Quick guide to clotting in long COVID

Harriet A. Carroll, PhD
Long Covid Scientific Consultancy
www.LC-SC.co.uk
✉ harriet@lc-sc.co.uk

What is clotting in long COVID?

Whilst more typical clotting can occur in long COVID and similar post-vaccine syndromes, we often see much smaller clots, commonly called microclots. Microclots have an amyloid structure, are difficult to break down, and are small enough to block the microvasculature. Research suggests these properties can lead to poor oxygen extraction, continued immune activation, and may lead to widespread "micro" ischaemia-reperfusion injuries.

Microclots in long COVID are often accompanied by hyperactivated platelets an endotheliitis. Chronic platelet hyperactivation is found in other neurological diseases such as Parkinson's and Alzheimer's, and, in addition to clotting, may directly contribute to the disease via inflammation, inappropriate neurotransmitter secretion, and exacerbation of endotheliitis. The endothelium regulates vaso-activity and has a bidirectional relationship with the nervous and immune systems. Markers of endotheliitis are a common finding in long COVID.

There are currently no clinical guidelines for clotting in long COVID; this quick guide aims to outline this pathology based on current research findings.

What are the symptoms of clotting in long COVID?

We do not have enough evidence to confidently describe symptoms that are directly caused by the type of clotting seen in long COVID. As such, the below provides a description of some common symptoms and conditions with an explanation of why these could be caused by microclots and related pathology:

General:

Allergy symptoms: Histamine release from activated platelets

"COVID toes", Raynaud's-like phenomena: Poor blood flow to peripheries

Insomnia: Histamine release from activated platelets

Exercise intolerance: Impaired oxygen extraction reducing anaerobic threshold, skeletal muscle abnormalities

Post-exertional symptom exacerbation: Widespread "micro" ischaemia-reperfusion injuries
Xerostomia: Reduced sublingual vasculature/blood flow

Lungs & cardiovascular:

Chest pain: Microvascular ischaemia
Dyspnoea: Pulmonary microthrombi

Genitourinary:

Period changes: Hypercoagulability (may also drive mast cell activation)

Ears & eyes:

Tinnitus: Poor blood flow to auditory nerves
Vision problems: Reduced retinal vasculature/blood flow

Neurological:

Cognitive dysfunction: Poor oxygen extraction, neurotransmitter disturbances
Headaches: Ischaemia, inappropriate vaso-activity
Paraesthesia: Nerve ischaemia
Slowness, weakness: Poor oxygen extraction, neurotransmitter disturbances

Clotting in long COVID may also cause or contribute common co-pathologies found in long COVID:

Autoimmunity: Misfolded proteins may not be recognised as "self"

Mast cell activation syndrome (MCAS): Many mast cell mediators have roles in (anti-)coagulation, such as tryptase (fibrinolytic properties); VEGF (angiogenesis); heparin (anticoagulant); prostaglandins (pro- and anticoagulant effects); histamine (promotes tissue factor expression, platelet aggregation). As such, MCAS could be a response to, or a cause of, clotting in long COVID.

Postural orthostatic tachycardia syndrome (POTS): POTS is associated with endothelial disease, platelet pathology, tissue hypoxia, and thromboinflammation. Clotting could cause nerve damage via nerve ischaemia and/or the neurotoxic effects of amyloid proteins; microcirculatory disturbances may cause sympathetic overcompensation, exacerbated by greater damage to parasympathetic fibres in the endothelial layer; hypoxia and cerebral hypoperfusion may trigger tachycardia.

Myalgic encephalomyelitis (ME): Poor perfusion; widespread micro-reperfusion injuries; hypoxia resulting in dysmetabolism

What tests are there for clotting in long COVID?

It is important to investigate and treat common co-pathologies (e.g. ME, POTS, MCAS) according to relevant guidelines. There are currently no clinically validated tests for the clotting found in long COVID. However, in no other situation is clotting left untreated; thoroughly checking for overt signs of clotting pathology therefore seems prudent. Depending on availability, tests may include:

Blood tests to check for overt signs of clotting

- aPTT or PTT
- Antiphospholipid syndrome biomarkers (lupus anticoagulant, anti-cardiolipin, anti-beta-2-glycoprotein-1)
- D-dimer
- Factor V
- Fibrinogen
- INR
- Platelet count
- Proteins C & S
- Prothrombin time
- ROTEM

These may all come back normal; in the context of long COVID, normal clotting tests do not rule out microclots, platelet hyperactivation, or endothelial dysfunction

Other tests (clinically available)

- Pulmonary function tests
- Ventilation/Perfusion (V/Q) or dual-energy computed tomography (DECT) imaging

These can be particularly helpful for patients with breathlessness. If DLco (also called TLco) comes back low, a V/Q or DECT scan may be an appropriate next step; these are more sensitive than CTPA to detect the microthrombi found in long COVID

What treatments are there for clotting in long COVID?

If any of the aforementioned tests show a clotting abnormality, these should be treated appropriately. There are currently no clinically approved treatments for the type of clotting often seen in long COVID/similarly presenting post-vaccine syndromes.

Prominent clinicians in the field promote the use of combined therapy, usually employing one anticoagulant plus two antiplatelet medications ("triple therapy"), sometimes with the inclusion of another relevant medication, described below (e.g. a statin). This is because clotting in long COVID involves several pathologies that all interact and exacerbate each other; as such, only addressing one pathway may not be adequate.

Some medications may be preferred over others due to their unique properties, or contraindications, for example:

- Many MCAS patients cannot tolerate aspirin
- Many people have a genetic mutation that makes clopidogrel ineffective
- Dabigatran has enhanced fibrinolytic properties *versus* other DOACs
- Sulodexide has evidence for efficacy in both tinnitus (a common long COVID symptom) and long COVID

Fibrinolytic supplements

- Nattokinase (this is a fermented soy product which many MCAS patients react badly to)
- Serrapeptase
- Lumbrokinase
- Bromelain

Unlike anticoagulants which inhibit the clotting cascade, fibrinolytic supplements directly break down fibrin. Research in other contexts suggests these are safe especially in the short-to-medium term

Supportive treatments with relevant pleiotropic effects

- **Statins:** Anti-inflammatory, anticoagulant, antiplatelet, mast cell stabilising, and endothelial-supporting effects; can increase cortisol which is often low in long COVID
- **Metformin:** Anti-inflammatory and antiviral properties
- **Selective serotonin reuptake inhibitors:** Anti-inflammatory, antiplatelet, mast cell stabilising, and endothelium-supporting effects
- **Omega 3:** Antiplatelet effects

Exercise may be harmful

Exercise or increasing physical activity (including graded exercise therapy) is contraindicated in ME (a common diagnosis in long COVID) which may be caused or exacerbated by coagulopathy. Exercise in those with ME can result in permanent worsening of the patient's condition. In the context of difficult to diagnose coagulopathy, exercise may risk clot dislodgement.

Pulmonary rehabilitation may be harmful

Breathing problems in long COVID can be due to a multitude of factors, including dysautonomia and coagulopathy. As the clotting in long COVID can be difficult to find with current clinically available tests, there is a concern that improving breathing through rehabilitation may lead to an artefactual improvement, which delays further testing by masking symptoms. Therefore, the use of pulmonary rehabilitation should be carefully considered in long COVID.

Further considerations

As this is an emerging treatment in long COVID that is not clinically recognised, there are several nuances that need consideration:

- **Bleed risk mitigation:** PPIs and H2 blockers should be considered to reduce bleed risk. PPIs can be less well tolerated by long COVID patients; H2 blockers may have added benefits of being a MCAS-targeted therapy too
- **Protocol:** Whilst prominent clinicians/researchers in the field use and promote triple therapy, some patients get significant improvements on dual therapy (either two antiplatelets, or one antiplatelet + one anticoagulant). It is not clear if this proffers an improved safety profile, or what regime is optimal for who
- **Treatment length:** Some patients (usually those who have been sicker longer) require longer treatment times than others, including some being on treatment indefinitely. It is not clear who requires longer or shorter treatment time. For those with clear evidence of bloods clots (e.g. V/Q scan), the DASH score may be helpful to assess long-term prophylactic treatment
- **Stopping the treatment:** If treatment is stopped too soon, patients can in some cases decline to a new, worse, baseline
- **Treatment-induced relapse:** It seems common that patients relapse upon starting aggressive clot-targeting therapies, usually around weeks 2-4 (though this is variable). Based on clinical experience, those who "push through" this relapse tend to respond well to treatment, but this may not always be the case
- **Generalisability:** Without access to research-grade tests, it can be difficult to establish whether clot-targeted therapies are the right course of action for any individual patient, particularly if standard tests come back clear. Long COVID is heterogeneous, so some patients will not have coagulopathy at the core of their disease

Resources

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