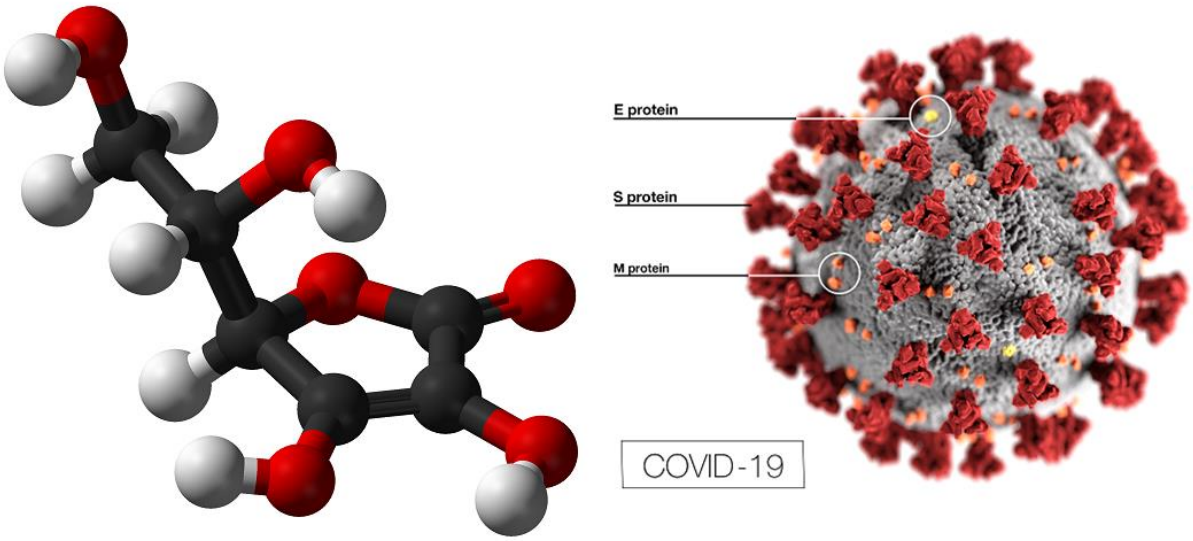
Vitamin C evidence for treating complications of COVID-19 and other viral infections

- For medical professionals, COVID-19 patients and their relatives/families and anyone willing to learn more about vitamin C. A bit of information on vitamin D3, zinc and melatonin is included, too.



L-Ascorbic Acid molecular structure 3D and electron microscope photography of SARS-CoV-2 virus.

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Read this before reading:
The document does not substitute reading the sources provided herein. Most of the document is a reading guide for most relevant sources on Vitamin C and D for prevention and treatment of complications from COVID-19 and other viral infections.
I also highly encourage anyone reading this document, especially the medical professionals, to keep an open mind. I'm therefore hoping you will search for information about other micronutrients, supplements and/or pharmaceutical drugs that play an important role in immune function and possible prevention and treatment of COVID-19 and or other viral respiratory illnesses.
A nonexhaustive list of these micronutrients: Vitamin C, D, E and A, zinc, selenium, magnesium, vitamin B6, iron and copper.

Abbreviations used:
IV-C: Intravenous Vitamin C
HDIV-C: High Dose Intravenous Vitamin C
NIH: National Institute of Health
CAM: Complementary and Alternative Medicine
RCT: Randomized Controlled Trial
HAT therapy/protocol: Hydrocortisone, Vitamin C and Thiamine therapy/protocol
SA: Sodium Ascorbate
AA: L-Ascorbic Acid
LEV-C: Liposomal Encapsulated Vitamin C
IV: Intravenous

Update log:

v5.0 1.5-2020 vs v.4.2 18.4-2020

- **Major changes:**
- Major addition to the reference list. In total 51 new references have been added and the reference count is now 152.
- Major update and revision of chapter 1. New info about G6PD added, and toxicology, upper limit for intake and cases of ultra high dose IV-C used in clinical practice added. 4 references added.
- Update of chapter 2. Info from Fonorow study explained in far greater detail and 1 reference added.
- Chapter 3 has been updated. 3 references added providing new info and a new COVID-19 treatment protocol (MATH+).
- Major revision and update of chapter 4. New info added to some existing RCT's and studies, and new RCT's and studies additions. In total 15 references added (chapter 4.1 = 11, chapter 4.3 = 1, chapter 4.4 = 3).
- 4 new trials listed under chapter 5, and preliminary findings for the first vitamin C COVID-19 RCT added. 5 references added.
- Chapter 6.2 and 6.3 has been expanded. New scientific papers and articles listed. In total 6 references added (6.2 = 4, 6.3 = 2)

- New chapter added titled “7. Case reports and anecdotes on vitamin C, other nutrients and melatonin for treating COVID-19”. This chapter compiles all the reports of success of Vitamin C and use of vitamin C for treating covid outside of trials and studies. 12 references added.
- Update to chapter 8. New studies about vitamin D and the importance of optimal nutrition and nutrient supplementation. 4 references added.
- **Minor changes:**
- Subchapter 4.1 has been split up in four subchapters.
- Chapter 5 renamed to “5. Studies and RCT’s on Vitamin C for Treatment of COVID-19”.
- Subchapter 6.2 has been split up in three subchapters.
- Chapter 7 moved back. Now it’s called chapter 9.
- Chapter 8 renamed to “8. Immunoregulatory and Antiviral Properties of Vitamin D, Zinc, Miscellaneous Micronutrients and Melatonin”.
- One reference added to Chapter 9.

v4.2 18.4-2020 vs v.4.1. 17.4.2020.

- Errors in G6PD mentions corrected. Some of them were GP6D.
- Addition to chapter “2. Efficacy and Benefits of IV vs Oral Vitamin C” about G6PD and IV-C dose.

v4.1 17.4-2020 vs. v.4.0 17.4.2020

- Proofreading: minor edits to text and error correction

v4.0 17.4-2020 vs v.3.1 16.4.2020

- **Major changes:**
- Major addition to chapter “8. Immunoregulatory and Antiviral Properties of Vitamin D, Zinc and Melatonin” about zinc and vitamin D. 8 references added [93-100].
- Hyperlinks added in the entire document (>100 instances), in most instances replacing “link URL: [weblink]” format.
- Major update to reference rules and improved reference consistency. All published and peer reviewed research articles and submissions for research abide to reference rules for research.
- **Minor changes:**
- One reference added [92] to chapter “4.4. Miscellaneous Articles”.
- One reference added [101] to chapter “6.3. Large Folders (ZIP), Link Collections and Comprehensive Articles on Multifaceted Orthomolecular Treatment of Viral Disease”.
- Reference nr. 55 moved from subchapter “6.2. Miscellaneous Research Papers, Articles and Slideshows on Vitamin C” to subchapter “6.3. Large Folders (ZIP), Link Collections and Comprehensive Articles on Multifaceted Orthomolecular Treatment of Viral Disease”.
- Subchapter 6.3 renamed to “6.3. Large Folders (ZIP), Link Collections and Comprehensive Articles on Multifaceted Orthomolecular Treatment of Viral Disease”.
- Chapter 8 renamed from “8. Sources on Vitamin D and Melatonin” to “8. Immunoregulatory and Antiviral Properties of Vitamin D, Zinc and Melatonin”.
- Reference 41 was erroneously removed in an earlier version. Therefore references $\geq$41 has been increased by 1. For example: Ref. 54 = 55, ref. 90 = 91 etc.

v3.1 16.4-2020 vs v.3.0 16.4.2020

- Minor aesthetic fixes to link appearance, faulty ones changed to blue.
- Text font for changed to arial 11, arial 10 for remainder text

v3.0 16.4-2020 vs v2.0 14.4-2020.

- New chapter added: “5. Studies and Trials on Vitamin C for Treatment of COVID-19”. 8 new references added [84-91]

- New subchapter added: “6.3. Shared Large Folders (ZIP) With Multiple Documents”. One new reference added [82]
- Two new references added for the remainder of the paper, one in subchapter “6.2. - Miscellaneous Research Papers, Articles and Slideshows on Vitamin C” [81] and one in subchapter “4.1. RCT’s and Studies” [83].

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1. Vitamin C Safety Oral and Intravenous

This chapter contains carefully selected and compiled information on the safety of oral and intravenous (IV) vitamin C.
Let it be said right away that the LD50 or median lethal dose for vitamin C determined from rat experiments is remarkably high at 11,900mg/kg of bodyweight. This is determined by administering at once, not over a 24 hour period [103]. For a adult human body weight range of 60-100kg this equates a LD50 range 714-1190g.
Extraordinarily high daily oral and IV dosages, although not anywhere near the LD50 level, has safely been administered in humans and will be reported on later in this chapter.

1.1. Safety of Oral Vitamin C

Oral supplementation of vitamin C is safe and well tolerated when not taken beyond bowel tolerance. Bowel tolerance is indicated by mild gastrointestinal symptoms such as: flatulence, belching, mild rumbling from the gastrointestinal tract, increased bowel movement and loose stools. Bowel tolerance is not indicated by severe gastrointestinal issues like diarrhea, abdominal pain, cramping and bloating and nausea. That's taking vitamin C past bowel tolerance, and it's not recommended unless the goal is to cleanse the gastrointestinal tract.
When taking very large and frequent (many times per day) oral dosages of vitamin C it could be potentially dangerous not to follow Dr. Robert F. Cathcart's advice on the symptoms of bowel tolerance and titrating Vitamin C to bowel tolerance [1].

The original 1981 research paper by Cathcart discussed titrating to bowel tolerance with l-ascorbic acid (AA) – this was Cathcart's preferred variant of vitamin C. Cathcart said AA was the only form of oral vitamin C that could achieve a "clinical ascorbate effect".

According to Cathcart the usual bowel tolerance dosage depends on the severity of the disease. The dosage required to hit this level could be anything from 15g/day to +200g/day [1]. The severity of the disease is measured as the amount of inflammation and oxidation caused by reactive oxygen and nitrogen species (ROS/RNS). A 2007 literature review titled "Vitamin C may affect lung infections" reported this about the high bowel tolerance vitamin c dosages Cathcart had observed in his clinical practice [71]:
"Furthermore, it has been stated that patients with pneumonia can take up to 100 g/day of vitamin C without developing diarrhoea, possibly because of the changes in vitamin C metabolism caused by the severe infection."

The most massive oral bowel tolerance vitamin C dose in g/kg/day Cathcart observed was a young librarian with severe mononucleosis [1]:
"Early in this study a 23-year-old, 98-pound librarian with severe mononucleosis claimed to have taken 2 heaping tablespoons every 2 hours, consuming a full pound of ascorbic acid in 2 days."

One pound is ~454g, so she consumed 227g/day for two days straight yielding an intake of 5.11g/kg/day. For a 100kg person suffering from a similar and as severe mononucleosis infection this would result in daily bowel tolerance vitamin C dosage of +500g/+1.1lb.

1.2. Safety of IV-C

For nearly all people high dose intravenous vitamin C (HDIV-C) appears to be remarkably safe, well tolerated and without any serious adverse events in clinical trials and clinical practice of practitioners using it.
One of the lead National Institute of Health (NIH) nutrient researchers Sebastian J. Padayatty and colleagues came to the following conclusion in a study from 2010 about use of IV-C by integrative medicine practitioners [2]:
"Other than the known complications of IV vitamin C in those with renal impairment or glucose 6 phosphate dehydrogenase deficiency, high dose intravenous vitamin C appears to be remarkably safe"

The NIH – National Cancer Institute's article titled "High-Dose Vitamin C (PDQ®)–Health Professional Version" about HDIV-C treatment for cancer had this to say about side effects [3]:
"Intravenous (IV) high-dose ascorbic acid has been generally well tolerated in clinical trials.[1-8] Renal failure after ascorbic acid treatment has been reported in patients with preexisting renal disorders.[9]
Case reports have indicated that patients with glucose-6-phosphate dehydrogenase (G-6-PD) deficiency should not receive high doses of vitamin C because of the risk of developing hemolysis.[10-12]
Vitamin C may increase bioavailability of iron, and high doses of the vitamin are not recommended for patients with hemochromatosis.[13]"

The article's section "Human/Clinical Studies" appears to indicate that the NIH has not yet been able to establish an upper limit for dosing and infusion rate for HDIV-C. This applies only to people without existing renal disorders, hemochromatosis or G6PD deficiency, since people suffering from any of these illnesses were excluded from the clinical trials.
The current largest vitamin C infusion dosage and infusion rate investigated for cancer patients in clinical trials is 1.5g/kg and 1g/minute respectively. They did not appear to cause any serious adverse events [3]. Hence, to date no upper limit on dose and infusion rate for vitamin C has been established in clinical trials.
Therefore, the NIH concluded the following [3]:
"Studies have shown that vitamin C can be safely administered to healthy volunteers or cancer patients at doses up to 1.5 g/kg and with screening to eliminate treating individuals with risk factors for toxicity (e.g., glucose-6-phosphate dehydrogenase deficiency, renal diseases, or urolithiasis)."

It's important to note that the 1.5g/kg dose limit is for a single infusion, not a upper limit for around the clock protocols given q6h or q8h. Because NIH has stated the following about the previously mentioned studies (1.5g/kg) [3]: *"...plasma concentrations of vitamin C are higher with IV administration than with oral administration and are maintained for more than 4 hours."* … It's not unreasonable to think that these large dosages couldn't be administered q6h or q8h, yielding a IV dose of 4.5-6g/kg/24h.
While this hasn't been studied in clinical trials, similar extremely high doses have been

administered by integrative medicine doctors with little to no minor side effects. Prof. Ian Brighthope has administered up to 250.000mg/day for cancer patients with only minor side effects like thirst and those indicating hypoglycemia being observed [104]. Dr. Charles Mary Jr. said he once treated a immunocompromised ICU patient with a severe bacterial infection. The patient had severe bacterial pneumonia and encephalitis and was declared dead and not able to rescue by other doctors. Dr. Charles Mary Jr. at one point administered 400.000mg/24h of vitamin C. The patient made a remarkable recovery and didn't have any serious adverse events caused by vitamin C [102].

A review about critically ill patients with sepsis and septic shock by Markos G. Kashiouris, Alpha A. Fowler and colleagues reported the following about intravenous vitamin C (IV-C) and side effects:
"In all the sepsis trials mentioned above, HDIVC was found to be safe and no significant side-effects were identified. Additionally, two studies in non-medical patients did not report adverse side effects."
The trials mentioned in the review excluded those with renal impairment, hemochromatosis & G6PD deficiency [4].

1.3. Vitamin C and Kidney Stones

A prospective case series study conducted by Melissa Prior et al., which was the first long term study to examine the relationship between IV-C administration and renal stones, reported the following [5]:
"No renal stones were reported by any patients in the study, despite 8% of the patients having a history of renal stones. In addition, the majority of patients investigated had stable renal function during the study period as evidenced by little change in serum creatinine levels and estimated glomerular filtration rate (eGFR) following IVC. In conclusion, IVC therapy was not associated with patient-reported renal stones."

In the previously mentioned septic shock article the researchers reported that vitamin C hasn't caused renal stones or hyperoxaluria in any clinical trials [4]:
"One proposed side effect of HDIVC is an increased propensity for oxalate kidney stone production, but this has not been shown in any clinical trials to date."
In addition, case reports of Vitamin C therapy causing renal stones or renal failure are rare [2].

The limited evidence in the medical literature on vitamin C induced renal stones suggests vitamin C will only cause renal stones in patients with renal insufficiency.
It's therefore plausible to conclude it's highly unlikely for HDIV-C or daily multigram oral supplementation to cause renal stone precipitation in people without renal insufficiency.

1.4. G6PD Deficiency and Vitamin C

While IV-C is usually not recommended for patients with G6PD deficiency Ron Hunninghake of the Riordan Clinic Research Institute has said IV-C appears to be safe for patients with G6PD deficiency at moderate infusion dosages of 25g [6] (s. 4 p. 14):

"Hemolysis has been reported in patients with G6PD deficiency when given high-dose IVC (Campbell, et al., 1975). The G6PD level should be assessed before beginning IVC. (At the Riordan Clinic, G6PD readings have yielded five cases of abnormally low levels. Subsequent IVC at 25 grams or less showed no hemolysis or adverse effects.)"

Paul E. Marik wrote an editorial about G6PD deficiency and IV vitamin C, where he investigated the following question: *"Is intravenous vitamin C contraindicated in patients with G6PD deficiency?"* He looked at the sparse reports of vitamin C induced hemolysis of G6PD caused by IV-C doses of >60g and the case reports and case series of IV-C 1-10g q6h with being used as an effective treatment of methemoglobinemia and hemolysis on G6PD deficiency paitnets [105]. He concluded that low to moderate doses of IV-C *"...should not be considered contraindicated in patients with known or suspected G6PD deficiency"*.
Hence Marik's findings seems to coincide with those of the Riordan Clinic. They both state that while large pharma dosages of IV-C should be avoided in G6PD deficiency patients, low to moderate doses of IV-C can be administered without adverse events in people with G6PD deficiency [6] [105].

This evidence, while limited, seems to indicate IV-C at moderate infusion doses of 25g appears to be safe and well tolerated in patients with G6PD deficiency.
The Riordan Clinic recommends checking red blood cell G6PD levels prior to onset of IV-C therapy [6] (s. 3 p. 13.).

1.5. Vitamin C and Hemochromatosis

The relationship between Vitamin C and hemochromatosis appears to be based on the theory of "iron overload" as stated here by the NIH [3]:
"Vitamin C may increase bioavailability of iron, and high doses of the vitamin are not recommended for patients with hemochromatosis.[13]"

While there are reports of vitamin C therapy causing "iron overload", these are rare. In addition, no studies on Vitamin C supplementation in people with hemochromatosis have been conducted to date. Some evidence from the Riordan Clinic seems to conflict with the theoretical premise of Vitamin C and "iron overload". Ron Hunninghake, MD from the Riordan Clinic reported the following [6] (s. 9 p. 15):
"There have been some reports of iron overload with vitamin C therapy. We have treated one patient with hemochromatosis with high-dose IVC with no adverse effects or significant changes in the iron status."

Steve Hickey PhD had the following to say about high dose vitamin C and hemochromatosis [7]:
"There is a theoretical danger but the actual reports are sparse and unclear. I expect that if vitamin C really did have such a side-effect, its detractors would have had a field day. Having read much of the available evidence, I consider the benefits of high dose vitamin C to exceed greatly any (largely theoretical) side-effects." - from the book "Ascorbate: The Science of Vitamin C", by Hickey S and Roberts H.

The limited evidence in the medical literature on megadose vitamin C and hemochromatosis suggests vitamin C is fairly safe, and the evidence to discourage its use appears to be weak, largely unfounded and based on theory, not reality.
Despite this, caution is still advised for patients with hemochromatosis using IV-C therapy, and blood levels should be monitored during treatment.

Another word of caution for oral supplementation: People with hemochromatosis taking large multigram daily doses of oral vitamin C should be taking it between meals. Additionally, they should take measures to lower blood ferritin levels like blood donation or lowering dietary iron intake.

1.6. A Final Note

We can conclude that vitamin C is a very safe biomolecule, and it can be used in massive dosages by those not suffering from G6PD deficiency, hemochromatosis or renal insufficiency.
It also appears vitamin C will only cause renal stones in people with renal insufficiency.

For patients with G6PD deficiency, limited patient data from the Riordan Clinic showed that:
"Subsequent IV-C at 25 grams or less showed no hemolysis or adverse effects"
For people with hemochromatosis, while caution is still advised vitamin C appears to be fairly safe, and the evidence to discourage its use appears to be weak, largely unfounded and based on theory, not reality.

Decades of science has proven that Frederick Robert Klenner was right when he said:
"Vitamin C is the safest substance available to the physician."

2. Efficacy and Benefits of IV vs Oral Vitamin C

In mainstream medicine and some of the integrative and orthomolecular medicine community there's a strong consensus that oral vitamin C cannot achieve the clinical effects associated with pharmacological ascorbate (1-100mM/L) blood levels but at most blood concentrations of 0.22mM/L. This notion is based on research that investigated vitamin C blood levels following oral and IV administration [8].
In mainstream medicine there's also another widely accepted notion that only 200-250mg/day of oral Vitamin C can be absorbed. However decades of clinical experience from Robert F. Cathcart, a prominent practitioner advocating for oral megadoses of vitamin C, and new research seems to strongly contradict these notions about oral AA [9].

Owen Fonorow did a case study on a diabetic 61 year old male. He monitored blood Vitamin C concentrations every minute following ingestion/infusion – something that's never been done before. Since vitamin C absorption into cells is insulin dependent due to its remarkable resemblance of glucose, and because the cellular uptake is dependent on the same membrane transporter as glucose a diabetic study participant is ideal.
Based on findings from the case study Fonorow stated that *"...our results suggest that up to 4,000 mg of ascorbic acid taken by mouth can produce the same rapid increase in plasma concentration as an intravenous infusion"*.

The paper also mentioned AA absorption was efficient [9]:
"Indeed, the initial oral measurements appear slightly greater than were obtained with the IV/C suggesting an efficient absorption through the stomach wall."

While exact vitamin c blood serum levels were not monitored, since the reading was glucose + vitamin C in experiment no. 1-4, for now it's reasonable to assume baseline glucose levels were 110mg/dl. This assumption is based on the data from the fifth experiment [9]. Baseline vitamin C levels (estimated at 60-80μM/L) in mg/dl won't be subtracted from the baseline glucose reading, because these at 1-1.4mg/dL are too small to have a noticable influence results.
Data from experiment 2 that looked at vitamin C blood levels following IV-C 10g infused at 250mg/minute showed the glucose meter blood level reading peaking at 30-34 minutes (see figure 1) at 210mg/dL (see figure 2) [9]. 210-110 = 100mg/dL and since the molar mass of SA is 198,11g/mol, IV-C blood levels peaked at 5.23mM/L.

In the third and fourth experiment absorption and blood levels were monitored following oral ingestion of a 10g gulp of AA (experiment 3) or 11.3g of SA (experiment 4). AA had rapid absorption and achieved relatively stable and high vitamin C blood levels in the millimolar range (>1mM/L) (see figure 4). At 2-9 minutes glucose meter blood level readings (average of 3 tests) were peaking at 225-240mg/dL (see figure 4). This is AA levels at 115-130mg/dL or in millimolar 6.53-7.38mM/L, higher than the peak IV-C blood level at 5.23mM/L.
What's even more interesting is to look at the first IV-C blood level peaks in the three tests (see figure 3). A, B and C-oral achieved peak glucose meter blood levels readings of ~245mg/dL at ~1 minutes, ~280mg/dL at ~6 minutes and ~305mg/dL at ~2 minutes respectively. Converted to AA levels this is 135-195mg/dL or in millimolar 7.67-11.07mM/L, which is evidently significantly higher than the IV-C SA blood levels.

This rapid absorption was not seen for SA which had significantly slower absorption – that was more like a timed release. Nonetheless, SA did achieve vitamin C levels close to 1mM/L or >1mM/L). The levels were above 20mg/dL (glucose meter reading = 130mg/dL) the majority of the time after 2-3 minutes 10 minutes, and peaking at ~14 minutes at 40mg/dL (glucose meter reading = 150mg/dL) or 2.02mM/L.

Furthermore, Fonorow investigated the relative vitamin C blood level increase over the 60 minute period (see figure 6, p. 85), and the data clearly indicates AA is being recycled multiple times [126]. This phenomenon can be seen in figure 3 and 4, where there's three peaks following each 10g gulp of oral AA [9]. An article by Doris Loh explains this AA recycling in great detail [79].

The rapid and early absorption and utilization of AA presented in the article by Fonorow may help explain what Cathcart reported from his clinical practice. While the sample size from this case study is tiny, the remarkable pharmacokinetics of AA observed does seem to confirm the clinical observations Cathcart got in his decades of clinical practice [9] [1].
Fonorow ended the article by stating the following about Cathcart [9]:
"Cathcart also reported that he could only obtain 'a clinical ascorbate effect' orally with ascorbic acid, not mineral ascorbates. We might speculate that an increased stomach acidity in the sick can at least in part explain Cathcart's observations."

Some practitioners who have used LEV-C, including Thomas E. Levy, claim that in some instances it can have effects that are similar or superior to IV-C.
This could be due to the following unique features of LEV-C [10]:
1. It can be transported into the cells through the cell membrane without any energy consumption.
2. It has a high bioavailability.
3. The majority of LEV-C gets directly into the cell cytoplasm. This doesn't happen with oral non-LEV-C and IV-C, where only a small amount reaches cell cytoplasm and the majority gets excreted in urine before reaching cell cytoplasm.
4. It's absorbed and transported through the lymphatic system.

While the oral AA findings from the case study and the unique features of LEV-C sound impressive, HDIV-C can achieve much higher and more stable Vitamin C blood levels (>20mM/L) than oral vitamin C [3] [6]. Furthermore IV-C is more viable than oral SA and AA for hospitalized patients for multiple reasons.
First, titrating to bowel tolerance isn't possible for many ICU patients, some of whom are in critical condition. Second, it could be more convenient for hospitalized patients than oral vitamin C. Third, IV-C allows for higher and more effective doses of vitamin C. Fourth, the uptake into the bloodstream is 100%, and the rate of infusion can be controlled and fine tuned. And fifth, IV-C can be given to patients no matter how sick they're as long as they don't suffer from renal failure or preexisting renal disorders.
In addition, as previously mentioned, one 25g IV-C infusion can safely be used in patients with G6PD deficiency.

Many integrative medicine vitamin C advocates have recommended combining IV-C with oral supplementation when possible. The LEV-C – because of its aforementioned unique features – seems to be the best candidate for hospitalized patients [10]. Oral AA is the second best candidate.
If the clinician wants to use massive doses of vitamin C orally as an adjunct til IV-C, AA should be used instead of SA due to its superior pharmacokinetics and nonexistent sodium load, which makes titrating to bowel tolerance an easier and more effective strategy [9].

A word of caution: Hospitalized patients should not take oral vitamin C past bowel tolerance.

3. IV-C Protocols, Administration, Cost and Dosing

Given the relatively novel nature of IV-C in mainstream medical research, most of the information in the articles listed here is based on clinical experience of medical practitioners using megadose vitamin C. The safety aspect of vitamin C was explained in a previous chapter titled "1. Vitamin C Safety Oral and Intravenous".

The recommended IV-C dosages for treating COVID-19 infection in hospitalized patients varies. The lowest dosages are 6gram/day, 50-100mg/kg/day [11] [12] [17]. Moderate dosages are 200mg/kg/day, 12gram/day and 25gram/day [11] [12] [14] [17]. The HDIV-C are 30-60g/day [18], and as high as >1g/kg/day for mild and moderate cases and >3g/kg/day for severe cases [14].
The IV-C administration strategies are different in other aspects. Some protocols have used multiple hour continuous infusion of IV-C two times per day [85], while others have used 1-2x 30-60minute infusions per day [14]. Most of the protocols use IV-C infusions every 6-8 hours [14] [17].

The duration of IV-C treatment and dosages required depends on the severity and progression of the COVID-19 infection. Hence, the course of the illness should be closely monitored and IV-C dosages should be adjusted accordingly.

Below are included some IV-C articles explaining how to best administer it. Articles with useful information about how to make IV-C solutions and dosage recommendations for treating COVID-19 in hospitalized patients are listed too:

1. Shanghai Expert Group on Clinical Treatment of New Coronavirus Diseases. Expert Consensus on Comprehensive Treatment of Coronavirus Diseases in Shanghai 2019 [J / OL], *Chinese Journal of Infectious Diseases*, 2020,38 (2020-03-01) , doi: 10.3760 / cma.j.issn.1000-6680.2020.0016. [Pre-published online]
   Description [11]: This is the official Shanghai Expert Group on Clinical Treatment of New Coronavirus Diseases and Shanghai Medical Association consensus pre-published. This consensus was formed by 30 leading medical experts in Shanghai [147]. The treatment plan called the “Shanghai Plan” recommends 50-100mg/kg/day of IV-C for mild to moderate cases of hospitalized COVID-19 and 100-200mg/kg/day of IV-C as part of a multifaceted protocol for prevention and treatment of “cytokine storms”.
   - Most of the article can be found translated by Dr. Richard Cheng on his website [12].
   - Comment: According to Dr. Richard Z. Cheng who was in Shanghai when this consensus was published, the consensus is official and supported by the Shanghai government and not merely a consensus between the Shanghai Medical Association and the Shanghai Expert Group. This is supported by a comment from the Shanghai Medical Association, where they talked about Chinese state TV had a news about the treatment plan [147].
   A similar consensus, where IV-C and other similar drugs were recommended for treating “cytokine storms”, was issued by the Guangdong Provincial Health Commission back in March 2020 [106].
2. Medical Information/COVID Care Protocol, EVMS Medical Group, Eastern Virginia Medical School, EVMS.edu.
   Description [17]: This is medical information about COVID-19 and the COVID Care Protocol provided by the EVMS Medical Group led by Dr. Paul E. Marik. The resources and protocol are frequently updated and thus, subject to change.
   - The COVID Care Protocol is a comprehensive protocol, and it’s explained in great detail in a downloadable PDF document. It recommends the clinician consider various nutritional and pharmaceutical compounds for treatment of COVID-19. The compounds and dosages recommended depends on the severity of COVID-19.
   - A one page PDF summary of the protocol is provided, too.
3. Treatment protocol, Frontline COVID-19 Critical Care Working Group, Covid19CriticalCare.com.
   Description [107]: This is the COVID-19 treatment protocol developed by the Frontline COVID-19 Critical Care Working Group. The protocol is based on *“...available research, the experience in China reflected by the Shanghai expert commission, and their decades-long professional experiences in Intensive Care Units around the country”*. FLCCC Working group is made up of *“leading critical care specialists at academic centers or major hospitals”* in United States. The protocol is called MATH+, which stands for Methylprednisolone, Ascorbic Acid, Thiamine (optional) and Heparin + additional optional components like Vitamin D, Zinc and melatonin.

4. Intravenous Ascorbic Acid (IVAA) for COVID-19 Supportive Treatment in Hospitalized COVID-19 Patients (Based on use in China and US settings), Dr. Paul S. Anderson, Isom.ca, March 24, 2020.
   Description [13]: This is a medical document for health professionals on IV-C and the rationale for using it to treat hospitalized COVID-19.
   It includes pharmacy and nursing details and an approximation of drug cost of IV-C dosages recommended in the Shanghai treatment plan.
5. Rationale for Vitamin C Treatment of COVID-19 and Other Viruses, Orthomolecular Medicine News Service Editorial Review Board, Orthomolecular Medicine News Service, Orthomolecular.org, April 3, 2020.
   Description [18]: This article is urging *"The world's political, scientific, medical and industrial leaders need to consider this* (Vitamin C) *very carefully"*. Different dosages and route of administration (oral or IV) are listed, and a short note on Vitamin D and zinc is provided, too.
   - They recommend the following for treatment of "cytokine storm":
   "In severe lung infections, a "cytokine storm" generates reactive oxygen species (ROS) that can be effectively treated with doses of 30-60 g of vitamin C. At the same time the relatively high level of vitamin C can promote an enhanced chemotaxis of white blood cells (neutrophils, macrophages, lymphocytes, B cells, NK cells)."
   - The article has a section on IV-C side effects and precautions that's useful for medical professionals.
6. Role of Ascorbic Acid in Covid 19 Management, Dr Yuen Chuen Fong Raymond, Doctoryourself.com.
   Description [14]: This is a comprehensive slideshow answering the most important questions about vitamin C. It provides evidence and rationale for using vitamin C in treatment and prevention of many different diseases, including COVID-19.
   - Slides concerning "Protocol – High Dose AA for Covid19" is at slide no. 116-120. This is the previously mentioned protocol using >1g/kg/day for mild and moderate cases and >3g/kg/day for severe cases.
   - The recommendations made by the Japanese College of Intravenous Therapy (JCIT) are at slide no. 115. JCIT recommends IV-C 1-2x per day of 12.500-25.000mg per day for treatment of acute viral infections.
7. The Riordan IVC Protocol for Adjunctive Cancer Care Intravenous Ascorbate as a Chemotherapeutic and Biological Response Modifying Agent, Ron Hunninghake et al., Riordan Clinic Research Institute, 2014.
   Description [6]: This is a thorough research document describing the Riordan Clinic's IV-C protocol for cancer.
   - Check "Precautions and Side Effects" at page 14-15 and the concise "cheat sheets" for IV-C solutions at page 15-16.
   - A website version of the PDF is available here at the Riordan Clinic website [15].
8. A Guide to the Optimal Administration of Vitamin C, Thomas E. Levy, MedFox Publishing.
   Description [16]: Here is an exhaustive guide on IV-C administration. It is written by Thomas E. Levy, MD. He is hailed as the "Vitamin C expert" in orthomolecular and integrative medicine circles.
   - Contains information on the *"Important Factors in the Effective Administration of Vitamin C".* These are: Dose, route, rate, frequency, duration of treatment period, type of vitamin C, adjunct therapies, safety and quality of overall protocol.

9. Preparation of Sodium Ascorbate for IV and IM Use, Robert F. Cathcart III, M.D, Edited 2011 by Owen Fonorow, Vitamin C Foundation, VitaminCFoundation.org.
   Description [19]: This is a useful document for hospital pharmacies willing to make their own IV-C SA solutions and bags. In this document Robert F. Cathcart outlines how to make IV-C SA solutions and bags.
   - The document contains information about dosage guidelines (Dr. Levy), rate of infusion and hypoglycemia. The following comment about dosage is important:
   "Dosage is always empirical, as in give more if the clinical response, especially in infections or poisonings, is not adequate." - Thomas Levy, MD.
   - Dr. Cathcart's video instructions can be found here on the Vitamin C Foundation's YouTube Channel [20].

4. Significant RCT's, Reviews, Meta-analyses and Articles on Vitamin C

Note: Research material by integrative and orthomolecular medicine practitioners and advocates have been excluded from this chapter. These studies can be found under the chapter titled "6. Orthomolecular Clinical Experience, Studies and Articles on Vitamin C". Ongoing research announced investigating IV-C for treating COVID-19 can found under the chapter titled "5. Studies and Trials on Vitamin C for Treatment of COVID-19".
For articles on safety, efficacy and administration of vitamin C go to references or the previous chapters titled: "1. Vitamin C Safety Oral and Intravenous", "2. Efficacy and Benefits of IV vs Oral Vitamin C" and "3. IV-C Protocols, Administration, Cost and Dosing".

It should be noted that the vitamin C research listed here is built upon a mountain of in vitro and in vivo studies and clinical research. In addition, it builds upon decades of clinical experience from medical doctors who at some point began using orthomolecular medicine in their clinical practice. These doctors were Frederick R. Klenner, Robert F. Cathcart, Archie Kalokerinos, Hugh Riordan, Ron Hunninghake, Thomas E. Levy and many more.

4.1. RCT's and Studies

The following subchapter lists RCT's and studies that investigate Vitamin C. It's been divided into sub-subchapters due to the length of this chapter.

4.1.1. IV Vitamin C Monotherapy RCT's

Alpha A. Fowler III et al., Effect of Vitamin C Infusion on Organ Failure and Biomarkers of Inflammation and Vascular Injury in Patients With Sepsis and Severe Acute Respiratory Failure – The CITRIS-ALI Randomized Clinical Trial, *Journal of the American Medical Association* (JAMA), 2019;322(13):1261-1270 (Epub 2019 October 1), doi:10.1001/jama.2019.11825
Description [21]: This is the first RCT (167 participants and quadruple blinded) to date to investigate the effects of moderate dosages (≥200mg/kg/day) of IV-C on patients with sepsis and severe acute respiratory failure (ARDS). The trial could not detect any significant or noticeable differences in the primary endpoint outcomes between the vitamin C and placebo group. Primary

endpoints were: SOFA scores, C-reactive protein levels and thrombomodulin levels.
However, there were some encouraging results in of many of the secondary endpoint outcomes. Some of these were statistically significant:

1. **28-day mortality:** *"At day 28, mortality was 46.3% (38/82) in the placebo group vs 29.8% (25/84) in the vitamin C group (χ2 = 4.84; P = .03; between-group difference, 16.58% [95% CI, 2% to 31.1%])"*
   This is a 17.5% reduction in mortality or a 35.6% reduction in the total number of deaths in the IV-C group vs control.
2. **Kaplan-Meier survival curves:** "*The Kaplan-Meier survival curves for the 2 groups were significantly different by the Wilcoxon test (χ21 = 6.5; P = .01)."*
3. **Ventilator-free days:** *"The number of ventilator-free days was 13.1 in the vitamin C group vs 10.6 in the placebo group (mean difference, 2.47; 95% CI, −0.90 to 5.85; P=.15)"*
4. **ICU-free days:** *"The number of ICU-free days to day 28 was 10.7 in the vitamin C group vs 7.7 in the placebo group (mean difference, 3.2; 95% CI, 0.3 to 5.9; P = .03)"*
5. **Transfer out of the ICU by hour 168:** *"Transfer out of the ICU by hour 168 or less occurred in 25% of patients in the vitamin C group (21/84) vs 12.5% in the placebo group (10/83) (χ2 = 4.63; P = .03; difference, 12.95% [95% CI, 1.16% to 24.73%; P = .31])"*
6. **Hospital free days:** "*The number of hospital-free days in the vitamin C group vs the placebo group was 22.6 vs 15.5, respectively (mean difference, 6.69; 95% CI, 0.3 to 13.8; P = .04)"*

What probably was most significant was the Kaplan Meier Mortality curves for this trial and the dramatic differences between IV-C and placebo in mortality and ICU graduations at 96 hours. At 96 hours, there was 19 and 4 deceased people in the placebo and IV-C group respectively. This resulted in a mortality of ~4-5% in the IV-C group and ~23% in the placebo group. Past 96 hours the two mortality curves parallelize all the way to day 28, where the IV-C and placebo group 28-day mortality is 29.8% and 46.3% respectively. In addition there was a remarkable difference in ICU graduations at 96 hours, where 9 in the IV-C group and only 1 in the placebo group had graduated.
- Comment: This RCT faced criticism due to alleged survivorship bias, because the article didn't measure the SOFA scores of deceased study participants. This criticism came from many people, one of which was none other than the creator of the SOFA score Dr. Jean-Louis Vincent. In response to the letter sent to the editor of JAMA by Harm-Jan de Grooth, MD; Paul W. G. Elbers, MD, PhD; Jean-Louis Vincent, MD, PhD, Alpha A. Fowler III, MD; Bernard J. Fisher, BS, MS; Markos G. Kashiouris, MD, MPH recalculated the SOFA score post hoc [108] [109]. They calculated a mortality adjusted mSOFA score, and ICU graduations and deceased participants in the first 96 hours (treatment period) of the trial were given a mSOFA score of 0 and 20 respectively. This resulted in a significant ($p<0.026$) difference between the IV-C and placebo group in mSOFA score at 96 hours [109].
- Further reading:

- Dr. Fowler presents the trial's findings on JAMA Network's YouTube channel [22].
- A similar albeit more comprehensive presentation of the CITRIS-ALI trial by Dr. Fowler and an editorial was presented at CCR 2020 in Belfast. It includes a presentation of the mSOFA score recalculation. It can be accessed using Vimeo [110].
- A brilliant article about the CITRIS-ALI trial written by Dr. Daniel Nichita can be found at Escavo.com [111].

Alpha A. Fowler et al., Phase I safety trial of intravenous ascorbic acid in patients with severe sepsis, *Journal of Translational Medicine*, 2014; 12: 32 (Epub 2014 January 31), doi: 10.1186/1479-5876-12-32

Description [23]: This was the first RCT to investigate IV-C for severe sepsis (septic shock). It enrolled 24 patients and was quadruple blinded. It detected significant IV-C dose dependent reductions in SOFA scores and no adverse events in patients receiving IV-C.

Following quote is from the abstract:

"No adverse safety events were observed in ascorbic acid-infused patients. Patients receiving ascorbic acid exhibited prompt reductions in SOFA scores while placebo patients exhibited no such reduction. Ascorbic acid significantly reduced the proinflammatory biomarkers C-reactive protein and procalcitonin. Unlike placebo patients, thrombomodulin in ascorbic acid infused patients exhibited no significant rise, suggesting attenuation of vascular endothelial injury."

As previously mentioned the SOFA scores for the low (50mg/kg/day) and high IV-C group (200mg/kg/day) both decreased significantly ($p<0.05$ and $p<0.01$ respectively) more than placebo.

Mohadeseh H. Zabet et al., Effect of high-dose Ascorbic acid on vasopressor's requirement in septic shock, *Journal of Research in Pharmacy Practice*, 2016 Apr-Jun: 5(2): 94-100, doi: 10.4103/2279-042X.179569

Description [24]: This small placebo controlled RCT (28 participants) investigated the impact of administering 100mg/kg/day IV-C for 72 hours in surgical critically ill patients with septic shock. The researchers reported the following results:

"Mean dose of norepinephrine during the study period (7.44 ± 3.65 vs. 13.79 ± 6.48 mcg/min, P = 0.004) and duration of norepinephrine administration (49.64 ± 25.67 vs. 71.57 ± 1.60 h, P = 0.007) were significantly lower in the ascorbic acid than the placebo group. No statistically significant difference was detected between the groups regarding the length of ICU stay. However, 28-day mortality was significantly lower in the ascorbic acid than the placebo group (14.28% vs. 64.28%, respectively; P = 0.009)."

Furthermore, the duration of mechanical ventilation in the IV-C group was 22% shorter than placebo [38].

Nabil Habib T. and Ahmed I., Early Adjuvant Intravenous Vitamin C Treatment in Septic Shock may Resolve the Vasopressor Dependence, *International Journal of Microbiology & Advanced Immunology* (IJMAI), IJMAI-2329-9967-05-101, published 2020, July 28, doi: 10.19070/2329-9967-1700015

Description [112]: This RCT (open label) enrolling 100 study participants with severe septic shock. Treatment protocols were IV-C 1.5g q6h *"...in the first 24 hours after admission until ICU discharge plus conventional sepsis treatment"* in experimental group and conventional treatment only in control group. The researchers reported the following results in the abstract:

"There were no differences in duration on MV (p= 0.187), need for RRT (p=0.412), or ICU mortality (p=0.138). The mean number of days on vasopressor was significantly less in EVC group than in control group (2.30 Vs 6.50 days, p=0.001). There was a statistically significant difference in ICU stay between the two groups (p=0.04)."

Due to the relatively small size of the trial many of the endpoints that had sizeable differences between the control and IV-C group didn't reach statistical significance, but instead a trend towards better outcomes in the IV-C group.

One example was duration of mechanical ventilation (MV) was 4.6 days in the IV-C group and 7.87 days in the control group resulting in a massive 41.5% reduction in the duration of MV in the IV-C group compared to control.
Another example was ICU mortality was 24% in the IV-C group and 36% in the control group. In the IV-C group 33% (12 vs 18) fewer than in the control group died in the ICU
The length of ICU stay, which did reach statistical significance saw a reduction in the length of stay in the ICU of 4.1 days in the IV-C group vs control group (10 vs 14.1) or a 29.1% shorter length of stay in ICU in IV-C group than in control group.

4.1.2. Vitamin C HAT Therapy RCT's: Sepsis and Septic shock

Tomoko Fujii et al., Effect of Vitamin C, Hydrocortisone, and Thiamine vs Hydrocortisone Alone on Time Alive and Free of Vasopressor Support Among Patients With Septic Shock - The VITAMINS Randomized Clinical Trial, *Journal of the American Medical Association* (JAMA), 2020;323(5):423-431 (Epub 2020 January 17), doi:10.1001/jama.2019.22176
Description [28]: This is the largest RCT (216 participants and open label) to date to study HAT therapy for septic shock. The trial did not detect any significant or noticeable differences between the vitamin C and placebo group. The abstract reports these results:
"Time alive and vasopressor free up to day 7 was 122.1 hours (interquartile range [IQR], 76.3-145.4 hours) in the intervention group and 124.6 hours (IQR, 82.1-147.0 hours) in the control group; the median of all paired differences was –0.6 hours (95% CI, –8.3 to 7.2 hours; P = .83). Of 10 prespecified secondary outcomes, 9 showed no statistically significant difference. Ninety-day mortality was 30/105 (28.6%) in the intervention group and 25/102 (24.5%) in the control group (hazard ratio, 1.18; 95% CI, 0.69-2.00). No serious adverse events were reported."
- **Comment [29]:** This RCT faced criticism from Dr. Paul E. Marik during the presentation of the trial at CCR Belfast 2020. Marik claimed that it did not replicate real life clinical experience, because the treatment was delayed too much. The authors of the study reported HAT therapy was initiated on average ~12 hours past meeting eligibility criteria of septic shock. It's estimated that treatment that time from ED presentation to HAT treatment initiation was a minimum of 18-20 hours. According to Marik this delay in treatment rendered the HAT therapy ineffective.
Two ICU doctors using HAT therapy in their ICU's, one from Wisconsin (Pierre D. Kory, MD), and one from Norway (Dr. Eivind H. Vinjevoll), agreed with Marik's assessment of the trial.
Marik said based on his clinical experience with HAT therapy, that it has to be initiated <6 hours past septic shock presentation, preferably initiated at time of the first dose of antibiotics for optimal results. The doctor from Wisconsin affirmed that if HAT therapy is initiated >12 hours past ED presentation, it has an insignificant effect on mortality, and if >18 hours past ED presentation no effect on mortality. The >12 and >18 hour figures are based on research conducted by Pierre D. Kory and colleagues published in *Critical Care and Shock* [113] [114].
- Here's a video of VITAMINS trial presentation at CCR 2020 in Belfast on JAMA Network's YouTube channel [29].

Ping Chang et al., Combined treatment with hydrocortisone, vitamin C, and thiamine for sepsis and septic shock (HYVCTTSSS): A randomized controlled clinical trial, *Chest*, 2020 Mar 31. pii: S0012-3692(20)30552-3, doi: 10.1016/j.chest.2020.02.065.
Description [83]: This is the most recent RCT to date to investigate IV-C (HAT therapy) as a treatment for sepsis and septic shock. The trial is single-blinded, randomized and placebo controlled, and it had 80 participants. The researchers reported the following results in the abstract:

"No difference in 28-day all-cause mortality was observed (27.5% vs. 35%; P = 0.47), although treatment was associated with a significant improvement of 72-h ΔSOFA score (P = 0.02)."
"In prespecified subgroup analysis, patients of the treatment subgroup diagnosed with sepsis within 48 h showed lower mortality than those in the control subgroup (p = 0.02)."
- The subgroup analysis showed that those diagnosed with sepsis <48 hours past ICU admission fared much better than the rest of the IV-C study participants; some of the secondary outcome endpoints were statistically significant. The 28-day mortality was significantly lower in the IV-C group *"(13.6% vs.47.6%; RR, 0.29; 95% CI, 0.09 to 0.90; p = 0.02)"*, and 72 hour PCT clearance was significantly lower in the IV-C group *"(p = 0.02; 75.6% (62.3–92.0) vs. 58.9% (16.0–79.5)"*. The reported difference in survival rate of IV-C in the subgroup was slightly exceeded the one reported in Paul Marik's 2017 *Chest* study (34% vs 31.9%), albeit the IV-C group mortality was higher than in Marik's study (13.6% vs 8.5%).
- Comment [83]: The subgroup analysis, the first of its kind in a RCT investigating HAT therapy, strongly suggests that Marik's assertions on the importance of timely administration of the protocol are correct; HAT therapy is remarkably effective, albeit only effective when administered in the early stages of septic shock. As previously mentioned this assertion is backed up by research conducted by Pierre D. Kory and colleagues published in *Critical Care and Shock* [113] [114].

4.1.3. Vitamin C HAT Therapy Studies: Sepsis and Septic shock

Paul E. Marik et al., Hydrocortisone, Vitamin C, and Thiamine for the Treatment of Severe Sepsis and Septic Shock: A Retrospective Before-After Study, *Chest*, 2017 Jun;151(6):1229-1238 (Epub December 6, 2016), doi: 10.1016/j.chest.2016.11.036
Description [25]: Retrospective study conducted by Dr. Paul E. Marik and colleagues. It investigated their HAT protocol for treatment of septic shock. The study reported massive reductions in the vasopressor duration and hospital mortality in the vitamin C group. For the majority of HAT cohort patients, HAT therapy was initiated within 6 hours of ICU admission and many initiated in ED. The following is from the abstract:
"The hospital mortality was 8.5% (4 of 47) in the treatment group compared with 40.4% (19 of 47) in the control group (P < .001)" and *"All patients in the treatment group were weaned off vasopressors, a mean of 18.3 ± 9.8 h after starting treatment with the vitamin C protocol. The mean duration of vasopressor use was 54.9 ± 28.4 h in the control group (P < .001)."*
Furthermore patients treated with HAT had highly significant SOFA score reductions (-6 vs -1.1, p<0.001) compared to the retrospective cohort, that didn't receive HAT therapy.

Eric Wald et al., Hydrocortisone-Ascorbic Acid-Thiamine Use Associated with Lower Mortality in Pediatric Septic Shock, *American Journal of Respiratory and Critical Care Medicine*, 2020 April 1, Volume 201, Issue 7 (Epub January 9, 2020), doi: 10.1164/rccm.201908-1543LE
Description [26]: Retrospective study conducted at the Ann & Robert H. Lurie Children's Hospital of Chicago investigating HAT therapy for treating pediatric septic shock. HAT was administered a median 12 hours from PICU admission/vasopressor initiation. Because this is a retrospective study, the evidence is nowhere near the quality of evidence from RCT's. However, the researchers did some things to increase the quality of the evidence:
"Propensity score matching, IPTW, and Cox regression were used to reduce treatment selection bias, but unmeasured confounding variables may have been present."
- The following is from a study report published on the hospital's website (see link below):

"They found that while controls had mortality of 28 percent at 30 days, mortality in patients treated with the vitamin C combination protocol dropped to 9 percent in the same period. Treatment with hydrocortisone alone did not improve mortality (30 percent at 30 days). Similar reductions in mortality were seen at 90 days (14 percent with vitamin C protocol vs. 35 percent in controls and 37 percent in the hydrocortisone only group)."

This reported difference in mortality reached statistical significance at day 30 (*p≤0.03),* and they conducted a *"...sensitivity analysis using IPTW with a time epoch..."* resulting in a significantly lower 30-day mortality in the HAT group *"...compared to untreated controls (p=0.006) and hydrocortisone only patients (p=0.014)*".
- Here's a link to the study report on the hospital's website [27].

Micah T. Long et al., Early hydrocortisone, ascorbate and thiamine therapy for severe septic shock, *Critical Care and Shock*, 2020, 23:23-34.
Description [114]: This is a retrospective cohort study investigating HAT therapy as an early intervention in septic shock requiring vasopressors in ICU. APACHE was used to reduce selection biases in the HAT and conventional treatment cohort. 127 was included in the non iHAT cohort, and 79 in the iHAT cohort. The researchers reported the following results:
"Observed ICU mortality was lower in the iHAT cohort compared to SC as was APACHE-adjusted ICU mortality (OR 0.44, p=0.043)". A subgroup analysis revealed that "APACHE-adjusted ICU mortality was lowest when iHAT was initiated within 6 hours (OR 0.08, p<0.01)"
The ICU mortality in the <6 hour group (n=22) was 0%.The other endpoint outcomes APACHE-adjusted *"Hospital mortality* (p=0.8)*, vasopressor duration* (p=0.09)*, initiation of renal replacement therapy* (p=0.26) *and lengths of stay* (p=0.91) *were not significantly different between cohorts"*. The researchers concluded:
"There is a time-sensitive improvement in APACHE-adjusted ICU mortality in septic shock patients treated with adjunctive iHAt. The strong temporal benefit of iHAT therapy has important implications towards future studies"
- Comment [113][114]: These underwhelming results are likely explained by the delay in treatment in the majority of the iHAT cohort. Mean time to iHAT therapy after sepsis presentation was a mean of 10.9±7.0hours, and time to ICU admission after presentation was a mean of 7.6hours.
In a letter to the Editors of the unpublished VICTAS trial the authors of this study stated based on data from this trial that if HAT therapy is initiated >12 hours past sepsis presentation, it has an insignificant effect on mortality (see figure 1) [113]. If initiated >18 hours (subgroup >18-24hrs, n=12) past ED presentation there's actually an increase in mortality (O/E=1.2 = 20% increased mortality risk vs. no treatment) compared to expected mortality (estimated using APACHE). This is consistent with the findings of the VITAMINS trial (hazard ratio, 1.18). It must be noted that this is a tiny subgroup of only 12 patients, hence this evidence is far from conclusive.

Farid Sadaka et al., Ascorbic Acid, Thiamine, and Steroids in Septic Shock: Propensity Matched Analysis, *Journal of Intensive Care Medicine*, 2019 Jul 17:885066619864541, doi: 10.1177/0885066619864541
Link URL: https://www.ncbi.nlm.nih.gov/pubmed/31315499
Description [115]: This is propensity matched cohort study of HAT therapy in 62 patients (n = 31 control hydrocortisone, n = 31 HAT) with septic shock. Data was pooled from APACHE outcome

database, medical records, and *"Propensity analysis was used to match patients on age, gender, MV, APACHE III, APS, LA, and Cr"*. The researchers reported the following results:
"The ATS group had longer duration of VP (4.5: 4.0-6.0 vs 2.0: 1.0-2.0, P = .001), similar RRT for AKI (26% vs 29%, P = .8), similar MV-free days (10.2: 5.0-15.0 vs 10.2: 1.6-18.0, P > .9), lower intensive care unit mortality (9.6% vs 42%, P = .004), and a trend toward lower hospital mortality (29% vs 45%, P = .2) compared to the NO ATS group."
And concluded the following: *"The use of IV ascorbic acid, thiamine, and hydrocortisone might be beneficial in patients with SS"*

Saskya Byerly et al., Vitamin C and Thiamine Are Associated with Lower Mortality in Sepsis, *Journal of Trauma and Acute Care Surgery*, 2020, February 7, doi: 10.1097/TA.0000000000002613
Link URL: https://www.ncbi.nlm.nih.gov/pubmed/32039973
Description [116]: This is a study looking at a large ICU database using propensity matched pairs to investigate the effect of IV thiamine and IV vitamin C on sepsis (IV-C and IV-B1, n = 90, control (standard of care), n = 90) and septic shock on vasopressors (IV-C and IV-B1, n = 30; control (standard of care), n = 60). Furthermore *"Kaplan-Meier curves, logistic regression, propensity score matching and competing risks modeling were constructed"*.
The researchers reported in the sepsis group that *"...VitC+THMN (AOR:0.335 [0.13-0.865]) were associated with survival but not lactate clearance"*, and the number needed to treat (NNT) to save one life was 5. In the septic shock on vasopressors group *"...VitC+THMN were associated with lactate clearance (AOR:1.85 [1.05-3.24]) and survival (AOR:0.223 [0.0678-0.735])",* and the NNT to save one life and lactate clearance was 3.3 and 4.9 respectively.

4.1.4. Vitamin C Miscellaneous Studies and RCT's

Anitra C. Carr et al., Hypovitaminosis C and vitamin C deficiency in critically ill patients despite recommended enteral and parenteral intakes, *Critical Care*, 2017 Dec 11;21(1):300, doi: 10.1186/s13054-017-1891-y
Description [30]: Study about the widespread hypovitaminosis C and scurvy in critically ill patients. The following is from the abstract:
"Critically ill patients have low vitamin C concentrations despite receiving standard ICU nutrition. Septic shock patients have significantly depleted vitamin C levels compared with non-septic patients, likely resulting from increased metabolism due to the enhanced inflammatory response observed in septic shock."

Sawyer MAJ, Mike JJ and Chavin K, Marino P.L., Antioxidant therapy and survival in ARDS (abstract), *Critical Care Medicine*, 1989;17:S153. [Google Scholar]
Description [117]: This was the first RCT (32 participants) to investigate multiple gram/day IV-C dose for treating ARDS. The IV-C group got 1g q6h of vitamin c in addition to NAC, selenium, vitamin E also every 6 hours. This old trial from 1989 showed showed that the mortality in the IV-C group from 71% to 37%. In a clinical setting this means 47% fewer deaths.

Won-Young Kim et al., Combined vitamin C, hydrocortisone, and thiamine therapy for patients with severe pneumonia who were admitted to the intensive care unit: Propensity score-based analysis

of a before-after cohort study, *Journal of Critical Care*, 2018 Oct;47:211-218 (Epub 2018 July 5). doi: 10.1016/j.jcrc.2018.07.004
Description [73]: This is a significant *"Propensity score-based analysis of a before-after cohort study"* investigating HAT therapy as a treatment for severe pneumonia requiring ICU admission. The following results was reported in the abstract:
"In the propensity-matched cohort (n = 36/group), the treated patients had significantly less hospital mortality than the control group (17% vs. 39%; P = 0.04). The vitamin C protocol associated independently with decreased mortality in propensity score-adjusted analysis (adjusted odds ratio = 0.15, 95% confidence interval = 0.04-0.56, P = 0.005). Relative to the control group, the treatment group had a significantly higher median improvement in the radiologic score at day 7 compared with baseline (4 vs. 2; P = 0.045). The vitamin C protocol did not increase the rates of acute kidney injury or superinfection."

Anitra C. Carr et al., Patients with Community Acquired Pneumonia Exhibit Depleted Vitamin C Status and Elevated Oxidative Stress, Preprints, 2020, April 15, doi: 10.20944/preprints202004.0243.v1
Description [118]: This cohort study on CAP investigated vitamin C blood levels and blood levels of the oxidative stress marker protein carbonyl in a 50 patient pneumonia cohort and compared these to a 50 healthy community controls. Description from abstract of the pneumonia cohort:
"The pneumonia cohort comprised 44 patients recruited through the Acute Medical Assessment Unit (AMAU) and 6 patients recruited through the intensive care unit (ICU); mean age 68 ± 17 years, 54% male."
The researchers reported the following results:
"Patients with pneumonia had depleted vitamin C status compared with healthy controls (23 ± 14 µmol/L vs 56 ± 24 µmol/L, P <0.001). The more severe patients in the ICU had significantly lower vitamin C status than those recruited through AMAU (11 ± 3 µmol/L vs 24 ± 14 µmol/L, P = 0.02). The total pneumonia cohort comprised 62% with hypovitaminosis C and 22% with deficiency, compared with only 8% hypovitaminosis C and no cases of deficiency in the healthy controls."
"The pneumonia cohort also exhibited significantly elevated protein carbonyl concentrations compared with the healthy controls (P < 0.001), indicating enhanced oxidative stress in the patients."
- Comment: This does seem to confirm previous assertions (see "Vitamin C and Immune Function" and "Hypovitaminosis C and vitamin C deficiency in critically ill patients despite recommended enteral and parenteral intakes") about significantly increased vitamin C metabolism, depletion and requirement during illness, especially severe illness.

Tae K. Kim et al., Vitamin C supplementation reduces the odds of developing a common cold in Republic of Korea Army recruits: randomised controlled trial, *BMJ Military Health*, 2020 Mar 5. pii: bmjmilitary-2019-001384 (Epub ahead of print), doi: 10.1136/bmjmilitary-2019-001384
Description [31]: This is the first large scale RCT (1444 participants) to investigate if a high 6,000mg/day dose of oral vitamin C per day reduces the odds of developing a common cold. The researchers reported the following in the abstract:
"The vitamin C group had a 0.80-fold lower risk of getting a common cold than did the placebo group. Subgroup analyses showed that this effect was stronger among subjects in camp A, among never smokers and among those in physical rank 3."

H. Clay Gorton and Kelly Jarvis, The effectiveness of vitamin C in preventing and relieving the symptoms of virus-induced respiratory infections, *Journal of Manipulative and Physiological Therapeutics*, 1999 Oct;22(8):530-3, DOI: 10.1016/s0161-4754(99)70005-9
Description [32]: This is a *"prospective controlled study of students in a technical training facility"* investigating vitamin C's usage and efficacy for *"preventing and relieving the symptoms of virus-induced respiratory infections"*.
Is was a fairly large study: *"A total of 463 students ranging in age from 18 to 32 years made up the control group. A total of 252 students ranging in age from 18 to 30 years made up the experimental or test group."*
The treatment protocol in the test group was as follows: *"...those in the test population reporting symptoms were treated with hourly doses of 1000 mg of Vitamin C for the first 6 hours and then 3 times daily thereafter. Those not reporting symptoms in the test group were also administered 1000-mg doses 3 times daily."*
They gave 6 grams, The following is from the abstract:
"Overall, reported flu and cold symptoms in the test group decreased 85% compared with the control group after the administration of megadose Vitamin C."

Clare Hunt et al., The clinical effects of vitamin C supplementation in elderly hospitalised patients with acute respiratory infections, *International Journal for Vitamin and Nutrition Research*, 1994;64(3):212-9., PMID: 7814237
Description [33]: This small RCT (57 participants and double blinded) reported 80% fewer deaths in the 200mg/day vitamin C group than placebo. This RCT was included in the 1999 review "Vitamin C and acute respiratory infections" and the 2017 review "Vitamin C and Infections". These reviews can be found under the subchapter titled "4.3. Reviews".

Imran M. Khan et al., Efficacy of Vitamin C in Reducing Duration of Severe Pneumonia in Children, *Journal Of Rawalpindi Medical College* (JRMC), 2014;18(1):55-57, at Journalrmc.com.
Description [34]: This is a descriptive and placebo controlled trial of children under the age of 5 with pneumonia. 200mg/day of oral vitamin C was administered and control group received placebo drops matching color and taste.
The researchers reported the following results:
"Among 222 children, majority (61.71%) were male and 85(38.28%) were female. Majority (58.55%) were infants, 29.72% were between 1-3 years and 11.71% were between 4-5 years (15.14±7.76 months). Oxygen saturation was improved in ≤ 01 day (p=0.003) and respiratory rate was improved in ≤ 04 days (p=0.03) in vitamin C group".
They concluded that: *"Vitamin C is effective in reducing duration of severe pneumonia in children less than five years of age."*
- Available as a PDF here on Rawalpindi Medical College's website [35].

Ren Shiguang et al., Observation on the therapeutic effect of intravenous large dose of vitamin C on infants and young children with viral pneumonia, *Hebei Medicine,* 1978,4:1-3.

Description [36] [37]: This is an observational study on high dose vitamin C for treating infantile viral pneumonia. The researchers reported that high doses of vitamin C reduced mortality and shortened duration of the illness compared to no vitamin C.

4.2. Meta-analyses

Harri Hemilä and Elizabeth Chalker, Vitamin C may reduce the duration of mechanical ventilation in critically ill patients: a meta-regression analysis, *Journal of Intensive Care*, 2020; 8: 15 (Epub 2020 February 7), doi: 10.1186/s40560-020-0432-y
Description [38]: This meta-regression analysis investigated the effect of vitamin C on duration of mechanical ventilation. It was based in part on their earlier meta-analysis "Vitamin C Can Shorten the Length of Stay in the ICU: A Meta-Analysis". These results were reported in abstract:
"…vitamin C shortened the length of mechanical ventilation on average by 14% (P = 0.00001). However, there was significant heterogeneity in the effect of vitamin C between the trials. Heterogeneity was fully explained by the ventilation time in the untreated control group. Vitamin C was most beneficial for patients with the longest ventilation, corresponding to the most severely ill patients. In five trials including 471 patients requiring ventilation for over 10 h, a dosage of 1–6 g/day of vitamin C shortened ventilation time on average by 25% (P < 0.0001)."
The researchers concluded the following:
"We found strong evidence that vitamin C shortens the duration of mechanical ventilation, but the magnitude of the effect seems to depend on the duration of ventilation in the untreated control group."

Vitamin C Can Shorten the Length of Stay in the ICU: A Meta-Analysis, Harri Hemilä and Elizabeth Chalker, *Nutrients*, 2019 Apr; 11(4): 708 (Epub 2019 March 27), doi: 10.3390/nu11040708.
Description [39]: This meta-analysis investigated vitamin C's impact on length of stay in the ICU, and it reported the following in the abstract:
"In 12 trials with 1766 patients, vitamin C reduced the length of ICU stay on average by 7.8% (95% CI: 4.2% to 11.2%; p = 0.00003). In six trials, orally administered vitamin C in doses of 1–3 g/day (weighted mean 2.0 g/day) reduced the length of ICU stay by 8.6% (p = 0.003). In three trials in which patients needed mechanical ventilation for over 24 hours, vitamin C shortened the duration of mechanical ventilation by 18.2% (95% CI 7.7% to 27%; p = 0.001)."
In the paper the researchers reported that vitamin C's observed efficacy increases with the severity of the illness. Likewise this effect was observed in the mechanical ventilation meta regression-analysis from 2020:
"In seven trials with control group ICU stay from 1 to 2 days, corresponding to less sick patients, vitamin C reduced ICU stay by 5.7% (p = 0.027). In five trials with control group ICU stay from 3 to 5 days, corresponding to sicker patients, vitamin C reduced ICU stay by 10.1% (p = 0.0001)."
In the abstract the researchers concluded: *"Given the insignificant cost of vitamin C, even an 8% reduction in ICU stay is worth exploring. The effects of vitamin C on ICU patients should be investigated in more detail."*
- **Comment [39]:** It should be noted that none of the IV-C studies included in the calculation of the 7.8% figure used IV-C dosages >3g/day. In fact, only two IV-C studies used dosages >1g; one 3g/day and the other 2g/day. Three studies used 1 gram/day, and one used 0.5 gram/day, yielding a 1.42g/day average of IV-C (not mentioned in meta-analysis). Meanwhile the oral dosing was higher as mentioned by the researchers:

"For these six trials, the weighted mean dose of vitamin C was 2.0 g/day".
The case study conducted by Fonorow might help explain why oral vitamin C at only ~40% higher dose than IV-C (average) can lead to a similar reduction in length of ICU stay. Future clinical trials using much higher IV-C and oral AA dosages are warranted.

Harri Hemilä and Elizabeth Chalker, Vitamin C for preventing and treating the common cold, *Cochrane Database of Systematic reviews*, 2013 Jan 31;(1):CD000980, doi: 10.1002/14651858.CD000980.pub4.
Description [40]: This meta-analysis investigated the role of vitamin C for prevention and treatment of the common cold. The researchers reported the following results:
"In adults the duration of colds was reduced by 8% (3% to 12%) and in children by 14% (7% to 21%). In children, 1 to 2 g/day vitamin C shortened colds by 18%. The severity of colds was also reduced by regular vitamin C administration. Seven comparisons examined the effect of therapeutic vitamin C (3249 episodes). No consistent effect of vitamin C was seen on the duration or severity of colds in the therapeutic trials."

They concluded the following in the abstract:
"Nevertheless, given the consistent effect of vitamin C on the duration and severity of colds in the regular supplementation studies, and the low cost and safety, it may be worthwhile for common cold patients to test on an individual basis whether therapeutic vitamin C is beneficial for them."
- It should be noted that the abstract of the meta-analysis did not mention the two and only placebo controlled trials using high dose oral vitamin C (Karlowski (1975) and Anderson (1974)). These were later included in the abstract of a review from 2017 titled "Vitamin C and infections". This review can be found under the next sub-chapter "4.3. Reviews".
- A report of the meta-analysis can be found here on Cochrane's website [41].

4.3. Reviews

Markos G. Kashiouris et al.,The Emerging Role of Vitamin C as a Treatment for Sepsis, *Nutrients*, 2020 Feb; 12(2): 292 (Epub 2020 January 22), doi: 10.3390/nu12020292
Description [4]: Review on IV-C as a treatment for sepsis. It contains a comprehensive explanation of vitamin C's mechanisms of action relevant in ARDS and sepsis. This can be found in the article under a section titled "2.3 Vitamin C's Mechanism of Action in Sepsis and ARDS".

Harri Hemilä, Vitamin C and Infections, *Nutrients*, 2017 Apr; 9(4): 339 (Epub 2017 March 29), doi: 10.3390/nu9040339
Description [42]: This is an in-depth review investigating the evidence and importance of vitamin C for treatment and prevention of infections. The following is from the abstract:
"Two controlled trials found a statistically significant dose–response, for the duration of common cold symptoms, with up to 6–8 g/day of vitamin C. Thus, the negative findings of some therapeutic common cold studies might be explained by the low doses of 3–4 g/day of vitamin C. Three controlled trials found that vitamin C prevented pneumonia. Two controlled trials found a treatment benefit of vitamin C for pneumonia patients."
- The high dose Vitamin C trials (Karlowski (1975) and Anderson (1974) used 3/6g and 4/8g of oral vitamin C a day respectively. In the high dosage vitamin C group the trials reported a 17%

(Karlowski 1975) and 19% (Anderson 1974) reduction in the duration of cold infections vs placebo. In both trials the reductions in cold duration in the high dose C group were twice as much as the lower dose vitamin C group It should be noted that "*In the Anderson (1974) trial, vitamin C was administered only on the first day of the common cold"*. Despite this the trial reported that *"...in those taking 8 grams in the first day 46% had symptoms that only lasted for one day"*.
- Comment [125]: Dr. Harri Hemilä states there's strong evidence to support vitamin C usefulness as a therapeutic agent for treatment of the common cold and flu. He notes that it has to be given at the onset of symptoms, otherwise the effect will be minimal. It needs to be given regularly, which means in equally divided doses multiple times per day, and at a dose of 6g/day or more. Dr. Hemilä suggests future RCT's investigating different doses and higher doses than 8 grams/day are warranted, because the current evidence is not conclusive, and there's a clear dose dependent response.

Anitra C. Carr and Silvia Maggini, Vitamin C and Immune Function, *Nutrients*, 2017 Nov; 9(11): 1211 (Epub 2017 November 3), doi: 10.3390/nu9111211
Description [43]: Comprehensive review investigating vitamin C's role in and importance for immune function. In the abstract the researchers reported:
"In contrast, treatment of established infections requires significantly higher (gram) doses of the vitamin to compensate for the increased inflammatory response and metabolic demand."
The following was said about vitamin C and pneumonia:
*"There was also a positive effect on the normalization of chest X-ray, temperature, and erythrocyte sedimentation rate [*255*]. Since prophylactic vitamin C administration also appears to decrease the risk of developing more serious respiratory infections, such as pneumonia [*256*], it is likely that the low vitamin C levels observed during respiratory infections are both a cause and a consequence of the disease."*

Harri Hemilä and Robert M. Douglas, Vitamin C and acute respiratory infections, *International Journal of Tuberculosis and Lung Disease*, 1999 Sep;3(9):756-61, PMID: 10488881
Description [44]: Review investigating vitamin C's role for treatment and prevention of respiratory infections. The vast majority of the research in this review can be found in a newer review from 2017 titled "Vitamin C and infections". The following was reported in the abstract:
"In the four largest studies the duration of colds was reduced only by 5%. In two of these studies, however, absence from school and work was reduced by 14-21% per episode, which may have practical importance. Three controlled studies recorded a reduction of at least 80% in the incidence of pneumonia in the vitamin C group, and one randomised trial reported substantial treatment benefit from vitamin C in elderly UK patients hospitalized with pneumonia or bronchitis."

Harri Hemilä and Pekka Louhiala, Vitamin C may affect lung infections, *Journal of the Royal Society of Medicine*, 2007 Nov; 100(11): 495–498, doi: 10.1258/jrsm.100.11.495
Description [71]: Short literature review on vitamin C and lung infections. The paper reviews vitamin C's importance for immune function and the clinical research on vitamin C and lung infections. Most of the information in the review can be found in a newer review from 2017 titled "Vitamin C and Infections".

Harri Hemilä and Pekka Louhiala, Vitamin C for preventing and treating pneumonia, *Cochrane Database Systematic Review*, 2013 Aug 8;(8):CD005532, doi: 10.1002/14651858.CD005532.pub3.
Description [72]: Systematic review on the evidence on vitamin C for prevention and treatment of pneumonia. The following was reported in the abstract:
"We identified two therapeutic trials involving 197 community-acquired pneumonia patients. Only one was satisfactorily randomised, double-blind and placebo-controlled. That trial studied elderly patients in the UK and found lower mortality and reduced severity in the vitamin C group; however, the benefit was restricted to the most ill patients. The other therapeutic trial studied adults with a wide age range in the former Soviet Union and found a dose-dependent reduction in the duration of pneumonia with two vitamin C doses."

Yin Li and Guoping Li., Is Vitamin C Beneficial to Patients with CAP, *Current Infectious Disease Reports*, 2016 Aug;18(8):24. doi: 10.1007/s11908-016-0530-0.
Description [74]: Review investigating if vitamin C is beneficial to patients with community-acquired pneumonia (CAP). The following was reported in the abstract:
"First, we reviewed recent advances about the role of oxidative stress in CAP. Oxidative stress is a crucial component of the host defense system and inflammatory response. However, excessive oxidative stress can cause a systemic inflammatory response leading to tissue damage. The degree of oxidative stress has been associated with the severity of CAP."
"Administration of vitamin C decreases the duration of mechanical ventilation by decreasing oxidative stress."

Pramath Kakodkar et al., A Comprehensive Literature Review on the Clinical Presentation, and Management of the Pandemic Coronavirus Disease 2019 (COVID-19), *Cureus*, Cureus 12(4): e7560, 2020 April 6, doi: 10.7759/cureus.7560
Description [76]: This article is highly recommended for medical professionals. It's a comprehensive review on the current knowledge about COVID-19. A section near the end is dedicated to the following experimental treatments for COVID-19: Vitamin C and D, remdesivir, lopinavir, ritonavir, umifenovir, chloroquine, antepyretics, ACEi, ARBs and systemic corticosteroids. The article lists some of vitamin C's mechanisms of action relevant for COVID-19:
"Vitamin C reinforces the maintenance of the alveolar epithelial barrier and transcriptionally upregulates the protein channels (CFTR, aquaporin-5, ENaC, and Na+/K+ ATPase) regulating the alveolar fluid clearance [37]. HDIVC has been implicated in reducing plasma cell-free DNA formed from the neutrophil extracellular trap (NET) which is the facilitator of systemic inflammation in sepsis-induced multi-organ failure [38,39]. Interestingly, elevated levels of syndecan-1 in the plasma correlate with increased mortality in severe sepsis and ARDS, and this endothelial glycocalyx can be reduced significantly by HDIVC [39]."

Sebastian J. Padayatty and Mark Levine, Vitamin C physiology: the known and the unknown and Goldilocks, *Oral Diseases*, 2016 Sep; 22(6): 463–493 (Epub 2016 April 14), doi: 10.1111/odi.12446
Description [45]: Comprehensive review investigating vitamin C's physiology. Recommended for medical professionals.

4.4. Miscellaneous Articles

Michael A. Matthay et al., Treatment of severe acute distress syndrome from COVID-19, *The Lancet Respiratory Medicine*, 2020 March 20, doi:
Description [80]: A comment written by prominent researchers at The University of California and published in the prestigious medical journal *The Lancet*. It contains brief information on the *"Treatment for severe acute respiratory distress syndrome from COVID-19".*
Furthermore, it includes a recommendation of Vitamin C being used as a rescue therapy based on the mortality reduction (IV-C group: 29.8% vs placebo group: 46.3%) AA Fowler and colleagues observed in the CITRIS-ALI trial. The vitamin C recommendation reads as follows:
"Rescue therapy with high-dose vitamin C can also be considered."

PulmCrit- American research infrastructure is killing us: The misbegotten battle between the ivory tower academics and the rogue cowboys, Josh Farkas, April 29, 2020, PulmCrit (Emcrit), Emcrit.org.
Description [150]: This is an interesting article relevant for our current pandemic. The argument between Rogue Cowboys and Ivory Tower Academics is explored. In short it's about whether we should try new treatments potentially efficacious but also potentially harmful for COVID-19 and do rapid large scale pragmatic studies, or we should let people die and conduct RCT's from which the results will arrive next year or in 2022.
Then there's a long section on the failure of the American research infrastructure and the missed opportunities due to excessive bureaucracy and lack of approval streamlining.

iSepsis – Vitamin C, Hydrocortisone and Thiamine – The "Metabolic Resuscitation Protocol", Paul Marik, EMCrit.org - iSepsis Project (EMCrit), July, 16 2017.
Description [46]: In this article at EMCrit.org Paul E. Marik explains the rationale for HAT therapy. He lists the decades of evidence it builds upon and details the Hydrocortisone, Vitamin C and Thiamine (HAT) protocol.

Paul E. Marik et al., Hydrocortisone, ascorbic acid and thiamine for sepsis: Is the jury out?, *World Journal of Diabetes*, 2020 Apr 15; 11(4): 90–94 (Epub 2020, April 15), doi: 10.4239/wjd.v11.i4.90
Description [119]: Research paper by Paul Marik and colleagues where they present the biological rationale for HAT therapy and the increasing clinical evidence from RCT's and their astonishing results with HAT. Furthermore, they discuss the potential shortfalls of RCT's and how sometimes it's difficult to replicate real life clinical experience in RCT's.

PulmCrit- Metabolic sepsis resuscitation: the evidence behind Vitamin C, Josh Farkas, March 27, 2017, PulmCrit (EMCrit), Emcrit.org.
Description [120]: In this in depth and comprehensive article the creator of PulmCrit.org Josh Farkas looks at the clinical evidence and biological rationale of the vitamin C and thiamine components of HAT therapy.

Paul E. Marik and Michael H. Hooper, Doctor—your septic patients have scurvy!, *Critical Care*,

2018 Jan 29;22(1):23, doi: 10.1186/s13054-018-1950-z
Description [47]: Editorial by Paul E. Marik and Michael H. Hooper written in response to the study “Hypovitaminosis C and vitamin C deficiency in critically ill patients despite recommended enteral and parenteral intakes”. They provide evidence for why this antioxidant depletion occurs in critically ill patients, and they detail what happens if the deficiency is not corrected.

Adnan Erol, High-dose intravenous vitamin C treatment for COVID-19, preprint (not yet peer reviewed), 2020 February, doi: 10.31219/osf.io/p7ex8.
Description [92]: In this detailed research article, researcher Adnan Erol investigates the non-clinical research on the pathology of and immune response to SARS-CoV-2 virus. Furthermore, he describes the proposed action of vitamin C as an immunomodulatory, -regulatory and -suppressant, and he discusses IV-C treatment of COVID-19.

Salim Surani and Munish Sharma, Revisiting the Role of Vitamin C in Sepsis. Is it a Forlorn Hope or is there Still Dearth of data?, *The Open Respiratory Medicine Journal*, Bentham Open, Benthamopen.com, 2019 Dec 31;13:55-57, doi: 10.2174/1874306401913010055
Description [48]: Editorial on vitamin C for treating sepsis. It’s written in response to the CITRIS-ALI randomized controlled trial.

5. Studies and RCT’s on Vitamin C for Treatment of COVID-19

The following chapter has a description of each listed RCT and study. Preliminary, preprint and published findings of the RCT’s and studies have been listed, too.

To be listed here the trials and studies need to live up to all these criteria:

1. Enroll patients with suspected or confirmed COVID-19.
2. Use either IV-C or oral dose ≥1500mg/day.
3. Use it along with no more than 3 other drugs/compounds.
4. Be a therapeutic intervention study and not long term supplementation for prophylaxis.
5. The vitamin C dosage used has to be stated.
6. Vitamin C needs to be a treatment intervention not a placebo or control comparator.

As of today (April 30, 2020) 10 trials on vitamin C have been announced, and 6 of them are currently recruiting patients. 8 are active, while two have been cancelled.
A brief overview of the current vitamin C trials can be found under the section “Nutrients” in the following document from the Danish Medicines Agency titled “Overview of planned or ongoing studies of drugs for the treatment of COVID-19” [84].

ZhiYong Peng, Vitamin C Infusion for the Treatment of Severe 2019-nCoV Infected Pneumonia, Date of registration: February 11, 2020, ClinicalTrials.gov.
Description [85]: Look below.

- Study identifier: NCT04264533
- Study design: Phase II randomized triple-blinded placebo controlled trial (140 participants, experimental (n=70), control (n=70)).
- Description of participants: Serious or critical COVID-19 patients.

- Treatment protocol: Experimental group: 12g IV-C in 50mL sterile water solution q12h, 12mL/h (4.17h infusion), IV-C 24g/day. Placebo control group: 50mL sterile water solution q12h, 12mL/h (4.17h infusion). Administered for 7 days for both groups.
- Study location: Zhongnan Hospital, Hubei, China.
- Status of trial: Recruiting.
- Primary completion date: September 30, 2020
- Study completion date: September 30, 2020
- **Preliminary results [121]:** Dr. Zhiyong Peng reported the following preliminary results in a international video conference attended by multiple physicians:

1. *"HD-IVC seems to reduce the inflammation of Covid-19 significantly."* IL-6 and PF ratio was significantly reduced in the IV-C group vs placebo.
2. *"HD-IVC seems to reduce Covid-19 patients' ICU and hospital stays."*
3. *"HD-IVC may also reduce the mortality rate of Covid-19 patients, although the number of patients may be too small."* The mortality reported in the IV-C group and placebo control group was 24% and 35% respectively.

Jun Lin, A randomized, open, controlled trial for diammonium glycyrrhizinate enteric-coated capsules combined with vitamin C tablets in the treatment of common novel coronavirus pneumonia (COVID-19) in the basic of clinical standard antiviral treatment to evaluate the safety and efficiency, Date of registration: February 12, 2020, Chinese Clinical Trial Registry, Chictr.org.cn.

Description [86]: Look below.

- Study identifier: ChiCTR2000029768
- Study design: Randomized open controlled trial (60 participants, experimental (n=30), control (n=30)).
- Description of participants: COVID-19 patients.
- Treatment protocol: Experimental group: Vitamin C 0.5 g (3x day) + diammonium glycerrhizinate enteric coated capsules 150 mg 4x/day + and standard clinical antiviral treatment. Control: Standard clinical antiviral treatment. Duration of treatment not stated.
- Study location: Zhongnan Hospital, Hubei, China.
- Status of trial: Recruiting.
- Primary completion date: May 12, 2020
- Study completion date: n/a

Gao Defeng, An observational study of high-dose Vitamin C in the treatment of severe and critical patients with novel coronavirus pneumonia (COVID-19), Date of registration: February 17, 2020, Chinese Clinical Trial Registry, Chictr.org.cn.

Description [87]: Look below.

- Study identifier: ChiCTR2000029957
- Study design: Case series, observational study (66 participants).
- Description of participants: Severe or critical COVID-19 patients.
- Treatment protocol: High dose vitamin C (dose: n/a) + standard care. Dosages used reported by Dr. Richard Cheng: 6.000-12.000mg/day [91]. Duration of treatment not stated.
- Study location: Shaanxi and Hubei, China.
- Status of trial: Not yet recruiting, canceled by ethics committee on March 14, 2020.
- Primary completion date: ---||---

- Study completion date: ---||---

Gao Defeng, A randomized controlled trial for high-dose Vitamin C in the treatment of severe and critical novel coronavirus pneumonia (COVID-19) patients, Date of registration: February 24, 2020, Chinese Clinical Trial Registry, Chictr.org.cn.
Description [88]: Look below.

- Study identifier: ChiCTR2000030135
- Study design: Randomised controlled trial, blinding not stated (40 participants, experimental (n=26), control (n=13)).
- Description of participants: Severe or critical COVID-19 patients.
- Treatment protocol: Experimental group: high dose vitamin c (dose = n/a.). Control group: routine treatment. Duration of treatment not stated.
- Study location: Shaanxi and Hubei, China.
- Status of trial: Not yet recruiting, canceled by ethics committee on March 14, 2020.
- Primary completion date: ---||---
- Study completion date: ---||---

Salvatore Corrao, Use of Ascorbic Acid in Patients With COVID 19, Date of registration: March 26, 2020, ClinicalTrials.gov.
Description [89]: Look below.

- Study identifier: NCT04323514
- Study design: Single arm, open label (500 participants).
- Description of participants: Hospitalized patients with COVID-19.
- Treatment protocol: 10 grams IV-C, appears to be a single infusion.
- Study location: University of Palermo, Palermo, Sicily, Italy.
- Status of trial: Recruiting.
- Primary completion date: March 13, 2021
- Study completion date: March 13, 2021

Markos. G. Kashiouris and Alpha A. Fowler, Early Infusion of Vitamin C for Treatment of Novel COVID-19 Acute Lung Injury (EVICT-CORONA-ALI), Date of registration: April 14, 2020, ClinicalTrials.gov.
Description [90]: Look below.

- Study identifier: NCT04344184
- Study design: Quadruple blind randomized placebo controlled trial (200 participants, experimental (n=100), control (n=100))
- Description of participants: Patients with hypoxemia and suspected COVID-19.
- Treatment protocol: Experimental group: 100mg/kg/q8h (300mg/kg/24h) IV-C infusion. 12mL/h (4.17h infusion), IV-C 24g/day. Placebo control group: Dextrose 5% water q8h. Administered for up to 72 hours for both groups.
- Study location: Virginia Commonwealth University, Virginia, USA.
- Status of trial: Not yet recruiting
- Primary completion date: May 2021
- Study completion date: May 2021

François Lamontagne and Neil Adhikari, Lessening Organ Dysfunction With VITamin C (LOVIT), Date of registration: September 21, 2018, ClinicalTrials.gov.
Description [122]: Look below:

- Study identifier: NCT03680274
- Study design: Quadruple blind randomized placebo controlled trial (800 participants, experimental (n=400), control (n=400))
- Description of participants: Patient with septic shock admitted to ICU and treated with continuous IV infusion of vasopressors. Was recently changed to allow for enrollment of COVID-19 patients with septic shock.
- Treatment protocol: Experimental group: 50mg/kg/q6h (200mg/kg/24h) IV-C infusion. Placebo control group: Dextrose 5% in a water *(Dextrose 5% in water (D5W) or normal saline (0.9% NaCl)...".* Administered for 96 hours.
- Study location: Research Center of the CHUS, Quebec, Canada.
- Status of trial: Recruiting
- Primary completion date: December 31, 2021
- Study completion date: December 31, 2022

Milind Desai, Coronavirus 2019 (COVID-19)- Using Ascorbic Acid and Zinc Supplementation (COVIDAtoZ), Date of registration: April 13, 2020, ClinicalTrials.gov.
Description [123]: Look below:

- Study identifier: NCT04342728
- Study design: Single-center, prospective open label four arm randomized controlled trial (520 participants).
- Description of participants: Adult patients presenting to hospital who test positive for COVID-19, and *"Women of child bearing potential who have not had a menstrual period within the past 30 days, have not had previous sterilization or those who are perimenopausal (less than 1 year) who have a negative pregnancy test"*.
- Treatment protocol: Active comparator 1: AA 8000mg divided in 2-3 daily doses with food. Active comparator 2: Zinc gluconate (50mg) to be taken daily at bedtime. Active comparator 3: 8000mg AA divided into 2-3 daily doses with food and zinc (50mg) gluconate at bedtime daily. Arm 4: Standard of care.
- Study location: Cleveland Clinic, Ohio, United States
- Status of trial: Enrolling by invitation
- Primary completion date: September 30, 2020
- Study completion date: April 30, 2021

Brian C. Davis, Administration of Intravenous Vitamin C in Novel Coronavirus Infection (COVID-19) and Decreased Oxygenation (AVoCaDO), Date of registration: April 22, 2020, ClinicalTrials.gov.
Description [124]: Look below:

- Study identifier: NCT04357782
- Study design: Case-series (20 participants)
- Description of participants: COVID-19 patients with signs of worsening oxygenation and severe hypoxia group with acute hypoxemic respiratory failure requiring ventilator intubation.
- Treatment protocol: Mild deoxygenation: 50mg/kg/q6h (200mg/kg/24h) IV-C infusion for 4 days. Same treatment for severe deoxygenation.

- Study location: Hunter Holmes Mcguire Veteran Affairs Medical Center, Virginia, United States.
- Status of trial: Recruiting
- Primary completion date: June 1, 2020
- Study completion date: August 1, 2020

Dagan Coppock, Pharmacologic Ascorbic Acid as an Activator of Lymphocyte Signaling for COVID-19 Treatment, Date of registration: April 27, 2020, ClinicalTrials.gov.
Description [151]: Look below:

- Study identifier: NCT04363216
- Study design: Randomized controlled trial (open label), 2:1 randomization ratio (66 participants, 44 HDIV-C and 22 control).
- Description of participants: COVID-19 patients.
- Treatment protocol: Experimental group: IV-C infusion given over 2 hours once a day along with 1g/L magnesium chloride to reduce burning sensation. Escalating dose of 0.3g/kg, 0.6g/kg and 0.9g/kg on day 0, 1 and 2 respectively. On day 3-5 0.9g/kg. Control group: Routine care.
- Study location: n/a
- Status of trial: Not yet recruiting
- Primary completion date: April, 2021
- Study completion date: April, 2021

6. Orthomolecular Clinical Experience, Studies and Articles on Vitamin C

Below is a compilation of articles relevant to the current COVID-19 pandemic. This includes the clinical experience medical doctors, who are/were using orthomolecular medicine, have had with vitamin C and viral infections.
Other miscellaneous articles from orthomolecular medicine practitioners and advocates, including published and peer reviewed research are provided, too.

6.1. Clinical Experience and Observational Studies

Frederick R. Klenner reported remarkable results using IV-C and high dose oral vitamin C. Here are some of the papers he published and a detailed article about his research:

Clinical Guide to the Use of Vitamin C, Lendon H. Smith. M.D, AscorbateWeb, 1988.
Description [49]: This is a comprehensive article about *"The Clinical Experiences of Frederick R. Klenner, M.D."* and it's *"abbreviated, sumarized and annotated by Lendon H. Smith, M.D.".* Lendon H. Smith went through Frederick R. Klenner's over 27 papers from the 1940's to 1970's. The article is an adaption of the book "*Vitamin C as a Fundamental Medicine: Abstracts of Dr. Frederick R. Klenner, M.D.'s Published and Unpublished Work*". The book is written by Lendon H. Smith, too.
- The article details Frederick R. Klenner's observations on vitamin C's dosage, antitoxin, antiviral and antimicrobial properties and the many illnesses and ailments Klenner said he cured with megadose vitamin C.

Frederick R. Klenner, M.D, The Treatment of Poliomyelitis and Other Virus Diseases with Vitamin C, *Southern Medicine & Surgery*, Volume 111, Number 7, July, 1949, pp. 209-214.
Description [50]: This is an observational report on vitamin C being used to treat poliomyelitis and other viral diseases. In this paper Klenner reported curing many viral illnesses with IV-C and megadose oral vitamin C. During a poliomyelithis epidemic in North Carolina in 1948 Klenner reported curing 60 out of 60 cases of poliomyelitis with megadose vitamin C:
"With these precautions taken, every patient of this series recovered uneventfully within three to five days."

Frederick R. Klenner, M.D, Observations On the Dose and Administration of Ascorbic Acid When Employed Beyond the Range Of A Vitamin In Human Pathology, *Journal of Applied Nutrition*, Vol. 23, No's 3 & 4, Winter 1971.
Description [51]: This is a detailed research article in which Dr. Klenner laid out his thoughts and observations on vitamin C's mechanisms of action in many diseases. Furthermore, the article includes observational evidence from hundreds of treated patients from Klenner's own practice and other practitioners and researchers using megadose vitamin C.
- It includes a case report of a dying cyanotic patient (due to a toxin) being saved by 12 grams vitamin C IV push (extremely rapid infusion). In addition, there are hundreds of case reports of IV-C being successful in treatment of mononucleosis, viral encephalitis and many other illnesses.

And here are two important articles, one by Robert F. Cathcart, MD and one by Thomas E. Levy, MD:

Robert F. Cathcart, M.D, VITAMIN C, TITRATING TO BOWEL TOLERANCE, ANASCORBEMIA, AND ACUTE INDUCED SCURVY, *Medical hypotheses*, 1981, 7:1359-1376, Vitamin C Foundation.
Description [1]: This is the famous research article by Robert F. Cathcart, III, MD where he introduced the concept of titrating to bowel tolerance. It also includes the clinical observations made by Cathcart on the remarkably high daily vitamin C dosages required for certain illnesses to hit bowel tolerance. Cathcart reported sometimes +200g/day of oral AA was required to reach bowel tolerance. Cathcart estimated bowel tolerance doses for a wide variety of illnesses based on his clinical experience, too.
- And all the other publications by Robert F. Cathcart can be found on the Vitamin C Foundation's webpage [52].

The Clinical Impact of Vitamin C: My Personal Experience as a Physician, Thomas E. Levy, Orthomolecular Medicine News Service, Orthomolecular.org, September 3, 2014.
Description [53]: In this commentary Thomas E. Levy, MD compiled what he considered to be the most dramatic anecdotes about the power of megadose vitamin C. The majority of these were from his own practice.

6.2. Miscellaneous Research Papers, Articles and Slideshows on Vitamin C

This chapter contains a lot of papers, articles and slideshows on COVID-19 on vitamin C. Everything from published research and slideshows to articles and reports.

6.2.1. Vitamin C Miscellaneous

Richard Z. Cheng, Can early and high intravenous dose of vitamin C prevent and treat coronavirus disease 2019 (COVID-19)?, *Medicine in Drug Discovery*, 2020 March 26, doi: 10.1016/j.medidd.2020.100028
Description [54]: Editorial by Richard Z. Cheng on the mounting evidence indicating vitamin C could be useful in treatment of COVID-19.

Case for Vitamin C for COVID-19, Patrick Holford, PatrickHolford.com, March 29, 2020.
Description [77]: Short article by Patrick Holford on the *"...six compelling reasons why high dose oral (6gram+) and intravenous vitamin C (IVC) should be trialled on critically ill COVID-19 patients to speed up recovery time spent in ICU and reduce mortality"*.

COVID-19, Vitamin C, Vaccine and Integrative Medicine, Dr. Richard Cheng, Cheng Integrative Health Center Blog, April 16, 2020, DrWLC.com.
Description [128]: This is a great overview of all the information Richard Cheng has reported on so far. He has reported on the clinical trials in China, Wuhan family is saved from COVID-19 infection, IV-C endorsement from Shanghai Medical Association and the Guangdong Province Expert Panel, the remarkable 50 COVID-19 patient case series reported by Dr. Enqiang Mao in Shanghai and at last the preliminary findings of the first HD-IVC clinical trial on COVID-19.

Coronavirus Coverup — Vitamin C Dramatic Help against Infection in China, South Korea — Why Aren't We Told, Mara Leverkuhn, Medium.com, March 17, 2020.
Description [81]: This is an article translated from Romanian, which contains an interview with medical researcher and biophysicist Virgiliu Gheorghe on the topic of vitamin C. The interview contains information on the reports from China and South Korea and the censorship of these. Furthermore, Mr. Gheorghe answers additional miscellaneous questions about the safety of vitamin C and dosages.

Rationale for Vitamin C Treatment of COVID-19 and Other Viruses, Orthomolecular Medicine News Service Editorial Review Board, Orthomolecular Medicine News Service, Orthomolecular.org, April 3, 2020.
Description [18]: This article urges *"The world's political, scientific, medical and industrial leaders need to consider this* (vitamin C) *very carefully"*. It provides the evidence and rationale for vitamin C in treatment of COVID-19 and other viral infections.
Vitamin C's mechanisms of action are explained, and a short note on vitamin D and zinc is provided. Different dosage recommendations and route of administration (oral or IV) are outlined, too.

Arturo Hernández et al., Two known therapies could be useful as adjuvant therapy in critical patients infected by COVID-19, *Revista Española de Anestesiología y Reanimación*, 2020, April 14, doi: 10.1016/j.redar.2020.03.004
Description [129]: This article briefly reviews the evidence behind vitamin C and ozone therapy, and the authors say that they *"...could be useful for the treatment of severe acute coronavirus infection associated with acute respiratory syndrome (SARS-CoV-2)"*. The researchers lists a nutritional strategy for treatment of COVID-19 that includes HDIV-C, zinc, thiamine, vitamin D, vitamin E, melatonin.

Hospital-Based Intravenous Vitamin C Treatment for Coronavirus and Related Illnesses, Andrew W. Saul and Atsuo Yanagisawa, MD, PhD., May 2020, Orthomolecular News Service (OMNS), Townsend Letter, TownsendLetter.com.
Description [131]: This great article lists a IV-C treatment protocol made by the Japanese College of Intravenous Therapy (JCIT) (previously mentioned in chapter 3), and it debunks the "vitamin C is dangerous" argument. Furthermore, the majority of the article is dedicated to how to get IV-C in a hospital setting where there's resistance towards vitamin C.

And here's a transcript of a video conference where Dr. Enqiang Mao shared his experience with IV-C for treating hospitalized COVID-19 patients:

Successful High-Dose Vitamin C Treatment of Patients with Serious and Critical COVID-19 Infection, Richard Cheng, MD, PhD, Orthomolecular Medicine News Service, March 18, 2020.
Description [56]: This article is a transcribed online video conference, where a group of medical doctors, healthcare providers and scientists discussed vitamin C for the treatment of moderate to severe hospitalized cases of COVID-19.
- The key guest was Dr. Enqiang Mao *"...chief of emergency medicine department at Ruijin Hospital, a major hospital in Shanghai, affiliated with the Joatong University College of Medicine"*. He had successfully treated 50 moderate to severe COVID-19 patients with 10,000-20,000mg/day IV-C for 7-10 days. The mortality rate was 0%.
- A report of a rapidly deteriorating patient given a bolus of 50,000mg IV-C over 4 hours is included, too. The patient's oxygenation was reportedly improved in real time following initiation of HDIV-C therapy.

This is a useful article on how to get IV-C administered to a hospitalized patient:

How to Get Intravenous Vitamin C Given to a Hospitalized Patient: A Checklist, Andrew W. Saul, DoctorYourself.com, 2019.
Description [57]: For hospitalized patients and their families and relatives. It has all the information needed on *"How to Get Intravenous Vitamin C Given to a Hospitalized Patient"*. The document is not legal advice. If legal advice and action is required, contacting a lawyer is recommended.

6.2.2. Slideshows

And here are some interesting slideshows:

Vitamin C in the Prevention & Treatment of Covid-19, Richard Z. Cheng, M.D., Ph.D., DoctorYourself.com.
Description [127]: Excellent and concise, yet still comprehensive slideshow by Dr. Richard Cheng on the rationale for vitamin C for treatment of COVID-19, presented as part of a NIH online video conference. It contains clinical evidence, biological rationale based on mechanistic research and serves the function of an introduction to vitamin C for Covid-19 remarkably well.

Role of Ascorbic Acid in Covid 19 Management, Dr Yuen Chuen Fong Raymond, DoctorYourself.com.
Description [14]: This is a comprehensive slideshow answering most questions about vitamin C. It provides evidence and rationale for using vitamin C in the treatment and prevention of various diseases, including COVID-19.

Colds, Flus and COVID-19: Can Supplements Help?, Prof Kylie O'Brien PhD and Prof Ian Brighthope, Australasian College Of Nutritional And Environmental Medicine (ACNEM), ACNEM.org, 2020.
Description [58]: Slide show from ACNEM presenting multiple research findings about the efficacy of vitamin C, D and zinc for treating colds, flus and respiratory illnesses. The research findings suggest that IV-C could play an important role in treatment of COVID-19.
- The slide show has been presented in three video presentations: Part 1 - Vitamin C, Part 2 – Vitamin D and Part 3 – Zinc. These can be found on ACNEM's webpage [58].

6.2.3. In depth research by Doris Loh

And furthermore, here's some in-depth research material on COVID-19 by Doris Loh:

STOP ARDS NOW WITH ASCORBIC ACID, Doris Loh, Evolutamente.it, March 28, 2020.
Description [60]: Detailed slideshow explaining the mechanisms of action of oral AA and IV-C and their potential importance for treating COVID-19. It contains excerpts from the five text articles by Doris Loh listed here.
- The article puts a great emphasis on the unique mechanisms of action of AA.

COVID-19, ARDS & CYTOKINE STORMS – THE RECYCLING OF ASCORBIC ACID BY MACROPHAGES, NEUTROPHILS AND LYMPHOCYTES, Doris Loh, Evolutamente.it, April 5, 2020.
Description [79]: Detailed slideshow explaining SARS-CoV-2's virulent destruction of hemoglobin and red blood cells leading to a surge in cytotoxic cell-free hemoglobin. The slide show investigates vitamin C's importance for preventing and treating destruction and extracellular release of hemoglobin.
Furthermore, the slide show provides evidence for vitamin C's importance for treatment and

prevention of ARDS and “cytokine storms”.

MITOCHONDRIA & THE CORONAVIRUS – THE VITAMIN C CONNECTION (PART 3), Doris Loh, Evolutamente.it, February 1, 2020.
Description [61]: Detailed article on the mechanisms of vitamin C for mitochondrial function and its potential for prevention of “cytokine storm” and ARDS. ARDS and “cytokine storm” are strongly associated with severe cases of COVID-19.

COVID-19, FURINS & HYPOXIA – THE VITAMIN C CONNECTION, Doris Loh, Evolutamente.it, February 29, 2020.
Description [62]: In-depth article explaining the connection between vitamin C and COVID-19, furins and hypoxia. The significance of furins and HIF1a in COVID-19 are explained in great detail, too.

COVID-19 MUTATIONS, VACCINES & NITRIC OXIDE – THE VITAMIN C CONNECTION, Doris Loh, Evolutamente.it, March 7, 2020.
Description [63]: In-depth article investigating mechanisms of action of nitric oxide and vitamin C important for COVID-19. SARS-CoV-2 mutations and how they impact vaccine R&D are explored, too. Furthermore, the viruses SARS-CoV (SARS 2003) and SARS-CoV-2 (COVID-19) are compared.

COVID-19, PNEUMONIA & INFLAMMASOMES – THE MELATONIN CONNECTION, Doris Loh, Evolutamente.it, March 14, 2020.
Description [64]: In-depth article investigating the relationship between COVID-19, inflammasomes and pneumonia. The important role the mechanisms of action of melatonin play in COVID-19 is discussed, too.
- The article reports that melatonin, nitric oxide and ascorbic acid inhibit NLRP3 inflammasomes. NLRP3 inflammasomes play a significant role in the “cytokine storm” associated with severe COVID-19.
- A simple guide for melatonin and ascorbic acid supplementation is provided near the bottom of the article.

COVID-19, ARDS & CELL-FREE HEMOGLOBIN – THE ASCORBIC ACID CONNECTION, Doris Loh, Evolutamente.it, March 24, 2020.
Description [65]: Comprehensive article explaining the relationship between ARDS, cell-free hemoglobin and COVID-19 in great detail. The important role vitamin C plays in preventing and treating cell-free hemoglobin and ARDS is investigated.
- Furthermore, the article explains why oral AA is superior to oral SA.
- Near the end it gives an oral supplementation protocol for COVID-19.

6.3. Large Folders (ZIP), Link Collections and Comprehensive Articles on Orthomolecular Treatment of Viral Disease

BRIGHTHOPE CORONAVIRUS SHARE GENERAL, Dr. Ian Brighthope, available at Dropbox.com.
Description [82]: This is a storehouse of information (+70 PDF documents) from Australian physician Dr. Ian Brighthope about vitamin C, D, COVID-19 and viruses. The folder "VITAMIN C D AND VIRUSES" contains information on viral disease and vitamin C. In addition, the folder provides plenty of evidence from experimental and clinical research that strongly supports vitamin C's efficacy as a treatment of viral disease.

Safe and Effective Modalities For COVID-19 That Can Not Be 'Proven'", Dr. Charles Chun-En Hsu, M.D, Afternoon Health, April 1, 2020.
Description [55]: In-depth article explaining the potential benefits of magnesium, zinc, vitamin C and D, melatonin and NAC for prevention and treatment of COVID-19. The majority of the sources provided are in vitro and in vivo research papers on the mechanisms of action of the previously mentioned compounds.
- All these mechanisms of action play an important role in COVID-19. Hence, the compounds are speculated to be potentially beneficial for treatment and prevention of COVID-19

Published Research and Articles on Vitamin C as a Consideration for Pneumonia, Lung Infections, and the Novel Coronavirus (SARS-CoV-2/COVID-19), Graham Player, PhD et al., March 22, 2020, Orthomolecular Medicine News Service, Orthomolecular.org.
Description [101]: A comprehensive compilation of *"Published Research and Articles on Vitamin C as a Consideration for Pneumonia, Lung Infections, and the Novel Coronavirus (SARS-CoV-2/COVID-19)"*. A majority of the research of the extant articles is referenced in this document.

Alberto Boretti and Bimal Krishna Banik, Intravenous vitamin C for reduction of cytokines storm in acute respiratory distress syndrome, *PharmaNutrition*, Volume 12, June 2020, 100190 (Epub 2020, April 21), doi: 10.1016/j.phanu.2020.100190
Description [130]: This is a comprehensive review on *"...the effects of IV Vit-C on the immune system response, the antiviral properties of IV Vit-C, and finally the antioxidant properties of IV Vit-C to specifically address the cytokines' storm characteristic of the Acute Respiratory Distress Syndrome (ARDS) that occur in the later cycle of the Covid19 infectious disease"*. The review article contains 150 references and includes all the evidence including some case series and case reports from orthomolecular physicians.

COVID-19: News & Updates, Riordan Clinic, RiordanClinic.org.
Description [132]: News and updates about COVID-19, continuously updated by the Riordan Clinic. It lists news coverage for vitamin C that this Google Docs have excluded.

7. Case reports and anecdotes on vitamin C, other nutrients and melatonin for treating COVID-19

This chapter compiles all the reports on successful use of vitamin C for treating COVID-19 outside of trials and studies.

To date (30.4-2020) *"27 hospitals in New York, Wisconsin, Houston and East Virginia are using intravenous vitamin C and report remarkable improvement in symptom severity, duration and deaths"* [77]. These include the largest hospital chain in New York, Northwell which operates 23 hospitals, and the hospitals affiliated with the prominent emergency physicians who formed the Frontline COVID-19 Critical Care Working Group (FLCCC Working Group) and developed the MATH+ protocol (see chapter 3, no. 3) [107] [133]. Another major hospital chain in US, St. Luke's University Health Network, comprising of 10 hospitals, 6 in New Jersey and 4 in Pennsylvania has reported good results with their protocol that includes IV-C, zinc, atorvastatin and steroids, and taken measures to prevent and delay mechanical ventilation [134].

The first report of successful treatment of COVID-19 with vitamin C is all the way back from February 21th. In an official statement the The Second Affiliated Hospital of Xi'an Jiaotong University (Xibei Hospital), located in the neighbouring province of Hubei Shaanxi, stated the following [148] [149]:
"On the afternoon of February 20, 2020, another 4 patients with severe new coronaviral pneumonia recovered from the C10 West Ward of Tongji Hospital. In the past 8 patients have been discharged from hospital… High-dose vitamin C achieved good results in clinical applications. We believe that for patients with severe neonatal pneumonia and critically ill patients, vitamin C treatment should be initiated as soon as possible after admission... Early application of large doses of vitamin C can have a strong antioxidant effect, reduce inflammatory responses, and improve endothelial function. Numerous studies have shown that the dose of vitamin C has a lot to do with the effect of treatment... High-dose vitamin C can not only improve antiviral levels, but more importantly, can prevent and treat acute lung injury (ALI) and acute respiratory distress (ARDS)."

The second report and the first detailed case series of patients successfully treated with IV-C was from Dr. Enqiang Mao *"...chief of emergency medicine department at Ruijin Hospital"*. It was presented in a worldwide video conference attended by many prominent physicians, including Dr. Paul Marik and Dr. Alpha "Berry" Fowler [56] [128]. Dr. Mao reported a case series of 50 hospitalized patients with moderate or severe COVID-19 treated with 10,000-20,000mg/day of IV-C for 7-10 days. The case series had a 0% mortality rate and a 3-5 day shorter hospital stay than the the 30-day hospital stay for all COVID-19 patients. Patients with hypercoagulation issues was administered heparin [56].
A rapidly deteriorating patient was given *"...a bolus of 50,000mg IV-C over a period of 4 hours"*, and *"The patient's pulmonary (oxygenation index) status stabilized and improved as the critical care team watched in real time"*. No side effects were reported in the IV-C case series [56].

Dr. Andrew G. Weber used IV-C 1,500mg/q6h for treating COVID-19 ICU admissions and reported the following [133]: *"The patients who received vitamin C did significantly better than those who did not get vitamin C"*. and *"It* (IV-C) *helps a tremendous amount..."*.

The MATH+ therapy has been put to use in at least 4 hospitals, and the physicians using it are reporting remarkable benefits. One example is Dr. Joseph Varon, at United Memorial Medical Center in Houston, Texas. He reported (April 10, 2020) that his ICU had treated 24 COVID-19 patients with MATH+, and they had no deaths. He emphasized it's important to intervene early:
"You start it early and patients don't even need to be intubated."
Dr. Paul Marik reiterated the importance of early treatment initiation [135]:
"You have to intervene early and aggressively to prevent them from deteriorating."
In addition, Dr. Varon reported other physicians are getting very similar results from MATH+ [136]:
"We have a consortium of five intensive care doctors across the united states that are using this same protocol and we all have very similar results."

Another physician using MATH+ is Dr. Paul Marik of Eastern Virginia Medical School. He reported no deaths in the first 30 severe and critical COVID-19 patients treated in his ICU [77]. Marik did state that in the total 40 ICU COVID-19 patients treated so far (released 28.4-2020) there was only 2 deaths. Both were over 85 year and had severe comorbidities, one with end stage cirrhosis and another with end stage lung disease. Furthermore, at his ICU they managed to resurrect a dead cardiac arrest patient with COVID-19. In addition he had massive pulmonary embolism, and Marik reported that he walked out of the ICU last week (information released 28.4-2020)
The number of reported patients on a ventilator in the ICU was also very low in Marik's ICU [137]:
"Out of the 40, maybe 5-6 patients who actually went on a ventilator."
"...all of them have come off the ventilator. So we've not had a single patient patient, who has become ventilator dependant."

The remarkable results might not only be explained by the reported efficacy of the MATH+ protocol for treating COVID-19, but by the reversal of the extremely widespread clinical scurvy in some COVID-19 patients. Vitamin C levels in COVID-19 patients were measured by one of Marik's colleagues:
"They're undetectable, undetectable. The levels (vitamin C) are so low in all COVID patients they can't be detected. So we absolutely know that patients with COVID, apart from other benefits, these patients are absolutely and profoundly deficient in vitamin C."
"These people (COVID-19 patients) have a disease-induced scurvy" - Dr. Paul Marik.

As previously mentioned the St. Luke's University Health Network has had good results with their protocol. On April 24, 2020 they discharged their 500th COVID-19 patient and have already extubated about 50 patients from mechanical ventilation [134]. The *"infectious disease specialist Jeffrey Jahre, MD, St. Luke's Senior Vice President of Medical Affairs"* said the following about the 50 patient mechanical ventilation extubation figure [134]:
"These remarkable figures reflect the lifesaving care provided by our doctors, nurses and other caregivers and the incredible innovations…"

Furthermore, three significant cases of severe and critical COVID-19 reversed with IV-C combined with other experimental treatment have been included [138] [139] [140].

Dr. Jeff Brown, a Vascular Surgeon, was admitted to hospital in Hanover County, Virginia. He had moderate to severe COVID-19 and hospital, hypoxemia and was on the brink of organ failure. The doctors feared he would suffer from respiratory failure and require mechanical ventilation. He was treated with tocilizumab and IV-C, and already within *"...45 minutes he began to feel a change.*

Within two hours his discomfort had subsided. His fever diminished and his heart rate slowed". In only three days after the treatment was started he went home [138].

Dr. Ryan Padget, 45 and from Seattle, was admitted to hospital and rapidly deteriorated and within hours past admission he was on a ventilator. The New York Times reported that his condition only continued to worsen and *"By March 16, his heart was struggling, his kidneys were failing and his lungs were not providing enough oxygen to his body. The levels became so dire that he was on the verge of injuring his brain through oxygen starvation"*. On the same day he was ECMO intubated went into a medically induced coma, and after seeing signs of a "cytokine storm" they gave him tocilizumab and IV-C [139]. It took nearly 2 weeks before he woke up from the sedated coma. He graduated from the ICU, was discharged from hospital and went home [139].

Paz, 47 and a mother of five, was on the brink of requiring mechanical ventilation while in the ICU at Staten Island University hospital. The doctors gave her IV-C with IV antibiotic coupled with magnesium and potassium, and the disease progression stopped, and she avoided mechanical ventilation. She was in the ICU for 3 days and was discharged from hospital on day 15 [140].

Melatonin has been used by some physicians in high doses with good results [141] [142].
Dr. Richard Neel, an doctor in San Antonio, reported giving melatonin in high doses to 10 patients at his urgent care clinics. All of them have seen positive results and in one case was given 80mg/day of melatonin, and *"...all of them turned around in less than 24 hours"* [141].
And here's a what the Manila Doctors Hospital in Philippines, the world's first hospital *"...to try high-dose melatonin for high-risk COVID-19 patients"*, reported [142]:
"According to reports, several of the patients who were given the hormone already had adult respiratory distress syndrome prior to taking melatonin, but they all survived.
These impressive observational results align with the strong biological rationale for using melatonin in treatment of infectious diseases and COVID-19 [64] [78]. Trials and pragmatic studies exploring the potential and likely benefits of high dose melatonin are warranted.

8. Immunoregulatory and Antiviral Properties of Vitamin D, Zinc, Miscellaneous Micronutrients and Melatonin

This chapter will list important sources for vitamin D and melatonin, and it will include a piece of text on zinc's antiviral properties.
Antiviral and immunoregulatory effects of vitamin A, NAC, magnesium and other compounds won't be discussed here or in any other section of this document. Reference no. 55 talks about magnesium and NAC and can be found under subchapter "6.3. Large Folders (ZIP), Link Collections and Comprehensive Articles on Multifaceted Orthomolecular Treatment of Viral Disease".

Here are six sources on vitamin D3 and COVID-19:

William B. Grant et al., Evidence That Vitamin D Supplementation Could Reduce Risk of Influenza and COVID-19 Infections and Deaths, *Nutrients*, 2020 Apr 2;12(4):E988, doi: 10.3390/nu12040988
Description [143]: This is a detailed review about "Evidence that Vitamin D Supplementation Could Reduce Risk of Influenza and COVID-19 Infections and Deaths". The review *"…reviews the roles of vitamin D in reducing the risk of respiratory tract infections, knowledge about the epidemiology of influenza and COVID-19, and how vitamin D supplementation might be a useful measure to reduce risk"*. In addition it details that vitamin C can likely reduce the length of mechanical ventilation substantially.

Mark Alipio, Vitamin D Supplementation Could Possibly Improve Clinical Outcomes of Patients Infected with Coronavirus-2019 (COVID-2019), *SSRN*, 2020, April 9, doi: 10.2139/ssrn.3571484
Description [144]: This is a retrospective multicenter study that exames 212 laboratory confirmed cases of COVID-19 ", with data pooled from...database of three hospitals in Southern Asian countries". In the abstract Alipio reported:
"Serum 25(OH)D level was lowest in critical cases, but highest in mild cases. Serum 25(OH)D levels were statistically significant among clinical outcomes."
Furthermore Alipio reported that *"...for each standard deviation increase in serum 25(OH)D, the odds of having a mild clinical outcome rather than a severe outcome were approximately 7.94 times (OR=0.126, p<0.001) while interestingly, the odds of having a mild clinical outcome rather than a critical outcome were approximately 19.61 times (OR=0.051, p<0.001). The results suggest that an increase in serum 25(OH)D level in the body could either improve clinical outcomes or mitigate worst (severe to critical) outcomes, while a decrease in serum 25(OH)D level in the body could worsen clinical outcomes of COVID-2019 patients"*.

Covid-19 and Vitamin D Information, Dr Gareth Davies (PhD), Dr Joanna Byers (MBChB), Dr Attila R Garami (MD, PhD), Google Docs.
Description [69]: In-depth article on the rationale of vitamin D for COVID-19. It explains how and why *"...Vitamin D supplements could be effective in preventing Covid-19, and play a key role in treating patients if added to existing treatment plans, especially if this is done early in the disease progression."* - from the document's front page.
- This document is for medical professionals only.

Jaykaran Charan et al., Vitamin D for prevention of respiratory tract infections: A systematic review and meta-analysis, *Journal of Pharmacology & Pharmacotherapeutics*, 2012 Oct-Dec; 3(4): 300–303, doi: 10.4103/0976-500X.103685
Description [75]: Systematic review and meta-analysis on the role of *"Vitamin D for prevention of respiratory tract infections"*. Here are the results from the meta-analysis:
"Events of respiratory tract infections were significantly lower in vitamin D group as compared to control group [Odds ratio = 0.582 (0.417 – 0.812) P = 0.001] according to random model. Results were similar in fixed model. On separate analysis of clinical trials dealing with groups of children and adults, beneficial effect of vitamin D was observed in both, according to fixed model [Odds ratio = 0.579 (0.416 – 0.805), P = 0.001 and Odd ratio = 0.653 (0.472 – 0.9040, P = 0.010 respectively]."

Mihnea Zdrenghea et al., Vitamin D modulation of innate immune responses to respiratory viral infections, *Reviews in Medical Virology*, 2017 Jan;27(1) (Epub 2016 Oct 7), doi: 10.1002/rmv.1909
Description [93]: Comprehensive review about *"Vitamin D modulation of innate immune responses to respiratory viral infections"*. Contains information about vitamin D's immunomodulatory and antiviral activity, its role in acute respiratory infections and the impact of vitamin D deficiency and supplementation in preventing and treating acute respiratory infections (ARIs) and more.

Former CDC Chief. Dr. Tom Frieden: Coronavirus infection risk may be reduced by Vitamin D, Op-ed by Tom Frieden, M.D, Fox News, March 2020.
Description [70]: Op-ed written by former CDC chief Tom Frieden. He explains how and why vitamin D could play an important role in the current COVID-19 pandemic.

And here's a comprehensive piece of research on melatonin as a treatment for COVID-19:

Rui Zhang et al., COVID-19: Melatonin as a potential adjuvant treatment, *Life Sciences*, 2020 June 1; 250: 117583 (Epub 2020 March 23), doi: 10.1016/j.lfs.2020.117583
Description [78]: This is a comprehensive research article that *"...summarizes the likely benefits of melatonin in the attenuation of COVID-19 based on its putative pathogenesis"*.

And now a short word on zinc: Zinc is likely an effective and potent SARS-CoV-2 antiviral. It has been proven in multiple in vitro studies to inhibit viral replication [94] [95] [96] [97]. It's been proven in vitro to inhibit SARS-CoV (2003) [97]. The mechanism of action for zinc in viral infections is similar to remdesivir, because they both inhibit the RNA polymerase enzyme [97].
Zinc on its own won't have the same antiviral effect as when combined with a carrier ionophore. A carrier ionophore catalyzes ion transport across the cell membrane, leading to rapid intracellular ion accumulation and high intracellular concentrations of zinc ions. There are multiple known zinc ionophores, but the ones that get the greatest attention for COVID-19 are the pharmaceutical drugs hydroxychloroquine, chloroquine and the flavonol quercetin [98] [99] [100].

An excellent preprint research hypothesis by Martin Scholz and Roland Derwand from April 8, 2020 titled "Does Zinc Supplementation Enhance the Clinical Efficacy of Chloroquine/Hydroxychloroquine to Win Todays Battle Against COVID-19?" explains this in greater detail [100].

And at last here's two interesting articles about the importance of nutrient supplementation amid the COVID-19 pandemic. They detail the important immunoregulatory and antiviral effects of multiple different nutrients.

Philip C. Calder et al., Optimal Nutritional Status for a Well-Functioning Immune System Is an Important Factor to Protect against Viral Infections, *Nutrients*, 2020, *12*(4), 1181, published 2020, April 23, doi: 10.3390/nu12041181
Description [145]: This is a detailed review by prominent nutrient researchers about the *"...wealth*

of mechanistic and clinical data show that vitamins, including vitamins A, B6, B12, C, D, E, and folate; trace elements, including zinc, iron, selenium, magnesium, and copper; and the omega-3 fatty acids eicosapentaenoic acid and docosahexaenoic acid play important and complementary roles in supporting the immune system". This article is comprehensive and has 83 references, so it's a good introduction to the importance of *"Optimal Nutritional Status for a Well-Functioning Immune System..."*.

Amin Gasmi et al., Individual risk management strategy and potential therapeutic options for the COVID-19 pandemic, *Clinical Immunology*, 2020, Apr 7, doi: 10.1016/j.clim.2020.108409
Description [146]: This excellent and comprehensive (168 references) review by Amin Gasmi and colleagues about *"Individual risk management strategy and potential therapeutic options for the COVID-19 pandemic"*. The researchers conclude in the abstract:
"The careful individual assessment for the possible dietary, nutritional, medical, lifestyle, and environmental risks, together with the proper relevant risk management strategies, is the sensible way to deal with the pandemic of SARS-CoV-II."

9. Alan Smith H1N1 Story and an Enterovirus Case Report

Alan Smith, a New Zealand farmer with severe H1N1 Swine Flu resulting in coma and ECMO intubation, saved by HIDV-C and LEV-C. Watch Part 1 [66] and 2 [67]. Article available too [152].
Description [66] [67]: Alan Smith's H1N1 infection quickly worsened, and ECMO intubation was necessary. After a few weeks his condition was deteriorating, and the hospital doctors felt they had no recourse but to take him off ECMO and let him die.
Smith's family, however, contacted Dr. Thomas E. Levy and pushed for IV-C to be given to him. The hospital doctors reluctantly allowed HDIV-C to be administered. Massive IV-C doses of 25g and 50g (25g in the morning, 25g in the evening) were given, and Smith's "whitened lungs" cleared within days. Following that, the treatment dose was lowered to only a few thousand milligrams. Then treatment stopped and was resumed again at a smaller dose. This caused his condition to quickly worsen. The family decided to intervene by giving large doses of LEV-C, and the patient's condition improved. He made a full recovery and resumed his farmer life. Alan Smith continues to take high-doses of oral vitamin c daily.

Alpha A. Fowler et al., Intravenous vitamin C as adjunctive therapy for enterovirus/rhinovirus induced acute respiratory distress syndrome, *World Journal of Critical Care Medicine*, 2017 Feb 4; 6(1): 85–90 (Epub 2017 February 4), doi: 10.5492/wjccm.v6.i1.85
Description [68]: A case report of severe ARDS caused by enterovirus/rhinovirus and resulting in ECMO intubation. The researchers used their 200mg/kg/day IV-C protocol, and "*ECMO decannulation and extubation from ventilation occurred on ECMO day 7"*. The IV-C dose was gradually lowered on the two days following ECMO day 7: From 200mg/kg/day to 50mg/kg/day. The patient was sent home on hospital day 12. In the abstract the authors concluded:
"The patient's recovery was rapid. ECMO and mechanical ventilation were discontinued by day-7 and the patient recovered with no long-term ARDS sequelae. Infusing high dose intravenous vitamin C into this patient with virus-induced ARDS was associated with rapid resolution of lung injury with no evidence of post-ARDS fibroproliferative sequelae."

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