Operation Thiamine – Reducing the Need for Hospitalization of Patients with COVID-19

By Jeffrey Lubell[1]

Research is needed into the potential of high-dose thiamine to provide respiratory support to COVID-19 patients in the early (out-patient) and intermediate (stable, pre-ICU) stages of the disease. An in vitro study found that, in high doses, thiamine acts as a carbonic anhydrase inhibitor (CAI) with a potency approaching the better known acetazolamide (Diamox). Among other benefits, CAIs increase minute ventilation and blood oxygen levels, which could be helpful as an adjunctive therapy for individuals in the early phase of COVID-19 whose oxygen levels are beginning to drop. If research were to confirm the CAI properties of thiamine and its efficacy in mitigating respiratory distress, thiamine could be distributed to individuals soon after they contract the illness, potentially helping more people cope with COVID-19 on their own. This could reduce the burden on crowded hospitals.

A key first step is to conduct research to confirm whether thiamine has the CAI properties in people predicted by the in vitro study, as well as to test for other key properties. Assuming the CAI properties of thiamine are confirmed, the next step would be to test the protocol for safety and efficacy, with the goal of reducing the share of patients with COVID-19 who need to be hospitalized.

Because thiamine has fewer side effects than acetazolamide, it could be administered in increased doses and with greater frequency, potentially providing increased respiratory support for patients at intermediate stages of the illness, especially in third-world countries and other places where supplemental oxygen is in short supply. The efficacy of higher doses of CAIs for COVID-19 needs to be studied, but this testing could and should be done on an expedited basis, with a goal of reducing the share of hospitalized patients that require the ICU or a ventilator. It remains to be seen if thiamine has the pulmonary vasodilation properties of acetazolamide; if not, it may be desirable to combine acetazolamide and thiamine in the pre-ICU hospital phase of the protocol.

This working paper briefly outlines the evidence for this proposal, along with a proposed testing protocol. The first phase of the protocol -- verifying the CAI properties of thiamine -- could have great benefits for medicine, even if thiamine doesn't end up having the hypothesized benefits for COVID-19. If thiamine were confirmed to be an effective CAI, it could potentially be substituted for acetazolamide in a range of uses, such as glaucoma, Idiopathic Intracranial Hypertension and preventing high-altitude sickness, reducing harmful side effects for thousands of patients each year.

The hypotheses explored in this working paper all focus on the pre-ICU phase of the illness. The treatment of the more critically ill COVID-19 patients in the ICU is beyond the scope of this paper.

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[1] These ideas grow out of research I have been doing into a rare disease that affects my daughter. I am not a doctor or a medical professional. If you are interested in discussing these ideas further, please contact me at jefflubell@gmail.com or on Twitter at @JeffLubell_C19 .

1. In high doses, thiamine is likely a carbonic anhydrase inhibitor

Ozdemir et al. (2013) evaluated the relative efficacy in vitro of thiamine and several other compounds, including acetazolamide, in inhibiting three of the 16 (or more) carbonic anhydrase isoenzymes. They found that thiamine had effects similar to (though not quite as strong as) acetazolamide against all three of the isoenzymes studied.[2] Smithline et al. (2012) evaluated the bioavailability of oral thiamine HCL (one of the two more common oral thiamines available) and found that it is well absorbed. As they write, "oral thiamine hydrochloride when given over a 1-week period produce[s] blood levels that approach those obtained by intramuscular and intravenous administration" (ibid.)

Commenting on the results of Ozdemir et al. (2013) and Smithline et al. (2012), one Internet forum commentator noted the following: (I would appreciate confirmation that this interpretation is accurate.)

> The highest concentration of thiamine is required to inhibit hCA I and it is 380nM/L. This figure from a human study on the pharmacokinetics of thiamine shows that this concentration is achievable using a 1,500mg dose. The concentration[s] required to inhibit the other isoenzymes of hCA were 85nM and 62nM, which are easily achieved with a thiamine dosage of 300mg - 500mg.[3]

Since oral thiamine HCL has a half-life of about 3-5 hours (Smithline et al. 2012) and cerebral spinal fluid regenerates every 6-8 hours, thiamine would likely need to be administered 3-5 times per day to be of maximum effectiveness.

For more than ten years, Antonio Costantini and his colleagues in Italy have used high-dose thiamine to treat a range of neurological conditions. While they seem unaware of its CAI properties, the dosages they use (for most conditions, 600 to 1,800 mg of thiamine daily, rising to 4,000 mg of thiamine daily for Parkinson's Disease, in divided doses) are precisely those needed to reduce cerebral spinal fluid (CSF) flow in light of the findings of Ozdemir et al. (2013) and Smithline et al. (2012). I believe carbonic anhydrase inhibition provides a plausible explanation for the outcomes Costantini and his colleagues have observed, potentially in synergy with other pathways. Potential mechanisms for the effects observed by Costantini and his colleagues include reductions in intracranial hypertensions and ventral brainstem compression, increases in oxygen to the brain and inhibition of lactic acid through CO2 production. I've provided citations to many of the articles by Costantini et al. in the sources list.

Thiamine is included in the May 14, 2020 version of Paul Marik's EVMS COVID-19 protocol (Marik 2020) based on his earlier experience with a combination of vitamin C, thiamine, and hydrocortisone for sepsis (Marik et al. 2017). A more recent study of patients with septic shock found that a combination of thiamine, vitamin c and hydrocortisone reduced by more than half the length of time patients spent in the ICU compared with hydrocortisone alone (Mitchell et al. 2019).[4] Another randomized study found no

[2] In the text of the paper, the authors state that thiamine is more effective than acetazolamide in inhibiting the hCA I isoenzyme, butII read the table as showing that thiamine is somewhat less effective.

[3] https://raypeatforum.com/community/threads/thiamine-is-a-carbonic-anhydrase-inhibitor-as-effective-as-acetazolamide.6833/

[4] Reporting of the study has focused on the fact that there was no difference in mortality rates between the two groups, but the study had a very small sample (only 38 patients each in the control and treatment groups) making it difficult to detect statistically significant differences. Better outcomes were reported for the treatment group

difference from combined protocol (Fujii et. al. 2020), but ICU clinicians had discretion to give thiamine to control group patients, complicating interpretation of the results.

2. If its CAI properties are confirmed, thiamine could potentially help more patients to cope with COVID-19 at home by inducing respiration and increasing oxygen

As documented in Berthelsen and Dich-Nielsen (1987), the CAI acetazolamide increases blood oxygen content through the inhibition of carbonic anhydrase isoenyzmes. CAIs like acetazolomide appear to increase blood oxygen levels in a number of different ways, including through increases in minute ventilation and decreases in sleep periodic breathing. (Leaf and Goldfarb 2006). There is some evidence that the increased ventilation comes through increases in tidal volume, rather than respiratory frequency (ibid.). By raising oxygen levels, a CAI could potentially help patients with declining oxygen saturation levels to cope with COVID-19 on their own, without going to the hospital, or provide a useful adjunctive therapy to help newly hospitalized patients avoid the ICU and ventilators.

In addition to helping individuals take in more oxygen while their bodies fight off the infection, higher oxygen levels could potentially stave off organ damage that contributes to patients becoming critically ill. Low levels of oxygen in the blood (hypoxemia) can lead to low levels of oxygen in bodily tissues (hypoxia), which can damage organs such as the brain, kidneys, and lungs. For example, Frohlich, Boylan, and McLoughlin (2013) document the role that hypoxia plays in contributing to acute lung damage. Among other effects, low levels of oxygen in body tissue produce microvascular inflammation, mediated by mast cells (Steiner, Gonzalez, and Wood (2003).

CAIs do not induce hyperventilation. To the contrary, by producing carbon dioxide they counter the effects of hyperventilation, which causes respiratory alkalosis that inhibits respiration (Leaf and Goldfarb 2006). The carbon dioxide produced by CAIs can also help protect tissues and organs from the effects of hypoxia:

> Numerous other mechanisms potentially exist whereby CO2 protects the tissues from hypoxic-ischemic damage. An increase in blood pCO2 shifts the oxygen hemoglobin dissociation curve to the right (Bohr effect), the result of which is a decrease in the affinity of hemoglobin for oxygen. Therefore, at the capillary level, CO2 would tend to raise pO2, increase the gradient for any given oxyhemoglobin saturation, and facilitate transfer of O2 to the tissue for oxidative processes. CO2 might also preserve cardiac function during systemic hypoxia. The inhibition of systemic lactate production by CO2 inhalation during hypoxia would serve to maintain optimal cardiovascular function. (Vesela and Wilhelm 2002).[5]

While CAIs are seldom used today as stand-alone diuretics given the emergence of other diuretic drugs, they do have a diuretic effect (Imiela and Budaj 2017) that could be of potential additional value in reducing pulmonary and other edemas. Finally, there could also be independent benefits from thiamine administration given its importance in strengthening the body's ability to fight illness (Lonsdale and Mars, 2017) and the tendency of severely ill patients to have or develop thiamine deficiency (*ibid*. and Donnino et al. 2010).

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than the control group for each outcome studied, but they were not large enough to be statistically significant given the small sample.

[5] See Peat (2006) for a discussion of the beneficial biological effects of carbon dioxide.

If thiamine were proven to inhibit carbonic anhydrase isoenzymes as well in people as predicted in vitro, and to be effective in mitigating the respiratory distress experienced by some COVID-19 patients, my suggestion would be to have patients start at home with a starting dose of a thiamine before the disease reaches its more dangerous phase, and then gradually increase the dose based on certain defined markers of disease progression. By helping them maintain a high oxygen level, this would hopefully help them cope at home, but if necessary, they could be transferred to a hospital, where the lower side effects of thiamine might allow higher and more frequent dosages, with a goal of helping stable hospitalized patients to recover without needing to go into the ICU or be intubated. Acetazolamide likely works through several different mechanisms (Leaf and Goldfarb 2007). If thiamine proves to be a CAI but not to produce pulmonary vasodilation like acetazolamide, it might be useful to combine the two during the pre-ICU hospital portion of the protocol. No hypothesis is offered here about the relevance of thiamine to the care of critically ill patients in the ICU..

Given the anti-viral properties of Vitamin C (Biancatelli 2020), another safe and well-tolerated supplement, consideration should be given to including Vitamin C at all phases of the protocol. Another, broader, approach would be to start with a moderate dose of thiamine and the mast cell stabilizers quercetin, Vitamin C and aspirin upon first sign of COVID-19, followed by high-dose thiamine after a certain number of days or upon evidence of declining oxygen levels, supplemented by proning as needed.[6]

The ideas described in this working paper need to be tested. In the Appendix, I describe a proposed accelerated protocol for testing this approach. Preliminary results could be available within about a week to provide an early indication of its potential; full results would take several additional weeks.

While acetazolamide is the best known CAI, and could be used if thiamine's CAI properties are not confirmed, I believe thiamine may be a better option for the early phases of the disease due to the much lower incidence of side effects. If a CAI is to help newly diagnosed patients avoid hospitalization, we will need a high rate of compliance. With almost no side effects, thiamine could have a better compliance rate than acetazolamide.

3. Acetazolamide has been proposed as an adjunctive treatment for COVID-19 due to similarities between COVID-19 and high-altitude pulmonary edema (HAPE); there are differences of opinion, however, on how similar the two illnesses are

In recent weeks, frontline physicians have begun noting similarities between COVID-19 and high-altitude sickness and high-altitude pulmonary edema (HAPE). For example, Dr. Cameron Kyle-Sidell, an ER doctor in New York, describes COVID-19 as "some kind of viral-induced disease most resembling high-altitude sickness. It is as if tens of thousands of my fellow New Yorkers are in a plane at 30,000 feet and the cabin pressure is slowly being let out."

Solaimanzadeh (2020) documents the close resemblance of COVID-19 to high-altitude pulmonary edema (HAPE). As he explains: "Both COVID-19 and HAPE exhibit a decreased ratio of arterial oxygen partial pressure to fractional inspired oxygen with concomitant hypoxia and tachypnea. There also appears to be a tendency for low carbon dioxide levels in both as well. Radiologic findings of ground glass opacities are present in up to 86% of patients with COVID-19 in addition to patchy infiltrates. Patients with HAPE

[6] These multi-part treatment approaches would obviously complicate interpretation of the results of any trial, but given the crisis we are in, it may be better to test an easily distributed combined protocol first and worry later about how much each agent contributed to the results.

also exhibit patchy infiltrates throughout the pulmonary fields, often in an asymmetric pattern and CT findings reveal increased lung markings and ground glass-like changes as well. Widespread ground-glass opacities are most commonly a manifestation of hydrostatic pulmonary edema. Similarly, elevated fibrinogen levels in both conditions are likely an epiphenomenon of edema formation rather than coagulation activation. Autopsy results of a COVID-19 fatality revealed bilateral diffuse alveolar damage associated with pulmonary edema, pro-inflammatory concentrates, and indications of early-phase acute respiratory distress syndrome (ARDS). HAPE itself is initially caused by an increase in pulmonary capillary pressure and induces altered alveolar-capillary permeability via high pulmonary artery hydrostatic pressures that lead to a protein-rich and mildly hemorrhagic edema. It appears that COVID-19 and HAPE both discretely converge on ARDS."

As a note published by the Cochrane collaborative confirms (Vincent 2017), the CAI acetazolamide is effective in helping to prevent high-altitude sickness. Acetazolamide is also used for the treatment for HAPE. As Solaimanzadeh (2020) explains: "Acetazolamide has a myriad of effects on different organ systems. It potently reduces hypoxic pulmonary vasoconstriction. Improved minute ventilation and expired vital capacity has been shown in climbers taking Acetazolamide as well. Furthermore, over 70% of patients with COVID-19 had elevated lactate dehydrogenase levels; this too may be connected to hypoxia. Evidently, Acetazolamide has physiologic effects that delay plasma lactate appearance with no effect on ventilatory threshold."

Other experts have argued that there are important differences between HAPE and COVID-19 that make it inappropriate to apply HAPE treatments to COVID-19. For example, Luks, AM, Freer, L, Grissom, C.K., et al. (2020) take issue with Solaimanzadeh (2020)'s analogy to HAPE and argue that the HAPE treatments nifedipine and sildenafil are inappropriate for COVID-19. They do not address the applicability of acetazolamide, however, which was the primary adjunctive treatment recommended by Solaimanzadeh. In a separate article, two of the seven authors of this paper argue that acetazolamide is inappropriate for COVID-19 patients due to concerns with metabolic acidosis as well as an inability of patients with severely compromised lungs to respond to the respiratory stimulus provided by acetazolamide (Luks and Swenson 2020).

The debate about how best to treat the illness once patients become critically ill is extremely important, but beyond the scope of this paper. The proposed treatment protocol focuses solely on adjunctive therapy to help patients cope with the disease at the early (out-patient) and middle (stable, pre-ICU) stages of the disorder, reducing the need for hospitalization and admission to the ICU. In this respect, the suggestion advanced in this paper is similar to the proposal made by Khodarahmi and Sobhani (2020) to test acetazolamide as an adjunctive therapy for COVID-19 for the relief of respiratory distress in stable out-patients or in-patients. In their paper, they distinguish between the use of acetazolamide in stable versus critically ill patients:

> COVID-19 critically ill patients with severe ARDS may be unable to increase ventilation in response to a respiratory stimulant. The use of acetazolamide in such patients may expose them to all its adverse effects with no proper respiratory compensation. But low doses of acetazolamide (< 200 mg or 2.5 mg/kg) appear to be sufficient for complete renal CA inhibition to stimulate ventilation in stable patients. . . it is anticipated that acetazolamide administration for stable outpatients (and hospitalized COVID-19 patients as well) [could] lead to "respiratory distress relief" with no additional serious acid-base complications.

4. Higher and more frequent doses of CAIs should be tested

Drawing on the literature for high-altitude pulmonary edema, Solaimanzadeh (2020) suggests administering 250 mg of acetazolamide every 12 hours. Khodarahmi and Sobhani (2020) similarly recommend a low dose of less than 200 mg. Such doses may well be sufficient. But it may also be useful to test somewhat higher or more frequent dosages of CAIs to see if they would be even more effective against COVID-19 in the pre-ICU phases of the illness by further increasing oxygen levels. This hypothesis of course needs to be tested.

A recent randomized trial found that 500 mg of acetazolamide (or 1,000 mg when loop diuretics were co-administered) twice daily led to a 10% reduction in invasive mechanical ventilation of COPD patients, which was clinically substantial but not large enough to be statistically significant given the sample size (Faisy et. al. 2016). As the authors observe, in addition a larger sample, they may also have needed larger doses. More frequent administration could potentially also increase the effects.

Side effects are a potential problem with increasing the dosage of acetazolamide. Because thiamine has few side effects, it could facilitate larger and more frequent doses if they proved more efficacious than smaller dosages in outpatients and stable pre-ICU hospitalized patients.

Conclusion

In conclusion, research is needed into the potential of high-dose thiamine to help newly diagnosed patients cope with COVID-19 at home, reducing the demands on over-burdened hospitals. Research is also needed into whether higher and more frequent doses of CAI like thiamine or acetazolamide could help keep more newly hospitalized patients out of the ICU and off of ventilators. The first step in studying this hypothesis -- verifying the CAI properties of thiamine -- would take only a few days and could have great benefits for medicine, even if thiamine doesn't end up having the hypothesized benefits for COVID-19. If thiamine were confirmed to be an effective CAI, it could potentially be substituted for acetazolamide in a range of uses, such as glaucoma, Idiopathic Intracranial Hypertension and preventing high-altitude sickness, reducing harmful side effects for thousands of patients each year.

A proposed testing protocol is included in the Appendix.

Appendix: Proposed Testing Regime for Project Thiamine

The following is a proposed accelerated testing regime designed to determine whether it would be safe and efficacious to distribute thiamine to the public as a way to help more people recover at home, reducing the burden on the hospital system. The protocol would also test whether higher and more frequent doses of thiamine could reduce the share of hospitalized patients that need the ICU or a ventilator.

Step One: Assess whether IV thiamine is a carbonic anhydrase inhibitor

Test the extent to which thiamine functions in vivo as a carbonic anhydrase inhibitor, as predicted by the in vitro study of Ozdemir et al. (2013)

Methods: Three groups: (a) thiamine; (b) acetazolamide; and (c) controls. Measure the impacts of IV administration on key outcomes of interest, including: (1) respiratory outcomes and pulmonary vasodilation; (2) blood flow to the brain; (3) reduction in cerebral spinal fluid (CSF); and (4) metabolic acidosis.

My a priori guess is that you need about 20% more thiamine than acetazolamide to achieve the same basic CAI effects, but this should be ascertainable within a day or so. It is unclear whether thiamine will have the same pulmonary vasodilation effects as acetazolamide as it is hypothesized that those effects may have a different pathway.

While you should be able to move on to Step Two within a day, it would be useful to continue this experiment, to include a washout period and then crossover, to get more precise estimates of the relative CAI and other effects of the two agents.

Step Two: Measure CAI properties of oral thiamine

In the home setting, patients will be getting pills rather than IVs, so the effects of either agent will depend partly on absorption rates. It would therefore be useful to repeat the above experiment with pills to see what doses are needed to achieve the desired effects and what the timing of those doses need to be. Experience with oral thiamine HCL suggests a delay of a day or two in patient recognition of the effects of reduced CSF flow from introduction of the agent and changes in dose, but I would expect to see the respiratory and blood flow effects happening much sooner. I'd suggest separately trialing three forms of thiamine: thiamine HCL, thiamine mononitrate, and benfotiamine.

If desired, Steps One and Two could proceed simultaneously, with separate groups. You could skip Step One altogether and go straight to Step Two, losing only about a day. But there are independent benefits to understanding the effects of intravenous thiamine for a hospital setting, so I recommend both Steps One and Two.

If one or more of the oral thiamine agents proves effective as a CAI agent, this could potentially be a better choice than acetazolamide for home use by newly diagnosed COVID-19 patients given the reduced side effects. Since I don't know much about the absorption rates of acetazolamide, I don't have a prediction about how much oral thiamine you would need to have a similar effect as acetazolamide. However, I would expect that oral thiamine would be effective as a CAI agent and that a cost-effective therapeutic dosage could be established. It is unclear whether thiamine will have similar, better or worse effects on pulmonary vasodilation. If thiamine does not have the pulmonary vasodilation effects

of acetazolamide, it might be useful to combine the two at later stages of the home protocol and in the hospital protocol.

As with the IV experiment, it would be desirable to continue this experiment even after you've moved onto Step Three, adding a washout period and then crossover.

Step Three: Safety Testing

Thiamine is an over-the-counter supplement, so hopefully the safety testing could be done quickly. One approach to safety testing would be to have healthy volunteers start the proposed protocol and be a day or two ahead of a group of people who are newly diagnosed with COVID-19, and then a day or two ahead of patients newly admitted to the hospital, who all follow the same protocol. The advantage of this method is that you could stop the experiment at any time if problems are uncovered in the healthy volunteers, but the newly diagnosed group is only a day or two behind them, and the newly hospitalized group is only a day or two behind them, so you also get to see whether there are any complications in a COVID-19 population.

There appear to be few side effects associated with oral thiamine, even at high doses. Antonio Costantini's team in Italy has the most experience with high-dose thiamine, and he claims to have seen almost no side effects other than transient insomnia. He addresses the insomnia by giving the last dose at 5 p.m. I have found increased water intake to be helpful in addressing this problem in my daughter who takes 1,800 mg of thiamine daily for neurological issues in 3 divided doses; I hypothesize the insomnia is related to dehydration induced by the CAI process.

Costantini reports one episode of arrhythmia, which was addressed by lowering the dose. I've seen one case report each of allergic reactions to IV and oral thiamine, but neither seem common, at least based on my initial research (a more complete scan is warranted). Costantini reports a somewhat higher rate of allergies when thiamine is administered intramuscularly (4 in more than 2,500 cases), but presumably that will not be undertaken here.

As with any CAI agents, hypokalemia and kidney stones are issues to watch for, along with decreased efficacy of the CAI process when blood CO2 levels dip too low. I doubt these issues will be a problem in the duration of the experience here, but wanted to flag them.

Step Four: Testing Different Dosages

It is unclear what dosage of thiamine is best suited to combatting COVID-19. It would be useful to test the effects of different dosages. One potential group for testing would be patients who come to the hospital for COVID-19 treatment but do not yet have a severe enough case to warrant admission to the hospital. These are precisely the patients who we are trying to help overcome the illness on their own, reducing the rate of hospitalization. The idea would be to reduce the share of such patients who need to be admitted to the hospital or, if admitted to the hospital, who need to be moved to the ICU or placed on a ventilator. These patients could either be sent home with thiamine or kept in the hospital for observation and treated with thiamine, with certain pre-determined markers identified for assessing progress.

A second potential group would be people newly admitted to the hospital whose conditions have not yet progressed to the point where they are considered severe.

These tests could help provide evidence to inform the finalization of the protocol.

Step Five: Community Testing

This would need to be fleshed out more, but the basic idea for community-wide distribution of thiamine would be to distribute it either to individuals who come in for testing for COVID-19 or to all households in a selected community where the disease is prevalent. It would likely be preferable to test the protocol first in a smaller setting. For example, the protocol could be tested in one or more community settings (an apartment building, or a particular doctor's office) and then outcomes could be compared to those of similar settings in the same or similar communities – essentially a quasi-experimental design. Outcomes would be measured through a difference-in-difference design, with primary outcomes including: (a) calls to 911, (b) hospitalizations, (c) admissions to ICU, and (d) share requiring a ventilator. It might also be useful to measure other secondary metrics of those admitted to the hospital, such as various measures of respiratory effectiveness and inflammation.

Draft Treatment Protocol

Much more work is needed to refine this proposed treatment protocol, but I've noted some ideas below as an initial strawperson for consideration. The protocol assumes, for the time being, that the respiratory and other benefits of thiamine for COVID-19 patients increase with dosage and frequency, but those points still need to be confirmed through the earlier testing stages. The protocol should be modified if testing does not confirm greater benefit from higher dosages or if problems are observed associated with reduced CSF flow.

Given the anti-viral properties of Vitamin C (Biancatelli 2020), another safe agent suitable for community dissemination, it might be useful to combine thiamine with Vitamin C at all stages of the protocol. Another, broader, approach would be to start with a moderate dose of thiamine and the mast cell stabilizers quercetin, Vitamin C, and aspirin upon first sign of COVID-19, followed by high-dose thiamine after a certain number of days or upon evidence of declining oxygen levels, supplemented by proning as needed.

This protocol is obviously not suited to patients for whom CAIs are contraindicated, such as those with pre-existing intracranial hypotension or kidney disease.

At Home

1. As soon as the patient is diagnosed, 150 mg of thiamine HCL twice daily to strengthen the body's defenses against illness.

2. After a set period of time, such as five days after onset of symptoms (or when oxygen levels begin declining), start taking 300 mg of thiamine HCL twice a day (morning and at 5 p.m.)

3. After a second trigger point to be determined (such as further declines in oxygen or trouble breathing), increase to 300 mg of thiamine HCL three or four times per day.

If and when patient needs hospitalization, transfer to hospital.

Hospital (pre-ICU)

4. Once the patient is admitted to the hospital, switch to 500 mg of thiamine HCL three times a day (for a total of 1,500 mg / day)

5. If the patient worsens (criteria to be determined), increase to 500 mg of thiamine HCL four times a day (for a total of 2,000 mg / day)

NOTE: The protocol does not extend to care in the ICU.

This draft protocol is based on the following:

- The starting dose is grounded in the ideas of Derrick Londale and Chandler Mars about the important role that thiamine plays in strengthening the body's ability to fight illness (Lonsdale and Mars 2017). It will also help ensure that patients are not deficient in thiamine, a not uncommon problem in cases of severe illness, particularly in the elderly.

- The remaining home doses are based on the amount needed to inhibit one of the three carbonic anhydrase isoenzymes tested by Ozdemir et al. (2013).

- The proposed hospital doses should inhibit two of the three carbonic anhydrase isoenzymes tested by Ozdemir et al. (2013).

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