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Small Fiber Neuropathy in Long COVID: Pathophysiology, Clinical Manifestations, and Management

1. Pathophysiology and Evidence

Immune-Mediated Damage: Long COVID-related small fiber neuropathy (SFN) appears to be driven largely by immune dysregulation and inflammation triggered by SARS-CoV-2. Acute COVID-19 is associated with a surge of cytokines and activation of the innate immune system; in post-COVID SFN, these persistent inflammatory signals can activate skin macrophages, dendritic cells, and other innate immune cells, causing *neurogenic inflammation* and sensitization or damage of small nerve fibers [1] [2]. Recent evidence in an autoimmune SFN model (type 1 diabetic SFN) showed activated macrophages and Langerhans cells releasing pro-inflammatory mediators that sensitize intradermal nociceptors [1]. This mechanism is thought to be analogous in post-COVID SFN, where an *overabundance of cytokines* post-infection may lead to ongoing small-fiber injury even after the virus is cleared [1]. Notably, skin biopsies from long COVID patients confirm objective small-fiber loss, supporting an organic neuropathic process rather than a purely functional disorder [3]. Corneal confocal microscopy studies bolster this evidence: patients with long COVID show **reduced corneal nerve fiber density** and **increased corneal dendritic cell infiltration** up to 1–2 years post-infection [4]. These corneal findings indicate persistent neuroinflammation at the level of small autonomic fibers, providing a **direct, in-vivo** view of small nerve fiber damage in long COVID.

Autoimmune Responses: SARS-CoV-2 may also trigger *autoimmune mechanisms* that contribute to SFN. Molecular mimicry and post-viral B-cell dysregulation have been proposed to generate autoantibodies that attack components of the peripheral nervous system [5] [6]. Indeed, long COVID patients have higher rates of certain autoantibodies and are often ANA-positive, hinting at systemic autoimmune activation [7]. Specific small-fiber-related antibodies, such as **TS-HDS (trisulfated heparan disaccharide)** and **FGFR3 antibodies**, have been detected in roughly 20–50% of idiopathic SFN cases and in about one-third of post-COVID SFN patients [8] [9]. However, these markers are **nonspecific** – their presence suggests immune involvement but does not definitively prove causation [8]. Another line of evidence comes from *G-protein coupled receptor (GPCR) autoantibodies*: POTS, a common autonomic complication of long COVID, is associated with autoantibodies against β-adrenergic and muscarinic acetylcholine receptors [10]. Such antibodies could impair autonomic nerve signaling and contribute to orthostatic intolerance and tachycardia in these patients [10]. The **frequency of POTS and SFN in long COVID** (one cohort found POTS in 67% of long COVID patients) and their known association with GPCR autoantibodies supports an autoimmune etiology in at least a subset of cases [10]. It should be noted, though, that no single pathogenic autoantibody has been pinpointed for post-COVID SFN, and research is ongoing.

Persistent Virus and Dysregulation: Other hypotheses include persistent viral reservoirs and microvascular damage. SARS-CoV-2 proteins have been found lingering in some patients' bodies long after acute infection, and this could drive chronic immune activation [11] [12]. Some long COVID patients have **detectable viral spike protein** in the blood months later, suggesting an antigenic stimulus that continually

provokes the immune system [11] [12]. This ongoing immune response might contribute to neuropathic symptoms. Additionally, microangiopathic effects of COVID-19 – endothelial injury and microclot formation – could impair blood supply to small nerve fibers. Chronic endothelial dysfunction and microclots have been documented in long COVID and may cause ischemic damage to small fibers, compounding the immune-mediated injury [6] [13]. Overall, the pathogenesis is likely *multifactorial*: a combination of **post-infectious autoimmunity, neuroinflammation, and microvascular dysregulation** leads to damage or dysfunction of thin nerve fibers. This is consistent with what is seen in other post-viral neuropathies and in conditions like postural tachycardia, which often follow viral illnesses and share overlapping mechanisms [14] [10]. Importantly, **evidence of small-fiber pathology** in long COVID is now compelling – up to half of patients with long COVID pain syndromes have objective SFN on testing [15] – establishing that SARS-CoV-2 infection can indeed trigger an organic neuropathy.

2. Clinical Presentation and Symptoms

Neuropathic Sensory Symptoms: Long COVID-related SFN typically presents with symptoms of peripheral nerve hyperirritability or loss of function in small sensory fibers. Patients often report **distal limb paresthesias** such as burning pain, tingling ("pins-and-needles"), and numbness, often in a **stocking-and-glove distribution** (feet and hands) if the neuropathy is length-dependent [16] [3]. Allodynia (pain from light touch) and thermal sensory disturbances are common – patients may have heightened pain to mild warmth or cold due to involvement of thin myelinated Aδ and unmyelinated C fibers that carry temperature and pain signals [16]. While distal extremity symptoms predominate, long COVID SFN can also be **patchy or non-length-dependent**, producing sensory symptoms in the trunk, face, or proximal limbs [3]. For example, some patients experience tingling or burning in the abdomen or chest, or even neuropathic facial pain. This variability reflects the diffuse distribution of small fibers and, in some cases, dorsal root ganglion involvement. Notably, many long COVID patients with SFN also describe **"neurogenic" fatigue and post-exertional symptom flare-ups**. In one series, 92% had post-exertional malaise (exacerbation of fatigue and pain after activity) reminiscent of ME/CFS [17]. This suggests an overlap between small-fiber neuropathic pain and central fatigue pathways in long COVID.

Autonomic Dysfunction: A hallmark of post-COVID SFN is *dysautonomia* – dysfunction of the small autonomic fibers controlling cardiovascular, gastrointestinal, and sudomotor (sweat gland) functions. **Orthostatic intolerance** is frequently reported. Patients may develop **postural orthostatic tachycardia syndrome (POTS)**, defined by excessive heart rate increase on standing ($\geq$30 bpm) with symptoms like dizziness, palpitations, presyncope, and exercise intolerance. POTS and related orthostatic syndromes are commonly seen in long COVID; studies have found POTS in roughly 2/3 of long COVID patients evaluated for autonomic symptoms [18]. These individuals (often young to middle-aged adults) experience rapid heartbeat, lightheadedness, chest discomfort, and fatigue upon upright posture – often accompanied by acral vasoconstriction (cold, discolored feet) and, in severe cases, near-fainting. **Blood pressure dysregulation** can also occur: while POTS involves normal blood pressure or mild drops, a subset of patients have orthostatic hypotension (a significant BP drop on standing), leading to weakness or cognitive "fog" when upright. Alongside cardiovascular signs, **gastrointestinal dysautonomia** is common. Long COVID SFN patients frequently report GI dysmotility symptoms – e.g. early satiety, bloating, nausea (suggesting gastroparesis), alternating diarrhea and constipation (reflecting small-fiber involvement in enteric motility) [19]. Some develop **irritable bowel syndrome**-like symptoms post-COVID. Autonomic fiber damage can also lead to **urinary dysfunction** (bladder retention or urgency), **anhidrosis or hyperhidrosis** (abnormal sweating patterns on QSART testing), dry eyes and mouth, and even pupillary abnormalities. Indeed, *corneal small fiber loss* in long COVID correlates with **neuropathic ocular complaints** – patients

may have dry eye, blurry vision, or neuropathic corneal pain (a burning/gritty sensation in the eyes) as part of the SFN spectrum [20]. Autonomic symptoms often fluctuate, and can be exacerbated by triggers like heat, dehydration, or physical stress.

Sex Differences: Notably, **women comprise the majority of adult long COVID SFN/POTS patients**. Across cohorts, 75–85% of patients with post-COVID SFN and dysautonomia have been female [17] [21]. This mirrors the epidemiology of idiopathic POTS and many autoimmune disorders, which disproportionately affect women. Female patients not only are more likely to develop these syndromes, but may also experience a *greater intensity and variety of symptoms*. Studies have found that women with long COVID tend to report a higher number of persistent symptoms than men, independent of acute COVID severity [22]. For example, one analysis showed women with long COVID had more frequent **musculoskeletal pain**, while men more often reported **sleep disturbances** as a primary issue [23]. Women with POTS in particular endorse more pain symptoms (e.g. body aches, migraine) compared to men with POTS, who report relatively more sleep and cognitive issues [23]. The reasons are not fully clear but may involve hormonal influences on autonomic regulation and immune response. Regardless of sex, the **core clinical picture** of post-COVID SFN is consistent: a combination of **neuropathic pain and sensory abnormalities** plus **autonomic complaints** (cardiovascular, GI, sudomotor). However, clinicians should have a high index of suspicion in women presenting with this constellation after COVID-19, given their predilection, while not overlooking male patients who can certainly be affected. The timing of onset is typically **weeks to a few months after the acute infection** (median ~2–3 weeks in one series [24]), though some patients notice symptoms only later or after another trigger such as vaccination or illness. Importantly, these symptoms are often **independent of the severity of the initial COVID-19**. Even patients with mild acute illness can develop significant SFN/dysautonomia afterward – no strong correlation with acute COVID hospitalization or severity has been observed [25]. This unpredictable emergence highlights the need for all post-COVID patients (not just those who were severely ill) to be monitored for neuropathic complications if they have compatible symptoms.

3. Diagnosis

Diagnosing long COVID-related SFN requires a combination of clinical evaluation and specialized testing to document small fiber dysfunction. **Clinical screening** should include detailed neurological exam (often normal for strength and reflexes, since large fibers are intact) and **autonomic system review**. Bedside signs like heart rate/blood pressure changes on standing, distal color changes, or reduced distal pinprick sensation might raise suspicion. Definitive diagnosis, however, rests on objective measures:

- **Skin Biopsy for Intraepidermal Nerve Fiber Density (IENFD):** A **punch skin biopsy** is the gold standard for confirming small fiber neuropathy [26]. Typically taken from the distal leg (and sometimes thigh), the 3–4 mm skin sample is stained to count the density of small nerve fibers in the epidermis. Long COVID patients with SFN show **reduced IENFD** compared to age-matched norms, confirming the neuropathy [26]. This test has high specificity – a low fiber density definitively indicates small fiber loss – but sensitivity can be an issue if patchy distribution or early-stage disease is present [27] [28]. In fact, serial biopsies may be useful: one study followed initially biopsy-negative long COVID patients who later became positive as symptoms evolved, illustrating that SFN can develop over time [29]. Immunohistochemical analysis (per **Lauria's protocol**) can also evaluate sweat gland innervation to detect autonomic involvement [26]. While widely regarded as the diagnostic gold standard, limited access to expertise in performing and interpreting skin biopsies remains a challenge, and no standardized threshold specific to post-COVID etiology exists [27].

Nonetheless, a skin biopsy showing diminished small fibers provides strong, objective evidence of SFN in long COVID patients with otherwise unexplained neuropathic symptoms.

- **Corneal Confocal Microscopy (CCM):** This is an emerging **noninvasive imaging** technique to evaluate small fibers by scanning the cornea (which is densely innervated by Aδ and C fibers). CCM has proven particularly useful in research on long COVID. Studies using in-vivo confocal microscopy have identified **significant corneal nerve fiber loss** in long COVID patients, especially those with neurological symptoms, along with an increased density of **dendritic cells** in the cornea [4]. The presence of these immune cells alongside nerve loss provides a window into ongoing neuroinflammation. Corneal nerve fiber length and density are quantifiable, and long COVID cohorts show markedly lower values than controls ~20 months post-infection [4]. For patients with ocular symptoms (dry eye, pain) or if skin biopsy is not readily available, CCM offers a rapid, painless test that can support a diagnosis of SFN. Its sensitivity appears high in research settings, although normative databases and clinical availability are still limited. Clinically, an **abnormal corneal nerve morphology on CCM** in a post-COVID patient (especially if accompanied by **"microneuromas"** – bulbous nerve endings indicating regenerative attempts [4]) would strongly suggest small fiber neuropathy. This tool is being incorporated into some long COVID clinics and may become more mainstream as a diagnostic adjunct for SFN.

- **Autonomic Function Testing:** A battery of autonomic tests can objectively demonstrate dysfunction of small autonomic fibers:

- *Heart Rate and Blood Pressure Variability:* Analysis of **heart rate variability (HRV)** (at rest and with deep breathing or Valsalva) gauges cardiovagal function. Long COVID dysautonomia often shows reduced HRV, indicating blunted parasympathetic activity. **Tilt-Table Testing** is the gold standard to diagnose POTS or orthostatic hypotension. During a tilt test, patients with POTS will exhibit a >30 bpm jump in heart rate (or >120 bpm absolute) within 10 minutes upright, reproducing their symptoms, without significant BP drop. Orthostatic hypotension, in contrast, is confirmed by a >20 mmHg systolic BP drop. Tilt testing in long COVID clinics has revealed a high incidence of POTS and orthostatic intolerance (one series found 86% of long COVID patients had some form of autonomic dysfunction, median age ~32, majority female [21]). Documenting these changes is important for formal diagnosis and management planning. Additionally, **24-hour ambulatory BP/HR monitors** and exercise testing (e.g. *invasive CPET* used in the Yale study) can uncover neurocirculatory abnormalities consistent with dysautonomia [30].
- *QSART and Sudomotor Tests:* The **Quantitative Sudomotor Axon Reflex Test (QSART)** measures sweat output in response to acetylcholine delivered iontophoretically to the skin. Impaired sweating in the foot or distal leg is a sensitive indicator of peripheral autonomic (small fiber) neuropathy. Many post-COVID SFN patients show attenuated QSART responses, consistent with sympathetic sudomotor fiber loss. Similarly, a **Thermoregulatory Sweat Test** (using powder to visualize sweat patterns in a heated chamber) can show patchy or distal anhidrosis. These tests have moderate sensitivity and good specificity for autonomic SFN; combined with skin biopsy, they increase diagnostic yield of detecting any small fiber involvement (sensory or autonomic).
- *Cardiovagal and Adrenergic Function:* Tests like deep breathing HRV (for vagal function) and Valsalva maneuver (which assesses baroreflex and sympathetic adrenergic function) can further delineate which autonomic pathways are affected. Long COVID patients with SFN/POTS may have an exaggerated phase IV overshoot on Valsalva or blunted phase II, indicating sympathetic dysregulation. **Head-up tilt with transcranial Doppler** or cerebral blood flow monitoring is

sometimes done in research to confirm cerebral hypoperfusion during orthostasis, but that's specialized.

These autonomic tests help **quantify the dysfunction** (e.g., degree of vagal impairment, presence of vasomotor failure), guiding therapy. For instance, a patient with predominant cardioacceleratory POTS might benefit from beta-blockade, whereas one with blood pressure drops might need vasoconstrictors.

- **Laboratory and Antibody Testing:** Given the suspected autoimmune basis in many cases, a thorough **laboratory workup** is recommended to identify any treatable causes or immune markers:
- *General Laboratories:* Rule out other causes of neuropathy that could be masked by coincidental COVID. This includes testing for **diabetes or pre-diabetes (glucose tolerance, A1c)**, **vitamin B12 levels**, **thyroid function**, **B6 levels**, and **HIV/hepatitis serologies**. These are standard in any SFN workup, as conditions like glucose dysregulation or B12 deficiency can cause small fiber neuropathy.
- *Autoimmune Serologies:* A high proportion of long COVID SFN patients have positive **antinuclear antibodies (ANA)** [31], suggesting an autoimmune diathesis. Testing for **ANA and ENA panels, rheumatoid factor, ESR/CRP** is reasonable, especially if there are systemic symptoms (joint pain, rash) hinting at a connective tissue disease. In one report, long COVID SFN patients with concurrent new-onset arthritis had high ANA titers and responded to immunosuppressive therapy [7]. Markers for **Sjögren's syndrome** (SSA/Ro, SSB/La) are pertinent because Sjögren's can present with small fiber neuropathy and some long COVID complaints (e.g. sicca, dysautonomia) overlap with it.
- *Specific Neuropathy-Related Antibodies:* Tests for **TS-HDS and FGFR3 autoantibodies** can be sent (these are specialized ELISA assays available in some labs). As noted, ~30% of post-COVID SFN patients in one study had these antibodies [32]. Their presence might reinforce an autoimmune neuropathy diagnosis, but absence doesn't rule it out (and presence doesn't confirm causation). Likewise, **ganglionic acetylcholine receptor (gAChR) antibodies** (associated with autoimmune autonomic ganglionopathy) could be checked if a patient has severe diffuse autonomic failure – though this is rare in long COVID (gAChR Ab typically causes near-complete autonomic shutdown, more severe than POTS).
- *GPCR Autoantibody Panels:* Research assays (available in Europe via CellTrend, etc.) can measure IgG against **β1/β2 adrenergic receptors, α1 adrenergic, M2/M3 muscarinic receptors, and AT1 angiotensin receptors**. Long COVID POTS patients have been found to have elevated levels of some of these functional autoantibodies compared to controls [33] [10]. While these tests are not yet standard or FDA-approved, a high titer might support consideration of immunotherapy. Clinically, if strong suspicion of autoimmune POTS/SFN exists, some specialists might use this data (e.g. high adrenergic receptor Ab) as part of a decision to try immunosuppression.
- *Other tests:* Given links between long COVID and reactivation of viruses like EBV [5], checking **EBV serologies or PCR** and other herpesvirus panels can be considered in research settings, though clinical utility is unclear. **Cortisol levels** have been noted to be low on average in long COVID cohorts with fatigue [34], but this is a systemic finding not specific to neuropathy.

In summary, the diagnostic work-up combines **direct evidence of small fiber damage** (skin or corneal biopsy) with **functional tests** (autonomic testing) and **immune/infectious labs** to characterize the syndrome. Sensitivities and specificities: skin biopsy has high specificity (a positive biopsy virtually confirms SFN), but sensitivity may be in the range of ~75% (some early or focal cases can be missed) [27]. Autonomic tests vary – tilt table testing is very sensitive for POTS (if done properly), QSART is fairly sensitive for distal autonomic SFN (sensitivity ~80% in distal symmetric SFN in some series) but might miss pure small-fiber sensory neuropathy. Corneal confocal microscopy has shown promise as a sensitive marker in research (detecting changes in a majority of long COVID neuro patients), but its specificity is being defined (other

neuropathies can also cause corneal changes). **Clinical recommendations** are to confirm SFN with objective testing whenever possible before embarking on immunotherapy, since symptoms can be nonspecific. Neurology and autonomic specialty societies advise using skin biopsy and autonomic reflex testing to document neuropathy in post-COVID patients, both to solidify the diagnosis and to monitor responses to treatment [35] [26]. Once confirmed, patients should be counseled that they have an identifiable neuropathic complication of COVID (which often provides relief that "it's not all in my head") and this guides targeted management as described next.

4. Treatment

Management of long COVID SFN is *two-pronged*: **alleviating symptoms** (neuropathic pain and autonomic dysfunction) and, when possible, **modifying the underlying disease process** (e.g. immune therapies to promote nerve recovery). Given that no single therapy is universally effective, a **multidisciplinary, individualized approach** is recommended [36].

Symptomatic Treatment – Neuropathic Pain and Sensory Issues: Small fiber neuropathy pain can be debilitating, so aggressive symptom control is important for quality of life. **Neuropathic pain medications** are first-line: - *Gabapentinoids:* **Gabapentin** or **pregabalin** can reduce burning and tingling pain by decreasing neuronal excitability. These are commonly used in long COVID SFN patients, often providing partial relief [36]. Dosing is titrated to effect (e.g. gabapentin 300 mg up to 900–1800 mg/day as tolerated). - *SNRIs and TCAs:* **Duloxetine** (an SNRI) is effective for neuropathic pain and also addresses comorbid anxiety or depression; doses of 30–60 mg/day are typical [36]. It may also aid orthostatic intolerance by increasing sympathetic tone slightly. **Tricyclic antidepressants** like amitriptyline or nortriptyline (in low doses at night, e.g. 10–25 mg) can help with neuropathic pain and sleep, though side effects must be monitored, especially since these can worsen orthostatic hypotension in some. - *Topical agents:* Capsaicin 8% patches (applied to painful areas of feet/legs in a clinic setting) deplete substance P and can reduce pain for weeks by desensitizing peripheral nociceptors. Topical lidocaine or low-dose capsaicin creams applied at home are lower potency options for focal pain. - *Other adjuvants:* **Alpha-lipoic acid** (an antioxidant) and certain supplements have been tried (the MDPI review notes homotaurine and phosphatidylserine usage) [36], though evidence is anecdotal. They are generally safe and might be attempted as adjuncts for nerve health. **Acetyl-L-carnitine**, which can support mitochondrial function, is sometimes given empirically in post-viral neuropathies. - If pain is severe and refractory, **tramadol** (a weak opioid with SNRI properties) can be considered in moderation, but traditional opioids are usually ineffective for neuropathic pain and best avoided to prevent dependency.

Beyond medications, **non-pharmacological pain management** techniques can help. These include *transcutaneous electrical nerve stimulation* (TENS) for localized relief, and integrative approaches like acupuncture. **Physical therapy** is useful not only for deconditioning but also for pain – gentle exercise can release endorphins and improve blood flow to nerves. Patients should be counseled on pacing activity to avoid post-exertional flares (which can worsen both pain and dysautonomia).

Symptomatic Treatment – Autonomic Dysfunction: Treating POTS and related autonomic symptoms greatly improves function: - *Volume Expansion:* Nearly all POTS patients benefit from increasing **blood volume**. **Fluid loading** (aiming for 2–3 liters of water per day) and **high salt intake** (3–10 grams of sodium per day, via salt tablets or salted foods) are foundational strategies [37]. This helps mitigate orthostatic tachycardia by improving preload. Many patients also use **electrolyte solutions** (e.g. oral rehydration salts or sports drinks) to enhance fluid retention. - *Compression and Physical Countermeasures:* Compression

stockings (30–40 mmHg, waist-high) and abdominal binders can reduce venous pooling in the legs and abdomen, respectively, thereby increasing upright blood return. Patients are taught counter-maneuvers (leg crossing, squatting or tensing leg muscles) when dizzy. Gradual **tilt training** (e.g. standing against a wall incrementally longer each day) can improve orthostatic tolerance over time by conditioning the autonomic reflexes. - *Heart Rate Control:* **β-blockers** are a first-line pharmacologic treatment for POTS tachycardia [37]. Low-dose **propranolol** (10–20 mg taken 30 minutes before upright activities or exercise) can blunt the excessive heart rate and reduce palpitations and tremulousness. Longer-acting beta-1 selective agents (metoprolol, bisoprolol) are used as well, often at low doses (e.g. metoprolol 12.5–25 mg BID) to avoid dropping blood pressure too much. An alternative for those who cannot tolerate beta blockers (e.g. due to asthma or fatigue) is **ivabradine**, a sinus node inhibitor that lowers heart rate without affecting blood pressure. One small trial in POTS showed ivabradine improved symptoms, and it's being used off-label in some long COVID clinics. - *Vasoconstrictors and Volume Retainers:* If hypotension or pooling is an issue, **Midodrine** (an alpha-1 agonist) can be given to raise standing blood pressure and reduce dizziness. It's dosed at 2.5–10 mg three times daily (avoiding doses near bedtime to prevent supine hypertension). **Fludrocortisone** (a mineralocorticoid) at 0.05–0.1 mg daily can help the kidneys retain sodium and water, thus expanding plasma volume; it's useful in patients who can tolerate it (watching for hypokalemia or blood pressure increases). These can be combined with salt/fluid loading for synergistic effect. - *Other autonomic modulators:* **Pyridostigmine** (a cholinesterase inhibitor) has been used in POTS to enhance parasympathetic activity and splanchnic vasoconstriction – typically 30–60 mg once or twice daily. It can modestly improve orthostatic tachycardia and GI motility. Some hyperadrenergic POTS patients (especially those with significant tremor or anxiety) respond to central sympatholytics like **clonidine** or **methyldopa** in low doses, which temper the central sympathetic outflow. These require caution due to risk of worsening fatigue or depression.

For **GI dysmotility**: dietary measures (small, frequent meals; low-fat and low-fiber diet if gastroparesis) are first-line. Pharmacologically, **metoclopramide** or **domperidone** (if available) can help gastroparesis but long-term use is limited by side effects. Newer agents like **prucalopride** (a 5-HT4 agonist) may help colonic motility in constipation. For diarrhea-predominant dysfunction, **loperamide** PRN can be used. If nausea is prominent, antiemetics (ondansetron, promethazine) provide symptom relief. **Bethanechol** (a muscarinic agonist) is sometimes used to aid bladder emptying or GI motility in autonomic neuropathy, but evidence is anecdotal.

Disease-Modifying Therapies: Given the immunological underpinnings, several therapies aim to treat the *cause* of the neuropathy rather than just symptoms: - *Intravenous Immunoglobulin (IVIG):* IVIG has emerged as a promising option for post-COVID SFN, especially when an autoimmune process is suspected. A retrospective Yale study reported that **9 out of 9 patients** with long COVID SFN who received IVIG (2 g/kg monthly) experienced significant clinical improvement, whereas only 3 of 7 who did not get IVIG improved over the same period [30] [38]. By 6 months of therapy, 6 of the 9 had **complete resolution** of neuropathic symptoms and the other 3 had substantial improvement [39]. Patients noted reduced pain, restored sensation, less orthostatic intolerance, and even improvement in post-exertional malaise [39]. This dramatic response suggests IVIG may modulate the aberrant immune response – proposed mechanisms include neutralizing pathogenic autoantibodies and exerting an anti-inflammatory effect that allows regeneration of damaged small fibers [40]. That said, IVIG is not universally effective; outside of controlled trials, results have been **mixed** and it's costly. Two randomized trials in idiopathic SFN prior to COVID were **negative** (no significant benefit over placebo) [8], tempering enthusiasm. Nonetheless, the **Class III evidence** from case series is encouraging [41], and experts like Dalakas argue it can be justified in select long COVID SFN patients given the significant disability and lack of alternatives [42] [43]. IVIG is typically trialed for 3–

6 months and continued if clear improvement is observed. Some patients may require long-term maintenance IVIG if symptoms recur upon stopping [44]. - *Corticosteroids and Immunosuppressants:* In cases where SFN is accompanied by systemic autoimmune features (e.g. new connective tissue disease or high ANA), immunosuppressive therapy can be considered. **Corticosteroids** (prednisone or equivalent, e.g. 40–60 mg daily then tapered) can dampen immune-mediated nerve damage. There are reports of long COVID neuropathy patients (especially those with co-occurring inflammatory arthritis or autoimmune markers) responding to steroid courses [7]. One case series noted improvement in SFN symptoms with immunosuppressants like **methotrexate and azathioprine**, used in conjunction with treatment of autoimmune arthritis triggered by COVID [7]. These are not standard for isolated SFN but could be useful if SFN is part of a broader post-COVID autoimmune syndrome. **Mycophenolate mofetil** or **rituximab** might theoretically help if a specific antibody-mediated process (like ganglionic AChR Ab or a suspected connective tissue disease) is at play, but we lack data in long COVID for these at present. - *Plasmapheresis (PLEX):* Plasmapheresis can remove circulating autoantibodies and immune complexes. While no large studies exist yet for long COVID SFN, PLEX has shown benefit in some idiopathic autoimmune dysautonomias and POTS. Anecdotally, a few long COVID patients with severe POTS or neuropathy and high GPCR autoantibody titers have improved after plasma exchange – sometimes dramatically so (similar to what is seen in Guillain-Barré). This is an invasive treatment usually reserved for severe, refractory cases or as a trial in research settings. - *Low-Dose Naltrexone (LDN):* **Low-dose naltrexone** (e.g. 1.5–4.5 mg nightly) is an anti-inflammatory and glial cell modulating agent that has gained popularity for fibromyalgia and other central sensitization disorders. In long COVID, LDN is being used off-label to reduce neuroinflammation and pain. The *Nature Reviews* article highlights LDN as a potential therapy for neuroinflammation in long COVID [37]. Although formal trials are pending, many clinicians report that LDN can help symptoms of brain fog, fatigue, and diffuse pain – it likely works by reducing microglial activation and pro-inflammatory cytokine release in the nervous system. It is generally safe and well-tolerated (aside from vivid dreams or insomnia in some). - *Autonomic Rehabilitation:* While not a drug, **structured rehabilitation** targeting the autonomic nervous system can gradually improve the condition. This includes supervised **exercise programs** (recumbent aerobic exercise like rowing or cycling, to avoid orthostatic stress initially) with very slow progression, to recondition deconditioned patients and improve vascular tone. Some centers employ **Tilt Training** and **physical therapy specifically for dysautonomia**, which have shown to increase orthostatic tolerance over weeks to months. *Intravenous hydration* therapy (IV saline infusions) is occasionally given to provide temporary relief in severe POTS, but this is a short-term bridge rather than a lasting solution.

Evidence Base: As of 2024, high-quality evidence is still limited, but growing. The positive IVIG case-control study [30] [38] and others like it have prompted calls for **controlled trials** of immunotherapies in long COVID SFN. Indeed, experts are now advocating for an IVIG randomized trial given the retrospective improvements observed [45] [39]. Meanwhile, an NIH-funded trial (STARS study) is evaluating **beta blocker vs. pyridostigmine vs. placebo in long COVID POTS**, and others are investigating therapies like **anticoagulation (to address microclots)** and **antiviral treatments** for viral persistence. For now, clinicians must rely on existing knowledge of idiopathic SFN and POTS management, adapting it to the long COVID context. A reasonable approach is to start with **conservative measures and symptomatic treatments** (fluids, salt, compression, neuropathic pain meds, etc.) for all patients, and **escalate to IVIG or immunosuppressants** in patients who are severely affected or have evidence of autoimmunity and do not improve with initial therapy [37]. Multidisciplinary care is key: cardiologists or autonomic specialists for POTS, neurologists for neuropathy, rheumatologists if autoimmune disease is present, and physiatrists or physical therapists for rehab.

It's important to set expectations: many treatments result in **partial improvements** rather than total cure [36]. Patients often require a combination of therapies to address the spectrum of symptoms. For example, one might be on midodrine and compression for orthostasis, gabapentin for pain, and receive IVIG monthly for immune modulation. Close follow-up is needed to monitor efficacy and adjust the regimen. Encouragingly, some patients show major recovery – e.g. returning to exercise and normal activities – especially if therapies like IVIG are effective [39]. Others may remain limited but with better symptom control (e.g. able to stand longer with POTS under control, or sleep through the night once pain is managed). As research evolves, treatment protocols will be refined, but the current strategy is **symptom-driven supportive care plus immune therapy in selected cases**, aligning with expert consensus and case series evidence.

5. Prognosis

The long-term outlook for long COVID-associated SFN is still being elucidated, but early data and clinical experience provide some insight. **Overall, prognosis appears to be variable** – some patients recover significantly over time (with or without treatment), whereas others have persistent symptoms beyond a year or two. Unlike the acute post-viral neuropathies (e.g. Guillain-Barré, which often improve substantially in months), SFN in long COVID can follow a chronic, relapsing course in a subset of patients.

Natural History and Recovery: Small nerve fibers *can* regenerate, but slowly. In favorable cases, nerves regrow and symptoms abate over **6–18 months**. For example, a few long COVID SFN patients not treated with immunotherapy have reported gradual improvement in burning pain and autonomic function over the course of a year or more, presumably as inflammation subsides and nerve fibers reinnervate the skin. One longitudinal evaluation noted that, on average, patients had about **50% improvement in neuropathic symptom severity over time**, but notably *none* had complete resolution in that observation period [46]. This suggests partial recovery is common, while full recovery may be slower or incomplete in many cases. Supporting this, a recent follow-up of long COVID patients with SFN diagnoses found **no one was 100% back to normal** at their latest evaluation, though more than half reported at least some improvement [46].

On the other hand, when active immune treatment is given, outcomes can be quite positive. With IVIG therapy, a subset of patients achieved *total resolution* of SFN symptoms within 6–12 months [39]. These individuals essentially returned to their pre-COVID baseline, indicating that in an immune-mediated case, stopping the autoimmune attack can allow for nerve repair and excellent recovery. Even those who did not fully resolve often improved enough to resume many activities. The key point is that **reversibility is possible**, especially if the nerve cells (dorsal root ganglia and autonomic ganglia) remain intact and only the fibers are affected. Skin biopsies repeated post-treatment have shown *increased nerve fiber density* in some cases, correlating with symptom improvement, which is an objective sign of nerve regeneration.

Duration and Persistence: Unfortunately, some patients continue to suffer long-term. Particularly, if SFN is accompanied by conditions like **ME/CFS** or established **POTS**, these syndromes can be lifelong or very long-lasting for many. Experts caution that new-onset ME/CFS or POTS after COVID often "persists for years and can become a chronic life-long condition" in the absence of effective disease-modifying treatment [47]. This implies that if long COVID SFN falls into that phenotype (e.g. the patient meets criteria for ME/CFS with dysautonomia), the prognosis may be one of managing a chronic illness with gradual improvements at best. Some patients with pre-existing tendencies (for example, a young woman with hypermobile Ehlers-Danlos who develops POTS/SFN after COVID) might have ongoing symptoms for many years, since these conditions can wax and wane rather than simply resolve.

Factors Influencing Recovery: Several factors may modulate prognosis: - *Severity of Neuropathy:* Patients with **milder fiber loss** (on biopsy or QST) and less severe autonomic dysfunction likely recover faster and more fully than those with severe fiber depletion. Mild cases might even improve spontaneously over 6–12 months as inflammation diminishes. In contrast, severe cases (e.g. those with significant small fiber denervation on biopsy and frank autonomic failure) have more ground to make up and might be left with residual deficits. - *Time to Treatment:* Anecdotally, those who received immunotherapies (IVIG, steroids) earlier in the course (say, within 6–9 months of symptom onset) sometimes had better outcomes than those treated very late. Early intervention might halt immune damage before it becomes irreversible (fibrosis or permanent neuron loss). However, even patients treated late (e.g. 1.5 years after onset) have shown improvements [24] [39], so it's never "too late" to attempt therapy if significant symptoms persist. - *Autoimmune Features:* The presence of an active autoimmune process could cut both ways. On one hand, it often means more severe disease (as the immune system is actively attacking nerves), potentially prolonging symptoms. On the other hand, it offers a target for therapy – these patients may respond well to IVIG or immunosuppression and improve. For instance, in the Yale series, patients with positive autoantibodies (even nonspecific ones) did improve on IVIG [40]. Yet if the autoimmune process is not adequately suppressed, symptoms might continue or relapse when therapy is stopped [44]. Cases have been noted where discontinuation of IVIG led to symptom return, implying a need for ongoing therapy to maintain remission [44]. - *Comorbid Conditions:* Coexisting problems like diabetes, another neuropathy, or significant organ damage from acute COVID can worsen neuropathy or hinder recovery. For example, if a patient had undiagnosed pre-diabetes, the long COVID SFN might recover slower unless that metabolic issue is addressed. - *Sex and Hormonal Factors:* It's not clear if sex influences recovery, but given females have higher prevalence, it's worth noting hormonal changes (pregnancy, menopause) can affect autoimmune activity and POTS. Some women report fluctuations in dysautonomia severity with menstrual cycles. Pregnancy has unpredictably improved or worsened POTS in case reports. These aspects need more study in long COVID cohorts. - *Rehabilitation and Lifestyle:* Patients who engage in **graded exercise (as tolerated)** and **autonomic rehabilitation** often see functional gains over time, which can improve overall prognosis in terms of daily living – even if some neurologic deficits remain. Conversely, patients who are completely bedbound for long periods (due to severe symptoms) may develop secondary deconditioning that complicates recovery. **Strict pacing** to avoid crashes and gradually increase activity is associated with better functional outcomes in illnesses like ME/CFS, and likely holds true in long COVID SFN as well.

Long-Term Outcome: We are now ~3 years into the pandemic aftermath, and some longitudinal patterns are emerging. Many long COVID SFN patients still have ongoing symptoms 1–2 years out, but there is a slow trend towards improvement in a fraction of them. A medRxiv analysis of nearly 1,000 long COVID patients noted neuropathic symptoms improved by at least 3 points (on a 1–5 scale) in about 5/8 of those surveyed over time [48] – meaning some improvement in over half, though not necessarily full resolution. Importantly, small fiber neuropathy as a condition is not typically degenerative (unlike large-fiber neuropathies); if the inciting cause is removed or dies down, **stabilization and partial recovery** are the rule. We do not currently have evidence of post-COVID SFN progressing to involve large fibers or motor fibers in most cases – it tends to remain a small fiber issue without causing paralysis or major sensory ataxia, which is somewhat reassuring.

Follow-Up and Monitoring: Patients are usually followed with periodic clinical assessments. Some objective improvements can be tracked: for instance, a follow-up skin biopsy might show increased nerve fiber density after treatment, or repeat QSART may normalize sweating in areas that were previously abnormal. Improvements in tilt table results (e.g. a decrease in heart rate increment or ability to finish a 10-minute stand) can document autonomic recovery. Corneal confocal microscopy, in research, could be repeated to

see if nerve fibers are reappearing (in other neuropathies, corneal nerves do regenerate alongside clinical improvement).

If after 1–2 years a patient has only minimal improvement, it suggests a more chronic course and they may need long-term maintenance therapy (symptomatic meds indefinitely, or ongoing IVIG if it's the only thing controlling symptoms). Conversely, if a patient is steadily improving, medications can be tapered (for example, reducing IVIG frequency or weaning off midodrine when POTS signs normalize). Some experts predict that a subset of long COVID SFN patients will have **persistent, albeit manageable, dysautonomia** for many years – similar to idiopathic POTS – while others will essentially recover. Unfortunately, cases with overlapping **ME/CFS** features might have the toughest prognosis, as ME/CFS historically has low rates of full remission.

In summary, the prognosis for long COVID small fiber neuropathy is **guarded but not grim**. There is potential for meaningful recovery, especially with appropriate therapy: cases of full resolution have been documented [39]. At the same time, a considerable fraction of patients may experience a chronic course with partial improvements and relapses. Key factors like immune activity, treatment timing, and co-morbid syndromes influence the trajectory. Patients should be counseled that **improvements are often slow and incremental** – e.g. being able to stand 15 minutes longer after a few months of therapy, or pain decreasing from severe to mild – but these changes significantly enhance daily functioning. Continued research and **post-2023 clinical data** will hopefully clarify long-term outcomes. Early results from ongoing studies and patient reports emphasize the need for patience and comprehensive care. With time, some patients will regenerate small fibers and feel closer to normal, while others may need to adapt to a "new normal" and maintain treatments to keep symptoms in check. **Close follow-up, supportive care, and optimism tempered with realism** are essential in managing expectations for both patients and specialists navigating this novel post-viral neuropathy [49].

Bottom line: Long COVID-related SFN can be life-altering, but it is a *recognizable and often treatable complication* of SARS-CoV-2 infection. By understanding its immune-mediated mechanisms, clinicians can validate patients' experiences and pursue appropriate diagnostic tests. With a combination of symptom-directed treatments and immunotherapies, many patients achieve significant relief. Ongoing research (including high-quality studies published in 2024 and 2025) is rapidly informing best practices and giving hope that outcomes will continue to improve for those suffering from this condition [38] [37].

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