IDENTIFYING THE ETIOLOGY OF POST-ACUTE SEQUELAE SARS-COV-2 (PASC) INFECTION

An Undergraduate Research Scholars Thesis

by

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Research activities involving the use of human subjects, vertebrate animals, and/or biohazards must be reviewed and approved by the appropriate Texas A&M University regulatory research committee (i.e., IRB, IACUC, IBC) before the activity can commence. This requirement applies to activities conducted at Texas A&M and to activities conducted at non-Texas A&M facilities or institutions. In both cases, students are responsible for working with the relevant Texas A&M research compliance program to ensure and document that all Texas A&M compliance obligations are met before the study begins.

I, Perri Marshall, certify that all research compliance requirements related to this Undergraduate Research Scholars thesis have been addressed with my Research Faculty Advisors prior to the collection of any data used in this final thesis submission.

This project did not require approval from the Texas A&M University Research Compliance & Biosafety office.

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ABSTRACT

Identifying the Etiology of Post-acute Sequelae SARS-CoV-2 (PASC) Infection

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The viral illness coronavirus disease 2019 (COVID-19) has affected millions worldwide since its initial discovery in late 2019. After recovering from the primary viral infection, many have found themselves suffering new, ongoing, or recurrent COVID-19 symptoms in a condition referred to as long COVID or post-acute sequelae SARS-CoV-2 (PASC) infection. Presently, little is understood regarding the etiology of PASC.

This literature review analyzes current theories of PASC development in adult humans after initial COVID-19 disease. An understanding of PASC's developmental mechanism will pave the way for better-targeted therapies to treat patients diagnosed with this illness.

Proposed PASC origin theories for discussion include: (1) persistent SARS-CoV-2 remains after initial COVID-19 infection; (2) immunosuppression during COVID-19 disease leads to hyperinflammation and subsequent symptoms; (3) microclots cause organ damage. The

interplay between these theories reveals future study directions and implications. A deeper understanding of these PASC mechanisms allows research progression towards treatments that directly target the illness at its source.

DEDICATION

To my parents, for your endless support and love.

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NOMENCLATURE

α2-AP	α2-antiplasmin
CDC	Centers for Disease Control and Prevention
COVID-19	Coronavirus disease 2019
IFNγ	Interferon γ
IgG	Immunoglobulin G
IgM	Immunoglobulin M
IL-6	Interleukin-6
IVIG	Intravenous immunoglobulins
MERS	Middle East respiratory syndrome
MIS	Multisystem inflammatory syndrome
PASC	Post-Acute Sequelae of SARS-CoV-2
PD-L1	Programmed death-ligand 1 (PD-L1)
RBD	Receptor binding domain
SARS	Severe acute respiratory syndrome
SARS-CoV-1	Severe acute respiratory syndrome coronavirus 1
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2

1. INTRODUCTION

As the coronavirus disease 2019 (COVID-19) pandemic inflicts its reign of terror on the world, a lesser-discussed illness remains in its wake: post-acute sequelae of SARS-CoV-2 (PASC). Even after COVID-19 has inflicted its damage on its targets, a select number of affected individuals continue to suffer from lingering symptoms, termed PASC or long COVID, for a still unknown time period after recovering from their initial infection.

According to the Centers for Disease Control and Prevention (CDC), PASC is defined as "a wide range of new, returning, or ongoing health problems" experienced 4 or more weeks after initial infection with the COVID-19 virus.[1] Estimated PASC prevalence ranges as low as 10% up to 30% of patients reporting at least 1 lingering COVID-19 symptom.[2] Depending on patient's age or sex, one is more predisposed to experiencing certain PASC symptoms over others.[3] Predisposing risk factors that predict PASC are: female, having more than 5 early symptoms, and the initial severity of COVID-19 infection. Patients with more severe infections are found to be more likely to suffer tissue damage long-term.[4] Regardless of an individual's symptomatic status during COVID-19 infection, one is still vulnerable to later development of PASC. A wide variety of symptoms have been linked to PASC and are known to persist for varying lengths of time in different people.[1] Some symptoms associated with PASC include: breathing difficulties/breathlessness; fatigue; chest/throat pain; headache; abdominal symptoms; myalgia; cognitive issues; anxiety/depression.[3] Symptoms can continue for at least 6 months after initial symptom onset, but the maximum duration of PASC is still under investigation.[4]

1.1 Mechanism of COVID-19 in SARS-CoV-2 Infection

To better understand the pathology of PASC infection, the mechanism of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) should be understood. SARS-CoV-2, the causative agent of COVID-19, is a positive-sense single-stranded RNA virus.[5] The diversity of COVID-19 symptoms are reflective of SARS-CoV-2's ability to infect a variety of human cell types. The virus's functional receptor target is angiotensin converting enzyme 2 (ACE2), a protein found in a wide range of body areas, including vascular smooth muscle cells, the respiratory system, and brain endothelium.[6] This high expression of ACE2 helps explain why COVID-19 symptoms appear to center around these related organs. The highly common ACE2 target allows the virus to wreak widespread damage throughout the entire body, evading host immune responses through various methods.

SARS-CoV-2 may avoid host detection through pathogen pattern recognition receptors by replicating within double-membrane vesicles. This system disguises the virus, allowing it to enter other cells without being sensed. Normal host immune system functioning is likewise disrupted by SARS-CoV-2. The virus expresses proteins which diminish the production of interferons and/or escape from their actions that are typically important for the immune system to fight against viral infections. If SARS-CoV-2 is not controlled, increased numbers of proinflammatory cytokines, including interleukin-6 (IL-6), are produced, leading to hyperinflammation.[6] In severe cases, the body reaches a point of functional exhaustion and endures decreased numbers of T lymphocytes and natural killer cells.[5, 6]

1.2 A History of Other Viruses with Lingering Symptoms

COVID-19 is not novel in its ability to leave post-viral syndromes after the initial infection. Many viral and bacterial diseases have been linked to chronic symptoms in some

patients, such as Ebola and influenza.[3, 6] Other human coronavirus diseases found to leave lingering symptoms include Middle East Respiratory Syndrome (MERS) and severe acute respiratory syndrome (SARS).[4] Comparison of the characteristics of these viruses' chronic conditions may assist in a deeper understanding of the etiology and treatment necessary for long COVID.

1.2.1 A History of Other Coronavirus Infections with Lingering Symptoms

Some theorize that SARS-CoV-2 persists within the body after initial COVID-19 disease. This is not a unique characteristic of SARS-CoV-2; other coronaviruses have also been shown to be capable of persistence in the body.[6]

MERS was first discovered in Saudi Arabia in 2012.[7] Primary MERS is caused by the MERS-CoV virus and affects the lower respiratory tract.[8, 9] Symptoms manifest as coughing, fever, breathing difficulty, and pneumonia.[9] Studies conducted post-infection revealed a reasonable subset of those affected by MERS continued to suffer with psychiatric symptoms, chronic fatigue and abnormal chest radiographs.[7-9] These radiographs revealed continued lung fibrosis in patients four years post-MERS infection, a concerning omen for recovering COVID patients susceptible to PASC infection.[8]

SARS, discovered in South China in 2003, is caused by severe acute respiratory virus 1 (SARS-CoV-1).[7] Common symptoms include fever, myalgia, cough, and dyspnea.[10] Still, however, some symptoms linger after the initial viral infection. Post-initial infection symptoms include fatigue, shortness of breath, and lung lesions. Even 15 years after infection, affected patients continued to demonstrate abnormal chest radiographs. Like SARS-CoV-2, SARS-CoV-1 uses ACE2 to infect cells.[7]

The causative coronaviruses of MERS and SARS both cause strikingly similar symptoms to those of COVID-19. Like SARS-CoV-2, MERS-CoV and SARS-CoV-1 can continue to have lingering effects on patients for many years after initial infection. Although SARS-CoV-2 is still a relatively new virus, there is promising potential for future research to use past findings about the etiology of these other post-viral infections to better understand the mechanisms of PASC.

An understanding of the pathophysiology of PASC is necessary for the development of better-targeted therapies for this illness. With knowledge of how long COVID originates, treatments can be created to attack PASC directly at its source. COVID-19 has already infected millions worldwide; it is still unknown how many more will eventually be affected by PASC. It is therefore extremely important to begin studying the pathophysiology of long COVID now in preparation for the future.

2. METHODS

Literature searches were conducted periodically on PubMed, Google Scholar, and LitCovid beginning on September 19, 2021. Basic information about the characteristics of COVID-19, PASC, and other relevant diseases were researched specifically on the CDC website or PubMed. The general search terms used throughout the study for PASC-specific research are exhibited in table 2.1. Long-COVID and PASC both refer to the same illness, which allowed interchangeable use of these phrases in the search terms. Articles suggested by thesis reviewers were also used in this study.

Table 2.1. Search Terms Used Throughout Study

Study Search Terms
Long-COVID
PASC
Long-COVID pathophysiology
PASC pathophysiology
Long-COVID etiology
PASC etiology

Article titles and abstracts were initially scanned to identify studies with thorough and informative results. Emphasis was placed on reviewing studies that focused on adult cases of PASC. No explicit focus was placed on a certain geographical region. In some cases, references were identified by reviewing articles cited by the originally viewed search result. A document list was created as articles were found for later information collection. This master list housed notes about each article for later dissection. Commonalities in research findings between

different studies were then noted upon examination of gathered data. The final literature search was completed on March 31, 2022.

3. RESULTS

While long COVID does share the same causative viral agent with COVID-19, the two illnesses are not the same. PASC's symptoms are more chronic, whereas those of COVID-19 are generally temporary. Such discrepencies allow the two diseases to exist as separate entities. Table 3.1 displays some symptoms of each illness for comparison.

Table 3.1. Comparison of COVID-19 vs PASC Symptoms[11]

	COVID-19	PASC
Systemic Manifestations	Fatigue	Chronic malaise
	Weakness	Poor concentration
Respiratory Manifestations	Dyspnea	Dyspnea
	Pneumonia	Persistent radiological abnormalities
Cardiac Manifestations	Myocarditis	Heart palpitations
	Cardiomyopathy	Chest pain
Neuropsychiatric Manifestations	Sensory loss	Impaired taste and smell
	Delirium	Brain fog

Because of the range in PASC symptoms, some researchers have proposed that different subtypes of the illness may exist. Symptoms related to bodily myalgia (such as abnormal breathing, chest/throat pain, and fatigue) are usually interconnected and form early during PASC development. Connections between myalgia and cognitive symptoms, however, have weak connections. Thus, origins of PASC myalgia and cognitive symptomsmay differ, but further research is still necessary for this theory.[3] Some cognitive and immune PASC symptoms are shown in table 3.2.

Table 3.2. Immune- and Cognitive-Related PASC Symptoms[4, 12]

Immune Systems	Cognitive Symptoms
Myalgia	Cognitive mental disorders
Chest and joint pain	Headache
Cough	Insomnia
Sputum	Smell and taste dysfunction
Shortness of breath	Anxiety & depression
Increased risk of blood clotting	Fatigue

Several theories have already been put forward regarding the origin of PASC. As of time of publishing, the proposals with the strongestest evidence in affecting PASC etiology include:

1. SARS-CoV-2 persists in the body after initial COVID-19 disease and manifests as PASC symptoms.
2. Elevated levels of IL-6 and transforming growth factor-β promote a prolonged and excessive immune response.[12]
3. Microvascular COVID-19 lung vessels obstructive thromboinflammatory syndrome (microCLOTS) leads to elevated plasmin levels, which cause PASC symptoms.[13]

3.1 Persistent SARS-CoV-2 Remaining after Initial COVID-19

One particularly popular theory proposes that SARS-CoV-2 remains in certain body locations or tissue reservoirs after primary infection and COVID-19. In fact, evidence shows that many cases of COVID-19 patients continue to shed the virus from their system after recovery. Viral shedding continues for up to 2 months after infection, whereas respiratory shedding can occur up to 4 months. Patients can even continue to test positive through RT-PCR tests 3 months after their infection.[4] It would be expected that the persistence of viral RNA is unlikely because of the propensity of human cells to possess RNase enzymes for rapid RNA degeneration.[6] Therefore, consistent and prolonged RT-PCR positive results suggest the presence of intact viral particles in the patients. Multiple studies have found SARS-CoV-2 RNA in olfactory mucosa

and intestinal samples in patients 4 months after their own respective initial COVID-19 illness onsets.[14, 15] Additional research is thus necessary to confirm the presence of virus in these tissues.

COVID-19 antibody levels also demonstrate SARS-CoV-2's persistence after infection. In a study by Gaebler and colleagues, titers of immunoglobulin M (IgM) and immunoglobulin G (IgG) anti-spike protein receptor binding domains (RBD) decreased when comparing levels between month 1 and month 6 after SARS-CoV-2 infection.[6, 14] Typically, IgM and IgG assist in immune function and antigen clearance. Sustained low levels of these antibodies, especially IgM, after COVID-19 suggests that SARS-CoV-2 persists in the body..

In the same study, Gaebler and colleagues found that RBD-specific memory B cell levels remained consistent over the 6 months following infection.[6, 14] Through further examination, it was determined that these memory B cells *increased* in their potency and breadth between months 1 and 6.[14] The continued enhancement of these cells therefore suggests that SARS-CoV-2 remains within the body even after initial infection. Increased memory B cell potency demonstrates the immune system's continued efforts to clear the virus through constant antibody evolution to increase its binding strength.

Monocytes, another immunologic mediator, also reveal continued SARS-CoV-2 presence post-initial infection. There are three general monocyte groups: classical monocytes, intermediate monocytes, and non-classical monocytes. Classical monocytes and non-classical monocytes are most relevant concerning PASC etiology. Classical monocytes, which include the $CD14^{++}$ and $CD16^{-}$ phenotypes, express high levels of ACE2 and secrete proinflammatory molecules such as IL-6. Non-classical monocytes, meanwhile, include phenotypes $CD14^{lo}$ and $CD16^{+}$ and are generally known as anti-inflammatory cells. A study by Patterson and colleagues found that PASC patients have decreased levels of classical monocytes, but increased non-

classical monocytes.[2] Some individuals have even been found to retain a SARS-CoV-2 protein on their non-classical monocytes up to 15 months after infection. Interestingly, recent discoveries also reveal that non-classical monocytes can acquire a proinflammatory phenotype.[2, 16] If this mechanism is found to occur at higher levels in recovering COVID-19 patients, this characteristic may prove influential in affecting greater inflammation levels, leading to PASC.

While these studies demonstrate SARS-CoV-2 persistence for several months after first infection, they also show irregular immune cell levels. Such disruption can send the body into an immunosuppressed state.

3.2 Immunosuppression Leads to Hyperinflammation

Immunosuppression is the decrease in the body's ability to fight immune threats. Two major players in sustaining normal immune function are T and B lymphocytes. In healthy patients, $CD4^+$ T cells activate B cells, which then create a specific antibody against offending threats. $CD4^+$ T cells can also help in the activation of $CD8^+$ T cells, which can destroy the virus-infected cells.[5] In addition to destroying invading pathogens, T and B lymphocytes also assist with inflammation resolution. SARS-CoV-2 infection, however, causes lymphopenia (T and B lymphocyte deficiency), leading to unresolved hyperinflammation during COVID-19. In some patients, as T and B lymphocytes levels remain low following primary infection, the hyperinflammation manifests itself as PASC symptoms such as pain or fatigue.[4] Thus, when levels of these virus-fighting cells are decreased, the body can less effectively fight infection, perpetuating SARS-CoV-2's life in the host.

Studies demonstrate that, of the two lymphocyte types, SARS-CoV-2 predominantly affects T lymphocytes.[17, 18] As such, some have found decreased levels of/less response of patient T cells after infection. In a study by Qin and colleagues, $CD4^+$ T cell levels saw the

greatest decrease in number out of all other T cell types during initial COVID-19 infection.[18] Further research is needed to understand if $CD4^+$ levels remain decreased once PASC ensues in relevant patients. A study by Peluso and colleagues, meanwhile, found that patients with PASC four months after COVID-19 suffered lower $CD8^+$ T cell responses over time.[19] Such decreased T lymphocyte levels explain the concurrent depressed B lymphocyte levels seen in PASC patients.

A notable number of cases of multisystem inflammatory syndrome (MIS) have occurred alongside infection with SARS-CoV-2. In these cases, elevated levels of systemic proinflammatory markers, including IL-6, are seen. MIS is not immediate. It tends to manifest within 2-6 weeks of initial viral infection, again hinting at the dysregulation of the immune system. Yong and colleagues suggest that the remaining inflammation and symptoms of MIS occurring post-COVID-19 contribute to later PASC symptoms.[4]

SARS-CoV-2 has damaging effects on T and B lymphocytes levels in patients. Without these pathogen-clearing cells, inflammatory symptoms are able to flourish. Some propose that, when these cells are replenished after initial COVID-19, hyperinflammation occurs as a result of still unresolved inflammation.[4, 20] The inflammatory process is a recognized system that activates blood coagulation, another symptom of PASC.[12, 21]

3.3 Coagulopathy and Microclots

Inflammation and coagulation are two common defense responses used by the body to fight various infections. Generally, these systems balance each other, based on whichever process is more needed at a given time. When the body needs to decrease its cytokine levels, inflammation activates coagulation. Anticoagulant cascades then follow to destroy clots. As this occurs, members of the cascade simultaneously neutralize and make cells less responsive to

inflammatory mediators. Conversely, the coagulation system may increase inflammatory response by releasing mediators that promote cell-to-cell interactions. This communication promotes further inflammatory action as neighboring cells receive news of an immunological threat.[21]

Several studies point to microCLOTS as instrumental in the origin of long COVID.[13] "Microclots" is a relatively new term being used to describe the anomalous amyloid clots forming in individuals suffering with PASC. Normal blood clots are produced via polymerization of fibrinogen (a common soluble plasma protein) to fibrin. Thrombin, an enzyme, first acts on fibrinogen to remove two of its fibrinopeptides. This action thermodynamically favors fibrinogen's conversion to insoluble fibrin. Next, transglutaminase factor XIII cross-links into the developing clot while simultaneously cross-linking α2-antiplasmin (α2-AP) to the fibrin. Factor XIII thus serves as a coagulation factor which synthesizes clots.[22] Fibrinolysis, the process to break up clots, uses effector protease plasmin to degrade the fibrin.[23] Action of α2-AP, however, inhibits plasmin's functions.[22]

Microclots may initially form during initial COVID-19 infection but can also develop with PASC manifestation. Affected PASC patients present with anomalous amyloid fibrin deposits in their plasma that are unusually resistant to fibrinolysis. Studies show that these patients have abnormally high levels of factor XIII, plasminogen, and α2-AP. As previously discussed, each of these substances individually contribute to the initial formation and persistence of microclots.[23] Once formed, microclots can inhibit erythrocyte transport to the capillaries, thus blocking O_2 exchange. As a result, organs do not receive adequate supply of their required nutrients to maintain normal function. This mechanism is hypothesized to directly contribute to PASC symptoms and may explain how an initially respiratory-presenting virus can

cause organ dysfunction, myalgia, and related neurological disorders.[22] The finding that hyperbaric oxygen therapy (which involves intermittent breathing of 100% oxygen) alleviates long COVID symptoms like fatigue and cognition further supports the hypothesis of microclots' effects.[24]

The higher plasmin levels caused by increased plasminogen and α2-AP in PASC patients still raises further interest. Beyond plasmin's role in fibrinolysis and clot removal, this protease modulates other, unrelated immunological processes. Specifically, it removes misfolded proteins, maintains tissue homeostasis, and plays a role in pro-inflammatory activity. Because plasmin levels are elevated in PASC patients, the products of its actions (or lack thereof) are likewise heightened. These abnormal plasmin levels caused by the aforementioned factors is thus hypothesized to further contribute to PASC development because of the damaging effects it can elicit on tissue homeostasis and inflammatory actions.[23, 25]

4. CONCLUSION

PASC quietly follows behind COVID-19, inflicting its damage on a select number of recovering COVID-19 patients. As of March 25, 2022, the World Health organization reported 476,374,234 confirmed COVID-19 cases worldwide.[26] According to Patterson and colleagues, PASC has a 10%-30% incidence rate.[2] These findings therefore suggest that *at least* 47,637,423 of the confirmed COVID-19 cases will eventually acquire PASC infection. Ongoing research aims to study the evolution of SARS-CoV-2 from initial COVID-19 disease to its later manifestation as long-COVID.

This paper explores current research supporting three popular theories for PASC etiology: (1) lingering SARS-CoV-2 manifests as PASC; (2) compromised immune cell levels lead to immunosuppression and eventual hyperinflammation; (3) microclot formation damages organs. Substantial amounts of evidence support each individual theory. Upon further examination, these proposed theories show promising connections to each other.

A combination of the three theories appear to contribute to the development of PASC and its related symptoms. The path begins upon initial infection with SARS-CoV-2. After a brief incubation period, the viral infection manifests itself as COVID-19. Regardless of initial disease severity, in some patients, SARS-CoV-2 may evade the immune response and persist within the body for months following initial infection. While the virus remains in the body, it continuously depletes T and B lymphocyte levels, weakening the immune system. Because of decreased T and B lymphocyte activity, inflammation sustains and accelerates. As a result of inflammation, coagulative substances are recruited to neutralize inflammatory mediators and decrease cytokine levels. PASC patients, however, have been found to have unusually higher levels of plasminogen

and α2-AP, which contribute to the synthesis and persistence of clots. Large amounts of coagulation reap damage on the body and can negatively impact oxygen transport to tissues. With decreased oxygen, tissue homeostasis is disrupted and organ damage ensues. Thus, each proposed PASC origin theory demonstrates connections to another. The combination of these three proposals is, therefore, the hypothesized pathway of PASC development. This path is illustrated in figure 4.1.

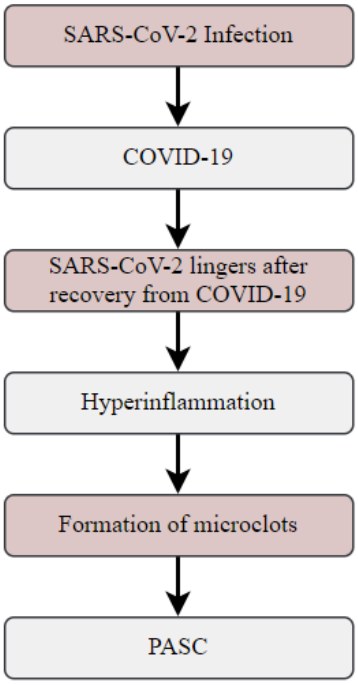

Figure 4.1. Proposed Theory of PASC Etiology

A few potential directions can be taken with regards to future PASC research. Some have suggested that the variability of the illness's symptoms and the co-occurrence of certain symptom types may be attributed to the existence of multiple long-COVID subtypes. Because this paper took a more body-wide research approach, future studies should more specifically examine potential neurological SARS-CoV-2 mechanisms during PASC. Furthermore, this

research may serve as a starting point for future research studies to make more concrete connections between the currently popular, proposed PASC etiology theories.

With a greater understanding of the developmental pathway of long-COVID, better therapies can eventually be created to directly target the disease at its root. Proactive research is urgently needed, before this illness creates long-term health problems on the large, susceptible population of individuals recovering from COVID-19.

4.1 Potential Treatment Options

No pharmaceuticals specific for PASC have yet been developed, nor have any preexisting drugs proven successful for alleviating symptoms.[4] Considering the proposed theories of long-COVID, however, several treatment methods may still prove viable for affected patients. The wide range of PASC symptoms on the body suggest that individualized treatment plans will be most successful. For general symptom management, Kell and colleagues suggest acetaminophen and non-steroidal anti-inflammatory drugs.[22] More aggressive, long-term treatment options generating interest, meanwhile, include immunomodulatory therapies and anti-coagulation medications.[22, 27]

As previously mentioned, SARS-CoV-2 infection causes a disruption in certain immune cell levels, such as in B lymphocytes, T lymphocytes, and IL-6. The resultant immunocompromised individual would thus benefit from immunomodulatory therapies such as receipt of programmed death-ligand 1 (PD-L1) inhibitors, interferon γ (IFNγ), and pooled intravenous immunoglobulins (IVIG).[27] PD-L1 serves to prevent immune cells from attacking host cells.[28] Thus, a PD-L1 inhibitor may prove useful in destroying host cells housing lingering SARS-CoV-2 virus. The cytokine IFNγ activates macrophages to initiate pathogen destruction.[29] T cells typically synthesize this protein, but due to the decreased levels of T cells seen in PASC

patients, these individuals also experience depressed IFNγ levels. Thus, IFNγ administration may prove helpful in destruction of persistent SARS-CoV-2. Furthermore, B lymphocytes typically synthesize immunoglobulins, which then assist in the destruction of foreign antigens. With the decreased B lymphocyte levels seen in PASC patients, however, less immunoglobulins can be created for viral destruction. IVIG therapy would allow for replacement of these deficient immunoglobulin levels. An additional positive potential side effect of PD-L1 inhibition, IFNγ, and IVIG administration may be increased ability to decrease inflammation due to these therapies' propensity to stabilize levels of related immunological cells/molecules to normal.

Anticoagulants also appear encouraging for successful PASC treatment. As a supportive treatment, blood thinners like rivaroxaban and apixaban can be used to destroy the microclots formed by SARS-CoV-2.[27] A triple anticoagulation treatment, however, demonstrates promise as an effective, long-term PASC therapy. Combination of a dual antiplatelet therapy, Apixaban, and a proton pump inhibitor has previously been shown to successfully treat thromboses.[22] Application of a similar treatment plan may thus diminish microclot formation as a result of PASC, alleviating the severity of microclots' related symptoms. Additional research is still needed to confirm these proposals.

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