia, (i.e., decrease in oxygenation, as outlined below)
5. New pulse oximetry saturation <93% on room air OR
6. Any new requirement of supplemental oxygen, with any device
7. In patients with supplemental oxygen at home, any increase in the requirement of supplemental oxygen.

Exclusion Criteria:

1. Allergic to Ascorbic acid
2. Dyspnea due to cardiogenic pulmonary edema
3. Pregnant or breastfeeding
4. Moribund patients not expected to survive 24 h
5. There is a state of tracheotomy or home oxygen therapy in the past
6. Previously complicated with end-stage lung disease, end-stage malignancy, glucose-6-phosphate dehydrogenase deficiency, diabetic ketoacidosis, and active kidney stone disease
7. The patient participates in another clinical trial at the same time
8. Glucose-6-phosphate dehydrogenase enzyme deficiency
9. Receiving mechanical ventilation >7 days
10. Did not have full support from patient/surrogate/physician
11. Alveolar hemorrhage (vasculitis)
12. Active kidney stone
13. Home mechanical ventilation via tracheostomy
14. Wards of the state (inmate, other)
15. Home 02 >2 L/min (except with CPAP/BIPAP)
16. Body mass index >40
17. Interstitial lung disease requiring continuous home oxygen
18. Diabetic ketoacidosis
19. No indwelling venous/arterial catheter in those taking insulin that requires glucose checks more than twice daily (continuous infusion, sliding scale)
20. Chronic Renal Failure (i.e., glomerular filtration rate less than 50 cc/minute)

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