Mount Sinai

Cohen Center for Recovery from Complex Chronic Illness



Infection-Associated Chronic Illnesses Provider Manual

First Edition



Table Of Contents

Important Medical Disclaimers 4
Chapter 1 | Introduction 5
About the Infection-Associated Chronic Illness (IACI) Manual 5
What Are IACIs? 7
Chapter 2 | Overview of IACIs 7
Mechanisms of Disease 8
Multiple Hits 9
Common Misconceptions about IACIs 11
What Is Recovery? 12
Chapter 3 | Current Research on the Drivers of IACIs 15
Drivers of Disease 16
Persistence of Pathogens in Tissue 17
Pathogen Reactivation Under Conditions of Immune Dysregulation 20
Mitochondrial Dysfunction 22
Coagulation & Vascular Dysfunction 24
Dysautonomia & POTS 26
Neuroinflammation & Cognitive Dysfunction 28
Immune Activation, Dysfunction, & Autoimmunity 30
Microbiome Imbalance & SIBO 30
Hormonal Imbalance 32
Mast Cell Activation & Immune Cell Priming 33
Chapter 4 | Clinical Care Guidance 36
Environmental Design: Creating a Cultivated Patient Experience 37
Securing an Appointment at CoRE & the Onboarding Process 39
Care Strategy at the CoRE 41
Follow-Up: Introduction to the Team Approach After the Initial Intake 44
In-Person Assessments at the CoRE 46
Optional Research Opportunities 46
Assessment Procedures & Treatment Recommendations Based on Clinical Findings 47
The Prevention of IACIs & When Reinfection Occurs 66
Chapter 5 | Allied Health Approaches to IACI Care 67
Psychology Services 67
Social Work 69



Physical Therapy & Autonomic Rehabilitation 70
Nutritional Guidance 72
Chapter 6 | At Home IACI Management Strategies 73
Pacing, Energy, & Assistive Technology in Complex Chronic Illness 73
Chapter 7 | Tick-Borne & Vector-Borne Illnesses 75
Overview of Tick-Borne & Vector-Borne Illnesses 75
Testing for Tick Borne & Vector-Borne Illnesses 76
Assessing & Treating Tick-Borne & Vector-Borne Illnesses 77
Appendix A | Billing & Coding at the CoRE 79
CoRE Assessment Order Sets & CPT Codes 79
Appendix B | Introduction Autonomic Rehabilitation 82
Autonomic Rehabilitation in Complex Chronic Illness 82
Spin Bike Upright Titration Protocol: A Symptom-Titrated Cardiovascular Training Framework for Autonomic Rehabilitation 90
Appendix C | Pacing, Energy, & Assistive Technology in Complex Chronic Illness 99
Pacing, Energy, & Assistive Technology in Complex Chronic Illness 99
Mobility Aids 105
Appendix D | Nutritional Guidance in Complex Chronic Illness 107
Nutritional Guidance in Complex Chronic Illness 107
Appendix E | Introduction to Hypermobility Spectrum Disorders & Hypermobility Testing 111
Hypermobility and Susceptibility in IACIs 111
Extracellular Matrix (ECM) Breakdown in hEDS & Post-Infectious Cases 111
Neurologic Manifestations Associated with Hypermobility 112
Subluxation & Dislocation Across the Body 115
Subluxation Reduction Guide for Hypermobility Disorders 125
Proprioception Training in Hypermobility Rehabilitation 128
Appendix F | Patient Reported Outcomes (PROs) 134
Appendix G | Blood Tests 152
Acknowledgements 157
From Our CoRE Team 157
Reviewers & Expert Contributors 158



Important Medical Disclaimers

The medical information provided in this manual is intended for educational purposes only and is designed specifically for licensed, legally practicing clinicians.

This manual is not to be considered a substitute for professional medical advice, diagnosis, or treatment.

The Infection-Associated Chronic Illness Provider Manual is not a replacement for personalized care tailored to individual patient needs.

Always consult relevant clinical guidelines and protocols and consider the unique circumstances of each patient when making treatment decisions.

For any specific medical concerns or emergencies, please refer to established medical protocols and seek guidance from appropriate healthcare professionals.

We encourage clinicians to apply their clinical judgment and expertise when utilizing the information contained in this manual into their practice.

Any mention of brand names in this manual are simply brands that are currently in routine use in the clinic. These mentions should not be viewed as endorsement.



Chapter 1 | Introduction

About the Infection-Associated Chronic Illness (IACI) Manual

The objective of this guide is to bridge the gap by providing:

- An overview of testing and treatments we have successfully implemented for IACI patients at the CoRE. These approaches address both root causes of disease and symptom management.
- Summaries of the latest research on key biological drivers of Long COVID and related IACIs, offering clinicians an evidence-based foundation for care.

We are the **Cohen Center for Recovery from Complex Chronic Illness** (the CoRE): a hybrid research and clinical care center focused on advancing the treatment of IACIs. At the CoRE, we specialize in managing Long COVID, chronic tick-borne and vector-borne illnesses, and other IACIs. Our mission is to combine cutting-edge research with patient-centered care, equipping healthcare providers with the tools and knowledge to better serve this often-overlooked patient population.

This manual is designed to provide healthcare practitioners with actionable strategies and practical guidance based on the latest scientific research as well as our own clinical experience. Over the past few years, global networks of researchers have collaborated on thousands of high-quality, peer-reviewed studies that illuminate biological contributors to IACIs, including viral persistence, clotting abnormalities, neuroinflammation, and immune dysregulation. Yet, much of this knowledge has not been effectively translated into clinical practice. This gap in care leaves patients struggling to find relief and clinicians without clear frameworks to address their needs. It is our hope that creating a manual of this nature will empower more clinicians to feel confident in caring for the millions of people with IACIs who have so few options when it comes to accessing evidence-informed care.

Since we are learning along with everybody else, this guide is by no means intended to be a fully comprehensive "final word" on the topic of IACI care. Our intention is to add to it each year and work together collaboratively with health care providers, subject matter experts, patients, and other stakeholders to include knowledge updates and new topics of immediate interest. Similarly, this manual is designed to be approachable to healthcare providers who may not have extensive knowledge or experience in identifying or managing IACIs.

At the CoRE, we work to translate emerging scientific findings into therapeutic interventions. One example of our innovations is our clinical trials, testing drugs such as Truvada, Maraviroc, and low-dose rapamycin for the treatment of Long COVID. As new results become available, this manual will be regularly updated to ensure clinicians have access to the most current information.

As you engage with this manual and consider incorporating its insights into your practice, we encourage you to approach your patients with empathy, patience, and a willingness to listen. Our shared goal is to provide care that not only addresses



symptoms but restores dignity and hope to those impacted by these conditions.

Thank you for your dedication to this work and your role in building a more compassionate and informed healthcare community.



What Are IACIs?

IACIs refer to a spectrum of persistent health conditions that can develop after infections caused by various pathogens, including viruses, bacteria, and fungi. These conditions can lead to debilitating symptoms that significantly impair the quality of life for affected individuals. Collectively, IACIs have also been referred to as post-acute infection syndromes or IACCs. Pathogens including Ebola virus, Zika virus, Dengue virus are also connected to IACIs, however management of these IACIs will not be covered in this manual.

MEDICAL EDUCATION VIDEO: Building Blocks of Post-Acute Infection Syndromes

Long COVID: A condition that affects a subset of individuals infected with the SARS-CoV-2 virus. These individuals may develop new symptoms or experience symptoms or lingering sequelae that do not resolve for months or years. The US CDC estimates that ~6% of US adults suffer from new symptoms lasting three or more months after contracting COVID-19. Common Long COVID symptoms include fatigue, flu-like symptoms, autonomic dysfunction, trouble with memory or concentration, and post-exertional malaise (PEM) (worsening of symptoms following exertion). However, dozens of Long COVID symptoms have been documented, and symptom presentation can differ from person to person.

Tick-borne/Vector-borne Illnesses: Similarly, a subset of individuals infected with tick-borne/vector-borne pathogens also develop chronic symptoms that can result in substantial disability. These pathogens include *Borrelia burgdorferi* (the agent of Lyme disease), but also the parasite *Babesia*, and intracellular bacterial pathogen *Bartonella*.

Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS): For decades, millions of individuals have also been diagnosed with ME/CFS, an IACI characterized by severe fatigue, musculoskeletal pain, and PEM. Many cases of ME/CFS begin with a viral infection or involve multiple exposures to viral and bacterial pathogens over time. Pathogens most implicated in ME/CFS development include the herpesviruses and enteroviruses.

Chapter 2 | Overview of IACIs



Mechanisms of Disease

Thousands of papers document clear biological abnormalities in Long COVID and other IACIs. Drivers of disease include the following and may differ from patient to patient. Importantly, each driver of disease is interconnected: for example, persistent reservoirs of the SARS-CoV-2 virus and its spike protein can drive fibrin deposition and inflammation that might contribute to the formation of clotting disorders, reduced tissue perfusion and small fiber neuropathy.

Depending on how these factors present, different therapeutic approaches are required. Approaching IACIs with a "one size fits all" mindset to clinical care is unlikely to yield favorable results. Thus, to the greatest capacity possible we strive for personalized and precision medicine at the CoRE.

Complex Chronic Illness Mechanisms of Disease
Pathogen persistence in tissue or host cells
Pathogen reactivation under conditions of immune dysregulation
Autonomic dysfunction
Coagulation issues and vascular dysfunction
Microbiome imbalance
Neuroinflammation and cognitive dysfunction
Mitochondrial dysfunction
Immune dysfunction and autoimmunity
Joint hypermobility
Mast cell activation



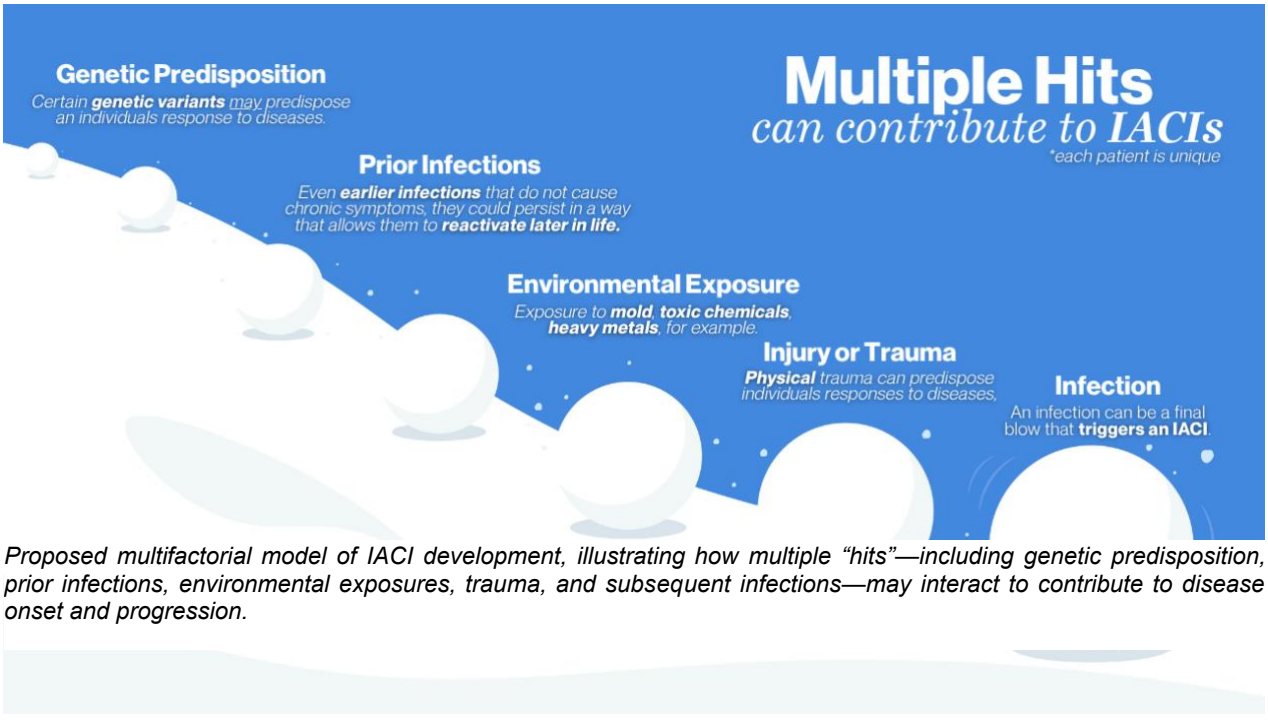
Multiple Hits

Treatment protocols that identify and address multiple infectious or inflammatory insults in patients with Long COVID or other IACIs are often required for optimal treatment.

This is because multiple infections, exposures, or other “hits” can contribute to the development of patient chronic symptoms over time. For example, a recent study found that priming of inflammatory processes in the brain by a SARS-CoV-2 protein can potentiate the effects of a subsequent inflammatory challenge such as a bacterial infection. The findings suggest that multiple infectious “hits” (viral and bacterial) may amplify long-term neuroinflammatory or neuroimmune symptoms in patients with Long COVID. Similar priming of inflammatory processes and/or immune dysregulation may additionally be impacted by chemical or mold exposures or injuries (e.g., a concussion) across a spectrum of IACIs.

While single infections can drive an IACI, treatment protocols that identify and address multiple infectious or inflammatory insults in patients with Long COVID or other IACIs are often required for optimal treatment.

This is because multiple infections, exposures, or other “hits” can contribute to the development of patient chronic symptoms over time. Each of these "hits" can dysregulate the immune response, potentially making the next infection, exposure, or other “hit" harder for the patient to manage. For example, a recent study found that priming of inflammatory processes in the brain by a SARS-CoV-2 protein can potentiate the effects of a subsequent inflammatory challenge such as a bacterial infection. The findings suggest that multiple infectious “hits” (viral and bacterial) may amplify long-term neuroinflammatory or neuroimmune symptoms in patients with Long COVID. Similar priming of inflammatory processes and/or immune dysregulation may



Proposed multifactorial model of IACI development, illustrating how multiple “hits”—including genetic predisposition, prior infections, environmental exposures, trauma, and subsequent infections—may interact to contribute to disease onset and progression.



additionally be impacted by chemical or mold exposures or injuries (e.g., a concussion) across a spectrum of IACIs.

MEDICAL EDUCATION VIDEO: Understand Different Infections, Exposures, and Hits



Common Misconceptions about IACIs

An unfortunate reality in IACI care is that many IACI patients take several years to receive a correct diagnosis if they can receive one at all. This can be attributed to several reasons, one being the existence of misconceptions about IACIs. Regardless of your experience level in managing IACI patients, it is important to challenge potential misunderstandings about these complex chronic conditions.

MISCONCEPTION: Exercise is a safe, effective treatment for people with IACIs who are experiencing fatigue and post-exertional malaise
FACT: The original research supporting the use of graded exercise therapy for ME/CFS, and by extension Long COVID, is heavily flawed.
FACT: Many people with IACIs develop PEM. Dosing exercise incorrectly can lead to a worsening of symptoms within 48-72 hours. Pacing and rest are safer, effective alternatives.

MISCONCEPTION: Cognitive behavioral therapy (CBT) is an effective treatment for IACIs.
FACT: As with exercise, the original research supporting the use of certain forms of CBT are heavily flawed. While CBT and other psychological treatment techniques may help people cope with adjustment to their chronic illness diagnosis or new disability status, these techniques are not effective in treating IACIs.

MISCONCEPTION: Most people who are diagnosed with IACIs recover.
FACT: Most people who are diagnosed with an IACI will experience chronic symptoms that can last for many years.
FACT: IACIs cause dynamic disability, meaning that symptoms can improve or worsen over time, while others might experience a remitting/relapsing pattern where symptoms can fluctuate and worsen for days, weeks or months before returning to a baseline.



MISCONCEPTION: IACIs are rare.
FACT: Though IACIs are historically understudied and underdiagnosed, they are not rare conditions. The most common among them, Long COVID, affects an estimated 400 million individuals worldwide while ME/CFS affects more than 4 million Americans.

MISCONCEPTION: IACIs do not affect healthy people.
FACT: Even excellent health is no guarantee of protection from IACIs. Previously fit and healthy individuals such as high performance athletes and active duty military members are at risk of developing these conditions just like members of the general population.



MISCONCEPTION: A person with an IACI is not at risk from future infections.
FACT: Multiple infections often worsen IACI symptoms, reactivate dormant pathogens, and create further immune dysregulation. While infection mitigation efforts are important for anyone seeking to prevent IACIs, they are of particular concern for current IACI patients.

MISCONCEPTION: Regular infection with pathogens is necessary to maintain a healthy immune system.
FACT: In addition to causing widespread general health consequences, every infection your body sustains can dysregulate and even weaken your immune system. While becoming infected with a pathogen may confer temporary immunity, there are easier and safer ways to protect oneself from infection, and we continue to discover new long-term risks associated with even mild acute infections.

What Is Recovery?

At the Cohen Center for **Recovery** from Complex Chronic Illness, our focus is to help our patients live a fulfilling life despite the limitations of chronic conditions.

While a cure may not always be possible, recovery focuses on achieving the best possible quality of life by addressing not only physical symptoms but also emotional resilience and social well-being.



For patients, this often means learning to navigate their new reality with the support of healthcare professionals, social networks, and tailored care strategies. For providers, this means a multidisciplinary approach to care.

Recovery isn't One-Size-Fits-All

Recovery is about helping individuals reclaim control over their lives and find ways to thrive, even in the presence of ongoing health challenges. Recovery is a multifaceted, deeply personal process that varies between individuals. It does not necessarily mean a complete cure or the elimination of symptoms. It encompasses the restoration or improvement of various aspects of life—including physical health, emotional well-being, social connections, and overall functionality.

Recovery Does Not Equate to a Cure

The goal is to help patients move from a state of overwhelming symptoms to one where their condition is stabilized and more manageable. Recovery is still attainable in the sense of improving functionality, managing symptoms effectively, and adapting to a new normal.

Recovery of Function

For some patients, recovery involves regaining the ability to participate in meaningful activities like work and hobbies. This requires medical interventions, physical therapy (PT), and energy management strategies (pacing). The goal is to help patients rebuild practical aspects of their lives and engage in what matters most. Recovery includes regaining strength, mobility, and endurance, approached carefully to prevent setbacks. For IACIs, pacing rest are essential to manage energy and avoid flares. Tailored exercise and medical therapy support improved function over time, with each small step contributing to a better quality of life.

Mental and Social Health as Part of Recovery

Social support is vital for recovery as social isolation and loneliness can have profound effects on many aspects of physical and mental health, including immune and hormonal health. Social health interventions need to be tailored to an individual's personal energy and comfort level, with some preferring in-person gatherings and others benefiting from online communities. Chronic illness can significantly impact mental health, leading to anxiety and depression, making mental health support essential. Therapy, mindfulness practices, and connecting with professionals can help



The Importance of the Right Environment

Recovery is influenced not only by medical interventions but also by the environment in which patients live, work, and heal. Creating a supportive environment—both physically and socially—is vital. This includes ensuring spaces are comfortable, accessible, and stress-free, as well as fostering social environments that emphasize understanding, compassion, and encouragement.



Chapter 3 | Current Research on the Drivers of IACIs

IACIs are often incorrectly referred to as "mysterious" due to a perception that we do not understand why people who are diagnosed with IACIs are actually sick and what may be driving their symptoms. Rather than thinking of IACIs as "mysterious" we would urge providers to think of them as *"complex."* This is because many of the drivers of IACI symptoms and pathobiology have been established through literally thousands of high-quality, peer-reviewed research studies.

While we are starting to better understand these drivers in detail, the *complexity* of treating IACIs comes from the fact that a person diagnosed with an IACI may be experiencing many of these drivers all at once, or just once. They may be experiencing just these drivers with no other relevant past medical history, or they may be managing multiple comorbidities and chronic illnesses alongside their IACI, and frankly, we do not have a detailed understanding of how these chronic illnesses intersect with one another. The purpose of this chapter is to dive into the details of some of the most well-established drivers of symptoms and pathobiology in IACIs, so that we can pave the way to better strategize actionable treatments.

Please see drivers of disease on the following page.



Drivers of Disease

Understanding drivers of IACIs is imperative for HCPs. These factors clarify the complex biological mechanisms underlying persistent symptoms associated with IACIs and enable HCPs to strive for the best diagnostic and therapeutic approaches.

Driver	Description
Persistence of pathogens in tissue	Chronic symptoms may result from the inability to fully clear infections, leaving pathogens in tissue or host cells as reservoirs that drive ongoing inflammation and other downstream effects. These reservoirs are often difficult to detect with standard blood tests.
Pathogen reactivation	Dormant pathogens, such as herpesviruses or *Bartonella*, can reactivate under stress or immune suppression, contributing to chronic illness symptoms like fatigue, inflammation, and vascular dysfunction.
Mitochondrial dysfunction	Pathogens and the inflammation that they cause can severely disrupt mitochondrial function, reduce energy production, and increase oxidative stress, which can lead to fatigue, inflammation, and other chronic symptoms.
Coagulation and vascular dysfunction	Pathogen-induced hypercoagulation, microclots, and endothelial dysfunction impair blood flow, oxygen delivery and tissue perfusion, exacerbating symptoms like fatigue, pain, and organ dysfunction.
Autonomic dysfunction	Disruptions in the autonomic nervous system, including conditions like postural orthostatic tachycardia syndrome (POTS), cause issues with heart rate, blood pressure, and other involuntary processes, leading to symptoms such as dizziness, fatigue, and nausea.
Neuroinflammation and cognitive dysfunction	Chronic inflammation in the brain, often linked to vascular abnormalities and/or persistent pathogen reservoirs, contributes to cognitive impairment, fatigue, and neuropsychiatric symptoms.
Immune activation, dysfunction, and autoimmunity	Persistent immune activation, often driven by pathogen presence, can lead to T-cell exhaustion, autoantibody production, and systemic inflammation, worsening chronic illness symptoms.
Microbiome imbalance and small intestinal bacterial overgrowth (SIBO)	Disruptions in gut microbiota and increased intestinal permeability ("leaky gut") lead to systemic inflammation, hormonal imbalances, and immune dysregulation, contributing to chronic symptoms.
Hormonal imbalance	Pathogen-driven changes in hormone production, such as cortisol, testosterone, estrogen and serotonin, contribute to systemic symptoms like fatigue, mood changes, and metabolic dysfunction, with sex-specific immune response differences noted in some conditions.
Mast cell activation and immune cell priming	Overactive mast cells and glial cells, often responding to persistent pathogen reservoirs or microbiome imbalances, can become perpetually over-active, amplifying inflammation and immune responses and contributing to chronic symptoms like pain, fatigue, and sensory sensitivities.



Persistence of Pathogens in Tissue

One of the most straightforward drivers of chronic symptoms following an infection is pathogen persistence.

Some IACI patients do not fully clear the viral or bacterial infections they sustain. Instead, a small amount of the pathogen persists in their tissue or host cells in a "reservoir."

Dozens of studies now support the existence of a SARS-CoV-2 reservoir in at least a subset of people with Long COVID. For example, SARS-CoV-2 double-stranded RNA suggestive of replicating virus has been identified in Long COVID gut tissue over two years post- infection.

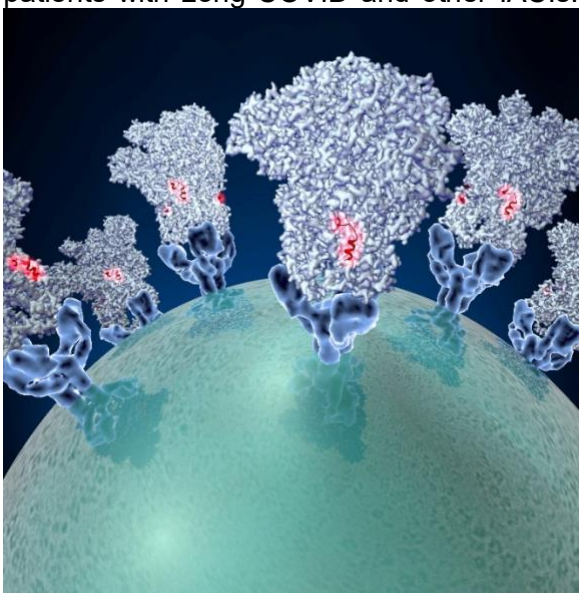
Similarly, enteroviral RNA has been identified in brain, skeletal muscle, and stomach tissue specimens of certain patients



Borrelia burgdorferi *under a microscope (Source: CDC).*

with ME/CFS. *Borrelia burgdorferi* has been detected in the heart and other tissues of animals months after initial infection, even after routine treatment with the antibiotic doxycycline. Pathogen reservoirs are often localized to tissue, meaning that the persistent pathogen often cannot be detected via a blood test alone. Some groups can perform biopsy procedures to collect tissue (gut, lymph node, etc.) from IACI patients for pathogen detection, but these procedures are not routine at most sites.

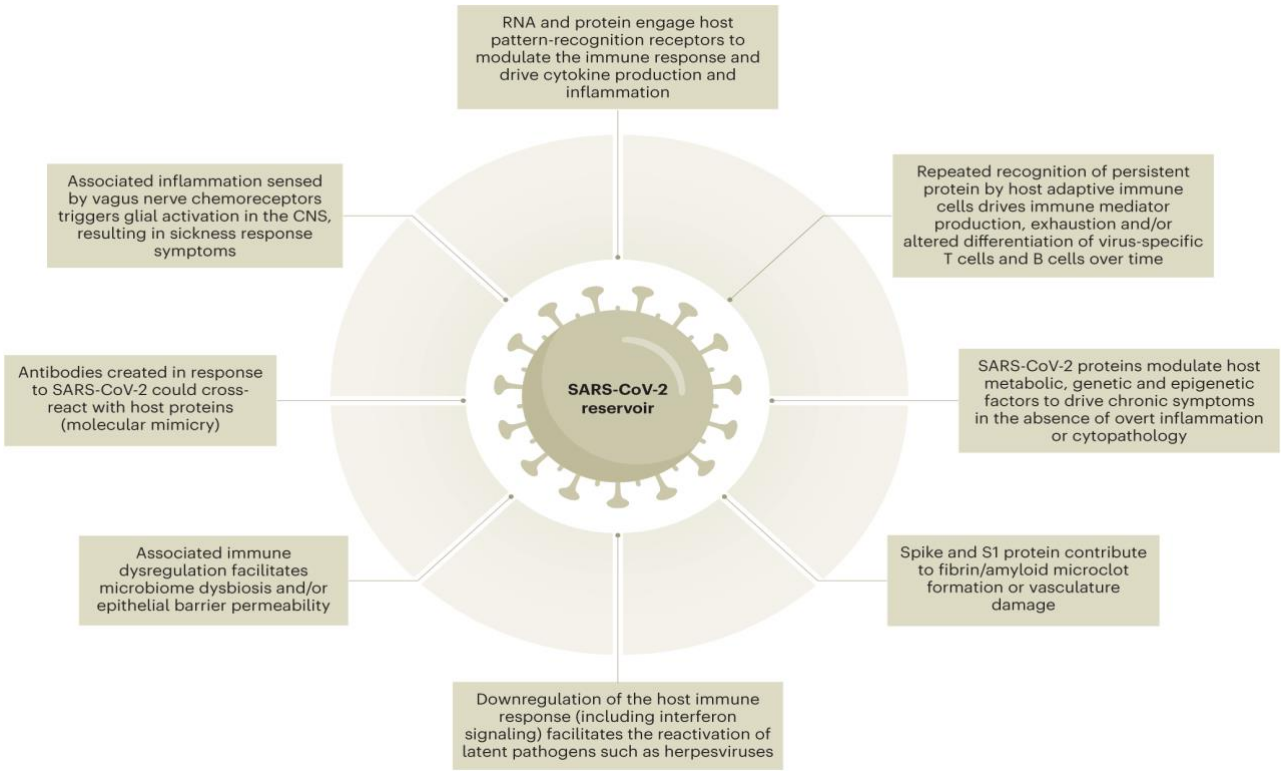
For chronic tick-borne/vector-borne disease some testing can be done, although the most comprehensive testing requires out of pocket labs (see the Tick-Borne/Vector-borne Illness section). It is important to note that pathogen persistence can be a driver of many of the other issues documented in patients with Long COVID and other IACIs.



SARS-CoV-2 spike protein.

For example, the figure on the following page documents mechanisms by which a persistent SARS-CoV-2 reservoir can



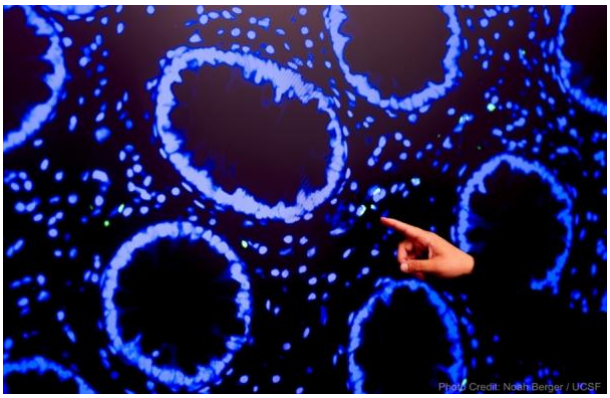


Mechanisms by which a SARS-CoV-2 reservoir may contribute to PASC (Source: Proal et al. 2023).

contribute to inflammatory, coagulation, microbiome, and other issues. A combination of therapies geared at targeting pathogen reservoirs in concert with treatments that also impact downstream sequelae driven by the reservoir is an option for patient care.

Multiple studies have found circulating SARS-CoV-2 proteins in the blood of 20-60% of participants with Long COVID. This protein may be derived from viral reservoirs in tissues such as the gut but leaks into blood where it can be measured. However, the ultrasensitive tests researchers are using to find circulating spike protein in Long COVID blood are not yet available to be ordered in a standard clinical setting.

Dozens of clinical trials are underway to test therapeutics capable of targeting SARS-CoV-2 reservoirs or their sequelae in Long COVID. An overview of some of these trials was recently published in the journal *Lancet Infectious Diseases*. As an example, a clinical trial at Harvard Medical School is testing if the drug larazotide, which has been shown to repair gut barrier tight junction permeability ("leaky gut"), can improve Long COVID symptoms and/or blood spike protein leakage from SARS-CoV-2 reservoirs in



The green shows SARS-CoV-2 spike RNA (a viral reservoir) in gut tissue collected from a patient with Long COVID. Image courtesy of the UCSF LIINC study.



Long COVID. Other teams are running clinical trials of monoclonal antibodies or antivirals in Long COVID.

The CoRE is also currently conducting a blood draw study that aims to investigate whether patients with complex chronic illnesses, including Long COVID, ME/CFS, post-treatment Lyme disease syndrome, and connective tissue disorders may carry tick-borne or vector-borne pathogens in their blood.

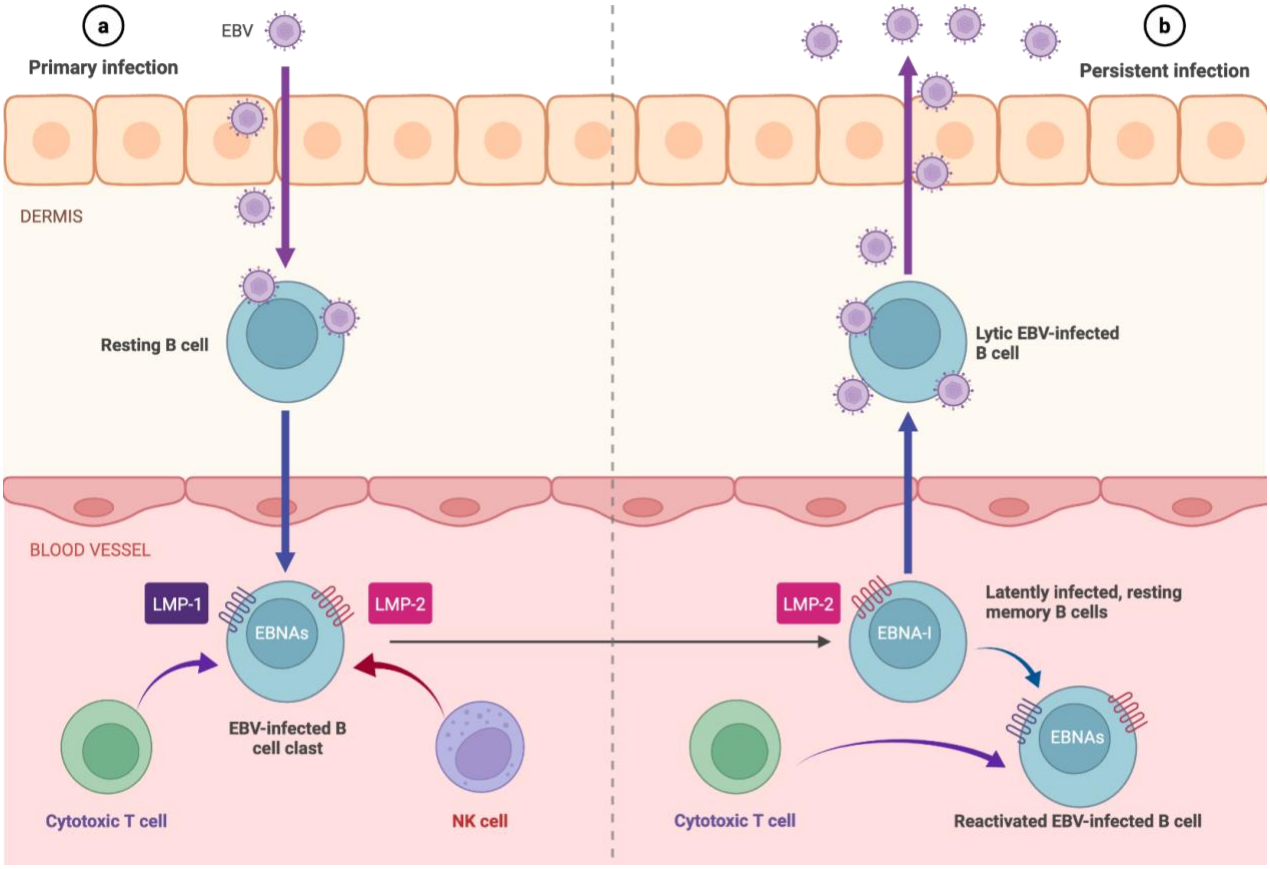
ASSESSMENTS & TREATMENTS: How We Assess and Treat Persistence of Pathogens in Tissue



Pathogen Reactivation Under Conditions of Immune Dysregulation

Another driver of IACI symptoms is that an infection can disable the immune system in a manner that allows previously dormant pathogens to reactivate. It is well understood that humans accumulate persistent viruses over the course of a lifetime (referred to as the "human virome"). These viruses, which can include herpesviruses such as the Epstein Barr virus (EBV), generally persist in dormant or latent states. However, these dormant viruses can reactivate under conditions of stress, immune dysregulation, or immunosuppression. SARS-CoV-2 creates multiple proteins that disable the host immune response, meaning that during acute COVID-19, viruses can more easily reactivate and drive chronic symptoms. The same pattern is true of other pathogens that disable the immune response to survive.

Multiple studies have documented herpesvirus reactivation in acute COVID-19 or Long COVID. For example, an extensive Long COVID immune profiling study found higher antibody responses directed against EBV proteins in a subset of participants. Increased herpesvirus presence has also been documented in ME/CFS. For example, one study found higher Human Herpes



EBV infection.



Virus-6B and Human Herpesvirus-7 viral loads in people with ME/CFS compared to healthy controls.

Like viruses, many bacterial, fungal, and parasite pathogens also change their activity to increasingly drive disease under conditions of immune dysregulation or stress. These include vector-borne bacterial pathogens capable of persistence such as *Bartonella*.

Bartonella can drive blood vessel dysfunction by infecting vascular endothelial cells, so increased activity of the pathogen in patients additionally infected with SARS-CoV-2 could augment vasculature or circulatory symptoms. One study documented post-COVID reactivation of *Bartonella henselae* in a patient diagnosed with a Long COVID, whose symptoms improved with antibiotic treatment.

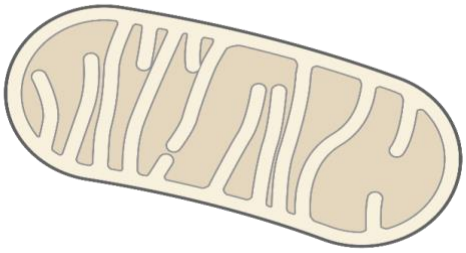


Mitochondrial Dysfunction

Dysfunction of the mitochondria has been documented in Long COVID, ME/CFS and other IACIs. Mitochondria are often called the powerhouses of the cell. They are responsible for producing energy through oxidative phosphorylation.

Mitochondria also play a role in managing oxidative stress, controlling programmed cell death (apoptosis), and influencing immune responses. Proper mitochondrial function is essential for maintaining balance within cells and the body. When mitochondria are not functioning well, energy production drops, harmful molecules (reactive oxygen species, or ROS) increase, and inflammation can begin, all of which may lead to chronic symptoms.

All viruses, and many bacterial, and fungal pathogens reprogram host mitochondrial metabolism to increase the supply of energy, nutrients, and metabolites required for their survival and proliferation. Indeed, viruses are obligate intracellular parasites that require the induction of an altered metabolic state in host cells to successfully replicate and complete their life cycles.

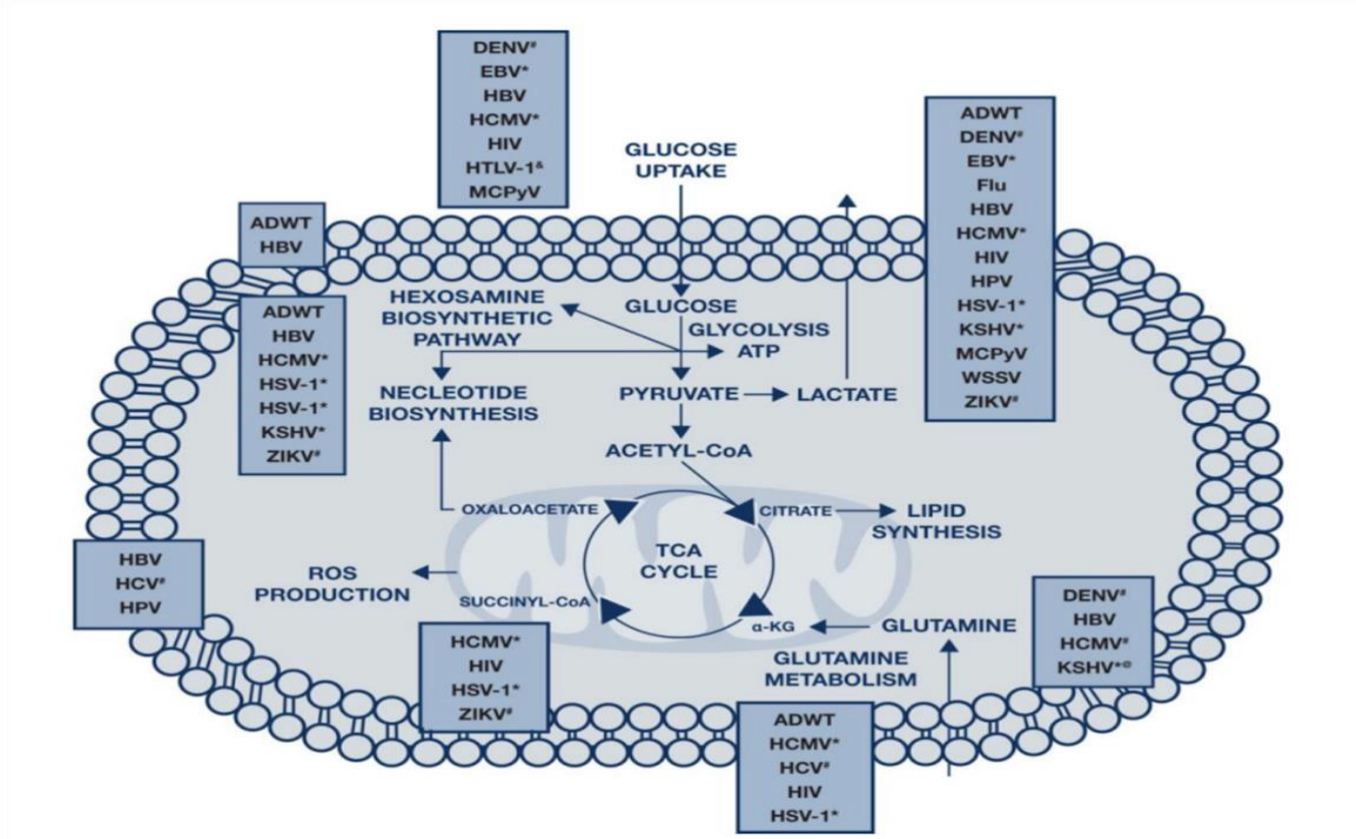


Several studies have documented mitochondrial dysfunction in individuals suffering from Long COVID. For instance, research has identified abnormalities in mitochondrial respiration and bioenergetics and mitochondria-related gene expression in peripheral blood mononuclear cells (PBMCs) from Long COVID patients.

Lyme *borreliosis* has also been connected to an increase in mitochondrial superoxide, suggesting a state of mitochondrial dysfunction. Indeed, *Borrelia burgdorferi* has been shown to hijack host cell mitochondrial metabolism in a manner that increases inflammatory cytokine production.

Pathogens **are major drivers** of mitochondrial dysfunction.

ASSESSMENTS & TREATMENTS: How We Assess and Treat Mitochondrial Dysfunction



Different viruses all hijack components of host mitochondrial metabolism. Image copied with permission from: https://wap.hapres.com/htmls/IJ_1341_Detail.html.

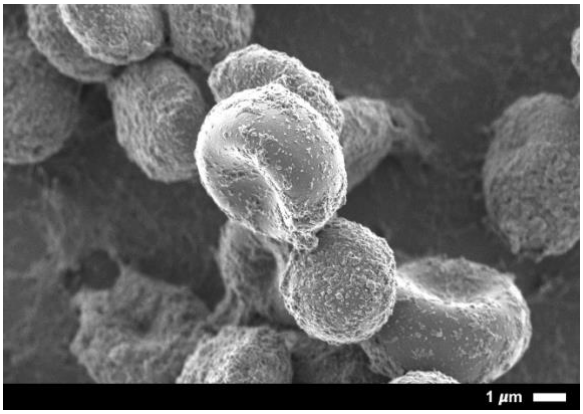


Coagulation & Vascular Dysfunction

The release of pathogen products during acute or chronic disease can contribute to hypercoagulation, platelet hyperactivation, and blood vessel dysfunction in a manner that can impact IACI symptom development.

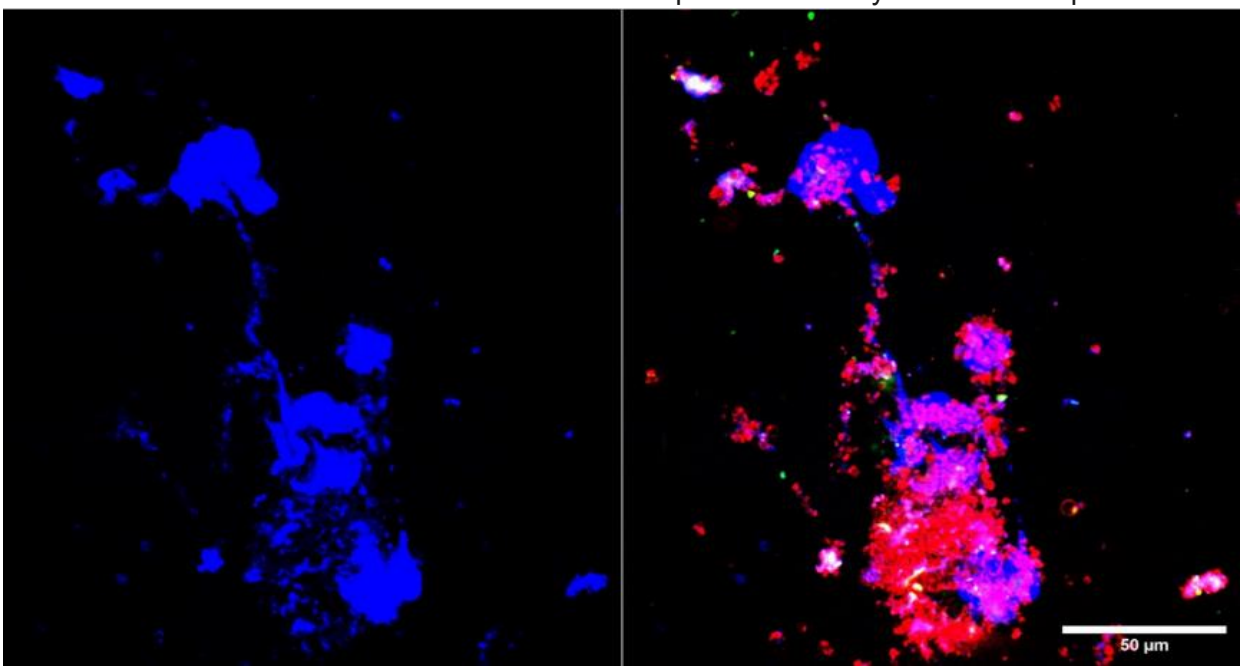
Long COVID is strongly tied to clotting and blood vessel issues. Multiple teams have identified fibrin/amyloid "microclots" resistant to fibrinolysis (indicative of hypercoagulation) in Long COVID plasma. In some cases, formation of these microclots could be triggered by circulating SARS-CoV-2 spike or S1 protein, which have been detected in Long COVID blood up to 14 months post-infection.

In addition, SARS-CoV-2 spike protein can bind to fibrinogen and induce structurally



Scanning electron microscope image of red blood cells covered in a meshwork of fibrin. Photo contributed by Resia Pretorius.

inflammatory activity. Persistence of spike or S1 protein in Long COVID plasma may also stimulate the activity of platelets (cell fragments in blood involved in clotting processes) or trigger formation of proinflammatory immune complexes and/or



Neutrophil extracellular traps (blue) co-localized with activated platelets (red/green) in Long COVID blood. Image courtesy of the VanElzakker lab, Harvard Medical School.

abnormal blood clots with heightened



neutrophil extracellular traps that can also contribute to clotting processes.

Bacteria like *Borrelia burgdorferi* also have potential to contribute to coagulation processes involving fibrin. During both acute and chronic disease *Borrelia burgdorferi* has been shown to shed peptidoglycan, a major component of the bacterial cell wall envelope. This peptidoglycan can activate immune cells in plasma, including neutrophils and platelets.

MEDICAL EDUCATION VIDEO: Mechanisms of Downstream Pathology: Coagulation and Endothelial Dysfunction

ASSESSMENTS & TREATMENTS: How We Assess and Treat Coagulation and Vascular Dysfunction

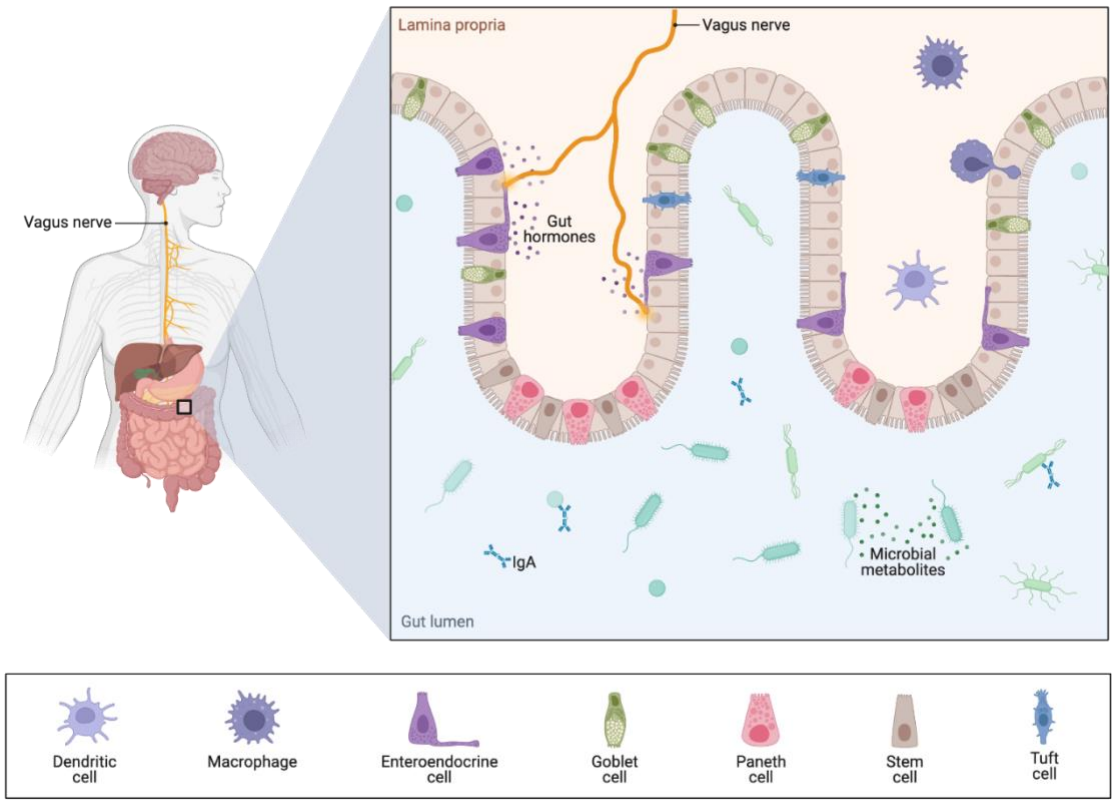


Dysautonomia & POTS

Many IACI patients report common symptoms including dizziness, heart palpitations, headaches, pre-syncope, pain, sleep problems, flu-like symptoms, difficulty concentrating, cognitive impairment, nausea, constipation, diarrhea, and other GI symptoms. The brainstem, which plays a central role in autonomic control, sickness behavior, and arousal, is thought to be involved in these symptoms.

One of the most common manifestations of dysautonomia is POTS, which is clinically present in a large percentage of people with IACI diagnoses. POTS occurs when the autonomic nervous system is unable to appropriately regulate blood pressure, heart rate and tissue perfusion. These symptoms can be especially prominent when the heart and circulatory system are trying to manage a workload against gravity, meaning that symptoms may be worse during positional changes (e.g., moving from sitting to standing or lying supine to sitting) or positions where gravity is playing more of a factor (i.e., standing will often be more symptomatic than sitting which will be more symptomatic than lying flat).

ASSESSMENTS & PROCEDURES: How We Assess Dysautonomia and POTS





Dysfunctional brainstem signaling and neuroinflammation may be a key factor in IACI-related dysautonomia symptoms. The vagus nerve, which transmits inflammatory signals from the organs of the body to the brainstem, plays a critical role in this process. When the vagus nerve detects inflammation, it triggers a "sickness behavior" response in the brainstem, leading to symptoms like fatigue, POTS, and pain.

The vagus nerve "sickness behavior" response can be triggered or sustained by ongoing inflammation from various causes, including pathogen reservoirs, immune activation, or microbiome imbalances, which could explain why different IACI patients may experience similar symptoms even if the underlying causes differ.

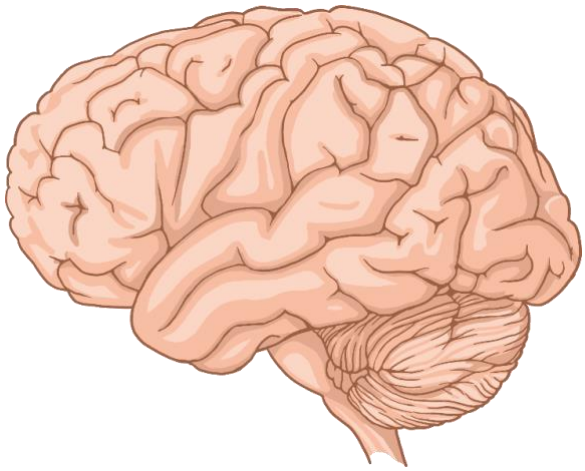
LEARN MORE: Guidance on Managing Dysautonomia and POTS

MEDICAL EDUCATION VIDEO: Mechanisms of Downstream Pathology: Autonomic Dysfunction, and PEM

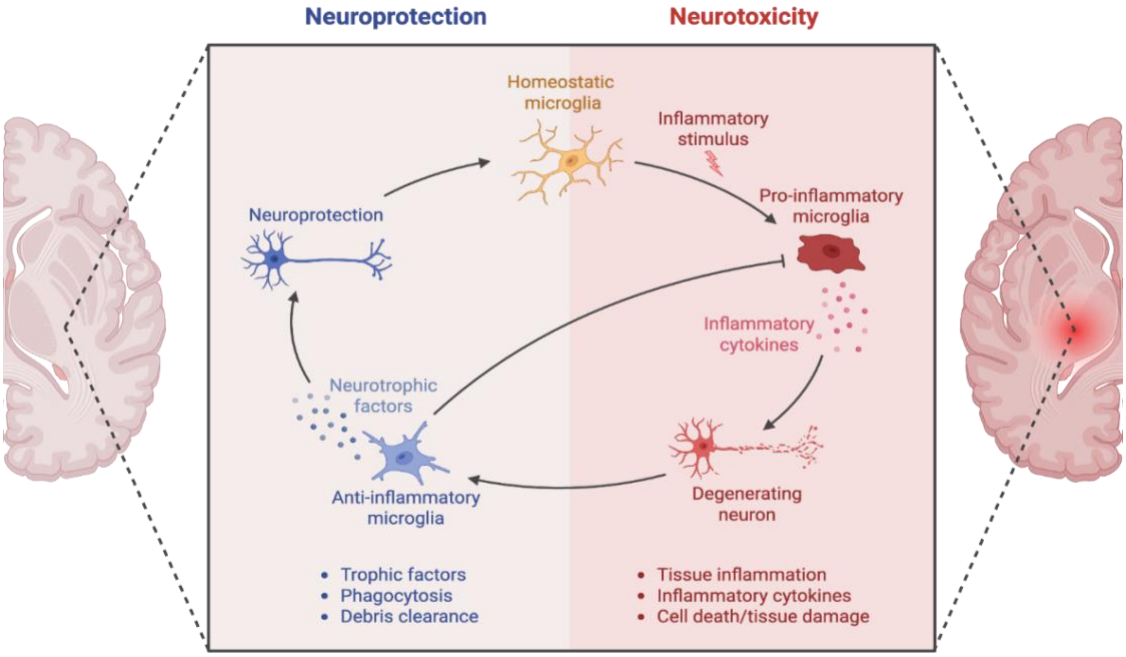


Neuroinflammation & Cognitive Dysfunction

Neuroinflammation has been documented in Long COVID, Post Treatment Lyme Disease Syndrome, and ME/CFS. One brain imaging study found that individuals with Long COVID had increased neuroinflammation compared to healthy study participants. This neuroinflammation was in some brain areas that are exposed to circulating blood factors via gaps in the "blood-brain barrier" of the brain's blood vessels. The researchers consequently measure a selection of blood factors related to vascular health or damage. They found that six such factors showed a correlation with the neuroinflammation signal in the brains of the Long COVID study participants.



These factors included fibrinogen, a protein seeded by the SARS-CoV-2 spike protein and involved in forming blood clots in the body, and sL-selectin, a molecule that helps immune cells attach to vasculature during inflammation. This suggests that the neuroinflammation in Long COVID patients may be connected to vascular problems.



Roles of microglia in neuroinflammation.



Indeed, as described in other sections of this manual, fibrin/amyloid "microclots" or circulating SARS-CoV-2 proteins have been found in the blood of Long COVID patients. These factors could reach the brain and contribute to neuroinflammation. But more research is needed to fully understand how blood clotting, viral persistence, and brain inflammation in Long COVID may be interconnected.

ASSESSMENTS & PROCEDURES: How We Assess Neuroinflammation and Cognitive Dysfunction

MEDICAL EDUCATION VIDEO: Mechanisms of Downstream Pathology: Neuroinflammation and Neuropsychiatric Symptoms



Immune Activation, Dysfunction, & Autoimmunity

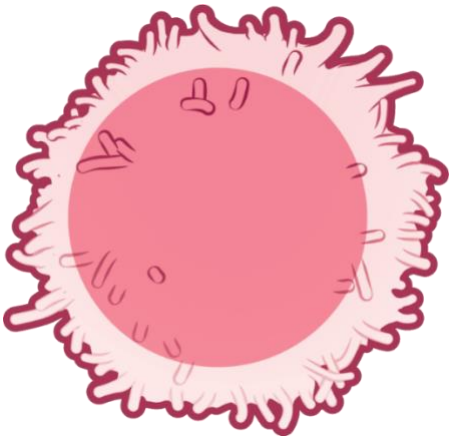
T-cell Exhaustion

Cells struggle to respond to persistent infection and become exhausted in the process. One study found that Long COVID patients showed differences in the distributions of their T cells, implying ongoing immune responses. The team also documented a mis-coordination between the SARS-CoV-2-specific T and B cell responses of participants.

Participants in the study additionally displayed increased frequencies of CD4+ T cells poised to migrate to inflamed tissues. This migration could represent an attempt by the immune cells to recognize and target SARS-CoV-2 reservoirs in such sites. Long COVID patients also showed exhausted SARS-CoV-2-specific CD8+ T cells and higher levels of SARS-CoV-2 antibodies. The findings are consistent with potential ongoing stimulation by persistent viral reservoirs in patient tissue.

Autoimmunity

Certain patients with Long COVID have been shown to have high levels of certain autoantibodies (AABs). One study found



Long COVID patients with neurocognitive and neurological issues had elevated AABs targeting proteins in the nervous system. When the researchers tested IgG antibodies, they reacted with tissue from the human brainstem and were also active against mouse nerves and spinal cord.

The antibody response in the sciatic nerves and meninges was related to headaches and confusion reported by the patients. When participant antibodies were transferred into mice, the animals showed increased pain sensitivity and symptoms similar to the patients', such as balance problems and dizziness. The results suggest that treating AABs may help some people with Long COVID.

Microbiome Imbalance & SIBO

ASSESSMENTS & TREATMENTS: How We Assess and Treat Immune Activation, Dysfunction, and Autoimmunity

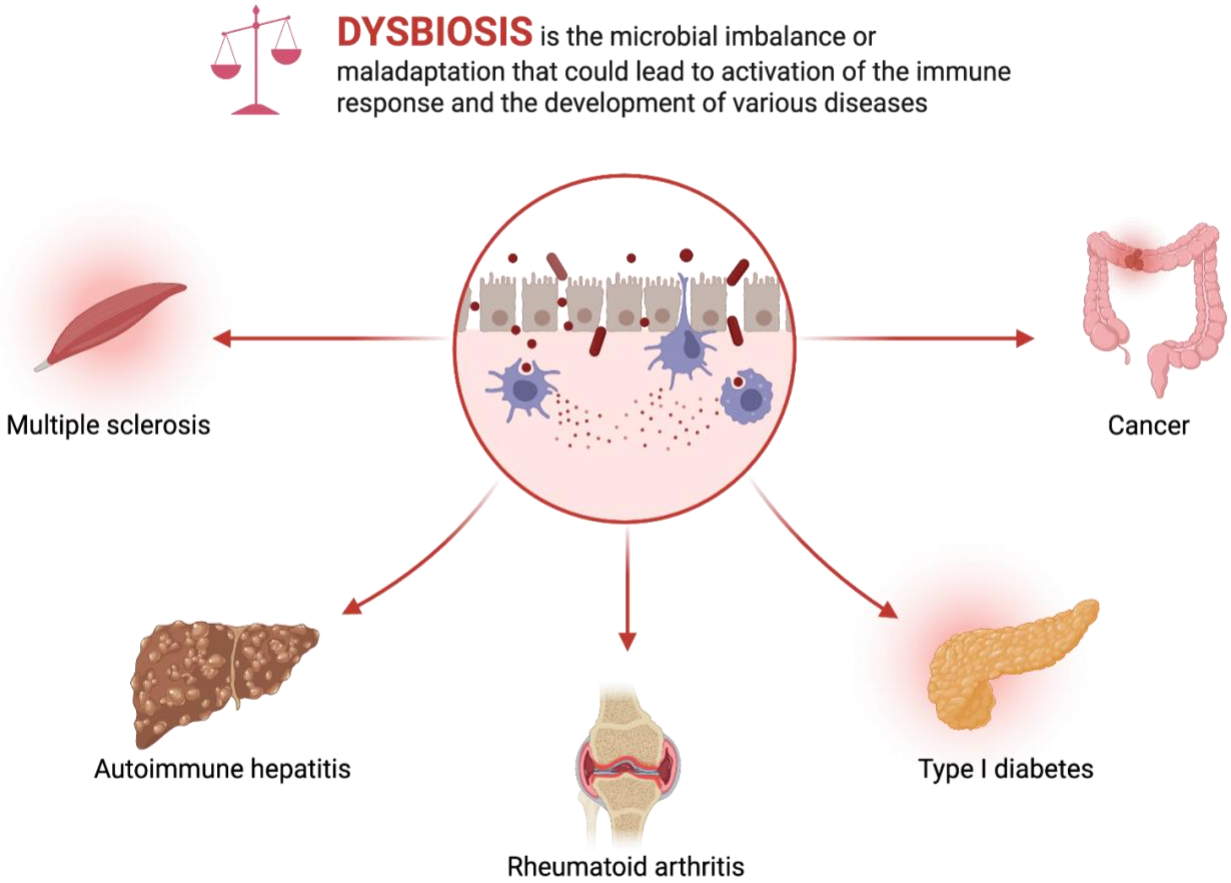
LEARN MORE: A recent study found that T cells in ME/CFS cases are epigenetically predisposed toward terminal exhaustion and that exhaustion markers are upregulated following exercise challenge. The findings are consistent with the hypothesis that chronic viral infection is a factor in ME/CFS.

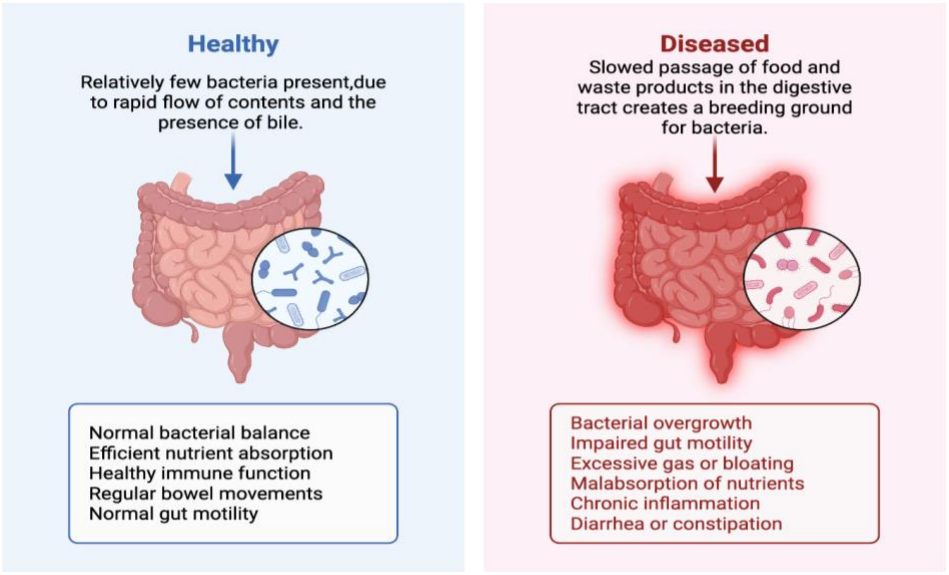


Humans harbor ecosystems of trillions of bacteria, fungi, and other organisms, including robust communities in the gut. These ecosystems are referred to as the human microbiome. Under conditions of health microbiome organisms persist in a state of balance or homeostasis. However, under conditions of imbalance or immune dysregulation they can change their composition or activity to promote disease (called dysbiosis). Microbiome imbalance or dysbiosis has been documented in IACI patients.

For example, one study found that patients with PTLDS have a distinct microbiome signature, characterized by an increase in the bacterial genus *Blautia*, a decrease in the bacterial genus *Bacteroides*, among other changes.

Microbiome imbalance can have a profound impact on host immune, metabolic, and hormonal signaling. That is because most proteins and metabolites in the human body are produced or modified by the microbiome. For example, one study documented a large





effect of the gut microbiome on blood metabolites. Indeed, one study of microbiome dysbiosis in ME/CFS identified reduced microbial butyrate biosynthesis and a reduction in plasma butyrate, bile acids, and benzoate.

Human bacteria have also been shown to produce and/or consume a wide range of mammalian neurotransmitters, including norepinephrine, dopamine, and serotonin. It follows that gut microbiome changes can impact hormonal signaling and symptoms.

Microbiome imbalance is also often accompanied by inflammation that can lead to dysfunction or breakdown of oral barriers such as the gingiva, the epithelial lining of the gut, or related barriers. This increased epithelial or oral barrier permeability allows pathogens or their products in such communities to translocate into the blood, where their presence can sustain a range of systemic inflammatory processes. This has been documented in patients with acute COVID, Long COVID, and ME/CFS. SIBO occurs when there is an abnormal increase in the overall bacterial population in the small intestine, particularly types of bacteria not commonly found in that part of the digestive tract. Causes of SIBO include:

- Post-infectious (following food poisoning or GI infections)
- Low stomach acid (including long-term use of PPIs)
- Impaired small intestine motility due to medications, hypothyroidism, dysautonomia, Sjögren's syndrome, CTDs, disordered eating/eating disorders, chronic small intestine inflammation from Crohn's disease, excessive NSAID use, undiagnosed or poorly managed celiac disease, low pancreatic enzyme production.

Hormonal Imbalance

ASSESSMENTS & TREATMENTS: How We Assess and Treat Microbiome Imbalance and SIBO



Hormonal imbalances have been documented in patients with Long COVID and other IACIs. One early study found that people with Long COVID had much lower cortisol levels than those without. Another study found that Long COVID was associated with serotonin reduction in blood and persistent SARS-CoV-2 RNA in stool. There are several possible drivers of serotonin reduction in Long COVID. Sex differences impacting the immune response are also increasingly being documented in Long COVID. For example, one study identified different sets of immune features that characterized Long COVID in females and males. Males with Long COVID had decreased frequencies of monocyte and dendritic cell populations, elevated natural killer cells, and plasma cytokines. Females with Long COVID had increased frequencies of exhausted T-cells, cytokine-secreting T cells, higher antibody reactivity to latent herpesviruses including EBV and Cytomegalovirus, and lower testosterone levels than their control female counterpart

FEMALE

Significantly higher symptom burden; wider variety of symptoms across multiple organ systems.

Common Symptoms

Fatigue
One of the most debilitating symptoms.

Neurological Symptoms
Higher incidence of headaches, confusion, and memory problems.

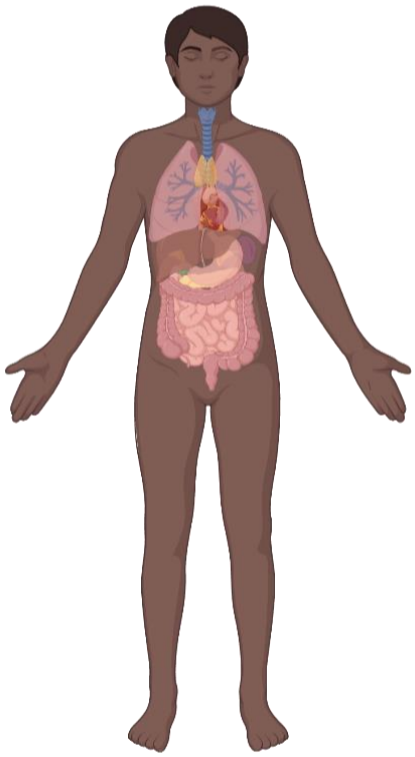
Gastrointestinal Symptoms
Increased reports of bloating, nausea, and abdominal pain.

Hair Loss
Notably higher prevalence compared to males.

Immune Profile
Increased frequencies of exhausted T cells and higher antibody reactivity to latent herpesviruses (e.g., EBV, CMV).

Hormonal Influence
Hormonal dysregulation linked to increased symptom severity. Lower testosterone levels compared to control females.

Comorbidities
Higher rates of asthma and gastrointestinal conditions.



MALE

Lower symptom burden compared to females; significant impacts on mood and post-exertional malaise.

Common Symptoms

Sexual Dysfunction
Higher prevalence reported.

Respiratory Symptoms
Increased reports of cough and dyspnea.

Neurological Symptoms
Confusion and brain fog, but less frequently than females.

Immune Profile
Elevated NK cells and certain cytokines (e.g., IL-8, TGF-β). Lower frequencies of monocyte and dendritic cell populations.

Hormonal Influence
Lower testosterone levels associated with higher symptom burden.

Comorbidities
Higher rates of cardiovascular conditions and respiratory issues.

Mast Cell Activation & Immune Cell Priming

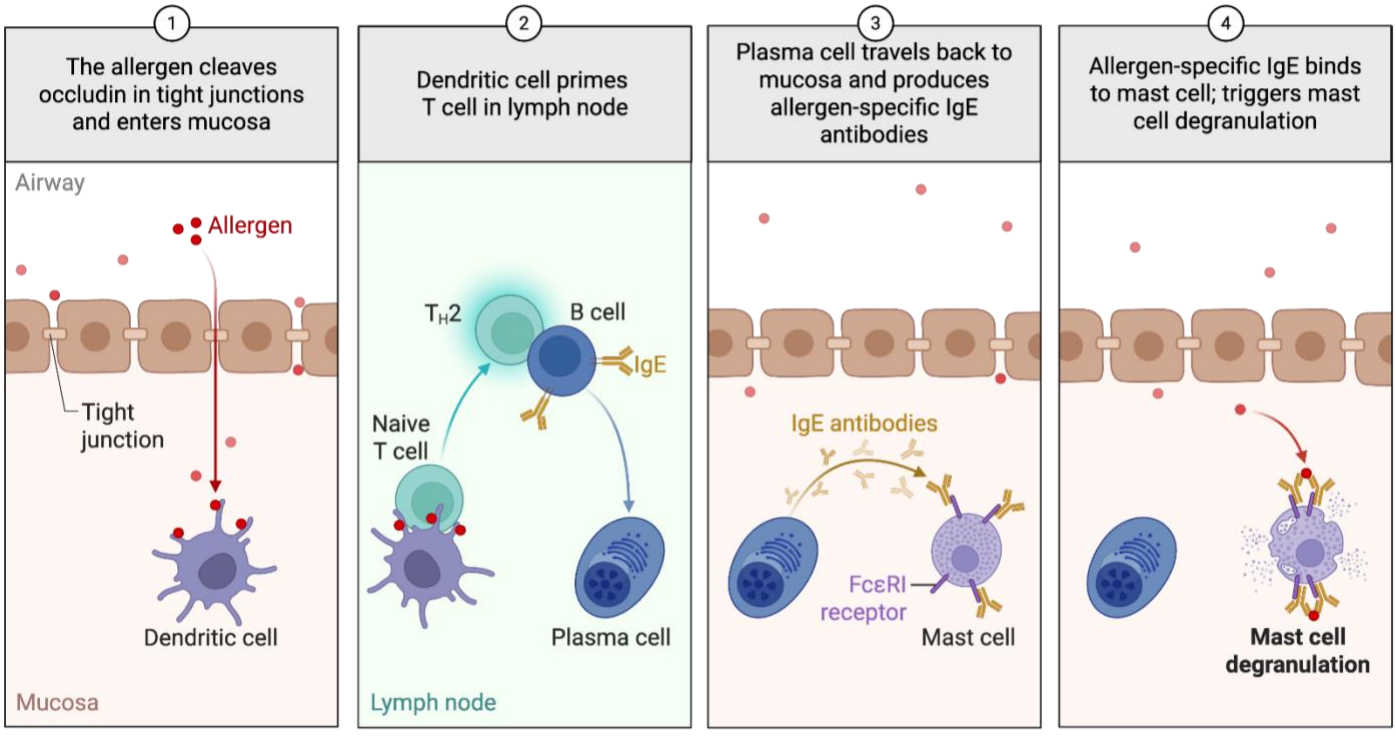


Persistent or reactivation pathogens can trigger inflammatory symptoms by activating immune and metabolic signaling pathways in a feedback loop. Mast cells and glial cells are key players in amplifying these immune responses during infections or injuries. When activated by pathogens, allergens, or injury, mast cells release various proinflammatory substances like histamine, cytokines, and lipid mediators to help fight the infection. For example, during influenza A infection, mast cells release these substances to try to control the virus. However, if the infection worsens or the immune response becomes too strong, mast cells can contribute to harmful inflammation instead.

In the central nervous system, mast cells work closely with microglia, the brain's immune cells, to respond to infection or injury. Upon activation, microglia change shape and release inflammatory substances, becoming "primed" to react more strongly to future challenges. Both mast cells and glial cells can become increasingly sensitive to multiple inflammatory events, leading to chronic inflammation.

This ongoing immune response can worsen neuroinflammation-linked IACI conditions like Long COVID or ME/CFS, contributing to symptoms like sensory sensitivity. The "primed" state of mast cells and glial cells is a crucial factor in sustaining inflammation and immunopathology in these patients.

Activation of Allergic Responses





ASSESSMENTS & TREATMENTS: How We Assess and Treat Mast Cell Activation and Immune Cell Priming



Chapter 4 | Clinical Care Guidance

The following section on clinical care guidance comes from our center's own practices. We are sharing our practices transparently in the hope that other locations may find them helpful and adopt them so that more people who are living with IACI diagnoses can access skilled and evidence-based care.

Some of our processes utilize specialized technology, software or expertise and we acknowledge that this may not be accessible to all clinics, but where possible we attempt to provide alternatives to these methods and services so that a basic level of care can always be provided. In other cases, some of the care we are providing may be incomplete or developing compared to what readers of this section are already providing. In which case, we appreciate you reaching out to us with advice and recommendations for techniques and services that we can include in our own center.



Environmental Design: Creating a Cultivated Patient Experience

Patient-Centered Physical Clinic Design



The main hallway in the CoRE features soft floor lighting and neutral, earth-toned colors which craft a calming atmosphere while patients receive care at our center.

The CoRE space was designed by Studio Elsewhere in collaboration with patients, providers and other stakeholders to create an environment that is intended to be comforting to patients, conducive to healing, and minimizes the likelihood of symptom flares while at our center. Features of the physical design of our center include:

- Soft, non-fluorescent lighting that can be easily adjusted to accommodate patient needs.
- Walls and ceilings that are painted with soothing natural tones to encourage a calming experience.
- Avoidance of using any artificial scents that may trigger mast cell reactions in sensitive patients.
- Environmental control that allows clinicians to adjust temperature based on patient preferences.
- Dedicated space for a patient to lay flat in a calm environment if they experience severe symptoms.

A Commitment to Infection Prevention

It is our philosophy that all clinical care settings, not just those that manage the care of IACI, should take a proactive approach in minimizing the chance that patients may sustain an infection whilst receiving care in location-based settings. To this end, we have established a series of steps and guidelines to keep our patients safe when they access care at the CoRE.

Current CDC guidelines make it challenging to mandate mask usage across an entire clinical facility. In NY State, we cannot legally require that our patients, staff, or visitors wear high-quality masks in our clinical spaces. However, we do take care to inform patients about what to expect to ensure that they are adequately prepared for their visit. If IACI patients are particularly conscious of infection-prevention protocols, we do take care to ensure that they are met with providers who are respectful of these needs, and we make every effort to provide them with private spaces where they do not need to share space with unmasked individuals. Our clinic also always stocks good-quality N95 masks onsite in easily accessible locations.



However, since mask mandates are challenging to enforce and practice daily due to state and federal law, the CoRE has also invested heavily in maintaining clean air in clinical spaces. We have equipped our center's HVAC system with HEPA filters that continuously purify the air throughout the CoRE space. In addition, we have installed far-UVC lighting has been installed in all patient-care areas of the CoRE. Far-UVC has antimicrobial properties that effectively eliminate airborne pathogens. Between regular testing, masking, air filtration systems and far-UVC lighting infrastructure in clinical environments, our clinic is well-positioned to maintain patient safety and minimize chances of reinfection during a clinical visit.



At the time of writing this guide, all clinicians who have direct patient contact wear N95 masks when interacting with patients, and all administrative staff mask in common clinical spaces.



Securing an Appointment at CoRE & the Onboarding Process

Initial Onboarding

Patients typically initiate contact with us via our email or our clinic phone number. We also accept referrals from other clinicians. Upon receiving a patient inquiry, our medical secretaries assess their immediate needs and schedule an initial intake appointment for the clinic.

The CoRE uses Epic as its Electronic Health Record, and appointments are made through the Epic MyChart app. Patients with smartphones are encouraged to download this app for ease of access, but this is not required.

To facilitate a productive and smooth initial intake appointment, our medical secretaries will provide all patients with a list of well-validated Patient Reported Outcomes (PROs) digitally to complete prior to their initial intake appointment. This allows our intake clinicians to begin discussions on symptom severity and prioritize care effectively.

Our Medical Billing Model & Insurance Pre-Authorization

At the CoRE, IACI patients undergo comprehensive assessments that objectively evaluate autonomic, cognitive, respiratory, and metabolic function. This approach provides us with a detailed picture of each patient's physiology, allowing us to tailor treatment plans to meet everyone's unique needs. We also understand that chronic illness impacts all facets of life, including social factors. For this reason, we also provide mental health services and support groups for patients and their caregivers.

The CoRE strives to accept insurance wherever possible. As a center, our goal is to make our services accessible to the millions of Americans living with IACIs. Before the first appointment, our medical secretaries run each patient's insurance to verify coverage. Our team will aim to provide each patient with realistic estimates of copays and other out-of-pocket expenses prior to each scheduled appointment or procedure.

Later in the guide, we will discuss the use of supplements as evidence-based interventions for certain disease drivers of IACIs. Unfortunately, the cost of supplements is rarely covered by insurance. In these cases, considering the use of supplement prescription platforms such as Fullscript can be useful in helping providers to reduce the cost of certain supplements to the patient. Similarly, you may find that sometimes the evidence-based use of off-label medications will be the best course of action. Again, this may present a cost barrier to some of your patients. To address this, our providers will often refer patients to compounding pharmacies such as Cost Plus Drugs that can offer these medications at a fraction of the regular cost to the patient.

REFER TO APPENDIX: We use a digital platform called REDCap for digital PRO intake. If patients are unable to access the digital platform, they can complete PRO intake by phone or via digital device in our waiting room. For a comprehensive list of the PROs used by the CoRE, please see the appendix.



The CoRE Clinical Registry

The CoRE utilizes patient data as part of a clinical registry to better understand IACI presentation and improve the quality of services that we can provide. To do this, we have consulted with our local ethics committee and obtained permission to retrospectively analyze acquired clinical data, **so long as patients provide consent that it is ok to do so**. Our medical secretaries offer patients the option to sign a consent form and become part of our clinical registry at the time of initial appointment scheduling, allowing for their data to be used for ongoing research. It is essential to clearly communicate that their access to care will not be affected by their decision to participate in research.

REFER TO APPENDIX: In Appendix A, you will find a listing of billing codes that we use to administer services that are covered by insurance. Please understand that these codes are shared for guidance purposes only and that you may have to find billing strategies that meet your clinic's needs.



Care Strategy at the CoRE

Overall Care Strategy

Our general care strategy has been developed with the complexity of IACIs in mind, understanding that although many people with IACIs may have similar symptoms (such as fatigue, PEM, cognitive impairment), the drivers/root causes of these symptoms may differ significantly from person-to-person and therefore require personalized care. To remember this, our overarching care strategy can be best described by the LIFT acronym:

Onboarding & Initial Intake

To minimize unnecessary exertion, an NP or physician generally conducts our initial intake virtually, unless the patient specifically requests an in-person visit. As we are an insurance-based clinic and we must adhere to certain efficiency standards, we aim to keep these initial intakes to a 30-minute period, but it may take some experience with IACI patient care before newer providers feel ready or comfortable to complete an initial intake in less than 45-60 minutes. On particularly busy days, our medical assistants may assist by completing portions

L – Listen

Engage with empathy. Hear the patient's story without assumptions.

I – Investigate

Measure all symptoms and gather data to assess severity.

F – Find the cause

Look deeper into your patient's physiology to identify the root of the problem.

T – Treat

Tailor a plan based on findings to support recovery and health.



of the subjective intake for our NP or physician.

Prior to their first intake session, all patients at the CoRE have been asked to complete a series of PROs during scheduling, which provide the clinician with a clear understanding of each person's most prominent symptoms and their severity, and to help guide the subjective intake process. While this intake session serves as a valuable opportunity to actively listen to the patient's history and symptoms, most patients with IACIs that we see have already received a diagnosis and have sought care from multiple other clinics in attempts to access care, so their narratives can often be complex and lengthy.

To effectively determine the next steps after the initial clinical intake, our NP or physician has already performed a medical record review to evaluate previous blood tests and results, previous clinical testing and results, and recommendations from past specialty appointments to ensure coordinated care. We find that it helps to try to reassure patients that this level of review has already occurred, and to target our initial subjective intake to how we can best get to targeted and effective treatment given the most pressing symptoms that are currently being experienced. We discuss the PRO results with the patient during the initial intake, highlighting normal and abnormal values and their meaning.

Diagnosis

Most patients who access care at the CoRE have already received a diagnosis, but we are often required to make diagnoses of IACIs as well. Based on the information obtained during the patient's intake, our practitioners do their best to link presenting symptoms to a potential triggering event and subsequently an appropriate diagnosis. The CoRE most frequently sees patients with Long COVID, ME/CFS, chronic tick- and vector-borne illness, and joint hypermobility spectrum disorders.

In undiagnosed individuals, our practitioners will use the initial intake appointment attempt to identify whether their patient's presenting symptoms can be linked to a specific event, and this can be used to guide the appropriate diagnosis.



In addition to the above PROs, we find it helpful to explore the patient's perspective on the following questions:

- What **past medical history** do you feel might be relevant?
- What **treatments or interventions** have you already tried?
- What has made you feel **better** and what has made you feel **worse**?
- What medications are you **currently taking**?
- What is the **most important symptom** that we can manage to improve your quality of life, and what are your **most immediate needs**?



In all cases, we strive to utilize existing, evidence-based consensus guidelines to make our diagnoses:

- For the diagnosis of Long COVID, we use guidelines that were set forth by the **National Academy of Science, Engineering and Medicine (NASEM)** clinical case definition.
- For the diagnosis of ME/CFS, we diagnose using the **Canadian Consensus Criteria**.
- For the diagnosis of chronic tick- and vector-borne illness, we use a variety of guidelines and protocols depending on the pathogens we suspect may be responsible for each patient's symptoms, including criteria put forth by research collaboratives as well as other guidelines and objective testing protocols.
- For the diagnosis of hypermobility spectrum disorders, we follow guidelines put forth by the **Ehlers-Danlos Society**.



Follow-Up: Introduction to the Team Approach After the Initial Intake

Connection to a Patient Navigator

Following the initial intake, patients can be connected to a patient navigator if needed. The navigator assists patients to schedule their appointments and manage the administration around care access.

Scheduling an In-Person Assessment

Following, and based upon, the results of the initial intake, our NP or physician will refer the patient back to our medical secretaries to schedule a series of in-person clinical and blood tests that will guide further intervention.

Our medical secretaries strive to schedule the in-person assessment within two weeks of the initial intake and to ensure that insurance pre-authorization or pricing for the tests is confirmed and transparent prior to the patient's next visit. Also, as a point of practice, our schedulers will always work with the patient to complete as many in-person tests as possible in a single visit to minimize multiple unnecessary visits, especially when PEM is a factor.

As-Needed Referrals

Typically, we wait until all assessments are completed before beginning the referral process, and we also try to treat in parallel to making specific referrals outside of the clinic. However, if the physician or NP identifies an immediate need for a specialty referral outside of the CoRE during the initial intake (such as cardiology or neurology for particularly troubling reports of cardiovascular or cognitive symptoms), that referral will be made right away.

The CoRE is staffed by a team of professionals that each play essential roles in providing comprehensive care. In addition to our in-house team, we collaborate with a wide network of specialists, including but not limited to gastroenterologists, neurologists, cardiologists, psychiatrists, endocrinologists, neurosurgeons and many other professionals, as needed. To prevent fragmentation of care, we attempt to manage as much care as possible in-house but also acknowledge the need for skilled and compassionate comprehensive care.

MEDICAL EDUCATION VIDEO: Effective Social Support for IACI Patients



In-house CoRE providers that provide comprehensive care for our patients:

Role	Responsibilities
Medical Secretaries	Manage patient scheduling, insurance authorizations, and billing.
NPs	Conduct initial clinical intakes, follow-up appointments, order labs and clinical tests, refer to specialists, and liaise with the medical team.
Physicians	Work with both physiatrists and primary care providers (PCPs) as first-contact physicians for IACI patients and collaborating with NPs to manage complex care.
Medical Assistants	Perform specialized clinical testing under the general supervision of the NP and assist in patient navigation.
Patient Navigator	Guide patients through their appointments and referrals, ensuring that they do not feel “lost” in the system while navigating complex care. Ideally, these individuals have both clinical backgrounds and lived experience.
Physical Therapists	Provide care for patients dealing with joint hypermobility, autonomic rehabilitation, breathwork, pacing education and pain management.
Neuropsychologists	Provide care for patients dealing with cognitive impairment and emotion dysregulation as a result of their diagnosis and subsequent adjustment to disability status.
Social Workers	Assist with applications for short- and long-term disability, manage our peer and caregiver support groups, and liaise with psychological services as needed.
Registered Dietician	Assist patients with a plan to consume adequate nutrition whilst also managing new onset food and drink sensitivities and allergies that often emerge in people with IACIs.



A specialty IACI clinic must excel at completing comprehensive assessments to determine how to best support each patient, but knowledgeable providers without specialized equipment can still make a huge difference in an IACI patient's daily function.



In-Person Assessments at the CoRE

Blood Testing

By the time the patients arrive for their CoRE in-person assessment, the NP or physician will have prepared all blood test orders, allowing for testing to occur on the same day as clinical evaluations.

Clinical Testing

Based on the patient's symptoms and the findings from the initial intake, a series of multisystem clinical tests will be ordered to provide objective data to guide clinical intervention. Specific details about these tests are provided later in the guide.

The in-person clinical testing is comprehensive and specifically designed to attempt to identify dysfunction associated with some of the drivers of IACI, including:

- **Autonomic nervous system**: Active Stand Test (Tier 1), Tilt Table Test (Tier 2)
- **Endothelial function**: EndoPAT
- **Metabolic health**: Resting Metabolic Rate
- **Cognitive function**: Quantitative EEG, neuropsychological testing
- **Joint mobility**: Testing for joint hypermobility and cervicocranial instability

Optional Research Opportunities





Since we are a hybrid center that engages in both research and clinical practice, patients will usually spend time meeting with a clinical research coordinator or another staff member who can inform them about open clinical trials and research opportunities. We have found that many people living with IACIs are eager and enthusiastic about participating in research opportunities. If your clinic is near or part of an academic research center, it may be beneficial to reach out to see if there are research opportunities and study flyers that you can feature in your clinic to assist in the completion of important IACI research.

After the Visit

After the in-person assessment, patients will be scheduled for a follow-up with the NP. This appointment will focus on discussing the blood and in-person testing results, as well as collaboratively working toward a treatment plan.

Active Patient Follow-Up

With complex patients who are receiving multiple referrals to various providers comprehensive care can be overwhelming and it can be easy to lose track of people and have them experience fragmentation. As with most busy clinical practices, this has been an issue at the CoRE in the past, and our clinical administration team is working to solve the issue with a focus on pro-actively tracking patient progress on a regularly to ensure no one is left behind.

Monthly Patient Reports

Each month, we pull together a report on our active patients using our Epic, which is the EHR software that is used across the Mount Sinai Health System. This helps us identify anyone who hasn't been contacted or hasn't had a follow-up scheduled. Good communication is essential for quality care. Here's what we focus on:

- It's important for patients to know what they should expect after their appointments or treatments.
- Regular check-ins help foster a trusting relationship, making it easier for patients to voice their concerns or ask questions.
- When patients are kept in the loop, they feel more confident taking an active role in their own healthcare.

Note for Managing Cognitively Impaired Patients

For those dealing with cognitive impairment, consistent follow-ups are even more important. This group may need extra support, including access to patient navigators, health coaches or patient advocates. We prioritize reaching out frequently to ensure everything is on track and that patients are managing their conditions and helping them to secure advocates where needed or appropriate.

Assessment Procedures & Treatment Recommendations Based on Clinical Findings

MEDICAL EDUCATION VIDEO: Patient Intake, Assessment, and Guidance

Pathogen Persistence & Reactivation



Basic Concepts & Testing

The world of assessing pathogen persistence is evolving with the emergence of new technologies that can detect pathogens that may be lingering in tissues, blood or other bodily fluids, but we have a long way to go before testing is mainstream and accessible. As part of their subjective intake, our providers will often start with the patient's medical history to determine whether the patient may have been exposed (through living circumstances, travel, work or lifestyle) to pathogens that may persist.

Where pathogen persistence or reactivation is suspected, providers should of course consider ordering serology testing for various pathogens (our standard blood testing panel). A positive serology test may indicate the reactivation of dormant viruses (for example EBV, HSV or CMV to name a few), which could contribute to IACI symptomatology. However, providers should also know, for a variety of reasons, antibody production may be inhibited in people living with IACIs and so serology testing for persistent pathogens may not be reliable. In addition, pathogens may persist in tissue and immune-privileged sites, meaning that standard testing will not detect them.

CoRE Treatment Philosophy

Treatment approaches for persistent and reactivated pathogens remain somewhat experimental or ad hoc due to technological limitations in mainstream approaches to detecting persistent pathogens. If patient serology is positive in a way that indicates the presence of persistent or reactivated pathogens, our philosophy is quite simple: these patients should be actively treated for these pathogens. Therefore, depending on the findings of the test results, clinicians should treat per protocol. For example, if a specific *herpesvirus* reactivation is found, treat per that *herpesvirus* protocol.

Ongoing Research & Future Directions

The CoRE is currently engaged in clinical trials to identify targeted therapies for persistent and reactivating pathogens in people with IACIs. For instance, we are currently exploring the role of two repurposed HIV medications, Truvada and Maraviroc, in managing reactivation of viruses associated with Long COVID. Our team will also be watching the results of various monoclonal trials for Long COVID and will update the manual as needed. Furthermore, the role of combination antiviral protocols is also of interest to the team, meaning that we believe that protocols such as the Pridgen Protocol, which has previously shown promise in Fibromyalgia, may benefit from updating for other IACIs and clinical trials. In short, this is a rapidly growing field of research and the promise of many drug protocols, used either in isolation or combination, are yet to be adequately trialed. This is a promising area of research, and providers interested in IACI management should commit to closely watching emerging research.

REFER TO CHAPTER 7: For an overview of the CoRE testing and interventional procedures for tick- and vector-borne pathogens, please see Chapter 7.



Case Examples of the Treatment of Persistent or Reactivated Pathogens

Long COVID: In some cases, extended courses of Paxlovid are being prescribed to patients with Long COVID, and success varies by case, while larger-scale trials without highly selective inclusion criteria have failed to show benefit in large cohort. This indicates that a more detailed understanding of Long COVID physiology is needed to better understand who may benefit from therapies such as Paxlovid. Similarly, there have been cases of remission of severe forms of Long COVID following monoclonal antibody (MCA) infusions. In short, the instinct to trial a monoclonal or SARS-CoV-2 antiviral for a person with Long COVID would be considered "off-label" at this time, but highly feasible given the available literature. More research is needed, however, to better identify Long COVID patients who might be responsive to this sort of treatment approach.

ME/CFS*:* Other broad-spectrum interventions for the treatment of pathogen persistence in ME/CFS includes inosine pranobex (IP). Dosage recommendations for IP in cases of ME/CFS have been previously published in consensus documentation.



Mitochondrial Dysfunction

Basic Concepts & Testing

Mitochondrial dysfunction can be extremely difficult to measure, because direct measures of mitochondrial function and cellular respiration such as Seahorse may vary based on the tissue type that is tested. Therefore, we chose resting metabolic rate (RMR) as a proxy to measure overall mitochondrial function and energy utilization.

Practically speaking, RMR gives us an indication of how much energy is being used to maintain very basic bodily function and homeostasis, so we use advanced technology to measure energy expenditure when a patient is sitting restfully in a quiet environment. There are normative values for RMR that are based on a patient's height, weight, body composition, gender and several other variables. If a patient's RMR is higher than what we would expect (compared with predicted norms), then mitochondrial function is suspected by our team. The CoRE uses the Cortex Metamax or the COSMED BodPod to calculate RMR in our patients, but there are many well-validated devices that can be used to produce the RMR metric.



RMR being collected from a patient using the Cortex Metamax technology.

We understand that the equipment used to generate RMR is highly specialized, so if your facility does not have direct access to this technology, third party health and wellness vendors can often provide patients with their baseline RMR and retest as needed. In an ideal clinical intake, we advocate for RMR as it is an objective test that may give us an indication of whether mitochondrial dysfunction is involved in driving some of our patients' symptoms. Namely, some of the most common manifestations of mitochondrial function will be the symptoms of fatigue and PEM, but because these symptoms are general and can be caused by other drivers (e.g. dysautonomia or reactivated pathogens), RMR testing allows us to narrow down mitochondrial dysfunction as a possible driver and measure our patient's responses to targeted intervention.

However, if your clinic does not have access to these technologies and/or the patient is unable to afford or access third party testing, using some of the PROs that are recommended for fatigue and PEM to objectively gauge whether a patient's symptoms are responding to mitochondrial supplementation is more than adequate.

CoRE Treatment Philosophy

The universe of mitochondrial supplementation is vast and can be overwhelming. Many practitioners will advocate for a highly specific approach based upon blood and functional testing, while others may approach things more generally. For instance, nutritional supplements such as antioxidants and



cofactors are commonly used to mitigate oxidative stress (a by-product of energy production) and support mitochondrial function, allowing users to be more resilient to exertion. Common antioxidants frequently utilized by people with IACIs include supplements such as CoQ10, oxaloacetate, and creatine. By contrast, amino acids and their derivatives such as arginine, citrulline, and carnitine are used to enhance nitric oxide production and facilitate fatty acid transport into the mitochondria, making mitochondria more efficient at producing energy. A comprehensive guide detailing the available peer-reviewed evidence for supplements can be found here and later in this manual, we will also discuss how dietary changes can contribute to increasing intake of these compounds.

Simply put, when it comes to mitochondrial dysfunction as a driver of IACI symptoms, our treatment philosophy is to identify patients who are reporting significant fatigue and PEM, who also have an RMR that is greater than 10-15% of their predicted RMR and work with our patients to develop a supplementation plan. Because supplements are not covered by insurance and they tend to be expensive, our providers ensure that they only recommend trusted brands that have gone through rigorous third-party testing.

We also ask providers to be aware that supplements can interact with other medications, comorbidities and can also trigger medication sensitivities or MCAS, so proceeding carefully with particularly complex patients is strongly recommended. After 1-2 months on the supplementation plan, we reassess both PROs and RMR to determine whether these supplements have made a difference to the patient's overall energy levels and resilience to exertion.

Ongoing Research & Future Directions

Exploring the role of drugs such as metformin and low-dose rapamycin to support mitochondrial function are ongoing. Metformin is a known promoter of mitochondrial function and is emerging as a useful medication in many disease states. Although studies do not yet exist to support the use of metformin or low-dose rapamycin in this way for people diagnosed with IACIs, they may be off-label use options for some patients as appropriate. Looking further into the future, the use of emerging techniques and technologies such as mitochondrial transplantation is an area of great promise for IACI patients who experience energy-limiting symptoms.



Coagulation & Vascular Dysfunction

Basic Concepts & Testing

Many patients with IACIs experience endothelial dysfunction and clotting abnormalities that may be driven by various other factors. Unfortunately, many of the mainstream laboratory tests for clotting and hypercoagulation are too insensitive to identify when micro-thrombotic mechanisms are at play. That said, we still recommend mainstream blood testing for hypercoagulation risk factors because people with IACIs, especially Long COVID,



It should be noted that arginine can worsen asthma symptoms, so avoid prescription if your patient is asthmatic.



have been identified being at higher risk for thrombotic events. To this end, we typically test for CRP and hs-CRP, Fibrinogen, D-Dimer, VEG-F, Von Willebrand Factor, Factor VIII and a full lipid panel (see Appendix G). If any of these tests are abnormally elevated, we recommend either treating per protocol or referring directly to a hematologist or cardiologist for per protocol care.

However, in the case that mainstream blood testing returns within normal limits (which is common), our team recommends testing patients for evidence of endothelial dysfunction as a proxy for micro-thrombotic issues and platelet hyperactivation.

In the CoRE, we utilize a device known as the EndoPAT for this, which is an FDA-approved device that non-invasively produces a measure of endothelial function called the reactive hyperemia index (RHI). RHI specifically measures the ability of blood vessels to dilate in response to a brief period of restricted blood flow, calculated using peripheral arterial tonometry (PAT; a measure of small pulse amplitude changes in the fingers).

Briefly, a blood pressure cuff is inflated to cut off blood supply to the arm below the cuff for a brief period, and a sensitive probe is placed on each index finger (pictured). The cuff is then deflated, and the probes measure how quickly blood returns to the fingers. A low RHI score (based on well-validated normative values for age and gender) indicates that a patient's endothelial dysfunction is abnormal and may be affecting tissue perfusion and even organ function.

CoRE Treatment Philosophy

For treating endothelial dysfunction, the evidence base is unfortunately sparse, but there are some available options. When it comes to managing endothelial dysfunction, the mechanism of action for most of these evidence-based options appears to relate back to our ability to manage a patient's oxidative stress levels using antioxidant compounds, but evidence-based options that have specifically been shown to benefit endothelial function or RHI in other populations include supplementation with lycopene, pycnogenol, vitamin C, and resveratrol. When abnormal RHI values are seen on EndoPAT testing, these four supplements are first-line interventions at the CoRE.

In addition, if we are seeing endothelial dysfunction, our providers will often suspect that microclots or platelet hyperactivation may also be part of the clinical picture. As such, when appropriate, our providers will also recommend trialing proteolytic enzymes such as nattokinase or lumbrokinase to treat coagulopathy by breaking down fibrinogen. In addition to the clinical evidence that these compounds can degrade fibrinogen and



fibrin, in a patient-led survey of people with Long COVID and ME/CFS, nattokinase and lumbrokinase were identified as interventions that were most often associated with driving at least some improvement, so proteolytic enzymes often



form part of our interventional approach. Similarly, our providers will frequently prescribe Aspirin as a safe and low-cost anti-platelet therapy when endothelial dysfunction is identified, as well as berberine, which has been shown to inhibit platelet activation as well as having potential fibrinolytic properties.

Ongoing Research & Future Directions

Continuing research to better understand the role, dosage and effects of many of these fibrinolytic and anti-platelet therapies is crucial.

There are other promising compounds for endothelial dysfunction such as sulodexide that is not currently available in the US or easily accessible elsewhere, but should be researched more in order to make a potentially promising intervention more readily available.

Finally, more aggressive approaches to combatting abnormalities in coagulation and platelet hyperactivation such as dual-antiplatelet therapy, anti-coagulation therapies (and various combinations of these approaches), as well as blood filtration approaches such as H.E.L.P apheresis may hold promise. However, given the high-risk nature of these technologies, until there is good-quality research data to support these approaches, they are not recommended at CoRE.

LEARN MORE: The CoRE team is currently engaging in an open-label trial of lumbrokinase to better understand how people with different IACIs respond to the supplement & why.



Dysautonomia & POTS

Basic Concepts & Testing

Many patients with IACI experience a significant number of symptoms due to dysautonomia and POTS. Although POTS can be relatively simple to identify, one of the most common errors we encounter when educating about the treatment of POTS is the assumption that POTS is simply an abnormal change in blood pressure and/or heart rate during positional changes and that when it is detected, it should always be treated in the same way. This is an oversimplification and can lead to poor patient outcomes. Our team tends to think about a POTS diagnosis as fitting one of three categories: hypovolemic, neuropathic, or hyperadrenergic POTS.

Our first-line assessment for all patients that we suspect of having POTS is called the active stand test. We like it because it is simple, gives a lot of information to guide treatment and requires minimal specialty equipment. If a patient has been working with us for 2-3 months and we are unable to make a difference in managing their POTS symptoms, then we may send them for more advanced POTS testing including a tilt table test, cardiovagal testing and sudomotor testing.

Cause	Excessive sympathetic nervous system activity
Key features	• Symptoms include tremors, anxiety and palpitations when upright • The longer a patient stands, the higher their blood pressure will climb • May have much more extreme tachycardia standing due to overactive adrenergic response • Marked increase in plasma NE levels (>600 pg/mL) upon standing (requires a specialized blood test testing NE levels in supine followed by standing)
Neuropathic POTS	
Cause	Partial autonomic denervation, especially in the lower limbs
Key features	• Impaired vasoconstriction leads to blood pooling in the legs especially during standing • Symptoms include cold or discolored feet, reduced sweating in lower extremities • May show increased heart rate and systolic blood pressure during standing • Typically normal or low norepinephrine levels
Hypovolemic POTS	
Cause	Reduced blood volume despite normal renal and adrenal function
Key features	• Symptoms include fatigue, dizziness, and lightheadedness on standing • Systolic and diastolic blood pressure will either stay the same or decrease during standing • Low circulating plasma volume and blood volume (this is not routinely tested but is noted in the literature) • Low aldosterone and renin activity may be present

Hyperadrenergic POTS



Tier 1- The Active Stand Test

The active stand test assesses orthostatic intolerance by measuring heart rate and blood pressure changes as the patient transitions between supine and standing positions. All you need for this test is a blood pressure cuff for monitoring blood pressure and heart rate and a method for physical (pen and paper) or digital (tablet) documentation of data. First, the patient will lie down for a few minutes. Then, the patient will be asked to sit up and then stand. Blood pressure and heart rate will be checked after different positional changes, and then every minute during the 10-minute stand period.

Tier 2- Tilt Table Testing, Cardiovagal Function, & Sudomotor Testing

When performing a comprehensive assessment of autonomic nervous system function, we typically perform autonomic testing in three phases:

1. The tilt table test, which involves lying the patient on a motorized table that tilts to different angles (typically from horizontal to fully vertical), while sensors monitor their heart rate and blood pressure to observe how they react to changes in position.
2. Cardiovagal function testing, where we evaluate how much one's heart rate changes during deep breathing (respiratory sinus arrhythmia) and how their heart and blood vessels respond to increased pressure inside the chest (utilizing the Valsalva maneuver)
3. Sudomotor testing, or Quantitative Sudomotor Axon Reflex Test (QSART), which allows us to measure a patient's ability to produce sweat in response to certain stimuli.

Based on responses to these three testing paradigms, we score patients on three indices: cardiovagal, adrenergic and sudomotor – and then create an aggregate score using the Composite Autonomic Severity Score (CASS). We use specific testing results to guide treatment selection.

CoRE Treatment Philosophy

Compression and fluid support is advised for management of POTS and dysautonomia. Regarding rehabilitation, patients should be referred to a knowledgeable physical therapist that can utilize autonomic rehabilitation techniques.



Patient is positioned upright during the tilt table test.

If your patient feels dizzy, faint, or develops any worsening of symptoms, document the point at which these symptoms occurred and take appropriate medical precautions right away. The active test can potentially make a patient's symptoms temporarily worse, so use your clinical judgement to determine if this test is appropriate or needs to be stopped.



If conservative management of POTS and dysautonomia are unable to stabilize symptoms, medical management may be indicated. Please note that medical management of POTS and dysautonomia can vary patient-to-patient and you may sometimes have to try different combinations of medications to get the desired effects.

Based on the type of POTS observed, different first-line medical management approaches may be indicated:

- **Hyperadrenergic POTS**: Managing tachycardia with beta-blockers such as propranolol or bisoprolol. Similarly, ivabradine can assist with an elevated heart rate. Finally, central sympatholytics such as guanfacine can also help to manage symptoms of hyperadrenergic POTS.
- **Neuropathic POTS**: The best evidence-base exists for trialing midodrine and pyridostigmine as first-line interventions. In cases that are non-responsive to first-line medications, IV or SC immunoglobulin can be considered. The best evidence-base exists for trialing midodrine and pyridostigmine as first-line interventions. In cases that are non-responsive to first-line medications, IV or SC immunoglobulin can be considered.
- **Hypovolemic POTS**: Fludrocortisone is recommended as a fluid expander for patients with hypovolemic POTS.

Ongoing Research & Future Directions

Research at the CoRE for autonomic dysfunction includes new rehabilitation strategies. The CoRE is evaluating the feasibility, safety, and physiological impact of a passive, position-based ischemic preconditioning (IPC) protocol designed to mimic the cardiovascular stress of upright posture through limb occlusion, potentially enhancing baroreflex function, improving venous return via the Frank-Starling mechanism, and priming autonomic and vascular adaptation in patients unable to tolerate conventional exercise.

Additionally, the CoRE is seeing promising results utilizing supplemental oxygen in various states of work, from rest all the way to upright titration training therapy, allowing PTs to make more progress with their patients with dysautonomia with less symptoms and consequences. Finally, we are in the process of exploring vagus nerve stimulation for patients with POTS and dysautonomia in subsequent versions of this handbook.



Connective Tissue Disorders (CTDs)

Basic Concepts & Testing

Patients with IACIs commonly present additional joint hypermobility as a key feature of CTDs. There are several CTDs, including but not limited to hypermobile Ehlers-Danlos syndrome (hEDS) and hypermobile spectrum disorder (HSD), where the key characteristic is excessive joint instability. As there are several different connective tissue disorders, and even several types of Ehlers-Danlos syndromes, their pathologic factor of connective tissue is not always consistent across all patients with this presentation. This said, it seems that some collagen mutations are most common in causing this widespread laxity, however which type of collagen is still not consistent.

A bidirectional relationship is present in those with IACIs and joint hypermobility. In many cases, we are finding that many with pre-existing hypermobility, even if non-syndromic, may be more susceptible to these IACIs, as well as the widespread inflammation and mast cell activation caused by the persistent infection may worsen existing hypermobility, evolving and non-syndromic case to a severe laxity and instability or worsening existing CTDs, or in other cases,$ causing the onset of noticed hypermobility.

The standard for testing for generalized hypermobility is currently the Beighton Scale. The conventional thought with hypermobility is that these patients would present as a very flexible person, which is often the case, but many are limited by their pain, inflammation and musculotendinous adaptive shortening to protect against their instability and therefore are not as flexible as one may anticipate. For that reason, the limitations of the Beighton Scale are filtering out some of those that lack the conventional (musculotendinous) hyperextensibility and are missing the articular instability caused by ligamentous laxity. See ongoing research to incorporate a new series of tests, the Iovine Cluster, to capture this specificity in the most affected joints.

Living with a CTD can affect nearly every system in the body.

Complications may involve neurological problems such as headaches, nerve compression, or spinal instability, and allergic-like responses due to mast cell activation. There are several predispositions seen between CTDs and neurological manifestations. Upper cervical instabilities (UCI) being a cardinal neurologic manifestation, include craniocervical instability (CCI), where there is pathology of

Common symptoms of CTDs include:

- Joint instability, frequent dislocations or subluxations
- Widespread pain
- Fatigue
- Dizziness (and other signs of autonomic dysfunction)
- Digestive issues (such as gastroparesis/delayed gastric emptying)
- Skin fragility
- Proprioceptive disorder



the tissues holding the occiput to C1 as well as atlantoaxial instability (AAI), where pathology lies in the connection from C1-C2.

WWhile the presentation of this pathology is vast, UCIs often cause positional headaches, a "bobble-head" sensation, neck instability, difficulty holding the head up, visual disturbances, and fainting or pre-syncope with head movement—distinct signs of brainstem and cranial nerve involvement. outpatient testing includes the alar ligament stress test, sharp-purser test and upper quarter screen while imaging includes upright flexion and extension MRI and rotational CT scans.

CoRE Treatment Philosophy

The CoRE treatment philosophy for CTDs emphasizes stabilization, energy conservation, and interdisciplinary care tailored to the unique challenges of tissue fragility, joint instability, and systemic involvement. Recognizing that symptoms often span musculoskeletal, autonomic, GI, and neurologic domains, we focus on whole-body assessment and treatment, prioritizing function over force and endurance over intensity. Patient education, joint protection, and proprioceptive retraining are central, as is adapting interventions to individual tolerance, pacing needs, and comorbidities like POTS or MCAS. By validating lived experience and tailoring care to each person's baseline, we help patients build safer movement patterns and reclaim quality of life. Subluxation corrections are what truly set apart classic rehabilitation techniques from specialized hypermobility care in addition to recognizing that regional interdependence is paramount in this population, as any joint being out of place can affect the position of any other articulations up or down the kinematic chain. An example is in treating UCIs, assessing pelvic stability and position is very important to ensure spinal neutrality. Also note that joint hypermobility disorders may have misleading nomenclature, as some tissue can become very adhered and tight. This still requires attention to fully address the presentation.

Infections as Drivers of Connective Tissue & Vasculature Problems

It is important to note that many of the viral or bacterial pathogens that initiate or exacerbate symptoms in IACI patients degrade connective tissue and/or infect and dysregulate the vasculature as part of their potential survival in tissue reservoirs. For example, *Borrelia* has been shown to damage collagen and elastic fibers as part of its activity. *Bartonella* can infect endothelial cells and red blood cells, which can lead to vascular pathologies. Thus, patients with CTDs should be tested for tick-borne/vector-borne infections as described here.

Ongoing Research & Future Directions

Current research by the CoRE for hypermobility includes an expert consensus study to address the key differences in rehabilitation for patients with CTDs, as well as investigating and validating the Iovine Cluster. Other studies that will benefit this population can be seen in the Autonomic Research section.



Neuroinflammation & Cognitive Dysfunction

Basic Concepts & Testing

Cognitive dysfunction in IACIs can occur for a myriad of reasons including disordered sleep, POTS/dysautonomia, neuroinflammation/MCAS, and mitochondrial dysfunction to name just a few. As such, cognitive dysfunction must be assessed, placing the assessment results of the other drivers of IACI into context as well. An added complication regarding cognitive dysfunction in IACI is that it can often be challenging to assess since we rarely have baseline data related to cognition prior to the onset of an IACI. Cognitive testing is rarely conducted in young adults, and most modes of cognitive testing have ceiling effects for younger patients, meaning that even if these patients have experienced significant cognitive loss, they will still score "within normal limits" on a test designed to identify cognitively impaired older adults. As such, we explain to patients that the cognitive testing paradigms we use at the CoRE are



implemented to establish a baseline for their cognition in the moment, and our goal is to show improvement over time in these scores, even if they are testing "within normal limits" at their baseline assessment.

In addition, if a patient is reporting sleep disruption, which can manifest as difficulty falling asleep, staying asleep or experiencing refreshing sleep despite adequate sleep time, cognition is likely going to be affected. If this is the case, CoRE providers will refer patients for a sleep study to identify whether

We evaluate cognition in three ways:

- We perform neuropsychological assessment using well-validated cognitive testing paradigms such as the Stroop, Trails A/B, and others. We utilize computerized testing platforms such as BrainCheck that allows for consistency in testing protocols as well as the ability to test patients virtually if they're unable to travel to the clinic.
- Quantitative EEG assessments via platforms such as the NeuroCatch that allow us to evaluate a patient's cognitive effort associated with conscious and unconscious processing of auditory inputs.
- PROs such as the Neurological Quality of Life (NeuroQOL) that allow us to understand the extent to which a patient's reported cognitive impairment is affecting their activities of daily living and quality of life.



disordered sleep is present. Medical management of disrupted sleep can make a significant difference to daily function and quality of life.

CoRE Treatment Philosophy

First and foremost, if a patient's cognition is severely affected and they are scoring extremely low (below the 30th percentile) on cognitive testing, our team will refer to neurology for imaging and formal assessment to rule out other causes of cognitive dysfunction.

Once other pathologies have been ruled out, CoRE providers work with the patient to understand the contributions of different IACI drivers to reported cognitive dysfunction. For instance, some patients will experience significant cognitive improvements in response to antihistamines that address MCAS, while others can experience cognitive benefits from maintaining adequate hydration. Many people with IACIs experience unrefreshing sleep and subsequent cognitive impairment because of impaired slow wave sleep. If confirmed on sleep studies, this can be potentially be well-managed with sleep medicine collaborations and use of some first-line sleep medications.

In addition to these strategies, while our providers are working to determine the drivers that could potentially be contributing to cognitive dysfunction, we also refer out to colleagues in neuropsychology to help patients with cognitive remediation therapies to help them manage the cognitive dysfunction that they are experiencing in the moment. In severe cases where patients are reporting significant difficulty with speech and word-finding, a referral to speech therapy may also be helpful.

Ongoing Research & Future Directions

Research investigating the role of different interventions for cognition are currently underway, including interventions such as hyperbaric oxygen therapy and microtesla magnetic therapy. In addition, given the seriousness and severity of cognitive impairment associated with IACIs, there is a critical need for research exploring the efficacy of combination therapies (e.g., hyperbaric oxygen therapy paired with antihistamines).



Immune Dysfunction & Autoimmunity

Basic Concepts & Testing

Immune dysregulation, including T-cell exhaustion, impaired natural killer cell function and altered interferon signaling is a common research finding in cases of IACI. Similarly, a subset of people with IACI will often test positive for blood biomarkers consistent with autoimmunity. Part of the blood testing protocol at the CoRE includes testing IACI patients for evidence of autoimmunity.

CoRE Treatment Philosophy

If immune dysregulation detected is characterized by features such as low albumin, elevated inflammatory cytokines such as IL-6, and an elevated neutrophil-to-lymphocyte ratio, the patient may be responsive to IV or SC immunoglobulin.

Another medication with anti-inflammatory and immunomodulatory properties that has shown benefit in some Long COVID and ME/CFS cases is low-dose naltrexone (LDN). One retrospective clinical cohort study found that use of LDN in Long COVID was associated with improved clinical symptoms including fatigue, PEM, and unrefreshing sleep. Another series of three case reports demonstrated improvement of some ME/CFS symptoms with LDN use. LDN must be obtained from a compounding pharmacy, with dosages of between 1-4 mg commonly used in IACI treatment (although in some cases dosage has been raised up to 12 mg). Patients often benefit from starting LDN in a very low dose and slowly increasing dosing over time until the medication is optimally tolerated.

In more complex cases of immune dysregulation or evidence of autoimmunity, our team refers out to rheumatology for medical management.

Ongoing Research & Future Directions

Researchers at the CoRE are currently investigating the role of functional autoantibodies in driving symptomatology in Long COVID and other IACIs. In addition, multiple groups including ours are exploring the role of low-dose rapamycin as an immune modulator that can correct some observed patterns of immune dysregulation in people with IACIs.



Microbiome Imbalance & SIBO

Basic Concepts & Testing

Common symptoms of SIBO include excess gas and painful bloating, diarrhea or constipation, acid reflux, low B12 levels, unintentional weight changes, and brain fog. If these symptoms are noted in an IACI patient, we refer to a gastroenterologist. The specialist will perform SIBO testing and treatment with considerations briefly summarized below. Breath testing (with proper preparation) is the standard diagnostic method.

Treatment considerations for SIBO:

- Treatment depends on whether SIBO is methane- or hydrogen-dominant.
- The success rate of a single course of antibiotics is approximately 50%, meaning some patients may require a second round or an alternative medication.
- Dietary changes alone won't cure SIBO, but limiting alcohol may be beneficial.
- A registered dietitian specializing in GI disorders can help manage symptoms without excessive restriction, improving quality of life and nutritional adequacy.

CoRE Treatment Philosophy

The composition of the gut microbiome differs greatly from person to person based on factors such as geographical region, diet, and time of day. Thus, CoRE protocols for gut related abnormalities or treatments focus more specifically on the measurement of metabolites or products commonly created by gut microbes.

Ongoing Research & Future Directions

Research is underway to understand if certain forms of probiotics might improve IACI symptoms. This includes use of the probiotic VNELLA in some of our IACI patients. VNELLA contains the bacterial strain *Veillonella atypica*. The microbe metabolizes lactic acid (a byproduct of exertion and in some cases mitochondrial dysfunction) and converts it into short chain fatty acids (compounds shown in some studies to have anti-inflammatory properties).

There is also a clinical trial of larazotide in Long COVID underway. Larazotide has been shown in some studies to improve gut barrier permeability. One case series in the pediatric post-COVID condition multisystem inflammatory syndrome reported significantly improved time to resolution of gastrointestinal symptoms in larazotide treated children. Larazotide cannot currently be ordered from a compounding pharmacy. However, if the Long COVID larazotide trial is successful, efforts may be increased to provide clinicians with access to the medication. Other compounds currently used in some cases to improve gut barrier permeability are zinc carnosine, l-glutamine, and aloe vera.



Mast Cell Activation

Basic Concepts & Testing

MCAS occurs when mast cells release excessive or inappropriate amounts of chemical mediators, resulting in widespread and fluctuating symptoms. This mast cell activation often occurs in response to pathogen persistence, pathogen reactivation, microbiome imbalances or other factors that activate the innate immune system. Unlike systemic mastocytosis, MCAS does not involve mast cell proliferation, but rather hyperactivation of mast cells that are structurally normal but inconsistently triggered to various degrees. These cells, present in connective tissue and near blood vessels and nerves, release mediators such as histamine, prostaglandins, leukotrienes, and tryptase, contributing to both acute reactions and chronic inflammation.

Diagnosis is based on three pillars: characteristic symptoms across multiple organ systems, objective evidence of mast cell mediator release, and a positive clinical response to medications that inhibit mast cell activity. Elevated baseline serum tryptase may support the diagnosis but is often normal in MCAS. More reliable indicators include elevated urinary levels of N-methylhistamine, prostaglandin D2 metabolites (e.g., 11β-prostaglandin F2α), and leukotriene E4, ideally collected during or shortly after symptom flares. Because mediator release can be episodic, repeated testing may be necessary.

We typically start with histamine receptor blockers, including:

- H1 antihistamines (e.g., cetirizine, loratadine, hydroxyzine) to address skin, respiratory, and neurological symptoms.
- H2 antihistamines (e.g., famotidine, ranitidine) to target GI and CV manifestations.

In addition to receptor blockade, we have found that stabilizing the mast cells can have an effective long-term response:

- Cromolyn sodium most often, or ketotifen (or natural bioflavonoids like quercetin or luteolin), which help regulate mediator release and reduce flare frequency over time.

In parallel, we emphasize histamine avoidance and trigger identification through symptom tracking and elimination strategies. Patients are supported in identifying personal triggers—such as specific foods, environmental exposures, medications, temperature changes, or hormonal shifts—and guided through tailored avoidance plans that balance stability with quality of life.



CoRE Treatment Philosophy

At the CoRE, we approach MCAS as a dynamic, multisystem condition that requires an individualized and layered treatment plan. Our philosophy focuses on reducing overall mast cell activation through targeted symptom management, lifestyle modification, and systemic support. Treatment begins with patient education and the introduction of low-risk pharmacologic interventions.

We recognize that MCAS rarely exists in isolation. Many patients also face overlapping diagnoses like POTS, hypermobility, or post-infectious syndromes. Our team works to restore autonomic, GI, and neuroimmune balance, always advancing treatment in a stepwise, symptom-informed way. This empowers patients to regain control through precision, pacing, and collaborative care.

Ongoing Research & Future Directions

As articulated in the Autonomic Research section, those with MCAS as additionally responding well to supplemental oxygen. We generally recommend starting with 2–5 liters per minute of oxygen flow, used in short bouts totaling about one hour per day, such as three 20-minute sessions, adjusting timing based on how your body responds. This moderate, intermittent use is safe, well-tolerated, and provides a meaningful oxygen boost—far below the levels associated with oxygen toxicity—making it both effective and comfortable for most users without the need for high-flow systems.

On the following page, please see a table for a comprehensive list of signs of mast cell activation.

Recommended management:

- Avoid known or suspected anaphylaxis triggers
- Histamine receptor-1 and histamine receptor-2 blockers
- Mast cell stabilizing agents
- Consider corticosteroids for severe or persistent cases
- Detailed recommendations for different subtypes of MCAS here
- Address and treat underlying infections that active and prime mast cells

MEDICAL EDUCATION VIDEO: Downstream Drivers of Post-Acute Infection Syndromes/MCAS



Signs of Mast Cell Activation	
Neuropsychiatric	Headache disorder Mood disorder (anxiety or depression) Pain syndrome Tingling, paresthesia, weakness Difficulty concentrating, memory, or balance
Eyes, ears, nose, sinus, throat	Watery running nose or sneezing fits Nasal obstruction Itchy nose Feeling unable to breathe through nose Fullness/pain in ears Watery, itchy eyes
Lungs	Trouble breathing Shortness of breath Coughing episodes Wheezing episodes Inhaler use
GI screen	Abdominal pain or discomfort Frequent bowel movements or episodes of constipation Bloating or abdominal distress after eating Needing to rush to the bathroom because of a sudden urgent bowel movement
Urogenital tract	Pain in bladder or pelvis including vagina, lower abdomen, urethra or perineum Pain or urge to urinate Need to get out of bed frequently to urinate
Urogenital problems in girls/women	Dyspareunia (pain during or after intercourse) Recurrent bouts of vaginitis Heavy/spontaneous vaginal bleedings
Skin	Urticaria (hives) Angioedema (swelling of tongue) Pruritus (Persistent itch without rash) Flushing (redness, heat sensation of the skin)
Cardiovascular	Heart palpitations or extra heartbeats Episodes of low BP Episodes of lightheadedness or near fainting
Musculo-skeletal system and joints	Frequent Joint pain or swelling Frequent muscle cramps Muscle weakness
Anaphylaxis	Patient has been treated for anaphylaxis Patient has been prescribed an EpiPen or auto-injector



The Prevention of IACIs & When Reinfection Occurs

Reduce Risk of Infection

COVID-19

The COVID-19 pandemic presents not only unprecedented challenges, but also opportunities to refine our approach to prevention, treatment, and IACI patient support. At the CoRE, we've adopted air quality improvements, and proactive testing to prevent respiratory infections/reinfections in individuals affected by Long COVID and related IACIs. Our staff additionally wear N95 masks to decrease the spread of respiratory pathogens.

Tick & Vector-Borne Illness

To avoid tick bites, wear protective clothing like long sleeves and pants tucked into socks, use insect repellent, and avoid areas with high grass and leaf litter if possible. See further guidance here. A helpful poster on Lyme disease basics can be downloaded here. Overall:

- It's a common misconception that you'll always feel a tick bite when it happens. Many tick bites are painless.
- Not everyone who develops Lyme disease will get a bull's eye rash.
- There is a misconception that ticks are only found in rural areas, when in fact, ticks are found in rural and suburban areas as well, especially where there's grass and weeds.
- If a patient suspects they're bitten by a tick, they should be treated immediately. Prophylactic treatment after a tick bite may reduce the risk of developing Lyme disease and persistent symptoms thereafter.

Reducing Severity of Infection

Vaccination

It has been shown that vaccination may prevent severe acute COVID-19, which in some cases, can lower Long COVID risk. However, it is noted that in some cases, vaccination makes Long COVID or other IACI patients feel worse.

Reinfection Happens

Understanding the Emotional Burden of Reinfection

First and foremost, *it is important to honor that reinfection can be frightening for some IACI patients.* Being reinfected often leads to anxiety and uncertainty about their health. It's important to recognize how overwhelming this experience can be and to reassure them that you will be a supportive figure to them in their health journey.

Encouraging patients to reach out to their support networks—whether it's family, friends, or community groups—can be incredibly beneficial.

Be sure to connect them with mental health resources can provide extra support as they navigate these tough feelings, helping them

The best way to prevent IACIs is to prevent the infection. A broad approach that emphasizes multiple preventative strategies including vaccination, masking (using an N95 or equivalent) and improving air filtration and ventilation is needed. People living in areas with lots of ticks or mosquitoes should wear longer clothes when outdoors and check for ticks or bites afterward.



build resilience and cope better during this challenging time.

LEARN MORE: Our center was thoughtfully designed to reduce patient triggers, and combat reinfection.

Chapter 5 | Allied Health Approaches to IACI Care

Psychology Services

As healthcare practitioners, it's essential to recognize the profound impact that a complex chronic illness can have on a patient's life. Beyond medical treatment,

Prophylactic medications:

- Studies have linked reinfection with an increased probability of developing Long COVID. There is evidence that use of Paxlovid or metformin during acute COVID-19 can reduce the risk of a person developing Long COVID. However, patients may experience GI side-effects when taking metformin. The dosages for metformin are outlined in this study. You may want to consider ramping up the dose carefully to account for medication sensitivity.
- Availability and appropriateness of SARS-CoV-2 prophylaxis medications continue to change as the virus mutates and the regulatory landscape attempts to keep pace with new medications. Physicians should stay informed about the availability of different prophylactic medications such as Pemgarda, which at the time of writing this, has an EUA from the FDA to be used for SARS-CoV-2 infection prophylaxis in immunocompromised patients.
- The SARS-CoV-2 virus can enter the body through the nasal pathway, infecting respiratory pathways. Thus, applying prophylactics to these areas should be considered. It has been found that applying Neosporin to the nasal passageway triggers a swift immune response by interferon-stimulated genes in the nose. Antihistamine nasal sprays have been shown to reduce both rate and severity of COVID-19 infection, and an efficacious, safe, and well-tolerated treatment of mild COVID-19 infection.

Be prepared to help patients:

- Cope with chronic symptoms and changes in self-identity
- Learn strategies to manage anxiety, depression, or cognitive dysfunction
- Develop strategies to reduce isolation or loneliness without putting themselves at risk



patients often need robust social support to help them adjust to their new reality, which is where the CoRE neuropsychology program is a useful tool for our providers. Of note, however, we must acknowledge that many patients with IACIs may also experience intense neuropsychiatric symptoms as a result of physiological processes such as neuroinflammation, MCAS, autoimmunity, sleep dysregulation and other direct and modifiable drivers of altered brain health. It is important that skilled psychological providers can identify when emotional dysregulation and neuropsychiatric symptoms may be led by highly treatable drivers rather than issues related adjustment to a new disability status and make the appropriate referrals and recommendations to the lead clinical provider.

On an emotional level, a diagnosis with an IACI can be very overwhelming. *With no FDA-approved cures for any IACIs currently available*, treatment primarily focuses on symptom management and helps most patients to achieve a manageable and stable disease state. This reality can be daunting, as patients must navigate significant physical health symptoms, but also the emotional toll and subsequent mental health challenges of redefining their identity considering their chronic condition. Healthcare practitioners must recognize that patients often must manage feelings of loss and uncertainty and ensure that they are appropriately supported.

The CoRE team refers patients to psychologists and neuropsychologists that are experienced in validating and treating patients with complex chronic illness, but also who are skilled in advising patients on the topic of cognitive remediation therapy. Although cognitive remediation therapy may not improve cognitive impairment caused by IACI, it can provide people with IACIs with actionable strategies to successfully manage and navigate daily life with reduced disability because of their cognitive impairment.

You may be able to find the appropriate therapist on the COVID Conscious Therapists' Directory. Check that the mental health provider is licensed in the state.

MEDICAL EDUCATION VIDEO: CoRE Psychologist Eric Watson Discusses Brain Health After Long COVID



Social Work

The adjustment process to becoming newly disabled can lead to adjustment disorders, social isolation and loneliness, making the establishment of social support programs essential for comprehensive care. Furthermore, it is now well-established that social health is a crucial dimension of overall health that can profoundly affect physical and mental health and newfound chronic illness can be highly isolating.

To this end, CoRE patients are also given the opportunity to join peer support groups facilitated by a social worker. These groups offer a 12-month, curricular program, designed to help IACI patients adjust to new or worsening disabilities, helping patients come to terms with their diagnosis and the changes it brings to their lives. All sessions are co-signed by a psychologist or neuropsychologist and covered by most insurances, including Medicare and Medicaid. However, it is also a goal of our peer support programs to facilitate improved social health. Participants connect with others who have similar diagnoses, fostering social connections with the intention of reducing feelings of loneliness and social isolation that may be brought about by their diagnosis.

Practical assistance is equally important, so our social workers are trained to identify those in need of one-on-one case work during the group sessions. This case work will ensure providing resources to help patients navigate daily life with chronic conditions such as accessing disability benefits or workplace accommodations—can make a significant difference. Skilled social workers can often be the difference between a patient receiving or being declined disability benefits to which they are entitled, so we view this as a crucial element of our program.



In future versions of this handbook, our IACI social health program curriculum will be made available.



Physical Therapy & Autonomic Rehabilitation

All movement counts, including small range assisted exercises or breathwork in bed. Progress is progress.

Autonomic dysfunction is a common, debilitating feature of IACIs, including Long COVID, POTS, ME/CFS, and tick-borne disease. Symptoms like dizziness, palpitations, blood pooling, and exercise intolerance reflect impaired regulation of vascular tone and cardiac output—not simple deconditioning. Traditional exercise protocols often fail these patients, and in some cases, worsen symptoms through PEM.

Our approach to autonomic rehabilitation emphasizes symptom-guided pacing, upright tolerance retraining, and gradual cardiovascular reconditioning. Patients begin at their current level of positional tolerance (often supine) and progress through phases that reintroduce upright positions, aerobic movement, and neuromuscular control—always below the patient's crash threshold.

Moving Beyond Graded Exercise Therapy (GET)

Rigid GET programs can cause harm in patients with PEM or dysautonomia. Instead, we promote pacing and recovery-based progression using symptom-guided thresholds (modified Borg RPE scale, VAS symptom tracking), positionally modified exercises (e.g., supine to upright transition), adaptive breathwork to regulate arousal and stabilize autonomic tone and therapist comfortability with small, even active assisted movements when needed and progressing based on symptom tolerance.

Foundation Protocols & Adaptations

Our team draws from established protocols (Dallas, CHOP-Modified Dallas, Levine) and adapts them for infection-associated presentations. Early rehab often includes recumbent cardio (e.g., spin bike with reclining chair in supine and progressing through semi-reclined positions, recumbent and then upright bike and standing on pedals), compression and fluid loading, low-load neuromuscular control in gravity-minimized positions and vagal-supportive breathwork.

Breathwork as a Cornerstone

Breathing techniques improve parasympathetic tone, reduce orthostatic symptoms, and support safe movement. Patients are trained in diaphragmatic, pursed-lip, box, and VNS-based breathwork as part of every phase. These tools not only stabilize physiology but also provide real-time feedback on readiness to engage in activity.

Supporting Success

Autonomic rehabilitation is most effective when integrated with gentle neuromuscular training for core and scapular stabilization, energy conservation and pacing education, structured breathwork for readiness and recovery (see more information in appendix), careful symptom tracking (e.g., RPE/VAS scales) and flexible program design and language that honors each patient's path.

Progress isn't linear. Patients may fluctuate between phases depending on fatigue, flare, or other factors. Providers are encouraged to meet patients where they are and avoid pushing through PEM.



Patients with connective tissue disorders (e.g., hEDS/HSD) require additional stabilization strategies to protect joints and manage subluxation risk throughout positional rehab.

We encourage providers to reference the Pacing and Hypermobile Rehabilitation sections for additional considerations when treating these patients.



Nutritional Guidance

Nutrition plays a critical role in managing complex chronic illnesses such as POTS, MCAS, post-infectious syndromes, and connective tissue disorders. At the CoRE, dietitians help patients maintain nutritional adequacy, avoid over-restriction, and make informed decisions about supplements and food-based interventions.

Many patients take overlapping supplements—such as multivitamins, green powders, or amino acids—without realizing they may exceed safe intake levels or cause side effects. Our dietitians assess for redundancy, potential interactions, and opportunities to transition to food-first strategies when possible. For example, nutrients like alpha lipoic acid, CoQ10, or arginine can often be obtained from spinach, fatty fish, or pumpkin seeds.

For those who require supplements, we recommend only third party-tested products to ensure quality and safety, while also balancing cost and long-term sustainability. Attention is also given to nutrient timing and bioavailability, such as taking curcumin with fat and piperine to enhance absorption or monitoring tolerance to supplements like arginine or citrulline in patients with GI or metabolic concerns.

Targeted guidance is available for patients with POTS, where small, frequent meals help minimize postprandial blood pooling and reduce orthostatic symptoms. In patients with MCAS, we work to identify food triggers without unnecessary elimination, support histamine management when appropriate, and reduce the risk of malnutrition or disordered eating from chronic restriction.

Ultimately, our nutrition program supports safe, individualized care by blending science-based strategies with patient-specific tolerances. In future versions of this handbook, nutrition trackers and meal-planning tools will be made available to help guide sustainable and symptom-informed eating.



Chapter 6 | At Home IACI Management Strategies

Pacing, Energy, & Assistive Technology in Complex Chronic Illness

Pacing is a cornerstone strategy for managing chronic symptoms in individuals with infection-associated conditions such as Long COVID, POTS, ME/CFS, and tick-borne illnesses as well as CTDs. It is a proactive approach to managing exertion—physical, cognitive, and emotional—by staying within an individual's physiological limits to prevent crashes, symptom flares, and functional decline.

Unlike traditional exercise programs, pacing emphasizes proactive energy management, helping patients stay within their physiological limits to avoid PEM. This approach applies to physical, cognitive, and emotional exertion and is critical in preventing setbacks that can last days or weeks.

PEM, fatigue, and malaise are distinct phenomena that often coexist. Fatigue is a baseline exhaustion not relieved by rest. Malaise is a flu-like sickness that signals systemic overload. PEM is a delayed worsening of symptoms following exertion. Understanding and differentiating these symptoms help clinicians adapt rehabilitation accordingly.

The term “exercise intolerance” is likely overused in this population; in many cases, patients are not truly intolerant of all activity but rather have been exposed to poorly dosed exertion that repeatedly exceeds their threshold for PEM. When movement is introduced in symptom-titrated, incremental doses, even those with significant limitations can often build tolerance over time.

To support patients in honoring their energy envelope, CoRE providers utilize familiar metaphors such as the Energy Envelope and Battery Theory and the Spoon Theory to guide communication and expectations. All these analogies stand to reason that there is a finite amount of energy that these patients have each day. These models allow for collaborative planning, realistic goal setting, and validation of the patient experience—particularly for those whose symptoms fluctuate or worsen with minimal activity.

Assistive technology plays a vital role in making pacing achievable and sustainable. Rather than being a sign of failure, mobility aids and sensory tools support independence and reduce the physiological burden. Items such as forearm crutches, rollators, or wheelchairs can help patients conserve energy and remain engaged in their communities. Sensory supports like noise-canceling headphones and blue light glasses may reduce symptom flares in overstimulating environments. Ergonomic adaptations such as reclining chairs, footrests, or lap desks support upright tolerance and allow patients to work, study,



PEM and PESE describe similar phenomena involving symptom flares following physical, cognitive, or emotional exertion. For consistency, this manual uses the term PEM, but all guidance provided applies equally to individuals who identify with or use the term PESE.



or rest in positions that do not provoke symptoms. Individual workstations can be created to meet the patients where they are if they are looking to add small doses of their career back into their lives as they recover.

Ultimately, pacing and adaptive tools allow patients to engage in life more safely and consistently, even when energy or upright tolerance is limited. In future versions of this handbook, examples of flare-friendly and accommodating desk spaces and patient pacing plans will be included.

Clinicians are encouraged to frame these tools as empowering, not regressive. For example, a rollator that doubles as a transport chair can allow a patient to walk when able and be pushed when not—preserving energy without compromising safety. Many patients benefit from having multiple workstation setups for use during flares versus periods of stability if able to work.



Chapter 7 | Tick-Borne & Vector-Borne Illnesses

Overview of Tick-Borne & Vector-Borne Illnesses

Tick and mosquito bites can transmit various infectious microbial organisms like bacteria, viruses and protozoans. One in 10 people do not fully recover from tick and vector-borne illnesses, leading to persistent symptoms that overlap with Long COVID and ME/CFS.

Diagnosis can be challenging, particularly in early stages, and may require a combination of clinical, epidemiological, and laboratory approaches. Note that different serological tests have varying levels of positive predictive value, false positives, and false negatives that confound assessment.

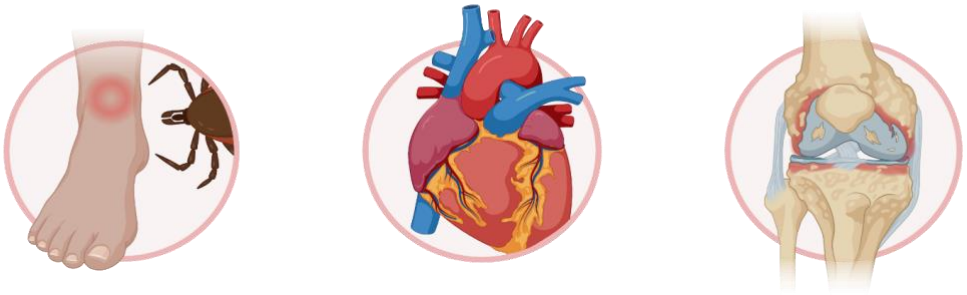
Patients who can link their symptom onset to a tick bite, bug bite or an activity that carries a high-risk of tick or other vector exposure (such as camping) should be strongly considered for a diagnosis of chronic tick- and vector-borne illness. However, people with financial or social

disadvantages may not be able to access *Borrelia* or other testing during acute infection, making it likely that documentation of infection is missing. Similarly, the erythema migrans rash associated with *Borrelia* infection can be difficult to recognize in individuals with darker skin. Thus, any

MEDICAL EDUCATION VIDEO: Diagnosing Post-Acute Infection Syndromes

RESOURCE: Invisible International

Symptoms of Lyme Disease



Early phase	Early dissemination	Late dissemination
(first days - weeks)	*(weeks - months after infection)*	*(weeks - months after infection)*
Symptoms can include fever, headache, fatigue, and a characteristic skin rash called erythema migrans (bullseye).	The bacteria can spread to tissues in the heart brain and/or joints.	If the symptoms remain undetected and untreated, the disease can progress, and often presents as chronic arthritis.



patient with symptoms consistent with tick-borne/vector-borne chronic illness should be considered for diagnostic testing.

Unfortunately, there are no specific ICD-10 codes for chronic tick- and vector-borne illnesses, but coding that is focused on specific infections can be used. For instance, codes such as A69.29 ("Other conditions associated with Lyme disease") or A69.20 ("Lyme Disease: Unspecified") can be used if persistent *Borrelia* infection is suspected, or A44.8 ("Other forms of *Bartonellosis*") can be used if persistent *Bartonella* infection is suspected.

The CoRE uses both blood testing and questionnaires to identify the persistent pathogens that are driving symptoms.

Multiple tick and vector-borne diseases can cause IACIs through multiple mechanisms including immune dysfunction and bacterial, viral, and parasite persistence. Common symptoms include fatigue, pain, and cognitive dysfunction. Clinicians should assess autonomic and cognitive function, in addition to other symptoms.

Since there are many different, understudied tick and vector-borne diseases, it is difficult to estimate the impact on patient quality-of-life.

Depending on the pathogen causing the symptoms, mechanisms may include pathogen persistence, immune dysfunction, microbial imbalance.

Disease	Species	Vector	Symptoms
Chronic Lyme/post-treatment Lyme disease	*Borrelia burgdorferi*	Blacklegged ticks also known as deer ticks	Fatigue, arthritis, joint pain, cognitive dysfunction
Bartonellosis	*Bartonella henselae*	Domestic or fetal cats, fleas, spider bites	Low-grade fever, eye problems, bone pain, anemia, cognitive dysfunction
Babesiosis	*Babesia microti*	*Ixodes* ticks	Similar to mild to moderate viral illnesses, in rare cases, can cause GI symptoms and mood swings
Rickettsial disease	*Rickettsiae*	Ticks, lice, fleas, mice, and other mammals	Fever, headache, muscle pain, fatigue, nausea and vomiting, thrombocytopenia
West Nile fever	West Nile virus	Mosquito	Fatigue, memory loss, depression, other neurological issues such as dysautonomia

Testing for Tick Borne & Vector-Borne Illnesses

The following tests are recommended by CoRE. Tier 1 testing is often ordered alongside a tier 2 *Bartonella* immunoblot.

Tier 1 Testing for Tick-Borne & Vector-Borne Illnesses

Before ordering these tests for your patient, ensure that Quest and MDL are in network for insurance.



- Lyme Western blot
- *Bartonella henselae* antibodies (this test is currently only available for research use in NY State)

The CoRE recommends the following assessments in addition to serology testing:

- Autonomic nervous system tests
- Cognitive function tests
- Resting metabolic rate tests

Testing Offered by Quest Diagnostics

- *Borrelia miyamotoi* antibodies (IgG, IgM), immunoassay
- Rickettsial antibody panel
- *Anaplasma phagocytophilum* and *Ehrlichia chaffeensis* antibody panel
- *Toxoplasma* antibodies
- *Bartonella* antibody panel (almost always negative)
- Lyme Western blot
- Vitamin D
- CMP
- CBC with diff
- *Babesia microti* and *Babesia duncani* antibodies
- *Brucella* antibodies

For Intravenous Immunoglobulin (IVIG) Consideration/Authorization

- Quantitative immunoglobulins
- IgE
- IgG subclasses
- Tryptase and plasma histamine when mast cell activation is suspected.

For Children & Suspected PANS/ PANDAS

PANS and PANDAS:

- *Mycoplasma* antibodies
- *Strep* antibodies (ASO, DNASE B)
- Medical Diagnostic Laboratories
- Lyme C6 peptide ELISA

Tier 2 Testing for Tick-Borne & Vector-Borne Illnesses

Please note that this tier of testing is not covered by insurance.

- Quantitative immunoglobulins
- iGeneX
- 4 immunoblot panel (*Babesia*, *Bartonella*, Tick-borne relapsing fever *Borrelia* and Lyme *Borrelia*) for about $1300
- The County of Sonoma Public Health Laboratory: *Babesia duncani* test (WA1) IFA test for about $72

Advice for ordering tier 1 and tier 2 tests:

- For Quest Diagnostics tests can be ordered by anyone without needing an account setup. For MDL, account set up is required.
- For iGeneX, an address is required by the requisition, even if doctor is only licensed in NY, and if blood is drawn in NY. If patient only has an NY address, blood needs to be drawn outside of NY as a few of the tests are not yet approved by the NY Department of Health.

Assessing & Treating Tick-Borne & Vector-Borne Illnesses

There are no drugs currently approved for treating IACIs caused by chronic tick and vector-borne illness. Some cases can be



prevented by treating promptly after a suspected tick or mosquito bite.

If Bartonella is positive through MDL testing, an additional positive FISH test may confirm an active infection which can be treated with combination doxycycline/rifampin. Early data also shows that a combination of tafenoquine and atovaquone may be effective in the treatment of *Babesia*.

At CoRE, we emphasize treating the specific drivers of IACIs identified through assessments and detailed earlier in this manual. Clinicians may consider medication to help relieve their patients with pain and inflammation and physical therapy to address muscle weakness and joint pain in those without PEM.

For more information on chronic tick-borne/vector-borne illness diagnosis and treatment, consult this CME course from VectorWise.



Appendix A | Billing & Coding at the CoRE

CoRE Assessment Order Sets & CPT Codes

These are some of the CPT codes and order sets that CoRE clinicians will bill to ensure that the comprehensive testing we are conducting to guide personalized treatments are covered by insurance. This is arguably one of the most important sections of the guidebook – ensuring that care is accessible and affordable to our patients! Please note, however, that these CPT Codes and order sets are shared to provide general guidance only: please check with your own billing and coding team to ensure that these codes are permissible and appropriate at your practice according to your location, and the licensing and real estate zoning status of your clinic and practitioners. In future versions of this manual, we will continue to update this section.

Resting Metabolic Rate

CPT Code: 94690
CPT Code: 94680

BrainCheck

When billed with E&M code add a 25 modifier.

CPT Code: 96116
CPT Code: 96121
CPT Code: 96132
CPT Code: 96136
CPT Code: 96137
CPT Code: 96138
CPT Code: 96139

NeuroCatch

CPT Code: 92653
CPT Code: 95813- requires 26 modifier
CPT Code: 92650

CPT Code: 92651

Autonomic Testing

CPT Codes:
95921
95922
95923
95924

Endovascular Assessment

CPT Codes: 93998, 93922, 93923



CPT Code	CPT Codes Description	Global	Incident to?
96116	Neurobehavioral status exam (clinical assessment of thinking, reasoning and judgment, [e.g., acquired knowledge, attention, language, memory, planning and problem solving, and visual spatial abilities]), by physician or other qualified HCP, both face-to-face time with the patient and time interpreting test results and preparing the report; first hour.	Services must be performed by a physician or other qualified HCP.	NO
96121	Neurobehavioral status exam (clinical assessment of thinking, reasoning and judgment, [e.g., acquired knowledge, attention, language, memory, planning and problem solving, and visual spatial abilities]), by physician or other qualified HCP, both face-to-face time with the patient and time interpreting test results and preparing the report; each additional hour (List separately in addition to code for primary procedure).	Services must be performed by a physician or other qualified HCP.	YES
96132	Neuropsychological testing evaluation services by physician or other qualified HCP, including integration of patient data, interpretation of standardized test results and clinical data, clinical decision making, treatment planning and report, and interactive feedback to the patient, family member(s) or caregiver(s), when performed; first hour.	Services must be performed by a physician or other qualified HCP.	
96136	Psychological or neuropsychological test administration and scoring by physician or other qualified HCP, 2 or more tests, any method; first 30 minutes.	Services must be performed by a physician or other qualified HCP.	
96137	Psychological or neuropsychological test administration and scoring by physician or other qualified HCP, 2 or more tests, any method; each additional 30 minutes (List separately in addition to code for primary procedure).	Services must be performed by a physician or other qualified HCP.	
96138	Psychological or neuropsychological test administration and scoring by technician, 2 or more tests, any method; first 30 minutes.	04 - Physician supervision policy does not apply when procedure is furnished by a qualified, independent psychologist or a clinical psychologist; otherwise, must be performed under the general supervision of a physician.	



CPT Code	CPT Codes Description	Global	Incident to?
96139	Psychological or neuropsychological test administration and scoring by technician, 2 or more tests, any method; each additional 30 minutes (List separately in addition to code for primary procedure).	04 - Physician supervision policy does not apply when procedure is furnished by a qualified, independent psychologist or a clinical psychologist; otherwise, must be performed under the general supervision of a physician.	NO
92650	Auditory evoked potential; screening of auditory potential with broadband stimuli, automated analysis.	02-Procedure must be performed under the direct supervision of a physician.	NO
92651	Auditory evoked potentials; for hearing status determination, broadband stimuli, with interpretation and report.	02-Procedure must be performed under the direct supervision of a physician.	Yes
95924	Testing of autonomic nervous system function; combined parasympathetic and sympathetic adrenergic function testing with at least 5 minutes of passive tilt.	--	Yes



Appendix B | Introduction Autonomic Rehabilitation

Autonomic Rehabilitation in Complex Chronic Illness

Autonomic dysfunction is a common and disabling feature of infection-associated conditions including Long COVID, POTS, ME/CFS, and tick-borne illness. Symptoms such as orthostatic intolerance, tachycardia, dizziness, blood pooling, shortness of breath, and exercise intolerance are not simply deconditioning—they reflect impaired autonomic control of vascular tone, cardiac output, and respiratory regulation.

Autonomic rehabilitation aims to restore tolerance to upright posture and improve functional capacity through a gradual, symptom-responsive approach. Effective rehabilitation must account for impaired baroreceptor reflexes, altered vascular responsiveness, and energy production deficits that cannot be pushed through without risk of worsening symptoms—especially PEM.

1. Moving Away from GET

Traditional GET models assume linear progress with progressive loading over time. However, in infection-associated autonomic conditions, this model often fails and may cause harm. Many patients experience nonlinear recovery, delayed symptom exacerbation, and PEM, which are not accounted for in rigid stepwise programs.

Modern autonomic rehab now emphasizes:

- Symptom titration, not timeline thresholds
- Subjective fatigue ratings (e.g., modified Borg Scale), not fixed vital-based progression
- Adaptability based on recovery capacity, not calendar timelines

Rehabilitation must start below symptom threshold, with patient-specific pacing and positional adaptation guiding progression.

2. Foundation Programs: Dallas, CHOP-Modified Dallas, & Levine Protocols

A. The Dallas Protocol

Initially developed for patients with POTS, the Dallas protocol recommends:

- Recumbent or semi-recumbent cardio (e.g., recumbent bike, swimming) to minimize orthostatic stress in early phases.
- Compression garments and fluid/sodium intake to support preload.
- Structured progression toward upright activity over months.

This protocol demonstrated benefits in improving stroke volume and reconditioning autonomic response but can be overly rigid for many infection-associated presentations.



B. CHOP-Modified Dallas

Children's Hospital of Philadelphia adapted the Dallas protocol for pediatric and post-viral populations by:

- Allowing more flexibility in pacing.
- Prioritizing patient-reported symptoms.
- Reducing cardiovascular loading in early phases.
- Incorporating core and diaphragm-focused exercises to support central stability and vagal tone.

This model provides a helpful bridge between structure and flexibility, particularly in patients who experience frequent flares.

C. The Levine Protocol

The Levine protocol was created with a strong focus on cardiovascular reconditioning. It includes:

- A 5-month structured program with aerobic training and resistance exercises.
- Target heart rate zones, increased volume over time, and specific exercise prescriptions.

While this protocol has been beneficial for some with POTS, it assumes a more athletic baseline and may be too aggressive or inflexible for patients with PEM or multi-system involvement.

3. Symptom-Titrated Upright Titration

A more individualized model is now being embraced—upright titration through small, progressive shifts in posture and exertion, driven by symptom tolerance, not vitals alone.

Key Principles

- Begin fully supine (meet their patient in the position that they can tolerate) and only progress when tolerated.
- Gradually move from supine → semi-reclined → recumbent seating → upright seated→ standing → walking → upright aerobic activity.
- Prioritize low-resistance, low-load exercises in early stages.
- Symptom severity and recovery windows dictate when progression is safe.

Symptom Monitoring

- Use Modified Borg Rating of Perceived Exertion (RPE) scale.
- Track post-session PEM, orthostatic symptoms, and cognitive fatigue.
- Watch for delayed crashes, not just in-session tolerability.

This titration process may take several months, depending on baseline severity, comorbidities, and recovery rate.



4. Breathwork as a Cornerstone

Breathwork is an essential and often underutilized foundation in autonomic rehabilitation. It supports autonomic regulation, oxygenation, and interoceptive awareness—especially critical in patients with dysautonomia, CCI, or impaired vagal tone.

Key Benefits

- Enhances parasympathetic activation and vagal tone.
- Improves mechanical efficiency of breathing, reducing accessory muscle overuse.
- Supports cardiac and baroreceptor regulation via improved diaphragmatic motion.
- Reduces symptoms of air hunger, palpitations, and dizziness during reconditioning.

Types of Breathwork to Incorporate

Breathwork is foundational in autonomic rehabilitation for conditions like Long COVID, POTS, ME/CFS, and tick-borne illness. These techniques help shift the autonomic nervous system from sympathetic ("fight or flight") to parasympathetic ("rest and digest") dominance, improve respiratory mechanics, and reduce symptom severity during reconditioning.

Diaphragmatic Breathing

Purpose: Supports vagal tone, improves mechanical efficiency of breathing, and promotes parasympathetic dominance.

Physiological Rationale: Deep, slow breathing activates baroreceptors and the vagus nerve via diaphragm excursion. It reduces reliance on accessory breathing muscles, decreases heart rate, and improves oxygen delivery.

How to Perform

- Begin in a supine position with knees bent or supported under a bolster.
- Place one hand on the chest and one on the belly.
- Inhale slowly through the nose for 4 seconds, expanding the belly.
- Exhale through the mouth for 6–8 seconds, allowing the belly to fall.
- Breathe quietly and smoothly. Avoid breath-holding or forced effort.
- Practice 5–10 minutes daily, particularly before or after rehab activities.

Pursed-Lip Breathing

Purpose: Maintains airway pressure during exertion, improves ventilation, and calms the nervous system.

Physiological Rationale: This technique slows exhalation and prevents airway collapse, reducing the work of breathing and improving gas exchange. It also promotes parasympathetic activity via prolonged exhalation.



How to Perform

- Inhale gently through the nose for 2–4 seconds.
- Purse the lips as if blowing out a candle and exhale slowly for 4–6 seconds.
- The exhale should be longer and more controlled than the inhale.
- Use during upright activity, walking, or transitions to mitigate air hunger and postural symptoms.

Box Breathing (4–4–4–4)

Purpose: Regulates breathing rhythm, reduces anxiety, and supports parasympathetic control.

Physiological Rationale: Rhythmic breathing reduces cortical excitability and modulates the hypothalamic-pituitary-adrenal (HPA) axis. Brief breath holds improve CO_2 tolerance and may increase baroreflex sensitivity.



How to Perform

- Inhale through the nose for 4 seconds.
- Hold the breath for 4 seconds.
- Exhale through the mouth for 4 seconds.
- Hold at the bottom of the breath for 4 seconds.
- Repeat for 1–3 minutes initially, increasing as tolerated.
- Use in seated or reclined positions to promote relaxation and readiness for upright activity.

Stacked or Resisted Breathing

Purpose: Enhances breath capacity, expands rib mobility, and strengthens respiratory musculature.

Physiological Rationale: Stacked breaths gradually stretch the thoracic cage and improve lung inflation. Resisted breathing increases diaphragm engagement and may improve intercostal muscle recruitment. Both techniques enhance thoracic mobility and may support orthostatic tolerance.

How to Perform Stacked Breathing

- Take a small inhale, pause.
- Without exhaling, add another small inhale. Pause again.
- Repeat for 3–4 mini-inhales until comfortably full.
- Exhale slowly and completely.
- Avoid breath-holding if it causes lightheadedness.

Vagus Nerve Stimulation (VNS) Breathwork

Purpose: Calms tachycardia, improves vagal tone, and downregulates autonomic arousal through vibrational stimulation.

Physiological Rationale: Voiced exhalation (e.g., humming, chanting) vibrates the vocal cords and stimulates the auricular and recurrent laryngeal branches of the vagus nerve. These vibrations activate parasympathetic pathways, are thought to improve heart rate variability (HRV), and reduce sympathetic dominance. The combination of extended exhalation, vocal tone, and breath retention supports baroreceptor sensitivity and real-time nervous system regulation.

How to Perform

- Inhale gently through the nose for 4 seconds.
- Hold the breath for 2 seconds.
- Begin exhaling with the sound “Oooooooo” for the first 4 seconds to prime resonance in the chest and throat.
- Transition to “Mmmmmm” for the remainder of the breath (6–8 seconds total), creating nasal and facial vibration.
- Allow the resonance to guide a slow, natural exhale.



- Use during tachycardia episodes, postural stress, or emotional overload.

Breathwork can also serve as a daily readiness assessment tool—patients can track changes in respiratory pattern, rate, or effort to predict their tolerance for upright activity.

5. Other Foundational Elements

Compression and Fluid Loading

Use waist-high compression garments or those that are best suited for the patient and high sodium/fluid intake when appropriate to improve preload and blood pressure regulation.

Neuromuscular Training

Once upright tolerance improves, patients may begin low-load core, hip, and scapular stability exercises in gravity-minimized positions to reduce joint strain while building motor control. Postural control once upright will be key.

Energy Conservation & Pacing

Even during rehab, patients must pace within their energy envelope, integrate frequent rest, and avoid cumulative cognitive or physical overload.

Example Schematics for Autonomic Rehabilitation

Introduction to Phased, Symptom-Titrated Autonomic Rehabilitation

The intention behind the phased, titrated therapy outlined below is to gently prime the body for movement and gradually improve tolerance to activity following periods of reduced function or bedrest. This structured approach is designed for individuals with autonomic dysfunction (e.g., POTS, ME/CFS, Long COVID) who may experience PEM, orthostatic intolerance, or profound fatigue.

Each phase begins with low-level, supine exercises. Not that in the beginning if they need to be partial range and active assisted activities, which is an okay place to start. Examples for Phase 1A include:

- Heel slides
- Straight leg raises
- Supine hip abduction
- Glute bridges

These movements may be substituted with other similarly gentle, recumbent exercises based on individual needs and capabilities. Each exercise is performed in timed intervals (e.g., 30 seconds) rather than repetitions or sets, allowing for complete customization.

Even if a patient performs only half of an assisted heel slide within the first 30-second interval, that is still considered a successful starting point. Exercises may begin fully assisted, progressing



toward independent execution as tolerated. The focus is on quality and symptom stability, not volume.

If a patient is bedbound or severely limited, it is completely appropriate to begin with just one exercise and the associated breathwork technique. Seated breathwork may also be adapted to supine if upright positioning is not yet tolerated.

Progression is based on symptom response, not a predetermined timeline:

- A patient should demonstrate the ability to complete all exercises in Phase 1A in a single session without triggering a crash and do so twice on separate occasions before advancing to Phase 1B.
- This graded exposure framework ensures that each phase builds sustainable tolerance while minimizing the risk of setbacks.

This approach honors the pacing principles necessary in autonomic rehabilitation, meeting the patient where they are, and guiding them forward one breath, one movement, and one phase at a time.



Phase IC: Standing Symptom Titrated Therapy

Exercise	Intensity	Target RPE	Stop Protocol
Standing Marches	4x60 seconds	<4/10	-RPE >3/10 -Symptom Exacerbation >3 points from initial VAS of score -Patient Requests to Stop -Rest Break > 5 minutes between sets or exercises
Standing 4-6 Nasal Breathing Exercise (diaphragmatic breathing)	x2minutes		
Sit to/from Stand	4x30 seconds		
Standing 4-6 Nasal Breathing Exercise (diaphragmatic breathing)	X2 minutes		
10 Meter Walk	X5		
Standing 4-6 Nasal Breathing Exercise (diaphragmatic breathing)	X2 minutes		

Phase IA: Supine Symptom Titrated Therapy

Exercise	Interval Duration	Target RPE	Stop Protocol
Supine Heel Slide	1x30 Seconds	<3/10	-RPE >3/10 -Symptom Exacerbation >3 points from initial VAS of score -Patient Requests to Stop -Rest Break > 5 minutes between sets or exercises
Seated 4-6 Nasal Breathing Exercise (diaphragmatic breathing)	2-3 minutes		
SLR	1x30 seconds		
Seated 4-6 Nasal Breathing Exercise (diaphragmatic breathing)	2-3 minutes		
Supine Hip Abduction AROM	1x30 seconds		
Seated 4-6 Nasal Breathing Exercise (diaphragmatic breathing)	2-3 minutes		
Bridges	1x30seconds		
Seated 4-6 Nasal Breathing Exercise (diaphragmatic breathing)	2-3 minutes		

Phase IB: Seated Symptom Titrated Therapy

Exercise	Interval Duration	Target RPE	Stop Protocol
Seated LAQ	2x30 Seconds	<3/10	-RPE >3/10 -Symptom Exacerbation >3 points from initial VAS of score -Patient Requests to Stop -Rest Break > 5 minutes between sets or exercises
Seated 4-6 Nasal Breathing Exercise (diaphragmatic breathing)			
Seated Hip Adduction Isometric	2x30 seconds		
Seated 4-6 Nasal Breathing Exercise (diaphragmatic breathing)			
Seated Marches	2x30 seconds		
Seated 4-6 Nasal Breathing Exercise (diaphragmatic breathing)			



Spin Bike Upright Titration Protocol: A Symptom-Titrated Cardiovascular Training Framework for Autonomic Rehabilitation

Overview

The Spin Bike Upright Titration Protocol is a structured, positionally progressive exercise program developed to retrain cardiovascular and autonomic regulation in patients with POTS and other forms of dysautonomia. Grounded in the principles of the Levine and CHOP-Modified Dallas protocols, this program integrates symptom-guided pacing, upright tolerance training, and progressive cardiovascular activation using a single spin bike setup with an adjustable reclining chair.

Rather than targeting heart rate zones or performance metrics, this protocol uses the RPE and VAS to titrate exercise intensity based on how the patient feels during activity. This approach accommodates the variable physiology seen in dysautonomia—including blunted heart rate responses, medication effects, and PEM/PESE risks—while promoting safe reconditioning.

Core Objectives

- Improve upright tolerance through progressive positional challenge
- Recondition the cardiovascular system with controlled exertion
- Stimulate vascular smooth muscle to enhance autonomic signaling
- Foster adaptability of the autonomic nervous system through multi-position, multisensory inputs
- Avoid PEM/PESE through close symptom monitoring and patient-centered pacing

Protocol Design & Rationale

The protocol is structured in 11 progressive phases, beginning with fully supine cycling and gradually advancing to seated upright, standing-pedaling, and ultimately functional return-to-sport. Each phase contains subphases (a–f) with incremental time and intensity goals.

Setup: A spin bike is paired with a 5-position adjustable reclining chair to simulate a recumbent-to-upright continuum without the need for multiple equipment types.

- Early phases focus on low-gravity demand positions to safely introduce cardiovascular stress.
- Later phases increase orthostatic load, resistance, cadence, and vestibular challenges.

Progression is based on:

- Completion of subphase duration and intensity (RPE) without significant symptom increase
- Achieving two successive successful sessions before advancing



- Maintaining symptoms below 5/10 on the VAS or avoiding a >3-point increase in VAS within-session

Each phase is intended to work up to tolerance of the specified schematic, not to enter at that level.

Why Not Base This on Heart Rate?

Patients with dysautonomia often have:

- Blunted or erratic heart rate responses
- Use of beta blockers or other heart rate-modulating medications
- Heart rate elevations that are not aligned with perceived exertion or true overload

Instead, we rely on:

- RPE to gauge subjective workload
- VAS to assess symptom provocation and guide pacing

This ensures the protocol remains tolerable, flexible, and adaptive across a wide clinical spectrum.

Managing PEM/PESE

Patients prone to PEM exacerbation must be closely monitored. If symptoms increase:

- Pause the protocol and rest until symptoms resolve.
- Reduce duration, RPE, or percent upright on resumption.
- Reintroduce activity below symptom threshold and increase gradually.

Setbacks are expected and not a sign of failure, they are feedback. Pacing and flexibility are essential to sustainable progress.

Pushing Through: What's Appropriate?

Mild, transient discomfort is expected as conditioning improves. It is safe to continue with:

- Mild fatigue
- Slight muscle soreness
- Minimal dizziness that resolves quickly

Do not push through:

- Severe fatigue
- Prolonged post-exertional crashes
- Neurologic, cardiac, or vestibular symptoms that intensify during or after sessions



Tools for Monitoring and Progression

RPE:

- 0 = rest
- 1–2 = light
- 3–5 = moderate
- 6–7 = heavy
- 8–10 = extremely taxing

VAS: Used to track symptom burden (dizziness, fatigue, palpitations, etc.). Target = ≤5, or no more than 3-point increase during sessions.

Positionally-Titrated Phases

Phases progress from supine (0% upright) to fully upright, then include standing and VOR (Vestibulo-Ocular Reflex) challenges. Detailed subphase instructions (1a–11f) provide clear time and RPE goals.

Key Highlights by Phase:

- **Phase 1–6:** Recumbent cycling with incremental upright angles (0%–100%)
- **Phase 7–8:** Upright spin bike with seated endurance and "bike-ups"
- **Phase 9–10:** Alternating seated and standing pedaling, introduction of VOR exercises
- **Phase 11:** Return to independent cycling or phased sport reintegration

Rehabilitation Integration

This protocol addresses the cardiovascular-autonomic axis. Patients with connective tissue disorders, such as hEDS, should integrate stabilization training in the same positional tier as their current cycling phase. This ensures neuromuscular demands remain consistent with autonomic load and minimizes flare risk.

Encourage patients to:

- Maintain alignment and joint protection
- Coordinate with a hypermobility-informed physical therapist
- Monitor for subluxation-related triggers

Clinical Notes for Implementation

- **Frequency:** 3–4x/week, adjusting for PEM risk
- **Individualized starting point:** Based on upright tolerance and orthostatic symptoms
- **Regression is not failure:** It is feedback and part of the recovery cycle
- **Equipment:** Magnetic resistance spin bike + 5-position adjustable reclining chair



Phase 1: Supine on Adjustable Chair

In this phase, you will be 0% upright, lying on your back in the adjustable seat. Place the seat close to the spin bike so that your legs can comfortably pedal in front of you from the chair and ensure its stability before sitting. Lie the chair back flat and strap onto the pedals in front of you.

If not clipping in, it recommended to strap your foot to the pedal tightly, allowing the face of the pedal to follow your foot since the bike is being used in a recumbent position rather than upright. RPE recommendations should be achieved via changing the cadence of your pedaling in this phase.

- **1a**: Work up to 10 minutes in **light RPE** (RPE 1-2).
- **1b**: Alternate 2 minutes of **light RPE** with 1 minute of **moderate RPE** (RPE 3-5), totaling 9 minutes.
- **1c**: Alternate 2 minutes of **moderate RPE** with 1 minute of **light RPE**, totaling 9 minutes.
- **1d**: Work up to 10 minutes in **moderate RPE**.

Phase 2: 20% Upright on Adjustable Chair

If you are utilizing a 5-position-adjustable chair, this phase is to be completed 1 notch more upright than lying flat, or in other words, 20% upright in the recumbent position. Place the seat behind the spin bike and ensure its stability before sitting. Adjust the seat to 20% upright and clip onto the pedals in front of you.

If not clipping in, it recommended to strap your foot to the pedal tightly, allowing the face of the pedal to follow your foot since the bike is being used in a recumbent position rather than upright. RPE recommendations should be achieved via changing the cadence of your pedaling in this phase.

- **2a**: Work up to 10 minutes in **light RPE** (RPE 1-2).
- **2b**: Alternate 2 minutes of **light RPE** with 1 minute of **moderate RPE**, totaling 9 minutes.
- **2c**: Alternate 2 minutes of **moderate RPE** with 1 minute of **light RPE**, totaling 9 minutes.
- **2d**: Work up to 10 minutes in **moderate RPE**.

Phase 3: 40% Upright on Adjustable Chair

If you are utilizing a 5-position-adjustable chair, this phase is to be completed 2 notches more upright than lying flat, or in other words, 40% upright in the recumbent position. Place the seat behind the spin bike and ensure its stability before sitting. Adjust the seat to 40% upright and clip onto the pedals in front of you.

If not clipping in, it recommended to strap your foot to the pedal tightly, allowing the face of the pedal to follow your foot since the bike is being used in a recumbent position rather than upright. RPE recommendations should be achieved via changing the cadence of your pedaling in this phase.

- **3a**: Work up to 10 minutes in **light RPE** (RPE 1-2).
- **3b**: Alternate 2 minutes of **light RPE** with 1 minute of **moderate RPE**, totaling 9 minutes.
- **3c**: Alternate 2 minutes of **moderate RPE** with 1 minute of **light RPE**, totaling 9 minutes.



- **3d**: Work up to 10 minutes in **moderate RPE**.

Phase 4: 60% Upright on Adjustable Chair

If you are utilizing a 5-position-adjustable chair, this phase is to be completed 3 notches more upright than lying flat, or in other words, 60% upright in the recumbent position. Place the seat behind the spin bike and ensure its stability before sitting. Adjust the seat to 60% upright and clip onto the pedals in front of you.

If not clipping in, it recommended to strap your foot to the pedal tightly, allowing the face of the pedal to follow your foot since the bike is being used in a recumbent position rather than upright. RPE recommendations should be achieved via changing the cadence of your pedaling in this phase.

- **4a**: Work up to 15 minutes in **light RPE** (RPE 1-2).
- **4b**: Alternate 2 minutes of **light RPE** with 1 minute of **moderate RPE**, totaling 15 minutes.
- **4c**: Alternate 2 minutes of **moderate RPE** with 1 minute of **light RPE**, totaling 15 minutes.
- **4d**: Work up to 15 minutes in **moderate RPE**.

Phase 5: 80% Upright on Adjustable Chair

If you are utilizing a 5-position-adjustable chair, this phase is to be completed 4 notches more upright than lying flat (1 notch away from full upright), or in other words, 80% upright in the recumbent position. Place the seat behind the spin bike and ensure its stability before sitting. Adjust the seat to 80% upright and clip onto the pedals in front of you.

If not clipping in, it recommended to strap your foot to the pedal tightly, allowing the face of the pedal to follow your foot since the bike is being used in a recumbent position rather than upright. RPE recommendations should be achieved via changing the cadence of your pedaling in this phase.

- **5a**: Work up to 15 minutes in **light RPE** (RPE 1-2).
- **5b**: Alternate 2 minutes of **light RPE** with 1 minute of **moderate RPE**, totaling 15 minutes.
- **5c**: Alternate 2 minutes of **moderate RPE** with 1 minute of **light RPE**, totaling 15 minutes.
- **5d**: Work up to 15 minutes in **moderate RPE**.

Phase 6: 100% Upright on Adjustable Chair

If you are utilizing a 5-position-adjustable chair, this phase is to be completed 100% upright in the recumbent position, the final notch that has the seat sitting all the way up. Place the seat behind the spin bike and ensure its stability before sitting. Adjust the seat to 100% upright and clip onto the pedals in front of you.

If not clipping in, it recommended to strap your foot to the pedal tightly, allowing the face of the pedal to follow your foot since the bike is being used in a recumbent position rather than upright. RPE recommendations should be achieved via changing the cadence of your pedaling in this phase.

- **6a**: Work up to 15 minutes in **light RPE** (RPE 1-2).



- **6b**: Alternate 2 minutes of **light RPE** with 1 minute of **moderate RPE**, totaling 15 minutes.
- **6c**: Alternate 2 minutes of **moderate RPE** with 1 minute of **light RPE**, totaling 15 minutes.
- **6d**: Work up to 15 minutes in **moderate RPE**.

Phase 7: Seated on Upright Bike

This phase is to be completed in the 100% upright position on an upright bike, (legs beneath the rider makes this more of an upright challenge than the upright recumbent position). Remove the seat from behind the spin bike from previous phases.

In this position, the RPE can be manipulated via changing cadence (speed of pedaling) or resistance or a balance of both. This decision is up to the rider in order to meet the recommended rate of perceived exertion.

- **7a**: Gradually increase time until 10 minutes of **light RPE** (RPE 1-2) is achieved.
- **7b**: Alternate 2 minutes of **light RPE** with 1 minute of **moderate RPE** (RPE 3-5), totaling 9 minutes (achieved by increased speed or resistance).
- **7c**: Alternate 2 minutes of **moderate RPE** with 1 minute of **light RPE**, totaling 9 minutes.
- **7d**: Work up to 2 minutes **light RPE** to warm up, 7 minutes **moderate RPE**, and 1 minute **light RPE** to cool down.
- **7e**: Work up to 3 minutes **light RPE** warm-up, 10 minutes **moderate RPE**, and 2 minutes **light RPE** cool-down.
- **7f**: Alternate 2 minutes of **moderate RPE** with 1 minute of **hard RPE** (RPE 6-7), with a warm-up and cool-down. Work up to a total of 11 minutes.

Phase 8: Seated on Upright Bike with "Bike Ups"

This phase is to be completed in the 100% upright position on an upright bike, (legs beneath the rider makes this more of an upright challenge than the upright recumbent position). The positional changes challenge the positional accommodations while upright.

In this position, the RPE can be manipulated via changing cadence (speed of pedaling) or resistance or a balance of both. This decision is up to the rider in order to meet the recommended rate of perceived exertion.

- **8a**: Work up to 10 minutes in **light RPE** (RPE 1-2), completing 5 "bike ups" per minute. (Bike ups = pushing up from handlebars to a more upright position and back down, similar to a push up, on the bike.)
- **8b**: Alternate 2 minutes of **light RPE** with 1 minute of **moderate RPE** (RPE 3-5), completing 5 bike-ups per minute. Progress to 10 bike-ups per minute.
- **8c**: Alternate 2 minutes of **moderate RPE** with 1 minute of **light RPE**, completing 5 bike-ups per minute. Progress to 10 bike-ups per minute.
- **8d**: Work up to 2 minutes of **light RPE** warm-up, 7 minutes of **moderate RPE**, and 1 minute **light RPE** cool-down. Complete 5 bike-ups per minute, progressing to 10 bike-ups.
- **8e**: Work up to 3 minutes **light RPE** warm-up, 10 minutes **moderate RPE**, and 2 minutes **light RPE** cool-down. Complete 10 bike-ups per minute, progressing to 20 bike-ups per minute.



- **8f**: Alternate 2 minutes of **moderate RPE** with 1 minute of **hard RPE** (RPE 6-7), totaling 11 minutes. Complete 5 bike-ups per minute, progressing to 20 bike-ups.

Phase 9: Seated & Standing on Upright Bike

This phase is to be completed in the 100% upright position on an upright bike, (legs beneath the rider makes this more of an upright challenge than the upright recumbent position). The positional changes challenge the positional accommodations to stand functionally.

In this position, the RPE can be manipulated via changing cadence (speed of pedaling) or resistance or a balance of both. This decision is up to the rider in order to meet the recommended rate of perceived exertion.

- **9a**: Alternate 2 minutes of **light RPE** with 1 minute of **moderate RPE** and 30 seconds of standing-pedaling. Progress to 1 minute standing-pedaling, totaling 12 minutes.
- **9b**: Alternate 2 minutes of **moderate RPE** with 1 minute of **light RPE** and 1 minute of standing-pedaling. Total 12 minutes.
- **9c**: Work up to performing the previous step twice within one session, totaling 24 minutes, with a break in between.
- **9d**: String together as much of the 24-minute interval without breaks as possible.
- **9e**: Increase to 2 minutes of standing-pedaling, 1 minute of **light RPE**, and 1 minute of **moderate RPE**, totaling 24 minutes.
- **9f**: Progress to an irregular pattern of standing, light, and moderate RPE to remove predictability.
- **9g**: Introduce **heavy RPE** (RPE 6-7) in seated upright. Alternate 1 minute of **light RPE**, 1 minute of **moderate RPE**, 1 minute of **heavy RPE**, 1 minute of **moderate RPE**, and 1 minute of standing-pedaling. String this pattern together for a total of 5 rounds.

Phase 10: Seated & Standing with VOR

This phase is to be completed in the 100% upright position on an upright bike, (legs beneath the rider makes this more of an upright challenge than the upright recumbent position). The positional changes challenge the positional accommodations to stand functionally and tolerate changing head position.

In this position, the RPE can be manipulated via changing cadence (speed of pedaling) or resistance or a balance of both. This decision is up to the rider in order to meet the recommended rate of perceived exertion.

- **10a**: Repeat Phase 9 but introduce **VOR (Vestibulo-Ocular Reflex) exercises** in every **light RPE** phase. VOR exercise: Focus on an object across the room. Keep your eyes on the target while moving the head side to side and up and down if neck allows. (In case of cervical instability or fusion, it is ok to skip this phase or complete in a limited range)
- **10b**: Progress to including VOR exercises in both **light** and **moderate RPE** phases.

Phase 11: Independent Cycling Class or Return to Sport

Begin by incorporating independent cycling classes into your weekly routine for maintenance. Choose classes that are tailored to your current fitness and symptom tolerance levels. Start with



shorter sessions and gradually increase duration as tolerated. Continue as a form of continue therapy to manage your upright tolerance associated with dysautonomia.

For those returning to sport- it is advised to break down complex multi-part maneuvers into smaller pieces and build the composite movements back up.

Example: Dancers- break down turns and twists, focusing on pieces of the full move that are heavy in head turns, visually spotting and high to low/ low to high transitions, String more and more of the activity together in pieces.

Closing Summary: Principles of Safe & Supportive Autonomic Conditioning

Autonomic rehabilitation is not about intensity, it's about intentionality. The cornerstone of this process is slow, symptom-titrated exposure to upright posture, guided by body awareness, breath regulation, and progressive tolerance, not by performance metrics or fixed timelines.

Breathwork as a Foundation

Breathwork is not just a warm-up, it is the *first exercise*. Diaphragmatic and vagus nerve-stimulating breath techniques play a crucial role in priming the autonomic nervous system, improving parasympathetic tone, reducing baseline arousal, and stabilizing the system before, during, and after upright activity. Patients should be encouraged to lean on these practices not only as a warm-up or cooldown, but as a daily regulation tool.

Titrating Toward Upright

True upright tolerance isn't binary. Between lying down and sitting upright lies a spectrum of semi-reclined positions—many of which require creative accommodation:

- Pillows, wedges, adjustable chairs, and bed risers can help patients find and build tolerance in intermediate angles.



- The transition from a recumbent position (back supported, legs forward) to a truly upright seated position (legs beneath the torso) is a major jump. The latter introduces gravitational



blood pooling, making it significantly more demanding for the autonomic system—even if the back is supported.

Recognizing and respecting the nuance of position is vital. The difference between 60% reclined and upright may be the difference between tolerability and crash. Providers must tailor progressions to the individual—not the protocol.

PEM

Infection-associated dysautonomia often includes PEM or post-exertional symptom exacerbation. Patients may feel well during or immediately after activity, only to experience a crash hours or days later—manifesting as overwhelming fatigue, pain, dizziness, or cognitive fog. This delayed feedback loop makes pacing and post-activity monitoring essential.

PEM is not a setback—it is a physiological signal. When it occurs, the protocol should be adjusted by:

- Reducing duration, intensity, or upright angle
- Increasing rest time
- Reintroducing activity only once the body has stabilized

Any Movement is Progress

For some patients, what appears to be “exercise” may feel inaccessible or even intimidating. For those who are bedbound or severely deconditioned, a breath, a stretch, or a single assisted heel slide *is* progress. Language providers use matters. Avoid terms like “just walking” or “simple exercise.” Instead, validate that all movement counts and emphasize that healing is nonlinear.

At the CoRE, we are currently conducting research on ischemic preconditioning (IPC) using blood flow restriction (BFR) as a potential bridge for patients who are bedbound or unable to tolerate traditional upright rehabilitation. By applying brief, low-pressure occlusion to the limbs while fully at rest, IPC may simulate the cardiovascular and metabolic effects of exercise and positional changes—stimulating vascular responsiveness, promoting nitric oxide release, and enhancing autonomic conditioning *without movement*. This approach offers a promising tool to gently prime the system before transitioning into positional or active therapies. More information to come on this as it becomes available.

Above all, meet patients where they are.

Empower them with tools, support them with flexible structure, and honor the complexity of their condition. Autonomic rehabilitation is not about pushing through—it's about building capacity one supported position at a time.



Appendix C | Pacing, Energy, & Assistive Technology in Complex Chronic Illness

Pacing, Energy, & Assistive Technology in Complex Chronic Illness

Pacing is a cornerstone strategy for managing chronic symptoms in individuals with infection-associated conditions such as Long COVID, POTS, ME/CFS, and tick-borne illnesses as well as connective tissue disorders. It is a proactive approach to managing exertion—physical, cognitive, and emotional—by staying within an individual's physiological limits to prevent crashes, symptom flares, and functional decline.

Unlike traditional models of graded activity or endurance training, pacing is symptom-contingent, not performance-driven. It emphasizes consistency, strategic rest, and self-awareness to minimize the risk of PEM while maximizing function within one's energy envelope.

PEM and PESE describe similar phenomena involving symptom flares following physical, cognitive, or emotional exertion. For consistency, this handbook uses the term PEM, but all guidance provided applies equally to individuals who identify with or use the term PESE.

Fatigue

Fatigue in this population is not the same as ordinary tiredness. It is a whole-body exhaustion, often physical, cognitive, and emotional—that persists even after sleep or rest. Fatigue may limit engagement in everyday tasks and accumulate over the course of the day, especially in response to environmental stimuli or internal stressors.

Key characteristics:

- Can be present at baseline.
- Exacerbated but not necessarily caused by exertion.
- Often only partially relieved by rest.
- Described as heaviness, slowness, or lack of energy.

Malaise

Malaise is a generalized feeling of illness, discomfort, or bodily unease that can accompany infection-associated chronic illnesses. It is more than tiredness—it often feels like a flu-like state with deep, aching fatigue, temperature dysregulation, and a sense of being unwell, even in the absence of fever or lab abnormalities.

Key characteristics:

- Often described as feeling "poisoned," "toxic," or like "a sickness coming on."



- It can occur at rest or be triggered by exertion, emotional stress, or environmental exposures.
- May be accompanied by low-grade fever sensations, chills, nausea, or pain.
- Signals systemic stress and should prompt rest and down-regulation, not escalation.

PEM

PEM is a defining and disproportionately disabling symptom of post-infectious syndromes or other complex chronic illnesses. It is not synonymous with fatigue. Instead, it is a delayed, profound worsening of symptoms following even minor physical, cognitive, or emotional exertion.

Key characteristics:

- Onset is delayed (often 12–48 hours post-trigger).
- Symptoms are severe, widespread, and often include cognitive shutdown, pain, and orthostatic issues.
- Rest rarely provides immediate recovery.
- Triggers include walking, reading, talking, or emotionally intense events.

Understanding the Differences: Fatigue, Malaise, & PEM

While fatigue, malaise, and PEM are often mentioned in the same breath, they describe fundamentally different symptom experiences, each with unique timing, physiology, and implications for care.

Fatigue refers to a persistent, whole-body exhaustion that builds with activity and rarely resolves with rest. It is present even at baseline and can be physical, cognitive, or emotional. Malaise, on the other hand, is more of a sick, sensational flu-like systemic, sometimes spontaneous feeling of being unwell that may emerge even in the absence of exertion. It often signals internal stress, immune activation, or environmental overload and may include chills, low-grade fever sensations, or a “toxic” feeling that prompts the need for full-body rest.

PEM, however, is distinct in both mechanism and trajectory. It is a delayed crash, occurring hours or even days after minimal exertion—physical, cognitive, or emotional—and is characterized by a worsening of multiple systems, not just fatigue. The hallmark of PEM is that it is out of proportion to the activity that caused it and can take days or weeks to resolve. Rest does not immediately reverse it, and “pushing through” often leads to a deeper, more prolonged crash.

Differentiating these symptoms isn’t just diagnostic directly informs treatment. Fatigue may be gently rehabilitated. Malaise requires system-calming and sensory relief. PEM demands strict pacing and symptom titration. Recognizing the differences helps prevent harm, validate patient experience, and guide truly individualized care.

Cognitive Dysfunction

Cognitive symptoms in post-infectious illness may occur independently or as part of PEM. They are often described as:



A. Brain Fog

- Mental haziness, reduced clarity, trouble focusing.
- Described as “thinking through mud” or “not being mentally present.”

B. Mental Exhaustion

- Worsening symptoms with prolonged cognitive activity.
- Tasks like reading, holding conversations, or planning cause rapid burnout.
- Mental stimulation can cause very legitimate physical and physiological changes.

C. Word-Finding & Memory Issues

- Trouble retrieving words, losing train of thought, forgetting tasks mid-action.

D. Sensory-cognitive Overload

- Difficulty processing multiple stimuli (e.g., sounds, visuals, crowds).
- May cause rapid cognitive shutdown or symptom flare.

Emotional & Sensory Triggers

Heavy emotional conversations, loud environments, or social overstimulation can act as significant cognitive and energetic stressors.

These may worsen:

- Cognitive dysfunction (via overload or dysregulation),
- Fatigue (due to cumulative mental strain),
- PEM (if recovery capacity is surpassed).

Validating these experiences as real and physiologically rooted is crucial for clinical care. There is a bidirectional relationship between these symptoms on mental health and mental health creating worsened states of these symptoms. Please see the mental health section.

Understanding Energy Management: Tools for Patient-centered Fatigue Framing

Fatigue in chronic illness is often invisible, misunderstood, and mischaracterized. These three metaphors help clinicians and patients better communicate and plan around energy limitations in a way that’s both tangible and empowering.

The Energy Envelope

Definition: The Energy Envelope model is a foundational pacing principle for ME/CFS and post-viral illness. It represents the safe range of activity a person can perform without causing symptom escalation, especially PEM.



Key concept:

- Each person has a fluctuating "envelope" based on their available energy that day.
- Exceeding the envelope leads to symptom crashes—often delayed by hours or days.
- Staying within the envelope requires careful self-monitoring, rest periods, and activity adjustments.

Clinical use:

Help patients identify:

- Baseline limits (before symptoms increase),
- Early warning signs of envelope breach (e.g., subtle cognitive slowing, dizziness),
- Strategies to widen the envelope slowly over time through symptom-titrated rehabilitation.

Spoon Theory

Origin: Developed by Christine Miserandino to explain energy limitations in lupus, now widely used across chronic illness communities.

The analogy: Imagine you start the day with a limited number of spoons—say, 12. Bu this amount changes each day. Every activity costs spoons:

- Shower = 2 spoons
- Making breakfast = 1 spoon
- A medical appointment = 3 spoons
- Having a difficult conversation = 2 spoons

When the spoons run out, you're not just tired—you're done. And borrowing spoons from tomorrow leads to crashes.

Why it helps: It gives patients a simple language to communicate boundaries and plan their day without feeling the need to justify their limitations.

Example for clinicians: If a patient says, "I'm out of spoons," it signals they're beyond their energy threshold and require immediate rest or modification of the treatment plan.

The Battery & Unreliable Charger Theory

Analogy:

- A healthy person's body is like a new phone battery; it charges overnight and is good to go in the morning.
- In contrast, a patient with chronic illness has a worn-out battery that doesn't charge fully—and may drain unpredictably, even with minimal use.
- Worse, the charger itself is unreliable, some days it works better, and some days it doesn't work at all.



Clinical takeaway: This metaphor reflects:

- Nonlinear recovery from activity
- Fluctuating baseline capacity
- The need to reframe expectations around rest, productivity, and rehabilitation pacing

When to use: This is particularly effective for discussing activity tolerance with tech-savvy or younger patients who may not relate as much to spoon theory.

Putting It All Together

Each of these models reinforces key truths:

- Energy is finite, unpredictable, and non-renewable on demand in this population.
- Recovery from overexertion is slow and nonlinear.
- Patient-centered care must involve pacing, validation, and flexible rehab frameworks that honor these realities.

Assistive Technology & Accommodations in Complex Chronic Illness

When pacing and positional tolerance are limited, assistive technology can provide a critical bridge to independence, symptom control, and meaningful participation in daily life. Rather than representing regression or dependency, these tools reflect strategic adaptation, allowing patients to function within their physiological limits while reducing symptom burden and energy expenditure.

Sound & Sensory Tools

- Sound machines and white noise apps can help manage tinnitus or reduce overstimulation in environments with unpredictable noise.
- Noise-canceling headphones or earplugs may assist individuals with sound sensitivity, common in those with neuroinflammatory or dysautonomia-related sensory processing changes.
    - Brand examples of this include Loop Earplugs
- Dimming filters, blue light glasses, or visual breaks can help reduce visual overload and support cognitive endurance.

Hearing Aids & Communication Supports

- Hearing aids may benefit individuals with auditory processing difficulties or subtle hearing loss exacerbated by autonomic dysfunction, especially in overstimulating environments.
    - Smart phones often have a feature that can help with this as well, utilizing earbuds and the phone microphone.
- Speech-to-text apps and closed captioning tools are useful when cognitive fatigue impairs verbal communication or word retrieval.





Mobility Aids

The Power of Mobility Aids: Tools for Freedom, Not Failure

Mobility aids do not signify failure or giving up, they represent strategic empowerment. For individuals with autonomic dysfunction, fatigue, joint instability, or post-exertional malaise, upright activity can be a drain on limited energy resources. Rather than being a last resort, mobility tools like canes, crutches, rollators, or wheelchairs allow patients to conserve energy, reduce pain, and participate meaningfully in their own lives.

These devices don't confine a person—they expand their world. A forearm crutch may allow someone to enjoy a museum without collapsing halfway through. A wheelchair may make it possible to attend a family outing, go to school, or navigate a large hospital campus. A scooter may mean the difference between isolation and independence.

Importantly, mobility needs fluctuate. One patient may walk unaided at home but need a rollator in the community. Another may use a wheelchair during flares but ambulate freely during good periods. The freedom to choose the right tool for the right day allows people to live more fully within their limits, without crashing or hiding.

Clinicians and caregivers should frame mobility aids not as signs of regression, but as bridges to function. They protect the body, honor the energy envelope, and allow patients to show up in the world with greater dignity, agency, and safety.

Common supports include:

- Forearm crutches, canes, and rollators to offload joints, improve stability, and reduce energy expenditure.
- Wheelchairs or mobility scooters for patients with profound orthostatic intolerance, PEM, or joint instability.
    - Drive Nitro makes a rollator that can double as a transport chair. This allows the patient to be independently upright as able but gives them a seat or option to be pushed like a wheelchair if orthostatic or energy symptoms flare.

Encourage patients to think of mobility aids as tools that give back movement rather than take it away. With energy limitations and orthostatic symptoms, many individuals may need different tools on different days.

Ergonomic Supports & Workplace Adaptations

Ergonomics in complex chronic illness is not just about comfort, it is a critical part of energy conservation, postural management, and preventing symptom flare-ups like fatigue, pain, orthostatic intolerance, and PEM. By supporting the body in efficient, neutral positions, ergonomic tools enable patients to function in both home and workplace settings, regardless of baseline limitations.



Home & Rest-Based Ergonomics

- Seat cushions, wedge pillows, and lumbar rolls reduce joint strain, support spinal alignment, and help offload pressure points during prolonged sitting.
- Reclining chairs, zero-gravity loungers, and adjustable bed risers support graded upright tolerance, allowing patients to find semi-reclined positions during flares or rehabilitation.
- Footrests, lap desks, and over-bed tables facilitate functional use of a laptop, tablet, or paperwork in reclined or bed-based positions—critical for maintaining work or school engagement during flares.

Workplace & Desk-Based Ergonomics

For patients who are able to return to work in-person or remotely, workstation setup can make or break symptom stability:

- **Adjustable sit-stand desks** allow for gradual upright exposure without forcing prolonged seated or standing time. A chair with dynamic recline options can help those who fatigue easily in standard upright postures.
    - An adjustable height desk, pulled up to something like a wing back chair may aid in head support and comfort.
    - Gamer's chairs are often a very ergonomic and supportive desk chair option.
- Chair adaptations such as coccyx cutout cushions, lumbar support pillows, or ergonomic armrests reduce musculoskeletal strain for patients with joint hypermobility or spinal pain.
    - This is applicable not only for work but bringing cushions when going out to a restaurant as well.
- Monitor risers, keyboard trays, and split keyboards promote neutral neck and wrist alignment, especially important for those with cervical instability, neuropathy, or connective tissue disorders.
    - This is key to good ergonomics.
    - The common forward head and rounded shoulders with a slumped posture is often a result of sinking closer and closer to the computer screen. Raising it to eye level and having the screen closer to your eyes may aid in better bodily positions,
- Anti-fatigue mats and foot pedals can assist with postural shifts and blood pooling management for those with POTS or orthostatic intolerance.
    - This exertion of pedaling can be overdone though, watch for fatigue.
- Lighting control (e.g., adjustable lamps or blue-light filtering glasses) and sound dampening options can reduce sensory overload, which commonly worsens fatigue and brain fog in this population.

Flexible & Flare-friendly Workstations

Many individuals with IACI or hypermobility conditions benefit from multi-location work setups. This might include:

- A formal seated workstation with ergonomic adaptations for focused work



- A reclined setup for use during flares (e.g., working from a zero-gravity chair with a laptop tray)
- The option to lie fully flat and work from a mobile device or voice dictation if symptoms escalate

Encourage patients and employers to build in movement breaks, visual rest, and position changes throughout the day as part of a reasonable accommodation strategy.

Ergonomic supports are not luxuries—they are part of a clinical care strategy. For patients with autonomic dysfunction, fatigue syndromes, CTDs, and neuroinflammatory conditions, posture, pressure, and positioning directly impact vascular stability, pain, focus, and stamina.

Creating flexible environments that meet the body's needs reduces the risk of symptom provocation, facilitates pacing, and improves quality of life. Thoughtful ergonomic planning empowers patients to work, rest, and participate more safely, even when upright tolerance or energy is limited.

Why This Matters

Assistive technologies are not just about comfort—they are essential tools that enable pacing, preserve upright tolerance, reduce triggers, and promote self-efficacy. Choosing the right supports and rotating them as needed can extend functional capacity, prevent symptom escalation, and support long-term rehabilitation.

When recommended early and framed positively, assistive technology can empower patients rather than discourage them—creating space for healing and participation without constant physiological compromise.

Appendix D | Nutritional Guidance in Complex Chronic Illness

Nutritional Guidance in Complex Chronic Illness

Nutrition plays a pivotal role in managing complex chronic illnesses, particularly those involving dysautonomia, MCAS, GI dysfunction, and post-infectious syndromes. Dietitians are essential partners in helping patients maintain adequate nutrition, avoid harmful restriction, and support metabolic and immunologic function.

Supplement Recommendations

Before recommending supplements, clinicians must evaluate nutrient overload, redundancy, and potential interactions. Many patients take multiple supplements—often influenced by healthcare providers, social media, or online sources—without realizing that overlapping products may exceed safe intake levels. Common hidden sources include:



- Multivitamins (may already contain CoQ10, vitamin C, or B-complex vitamins)
- Green powders and meal replacements (often enriched with amino acids or herbal extracts)
- Fortified foods (cereals, protein bars, and beverages)
- Energy drinks (frequently contain excess B vitamins, amino acids, or stimulants)

Patients should have their full supplement list reviewed by a registered dietitian to ensure safety, prevent side effects, and identify unnecessary additions.

Prioritize Whole Foods

Whole food sources provide not only essential nutrients but also bioactive compounds, fiber, and antioxidants that improve absorption and reduce oxidative stress. Examples include:

- **Alpha Lipoic Acid** → Spinach, broccoli, tomatoes
- **CoQ10** → Fatty fish, nuts, seeds
- **Arginine** → Turkey, soybeans, pumpkin seeds
- **Vitamin C** → Citrus fruits, bell peppers, strawberries

Whenever possible, food-first strategies are preferred over high-dose supplements.

Supplement Quality & Cost

If supplementation is necessary, patients should be guided toward third-party-tested products (e.g., USP, NSF, Informed Choice). Over-the-counter supplements often contain fillers, contaminants, or poorly disclosed dosing. Given that high-quality products may be costly and not covered by insurance, clinicians should consider more affordable, nutrient-dense food alternatives or low-cost supplement brands to support long-term adherence.

Monitor for Tolerance

Some supplements, particularly amino acids like arginine or citrulline, can cause gastrointestinal symptoms such as cramping, bloating, or diarrhea. Patients with metabolic conditions (e.g., diabetes, insulin resistance, or dysautonomia) may also respond differently to amino acid-based supplements. Dietitians can guide dosing and monitor tolerance.

Optimizing Absorption

Some nutrients, such as curcumin, have poor bioavailability and require specific timing or delivery methods to be effective. For example:

- Curcumin should be taken with a fat-containing meal and may be paired with piperine (black pepper extract) to enhance absorption.
- It should be used cautiously in patients with gallbladder disease, kidney stones, diarrhea, or pancreatic insufficiency.



Dietitians' Role in Supplement Management

- **Comprehensive evaluations** to eliminate redundancy and avoid harm
- **Food-first strategies** before high-dose supplementation
- **Patient education** to correct misinformation and optimize nutrient delivery

Targeted Nutritional Strategies for Dysautonomia/POTS

Patients with POTS often benefit from specific nutritional strategies to support blood volume, vascular tone, and autonomic regulation. One key recommendation is to consume **small, frequent meals** to reduce postprandial blood pooling. Large meals can divert blood to the GI tract, lowering central blood volume and exacerbating symptoms such as dizziness, fatigue, and tachycardia.

Additional strategies—such as adequate fluid and sodium intake—are covered in more detail in the POTS section of this handbook.

Nutritional Support for MCAS

MCAS nutrition management is highly individualized. Patients often face complex food triggers and a risk of over-restriction. Dietitians trained in MCAS help patients identify tolerances while maintaining nutritional adequacy.

Key Areas of Support:

Identify Food Triggers Without Excess Restriction: Unnecessary elimination can worsen nutrition status and increase food anxiety.

Manage Histamine Load: A low-histamine diet or DAO enzyme may help, but these should only be pursued with guidance.

Ensure Nutrient Adequacy: GI symptoms and restricted diets often lead to nutrient deficiencies, especially without supervision.

Prevent Malnutrition and Disordered Eating: Chronic restriction increases anxiety, MCAS flare risk, and undernourishment.

Individualized Trigger Management

Triggers vary widely but may include:

- Alcohol
- Heat or sun exposure
- Mold
- Additives/dyes in medications
- Exercise or physiological stress (including from malnutrition)



MCAS management should aim to reduce symptoms while preserving quality of life and dietary variety.

Diagnostic Clarity

Histamine intolerance is not an allergy. It occurs when the body can't break down histamine efficiently, leading to symptoms. Diagnosis should be guided by a gastroenterologist or immunologist—not unvalidated IgG or food sensitivity panels, which can cause excessive, unnecessary avoidance.



Appendix E | Introduction to Hypermobility Spectrum Disorders & Hypermobility Testing

Hypermobility and Susceptibility in IACIs

Patients with joint hypermobility – including those with or HSD – appear to be particularly susceptible to prolonged or worsened illness after certain infections. In some cases an infection can trigger or unmask previously asymptomatic hypermobility, leading to a new diagnosis of hEDS/HSD that was not evident before. For example, significantly higher rates of joint hypermobility have been observed in conditions like ME/CFS, POTS, fibromyalgia, and Long COVID compared to the general population. The immune activation from an infection (such as a virus) may damage connective tissue via inflammation – for instance, mast cell activation and hyperinflammation can degrade collagen and other matrix components, inducing hypermobility in people who were not previously hypermobile. In hypermobile patients, we often see more severe dysautonomia after infections, such as new or worsening POTS following a viral illness. This dynamic interplay – infection stressing already lax connective tissue – can result in persistent symptoms and lasting disability if the post-infectious syndrome triggers widespread chronic pain, fatigue, or autonomic instability.

It is important to note that hypermobility in hEDS is genetic and often runs in families, but there may be variability in how it manifests. Some individuals with congenital hypermobility remain relatively asymptomatic for years, possibly due to compensatory genetic or adaptive factors that support their connective tissue. In other words, certain genetic modifiers might allow a hypermobile person to function without major issues until a significant stressor (like an infection, injury, or hormonal change) causes their underlying connective tissue fragility to become apparent. Clinicians should be aware that a patient who develops POTS or chronic fatigue after an infection could have had an underlying hypermobility disorder that made them more vulnerable to an infection-associated chronic illness. Recognizing this susceptibility is key to providing appropriate management and avoiding dismissal of the patient's post-infectious symptoms as "just anxiety." Early identification of joint hypermobility in the context of IACIs can prompt screening for related issues and guide a more tailored rehabilitation plan.

Extracellular Matrix (ECM) Breakdown in hEDS & Post-Infectious Cases

One of the core problems in hEDS/HSD is an instability of the extracellular matrix (ECM) – the network of collagen, elastin, and other proteins that support connective tissues. Recent research has shown that patients with hEDS/HSD have disorganized ECM in their skin fibroblast cells, including abnormal patterns of fibronectin, type I collagen, and tenascin, along with excessive fragmentation of these proteins by matrix metalloproteinases (MMPs). Recent findings show that people with hEDS/HSD have a distinctive fingerprint of collagen I and fibronectin fragments in their bloodstream, generated by overactive MMP enzymes breaking down the matrix. This not only offers a potential biomarker for hypermobility disorders but also provides insight into the disease mechanism: the connective tissue in these patients is prone to degradation.



In hEDS, there seems to be a vicious cycle where a fragile ECM leads to microscopic damage, which in turn triggers the body to produce more MMPs and inflammatory molecules, causing further ECM breakdown. Fragments of collagen and fibronectin can act as danger signals (DAMPs) that drive chronic inflammation. Studies of hEDS patient fibroblasts show upregulation of multiple MMPs (such as MMP-1 and MMP-3) accompanied by downregulation of the natural MMP inhibitor (PI16), tipping the balance toward matrix destruction. This comes with an elevation of pro-inflammatory cytokines and aberrant cell signaling pathways in connective tissue cells. Essentially, a feedback loop develops: an unstable ECM leads to inflammation, which leads to more enzymatic breakdown of the ECM, and so on. In infection-triggered chronic illness, a similar process may occur – the infection's inflammatory response can initiate excess collagen breakdown. The result is connective tissue that doesn't heal properly after the infection, potentially explaining why some patients develop long-lasting joint pain, orthostatic intolerance, and connective tissue-related symptoms following viruses like Epstein-Barr or SARS-CoV-2. Supporting this idea, one study noted that treating hypermobile patients' cells with an MMP inhibitor (doxycycline) helped restore more normal ECM organization. Ongoing research is actively investigating these pathways, which could lead to treatments aimed at stabilizing the ECM in hypermobile patients who suffer infection-associated relapses or flares.

Neurologic Manifestations Associated with Hypermobility

Hypermobility disorders can affect not only joints and skin but also the nervous system, often in complex ways. Connective tissue laxity in ligaments and dura can lead to various neurological complications that healthcare providers should keep in mind, especially in patients whose chronic illness began or worsened after an infection.

Upper Cervical Instabilities (UCIs)

Craniocervical Instability (CCI): This refers to excessive mobility where the skull meets the cervical spine due to loose ligaments. CCI can allow the skull or upper vertebrae to slip and compress the brainstem, causing cervicomedullary syndrome. Symptoms include severe headaches (often worsened by upright posture, sometimes described as a "bobble-head" feeling), neck pain, balance problems, cranial nerve signs (e.g. trouble swallowing, tinnitus), and dysautonomia (such as tachycardia, orthostatic intolerance). Patients may also experience pressure headaches if CCI contributes to reduced cerebrospinal fluid (CSF) flow, leading to intracranial hypertension. CCI is typically diagnosed via dynamic imaging – an MRI of the craniocervical junction with flexion, extension, and rotation views (often done upright) to demonstrate abnormal movement. Some experts use a CT scan with the head turned side-to-side to catch subtle instability. In hypermobile patients, CCI can occur spontaneously (ligament laxity from EDS) or after trauma; notably, it's also seen after Chiari decompression surgery if the ligaments were already weak. Treatment ranges from conservative (neck bracing, physical therapy to strengthen neck muscles) to, in severe cases, surgical fusion of the skull to the upper cervical spine to prevent life-threatening brainstem compression.

Atlantoaxial Instability (AAI): AAI involves instability between the first two cervical vertebrae (C1–C2, the atlas and axis). This can occur along with CCI or in isolation. Because C1–C2 allow head rotation, patients with AAI often report symptoms worsening when turning their head (due to transient compression of arteries or nerves). Symptoms overlap with CCI – headache, neck pain, dizziness, neurological deficits – and can include fainting or near-fainting when looking



sharply to the left or right (as blood flow to the brainstem is compromised). Diagnosis of AAI also relies on rotational imaging (e.g. a rotational CT or MRI) to see if C1 slips excessively on C2. Like CCI, initial management is conservative, but a severe AAI may require C1–C2 fusion surgery in cases that have failed exhaustive conservative care, including but not limited to specialized physical therapy and pain management.

Structural Changes

Chiari I Malformation (CMI): Chiari I is a condition where the cerebellar tonsils extend down into the spinal canal, often leading to crowding at the base of the skull. Chiari can be congenital, but it appears to occur more frequently or at younger ages in those with hypermobility (hEDS). Overlap of Chiari and EDS is well recognized – a hypermobile neck may exacerbate the impact of a borderline Chiari, and some patients have both CCI and Chiari, compounding brainstem compression issues. Symptoms include intense pressure headaches (especially with coughing/straining), neck pain, dizziness, and even neurologic deficits or spinal fluid flow obstruction on MRI. In EDS patients, managing Chiari is nuanced because after a decompression surgery, the persistent ligament laxity can contribute to CCI or even CSF leaks. If a hypermobile patient has Chiari with neurological impairment, neurosurgery may be needed, but the surgeon should also assess craniocervical instability before and after decompression. Chiari and related CSF flow issues can also tie into idiopathic intracranial hypertension (described below).

Tethered Cord Syndrome (TCS)

TCS occurs when the spinal cord is abnormally attached (tethered) within the spine, often by a thickened or shortened filum terminale (the fibrous cord at the bottom of the spinal cord). This results in the cord being stretched, especially with movement, causing neurologic symptoms in the lower body. In hypermobile EDS, there is emerging evidence that the filum terminale can have intrinsic collagen abnormalities that aren't visible on standard MRI. Many hEDS patients with TCS report low back pain, sciatica-like leg pain or weakness, numbness, and bowel/bladder dysfunction (incontinence or urinary retention). Often these symptoms are chronic and unexplained by routine scans ("occult" tethered cord). Dr. Petra Klinge's 2022 study found that even when MRI does not show a classic tethered cord, EDS patients can have a functionally tethered cord due to the abnormally elastic filum – and that surgical release of the filum significantly improved pain and bladder symptoms in many cases. In summary, EDS is a risk factor for tethered cord; providers should consider a neurosurgical evaluation for TCS in a hypermobile patient with compatible symptoms, even if the imaging is inconclusive, as timely surgery can be life changing.

Tarlov Cysts

Tarlov cysts (also called perineural cysts) are fluid-filled sacs that form in the nerve root sheaths, usually in the sacral (lower spine) region. They are actually pockets of CSF that bulge out around the nerves. These cysts are found in the general population often incidentally, but they appear to be more common (and more often symptomatic) in people with connective tissue disorders like EDS. Most Tarlov cysts don't cause symptoms, but if they grow large or press on nearby nerve roots, they can cause low back and pelvic pain, sciatica, and bowel/bladder control problems. A hypermobile patient with unexplained sacral pain or nerve symptoms might benefit from an MRI to check for these cysts. Treatment of symptomatic Tarlov cysts can be challenging – options



include CT-guided drainage and fibrin glue injection, or surgical fenestration, with varying success. Outcomes from case series show symptom improvement in ~80% of patients who undergo interventions on painful Tarlov cysts. Given the overlap in EDS, neurologists and pain specialists should include Tarlov cysts in the differential if an EDS patient has refractory pelvic nerve pain.

Eagle Syndrome

Eagle syndrome is less common, but worth mentioning as it can overlap with hypermobility in the neck. It is caused by an elongated styloid process (a small, pointed bone just below the ear) or a calcified stylohyoid ligament. This can lead to sharp, neuralgic pain in the throat, face, or jaw, especially with head movement, as the elongated bone presses on nerves or blood vessels. Patients might have throat pain when swallowing, ear pain, or even dizziness if vascular structures are compressed. In the context of EDS, there are patient reports that cervical instability can aggravate Eagle syndrome (or be mistaken for it). Diagnosis is by imaging (often a CT scan of the neck) showing a long styloid process. Treatment is typically surgical removal (partial styloidectomy) if the pain is debilitating. Eagle syndrome is another example of how structural anomalies can compound the pain burden in someone with underlying hypermobility.

Pressure Changes

Idiopathic intracranial hypertension (IIH): IIH (also known as pseudotumor cerebri) involves increased intracranial pressure without a brain tumor or other obvious cause. It classically causes daily headaches (often with a pressure quality), visual changes (transient blindness or blurred vision due to optic nerve swelling), pulsatile tinnitus, and sometimes dizziness or nausea. While IIH is most common in young women with obesity, there are reports suggesting an association between hypermobility/EDS and IIH. One theory is that connective tissue laxity could affect venous drainage of the brain or CSF absorption, contributing to pressure buildup. In fact, up to 93% of IIH patients have MRI evidence of venous sinus narrowing, which might be more likely in those with connective tissue differences. Clinicians should be mindful that a hypermobile patient with chronic headaches and papilledema (optic disc swelling) might have IIH requiring neurologic referral. This is vital as the prolonged increased pressure does put the patient at risk of losing their vision. Treatment of IIH can include carbonic anhydrase inhibitors (acetazolamide), repeated lumbar punctures, or shunt surgery in refractory cases – weight loss is also recommended when applicable. It's not fully understood how often EDS and IIH co-occur, but vigilance is warranted.

Cerebrospinal fluid (CSF) leaks: Spontaneous CSF leaks (especially spinal leaks) are another neurologic complication seen more frequently in the hypermobile population. Weak connective tissue in the dura (the tough membrane around the brain and spinal cord) can lead to tears, allowing CSF to leak out. This causes intracranial hypotension with classic orthostatic headaches (headache that is worse sitting/standing and improves very quickly when lying flat), often accompanied by neck pain, nausea, and even cognitive difficulty. hEDS patients are more prone to spontaneous CSF leaks, likely due to the inherent tissue fragility. Chronic headaches in a hypermobile patient that are relieved by lying down should prompt consideration of a CSF leak. These leaks can sometimes be detected via MRI myelogram or CT myelogram showing contrast leaking along the spinal cord. Interestingly, there is a connection between CSF leaks and Chiari/IIH: an over-draining leak can cause the brain to sag (sometimes mimicking a Chiari on MRI), and conversely, high pressure (IIH) can lead to leaks – some EDS patients juggle both high



and low pressure at different times. Treatment for CSF leaks may involve bed rest, hydration, caffeine, and often epidural blood patch procedures to seal the leak. In refractory cases, surgery may be needed to repair the dura. Recognizing a CSF leak is critical, as it's a treatable cause of headaches that might otherwise be misattributed to "just migraine" in a hypermobile patient.

Subluxation & Dislocation Across the Body

One hallmark of hypermobile EDS and HSD is that joint instability is not limited to one area – it can affect virtually any joint in the body. Patients often experience frequent subluxations (partial dislocations where the joint slides out of place and back in) or even full dislocations with minimal trauma. Shoulders, knees, ankles, fingers, ribs, and jaw (TMJ) are common culprits in addition to the spine. These events can be extremely painful and damaging over time or joints can be sitting out of place for a prolonged period of time, patients not realizing that it's not normal and resulting in changes due to regional interdependence moving up and down the kinematic chain. Importantly, such widespread laxity is often overlooked in standard medical training – many providers are taught to think of dislocations only in the context of significant injury, not something that happens spontaneously during everyday activities. In hEDS/HSD, however, it is well documented that joints can dislocate or subluxate very easily- even spontaneously or with trivial forces due to defective connective tissue. For instance, an EDS patient might dislocate a shoulder turning over in bed, or an ankle might give out while simply walking on an uneven surface. These recurring subluxations lead to soft tissue damage, osteoarthritis, and often neuropathic pain from stretched nerves. Yet, patients report that their complaints of joints "popping out" are sometimes written off if imaging doesn't catch the transient subluxation. Any joint with a supporting ligament can be affected – from the small joints in the hands (causing grip difficulty) to the ribs at the sternum (costochondral subluxations that cause sharp chest pain). Education is needed so that providers realize the breadth of joint instability in hypermobility syndromes. Proper bracing, taping, physical therapy, and patient training in joint protection can reduce injury, but first the provider must take reports of "my joints dislocate easily" at face value. Being believed in these unusual symptoms is the first step for patients in receiving appropriate care. In summary, joint subluxations in hEDS/HSD can occur throughout the body, not just in the spine or major joints, and clinicians should maintain a high index of suspicion for such injuries in hypermobile patients even when the precipitating event seems minor.

Pain, Complexity, & Risk of Dismissal

Hypermobility-related disorders often produce a complex constellation of symptoms across multiple body systems. Patients may simultaneously deal with musculoskeletal pain, dysautonomic symptoms (fast heart rate, low blood pressure, GI dysmotility), allergic or mast cell disorder, fatigue, and neurological complaints. This complexity can unfortunately increase the risk of these patients being dismissed or misdiagnosed. Providers might see normal routine test results and be puzzled by the myriad of symptoms, sometimes incorrectly attributing them to anxiety or somatization. A patient with HSD, POTS, and mast cell activation might have debilitating nausea, tachycardia, and pain, yet endoscopies and cardiac workups are unremarkable – leading some doctors to conclude "nothing is wrong". This is where provider education is crucial: these syndromes are real and can cause significant disability even if conventional tests are normal.



Chronic pain in EDS/hypermobility is often underappreciated. Patients may have a mix of pain generators: acute pain from injuries or subluxations, chronic joint pain from degenerative changes, neuropathic pain from nerve compression or stretch, and central pain amplification. Migraine and headache disorders are also more common in EDS. Additionally, severe gastrointestinal dysmotility can occur – conditions like gastroparesis (delayed stomach emptying) and intestinal dysmotility are reported at higher rates in hypermobile patients, likely due to connective tissue laxity in the gut and dysautonomia affecting intestinal nerves. These GI manifestations (which can include irritable bowel syndrome, GERD, and pelvic floor dysfunction) add to the patient's symptom burden and often involve gastroenterologists in the care team.

Given the multi-system nature of hypermobility syndromes, an interdisciplinary approach is needed. Patients benefit from care teams that can address their cardiovascular issues (electrophysiologist or cardiologist for POTS), neurological issues (neurologist or neurosurgeon for Chiari/UCIs/TCS), gastroenterological issues (GI motility specialist for gastroparesis), allergic/immunologic issues (for mast cell activation), and of course rheumatology or genetics for the connective tissue disorder itself. Pain management specialists and physical therapists are also key players. However, assembling such a team can be challenging, and patients often encounter skepticism along the way. It is vital for healthcare providers to validate the patient's experiences and acknowledge the genuine, organic nature of their condition – these patients are not "faking it" or simply anxious. In fact, facing frequent medical dismissal can itself cause understandable anxiety and depression in anyone. Validating the patient's symptoms, educating them about the connections between hypermobility and their chronic post-infectious illness, and involving knowledgeable specialists will greatly improve patient outcomes. Equally important is patient education: helping individuals understand their condition (for instance, teaching them that their dizziness is from POTS and how to manage this, or that their abdominal pain may flare with mast cell triggers) can empower them in self-management and reduce panic. Overall, the mantra for providers should be "listen to the patient." These conditions are complex but very real, and compassionate management can prevent years of unnecessary suffering.

Onset Timing & Triggers

The age of onset for symptomatic hypermobility disorders can vary widely. Some patients are symptomatic from early childhood – for example, a child with congenital ligament laxity might walk later than peers, have frequent sprains or "growing pains," or show marked flexibility (like doing splits) along with pain. They may have developmental coordination delays or low muscle tone noted in infancy due to hypermobile joints. In other cases, individuals with underlying hypermobility go through childhood and adolescence relatively unaffected, only to see a major surge in symptoms later in life. Infection-associated chronic illnesses are one scenario in which a previously mild or asymptomatic hypermobility condition becomes dramatically evident. A classic story is about a young adult who handled their hypermobility well (perhaps they were even athletic due to their flexibility), but after a bad bout of mononucleosis or COVID-19, they develop chronic fatigue, POTS, widespread pain, and joint instability that doesn't resolve. The infection seems to flip a switch, turning a compensated hypermobility state into decompensated hEDS/HSD. Other common triggers include physical trauma (such as a car accident, causing whiplash might initiate a cascade of pain and instability in an EDS patient, unmasking CCI or other issues), surgery, or major hormonal events like pregnancy or menopause. Even severe psychological stress could potentially contribute to a flare of hypermobility-related problems, likely through inflammatory or mast cell pathways.



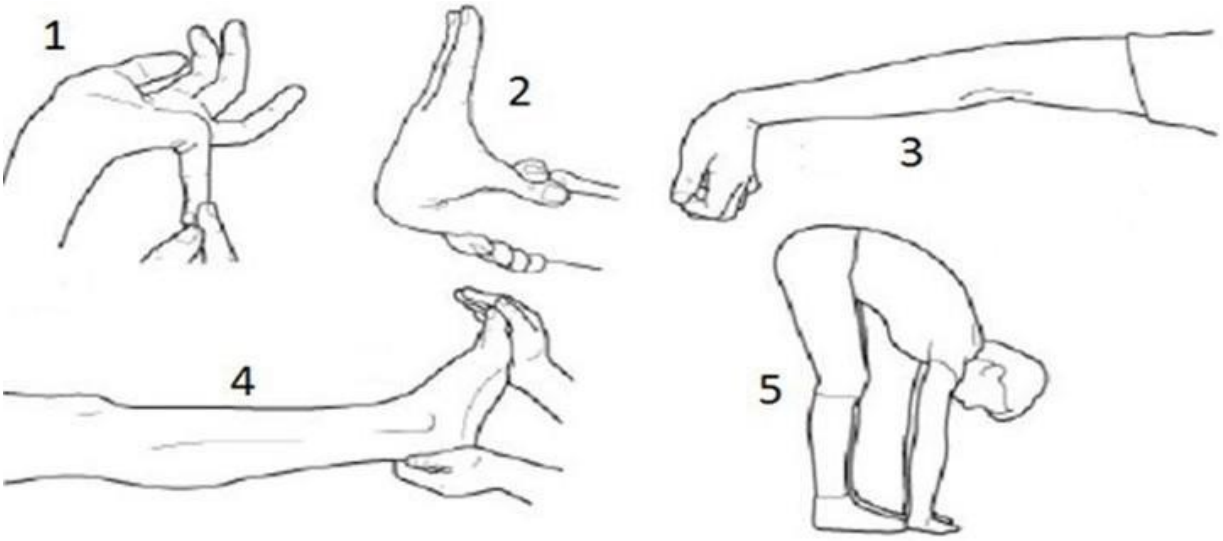
It's critical to acknowledge this broad range of onset. A hypermobile teenager with unexplained pain should be evaluated early – early diagnosis can lead to protective joint strategies that may reduce long-term injury. On the other hand, an adult patient with no history of joint problems should not be excluded from an hEDS/HSD diagnosis if they meet criteria now; their hypermobility may simply have gone unrecognized until a trigger occurred.

In summary, hypermobility and IACIs are intricately linked: a susceptible connective tissue framework can turn a temporary infection into a chronic, multisystem illness. By understanding the mechanisms (like ECM breakdown and dysautonomia) and the comorbidities (from CCI to mast cell issues), healthcare providers can deliver more empathetic, informed care. Early recognition and a multidisciplinary approach are essential. Above all, listening to and validating patients – whose symptoms may be invisible on standard tests – will foster better outcomes in this challenging intersection of infectious triggers and connective tissue disorder.



Screening

Beighton



The current gold standard of screening for hypermobility includes the Beighton Scale. The Beighton Scale is a 9-point scoring system that screens for widespread hypermobility. It does so by utilizing a point per side of elbow hyperextension beyond 10 degrees, knee hyperextension beyond 10 degrees, pink hyper extension beyond 90 degrees and thumb and wrist hyperflexion, allowing the thumb to reach the volar aspect of the wrist. The final point, creating this odd number total is 1 point is awarded if the patient can touch the floor with their legs straight and palms flat on the ground. The Beighton Scale, as well as a few modifiers asking “can you now, or could you ever [...]” is what is included as the first of 3 Criterion for a diagnosis of hEDS but is used for any hypermobility screening. While Beighton is a good, quick way to screen- the testing must go beyond Beighton as it is clouded by various confounding factors. In parts of the Beighton such as the elbow and knee hyperextension can be confounded by natural joint congruency such as a bony stop due to the olecranon at the elbow, or normal anatomical differences causing increased joint congruency, limiting knee hyperextension. Tests such as those at the hands and looking at reaching the palms to the floor are tests of musculotendinous length, which lends itself more so to flexibility rather than ligamentous, articular laxity, as seen in a connective tissue disorder. The difference between acquired musculotendinous flexibility vs. connective tissue and articular laxity is key in identifying those that may be at risk for the widespread effects of a connective tissue disorder, rather than those who have trained to become flexible. The Beighton Score may also be limited in cases of hypertonicity either from hypertrophy and strength or spastic, painful muscles, guarding as a natural accommodation to the clinical instability, in order to protect the joints. Many with hypermobility will come off as your classically “flexible” person, but it is not limited to those that do. Many individuals with an underlying connective tissue disorder may undergo a painful adaptive shortening of their musculature as accommodation to avoid subluxations and dislocations. These patients will score very low (or not at all) on the Beighton Scale. For this reason, Dr. Valerie Iovine Rogers has developed a new screening tool that looks purely at the articular hypermobility of select joints that are the most common complaints with tests that attempt



to utilize a good window into the status of the ligamentous laxity and are less confounded by the musculotendinous units.

Iovine Cluster

The Iovine Cluster combines existing, evidence-based tests and measures to compile a large-scale score for hypermobility. The tests included in Iovine Cluster are the Glenohumeral Load and Shift Test, the Sulcus Test, the Hip Dial Test, maintaining the Genu Recurvatum test from the Beighton, but adding the patellar translation evaluation to address the knee complex as well as an ankle inversion range of motion assessment and Navicular Drop Test. The scoring of these tests follows suit with the evidence-based and widely accepted structure utilized for the Glenohumeral Load and Shift Test, grading in a scaled manner from 0-3. Unlike Beighton's dichotomous scoring, this allows for a more nuanced and clinically relevant series of tests that is not limited by not reaching the maximally hypermobile grade for some credit towards the total.

Innovations in Hypermobility Testing at the CoRE: The Iovine Cluster

Instructions & Scoring

- Grading System:
  - Grade 0: Hypomobile
  - Grade 1: Normal - Mildly Hypermobile
  - Grade 2: Moderately Hypermobile
  - Grade 3: Severely Hypermobile

Load and shift test (reduction shift test): With the patient in a seated position with the arms relaxed, the provider grasps humeral head and slides it anteriorly and evaluates the hypermobility and then releases to assess if spontaneous reduction if subluxated. If the patient presents with an anteriorly subluxated shoulder, grade 3 is automatically attained.

- Grading:
  - Grade 0: Little to no movement of the humeral head
  - Grade 1: The humeral head could be shifted so that it started to ride up onto the glenoid labrum
  - Grade 2: The humeral head could be shifted off the glenoid but spontaneously relocated once the pressure had been eased
  - Grade 3: The humeral head could be shifted off the glenoid and remained dislocated once the pressure had been eased

Grade each side. Bilateral Load and Shift Total: __/6.

Sulcus sign: With the patient in a seated position with arms relaxed by the side, the provider grasps the patient's elbow and pulls down on the arm in an inferior only direction. If any gap appears in the subacromial area of the patient's shoulder, measure in centimeters. If the patient presents with a resting sulcus sign, grade 3 is automatically attained.

- Grading:
  - Grade 0: Little to no movement of the humeral head
  - Grade 1: The humeral head could be translated inferiorly < 2 cm (about 0.79 in)
  - Grade 2: The humeral head could be translated inferiorly 2- 2.5 cm (about 0.98 in)
  - Grade 3: The humeral head could be translated > 2.5 cm (about 0.98 in)



Grade each side. Bilateral Sulcus Sign Total: __/6.

Hip dial test: With the patient in supine, the most posterior aspect of the calcaneus on the treatment table, internally and externally rotate the hip via "rolling" the leg. Repeat rolling technique back and forth and release on an externally rotated directed force. Evaluate the level of rebound back to neutral.

- Grading:
  - Grade 0: Full rebound back to neutral, 0 degrees of rotation.
  - Grade 1: Some rebound towards neutral, hip comes to rest at less than 35 degrees of external rotation.
  - Grade 2: Little rebound, hip 35-45 degrees rotated.
  - Grade 3: No rebound, hips externally rotated > 45 degrees.

Grade each side. Bilateral Hip Dial Test Total: __/6.

Genu recurvatum: Have the patient stand and instruct them to "lock their knees all the way back" to evaluate knee hyperextension.

- Grading:
  - Grade 0: No hyperextension, knee achieves only 0 degrees of extension.
  - Grade 1: Slight hyperextension of the knee, -1 to -5 degrees present.
  - Grade 2: Moderate hyperextension of the knee, -6 to –10 degrees present.
  - Grade 3: Severe hyperextension of the knee, greater than –10 degrees present.

Grade each side. Bilateral Genu Recurvatum Total: __/6.

Patellar translation: With the patient in supine, have them relax their quadriceps and assess their mobility of the patella medially and laterally.

- Grading:
  - Grade 0: No patellar translation.
  - Grade 1: Normal patellar translation (7.2 to 17.6 mm laterally, 6.8 to 14.0 mm medially).
  - Grade 2: Greater than normal patellar translation with spontaneous reduction.
  - Grade 3: Greater than normal patellar translation without spontaneous reduction.

Grade each side. Bilateral Patellar Translation: __/6

Ankle inversion range of motion: With the patient in supine or long sit, feet completely cleared off the edge of the treatment table, assess passive inversion.

- Grading:
  - Grade 0: Ankle inversion ROM <20 degrees.
  - Grade 1: Ankle inversion ROM 20-30 degrees.
  - Grade 2: Ankle inversion ROM 31-40 degrees.
  - Grade 3: Ankle inversion ROM >40 degrees.

Grade each side. Bilateral Ankle Inversion Total: __/6

Navicular drop test: Have the patient seated with their bare feet on the floor, no weight bore through them. Palpate and mark the navicular with a marker. On an adjacent index card, mark



the level of the unweighted navicular. Have the patient come to a stand. Remark the level of the weight bearing navicular. Measure the distance on the index card.

- Grading
  - Grade 0: Navicular drops 5 mm (about 0.2 in) or less.
  - Grade 1: Navicular drops 6-10 mm.
  - Grade 2: Navicular drops 10-15 mm.
  - Grade 3: Navicular drops 15 mm (about 0.59 in) or more.
  - Grade each side.

Bilateral Navicular Drop Test Total: __/6

Iovine Cluster Score: __/42, 26 or more is positive.

Proprioceptive Deficits in the Hypermobile Population

Proprioception, the sense of joint position and movement in space, is often impaired in individuals with hypermobility disorders like hEDS and HSD. This deficit contributes significantly to motor incoordination, balance challenges, frequent injuries, and difficulty with postural control.

The underlying reason for proprioceptive impairment in this population stems from abnormal connective tissue structure, particularly within ligaments, joint capsules, and fascia, which house the mechanoreceptors responsible for proprioception. These include Ruffini endings, Pacinian corpuscles, and Golgi tendon organs, all of which rely on tension, stretch, and pressure cues from the ECM to send accurate feedback to the central nervous system. In hEDS/HSD, lax connective tissue due to collagen defects or ECM breakdown leads to mechanical instability and “noisy” or inconsistent feedback from these sensors. As a result, the brain receives degraded or delayed information about joint position and movement. This poor proprioception explains why this tends to be a clumsy population, misjudging their surroundings and also is the reason why many patients have trouble sitting still, tend to fidget and sit at end ranges. Since ligaments do not recoil, training against end range positions is key.

In short, proprioceptive deficits in hypermobile individuals are a predictable consequence of structural tissue fragility, and they represent a key therapeutic target in individualized, stability-focused rehabilitation.

The Regional Interdependence, Poor Proprioceptive Input Cycle (RIPPI Cycle)

The RIPPI Cycle (Regional Interdependence and Poor Proprioceptive Input) offers a framework to understand the self-reinforcing nature of dysfunctional movement in individuals with CTDs. It illustrates how excessive mobility in one region, compounded by impaired proprioceptive feedback, leads to instability, compensatory overuse, and further biomechanical dysfunction in adjacent areas.

This concept is crucial in both clinical evaluation and therapeutic planning for the hypermobile population, where subtle, repeated movement errors often underlie more overt joint pain, fatigue, and instability. The RIPPI Cycle reflects the dual challenge in CTDs: not only are joints unstable due to connective tissue fragility, but the sensory systems meant to detect and correct these instabilities are also impaired.



Mechanisms of the RIPPI Cycle

Excessive joint range of motion (ROM): In hypermobility disorders, ligaments and joint capsules allow a greater-than-normal range of motion, often without appropriate muscular control. Patients frequently and unintentionally move into these excessive end ranges, which the body cannot adequately stabilize. This leads to:

- Microtrauma to joint surfaces and surrounding soft tissues
- Repeated subluxations or excessive joint gliding
- Early joint fatigue during normal movement patterns

Compensatory overuse and regional underuse: Because hypermobile joints move more freely, they often become default movers within a kinetic chain. This creates a mismatch in joint contribution:

- Overuse of hypermobile segments increases strain and inflammation in those areas
- Underuse of adjacent, more stable joints leads to weakening or stiffness in those regions and painful tight muscles.
- The result is a loss of normal load-sharing across the kinetic chain, promoting dysfunction in remote areas (regional interdependence)

Proprioceptive deficits: Connective tissue houses mechanoreceptors critical for proprioception. In CTDs, abnormal or degraded connective tissue leads to:

- Inaccurate joint position sense
- Delayed neuromuscular response to instability
- Inability to self-correct during movement

This sensory deficit prevents the patient from recognizing when a joint is in a compromised position or approaching end range. Consequently, they are more likely to repeat maladaptive patterns, deepening the cycle.

Entrenchment of dysfunctional motor patterns: Over time, these factors lead to the engraining of poor motor control strategies. As the nervous system adapts to instability and abnormal input, faulty movement patterns become habitual. This contributes to:

- Global deconditioning
- Pain amplification
- Further loss of joint control

Clinical Implications

Breaking the RIPPI Cycle requires a multifaceted rehabilitation approach. Treatment should address both the mechanical and sensory components of dysfunction:

- Proximal stability training to reduce regional overuse
- Closed-chain and mid-range joint training to minimize end-range stress
- Balance and proprioception retraining to recalibrate sensory systems
- Gradual integration of underutilized joints to restore normal interdependence

Educating patients about the RIPPI Cycle can also foster better body awareness and promote adherence to activity modification and stabilization exercises. Clinicians should be mindful that



this cycle not only explains pain and joint dysfunction in individual joints, but also the systemic nature of instability in CTDs.

Rehabilitation Considerations in Hypermobility Disorders

Rehabilitating individuals with hypermobility requires a departure from conventional orthopedic protocols. These patients often present with pain or dysfunction in several joints, but even in the case of a singular joint priority, these are often affected by systemic instability, proprioceptive deficits, and multi-regional compensation patterns. A hypermobility-informed approach must treat the entire kinetic chain, not just the primary region of complaint.

Endurance of Local Stabilizers Over Maximal Strength

In hypermobile patients, large muscle groups are often recruited as global stabilizers to mask joint instability, while small stabilizing muscles remain underactive. Because connective tissues do not provide normal passive restraint, these patients rely more heavily on dynamic stabilization—making endurance of local stabilizers a primary goal of rehabilitation.

Focus should be placed on low-load, high-repetition training of intrinsic stabilizers (e.g., transversus abdominis, multifidus, deep neck flexors, rotator cuff).

Exercises must prioritize neutral joint positioning and mid-range control, avoiding excessive end-range loading.

Functional re-education of deep stabilizers should precede dynamic strengthening of global movers to reduce the risk of injury and recurrent subluxation.

Subluxation Screening, Correction, & Education

Joint subluxations, partial dislocations, are common in hEDS/HSD and may occur without overt trauma. Clinicians should be trained to:

- Routinely check for subluxations in symptomatic and adjacent joints
- Guide patients through safe self-reductions when appropriate (e.g., gently repositioning the shoulder or ribs)
- Use manual cues and postural retraining to restore optimal alignment before exercise initiation

Family and patient education is critical. Caregivers and patients should be taught how to recognize and reduce subluxations safely at home and instructed in joint protection strategies to avoid recurrence. Education should reinforce that subluxations are not signs of fragility, but indicators of instability that can be trained and supported with appropriate intervention.

The Pelvis as the Keystone

Regardless of the primary complaint, pelvic alignment must be assessed and corrected if necessary in every hypermobile patient. As the structural keystone of the body, the pelvis dictates both superior and inferior kinetic chain mechanics:



Multiplanar assessment is essential (anterior/posterior tilt, rotation, obliquity) as minor deviations in pelvic alignment can propagate dysfunction up and down the chain.

Common findings in HSD/hEDS include asymmetrical innominate rotation, SI joint instability, and lumbar compensation, which alter weight distribution and muscle activation patterns.

A poorly aligned pelvis disrupts central stability, amplifies lumbar lordosis, and creates adaptive strain through the thoracolumbar fascia and abdominal wall or can add to exaggerated scoliotic posture.

The Foot as the Foundation & Example of Regional Interdependence

The feet provide the primary base of support. In hypermobile patients, collapsed arches are common due to ligamentous laxity, and they have ripple effects through the entire system:

A collapsed medial arch contributes to ankle inversion and medial collapse of the knee, often leading to knee hyperextension.

This misalignment leads to inhibited activation of quadriceps and gluteal musculature, further destabilizing the pelvis.

Pelvic obliquity, even if subtle, alters spinal base support and can create a functional scoliosis in the spine.

Spinal misalignment leads to scapular tipping or winging, impairing the scapulothoracic rhythm and placing the glenohumeral joint in a vulnerable, gravity-dependent position—contributing to recurrent subluxation or dislocation.

As the shoulder drops or translates forward, tension is pulled through the cervical paraspinals and suboccipital musculature, contributing to upper cervical spine rotation or tilt. This can subtly shift the head off-axis, leading to compensatory gaze corrections and increasing strain on the atlantoaxial and craniocervical junctions—areas already prone to instability in this population.

One Joint, All Joints

Because of the structural and functional interdependence of joints in the hypermobile body, a complaint in a single region should always prompt a whole-body assessment. For example:

A shoulder that frequently subluxates may trace back to scapular instability, which may trace to pelvic tilt, which may trace to foot collapse.

Conversely, an ankle sprain may exacerbate pelvic asymmetry, causing ipsilateral thoracolumbar rotation, ultimately placing tension on the contralateral neck.

In other words, no joint functions in isolation in any population, but is very much so exaggerated in this population. Treating only the symptomatic region without addressing the chain of contributing dysfunction risks temporary improvement at best and exacerbation or injury elsewhere at worst.



Clinical Priorities in Hypermobility Rehabilitation

- Check pelvic alignment frequently, particularly if symptoms shift or are difficult to localize
- Encourage active foot posture, using cues to create and maintain the arch as a foundation
- Prioritize endurance and postural control over heavy resistance training
- Emphasize mid-range stability and proprioceptive retraining
- Reassess for subluxations regularly and correct prior to initiating loading
- Educate patients and families on the full-body implications of local instability and empower them with self-management techniques

By understanding the cascading biomechanical consequences of instability in the hypermobile body, clinicians can develop more effective, individualized treatment plans. The goal is not to strengthen a single joint in isolation, but to retrain a system built on unstable foundations.

Subluxation Reduction Guide for Hypermobility Disorders

In patients with hypermobility or connective tissue disorders such as HSD or hEDS, joint subluxations are a frequent source of pain and neuromuscular dysfunction. These events often occur without acute trauma and may not present as overt dislocations, but they still lead to significant mechanical disruption. Gentle, precise, and sustained joint repositioning techniques are preferred over forceful or repetitive mobilizations.

General Principles

- Palpation is key: Use anatomical landmarks and patient feedback to confirm malalignment.
- Sustained, directional pressure is more effective than repeated oscillations.
- Joint-specific knowledge of arthrokinematics (glides, rolls, spins) is critical for safe and effective reductions.
- Patient comfort and gentle touch are essential—many patients have comorbid MCAS and skin fragility. Communicate openly with your patient; they often know their bodies best.
- Skin taping (e.g., kinesiology tape) may help support alignment post-reduction but use with caution—many patients cannot tolerate adhesives due to MCAS and skin sensitivity and fragility.

Shoulder (Glenohumeral Joint)

Most Common Subluxation: Anterior

Assessment technique: With the patient's arm resting by their side, palpate with your thumb moving medial to lateral along the anterior shoulder. The humeral head should sit flush with the plane of the chest wall—not visibly prominent or anterior.

Reduction Technique

1. With the patient supine, gently abduct the affected arm to 45–90°.
2. Pin the patient's arm against your side for control and stabilization.



3. Place your hand just proximal to the elbow epicondyles to provide light axial distraction.
4. With your contralateral hand, place the heel of your hand on the anterior humeral head, ensuring contact is lateral to the joint line—crossing the joint line diminishes mechanical effectiveness.
5. Apply gradual, sustained posterior pressure, avoiding repeated mobilizations.
6. You may feel a subtle "clunk" or the return of the joint's suction mechanism - these are helpful cues but not necessary to confirm reduction.
7. Reassess by returning the arm to the patient's side and using the palpation technique above to check if the humeral head has returned to its anatomical position.

Note: Shoulder subluxations can occur in any direction. Adjust your mobilization direction accordingly and reassess scapular and thoracic mechanics post-reduction.

- Common dysfunctions: Innominate rotation, upslip, inflare, outflare

Pelvis

Assessment and correction: Pelvic assessment should be standard in all hypermobile patients due to the pelvis's central role in kinetic chain mechanics.

Anterior/Posterior Tilt & Rotation Correction

1. With the patient supine, palpate both Anterior Superior Iliac Spine (ASIS) for height symmetry.
2. Educate the patient to identify tilt themselves—an elevated ASIS usually indicates a posterior rotation, and a lower ASIS suggests an anterior rotation, but comparatively, it's difficult to identify the culprit. Typically, if there is a side with more pain or pressure, this is the one that did the moving.
3. Either way, the correction uses a bilateral muscle energy technique (MET).
4. Instruct the patient: "The high hip comes higher." That is, the leg on the high ASIS side pushes toward the face, and the opposite leg pushes away.
5. Classic setup (note there are many positional variations available for patient comfort): In semi-hooklying, have the patient:
    a. Raise one leg to 90/90 and press into their hands (hip flexor MET).
    b. Press the opposite foot into the table (hip extensor MET).
6. Hold each contraction concurrently for 6 seconds, repeat 5 times, and reassess after each set.
7. Watch for compensatory lumbar movement during isometric effort.

Inflare/Outflare Correction

1. Compare internal and external hip rotation with the patient supine and legs straight.
2. Be aware of potential confounders (e.g., femoral version, muscular imbalances).
3. If internal rotation is limited, this suggests an inflared innominate—correct with an isometric internal rotation in semi-hooklying.
4. If external rotation is limited, this suggests an outflare—correct with an isometric external rotation.
5. In either case: hold 6 seconds, repeat 5 times, reassess each time.
6. Watch for compensatory lumbar movement during isometric effort.



Upslip Correction

1. Wrap one hand around the anterior ASIS and guide the other around the posterior iliac crest.
2. Assume a split stance beside the patient, elbow locked straight.
3. Use your body weight to apply an inferiorly directed force (toward the patient's feet, not downward into the table).
4. Begin with 3–5 soft, low-grade mobilizations to take up slack.
5. Follow with a higher-grade mobilization without countdown, to avoid anticipatory guarding. Let the patient know you'll apply one firmer movement—but not exactly when.
6. Repeat the low- and high-grade cycle 3–5 times, then reassess.

Always confirm correction via ASIS, PSIS, and ischial tuberosity palpation. Note that complex compensatory patterns are common (e.g., a left anterior rotation may be paired with a left upslip and outflare, and a right inflare to re-stabilize the ring). Guard the patient carefully as they stand after correction—they may feel "off-center" after long-standing obliquities are addressed, especially the first time for the first few seconds.

Ribs

Common Subluxations: Anterior or Posterior (Subtle but Impactful)

Assessment & Correction

- Palpate for rib angle symmetry, tracing from posterior to anterior.
- Feel for step-offs, hypertonic intercostals, and deviation from the contralateral side.
- Apply a J-shaped mobilization:
- Anterior rib subluxation: Apply posterior-lateral force in a J or reverse-J pattern with patient supine.
- Posterior rib subluxation: Apply posterior-lateral force in the same directional curve with patient prone.
- Sustain gentle pressure and reassess motion and alignment.

Note: Rib subluxations can contribute to breathing dysfunction, autonomic symptoms, and thoracic outlet-like presentations. Rib checks should be standard in any upper thorax or scapular rehab.

Patella

Common Dysfunction: Lateral Tracking or Inferior Tilt

Reduction & Reinforcement

- Use gentle medial glides to realign the patella.
- Have the patient isometrically contract the quadriceps with the knee slightly flexed to avoid hyperextension.
- Hold for 5–6 seconds, repeat 5 times, optionally with therapist-assisted medial support during contraction.



Follow with neuromuscular re-education and gait retraining, emphasizing quadriceps control without hyperextension.

Clinical Pearls

- Unusual subluxations are common—be prepared to encounter instability in the TMJ, wrists, clavicle, costochondral junctions, and sacroiliac joints.
- Always assess multijoint contributions—e.g., wrist pain may stem from scapular asymmetry, or pelvic instability may originate from foot collapse.
- Apply manual therapy principles, anatomical precision, and clinical reasoning to identify and reduce even atypical subluxations.
- After reduction, always implement joint protection, stabilization strategies (e.g., braces, sleeves), and neuromuscular control training.

Caution on Kinesiology Taping

While taping can offer light support and proprioceptive input, it may not be appropriate for patients with MCAS, Ehlers-Danlos-related skin fragility, or dermatographism. If trialed:

- Always test on a small area first.
- Use hypoallergenic adhesives or apply skin prep/barriers.
- Consider alternatives such as compression sleeves, low-friction garments, or soft orthoses.

This guide offers a framework to help clinicians confidently and compassionately manage subluxations in hypermobile patients. By incorporating these techniques into routine care, providers can significantly reduce pain, improve alignment, and support stability for individuals with complex connective tissue disorders.

Proprioception Training in Hypermobility Rehabilitation

Individuals with hypermobility often present with impaired proprioception due to connective tissue laxity and disrupted sensory signaling from ligamentous structures. As a result, they struggle to accurately perceive joint position, movement, and muscular effort—challenges that are compounded by global instability and compensatory motor patterns.

Effective proprioceptive retraining is essential not only to improve posture and movement quality, but also to interrupt the RIPPI Cycle (Regional Interdependence and Poor Proprioceptive Input). This cycle describes how compensatory overuse and underuse patterns, driven by excessive range and inaccurate joint awareness, reinforce dysfunctional biomechanics throughout the kinetic chain.

Goals of Proprioceptive Retraining

- Re-educate joint position sense within collagen-typical (safe and functional) ranges
- Promote equal joint contribution across the kinetic chain to avoid compensatory overuse
- Improve postural awareness and dynamic control
- Restore appropriate muscle firing sequences and motor recruitment
- Prevent excessive reliance on end-range movement in hypermobile segments



Tools & Techniques

Laser Pointer Feedback

Using a laser attached to the head, wrist, or torso allows patients to visualize their movement on a wall or floor. This provides real-time feedback and helps retrain mid-range motor control.

- **Cervical training**: Place the laser on a headband; have the patient track slow movements within a target zone to improve cervical proprioception and gaze control. Placing the tongue to the roof of the mouth can help recruit the deep neck flexors at any time but is especially helpful in this intervention.
- **Lumbar/trunk training**: Affix a laser pointer to the low back to visualize spine movement during activities like seated pelvic tilts or cat-cows.
- **Shoulder and elbow control**: Laser alignment from the upper extremity can cue glenohumeral joint control and reduce reliance on compensatory thoracic motion.
- **Foot and ankle**: Secure the laser to the foot and have the patient follow a heavily side to side maze to train inversion and eversion proprioception

Mirror Therapy

Mirrors provide immediate visual feedback and reinforce body awareness.

- Ideal for retraining scapulohumeral rhythm, pelvic neutrality, and limb alignment.
- Helpful when addressing habitual knee hyperextension—most patients with hEDS are unaware of this until visually corrected.
- Encourages symmetrical joint usage and fosters proprioceptive recalibration through guided mid-range alignment.

Video Feedback

Short, recorded clips of functional movement can allow patients to see their habitual compensations (e.g., leaning into one hip, scapular elevation, rib flaring, hinging vs. segmental use of the vertebrae). Reviewing video in-session or at home:

- Reinforces correct motor patterns
- Improves body schema
- Enhances carryover into daily activities

Application Across the Kinetic Chain

Lower Extremity Re-Education

- **Knee control**: Teach patients to identify and avoid knee hyperextension. Cues include mirror feedback, tactile markers (like Theraband gently wrapped behind the knee), or laser guidance.
- **Foot posture**: Train patients to maintain an active medial arch. Collapsed arches lead to ankle inversion, tibial rotation, and knee hyperextension, contributing to proximal instability.
- **Equal loading strategies**: Encourage symmetrical weight-bearing to reduce overuse of one limb or reliance on hypermobile joints.



Upper Quarter Integration

- **Shoulder proprioception**: In patients with excessive glenohumeral joint (GHJ) mobility, retrain proper scapulohumeral rhythm to prevent impingement and thoracic outlet syndrome. Mirror or laser feedback can cue scapular depression and upward rotation during overhead tasks.
- **Thoracic mobility control**: Many hypermobile patients compensate with excessive thoracic hinging or rib flaring. Segmental cat-cow exercises, performed with controlled movement at each spinal level, help build awareness and reduce reliance on spinal extension during arm elevation or trunk movement or even help to use the segments equally with spinal movements.

Balance & Coordination

Proprioceptive deficits in hEDS often extend to dynamic balance and limb coordination.

- **Static balance training**: Begin with tandem or single-leg stance on flat surfaces before progressing to unstable surfaces (foam, BOSU).
- **Dynamic control**: Incorporate slow gait drills, obstacle stepping, or marching with arm movement to engage cross-body control and postural reflexes.
- Visual occlusion (e.g., eyes closed or reduced visual input) can be used once foundational control is established, but only under supervision.

Clinical Insight

Proprioceptive retraining is not about strengthening alone—it is about retraining the brain to recognize and correct joint position in real time. In hypermobility disorders, patients may look well-aligned externally while operating with poor internal control or faulty sequencing. Therefore:

- Always start with external feedback tools (mirror, laser, video)
- Prioritize mid-range joint control over end-range movement
- Reinforce movement quality, not quantity

By systematically retraining proprioception and neuromuscular awareness, clinicians can help hypermobile individuals move more confidently, reduce subluxation frequency, and minimize compensatory strain throughout the body.

Rehabilitation Considerations for

UCI is an underrecognized yet highly impactful complication in individuals with hEDS or HSD. Instability at the atlanto-occipital (AO) or atlantoaxial (AA) joints can result in compression or irritation of neural structures and vascular tissues, leading to symptoms such as neck pain, dizziness, headaches, visual disturbances, dysautonomia, and in some cases, cranial nerve involvement.

Due to the high-stakes anatomy in this region, particularly the brainstem, vertebral arteries, and cranial nerves, screening, stabilization, and gentle retraining must be done with precision and caution.



Screening & Clinical Examination

The screening techniques described herein, such as the Alar Ligament Stress Test and Sharp-Purser Test, should be applied only when clinically appropriate and with careful consideration of patient presentation. In individuals with suspected craniocervical or atlantoaxial instability, these tests may provoke symptoms or exacerbate underlying conditions. Clinicians are advised to use their professional judgment, modify, or defer testing when necessary, and refer for imaging or specialist evaluation when instability is suspected. Patient safety and comfort should always take precedence over confirmatory testing.

Alar Ligament Stress Test

This test assesses the integrity of the alar ligaments, which limit excessive rotation and side bending of the upper cervical spine.

Procedure:

- Patient is supine.
- Stabilize the C2 spinous process with a pinch grip.
- Gently, PT passively side-bends and/or rotates the head.
- **Positive test**: Excessive movement without C2 motion, or delayed motion of C2, may indicate ligament laxity or tear

Sharp-Purser Test

Used to assess atlantoaxial instability, specifically subluxation of the atlas (C1) on the axis (C2) due to transverse ligament insufficiency.

Procedure:

- Patient is seated with slight cervical flexion.
- The therapist stabilizes C2 with one hand and applies a posterior force on the forehead.
- **Positive test**: A clunk or reduction sensation (indicating prior subluxation) or marked symptom relief during the posterior glide.
- Can also be completed throughout the flexion range for a dynamic variable in the test.

Upper Quarter Neurologic Screen

Screening for neurologic involvement is essential prior to intervention. Include:

- Myotome testing (C1–T1)
- Dermatome and reflex testing
- Cranial nerve exam:
    - CN I (olfaction)
    - CN II (visual fields)
    - CN III, IV, VI (ocular tracking)
    - CN V (facial sensation)
    - CN VII (facial expression)
    - CN IX, X (gag, voice quality)
    - CN XI (trapezius and SCM strength)
    - CN XII (tongue movement)



Prerequisite: Pelvic Alignment and Global Postural Control

Before initiating upper cervical interventions, clinicians must ensure that global subluxations—especially at the pelvis—have been addressed. The pelvis serves as the foundation of postural alignment, and misalignments here can ascend through the spinal chain, altering head position and increasing strain on the suboccipital and cervical musculature. Even in cases where structural instability remains, functional alignment and postural symmetry must be optimized.

Deep Neck Flexor Retraining

Deep neck flexor (DNF) weakness is common in UCI and contributes to forward head posture, excessive loading of the upper cervical segments, and compensatory overuse of superficial musculature.

Tongue-to-Palate Cue

Cue the patient to place the tongue on the roof of the mouth (hard palate) to help:

- Facilitate DNF activation (longus capitis/colli)
- Reduce over recruitment of SCM and scalenes
- Reinforce cranio-cervical flexion pattern

Laser Training

- A head-mounted laser pointer can provide invaluable biofeedback:
    - Place the patient supine with the laser targeting a grid on the wall or floor.
    - Guide them to perform gentle cranio-cervical flexion ("nodding") while maintaining a stable laser path.
    - This improves motor control, proprioception, and reinforces midline control.
    - Place a target on the wall and have the patient turn their head very mildly. After a few repetitions with eyes open, attempt with eyes closed, aiming to get back to the center of the target, open eyes and correct the distance. Repeat for flexion/extension.
    - Place a target on the wall for the patient to maintain laser in target, in neutral position and introduce extremity movement.
    - Begin with hands linked and raising both arms overhead.
    - Progress to reciprocal arm movement.
    - Introduce reciprocal leg movement such as seated marching.

Bracing: Cervical Collar Use

Cervical orthoses may be used temporarily to provide mechanical support and reduce strain during flare-ups or until stabilization improves. This can be recommended for days with heavy activity or when in a situation with unexpected perturbations such as the passenger in a car, however, educate patients on over-reliance on bracing.

Aspen Vista: Preferred for its balance between support and adjustability.

Miami J: May be used in cases where TMJ involvement limits comfort with other collars.

Usage Guidelines:

- Should not be a substitute for neuromuscular retraining.



- Worn intermittently, ideally during symptom provocation, travel, or prolonged upright tasks.
- Educate patients on donning/doffing, skin checks, and avoiding dependence.

Stabilization Interventions

Controlled Head Perturbations

- With the patient in neutral alignment, introduce gentle, unpredictable perturbations to the head (tapping, light nudges).
- Instruct the patient to resist movement and maintain midline control.
- **Goal**: Improve cervical co-contraction and reactive stability.

Progressions:

- Perform with eyes closed
- Perform during light seated activity (e.g., reaching or lower limb movement)
- Transition to standing or dynamic balance tasks as tolerated

Summary

Upper cervical rehabilitation in the hypermobile population must be approached with clinical precision, patient education, and respect for biomechanical interdependence. It is essential to screen for instability and neurologic involvement, ensure pelvic alignment and postural control, and retrain the deep stabilizers of the cervical spine with visual feedback and graded proprioceptive challenges. In some cases, intermittent bracing can supplement the stabilization process.

When executed thoughtfully, this approach can significantly reduce headaches, dizziness, and neural symptoms while empowering patients with the tools to protect and support their own stability.

Note on positional and autonomic considerations: When working with individuals who have hypermobility, it's important to recognize that exercise selection may be limited not only by joint instability, but also by positional tolerance. For example, quadruped positions may be desirable for core and shoulder stabilization, but may be contraindicated due to glenohumeral subluxation, wrist pain, or cervical strain. Additionally, orthostatic intolerance (e.g., POTS or general upright intolerance) may limit a patient's ability to perform exercises in standing or even seated positions for extended periods.

Clinicians are encouraged to reference the Autonomic Rehabilitation section for a comprehensive framework on modifying and progressing exercises within this population, including strategies for graded positional exposure, orthostatic conditioning, and symptom-informed pacing. Integrating these considerations alongside structural rehabilitation supports a safer and more effective plan of care.



Appendix F | Patient Reported Outcomes (PROs)

CoRE Primary Survey (PROs)

Please complete the survey below at your convenience. Thank you!

Today's Date _____

About how you are feeling now...

Health Questionnaire

Under each heading, please tick the ONE box that best describes your health TODAY

MOBILITY	◯ I have no problems in walking about ◯ I have slight problems in walking about ◯ I have moderate problems in walking about ◯ I have severe problems in walking about ◯ I am unable to walk about
USUAL ACTIVITIES (e.g. work, study, housework, family or leisure activities)	◯ I have no problems doing my usual activities ◯ I have slight problems doing my usual activities ◯ I have moderate problems doing my usual activities ◯ I have severe problems doing my usually activities ◯ I am unable to do my usual activities
ANXIETY/DEPRESSION	◯ I am not anxious or depressed ◯ I am slightly anxious or depressed ◯ I am moderately anxious or depressed ◯ I am severely anxious or depressed ◯ I am extremely anxious or depressed
SELF-CARE	◯ I have no problems washing or dressing myself ◯ I have slight problems washing or dressing myself ◯ I have moderate problems washing or dressing myself ◯ I have severe problems washing or dressing myself ◯ I am unable to wash or dress myself
PAIN/DISCOMFORT	◯ I have no pain or discomfort ◯ I have slight pain or discomfort ◯ I have moderate pain or discomfort ◯ I have severe pain or discomfort ◯ I have extreme pain or discomfort

We would like to know how good or bad your health is TODAY
- 100 means the best health you can imagine
- 0 means the worst health you can imagine

Please mark on the scale how your health is TODAY

0 50 100

(Place a mark on the scale above)





CoRE Primary Survey (PROs)

Please complete the survey below at your convenience. Thank you!

Today's Date _____

About how you are feeling now...

Health Questionnaire

Under each heading, please tick the ONE box that best describes your health TODAY

MOBILITY

- ◯ I have no problems in walking about
- ◯ I have slight problems in walking about
- ◯ I have moderate problems in walking about
- ◯ I have severe problems in walking about
- ◯ I am unable to walk about

USUAL ACTIVITIES (e.g. work, study, housework, family or leisure activities)

- ◯ I have no problems doing my usual activities
- ◯ I have slight problems doing my usual activities
- ◯ I have moderate problems doing my usual activities
- ◯ I have severe problems doing my usually activities
- ◯ I am unable to do my usual activities

ANXIETY/DEPRESSION

- ◯ I am not anxious or depressed
- ◯ I am slightly anxious or depressed
- ◯ I am moderately anxious or depressed
- ◯ I am severely anxious or depressed
- ◯ I am extremely anxious or depressed

SELF-CARE

- ◯ I have no problems washing or dressing myself
- ◯ I have slight problems washing or dressing myself
- ◯ I have moderate problems washing or dressing myself
- ◯ I have severe problems washing or dressing myself
- ◯ I am unable to wash or dress myself

PAIN/DISCOMFORT

- ◯ I have no pain or discomfort
- ◯ I have slight pain or discomfort
- ◯ I have moderate pain or discomfort
- ◯ I have severe pain or discomfort
- ◯ I have extreme pain or discomfort

We would like to know how good or bad your health is TODAY

- 100 means the best health you can imagine
- 0 means the worst health you can imagine

Please mark on the scale how your health is TODAY

0 50 100

(Place a mark on the scale above)



Over the last 2 weeks, how often have you been bothered by the following problems?	Not at all	Several days	More than half the days	Nearly every day
Little interest or pleasure in doing things	○	○	○	○
Feeling down, depressed, or hopeless	○	○	○	○

PHQ-2 Score (0-6) _____

=>3 indicates that major depressive disorder is likely.

Over the last 2 weeks, how often have you been bothered by the following problem?	Not at all	Several days	Over half the days	Nearly every day
Feeling nervous, anxious, or on edge	○	○	○	○
Not being able to stop or control worrying	○	○	○	○
Worrying too much about different things	○	○	○	○
Trouble relaxing	○	○	○	○
Being so restless that it's hard to sit still	○	○	○	○
Becoming easily annoyed or irritable	○	○	○	○
Feeling afraid as if something awful might happen	○	○	○	○

GAD-7 Score (0-21) _____

0-4: minimal anxiety
5-9: mild anxiety
10-14: moderate anxiety
15-21: severe anxiety

If you checked off any problems, how difficult have these made it for you to do your work, take care of things at home, or get along with other people?

○ Not difficult at all
○ Somewhat difficult
○ Very difficult
○ Extremely difficult

Has COVID 19 affected existing pain or resulted in new-onset pain?

○ Yes
○ No

Please indicate your pain level , on the following scale from 0 to 10

0 (No pain) 5 10 (Worst pain imaginable)

(Place a mark on the scale above)

In the area where you have pain, do you also have "pins and needles", tingling or prickling sensations?

○ NO - I don't get these sensations
○ YES - I get these sensations



Does the painful area change colour (perhaps look mottled or more red) when the pain is particularly bad?	◯ NO - The pain does not affect the colour of my skin ◯ YES - I have noticed that the pain does make my skin look different from normal
Does your pain make the affected skin abnormally sensitive to touch? Getting unpleasant sensations or pain when lightly stroking the skin might describe this.	◯ NO - The pain does not make my skin abnormally sensitive to touch. ◯ YES - My skin in that area is particularly sensitive to touch.
Does your pain come on suddenly and in bursts for no apparent reason when you are completely still? Words like "electric shocks", jumping and bursting might describe this.	◯ NO - My pain doesn't really feel like this. ◯ YES - I get these sensations often.
In the area where you have pain, does your skin feel unusually hot like a burning pain?	◯ NO - I don't have burning pain ◯ YES - I get burning pain often
Gently rub the painful area with your index finger and then rub a non-painful area (for example, an area of skin further away or on the opposite side from the painful area). How does this rubbing feel in the painful area?	◯ The painful area feels no different from the non-painful area ◯ I feel discomfort, like pins and needles, tingling, or burning in the painful area that is different from the non-painful area.
Gently press on the painful area with your finger tip and then gently press in the same way onto a non-painful area (the same non-painful area that you chose in the last question). How does this feel in the painful area?	◯ The painful area does not feel different from the non-painful area. ◯ I feel numbness or tenderness in the painful area that is different from the non-painful area.
S-LANSS Score >=12 neuropathic mechanisms are likely to be contributing to patients' pain	_____
During the past 7 days, how would you rate your sleep quality overall? 0 = Terrible 1 to 3 = Poor 4 to 6 = Fair 7 to 9 = Good 10 = Excellent	◯ 0 ◯ 1 ◯ 2 ◯ 3 ◯ 4 ◯ 5 ◯ 6 ◯ 7 ◯ 8 ◯ 9 ◯ 10



How likely are you to doze off or fall asleep in the following situations, in contrast to feeling just tired? This refers to your usual way of life in recent times.

Even if you haven't done some of these things recently try to work out how they would have affected you. Use the following scale to choose the most appropriate number for each situation:

0 = would never doze
1 = slight chance of dozing
2 = moderate chance of dozing
3 = high chance of dozing

	Would never doze	Slight chance of dozing	Moderate chance of dozing	High chance of dozing
Sitting and reading	○	○	○	○
Watching TV	○	○	○	○
Sitting, inactive in a public place (e.g. a theatre or a meeting)	○	○	○	○
As a passenger in a car for an hour without a break	○	○	○	○
Lying down to rest in the afternoon when circumstances permit	○	○	○	○
Sitting and talking to someone	○	○	○	○
Sitting quietly after a lunch without alcohol	○	○	○	○
In a car, while stopped for a few minutes in the traffic	○	○	○	○

ESS Score (0-24) _____

0 to 10 = normal range of sleepiness in healthy adults
11 to 14 = mild sleepiness
15 to 17 = moderate sleepiness
18 to 24 = severe sleepiness.

Please respond to each item by marking one box per row.

	Never	Rarely	Sometimes	Usually	Always
I have trouble doing all of my regular leisure activities with others	○	○	○	○	○



I have trouble doing all of the family activities that I want to do	○	○	○	○	○
I have trouble doing all of my usual work (include work at home)	○	○	○	○	○
I have trouble doing all of the activities with friends that I want to do	○	○	○	○	○
I have to limit the things I do for fun with others	○	○	○	○	○
I have to limit my regular activities with friends	○	○	○	○	○
I have to limit my regular family activities	○	○	○	○	○
I have trouble doing all of the work that is really important to me (include work at home)	○	○	○	○	○

PROMIS Ability to Participate in Social Roles and Activities 8a Raw score _____

Cut-off points:

https://www.healthmeasures.net/score-and-interpret/interpret-scores/promis/promis-score-cut-points

T-scores:

https://staging.healthmeasures.net/images/PROMIS/manuals/PROMIS_Ability_to_Participate_in_Social_Roles_and_Activities_Scoring_Manual.pdf

Physical Activity

Currently, how frequently do you complete 150-minutes per week of moderate-intensity physical activity (like a brisk walking, slow biking, general gardening, or ballroom dancing)?

- ○ Every week
- ○ Most weeks
- ○ Some weeks
- ○ Very few weeks
- ○ Never
- ○ I do not know

Currently, how frequently do you complete 150-minutes per week of vigorous-intensity physical activity (like running, swimming laps, playing singles tennis, and fast bicycling)?

- ○ Every week
- ○ Most weeks
- ○ Some weeks
- ○ Very few weeks
- ○ Never
- ○ I do not know



Cognition	
In the past 7 days I had to read something several times to understand it	◯ Never ◯ Rarely (once) ◯ Sometimes (2-3 times) ◯ Often (once a day) ◯ Very Often (several times a day)
In the past 7 days my thinking was slow	◯ Never ◯ Rarely (once) ◯ Sometimes (2-3 times) ◯ Often (once a day) ◯ Very Often (several times a day)
In the past 7 days I had to work really hard to pay attention or I would make a mistake	◯ Never ◯ Rarely (once) ◯ Sometimes (2-3 times) ◯ Often (once a day) ◯ Very Often (several times a day)
In the past 7 days I had trouble concentrating	◯ Never ◯ Rarely (once) ◯ Sometimes (2-3 times) ◯ Often (once a day) ◯ Very Often (several times a day)
How much DIFFICULTY do you currently have for reading and following complex instructions (e.g., directions for a new medication)?	◯ None ◯ A little ◯ Somewhat ◯ A lot ◯ Cannot do
How much DIFFICULTY do you currently have planning for and keeping appointments that are not part of your weekly routine, (e.g., a therapy or doctor appointment, or a social gathering with friends and family)?	◯ None ◯ A little ◯ Somewhat ◯ A lot ◯ Cannot do
How much DIFFICULTY do you currently have managing your time to do most of your daily activities?	◯ None ◯ A little ◯ Somewhat ◯ A lot ◯ Cannot do
How much DIFFICULTY do you currently have learning new tasks or instructions?	◯ None ◯ A little ◯ Somewhat ◯ A lot ◯ Cannot do
Neuro-QOL Cognitive Function 8a Raw Score Scoring: https://www.sralab.org/sites/default/files/2017-06/Neuro-QOL_User_Manual_v2_24Mar2015.pdf Interpretation: https://www.healthmeasures.net/score-and-interpret/interpret-scores/neuro-qol/neuro-qol-score-cut-points	_____



Global Impression of Change	
Since beginning treatment at this clinic how would you describe the change (if any) in ACTIVITY LIMITATION, SYMPTOMS, EMOTIONS and OVERALL QUALITY OF LIFE, related to your overall condition? (select one box)	◯ No change (or condition has gotten worse) ◯ Almost the same, hardly any change at all ◯ A little better, but no noticeable change ◯ Somewhat better, but the change has not made any real difference ◯ Moderately better, and a slight but noticeable change ◯ Better, and a definite improvement that has made a real and worthwhile difference ◯ A great deal better, and a considerable improvement that has made all the difference
In a similar way, please select the number below, that matches your degree of change since beginning care at this clinic:	◯ 0 (Much Better) ◯ 1 ◯ 2 ◯ 3 ◯ 4 ◯ 5 (No Change) ◯ 6 ◯ 7 ◯ 8 ◯ 9 ◯ 10 (Much Worse)

POST-EXERTIONAL MALAISE

For each symptom below, please circle one number for frequency and one number for severity:

FREQUENCY

Throughout the past 6 months, how often have you had this symptom?

	None of the time	A little of the time	About half the time	Most of the time	All of the time
1. Dead, heavy feeling after starting to exercise	◯	◯	◯	◯	◯
2. Next day soreness or fatigue after non-strenuous, everyday activities	◯	◯	◯	◯	◯
3. Mentally tired after the slightest effort	◯	◯	◯	◯	◯
4. Minimum exercise makes you physically tired	◯	◯	◯	◯	◯
5. Physically drained or sick after mild activity	◯	◯	◯	◯	◯



SEVERITY **Throughout the past 6 months, how much has this symptom bothered you?**	Symptom not present	Mild	Moderate	Severe	Very severe
1. Dead, heavy feeling after starting to exercise	○	○	○	○	○
2. Next day soreness or fatigue after non-strenuous, everyday activities	○	○	○	○	○
3. Mentally tired after the slightest effort	○	○	○	○	○
4. Minimum exercise makes you physically tired	○	○	○	○	○
5. Physically drained or sick after mild activity	○	○	○	○	○

For each question below, choose the answer which best describes your PEM symptoms.	
6. If you were to become exhausted after actively participating in extracurricular activities, sports, or outings with friends, would you recover within an hour or two after the activity ended?	○ Yes ○ No
7. Do you experience a worsening of your fatigue/energy related illness after engaging in minimal physical effort?	○ Yes ○ No
8. Do you experience a worsening of your fatigue/energy related illness after engaging in mental effort?	○ Yes ○ No
9. If you feel worse after activities, how long does this last?	○ < 1 h ○ 2-3 h ○ 4-10 h ○ 11-13 h ○ 14-23 h ○ ≥ 24 h
10. If you do not exercise, is it because exercise makes your symptoms worse?	○ Yes ○ No

DSQ-PEM Scoring
- Scoring Step 1
Items 1-5: A frequency and severity score of 2, 2 on any items 1-5 is indicative of PEM.
• Scoring Step 2
Items 7, 8: Either item 7 or 8 must have an answer of yes to indicate an ME and/or CFS dx.



COMPASS-31	
In the past week, have you ever felt faint, dizzy, "goofy", or had difficulty thinking soon after standing up from a sitting or lying position?	◯ Yes ◯ No
When standing up, how frequently do you get these feelings or symptoms?	◯ Rarely ◯ Occasionally ◯ Frequently ◯ Almost Always
How would you rate the severity of these feelings or symptoms?	◯ Mild ◯ Moderate ◯ Severe
In the past week, have these feelings or symptoms that you have experienced:	◯ Gotten much worse ◯ Gotten somewhat worse ◯ Stayed about the same ◯ Gotten somewhat better ◯ Gotten much better ◯ Completely gone
	_____
In the past week, have you ever noticed color changes in your skin, such as red, white, or purple?	◯ Yes ◯ No
What parts of your body are affected by these color changes? (Check all that apply)	☐ Hands ☐ Feet
	_____
Are these changes in your skin color:	◯ Getting much worse ◯ Getting somewhat worse ◯ Staying about the same ◯ Getting somewhat better ◯ Getting much better ◯ Completely gone
	_____
In the past 5 years, what changes, if any, have occurred in your general body sweating?	◯ I sweat much more than I used to ◯ I sweat somewhat more than I used to ◯ I haven't noticed any changes in my sweating ◯ I sweat somewhat less than I used to ◯ I sweat much less than I used to
	_____
Do your eyes feel excessively dry?	◯ Yes ◯ No
Does you mouth feel excessively dry?	◯ Yes ◯ No



For the symptom of dry eyes or dry mouth that you have had for the longest period of time, is this symptom:	◯ I have not had any of these symptoms ◯ Getting much worse ◯ Getting somewhat worse ◯ Staying about the same ◯ Getting somewhat better ◯ Getting much better ◯ Completely gone
	_____
In the past week, have you noticed any changes in how quickly you get full when eating a meal?	◯ I get full a lot more quickly now than I used to ◯ I get full more quickly now than I used to ◯ I haven't noticed any change ◯ I get full less quickly now than I used to ◯ I get full a lot less quickly now than I used to
	_____
In the past week, have you felt excessively full or persistently full (bloated feeling) after a meal?	◯ Never ◯ Sometimes ◯ A lot of the time
In the past week, have you vomited after a meal?	◯ Never ◯ Sometimes ◯ A lot of the time
In the past week, have you had a cramping or colicky abdominal pain?	◯ Never ◯ Sometimes ◯ A lot of the time
In the past week, have you had any bouts of diarrhea?	◯ Yes ◯ No
How frequently does this occur?	◯ Rarely ◯ Occasionally ◯ Frequently ◯ Constantly
How severe are these bouts of diarrhea?	◯ Mild ◯ Moderate ◯ Severe
Are your bouts of diarrhea getting:	◯ Much worse ◯ Somewhat worse ◯ Staying the same ◯ Somewhat better ◯ Much better ◯ Completely gone
	_____
In the past week, have you been constipated?	◯ Yes ◯ No



How frequently are you constipated?	◯ Rarely ◯ Occasionally ◯ Frequently ◯ Constantly
How severe are these episodes of constipation?	◯ Mild ◯ Moderate ◯ Severe
	_____
Is your constipation getting:	◯ Much worse ◯ Somewhat worse ◯ Staying the same ◯ Somewhat better ◯ Much better ◯ Completely gone
	_____
In the past week, have you ever lost control of your bladder function?	◯ Never ◯ Occasionally ◯ Frequently ◯ Constantly
In the past week, have you had difficulty passing urine?	◯ Never ◯ Occasionally ◯ Frequently ◯ Constantly
In the past week, have you had trouble completely emptying your bladder?	◯ Never ◯ Occasionally ◯ Frequently ◯ Constantly
In the past week, without sunglasses or tinted glasses, has bright light bothered your eyes?	◯ Never ◯ Occasionally ◯ Frequently ◯ Constantly
How severe is this sensitivity to bright light?	◯ Mild ◯ Moderate ◯ Severe
In the past week, have you had trouble focusing your eyes?	◯ Never ◯ Occasionally ◯ Frequently ◯ Constantly
How severe is this focusing problem?	◯ Mild ◯ Moderate ◯ Severe



Is the most troublesome symptom with your eyes (i.e. sensitivity to bright light or trouble focusing) getting:	◯ I have not had any of these symptoms ◯ Much worse ◯ Somewhat worse ◯ Staying about the same ◯ Somewhat better ◯ Much better ◯ Completely gone
	_____
COMPASS 31 SCORE https://score.awellhealth.com/calculations/compass_31/documentation	_____

The UCLA 3-Item Loneliness Scale

	Hardly ever	Some of the time	Often
How often do you feel that you lack companionship?	◯	◯	◯
How often do you feel left out?	◯	◯	◯
How often do you feel isolated from others?	◯	◯	◯

UCLA Score	_____

Neurological Symptom Burden

Please use the slider below to rate the intensity with which you may experience the described symptom, 0 being not at all, 5 being severe intensity.

Hyperaccusis (Sensitivity to noise)	0, not at all. 5, severe. *(Place a mark on the scale above)*
Ringing in the ears	0, not at all 5, severe. *(Place a mark on the scale above)*
Loss of hearing	0, not at all 5, severe. *(Place a mark on the scale above)*
Balance disorder	0, not at all 5, severe. *(Place a mark on the scale above)*
Vertigo (room spinning around)	0, not at all 5, severe. *(Place a mark on the scale above)*
Dizziness/lightheadedness	0, not at all 5, severe. *(Place a mark on the scale above)*



Dystonias (Shaking episodes)	0, not at all	5, severe.
	(Place a mark on the scale above)	
Seizures	0, not at all	5, severe.
	(Place a mark on the scale above)	
Tremors	0, not at all	5, severe.
	(Place a mark on the scale above)	
Headache	0, not at all	5, severe.
	(Place a mark on the scale above)	
Neck pain	0, not at all	5, severe.
	(Place a mark on the scale above)	
Loss of consciousness/syncope	0, not at all	5, severe.
	(Place a mark on the scale above)	
Pre-syncope (feeling like you could faint, but don't lose consciousness)	0, not at all	5, severe.
	(Place a mark on the scale above)	
Concentration difficulties	0, not at all	5, severe.
	(Place a mark on the scale above)	
Memory loss	0, not at all	5, severe.
	(Place a mark on the scale above)	
Blurred vision	0, not at all	5, severe.
	(Place a mark on the scale above)	
Double vision	0, not at all	5, severe.
	(Place a mark on the scale above)	
Teichopsia (vision flashes)	0, not at all	5, severe.
	(Place a mark on the scale above)	
Photosensitivity (light sensitivity)	0, not at all	5, severe.
	(Place a mark on the scale above)	
Hyperolfaction (sensitivity to smell)	0, not at all	5, severe.
	(Place a mark on the scale above)	



Facial numbness	0, not at all	5, severe.
		(Place a mark on the scale above)
Paresthesia/tingling/sensory loss	0, not at all	5, severe.
		(Place a mark on the scale above)
Leg weakness	0, not at all	5, severe.
		(Place a mark on the scale above)
Arm weakness	0, not at all	5, severe.
		(Place a mark on the scale above)
Nausea/vomiting	0, not at all	5, severe.
		(Place a mark on the scale above)
Poor coordination	0, not at all	5, severe.
		(Place a mark on the scale above)
Speech difficulty	0, not at all	5, severe.
		(Place a mark on the scale above)
Hoarseness	0, not at all	5, severe.
		(Place a mark on the scale above)
Sensation of choking/ strangulation	0, not at all	5, severe.
		(Place a mark on the scale above)
Difficulty swallowing	0, not at all	5, severe.
		(Place a mark on the scale above)
Head/ neck pain worse over bumps in the car	0, not at all	5, severe.
		(Place a mark on the scale above)

Horowitz Lyme-MSIDS Questionnaire

	None	Mild	Moderate	Severe
Unexplained fevers, sweats, chills, or flushing	○	○	○	○
Unexplained weight change; loss or gain	○	○	○	○
Fatigue, tiredness	○	○	○	○



Unexplained hair loss	○	○	○	○
Swollen glands	○	○	○	○
Sore throat	○	○	○	○
Testicular or pelvic pain	○	○	○	○
Unexplained menstrual irregularity	○	○	○	○
Unexplained breast milk production; breast pain	○	○	○	○
Irritable bladder or bladder dysfunction	○	○	○	○
Sexual dysfunction or loss of libido	○	○	○	○
Upset stomach	○	○	○	○
Change in bowel function (constipation or diarrhea)	○	○	○	○
Chest pain or rib soreness	○	○	○	○
Shortness of breath or cough	○	○	○	○
Heart palpitations, pulse skips, heart block	○	○	○	○
History of a heart murmur or valve prolapse	○	○	○	○
Joint pain or swelling	○	○	○	○
Stiffness of the neck or back	○	○	○	○
Muscle pain or cramps	○	○	○	○
Twitching of the face or other muscles	○	○	○	○
Headaches	○	○	○	○
Neck cracks or neck stiffness	○	○	○	○
Tingling, numbness, burning, or stabbing sensations	○	○	○	○
Facial paralysis (Bell's palsy)	○	○	○	○
Eyes/vision: double, blurry	○	○	○	○
Ears/hearing: buzzing, ringing, ear pain	○	○	○	○
Increased motion sickness, vertigo	○	○	○	○
Light-headedness, poor balance, difficulty walking	○	○	○	○
Tremors	○	○	○	○
Confusion, difficulty thinking	○	○	○	○
Difficulty with concentration or reading	○	○	○	○



Forgetfulness, poor short-term memory	○	○	○	○
Disorientation: getting lost; going to wrong places	○	○	○	○
Difficulty with speech or writing	○	○	○	○
Mood swings, irritability, depression	○	○	○	○
Disturbed sleep: too much, too little, early awakening	○	○	○	○
Exaggerated symptoms or worse hangover from alcohol	○	○	○	○



Appendix G | Blood Tests

CoRE Blood Testing Wish List

Blood Test	Workflow	Can Quest Provide? (Y/N)	Test Code(s)	Notes on ICD-10 codes	Notes (other)
HORMONES/NEUROTRANSMITTERS					
Cortisol (morning, serum)	1st tier	Y	4212		Good first tier screen. If low, send to endocrinology for follow-up
Estradiol	1st tier (men only)	Y	4021		Good first tier screen for MEN only. If abnormal, send to endocrinology for follow-up
Progesterone		Y	745		
Serotonin (plasma)	1st tier	Y	818		Seeing this a lot in Long COVID (SNRIs can help) *4 mL whole blood submitted in a Serotonin Kit (provided by Quest Diagnostics) see detailed instructions here: Serotonin, Blood | Test Detail | Quest Diagnostics
Testosterone	1st tier	Y	15983 (total)		Good first tier screen. If low, send to endocrinology for follow-up
Free Testosterone	1st tier	Y	18944 (free)		Good first tier screen. If low, send to endocrinology for follow-up
TSH	1st tier (if not yet tested)				
T3	1st tier (if not yet tested)				
T4	1st tier (if not yet tested)				
Free T4	1st tier (if not yet tested)				
VITAMINS/MINERALS					
Folate	2nd tier	Y	466		Methyl folate can matter but don't know how to test for it
Ferritin	2nd tier	Y	457		
Iron	2nd tier	Y	571 (total)		
Magnesium	2nd tier	Y	622		
Vitamin B12	2nd tier	Y	927		
Vitamin D 25 OH	1st tier	Y	17306		If low give: https://systemicformulas.com/products/dv3/
LATENT VIRAL/BACTERIAL REACTIVATION					
Epstein Barr virus	1st tier	Y	8426; 8474; 8564		Consider Truvada if positive for 8426 Need more information/have a full EBV menu: Quest Diagnostics: Results for EBV
Herpes simplex virus 1	1st tier	Y			Can do serological /antibodies, or look for the pathogen itself (molecular); LDN?; Truvada? Need more information/have a full HSV-1 menu: Quest Diagnostics: Results for HSV 1
Herpes simplex virus 2		Y			Need more information/have a full HSV-2 menu: Quest Diagnostics: Results for HSV 2
Herpes simplex virus 3		Y			Need more information; full menu of HSV-3 (VZV) here: Quest Diagnostics: Results for VZV
Herpes simplex virus 4		Y			Need more information/have a full EBV menu: Quest Diagnostics: Results for EBV
Herpes simplex virus 5	1st tier	Y			Need more info/have a full CMV menu: Quest Diagnostics: Results for CMV
Herpes simplex	1st tier	Y			Need more info/have a full HHV 6 menu:



Blood Test	Workflow	Can Quest Provide? (Y/N)	Test Code(s)	Notes on ICD-10 codes	Notes (other)
virus 6					Quest Diagnostics: Results for HHV 6
Herpes simplex virus 7		Y			Need more info/have a full HHV 7 menu: Quest Diagnostics: Results for HHV 7
HPV	Referral to Gyn	Y			Need more info/full menu for HPV: Quest Diagnostics: Results for HPV
H Pylori (breath test)	Referral to GI for H Pylori and SIBO testing	Y	14839		
Human metapneumovirus (HMPV)		Y	40034		
Respiratory pathogen profile		Y	37444		
TICK-BORNE/VECTOR-BORNE ILLNESS					
Lyme disease (*Borrelia burgdorferi,, B. spielmanii, B. afzelii, B. mayonii, B. afzelii, B. garinii, B. bavariensis*)		maybe	39219	In our experience with payer engagement, reimbursement for speciating *Borrelia* beyond *B. burgdorferi* and *B. mayonnii* is not favorable. This is our best offering related to this request: *Borrelia* Species DNA, Real-Time PCR, with Reflexes, Blood | Test Detail | Quest Diagnostics	
Tick Borne Relapsing Fever (TBRF) (*Borrelia hermsii, B. lonestari, B. turicatae*)				Need more information; In our experience with payer engagement, reimbursement for speciating *Borrelia* beyond *B. burgdorferi* and *B. mayonnii* is not favorable. This is our best offering related to this request: *Borrelia* Species DNA, Real-Time PCR, with Reflexes, Blood | Test	



Blood Test	Workflow	Can Quest Provide? (Y/N)	Test Code(s)	Notes on ICD-10 codes	Notes (other)
				Detail | Quest Diagnostics	
Borrelia Miyamotoi Disease (*Borrelia miyamotoi*)		Y			Need more information; have a full menu of *B. miyamotoi* Quest Diagnostics: Results for *Borrelia miy*
Other *Borrelia* species (*B. andersonii, B. maritima, B. californiensis, B. bissettiae, B. lusitaniea, B. valaisiana, B. yangtzensis, B. turcica*)		maybe	39219	In our experience with payer engagement, reimbursement for speciating *Borrelia* beyond *B. burgdorferi* and *B. mayonnii* is not favorable. This is our best offering related to this request: *Borrelia* Species DNA, Real-Time PCR, with Reflexes, Blood | Test De	
Anaplasmosis		Y			Need more info/we have a full menu of antibody and molecular pathogen tests: Quest Diagnostics: Results for anaplasma
Babesiosis/Babesia (B. microti, B. duncani)		Y			Need more info/we have a full menu of antibody and molecular pathogen tests: Quest Diagnostics: Results for *babesia*
Bartonella infections *(henselae, elizabethae, quintana, vinsonii*)		Y			Need more info/we have a full menu of antibody and molecular pathogen tests: Quest Diagnostics: Results for *bartonella*
Human Monocytic Ehrlichiosis (HME) - *Ehrlichia chaffeensis*		Y			Need more info/we have a full menu of antibody and molecular pathogen tests: Quest Diagnostics: Results for *ehrlichia*
Rickettsiosis (*Rickettsia typhi, Rickettsia rickettsii*)		Y			Need more info/we have a full menu of antibody and molecular pathogen tests: Quest Diagnostics: Results for *rickettsia*
Rocky Mountain spotted fever		Y	6419		
Parvovirus		?			See below
Parvovirus B19	1st tier	Y			Need more information; we have a full menu for Parvovirus B19: Quest Diagnostics: Results for parvovirus
Cytomegalovirus		Y			Need more info/have a full CMV menu: Quest Diagnostics: Results for CMV
Toxoplasma gondii		Y			Need more info/have a full *T. gondii* menu: Quest Diagnostics: Results for *toxoplasma*
Anaplasma *phagocytophilum*		Y			Need more info/have a full *Anaplasma sp*. Menu: Quest Diagnostics: Results for Anaplasma
Tickborne Encephalitis Virus					Need more information on pathogen of interest. A high-level of our offering for viral encephalitis: Quest Diagnostics: Results for



Blood Test	Workflow	Can Quest Provide? (Y/N)	Test Code(s)	Notes on ICD-10 codes	Notes (other)
					encephalitis virus
Chlamydophila pneumoniae		Y			Need more info/we have a broad menu of antibody and molecular tests: Quest Diagnostics: Results for *chlamydo pneumo*
Mycoplasma pneumoniae		Y			Need more info/we have a broad menu of antibody and molecular tests: Quest Diagnostics: Results for *mycoplasma pneumo*
Human granulocytic anaplasmosis (HGA) - Anaplasma *phagocytophilum*		Y			Need more info/we have a broad menu of antibody and molecular tests: Quest Diagnostics: Results for Anaplasma phagocytophilum
Coxsackievirus		Y			Need more info/we have a broad meu of antibody and molecular tests: Quest Diagnostics: Results for coxsackie
West Nile Virus		Y			Need more info/we have a broad meu of antibody and molecular tests: Quest Diagnostics: Results for coxsackie
Powassan Virus		N			
Anti-Streptococcal A		Y	265		Anti-Streptolysin O Antibody (ASO) | Test Detail | Quest Diagnostics
INFLAMMATION					
CCL-5					
CCL-11					
G-CSF					
IL-1b					
IL-2					
IL-6					
IL-8					
IL-10					
IL-13					
Interferon gamma					
Pro-calcitonin					
SCD-40L					
TGF-b1					
TGF-b2					
TNF-a					
MMP-9					
IMMUNE					
Natural Killer Cell					LDN? Rapamycin?
CMP					
CBC with Diff					
	COAGULATION				
Alpha-2 macroglobulin					
D-Dimer					
Fibrinogen					
L-selectin					
E-selectin					
P-selectin					
VCAM-1					
Veg-F					
Von Willebrand Factor FVIII					





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