# Covid-19: Debunking the Hemoglobin Story

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In recent days, I've had a number of people ask me for my thoughts on a now-deleted Medium blog post entitled "Covid-19 had us all fooled, but now we might have finally found its secret." It seems that, even following its deletion, this post has become widely shared in an archived form, largely by people who seem to entirely accept its premise. That premise, to be very brief, is essentially that the SARS-CoV-2 virus harms patients entirely through its interactions with the oxygen transport protein hemoglobin (Hb). A Google search for the title will still turn up the post, should you wish to read (or re-read) it.

A bit about me, and why people have sent me this blog post: in December 2019, I completed my MD degree at the University of Pittsburgh through the Medical Scientist Training Program (MD/PhD program). As part of that same program, I spent 4 years completing a PhD in Bioengineering; the focus of my dissertation was the molecular biology, biochemistry, and physiology of mammalian heme globins. As a result, I've spent the last 7+ years at the intersection of clinical medicine and heme globin research and felt compelled to offer my perspective on this blog post. I've been assisted in writing this piece by Drs. Anthony DeMartino, PhD and Matt Dent, PhD, both postdoctoral scholars in the lab where I completed my PhD and both ten times better chemists than I could ever hope to be.

But back to the post: the Medium blog post in question simultaneously puts forth two related narratives, one "scientific" (or at least presented to give that appearance) and one clinical. Both are told with an overriding tone of authority and certainty;

unfortunately, both are also almost entirely incorrect in their overall conclusions and the specific details used to support those conclusions. As is so often the case, refuting this sort of misinformation requires a good deal more effort (and words) than propagating it, but we have done our best to address everything.

**The Purportedly "Scientific" Narrative**

Before getting into the details, I want to take a brief aside to describe hemoglobin. A single hemoglobin protein consists of two parts: heme (which itself is made up of a small chemical ring called a porphyrin + an iron atom in the center), and the globin, a large protein that holds the heme. The hemoglobin molecule in our red blood cells is actually comprised of four hemes and their four respective proteins (two alpha proteins and two beta) that are linked together to form a tetramer. In each of these chains, the heme is surrounded by its respective protein, which forms a small space referred to as the "heme pocket" around the heme. This pocket is just large enough to accommodate oxygen, carbon monoxide, and other small molecules that bind to the heme iron.

The blog post's "scientific" narrative begins with the SARS-CoV-2 virus entering red blood cells (RBCs). Once inside the RBCs, the post states that the virus rapidly removes the iron from RBC hemoglobin molecules, leading to 1) depletion of functional hemoglobin (with the virus bound to its porphyrin ring) and 2) accumulation of toxic iron in the bloodstream. All of the clinical manifestations of Covid-19 are subsequently attributed to this process, despite the fact that there's effectively no evidence to support such a mechanism of viral entry into RBCs and interaction with hemoglobin. Alarmingly, the blog post relies on a series of assumptions that have little to no support within the current scientific literature.

First, it is unclear that the virus enters red blood cells at all. Reviewing the currently published literature, I am unable to find any evidence for significant SARS-CoV-2 entry into red blood cells. While it is possible that interactions between the virus and RBCs may have been overlooked (the majority of research has understandably focused on lung disease), there is currently no evidence to suggest that red blood cells are a significant site of virus localization or replication. If the hypothesis is that most of this virus's toxic effect arises from interactions with Hb, documenting viral entry into RBCs would be an important first step.

That said, we do have some idea of where this virus is going. For example, one study examined lung tissue samples from a patient who died of Covid-19 and found results consistent with diffuse alveolar damage (damage to the small air sacs in the lungs where gas exchange occurs) [1]. The same study found that the virus itself localized primarily to the epithelial cells lining those same alveoli. While RBCs appear to have been washed out before the tissue samples were examined (leaving empty blood vessels), the blood vessels themselves, as well as the tissue between the air sacs, showed little to no virus. Overall, the study suggests that the virus, and the resultant damage, are found primarily in the lung alveoli.

The blog post author presumes that the virus does enter RBCs, and that viral "glycoproteins bond to the heme, and in doing so that special and toxic oxidative iron ion is 'disassociated' (released)." This spurious claim, for which the blog post author provides no evidence, seems to derive from a misinterpretation of a recent preprint of a paper in ChemRxiv. This pre-print manuscript proposes a possible mechanism for the virus to "attack" (a term they never define) hemoglobin and release the heme from the protein [2]. While the blog post author does not cite this work (or any other work, for that matter), the conclusions and language are similar enough that it seems very likely the scientific paper inspired the blog post.

On a close reading, the ChemRxiv paper is itself seriously flawed, and provides nothing that I or my colleagues consider meaningful evidence of a mechanism by which SARS-CoV-2 could "attack" hemoglobin. I do plan to work on a second piece further discussing the problems with this paper, but for now, here is a summary of that work: the authors claim to provide evidence that certain viral proteins can bind to isolated porphyrin (without the iron and not bound to any protein). They also argue that the virus may somehow force the heme out of the protein, and subsequently the iron out of the heme, to allow this sort of binding. This is all based on rather rudimentary analysis, relying solely on protein sequence similarity and questionable modeling of molecular docking. Notably, the work was entirely performed *in silico* (via computer models), which is usually an initial screening step that has to be verified with *in vitro* (experimental, *e.g.*, in a test tube or petri dish) data. The authors themselves state in their abstract that "[t]his paper is only for academic discussion, the correctness needs to be confirmed by other laboratories". Aside from this introductory disclaimer, the authors do a poor job of qualifying their results and emphasizing the highly preliminary nature of their work. It is

easy to see how a reader without a healthy dose of scientific skepticism could overinterpret the results given the strong language used throughout the manuscript.

Nevertheless, the Medium blog post seems to take this questionable work as hard truth and proceeds to extend the conclusion several steps further, claiming that the virus will go right into the heme pocket and replace the intact heme iron, all while the porphyrin remains bound to the protein. Beyond the questionable evidence for virus binding the porphyrin at all, the issue here is that the heme/porphyrin is still in the heme pocket, a space barely large enough for two-atom molecules like oxygen (O2). Despite that, the blog post author seems to believe the virus (which is larger than the entire hemoglobin protein) will be able to enter the pocket, kick out the iron, and bind the porphyrin while leaving the porphyrin and protein otherwise totally intact. To put it charitably, this would be an entirely novel and seemingly impossible sort of chemistry, and there is absolutely no scientific evidence that supports such a possibility. It's this seemingly impossible interaction that forms the foundation of the blog post's entire argument, and so the remainder of the conclusions drawn by the blogger simply don't carry any weight.

**The clinical story**

From here, using this faulty scientific narrative as a basis, the author creates an equally faulty narrative of the clinical progression of the disease. The failure of the scientific narrative largely invalidates the subsequent clinical narrative, which is almost entirely based on that faulty science. Thus, rather than pick apart the entire clinical model, I'm going to highlight some key points that I want to refute specifically. First, while this narrative is a bit more difficult to follow, I will attempt to summarize it herein.

***The blog post suggests (paraphrasing here outside of direct quotes):*** *As the patient's Hb loses iron, that patient will desaturate (lose oxygen from their hemoglobin). This desaturation has nothing to do with lung dysfunction as "there is no 'pneumonia' nor ARDS" and "the patient's lungs aren't 'tiring out', they're pumping just fine. The red blood cells just can't carry [oxygen], end of story". The free iron that has been released overwhelms the lung's defense mechanisms against this toxic free iron, leading to bilateral lung damage, which is held to be significant by the author because "Pneumonia rarely ever does that [causes damage in both lungs], but COVID-19 does… EVERY. SINGLE. TIME."*

Again, this probably sounds like a compelling, reasonable series of events to a lay person. In reality, it is essentially nonsense built upon a deeply flawed understanding of physiology and pathophysiology. Some key points, and my responses:

***Blog post says:*** *Patients desaturate as their hemoglobin loses iron*

**Reality:** Even if the virus were to eject the iron from hemoglobin (which it almost certainly does not), it would not likely result in a measurable desaturation. Saturation is most commonly measured via pulse oximetry (pulseox), which uses light to differentiate Hb with oxygen from Hb without oxygen. Both these forms of Hb, however, have the iron present, and most clinical pulse oximeters only work when these two forms — and **only** these two forms — of Hb are present [3]. A novel form of Hb with the virus in place of the iron would absorb light very differently from either of these forms, and such a protein (if it could exist) would almost certainly result in incomprehensible pulseox readings, not a desaturation.

Even ignoring these technical aspects, a far more likely explanation for a measured desaturation in Covid-19 patients would be inadequate oxygenation of the blood due to lung disease/damage (which we know is present). Indeed, we know that Covid-19 patients who are oxygenating poorly respond to supplemental oxygen, as the author seems to acknowledge when suggesting oxygen as a therapy. Improvement with more oxygen effectively rules out iron loss as a cause of this desaturation, as providing more oxygen will increase oxygen binding to normal Hb with intact iron but could not put iron back into Hb that had lost it.

***Blog post says:*** *Release of iron from Hb is the source of all observed pathology in Covid-19, including bilateral lung damage, which pneumonia "rarely ever" causes.*

**Reality:** There's simply no evidence that SARS-CoV-2 infection leads to the large-scale release of iron from Hb, or that such release would be sufficient to overwhelm the body's numerous mechanisms for regulation of free iron. Even if it did, however, I'm unable to find evidence that pure iron overload (in the absence of other pathologies) leads to significant lung damage, much less the bilateral pneumonia-like pattern seen in many Covid-19 patients [4]. In contrast, bilateral lung damage is actually a fairly common manifestation of pneumonia caused by viral infections [5].

***Blog post says:*** *"There is no 'pneumonia' nor ARDS. At least not the ARDS with established treatment protocols and procedures we're familiar with."*

**Reality:** Both are clearly present. The clinical picture, despite what the author might think, is generally consistent with viral pneumonia, and progression to ARDS has been well-documented. One study in China found that, out of 201 patients with confirmed Covid-19, roughly 42% developed a clinical picture consistent with ARDS [6]. The mortality rate among these patients was over 52%, while there were no deaths among those that did not develop ARDS. The blog post may be somewhat correct about the resultant ARDS being atypical. There is a letter out of Northern Italy suggesting that ARDS arising from Covid-19 may not require or could even be harmed by high-pressure mechanical ventilation [7], but this same letter suggests that intubation and mechanical ventilation without high pressures should be *prioritized* for patients who are struggling to breathe, not *avoided* as suggested in the blog post.

### Suggested treatments

Finally, and perhaps most troublingly, the author of the blog post, who has no medical background, suggests a number of therapies for their imagined mechanism of this disease.

### Treatment 1: "Max oxygen", or hyperbaric chamber with 100% O2 at multiple atmospheres of pressure

It's unclear what the author thinks this would achieve. If their model of virus-induced hemoglobin dysfunction via iron loss is true (it isn't, but **if** it was), the affected Hb absolutely CANNOT bind oxygen. Providing more oxygen, via a ventilator or a hyperbaric chamber, would not magically put the iron back in Hb. To take a generous interpretation, the author may be suggesting that free iron eventually causes lung damage, which subsequently prevents oxygen from getting into the blood, even though our current understanding is that this damage is in fact caused by the virus and our immune response. Regardless of the source of lung damage, however, intubation and mechanical ventilation remains the standard of care in critically ill patients with hypoxic respiratory failure, as even the report of atypical ARDS from Italy suggests [7].

EDIT, 04/13/2020: A reader, Dr. Merveldt-Guevara, brought to my attention that hyperbaric oxygen therapy (HBOT) likely would benefit patients with iron loss from Hb by allowing more oxygen to be dissolved directly in the blood without binding to hemoglobin. She is absolutely correct about this, and I want to thank her for setting me straight. While there remains no compelling reason to suspect such iron loss, HBOT is well-documented to increase the amount of oxygen that reaches the blood, and thus may have therapeutic potential for these patients even if their Hb remains entirely normal. I have reached out to some far more qualified colleagues for their opinions on this, and will update if I hear back.

**Treatment 2: Blood transfusion with "normal hemoglobin"**

The blog post is correct that a transfusion of donor red blood cells (or whole blood) would temporarily increase the oxygen carrying capacity of the blood. However, beyond the blog post's unfounded assertions, I can find no case reports or any other data suggesting that profound anemia or loss of oxygen carrying capacity exacerbates the effects of Covid-19 in patients, and so there's no reason to believe a transfusion of RBCs would result in clinical improvement.

Even if the author were correct, a red blood cell transfusion would likely do more harm than good after a brief initial improvement. For example, we know that some degree of hemolysis (RBC destruction) occurs during storage of blood and after transfusion, eventually leading to release of toxic byproducts such as free heme. Furthermore, if the core premise of the blog post is accepted, the transfused RBCs would also have their Hb attacked by the virus, negating any increase in oxygen carrying capacity and worsening the accumulation of iron in the blood. A transfusion, if we accept the author's argument about hemoglobin and iron, amounts to throwing logs onto a raging fire, claiming you're putting the fire out because those logs haven't burned up yet, and then watching the fire grow bigger as it consumes those logs as well.

Just to clarify, there is some evidence in favor of a plasma transfusion from recovered Covid-19 patients, as the antibodies contained therein can augment the recipient's immune function.The blog post, however, seems very dismissive of this therapy, suggesting it would be ineffective without a simultaneous transfusion of red blood cells despite the lack of any evidence to support this claim.

### Treatment 3: Hydroxychloroquine

The author of the blog post also recommends early treatment with hydroxychloroquine (HCQ), which in their words is "…suspected to bind to DNA and interfere with the ability to work magic on hemoglobin". A preface: I am not making a broader claim here about the effectiveness of HCQ in Covid-19, which remains under investigation. But this author's specific arguments about HCQ do not stand up to scrutiny.

For example, I'm not sure where the author found this "suspected" mechanism of action. The true mechanism of action of HCQ and other quinoline-based anti-malaria drugs has been studied extensively. It is known that these drugs prevent the malaria parasite from sequestering free heme (the result of hemoglobin consumption) in food vacuoles, where the toxic heme molecules are normally converted to relatively harmless, crystalline deposits of hemozoin [8]. Importantly, HCQ does not prevent the release of toxic iron from heme, nor does the drug prevent an interaction with hemoglobin (the protein component of which is still consumed by the parasite). Instead, HCQ disrupts formation of the inert hemozoin crystals, thereby allowing the accumulation of toxic heme (porphyrin and iron together), which causes oxidative damage that ultimately kills the parasite.

Also, the virus is a protein envelope surrounding a length of coding RNA (it's an RNA virus) and contains literally not a single piece of DNA anywhere, so a DNA binding mechanism would have no relevance here. Even beyond this virus, I cannot find anything suggesting DNA binding is a significant mediator of HCQ's effects on malaria, autoimmunity, or any other disease state. Its primary effect is thought to occur in lysosomes/food vacuoles, where it prevents acidification as a weak base and may otherwise inhibit hemozoin formation (in malaria) and antigen presentation/immune activation (in autoimmune disease) [9, 10]. As a final thought, HCQ being a weak base means that the author's statement that it "lowers the pH which can interfere with the replication of the virus" is certainly incorrect, as it is a base and thus would prevent lowering of pH (acidification).

### Final Thoughts

The above discussion is by no means an exhaustive list of the blog post's incorrect statements or conclusions. Nonetheless, I hope it has been sufficient to make clear that

the blog post, and even the scientific article that likely inspired it, should not be viewed as a source of any meaningful insight into SARS-CoV-2, how it affects patients, or how the virus might be treated. What I still don't know is why the blog post author, under a pseudonym, chose to present such an incorrect description of this disease and the underlying pathophysiology with such confidence. That they would go so far as to suggest treatments for the disease despite a lack of any medical training, and in virtually the same paragraph condemn "armchair pseudo-physicians" who push incorrect information, is truly mind-boggling. Tragically, whether it arises from genuine malice, unfounded arrogance, or just simple ignorance, this sort of misinformation about a deadly pandemic can genuinely put lives at risk, and it's up to those of us who work in this field to fight back against it in whatever way we can.

Finally, while I've been very critical of this blog post author, I do have to give them credit for making one very insightful comment, right near the end, that I want to single out for praise:

*"Whatever, I don't know the full breadth and scope because I'm not a physician."*

On this, at least, we can agree.

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