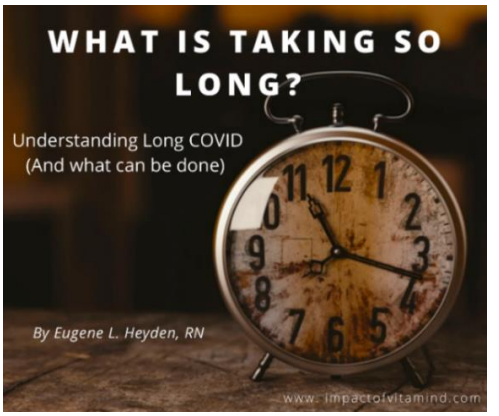

What is Taking so Long? Understanding Long COVID (And what can be done)

By Eugene L. Heyden, RN

Introduction

> *Studies have shown that long covid can affect the whole spectrum of people with covid-19, from those with very mild acute disease to the most severe forms.*
>
> *The symptoms of long covid include fatigue, dyspnea, cardiac abnormalities, cognitive impairment, sleep disturbances, symptoms of posttraumatic stress disorder, muscle pain, concentration problems, and headache.* **~Crook et al., 2021**

You can't help but be disappointed. You recovered from COVID-19 (or so they say), but the battle is far from over. For weeks to months, you are still having symptoms, symptoms you can feel but cannot explain. Looks like you are in it for the long haul. You, like so many others, have a continuation of the original disease (COVID-19), in a form know as Long COVID. Quite surprisingly, when it comes to its development, the degree of severity of the initial infection does not

seem to matter in the least. Long COVID can arise from even the mildest of COVID-19 cases.

> *Many patients with mild acute symptoms also develop long covid symptoms, in fact, studies show minimal differences between the prevalence of long covid symptoms between hospitalized and nonhospitalized covid-19 patients. (Crook et al., 2021)*

Here, in this article, we will explore what is really going on here and what can be done. But first, let's examine COVID-19 with the goal of seeing how you got from the acute infection stage to where you are today.

Understanding COVID-19

> *Severe SARS-CoV-2 infection mostly presents with coagulation abnormalities, pulmonary microvascular thrombosis, and severe inflammatory response.* **∼Fard et al., 2021)**

You know the story. COVID-19 is caused by the virus called SARS-CoV-2. An infection follows a successful interaction between the virus spike protein and a cell surface receptor known as ACE2, found abundantly (and invitingly) throughout the human respiratory tract and mucus membranes. Following spike protein/receptor interaction, the virus enters a target cell where it can replicate and create a host of clones with the freedom to leave to infect other cells or leave to infect another individual. It needs a host in order to replicate. Someone warm like you.

The virus in question is new to the human experience. So, we were caught off guard. But it is not as though we are defenseless. We have an array of innate immune responses engineered for times like these. We normally have antivirals such as lactoferrin, pre-positioned within the mucus that lines the target cells of the respiratory tract (Zanin et al., 2016; Pisani et al., 2020). And we normally have immune cells that enter the spaces between cells for the purpose of devouring and destroying viruses and other pathogens that have been placed under surveillance and pose an imminent threat (Budinger et al., 2021). These are but two of the many defenses we have at our disposal. But this new virus is crafty and can take advantage of defects and weaknesses present in our defenses, those that allow an infection to take hold. Besides, it is also very sneaky. The SARS-

CoV-2 spike protein is all dressed up in camouflage to avoid detection (Grobbelaar et al., 2021). And this seems to work all too well. Likely, the virus only wants to infect and replicate, not destroy. But destroy it has. Millions of lives have already been lost. More to follow.

Speaking of defenses, one of our more interesting and surprising defenses is known as **immunothrombosis** (Bonaventura et al., 2021). Likely you have never heard of it before, so I will let you in on this little secret. Simply put, when other defenses fail, allowing the virus to reach the capillary bed, the body strategically turns to clot formation, AKA thrombosis, to immobilize (freeze in place) the virus to prevent its advance into the circulation. Although this defense is quite effective, there is a price to be paid. Clotting within the capillary bed—a natural defense mechanism directed against viruses and bacteria that dare to enter the bloodstream—has the power to interfere with oxygen delivery to the very tissues it is trying to protect (Kell et al., 2022). This is the disease that the disease creates! SARS-CoV2 evokes clot formation which impairs tissue oxygenation at the capillary level. And from this, people need ventilators. And from this, people need prayers for recovery. And so begins a life-or-death struggle. This struggle invites the strong possibility that immune responses will become so intense, so frantic, that an individual can be taken from us by what is called a "cytokine storm."

> *The cause for which patients with severe COVID-19 die is not related to the damage caused by the replication of the SARS-CoV-2 virus but rather it seems to be linked to the so-called cytokine storm.* (Lete, 2021)

Above is the streamlined version of disease progression in COVID-19. Unfortunately, as COVID-19 transitions over time into a chronic form, the clotting continues. We call it Long COVID.

Long COVID is . . .

> *Coagulopathies [coagulation abnormalities], and especially the formation of* ***extensive microclots*** *in vivo, are* ***a hallmark of both COVID and long COVID****, and we have demonstrated that these microclots too are amyloid in character.*
>
> *Although the symptoms of Long COVID are multifarious, we here argue that the ability of these fibrin amyloid microclots (fibrinaloids) to block up capillaries, and*

thus to limit the passage of red blood cells and hence O2 exchange, can actually underpin the majority of these symptoms. **~Kell et al., 2022, emphasis added**

I have a suggestion. Before you continue, take the time to read my article *Taken by Storm: The Legacy of COVID-19 and the Future of Heparin*. It explains in detail the defense mechanism called immunothrombosis, as well as many aspects of COVID-19 that are not typically discussed but are highly relevant and should not be ignored. There are surprises in store. Don't miss out.

Now back to this thing we call Long COVID. Long COVID expresses itself in many ways, yet there is something fundamental to the variety of its presentations. It has been discovered, in Long COVID microclotting is occurring within the capillary bed, leading to impaired tissue oxygenation (Kell et al., 2022). *This* is the pathology that explains the persistent fatigue, the brain fog, the cognitive impairment, the shortness of breath, etc. And Long COVID remains long because the clots keep forming and intend to stay.

Of this we can be sure: We need to clot when we need to clot. And there are sophisticated mechanisms in play to keep us from clotting inappropriately and to dissolve clots when they are no longer of value. But unfortunately, in Long COVID the type of clot formed is structurally abnormal and resists breakdown and has been characterized as a fibrin amyloid microclot (Pretorius et al., 2021; Kell et al., 2022). Indeed, a fibrin amyloid clot is readily formed when whole blood is exposed to the SARS-CoV-2 spike protein, as depicted on the following page. You can see it with your own eyes! (And it is trouble.)

But before you turn the page, consider this:

Many pieces of research-level evidence suggest strongly that fibrin amyloid microclots, driven by the presence of the SARS-CoV-2 spike protein, are an inevitable accompaniment to (and a likely cause of) Long COVID. (Kell et al., 2022)

And this:

One source of the continuous production of a stimulus is represented by microbes, including virions, that persist in a largely dormant state (often in intracellular reservoirs) but can occasionally continue to replicate. There is now considerable evidence for the persistence of SARS-CoV-2. (Kell et al., 2022)

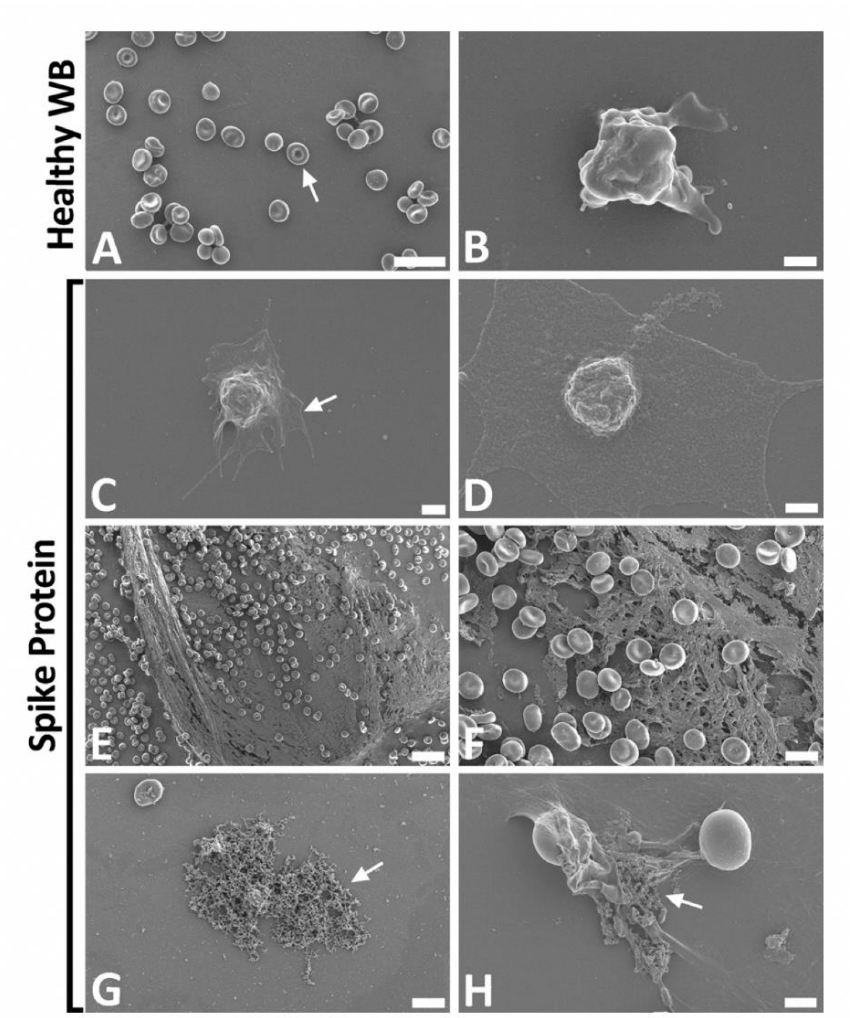

Figure 6. Whole blood sample of healthy volunteers, before and after exposure to spike protein

(**A–H**) Representative scanning electron micrographs of healthy control WB, with and without spike protein. (A,B) Healthy WB smears, with arrow indicating normal erythrocyte ultrastructure. (C–H) Healthy WB exposed to spike protein (1 ng.ml^{-1} final concentration), with (C,D) indicating the activated platelets (arrow), (E,F) showing the spontaneously formed fibrin network and (G,H) the anomalous deposits that is amyloid in nature (arrows) (scale bars: (E) 20 μm; (A) 10 μm; (F,G) 5 μm; (H) 2 μm; (C) 1 μm; (B,D) 500 nm).

Note: WB is an abbreviation for whole blood. An erythrocyte is a red blood cell. Images and description are from Grobbelaar et al., 2021. Use by author is permitted by the re-use policy of Portland Press.

Once it is understood that **COVID-19 is, fundamentally, a clotting disorder which interferes with the oxygenation of tissues**, Long COVID all makes sense. And why it lasts so long is two-fold: **1)** the stimulus for aberrant clotting persists and **2)** the clots themselves are resistant to normal degradation (Kell et al., 2022).

With respect to the stimulus, ***"There is now considerable evidence for the persistence of SARS-CoV-2."*** (Kell et al., 2022, emphasis added) It has been found that the SARS-CoV-2 virus, or parts thereof, can persist within the host for months! Indeed, one group of investigators discovered fragments of the SARS-CoV-2 pike protein within a circulating white blood cell called the monocyte—identified **15 months** following the original COVID-19 infection (Patterson et al., 2022; Kell et al., 2022). Great! The spike protein fragment is isolated within the body of a monocyte where it cannot evoke a regional immune response or initiate some sort of local, diabolical coagulation cascade. But, although the life of the monocyte is somehow prolonged past its typical one-day lifespan, the cell will eventually die (by the millions each day) and spill their contents (see Patterson et al., 2022). And likely, this is one of the mechanisms whereby sequestered spike protein fragments are repeatedly released into the circulation to evoke the host response that translates into fibrin amyloid clot formation, a lot of fibrin amyloid clot formation, and I mean a lot—leading to the extensive capillary blockage we see in Long COVID (Kell et al., 2022). So, although you have defeated the enemy, you are reacting to the body parts of the virus left behind.

> *It is important to note that the S1 [spike] protein detected in these patients appears to be retained from prior infection or phagocytosis of infected cells undergoing apoptosis [programmed cell death] and is not the result of persistent viral replication.* (Patterson et al., 2022)

To sum things up:

> *Many pieces of research-level evidence (especially suggest strongly that fibrin amyloid microclots, driven by the presence of the SARS-CoV-2 spike protein, are an inevitable accompaniment to (and a likely cause of) Long COVID.* (Kell et al., 2022)

So, you ask, "What can be done?"

H.E.L.P. is on the way

> *The procedure of therapeutic plasmapheresis is based on the fact that removal of abnormal accumulated substances such as cytokines or autoantibodies from the plasma can be therapeutic in certain situations.* **~Balagholi et al., 2020**

For the Long COVID patient, we can do nothing and hope this will all burn off and life will return to normal. Or we can seriously consider following in the footsteps of others. There is a way out.

During the beginning months of the pandemic, physicians (a few, not all), who were knowledgeable about a medical therapy called plasmapheresis, were quick to catch on that plasmapheresis could save the lives of the acutely ill COVID-19 patient, and do so by removing viruses, viral components, excess cytokines, and other harmful objects that accumulate in the bloodstream of those who have the disease. Therapeutic trials followed and impressive results were achieved. Indeed, emergency use authorization was granted by the FDA to treat COVID-19 patients with plasmapheresis and the WHO gave it its seal of approval (Sarfraz et a., 2020). So, this is not crazy stuff. Unfortunately, promising therapies, even approved therapies, often take forever to become standard practice.

Now with respect to Long COVID, once the phenomenon became noticeable, affecting those who were no longer acutely ill from COVID-19, it didn't take long to recognize (by the informed) that plasmapheresis could be an effective treatment here, too—in as much as plasmapheresis can remove from the bloodstream viral particles, proinflammatory cytokines, and abnormal or problematic clotting factors (Jaeger et al., 2021a; Balagholi et al., 2020). Seems just what is needed. And there was one form of plasmapheresis that was poised, ready to take on the challenge. It is called H.E.L.P. apheresis. Just so you know, H.E.L.P. is short for **H**eparin-mediated **E**xtracorporeal **L**DL **P**recipitation.

Briefly: H.E.L.P. apheresis was developed in 1984 to address metabolic disorders involving excessive fat and cholesterol in the bloodstream (Jaeger et al., 2021a). It is a treatment that requires access to the venous system, similar to blood donation or hemodialysis; and, with a special machine, tubing circuitry, and inline filters, the treatment processes the blood and returns it back to the patient. What is exciting here is that H.E.L.P. apheresis can remove from the bloodstream clotting factors such as fibrinogen (an important protein involved in coagulation), can remove viruses and the SARS-CoV-2 spike protein, and can remove pro-inflammatory cytokines that, when in excess, influence abnormal clot formation (Jaeger et al., 2021a). Importantly, H.E.L.P. apheresis inhibits the production of fibrinogen by reducing a stimulatory molecule called CRP and a pro-inflammatory

cytokine know as IL-6 (Jaeger et al., 2021a). It does this quickly, during a treatment lasting only a few hours. Indeed, when used during the acute COVID-19 infection phase,

> *HELP apheresis removes about 50% to 60% of fibrinogen, the most important coagulation protein, within two hours, that in turn immediately improves oxygen supply in the capillaries.* (Jaeger et al., 2021a)

And given the H.E.L.P. that they need, it is easy to see why the Long COVID patient can, in turn, breathe easier and be set on the path to full recovery.

To see it all in action, I have a great little video for you to watch. It is mandatory, so no squirming out. The video is in German but has English subtitles. It shows H.E.L.P. apheresis being performed in the clinical setting. And as a bonus, in the video you get to meet Katja and learn of her experience with long COVID. The video is on YouTube under the title *Help Apheresis for Long Covid Dr Beate Jaeger*. Here is the link: https://www.youtube.com/watch?v=zM8f-G1h3OQ. However, if you prefer your H.E.L.P. apheresis set to music, I invite you to watch the following video: https://www.mvcvideo1.com.

Welcome back! I thought these two little videos would present the concept and promise of H.E.L.P. apheresis better than a paragraph or two written by me. And all would agree, it was nice to meet Katja and hear her story. But she is not the only one who received great benefit from H.E.L.P. apheresis. There are other stories to be told.

Those who have gone before

> *While case reports are assigned limited level of evidence and are unable to deliver quantitative data, they still provide practical clinical real-world facts and are still indispensable for broadening medical knowledge.* **~Scarallo et al., 2021**

I have close to 20 case reports in front of me to share. I'll choose the ones that I feel best help make the case for H.E.L.P. apheresis as an effective treatment for Long COVID. And you never know, perhaps someday I will be telling your story. I'm sure it will be compelling.

Case 1

Case 1 is a 30-year-old gentleman who was infected with SARS-CoV-2 in November of 2020. While in quarantine, he developed a fever, *"complete exhaustion"* and profound weakness, *"barely able to make it from bed to kitchen."* His COVID-19 was described as "severe," but apparently not severe enough to require hospitalization. When the dust settled (a little) he was left with shortness of breath on exertion and limited waking endurance.

Approximately 2 ½ months out from the original infection, our gentleman received his first H.E.L.P. apheresis treatment. After the 1st apheresis, he was able to breath better and able to walk more than 40 steps rather quickly. And after his 2nd apheresis, he was *"completely symptom-free the day after."* On the following day, he resumed jogging, and was able to jog his usual 12 ½ miles. The use of an albuterol inhaler, previously required to help him manage his shortness of breath, was no longer needed, and was discontinued. (Jaeger et al., 2021b)

Case 2

Case 2 was 24 years old when he contracted COVID-19, confirmed by testing on 11/16/20. And it wasn't pleasant. In addition to a *"strong feeling of illness,"* he developed fever, high pulse rate of 140 beats per minute, loss of tase and smell, and extreme fatigue. *"Main symptoms: complete exhaustion, diarrhoea, shortness of breath during any lightest physical exertion."* After treatment with ampicillin, dexamethasone, and heparin for a period of 12 days, Case 2 was able to return to work as a caregiver, *"but was unable to climb 2 floors without air hunger."* Two and a half months into this was enough and he reached out for H.E.L.P. H.E.L.P. apheresis was performed twice, three days apart. Shortly after the second session, he was able to resume normal activities, including playing sports. (Jaeger et al., 2021b)

Case 3

This case outlines the experience of a 56-year-old pharmacist who contracted COVID-19 in March of 2020. It could have gone better, but it didn't go well. After the acute phase of the disease, she suffered shortness of breath *"lasting for months with cough, poor resilience, severe concentration disorders, memory*

lapses, sentence interruptions, temporary paralysis, skin symptoms on hands (blisters and peeling skin)." But H.E.L.P. was on the way. Her first apheresis occurred a year later, on March 30, 2021, and allowed her to breathe more easily and achieve noticeable improvement in her ability to concentrate. After her second apheresis on April 6, 2021, she felt like a new person, suffering less from her chronic Long COVID symptoms. Continual improvement followed her third and fourth apheresis, after which she *"completely recovered and could ride horses and play golf again, without shortness of breath."* Her ability to concentrate also steadily improved. (Jaeger et al., 2021b)

Case 4

Case 4 is a firefighter, age 35, who contracted COVID-19 on October 10, 2020. Initially, he ran a fever of up to 40°C [104°F] for a period of 6 days. During the acute illness phase he would become short of breath, even with talking, and his lips became cyanotic, and at times his blood pressure was seriously elevated. On two occasions, he felt like he was about to pass out. Before COVID, he could jog 10 miles at a stretch; however, during convalescence he could only walk a little over a mile before calling it quits. Shortness of breath persisted, and *"Every night had sleep disturbance, several times had to sit up and gasp for air."* Well, this can go on forever. Something needed to be done.

The first H.E.L.P. apheresis was performed on April 22, 2021, after which his breathing noticeably improved and he could sleep through the night. After the second and third apheresis session it was back to jogging again, but not as easily and as far as he did before contracting COVID. It would take yet another apheresis session before life would return to normal. The fourth apheresis was performed on June 1, 2021. Thereafter, he could jog 5 miles every other day and was considered fully recovered. He was allowed to return to work as a firefighter. (Jaeger et al., 2021b)

Case 5

Case 5 is a 21-year-old gentleman who was infected with SARS-CoV-2 in November of 2020. "*Symptoms comprised: fever, muscle/ancle pain, headache, coughing and gastrointestinal trouble."* Two days into the ordeal, he lost his sense of taste and smell and his lungs felt as though they were "full of sawdust."

Following the acute phase of the infection, fatigue, shortness of breath, persistent cough, fatigue, muscle weakness, and impaired concentration were persistent, and treatment was sought. Three H.E.L.P. apheresis treatments, conducted in within one week's time, *"reversed all symptoms."* So much so, the patient was able to resume jogging and resume playing the bugle, a testament to the power of H.E.L.P apheresis. (Jaeger et al., 2021b)

Case 6

The final case report in this series is a little different, in that the gentleman of our story did not get the H.E.L.P. he needed. Instead, he got something very close and arguably just a good, a plasmapheresis procedure called **T**herapeutic **P**lasma **E**xchange (TPE). In TPE, the patient's blood is separated into red blood cell and plasma fractions. The red blood cells are returned, but the plasma fraction is discarded and replaced with albumin or fresh frozen plasma. The plasma is what holds many the elements that sustain Long COVID, so its exchange offers welcomed relief. TPE is an approved treatment for COVID-19 (Balagholi et al., 2020). Then why not for Long COVID? The case could be made that both are really the same disease, one form transitioning into the other form.

In this case report we meet a 68-year-old attorney, an individual in a demanding position within his law firm and formally in good health. But this would all change. He began to feel ill on December 14, 2020, experiencing shortness of breath and fatigue. Four days later he would pay a visit to the emergency room out of concern for his persistent symptoms. Three day later he was hospitalized due to increased shortness of breath and increased fatigue. Treatment included remdesivir (antiviral), dexamethasone (steroid), and high-flow oxygen. Fortunately, he was never intubated and placed on a breathing machine. After an 11-day hospitalization, he was discharged for home to use supplemental oxygen as needed. Our patient had survived COVID-19 but would transition to Long COVID as symptoms would persist.

> *Over the following four weeks, he felt extremely fatigued. He could only walk to the bathroom and back to bed. He could not focus on anything cognitively, which he described as "brain fog". He was unable to do any work and could not even answer his emails. He reported he had no sense of smell nor taste.* (Kiprov et al., 2021)

On February 4, 2021, our attorney received his first TPE. Afterwards, he could breathe easier, and a persistent cough had subsided. The following morning *"he could walk and was not struggling for breath."* "*Two days later, he had no difficulty breathing and was able to walk 100 feet on a level surface but still had difficulty walking uphill."* He would need more TPE.

On February 6, the second TPE was performed, after which *"he was able to walk uphill with ease and even jog."* The brain fog had lifted, and our attorney was able to return to do what attorneys do. Furthermore, after this second plasmapheresis, his sense of smell and taste, previously lost, had returned. Would one more apheresis session be required?

Two months after his second TPE, *"the patient reported that he was back to work, feeling like his normal self, and able to exercise daily without shortness of breath."* Although markedly improved, it was felt that the patient could benefit from one final apheresis session. And so, a third and final TPE was performed. And here is where the case report ends. (Kiprov et al., 2021)

If you would like to watch an interview with an individual who received benefit from TPE for Long COVID, follow the link:
https://www.youtube.com/watch?v=L2L6iIOlxZY

Note: The above case report is from a paper coauthored by Dr. Dorbi Kiprov, a California physician and World-renowned authority on plasmapheresis. He operates a two plasmapheresis centers, one in California and the other in Florida, that currently treat Long COVID patients with TPE. Typically, the cost of each TPE session is approximately $5,000. The author is unaffiliated with Dr. Kiprov, his clinics or associates, nor profits in any manner from any form of association. For more information on plasmapheresis and services available, visit www.dobrikiprov.com.

On the horizon

There is an attractive alternative to both H.E.L.P. apheresis and TPE. It is a special blood filter called **Seraph-100**. And what is particularly nice, is that it can be used with an ordinary dialysis machine, likely making it more accessible, easier to perform, and perhaps less costly than plasmapheresis.

The Seraph-100 utilizes immobilized strings of heparin-coated beads to attract, trap, and remove from the bloodstream viruses and viral components

(think SARS-CoV-2 spike protein). The Seraph-100 is also capable of reducing both cytokines and fibrinogen, factors involved in aberrant blood clotting (Kelly et al., 2021). But there is a catch. While approved for use in acute COVID-19, its use in Long COVID has not yet been FDA approved. Encouragingly, a clinical trial for use in Long COVID is in the planning stages. The company involved in this award-winning medical device is ExThera Medical. Website: www.extheramedical.com. To become familiar with the Seraph-100 filter, watch the following video:

Treating Covid-19 with the Blood filter Seraph 100
https://www.youtube.com/watch?v=rX6UmHhRY9A

Another blood filter that shows promise for Long COVID is called **PentraSorb® CRP** (Torzewski et al., 2021). This filter specifically removes the molecule CRP from the bloodstream. One reason why this is relevant to Long COVID is that excess CRP circulating in the blood stream prevents the breakdown of fibrin (Torzewski et al., 2021). Notably, CRP has been found to be elevated in the Long COVID patient (Maamar et al., 2022). For more information, go to https://www.pentracor.de/en/. There, a nice little video awaits. Near the end of the video is a segment on COVID-19. My hope is that those familiar with this filter will consider its potential for Long COVID and act (with a sense of urgency).

Conclusion

If sufficiently motivated, the Long COVID patient can get the help that they need. Unfortunately, H.E.L.P. apheresis is not readily available, so this door may not be easily opened. However, TPE is readily available—widely used to treat a variety of medical disorders. But it won't be cheap. It may involve travel and lodging expenses, as well as treatment costs. It is doubtful that insurance will cover treatment costs, so expect to pay $5,000 or more out-of-pocket, per session. I know, this seems like a lot of money, but may be a small price to pay for getting your life back. Not to discourage you in any way but finding a facility that will perform plasmapheresis or TPE for Long COVID may not be easy. It's just not in the playbook . . . yet. Sorry. That's just the way it is. Hopefully, if I have anything to say about it, this will all change. Perhaps, circulating this article around will help speed things along (Hint!).

As far as accessibility to a yet-to-be-approved therapy, I should remind you there is this thing called **Right to Try**. You can apply for exemptions from the FDA

and may succeed in obtaining permission for H.E.L.P. apheresis, TPE, or access to the Seraph-100 filter or the CRP filter.

I wish there was an easier, less expensive way other than by plasmapheresis to deal with the problem of extensive fibrin amyloid clot formation in you, the Long COVID patient. There doesn't seem to be any easy answers. But there is H.E.L.P. and there is TPE, and both they are available now and both should be formally approved for the treatment of Long COVID.

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