CLINICAL CARE GUIDE

Managing ME/CFS, Long COVID, & IACCs

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CLINICAL CARE GUIDE:

Managing ME/CFS, Long COVID, and Infection-Associated Chronic Conditions (IACCs)

Acknowledgements

This guide is the product of a dedicated interdisciplinary team of clinicians, educators, researchers, and lived experience experts who share a common mission: to improve care for individuals living with ME/CFS, Long COVID, and other infection-associated chronic conditions (IACCs).

We are profoundly grateful to the contributors who brought their expertise, insight, and clinical experience to this project. Their thoughtful contributions reflect years of patient care and an ongoing commitment to expanding our collective understanding of these complex conditions. We also acknowledge the vital role of those living with these conditions. Their lived experiences have been central to the development of this guide and continue to inform how the medical community can grow in its approach to care.

Whether you are encountering these illnesses for the first time or building upon years of experience, we hope this guide offers you practical, thoughtful, and clinically useful tools. Above all, we hope it supports a shared commitment to compassionate, patient-centered care.

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INTRODUCTION

Across the world, a growing number of individuals are experiencing persistent symptoms following infection—most notably after SARS-CoV-2. Among these, a substantial subset of patients go on to meet the established diagnostic criteria for Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS). While Long COVID represents a broad and evolving category encompassing diverse pathophysiological processes, this Clinical Care Guide focuses specifically on the group of people whose clinical presentation aligns with ME/CFS and related infection-associated chronic conditions (IACCs).

This guide was developed by the Bateman Horne Center (BHC), a U.S.-based nonprofit organization and Center of Excellence dedicated to advancing clinical care, research, and education for ME/CFS, Long COVID, and related post-infectious conditions. We also recognize that people with similar clinical presentation, but lacking documentation of infection at onset, may also benefit from this approach to care.

The guide is designed primarily for healthcare professionals practicing within the United States, recognizing that health systems, medication access, insurance structures, and scopes of practice vary widely across states and countries.

Even so, the principles of care, diagnostic reasoning, and patient-centered approach outlined here are intended to be adaptable globally. We hope the underlying framework—emphasizing evidence-informed, multidisciplinary, and compassionate management—will support clinicians, researchers, and policymakers worldwide in improving care for this underserved patient population.

The intent of this guide is not to address every presentation or complication within the full spectrum of Long COVID (such as organ-specific damage, vascular or thromboinflammatory injury, or other sequelae requiring subspecialty evaluation). Rather, it aims to provide practical, immediately applicable clinical guidance for managing the functional, autonomic, and multisystem impairments characteristic of ME/CFS and overlapping post-infectious syndromes.

Effective care for these patients requires coordination among primary care providers, specialists, allied health professionals, and caregivers—and, most importantly, a therapeutic alliance grounded in mutual respect, shared decision-making, and acknowledgment of lived experience. Together, these efforts can reduce the burden of illness and improve long-term outcomes for individuals living with ME/CFS, Long COVID, and other IACCs.

This first edition of the Clinical Care Guide reflects current best practices and clinical experience. As scientific understanding evolves, future editions will expand and refine these recommendations to reflect emerging evidence, broadened collaboration, and the diversity of patient experiences across regions and healthcare systems.

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CHAPTER 1: NAVIGATING CLINICAL UNCERTAINTY

Zeest Khan, MD, March 2025

The practice of medicine is built on pattern recognition and evidence-based interventions, but post-infectious conditions like Long COVID and ME/CFS disrupt this framework. Their heterogeneous presentation, evolving research, and lack of established biomarkers leave clinicians facing diagnostic and treatment uncertainty—a discomforting challenge in a field that values precision. Yet, uncertainty does not mean inaction. As clinicians, our role is not just to provide definitive answers but to guide patients through structured, personalized, and evolving care, even when we do not have all the answers.

Challenges in Treating Long COVID & ME/CFS

Both patients and clinicians face significant obstacles in managing these conditions:

- Patients experience long wait times, limited treatment options, and medical skepticism/gaslighting. Many arrive at appointments exhausted, cognitively impaired, and wary of being dismissed.
- Clinicians must contend with evolving recommendations, limited patient visit times, the absence of definitive biomarkers, and the frustration of seeing patients who do not improve despite best efforts. Traditional diagnostic models often fail when dealing with multisystem dysfunction and fluctuating symptoms.

Given these challenges, a shift in clinical approach is necessary—one that moves beyond rigid protocols and toward patient-centered, adaptable, and collaborative care.

Embracing a Collaborative Care Model

In uncertain clinical landscapes, the patient-clinician relationship is one of the most valuable tools available. Instead of positioning clinicians as sole authorities, an integrated approach—where providers and patients share knowledge and decision-making—can enhance care quality.

- Recognize the patient's lived experience. Many patients have spent significant time tracking symptoms, researching treatments, and testing their own limits. Clinicians should validate and leverage this knowledge while providing a framework for safe, structured treatment trials.
- Trial-and-pivot over trial-and-error. Without clear guidelines, treatment often relies on carefully monitored interventions rather than definitive cures. Adjusting strategies based on patient response is not failure—it is informed decision-making.
- Set clear expectations. Patients and providers must establish realistic treatment goals, acknowledge that progress may be slow, and agree on boundaries—clinicians should not feel pressured to prescribe unproven treatments, and patients should not be criticized for declining interventions due to cost or side effects.

CHAPTER 1: NAVIGATING CLINICAL UNCERTAINTY

Zeest Khan, MD, March 2025

Building a Practical Clinical Framework

To navigate uncertainty effectively, providers can implement structured approaches to care:

1. Prioritize regular check-ins. Long COVID and ME/CFS symptoms fluctuate, making frequent assessments critical. Given time constraints, appointments should focus on one or two key issues per visit to ensure meaningful progress.
2. Support goes beyond prescriptions. Helping patients secure workplace/school/home accommodations, disability resources, and access to interdisciplinary care is just as crucial as medication-based management.
3. Referrals should be strategic. Given the multisystem impact of these conditions, interdisciplinary care is often needed. However, referrals should be intentional, with clear questions for specialists rather than a simple transfer of care.
4. Guide patients toward reputable resources. Patients inevitably turn to online sources, where accurate information coexists with misinformation. Clinicians should recommend trusted organizations to empower informed decision-making.

Redefining How We Approach Complex Illnesses

Long COVID and ME/CFS challenge conventional clinical practice, but they also present an opportunity to reshape how we approach medicine in the face of uncertainty. By embracing adaptability, patient collaboration, and evidence-informed clinical reasoning, providers can deliver meaningful care despite incomplete research.

Navigating uncertainty is not about waiting for perfect data—it is about using the best available knowledge, engaging in structured clinical reasoning, and remaining open to new insights. This mindset shift not only benefits patients with post-infectious conditions but strengthens our ability to manage other complex, poorly understood illnesses across medicine.

CHAPTER 2: BASICS OF LONG COVID, ME/CFS, AND COMORBIDITIES

Introduction

There is a growing subset of Long COVID patients who now meet the criteria for ME/CFS[178], resulting in an even greater need for clinicians to recognize these overlaps and apply ME/CFS care principles to both populations.

Understanding the ME/CFS diagnostic criteria is crucial for developing effective treatment strategies for Long COVID patients. ME/CFS serves as a blueprint for managing infection-associated chronic conditions (IACCs), offering structured assessment and management approaches that help improve function and quality of life. Even individuals who do not meet the full ME/CFS diagnostic criteria but share overlapping symptoms may benefit from these same care principles.

2.1 Defining Long COVID

The National Academies of Sciences, Engineering, and Medicine (NASEM)[125] defines Long COVID as:
"*Long COVID is an infection-associated chronic condition that occurs after SARS-CoV-2 infection and is present for at least 3 months as a continuous, relapsing and remitting, or progressive disease state that affects one or more organ systems*."

2.2 Defining ME/CFS

In the United States, the most widely used diagnostic criteria for ME/CFS are those established by the 2015 Institute of Medicine (IOM)[72], now known as the National Academy of Medicine (NAM). Internationally, other commonly referenced case definitions include the Canadian Consensus Criteria (CCC)[25] and the International Consensus Criteria (ICC).[26]

The NAM criteria outline the following core diagnostic features:
A patient must meet all the following criteria for a diagnosis of ME/CFS:

- Impairment of normal function accompanied by fatigue lasting at least 6 months
- Post-Exertional Malaise (PEM)*
- Unrefreshing sleep*
- Cognitive impairment* and/or orthostatic intolerance

*Must be moderate to severe and present at least 50% of the time.

More about the core criteria

1. A substantial reduction or impairment in ability to engage in pre-illness levels of activity (occupational, educational, social, or personal life) that:
    a. lasts for more than 6 months

b. is accompanied by fatigue that is:
   - often profound
   - of new onset (not life-long)
   - not the result of ongoing or unusual excessive exertion
   - not substantially alleviated by rest

2. Post-exertional malaise (PEM) refers to a significant worsening of symptoms and functional decline following physical, cognitive, or emotional exertion that would have been tolerable before illness onset. Key characteristics include:
   a. A delayed onset of symptom exacerbation, typically appearing 12-48 hours after the triggering activity.
   b. A prolonged recovery period lasting days to weeks, during which patients experience a "crash" state with intensified symptoms.
   c. Unpredictable triggers that may include minimal exertion, sensory stimulation (light/sound), or environmental stressors.
   d. A severity and duration of symptoms disproportionate to the triggering activity.
   e. PEM represents a pathological response to exertion that distinguishes ME/CFS from other fatigue-related conditions and serves as a cardinal diagnostic feature.
3. Unrefreshing sleep*
   a. Patients with ME/CFS wake unrefreshed after a full night's sleep.
   b. This may occur despite the absence of a primary sleep disorder.

Additional symptoms

To be diagnosed with ME/CFS, patients must have at least one of the symptoms below. These are in addition to the first three required criteria above.

1. Cognitive impairment* — problems with thinking, memory, executive function, and information processing. They also may have attention deficit and impaired psychomotor functions.
   a. All can be exacerbated by exertion, prolonged upright posture, stress, or time pressure.
   b. This may have serious consequences on a patient's ability to maintain a job or attend school full time.

2. Orthostatic intolerance (OI) — a worsening of symptoms upon assuming and maintaining upright posture. Reduced cerebral arterial blood flow has been consistently observed, but this testing is not readily available clinically.

Note: while heart rate and blood pressure changes may support a diagnosis of OI, it's not required.
   a. Symptoms including lightheadedness, fainting, increased fatigue, cognitive worsening, headaches, or nausea are worsened while upright (either standing or sitting). Symptoms are improved (though not necessarily fully resolved) with lying down.
   b. Orthostatic intolerance is often the most bothersome and functionally limiting manifestation of ME/CFS, especially among adolescents.

* The frequency and severity of these symptoms must be evaluated. The NAM committee specified, for diagnosis, patients should have symptoms at least half of the time (50%) with moderate, substantial, or severe intensity.

CHAPTER 2: BASICS OF LONG COVID, ME/CFS, AND COMORBIDITIES

2.3 Additional Symptoms Supporting Diagnosis[72,95]

Systems Affected	Symptoms
Immune System	Acute infection-like onset, flu-like symptoms, sore throat, tender lymph nodes, increased infections, new or worsened sensitivities (foods, medications, chemicals). Poor NK cell cytotoxicity correlates with severity
Neurological System	Impaired psychomotor function, muscle weakness, twitching, instability, ataxia, sensory sensitivities (light, noise, touch)
Autonomic & Endocrine Systems	Cold extremities, temperature dysregulation, excessive sweating, loss of appetite, alcohol intolerance, weight changes
Pain Manifestations	Headaches, myalgia, arthralgia, neuropathic pain
Gastrointestinal & Genitourinary Systems	IBS-like symptoms, gastroparesis, interstitial cystitis, chronic nausea

2.4 Common Comorbid Conditions of ME/CFS[12]

AUTONOMIC DYSFUNCTION **Postural Orthostatic Tachycardia Syndrome (POTS), Neurally Mediated Hypotension (NMH), Orthostatic Hypotension**	**RHEUMATOLOGICAL DISORDERS** **Fibromyalgia, Ehlers-Danlos Syndrome, Temporomandibular Joint Dysfunction, Sicca Syndrome (dry eyes/mouth)**	**NEUROLOGICAL DISORDERS** **Sensory Hypersensitivities (light, sound, touch, odors or chemicals), Poor Balance, Migraine Headaches, Peripheral Neuropathy, Small Fiber Neuropathy**
IMMUNOLOGICAL DISORDERS **New or worsened allergies, Mast Cell Activation Syndrome, Multiple Chemical Sensitivites, Chronic infections & immunodeficiencies**	**GASTROINTESTINAL DISORDERS** **Food Allergy and Intolerances, including to milk protein, Gut motility issues, Celiac Disease, Irritable Bowel Syndrome, Small Intestinal Bacterial Overgrowth**	**ENDOCRINE/METABOLOIC DISORDERS** **Hypothyroidism, Hypothalamus-Pituitary-Adrenal Axis dysregulation (low normal or flattened cortisol curve), Metabolic Syndrome**
SLEEP DISORDERS **Sleep Apnea, Restless Leg Syndrome, Periodic Limb Movement Disorder**	**PSYCHIATRIC DISORDERS** **Secondary Anxiety, Secondary Depression**	**GYNECOLOGICAL DISORDERS** **Endometriosis, Premenstrual Syndrome, Vulvodynia**
MISCELLANEOUS: Interstitial Cystitis, Overactive Bladder, Nutritional deficiencies. Vitamin B12 and D deficiencies, Obesity		

2.5 Assessment & Diagnosis

- The U.S. Clinician Coalition offers Tier 1, Tier 2, and Tier 3 diagnostic tests. For additional guidance and information, please visit: https://mecfscliniciancoalition.org/.
- **Symptom History & Functional Impact:**
  - Document PEM triggers and functional capacity over time.
  - Use validated symptom logs or PEM questionnaires.[32,77]
- **Key Diagnostic Tests:**
  - **Orthostatic testing:** 10-Minute NASA Lean Test (passive stand), Active Stand Test[112], Tilt Table Test (TTT)[133]
  - **Autonomic testing:** QSART, Valsalva, TTT if available
  - **Small fiber polyneuropathy testing:** Skin Biopsy[134]
  - **Standard labs:** CBC, CMP, thyroid function tests, vitamin B12 and folate, iron studies, ANA, ESR/CRP, rheumatoid factor, tissue transglutaminase (celiac testing), total immunoglobulins, vitamin D, AM cortisol and DHEA, phosphorus, magnesium, urinalysis, overnight sleep study

2.6 Management Strategy Overview

Please see the respective chapter for more details and guidance.

Area of Management	Key Interventions
Energy Management	Pacing, structured rest, preventing PEM crashes [79,182]
OI Management	IV saline, oral fluids, electrolyte supplements, compression clothing, pharmacological supports (see OI section)[17,112,161]
Neuroinflammation & Pain	Low-dose naltrexone (LDN), pyridostigmine, dextromethorphan (DM)[107,185]
GI & Nutritional Support	Low-FODMAP diet, low-histamine diet, probiotics, motility agents, anti-inflammatory diets[33,127]
Mast Cell Activation Syndrome	MCAS stabilizers, antihistamines, mast cell-directed biologics[55,117,118]
Sleep	Sleep hygiene, sedative-hypnotics, dual orexin receptor antagonists, benzodiazepines, melatonin receptor agonists (e.g., Remeron), antidepressants (e.g., doxepin, trazodone, mirtazapine, tricyclic antidepressants), herbals and supplements (e.g., magnesium glycinate), and antihistamines[12]
Cognitive Impairment	NAC and guanfacine, omega 3 fish oil, phosphatidylserine, phosphatidylcholine, *strategic* use of stimulants (be mindful of PEM)[124,171]

CHAPTER 3: ASSESSING IMPAIRED FUNCTION (CLINICAL EVALUATION)

Introduction

Patients with ME/CFS, Long COVID, and other infection-associated chronic conditions (IACCs) may experience profound impairments that often exceed those seen in conditions like multiple sclerosis, congestive heart failure, and chronic obstructive pulmonary disease. Unlike other chronic illnesses, these conditions are characterized by post-exertional malaise (PEM)—a worsening of symptoms and decline in function after minimal physical, cognitive, or emotional exertion.

Traditional diagnostic markers and lab tests often fail to capture the extent of disability in these patients. To accurately assess impairment, clinicians must rely on patient history, questionnaires, validated symptom screening tools, and objective tests for autonomic dysfunction and cognitive impairment.

This chapter outlines a structured clinical approach to evaluating impairment, incorporating key assessment tools, functional capacity measures, and considerations for documenting disability.

3.1 Assessment Tools

These instruments, while not ME/CFS-specific, support diagnosis and documentation of decreased function and symptom variability:

- Good Day/Bad Day Questionnaire: *captures function on baseline/good days and PEM/crashed/bad days and hours of upright activity (HUA)*
- 10-Minute NASA Lean Test **or Tilt Table Test**: *in-office passive standing test to assess for orthostatic intolerance*
- PROMIS Fatigue and Cognitive Function Questionnaires (4 or 7): *provides a validated measure of fatigue severity compared to population norms*
- SF-36 [RAND-36] Functional Assessment Scale: *measures health-related quality of life and daily limitations*
- **FUNCAP** – *assists in documenting support needs and loss of independence across multiple domains*
  - FUNCAP55: *offers more detail*
  - FUNCAP27: *shorter*

3.2 Clinical Documentation Tips

- Clearly **define limitations of function, impairment and PEM triggers.**
- Specify **tolerance for upright posture** (e.g., "Unable to stand for more than 10 minutes without symptoms").
- Emphasize **symptom variability & impact on daily life.**
- Use **objective tests** to supplement patient-reported symptoms.

3.3 Functional Capacity

Assessing Daily Function & Impairment

Functional impairment in ME/CFS and Long COVID is not simply about fatigue—it is a complex loss of energy production and autonomic stability that fluctuates unpredictably.

Key Functional Assessment Tools:

- **Hours of Upright Activity (HUA) Metric**
  - Documents total daily hours spent standing, walking, or ***sitting upright with feet on the ground.***
  - Provides an estimate of functional impairment over time.
- **Good Day (baseline day)/Bad Day (crashed/PEM day) Questionnaire**
  - Captures fluctuations in daily function and symptoms.
  - Is essential for disability documentation—patients may have occasional "good days" but remain severely impaired overall.
  - Helps define workplace, school, home modifications and accommodations.
- **DePaul Symptom Questionnaire**
  - Is helpful once a diagnosis of ME/CFS has been made.
  - Distinguishes PEM from generalized post-exertional fatigue seen in depression or deconditioning.
  - **The DSQ-PEM, Section 10 Questionnaire has been revised to improve specificity.**
  - Identifies the presence and severity of PEM.
- **PROMIS Fatigue Scale**
  - Provides a validated measure of fatigue severity compared to population norms.

3.4 Cognitive Dysfunction Screening

Assessment Approach

1. **Initial Symptom Interview (see Appendix B for assistive cognitive strategies)**
   - Consider referral to a neurocognitive specialist and/or speech therapist.
   - Patient self-reporting of cognitive symptoms is highly reliable and should be documented in detail.
   - Key screening questions:
     - "Do you experience problems with concentration, memory, word-finding, or mental clarity?"
     - "Do cognitive tasks trigger or worsen your other symptoms?"
     - "Have you noticed specific situations where your cognitive function is worse?"
     - "How has this affected your work, studies, or daily activities?"
   - Ask questions around iADLs like driving, medication management, appointment management, finances, household safety (i.e., leaving the stove on), etc.
2. **Practical Functional Assessment**
   - Document specific cognitive activities that:
     - Can no longer be performed.
     - Can only be performed for limited durations.
     - Can only be performed during "good" periods.
     - Trigger post-exertional malaise.

For severely impaired patients, cognitive assessments should be administered slowly and adapted to prevent PEM.

3.5. Autonomic Dysfunction & Orthostatic Intolerance (OI) Testing

OI is highly prevalent in ME/CFS and Long COVID, exacerbating functional impairment by reducing cerebral blood flow, worsening PEM, and contributing to cognitive dysfunction.[22,174]

The 10-Minute NASA Lean Test (a standardized passive stand test)

Purpose: Detects Postural Orthostatic Tachycardia Syndrome (POTS), Orthostatic Hypotension (OH), or blood pooling that contributes to impairment, and documents signs and symptoms during testing.

Procedure:

1. **Supine rest:** Measure heart rate (HR) and blood pressure (BP) after 5-10 minutes of quiet rest.
2. **HR & BP measurements:** Taken every minute while standing, leaning against the wall. See 10-Minute NASA Lean Test (NLT) instructions.
3. **Threshold for an established diagnosis of OI subsets:**
    - **POTS: HR increase ≥30 bpm (≥40 bpm in adolescents)** within 10 minutes with stable BP, or rise of HR> 120 bpm.
    - **OH: BP drop ≥20 systolic or ≥10 diastolic** within 3 minutes.
    - **Acrocyanosis** (purple discoloration of legs) or narrowed pulse pressure (<25% of systolic BP) suggest circulatory dysfunction.
4. **Pulse Pressure/SBP:** Calculate SBP (minus) DBP/SBP. Values < 25% indicates worsening venous return to the right side of the heart and decreased cardiac output. While not widely taken into consideration, this measure can provide added clarity to the NLT.

Clinical Implications:

- Many patients unknowingly reduce upright activity to avoid OI symptoms. Alternatively, if patients aren't recognizing their OI, they can continue the activity and further exacerbate and aggravate symptomatic consequences.
- Identifying OI allows targeted treatment (fluid loading, increased sodium intake, compression, medications).[17,106,112]
    - More on this in Chapter 7, Orthostatic Intolerance.

Conclusion

Assessing impairment in ME/CFS and Long COVID requires a shift away from traditional diagnostic frameworks and biomarkers toward careful evaluation of activity tolerance, sustainability, and symptom variability. These conditions often leave individuals unable to meet the demands of daily life, despite appearing physically intact during brief clinical encounters.

Through structured history-taking, validated questionnaires, cognitive and orthostatic testing, and attention to post-exertional malaise, clinicians can more accurately characterize the severity of impairment, support appropriate treatment strategies, and provide documentation necessary for accommodations or disability determinations. Above all, the focus should remain on assessing not only what a patient can do once, but what they can do consistently and without triggering physiological decline.

For more details and guidance, see the Disability and Accommodations chapter.

CHAPTER 4: POST-EXERTIONAL MALAISE (PEM)

Introduction

Post-exertional malaise (PEM) is the cardinal feature of ME/CFS and is present in a significant subset of Long COVID patients. PEM represents a distinct, pathological response to exertion that fundamentally differs from normal fatigue or post-exertional fatigue. It manifests as a multi-system deterioration following minimal physical, cognitive, emotional, orthostatic, sensory, or environmental exertions.[12]

For individuals with ME/CFS, exertion intolerance stems from documented abnormalities in energy metabolism at both cellular and systemic levels, not from deconditioning. This pathophysiological reality explains why graded exercise therapy (GET) is contraindicated in this population. Multiple studies have shown GET can trigger severe PEM episodes and potentially cause lasting functional deterioration in ME/CFS patients.[89,183]

Current evidence-based guidelines from the CDC, NICE, WHO, and other international health authorities recommend energy management and pacing strategies as the primary approach to activity management, specifically avoiding progressive increases in activity that characterize traditional graded exercise therapy.

This chapter provides:

- A structured framework for accurately identifying and assessing PEM in clinical practice.
- Validated screening tools and diagnostic questions to differentiate PEM from other forms of exertion intolerance.
- Evidence-based strategies for managing PEM through energy conservation, pacing, and appropriate activity modification.
- Patient education resources to support pacing and improve outcomes.

4.1 Key Characteristics of PEM

PEM is defined as a physiological, delayed, and prolonged worsening of symptoms and function following minimal activity. The key distinguishing features include:

- **Delayed onset:** Symptoms often appear 12 to 48 hours (and even up to 72 hours) after exertion, creating a temporal gap making it difficult for patients to link cause and effect.[32,35,77]
- **Prolonged recovery:** Worsening of symptoms can persist for days, weeks, or longer before returning to baseline.[77,99,177]
- **Multisystem manifestation:** PEM affects multiple body systems simultaneously, with worsening of:
  - Cognitive function (concentration, memory, word-finding difficulties)
  - Autonomic regulation (orthostatic intolerance, temperature dysregulation)
  - Immunological symptoms (flu-like symptoms, lymph node tenderness)
  - Neuromuscular function (muscle weakness, pain, unrefreshing sleep)[32,35]
- **Disproportionate severity:** The intensity and duration of symptom exacerbation are substantially out of proportion to the triggering activity, with even minor exertion potentially causing severe PEM episodes.[32]

- **Diverse triggering factors:** PEM can be provoked by:
  - Physical activity (even light housework or self-care/ADLs)
  - Cognitive exertion (reading, decision-making, screen time)
  - Social interaction (conversations, texting, meetings, gatherings)
  - Emotional experiences (both positive and negative)
  - Sensory stimulation (light, sound, motion)
  - Orthostatic stress (standing, sitting upright)
  - Environmental exposures (temperature extremes, chemicals, fragrances)

4.2 Pathophysiology of PEM

Impaired Energy Metabolism

PEM is characterized by disruptions in aerobic energy production, leading to reduced oxygen utilization, mitochondrial dysfunction, and early anaerobic threshold activation. This has been demonstrated in 2-day cardiopulmonary exercise testing (CPET), which shows a reproducible drop in VO_2 max and work capacity on the second day—an abnormal response not seen in deconditioning.[88,113,157]

Neuroimmune Dysfunction

- **Inflammatory cytokines (IL-6, IL-10, TNF-α)** increase following exertion, contributing to neuroinflammation and worsened symptoms.[23,35,99]
- **Autonomic dysfunction (orthostatic intolerance, heart rate variability changes)** impairs blood flow (perfusion) and oxygen delivery to tissues.[22,174]
- **Elevated oxidative stress and metabolic disturbances** interfere with normal ATP metabolism. There may also be too much ATP being released by some cells, leading to the cell danger response.[122]

These findings confirm that PEM is a distinct pathophysiological process, not simply "fatigue" or "deconditioning."

4.3 Screening Questions to Identify PEM

Clinicians can use the following **targeted questions** to differentiate PEM from other forms of exertion intolerance. When asking, allow the patient time to reflect, and offer the sub-bulleted examples as prompts if they have difficulty responding.

1. **What happens after you engage in activities you previously tolerated?**
   - Do you experience symptoms such as brain fog, dizziness, muscle pain, or flu-like feelings that were not present before?
2. **What symptoms do you experience while you are actively performing physical or cognitive activity?**
   - Do you experience in the moment/immediate symptoms of overexertion?

3. **Do you also experience a "payback" of new or worsening symptoms or declines in physical or cognitive functional ability later in the day or in the days that follow, even if symptoms experienced during exertion have resolved or regressed?**
   - Can it take **12-48 hours** before you experience a worsening of symptoms?
   - Note: When a patient is presenting with uncontrolled or poorly managed symptoms, the cause-and-effect relationship of PEM can be difficult for patients to recognize. For individuals with severe ME/CFS, delayed onset may be difficult to detect due to their severely limited baseline function and persistent high symptom levels.
4. **How long does it take for you to recover after overexertion?**
   - Do you remain symptomatic for days, weeks, or longer before returning to baseline?
5. **What activities trigger this response?**
6. **Do you experience push-crash cycles?**
   - Do you find yourself having "good" days when you overdo activity, only to "crash" for days afterward?

If the patient answers **yes** to these questions, **PEM is likely present**, and graded exercise should be avoided.

4.4 PEM Screening Tools:

Clinical Tools

- Good Day/Bad Day Questionnaire – Tracks variability in symptoms and function between Good Days (baseline illness) and Bad Days (PEM/crash days).
- Symptom Logs & Activity Diaries – Helps patients recognize PEM patterns.
- FUNCAP Questionnaires -Structured tools designed to assess functional capacity and disability across multiple domains, helping to capture the impact of PEM on daily life and support needs.

Validated Screening Tools

- DePaul Symptom Questionnaire (DSQ-PEM section, 10 question version) – The DSQ-PEM is a helpful tool to assess frequency and severity of PEM *once a diagnosis of ME/CFS is established*.
- PROMIS Fatigue Scales (4 and 7) – Measures fatigue impact.

4.5 Objective Testing (if needed)

While PEM is best diagnosed through clinical history, the 2-day CPET test can provide objective evidence of how physical exertion can lead to reduced energy production and PEM:

- **2-Day Cardiopulmonary Exercise Test (CPET)**
  - Demonstrates a drop in oxygen consumption (VO_2 max) and energy production on day 2[113,157]
  - Confirms metabolic dysfunction, autonomic dysregulation, and impaired recovery
  - Often not feasible due to limited access to professionals trained in CPET and the potential for severe or prolonged post-exertional malaise (PEM) following testing.
  - Can be useful for disability documentation

4.6 Preemptive and Recuperative Support for CPET Patients

Since CPET can induce severe PEM, proactive and recuperative strategies can help minimize risk.

Pre-test preparation:

- Hydration & electrolyte loading (e.g., modestly increased fluids and sodium)
- Mast cell stabilizers (antihistamines, montelukast, cromolyn, etc.) to reduce inflammatory response[118]
- Preemptive rest (limit activity in the days before testing)
- Consider alternative documentation for disability if CPET is not feasible

Post-test recovery:

- IV hydration therapy (saline + electrolytes)
- Neuroinflammation management (low-dose naltrexone, omega-3s, curcumin)
- Orthostatic support (compression garments, beta-blockers, fludrocortisone)
- Work and school accommodations (preemptive excused absences, flexible schedules)

4.7 Management of PEM

1. Pacing & Energy Conservation

The core principle of PEM management is staying within the "Energy Envelope" or the functional capacity to prevent crashes. The following can be used as basic guidance for your patients.[79,182]

Pacing Strategies:

- Activity shaping – Reduce task intensity, schedule structured breaks[79,182]
- Symptom-contingent rest – Learn early warning signs and symptoms of overexertion and stop, modify or adjust the activity when these signals occur.
- Heart rate-based pacing – Use wearables to prevent exceeding anaerobic threshold.
- Cognitive pacing – Limit screen time, reduce overstimulation, break complex tasks into smaller components, and schedule cognitive rest periods.
- Prioritization – Focus on essential activities, delegate when possible.
- Schedule pre-emptive and recuperative rest before/after activities.

Practical Tools:

- Timers – Enforce structured rest
- Postural adjustments – Perform activities seated, with feet elevated if possible, or lying down.
- Adaptive equipment – Shower chairs, mobility aids, reach tools
- Step count – Helps monitor physical activity limits
- Symptom tracking devices– Resting heart rate (RHR), active heart rate monitoring, heart rate variability (HRV), and sleep assessment tools – can help patients gauge their energy capacity at the start of each day.

2. Managing Crashes

There is no definitive treatment that can resolve an episode of PEM. Management of PEM relies upon a strategy of mitigating symptoms and reducing factors that contributed to the onset and prolongation of PEM with the goal of lessening the duration and intensity of the episode.

If PEM occurs:

- Immediate Actions:
  - Stop all activity and rest in a quiet, dark space
  - Increase hydration and electrolytes
  - Reduce sensory input (earplugs, eye masks, low-light room)
- Long-Term Prevention Strategies:
  - Plan rest days after exertion
  - Structure frequent rest in between exertional activities.
  - Identify early/in the moment signs of PEM and stop, rest, modify or delegate the activity.
  - Effective management of all other symptoms and comorbidities of ME/CFS is critical for helping patients avoid or reduce the frequency, intensity, and duration of PEM.

3. Supportive Interventions: To reduce intensity, severity, and duration of PEM

- IV hydration with IV NS 1-3 liters per week for more severe PEM episodes[17]
- Dampen excessive sympathetic nervous system signaling - consider benzodiazepines, alpha blockers, beta-blockers, etc.
- Techniques that increase vagal/parasympathetic tone – mediation, deep breathing techniques
- Sleep optimization and pain management[72]
- Dextromethorphan (DM) – 15 mg soft q4-6 hrs, up to TID dosing
- LDN (Low-Dose Naltrexone) – If initiated outside of PEM, may reduce neuroinflammation and PEM severity and frequency[107,185]

Share the **PEM Crash Survival Guidebook** with patients so they can plan and receive your help accordingly.

4.8 Key Takeaways

1. PEM is a hallmark of ME/CFS and occurs in a severe subset of Long COVID patients. It is a pathological response to exertion, not just fatigue or malaise.
2. Screening questions and validated tools help identify PEM.
3. Avoiding PEM improves symptoms and long-term function.
4. Graded exercise therapy (GET) nearly universally triggers PEM and is thus harmful and should not be used. For more, see Chapter 16, Allied Health Professionals.
5. Objective testing (e.g., CPET) can help document PEM, but history-taking remains the primary diagnostic tool.
6. Pacing is the key to managing PEM, focusing on staying within energy limits, using structured rest, and preventing crashes.[79,182]

CHAPTER 5: SLEEP CHALLENGES

Introduction

Sleep disturbances are common in ME/CFS and Long COVID. Primary sleep disorders need to be evaluated for, but are often not the cause of sleep disturbances. Sleep dysfunction in ME/CFS and IACCs is often driven by autonomic dysregulation, neuroinflammation, mast cell activation, and pain. Standard sleep hygiene recommendations alone are often inadequate in addressing these underlying pathophysiological factors.[25,26,72]

5.1 Assessment of Sleep Disturbances

Rule Out Primary Sleep Disorders

- Consider formalized sleep studies.
- If a primary sleep disorder is present (e.g., OSA), treat accordingly while continuing to address ME/CFS-related sleep dysfunction.

Identify Common ME/CFS Related Sleep Disturbances

- **Non-restorative sleep:** Patients wake up feeling unrefreshed despite adequate duration.[25,26,72]
- **Delayed Sleep Phase Syndrome (DSPS):** Difficulty falling asleep at a typical bedtime, leading to sleep-wake cycle dysregulation.[14,72]
- **Frequent night awakenings:** May relate to autonomic instability (POTS/OI)[22,106], pain, or mast cell activation.[54,163]
- **Hyperarousal & excessive sympathetic tone:** Patients often have difficulty "turning off" their nervous system at night. They may describe a "tired but wired" feeling.[51,136]

5.2 Management of Sleep Dysfunction

1. Address Underlying Drivers of Sleep Dysfunction

- **Autonomic dysfunction:**
  - **Alpha-adrenergic blockers** (e.g., clonidine, prazosin, guanfacine) may help reduce nighttime sympathetic overactivity, but could also worsen orthostatic hypotension (OI).[51,136]
  - **Beta-blockers** (e.g., propranolol, atenolol, metoprolol, etc.) can assist in reducing hyperadrenergic states contributing to insomnia.[106,111]
- **Neuroinflammation:**
  - **Low-Dose Naltrexone (LDN)** can modulate neuroinflammation and improve sleep quality.
    - Note: LDN can cause vivid dreams in some patients, morning dosing may be preferred.[107,185]
  - **Anti-inflammatory supplements:** Curcumin, omega-3s, flavonoids (e.g., quercetin).
- **Mast cell activation:**
  - **H1 and H2 blockers** (e.g., diphenhydramine, cetirizine, famotidine, hydroxyzine) may reduce histamine-induced night awakenings.[55,117,163]
  - **Cromolyn sodium or ketotifen** throughout the day and before bed can stabilize mast cells.[118,170]
- **Pain-related sleep disruption:**
  - **Low-dose amitriptyline or nortriptyline** can be used for pain modulation and sleep initiation.[23]
  - **Gabapentin or pregabalin** may help in patients with neuropathic pain impacting sleep.[43,109]

2. Optimize sleep hygiene (adjunctive, not standalone therapy)

- **Reduce blue light exposure:** Use blue-light blocking glasses or night mode settings 2-3 hours before bedtime.
- **Maintain a consistent sleep schedule:** Even if sleep quality is poor, maintaining routine sleep-wake times can help regulate circadian rhythm.
- **Control sleeping environment:**
  - Cool, dark, and quiet room
  - Weighted blankets for autonomic calming
  - White noise machines or ear plug to block disruptive stimuli

3. Pharmacological & Supplement Options

- **Melatonin:** Useful for DSPS but should be used in low doses (0.5-3 mg) as higher doses can be stimulating.
- **Magnesium Glycinate or L-Threonate:** Helps with muscle relaxation and nervous system calming.
- **Low-dose trazodone (12.5-50 mg):** Can aid with sleep initiation without suppressing REM sleep.
- **Mirtazapine (7.5-15 mg):** Helps with sleep maintenance and appetite stimulation if needed.
- **L-theanine & Glycine:** Can support GABAergic calming mechanisms.

CHAPTER 6: COGNITIVE IMPAIRMENT

Introduction

Cognitive impairment, often referred to by patients as "brain fog," is a hallmark feature of ME/CFS and Long COVID. It is characterized by difficulties with memory, processing speed, word retrieval, concentration, and executive function. Cognitive dysfunction in these conditions is multifactorial and influenced by post-exertional malaise (PEM), orthostatic intolerance (OI), neuroinflammation, mast cell activation syndrome (MCAS), dysregulated sleep, chronic pain, medications, etc.[72,77,95]

Unlike traditional cognitive disorders, cognitive impairment in ME/CFS and Long COVID fluctuates based on exertion, triggers, and comorbid conditions, making it essential for clinicians to assess these patients using symptom-contingent evaluations rather than standard neuropsychological testing alone.

6.1 Assessment of Cognitive Impairment

Key Symptom Domains[10,35,72,77,124]

- Memory deficits (short-term and working memory issues)
- Slow processing speed (difficulty multitasking, following conversations)
- Word-finding difficulties (difficulty recalling words or phrases)
- Reduced executive function (impaired planning, decision-making)
- Mental fatigue & difficulty sustaining attention
- Sensory processing issues (light, sound, and motion sensitivity)

Evaluation & Functional Assessment Tools

- Patient-reported questionnaires:
  - PROMIS Cognitive Function Scale
  - DePaul Symptom Questionnaire-Cognitive Section
  - Good Day/Bad Day Questionnaire (cognitive fluctuations)
- Orthostatic testing:
  - 10-Minute NASA Lean Test (to evaluate reduced cerebral perfusion in OI-related cognitive dysfunction)[22,174]
  - Tilt Table Test[133]
- Rule out coexisting conditions:[72]
  - Sleep disorders (refer to Chapter 5)
  - Medication side effects (anticholinergics, sedatives)
  - B12, iron, thyroid dysfunction, or autoimmune markers

6.2 Management of Cognitive Impairment

1. Address Underlying Physiological Drivers

- **Post-exertional malaise influence:**
  - Strict pacing strategies: Prevent cognitive crashes by limiting exertion.[79,182]
  - Energy conservation techniques: Encourage strategic activity-rest cycling.[79]

- **Orthostatic intolerance & cerebral hypoperfusion:**
  - Improve venous return[22,174]
  - Increase fluid and electrolyte intake (oral rehydration solutions, salt loading)[161]
  - Compression garments[17]
  - Medications: Midodrine, fludrocortisone, beta-blockers as needed[17,106,161]
- **Neuroinflammation & microglial activation:**
  - Low-dose naltrexone (LDN): Reduces neuroinflammatory cytokines[107,185]
  - Omega-3 fatty acids and curcumin: Help modulate inflammation
  - Antihistamines (H1/H2 blockers): If MCAS-related neuroinflammation suspected[117,170]
- **Mast Cell Activation Syndrome contribution:**
  - Mast cell stabilizers (e.g., cromolyn, ketotifen) to reduce neuroinflammation[118,170]
  - H1/H2 blockers for histamine-mediated cognitive symptoms[54,163]
  - Luteolin, Quercetin
- **Sleep-driven cognitive dysfunction:**
  - Address sleep disorders (refer to Chapter 5 for management options)[14,72]
  - Melatonin or low-dose trazodone for circadian regulation

2. Cognitive Pacing & Environmental Adaptations

- **Limit cognitive overload:**
  - Reduce screen time and exposure to bright lights
  - Break down tasks into smaller segments[79]
  - Use hearing protection in stimulating environments
- **Use assistive cognitive strategies:**
  - Voice-to-text applications
  - Written reminders and visual task lists
  - Recorded instructions for complex tasks
  - Perform cognitive tasks with feet elevated and wear compression garments.[17,22]
- **Adjust work & school environments:**
  - Offer flexible schedules and reduced workload
  - Allow extra processing time and rest breaks during mental tasks
  - Arrange cognitive rest periods throughout the day
  - Request less stimulating areas of classroom/work areas
  - Allow for virtual work when possible

3. Pharmacologic & Nutritional Support

- LDN (low-dose naltrexone): Modulates neuroinflammation and cognitive fatigue[107,185]
- Acetyl-L-Carnitine & CoQ10: Mitochondrial support for brain function
- Magnesium L-Threonate: Enhances synaptic plasticity and cognition
- Caffeine, modafinil or other stimulants ***(case-by-case basis)***: **May assist in improving alertness but should be used cautiously due to PEM risk.**

CHAPTER 7: ORTHOSTATIC INTOLERANCE (OI) & DYSAUTONOMIA

Introduction

Orthostatic Intolerance (OI) is a hallmark feature of dysautonomia, a condition of autonomic nervous system dysfunction that is prevalent in ME/CFS, Long COVID, and other infection-associated chronic conditions (IACCs). OI is characterized by an inability to maintain adequate blood flow and cerebral perfusion while upright, leading to dizziness, lightheadedness, cognitive impairment, fatigue, and worsening symptoms upon standing.[22,133,174]

OI is not a standalone issue but rather a symptom manifestation of broader dysautonomia—a dysfunction in autonomic regulation that also affects heart rate, blood pressure, digestion, immune function, temperature regulation, and pain processing. Addressing OI is a critical component of managing dysautonomia, **but clinicians must also recognize that dysautonomia is both a contributor to, and a consequence of, other comorbidities such as mast cell activation syndrome (MCAS), neuroinflammation, viral reactivation, sleep dysregulation, and small fiber polyneuropathy.**[93,136]

7.1 Assessment of OI and Dysautonomia

Clinical Presentation

- Dizziness, lightheadedness, or near-syncope upon standing[106,160]
- Cognitive impairment or "brain fog"[5,22,174]
- Fatigue exacerbated by being upright[22,134]
- Heart palpitations or tachycardia[106,112]
- Cold hands/feet, excessive sweating, or temperature dysregulation[134,136]
- Shortness of breath or chest discomfort[106]
- Sensory sensitivities[10,72]
- Tremors
- Sleep disruption, vivid dreams[14,25]
- Emotional lability, anxiety
- Nausea, bloating, or delayed gastric emptying (GI dysmotility)[33,127]

Diagnostic Testing

- **10-Minute NASA Lean Test** (passive standing test) or an Active Stand Test (in-office screening tool for OI, useful for diagnosis and monitoring effectiveness of interventions.)[8,112,174]
- **Tilt Table Test (TTT)** (gold standard diagnostic test, used when necessary to differentiate between POTS, OH, or NMH.)[133,160]
- **Ambulatory blood pressure and heart rate monitoring** (useful for detecting fluctuations associated with dysautonomia.)[106,136]

7.2 Management of OI and Dysautonomia

1. Address Underlying Autonomic Dysfunction

- **Fluids & electrolytes increase vascular volume:**[161]
  - Increase water intake (2-3L/day)
  - Increase Salt intake (8-12 g salt/day - which is equivalent to 3-5 g sodium **unless contraindicated**)
  - Consider varieties of electrolyte supplementation (oral rehydration solutions).

- **Compression garments:**[17,56]
  - Use high-waisted compression stockings/leggings to support venous return[15]
  - Abdominal binders may also help reduce blood pooling.
- **Physical countermeasures:**[17,56]
  - Encourage seated or reclined positions when possible.
  - Recumbent exercises (e.g., rowing, swimming, cycling, Pilates, yoga) – to strengthen core and lower extremities (**only if PEM is not induced**).[183,184]

2. Pharmacologic Interventions *(as needed and based on symptom severity)*

- **For POTS (Postural Orthostatic Tachycardia Syndrome) or Neurogenic Orthostatic Hypotension (nOH):**
  - **Fludrocortisone** – Enhances sodium retention and increases blood volume.[52,140]
  - **Midodrine** – Alpha-agonist that constricts blood vessels in the arms and legs and improves blood return.[136,156]
  - **Droxidopa (Northera)** – Increases norepinephrine to improve standing blood pressure. Better CNS effects than midodrine. Some cardiac inotropy support.[4,136]
  - **Pyridostigmine (Mestinon)** – Improves venous return to decrease preload failure and may improve systemic oxygen extraction.[83,136]
  - **Ivabradine** – Selective heart rate reduction without affecting blood pressure.[144,150,179]
  - **Beta-blockers (e.g., propranolol, atenolol, metoprolol)** – Reduce tachycardia and improve tolerance to standing. More for POTS presentation.[106,111,179]
  - **Atomoxetine (Strattera)** – Off label – SNRI selectively inhibits the reuptake of norepinephrine improving standing blood pressure. More for nOH presentation.[136]

3. Address Dysautonomia-Driven Comorbidities

- **Neuroinflammation:**
  - Low-dose naltrexone (LDN), omega-3s, curcumin[107,185]
- **Mast Cell Activation Syndrome (MCAS):**
  - H1/H2 blockers, cromolyn (compounded or liquid), ketotifen[93,117,118]
- **Sleep dysregulation:**
  - Melatonin, Alpha-adrenergic blockers (prazosin, clonidine, guanfacine, benzodiazepines – **used low dose and sparingly**)[51,136]
- **Small Fiber Polyneuropathy:**
  - IVIG, gabapentin, pregabalin, low-dose naltrexone (LDN)[43,50,134]

4. Non-Pharmacologic Interventions*

  - Vagus nerve stimulation techniques – deep breathing, meditation, cold therapy[51,85]

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CHAPTER 8: MAST CELL ACTIVATION SYNDROME (MCAS)/MAST CELL HYPERREACTIVITY

Introduction

Mast Cell Activation Syndrome (MCAS) is a condition of dysregulated mast cell activity that results in excessive and inappropriate release of mediators such as histamine, prostaglandins, leukotrienes, and cytokines.[55,117,170] MCAS is often intertwined with dysautonomia, neuroinflammation, orthostatic intolerance (OI), and post-exertional malaise (PEM)—meaning that a patient's overall symptom burden may be heavily influenced by underlying mast cell dysfunction.[92,93]

MCAS can present with system-wide symptoms, and it is frequently underdiagnosed due to the challenge of capturing biochemical markers during a flare.[117,170] Importantly, MCAS may not always show up on traditional testing unless the patient is experiencing a severe flare at the time of lab collection. Therefore, empiric trials of mast cell stabilizers and inhibitors serve as both diagnostic and therapeutic interventions.[180]

MCAS is frequently triggered or exacerbated by infections, including viral illnesses, which can lead to degranulation of mast cells and widespread inflammatory responses.[55,166] It is crucial to consider MCAS as a contributing factor in patients with ME/CFS and Long COVID who present with complex, multi-system involvement and fluctuating symptoms.[93,95]

Comorbid Conditions Associated with MCAS & ME/CFS[37,92,93,117,151,118]

- Postural Orthostatic Tachycardia Syndrome (POTS)
- Ehlers-Danlos Syndromes (EDS)
- Post-Lyme Syndrome
- Fibromyalgia
- Chronic Migraines
- Multiple Chemical Sensitivity Syndrome
- Irritable Bowel Syndrome (IBS)
- Post-Traumatic Stress Disorder (PTSD)
- Endometriosis
- Interstitial Cystitis
- Chronic Prostatitis
- Vulvodynia
- Cranio-cervical Instability (CCI)
- Atlanto-axial Instability (AAI)
- Occult Tethered Cord Syndrome

MCAS and Neuroinflammation

- Mast cells release over 130 different mediators, which can influence systemic and localized inflammation.[55,118,170]
- Mast cells communicate distress neurologically and immunologically, triggering downstream inflammatory effects.[169,172]
- Mast cells reside in critical brain areas: hypothalamus, thalamus, third ventricle, pituitary gland, and pineal gland.[46,188]

CHAPTER 8: MAST CELL ACTIVATION SYNDROME (MCAS)/MAST CELL HYPERREACTIVITY

- MCAS is often worsened by emotional stress due to the role of corticotropin-releasing hormone (CRH).[168]
- Mast cell mediators like histamine and tryptase can activate microglial cells, triggering neuroinflammation in conditions like ME/CFS and Long COVID.[38,188]

8.1 Diagnostic Criteria for MCAS

Diagnosing MCAS presents significant challenges due to its heterogeneous presentation and the technical difficulties in capturing mediator release during flares.[54,117]

Consensus Diagnostic Criteria[2]

A patient must meet all three of the following criteria:

1. **Characteristic clinical symptoms** involving ≥2 organ systems with recurrent or chronic features.[2,117]
   - Common systems affected include skin, gastrointestinal, cardiovascular, respiratory, neurologic, and musculoskeletal.
2. **Response to anti-mediator therapy**[2,117,180]
   - Substantial improvement in symptoms with H1/H2 antihistamines, mast cell stabilizers, leukotriene antagonists, or other medications targeting mast cell mediators.
   - Response should be clearly beyond placebo effect (typically considered >30% reduction in symptoms.)
   - Response could occur in more than one system, i.e., famotidine improves GI and upper respiratory symptoms. Reducing histamine activity in one system may translate into reduction of histamine activity in another.
3. **Objective evidence of mast cell mediator release**[2,117]
   - Elevated serum tryptase (>15 ng/mL or >20% + 2 ng/mL above baseline during or within 4 hours of a symptomatic period)
   - Elevated 24-hour urinary histamine metabolites (N-methylhistamine, prostaglandin D2 or its metabolite 11β-prostaglandin F2α)
   - Elevated plasma histamine or chromogranin A (if not taking PPIs)
   - Positive histochemical or immunohistochemical staining for mast cells in GI or urinary tract biopsies

Clinical Diagnostic Approach

Given the challenges of capturing laboratory evidence during flares, many clinicians adopt a pragmatic approach:[117,118,170]

1. **Detailed history and symptom inventory**[54,117]
   - Multi-system involvement with fluctuating symptoms
   - Symptoms can be present during PEM, or bad days, but not on good days
   - History of recurrent flu-like illnesses with no apparent diagnosis
   - History of IBS[33]
   - Triggers include foods, medications, environmental factors, temperature changes, exercise, stress
   - Family history of similar symptoms or diagnosed mast cell disorders

2. **Exclusion of other diagnoses**[2,117]
   - Rule out other conditions that could explain symptoms.
   - Consider systemic Mastocytosis if persistent elevation of tryptase >20 ng/mL.
3. **Laboratory testing**
   - **Serum tryptase:** Ideally measured during flare and compared to baseline.[108,117]
   - **24-hour urine collection:** Should be properly refrigerated during collection.[117]
     - N-methylhistamine
     - Prostaglandin D2
     - Leukotriene E4
   - **Plasma histamine** (requires special handling - chilled, spun down quickly)[117]
   - **Plasma heparin** (specialized testing)
   - **Chromogranin A** (if not on PPIs)[108]
4. **Special considerations for specimen collection**[117,118]
   - Collections ideally performed during symptomatic periods.
   - Proper specimen handling is crucial (chilled specimens, rapid processing).
   - Patients should avoid anti-inflammatory oral medications, creams and supplements for 1 week prior to testing.
5. **Therapeutic trial**[54,117,180]
   - Empiric trial of mast cell-targeted medications with clear documentation of response.
   - Systematic approach: Start with H1/H2 blockers, add mast cell stabilizers, then consider leukotriene antagonists.
   - Document response using validated symptom scales when possible.

Diagnostic Pitfalls to Avoid

- **Relying solely on tryptase:** Many MCAS patients never show elevated tryptase despite clear symptomatology.[54,117]
- **Inadequate specimen handling:** Improper handling of specimens is a common cause of false negatives.[117]
- **Testing during asymptomatic periods:** Mediator levels may normalize between flares.[54,117]
- **Failure to consider comorbidities:** Conditions like EDS, POTS, and ME/CFS frequently co-occur with MCAS.[92,93]
- **Dismissing diagnosis due to negative tests:** A therapeutic response to mast cell-targeted therapy with consistent symptomatology strongly suggests MCAS even with negative laboratory findings.[2,117,180]

Differential Diagnosis

- Systemic Mastocytosis
- Chronic infections
- Autoimmune disorders
- Carcinoid syndrome
- Pheochromocytoma
- Endocrine disorders

8.2 Management of MCAS

Goals of MCAS Management

- Reduce inflammation that increases vascular permeability, intestinal permeability, and neuroinflammation.[118,170,172]
- Prevent innate immune dysregulation that may drive ME/CFS pathophysiology.[95,124]
- Reduce triggers of neuroinflammation and headaches.[170,188]
- Mitigate dysautonomic dysfunction that contributes to OI, GI dysmotility, and sympathetic overdrive.[93,170]

1. Avoid & Mitigate Triggers[117,163]

- Environmental control (air purifiers, low-chemical exposure)
- Low-histamine diet
- Avoid unfrozen leftover foods
- Stress reduction techniques
- Eliminate other exposures (detergents, soaps, etc.)

2. Pharmacologic Management[117,118,170]

- **H1 Blockers:** diphenhydramine, fexofenadine, loratadine, cetirizine, levocetirizine
- **H2 Blockers:** famotidine, cimetidine
- **Leukotriene Blockers:** montelukast, zafirlukast
- **Mast Cell Stabilizers:** cromolyn sodium – liquid and compounded, ketotifen, quercetin, luteolin
- **Anti-IgE Biologics:** omalizumab (Xolair)
- **C-Kit Tyrosine-Kinase Inhibitors:** imatinib
- **Diamine Oxidase (DAO)** supplementation

CHAPTER 9: PAIN, NEUROINFLAMMATION, FIBROMYALGIA, SMALL FIBER POLYNEUROPATHY, MUSCULOSKELETAL PAIN IN hEDS/HSD

Introduction

Pain in infection-associated chronic conditions (IACCs) such as ME/CFS, Long COVID, fibromyalgia (FM), and hypermobility syndromes arises from a complex interplay of neuroinflammation, autonomic dysfunction, impaired pain modulation, and musculoskeletal instability.[23,43,93,136] Pain in these conditions is not purely musculoskeletal or inflammatory—it often involves central sensitization, small fiber polyneuropathy (SFPN), and dysregulated pain processing.[43,50,99]

While treatment remains symptom-focused, improving orthostatic intolerance, sleep quality, mast cell activation, and reducing PEM plays a critical role in mitigating pain severity. Multimodal pain management is often required, integrating pharmacologic and non-pharmacologic approaches.

9.1 Pain Management Approaches

Medication Class	Examples	Mechanism
Low Dose Naltrexone (LDN)	1.5–4.5 mg nightly	Reduces neuroinflammation, modulates microglial activation, and improves central pain processing[107,185]
Tricyclic Antidepressants (TCAs)	Amitriptyline, Nortriptyline, Desipramine	Enhances serotonin/norepinephrine levels, reduce neuropathic pain, improve sleep[23,72]
Serotonin-Norepinephrine Reuptake Inhibitors (SNRIs)	Duloxetine, Milnacipran	Modulates pain perception and fatigue[23]
Gabapentinoids	Gabapentin, Pregabalin	Reduces nerve hyperexcitability, manage neuropathic pain[43,134]
Muscle Relaxants	Cyclobenzaprine, Tizanidine	Reduces myofascial pain and muscle spasms
Migraine-Specific Therapy	Tryptans, CGRP Antagonists	Address neuroinflammatory-driven headaches and vascular dysfunction[75,76]

Key Considerations:

- **Gradual titration is critical,** as these patients often experience medication sensitivity.
- LDN is particularly effective in reducing neuroinflammation-related pain and should not be overlooked in ME/CFS and Long COVID.[75,76]
- Gabapentinoids and TCAs can be sedating and may worsen cognitive dysfunction—consider low-dose trials.

CHAPTER 9: PAIN, NEUROINFLAMMATION, FIBROMYALGIA, SMALL FIBER POLYNEUROPATHY, MUSCULOSKELETAL PAIN IN hEDS/HSD

9.2 Small Fiber Polyneuropathy (SFPN)

Key Clinical Features of SFPN in IACCs:

- Burning pain, tingling, numbness[43,134,50]
- Temperature dysregulation, sweating abnormalities[43,134]
- Worsening of autonomic symptoms (vascular function, GI function, etc.)[43,134,136]
- Heightened sensory sensitivities (light, sound, touch)[10,124]

Diagnostic Tools:

- Skin biopsy (gold standard) – identifies reduced small fiber nerve density. Must be done by an experienced clinician for proper biopsy location and depth and must go to a lab experienced in processing for SFPN diagnosis.
  - Variable sensitivity test despite good specificity when positive.[43,50,134]
- QSART (Quantitative Sudomotor Axon Reflex Test) – assesses autonomic nerve function.[3,134,136]
- Corneal Confocal Microscopy (CCM)

Treatment Strategies:

- LDN: neuroimmune modulation[107,185]
- IVIG (if autoimmune SFPN is suspected)[43,50]
- Alpha-lipoic acid, CoQ10, and acetyl-L-carnitine for mitochondrial support[35]
- Gabapentinoids, SNRIs, or TCAs for nerve pain[23,43,134]

9.3 Fibromyalgia Clinical Pearls

While some literature supports the idea of primary vs. secondary fibromyalgia, many experienced clinicians believe that fibromyalgia does not occur in isolation and occurs concurrent with (or present after) a chronic stimulus of somatic pain sources or continued inflammation.[23,99]

Key Takeaways:

- Fibromyalgia pain does not exist without underlying initial somatically–derived sensory triggers. Instead, signals that might otherwise be weak or easily ignored become amplified or given additional neurological salience than they might in other individuals.[23,99]
- Flare-ups do not occur randomly—they reflect an underlying physiological shift (e.g., worsening autonomic dysfunction, poor sleep, new inflammatory triggers).[23,136]
- Treat the underlying drivers of pain: unrefreshing sleep, dysautonomia, orthostatic intolerance, mast cell activation, SFPN, PEM, myofascial dysfunction, etc.[23,43,72,93]

Comprehensive Pain Reduction Requires:

1. Addressing central sensitization – LDN, TCAs, SNRIs, Gabapentinoids[23,43,107,185]
2. Improving autonomic function – Fluids, compression, dysautonomia treatment[17,93,136]
3. Managing mast cell hyper-reactivity – Antihistamines, mast cell stabilizers[3,117,118]
4. Optimizing sleep – Low-dose TCAs, melatonin, non-disruptive sleep aids[14,51,72]

9.4 Musculoskeletal Pain in hEDS/HSD

Hypermobile Ehlers-Danlos Syndrome (hEDS) and Hypermobility Spectrum Disorder (HSD) are common comorbidities in ME/CFS and Long COVID. These conditions result in structural joint instability, increased pain sensitivity, and higher rates of soft tissue injury. More details can be found in Chapter 11.[24,45,58]

CHAPTER 9: PAIN, NEUROINFLAMMATION, FIBROMYALGIA, SMALL FIBER POLYNEUROPATHY, MUSCULOSKELETAL PAIN IN hEDS/HSD

Clinical Identification Note:
Rather than relying solely on formal diagnostic criteria (which may miss many patients with clinically significant hypermobility), we recommend assessing for:

- Observable joint hyperextension during examination[24,27]
- Patient-reported history of dislocations or subluxations[24,27]
- Multisystem involvement (autonomic dysfunction, mast cell symptoms)[92,93]
- Evidence of tissue fragility (easy bruising, poor healing)[27,151]
- Family history of joint laxity or early-onset osteoarthritis[24,27]

This clinical approach identifies patients who benefit from hypermobility-focused interventions regardless of whether they meet formal diagnostic thresholds. In practice, the biomechanical principles of pain management apply to anyone with joint hypermobility, not just those meeting strict diagnostic criteria.

Biomechanical Considerations:

- Joint instability alters force distribution, leading to chronic pain and early-onset osteoarthritis.[24,67,116]
- Tendon laxity requires greater muscle exertion to stabilize joints.[24,67]
- Repetitive soft tissue injuries create a cycle of local inflammation and nociceptive pain.[24,27]
- Poor proprioception increases risk of injury.[24,56]

Common Injuries & Anatomical Complications:

- Joint hyperextensions, subluxations[24,27]
- Ligamentous laxity → recurrent sprains & dislocations[27,67]
- Spinal issues: kyphoscoliosis, spondylolisthesis, disc herniations[42,67]
- SI joint, hip, and pelvis malalignment[42,67]
- Hypertrophic or dystonic muscle compensation patterns[24,27]

Pain & Injury Prevention Strategies

1. Low-impact, joint-stabilizing physical therapy (avoid high-resistance exercises)[24,56]
2. Bracing and taping techniques for joint support[24,56]
3. Muldowney Protocol for EDS (gold standard PT approach)
4. Proprioceptive training to improve neuromuscular coordination.[24,56]
5. Manual therapy for myofascial pain relief[24]

Key Takeaway: Addressing hypermobility-related pain requires a biomechanical approach—treating regional joint pain without addressing the kinetic chain is ineffective.

Conclusion
Pain in ME/CFS, Long COVID, fibromyalgia, and hypermobility syndromes are multi-faceted, requiring an integrated approach. Optimizing autonomic function, neuroimmune regulation, sleep quality, and musculoskeletal stability is critical to long-term symptom management.[23,43,93,136]

CHAPTER 10: GASTROINTESTINAL DYSMOTILITY AND OTHER GI SYMPTOMS

Introduction

Gastrointestinal (GI) dysmotility is a common and often underrecognized feature of ME/CFS, Long COVID, and other infection-associated chronic conditions (IACCs). The autonomic nervous system (ANS) plays a central role in regulating GI motility, and disordered autonomic signaling and function can contribute to dynamic changes in gastrointestinal motility. In particular, patients may experience transient or waxing and waning symptoms of either delayed or accelerated gastric, intestinal, and colonic motility, often triggered or mediated by other factors (such as vascular dysregulation or anatomical upright vs supine positioning) that affect autonomic functioning.[128]

The GI tract is densely innervated by unmyelinated postganglionic autonomic small fiber nerves, and dysfunction, damage, or loss of these fibers (as part of SFPN) can result in wide ranging abdominal and digestive symptoms.[134] Gastrointestinal symptomatic presentations can also be mediated by additional factors related to mast cell activation syndrome (MCAS), alterations in gut microbiota composition with reduced microbial diversity and intestinal permeability ("leaky gut"), and features related to underlying connective tissue disorders including issues related to connective tissue integrity and motility as well as related structural vascular compression syndromes such as May Thurner's, Nutcracker's, Median Arcuate Ligament Syndrome, etc.) (See Chapter 12 for more information on Venous Congestion Syndromes & Structural Vascular Compression).

It should be noted that many patients with IACC's suffering from GI symptoms will meet the current diagnostic criteria for irritable bowel syndrome (IBS) and are frequently given this diagnosis by other medical professionals. Use of the diagnostic label "IBS", however, has often led to a lack of recognition of the extensive nature of the underlying functional GI disorders and pathology at the root of many of these symptomatic presentations, and often leaves patients with inadequate or incomplete diagnosis and treatment.

10.1 Key Contributors to GI Symptoms ME/CFS & Long COVID

Mechanism	Impact on GI Function
Dysautonomia	Impaired autonomic regulation disrupts motility and peristalsis.[93,136]
Small Fiber Neuropathy (SFN)	Damage to autonomic nerve fibers impairs gut motility and secretion.[43,134]
Mast Cell Activation Syndrome (MCAS)	Inflammatory mediators contribute to visceral hypersensitivity, nausea, and diarrhea. MCAS can also impact GI absorption of nutrients and medications.[93,117,163]
Hypermobility Syndromes (hEDS, HSD)	Connective tissue dysfunction leads to impaired gut structural integrity and motility issues.[27,92]
Post-Exertional Malaise (PEM)	Exacerbates nausea, bloating, and postprandial discomfort due to metabolic stress.[77,99]

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Symptoms

- Early satiety
- Nausea and vomiting
- Anorexia/weight loss (can be severe in some cases)
- Bloating, belching, flatulence
- Diarrhea (especially postprandial)
- Stool urgency
- Constipation
- Dysphagia
- Dyspepsia (especially postprandial)
- Colicky/cramping abdominal discomfort
- Severe postprandial pain (especially with MALS)
- Left flank or left pelvic pain (with venous congestion syndromes)
- Difficulty with stool evacuation
- Itching and flushing (especially postprandial)

10.2 Assessment & Diagnosis

- **Comprehensive History & Symptom Review:**
  - Assess for gastroparesis, irritable bowel syndrome (IBS), small intestinal bacterial overgrowth (SIBO), chronic nausea, and reflux.[33,127]
- **Autonomic Testing for Dysautonomia-Driven GI Dysfunction:**
  - Tilt Table Test, Active Stand or 10-Minute NASA Lean Test (passive stand) - to assess autonomic - instability[22,133,174]
  - QSART (Quantitative Sudomotor Axon Reflex Test) - for SFPN[43,134]
- **GI-Specific Testing:**
  - Gastric emptying study (for suspected gastroparesis)[127]
  - SIBO breath test (for chronic bloating, diarrhea, or constipation)[125]
  - Colonic transit study (if severe constipation is present)[127]
  - Endoscopy/colonoscopy with biopsies (can assess mast cell infiltration in MCAS patients with specialized CD 117 staining, as well as for celiac disease, H pylori, etc.)[54,117]
- **MCAS Evaluation:**
  - Serum tryptase, histamine, prostaglandins, and leukotrienes (when flaring)[54,117]
  - Empirical trial of mast cell stabilizers (Gastrocrom or other forms of cromolyn, quercetin, ketotifen, etc.) as diagnostic and therapeutic tools.[117,118,170]

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10.3 Management Strategies for GI Dysmotility

Target Mechanism	Intervention	Dosing Considerations
Upper GI Dysmotility	Metoclopramide	2.5-5 mg PO BID (black box warning for higher doses recommends limiting to 12 weeks continuous use)
	Prucalopride (Motegrity)	1-2 mg PO daily
	Pyloric Sphincter Botox/Myotomy	For refractory gastroparesis
	Gastric Pacing	For severe, medication-resistant gastroparesis
Impaired Cholinergic Transmission	Pyridostigmine	Dose every 4 hours during the day. Start with a low dose, increase dose gradually. Do not exceed 120 mg po every tid. ER formulations may have reduced side effects or improved efficacy, but do not exceed 360 mg ER daily.
Mast Cell Activation	Cromolyn Sodium	100-200 mg QID
	Gastrocrom (liquid Cromolyn)	1-5ml (up-titrate slowly to 5ml 3-4x/day; 15 minutes before meals and medications
	Ketotifen	1-2 mg at bedtime
	H1/H2 Blocker Combination	Famotidine 20 mg BID + Cetirizine 10 mg daily
	Low Histamine Diet	See dietary resources
Orthostatic Intolerance	Midodrine	2.5-10 mg TID (avoid within 4 hours of bedtime)
	Droxidopa	100-600 mg TID
	Fludrocortisone	0.1-0.2 mg daily (monitor electrolytes)

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Target Mechanism	Intervention	Dosing Considerations
Orthostatic Intolerance	Salt/Fluid Loading	2-3 oral fluid intake with 4-10g sodium daily
Constipation-Predominant	Linaclotide	145-290 mcg daily
	Lubiprostone	8-24 mcg BID with food
	Magnesium Supplements	400-800 mg at bedtime
Diarrhea-Predominant	Loperamide	2-4 mg PRN (max 16 mg/day)
	Cholestyramine	4g BID (separate from other medications)
	Low FODMAP Diet	See dietary resources
SIBO Management	Targeted Antibiotics	Based on breath test results
	Prokinetics	After antibiotic course
	Herbal Antimicrobials	For maintenance or recurrence

Key Considerations

- **Dysautonomia-driven GI dysfunction:** Addressing orthostatic intolerance, MCAS, and SFPN can significantly improve GI symptoms.
- **PEM and GI flare-ups:** GI dysfunction often worsens during PEM episodes, support pacing (home, work, school accommodations and modifications).
- **MCAS & GI symptoms:** Empirical trials of mast cell stabilizers and inhibitors can be both diagnostic and therapeutic.
- **Hypermobility & GI motility:** Hypermobility syndromes are strongly associated with gastrointestinal dysmotility presentations as well as other vascular structural abnormalities (such as MALS, May Thurner's, Nutcracker's) that can contribute to abdominal pain and GI dysfunction.

CHAPTER 11: HYPERMOBILITY AND CONNECTIVE TISSUE DISEASE

Introduction

Hypermobility spectrum disorders (HSD) and hypermobile Ehlers-Danlos syndrome (hEDS) are common comorbidities in ME/CFS, Long COVID, and other infection-associated chronic conditions (IACCs).[24,27,45] While hypermobility is often thought of as a benign trait, in many individuals, it is associated with systemic dysregulation, chronic pain, dysautonomia, mast cell activation syndrome (MCAS), and gastrointestinal dysfunction.[92,93,151] These overlapping conditions create unique diagnostic and management challenges that require a multidisciplinary approach to improve function and quality of life.

Not all patients with hypermobility meet the criteria for hEDS, but many experience significant joint instability, pain, and connective tissue-related complications that impact daily function.[27,67] Recognizing and appropriately managing hypermobility is crucial in patients with ME/CFS and Long COVID, as it influences physical stability, autonomic function, pain perception, and recovery strategies.[24,45,58]

This chapter outlines:

1. Understanding the spectrum of hypermobility disorders
2. Clinical presentation and key diagnostic features
3. Management strategies for pain, stability, and function

11.1 Understanding the Spectrum of Hypermobility Disorders

Hypermobility exists on a spectrum, ranging from asymptomatic joint hypermobility to generalized joint hypermobility (GJH), hypermobility spectrum disorder (HSD), and hEDS (Ehlers Danlos Syndrome).[27,45] Differentiating between these conditions is important, as it influences treatment and prognosis.

Condition	Key Features
Generalized Joint Hypermobility (GJH)	Impaired autonomic regulation disrupts motility and peristalsis. Increased joint range of motion in multiple joints without symptoms[27,67]
Hypermobility Spectrum Disorder (HSD)	GJH with musculoskeletal pain or instability, but does not meet hEDS criteria[27,67]
Hypermobile Ehlers-Danlos Syndrome (hEDS)	GJH plus systemic connective tissue involvement (e.g., skin hyperextensibility, easy bruising, autonomic dysfunction, GI dysmotility, chronic pain)[27,151]

Why It Matters:

- Patients with hEDS and HSD often experience pain amplification due to central sensitization and repeated soft tissue injuries.[23,27]
- Hypermobility can increase the risk of biomechanical complications, including joint subluxations, ligamentous injuries, and impaired proprioception, which contribute to chronic pain and postural instability.[67,116]
- Many individuals with hEDS experience neurological and autonomic symptoms, including dysautonomia, migraines, TMJ dysfunction, and neuropathic pain, making a multisystem approach essential.[92,93,151]

CHAPTER 11: HYPERMOBILITY AND CONNECTIVE TISSUE DISEASE

11.2 Clinical Presentation & Key Diagnostic Features

Patients with hypermobility often present with complex, multi-system symptoms beyond joint instability.[27,45,67]

Key Features Include:

A. Musculoskeletal Manifestations

- Joint instability, subluxations, and dislocations (often in shoulders, knees, and fingers)[27,67]
- Chronic widespread pain due to soft tissue strain and overuse.[24,27]
- Tendon and ligament injuries (often resistant to healing)[27,67]
- Spinal instability (can contribute to headaches, neuropathic pain, and autonomic dysfunction)[42,67]
- Fatigue and postural intolerance, often due to autonomic dysfunction.[24,27]

B. Autonomic Dysfunction & Dysautonomia

- POTS (Postural Orthostatic Tachycardia Syndrome) and orthostatic intolerance (OI)[93,106]
- Vasovagal syncope[133,160]
- Temperature dysregulation[134,136]
- Gastrointestinal dysmotility (gastroparesis, constipation, IBS-like symptoms)[33,127]

C. Mast Cell Activation Syndrome (MCAS)

- Histamine intolerance (food triggers, skin rashes, flushing)[117,163]
- Medication and environmental sensitivities[117,163]
- Frequent allergic-like reactions without clear IgE-mediated allergy.[117,170]

D. Neurological & Structural Concerns

- Frequent headaches and migraines (often due to cervical instability or mast cell activation)[37,75]
- TMJ dysfunction and orofacial pain[42,67]
- Peripheral neuropathy and paresthesias[43,134]
- Increased risk for Chiari malformation, CCI (cranio-cervical instability), and tethered cord syndrome (addressed in Chapter 12: Biomechanical Considerations)[37]

Screening Tools:

- **Beighton Score** (assesses joint hypermobility; ≥6/9 in children, ≥5/9 in adults suggests hypermobility)[27,67]
- **Brighton Criteria** (used to diagnose hEDS)[27]
- **Five-Point Questionnaire for Joint Hypermobility**[27]

11.3 Management Strategies for Pain, Stability, and Function

Management of hypermobility focuses on stabilization, pain control, autonomic regulation, and activity pacing.[24,56]

The following interventions are often helpful:

A. Musculoskeletal & Pain Management

Physical Therapy (PT) for Joint Stabilization *(monitor for PEM)*

- Focus on low-impact, isometric strengthening rather than dynamic movements.[56,183]
- The Muldowney Protocol is highly recommended for hEDS.[24]
- Avoid overstretching, as it can worsen instability.[24,56]

Medications for Pain Control

- Low-dose naltrexone (LDN) for central pain modulation.[107,185]
- Tricyclic antidepressants (TCAs) for neuropathic pain.[23]
- Gabapentinoids (Gabapentin, Pregabalin) for nerve-related pain.[43,134]
- Muscle relaxants (Cyclobenzaprine, Tizanidine) to address muscle tension from instability.

Bracing & Supportive Devices

- Kinesiology taping (watch for MCAS reactions), compression garments, and hypermobility-friendly orthotics can provide stability and reduce proprioceptive deficits.[24,56]
- Neck collars (for those with cervical instability).[37]

B. Autonomic Regulation & Dysautonomia Management

- Hydration and electrolyte support (e.g., salt tablets, IV saline, fludrocortisone)[17,52,161]
- Compression garments to improve circulation.[17,56]
- Beta-blockers or ivabradine for POTS.[106,179]
- Alpha adrenergic blockers for dysautonomia, sleep regulation.[51,136]
- MCAS treatment (antihistamines, cromolyn, leukotriene inhibitors)[117,118]

C. Activity Pacing & Lifestyle Adjustments

- Avoid prolonged static postures (e.g., standing, sitting for long periods).[56]
- Break up tasks into smaller activities to prevent fatigue.[79,182]
- Monitor PEM (Post-Exertional Malaise) carefully, as hypermobility may worsen post-exertional crashes.[77,99]
- Wear joint-supportive footwear to improve posture and reduce strain.[24,56]

CHAPTER 12: BIOMECHANICAL CONSIDERATIONS

This chapter will cover anatomical complications such as cranio-cervical instability (CCI), atlantoaxial instability (AAI), tethered cord syndrome, and venous congestion disorders in ME/CFS and Long COVID.

⚠ Clinical Disclaimer:

The anatomical and biomechanical considerations outlined in this chapter—including craniocervical instability (CCI), atlantoaxial instability (AAI), tethered cord syndrome, and venous congestion syndromes—should be considered only after a comprehensive evaluation and trial of less invasive, first-line interventions. These diagnoses are complex and require highly specialized imaging, clinical interpretation, and multidisciplinary expertise to assess accurately.

When a patient with ME/CFS or other infection-associated chronic conditions (IACCs) continues to experience persistent, function-limiting symptoms despite appropriate management of orthostatic intolerance, mast cell activation, post-exertional malaise, sleep dysfunction, and neuroinflammation, an underlying structural or biomechanical contributor may be present.

Referrals for further evaluation should be made to clinicians who are:

- Experienced in evaluating and managing these specific conditions.
- Skilled in distinguishing structural pathology from secondary or functional overlap.
- Sensitive to the fragility and complexity of ME/CFS and Long COVID populations.

Surgical interventions, where indicated, **should be approached with caution,** pursued only in **exceptionally selected cases,** and coordinated through teams with expertise in connective tissue disorders, complex dysautonomia, and neuroimmune conditions. Multidisciplinary collaboration is strongly recommended.

Introduction

Biomechanical abnormalities, including Cranio-Cervical Instability (CCI), Atlantoaxial Instability (AAI), Tethered Cord Syndrome (TCS), and Venous Congestion Disorders, are increasingly recognized in ME/CFS, Long COVID, fibromyalgia, and related post-infectious conditions.[37,42,60,116] While these conditions share some overlap with hypermobility spectrum disorders (HSD) and hypermobile Ehlers-Danlos syndrome (hEDS), they can occur independently of or as complications of generalized hypermobility.[27,37,67]

Why is this important?

- Structural instabilities in the spine can lead to neurological dysfunction, dysautonomia, pain, and worsening PEM.[37,42,60,116]
- Venous congestion and spinal cord tethering can impair cerebral blood flow, contributing to brain fog, orthostatic intolerance, and exertional crashes.[37,60]
- Biomechanical considerations are often overlooked in chronic illness, leading to prolonged diagnostic delays and unnecessary suffering.[37,42,60]

This chapter will discuss:

1. Cranio-cervical instability (CCI) & atlantoaxial instability (AAI)
2. Tethered cord syndrome (TCS)
3. Venous congestion disorders & jugular compression syndromes

CHAPTER 12: BIOMECHANICAL CONSIDERATIONS

12.1 Cranio-Cervical Instability (CCI) & Atlantoaxial Instability (AAI)

What is CCI & AAI?

- Cranio-cervical instability (CCI): Excessive mobility or structural weakness at the junction between the skull and cervical spine (C0-C1-C2), leading to brainstem compression and dysautonomia.[37,60,116]
- Atlantoaxial instability (AAI): Excessive motion between C1 (atlas) and C2 (axis), leading to instability in neck rotation and potential spinal cord compression.[37,116]

Why it Matters in ME/CFS & Long COVID

- CCI and AAI may lead to dynamic motion or neuroanatomical malpositioning that can irritate the brain stem, cranial nerves, and other neurological structures. Irritation of the brainstem in particular may lead to disruption of autonomic signaling that drives symptoms of orthostatic intolerance or GI dysmotility.[37,60]
- CCI and AAI can impair dynamic flow of the CSF and arteriovenous system of the head and neck sometimes resulting in abnormal intracranial pressure changes.[37,68,70]
- Conservative non-surgical management should always be prioritized before proceeding with surgical intervention.[37,42,60]
- Some patients have reported dramatic improvement in ME/CFS symptoms after CCI/AAI stabilization surgery, though surgery itself is not entirely or fully curative for ME/CFS.[37,68,70]

Key Symptoms of CCI/AAI

Symptoms

- Headaches (base of skull, pressure-like pain)[37,60]
- Dysautonomia (POTS, OI, Vagus nerve dysfunction)[37,60]
- Brain fog, memory loss, attentional deficits[37,60]
- Neck pain, cervical muscular dystonia, difficulty holding head upright[37,42,60]
- Notable symptom worsening with positional/postural change (supine vs upright) or with specific cervical positioning (cervical flexion, extension, rotation)[37,42,60]
- Visual disturbances (blurry vision, double vision, photophobia)[37,60]
- Vertigo, tinnitus, sensory sensitivities[37,60]

Diagnostic Workup

- Imaging tests: Imaging for these conditions vary depending on the preference of the neurosurgeon interpreting the images. If CCI/AAI is suspected, consult with the neurosurgeon you will be working with to determine appropriate imaging requirements.[37,116]
- Diagnostic clues:
  - If symptoms improve with a soft cervical collar, CCI/AAI may be contributing.[37,60]
  - If patients have severe brain fog, positional headaches, and worsening with upright posture, imaging should be considered.[37,60,70]

Treatment Approaches

Conservative Management:

- Targeted physical therapy with the goal of cervical stabilization.
  - May particularly focus on strengthening deep anterior neck flexors.[37,60]
- Tight mast cell activation control. MCAS inflammation appears to potentially exacerbate connective tissue integrity and healing.[37,92,117]
- Upright cervical stabilization in a neutral cervical position (no flexion, extension, rotation) may reduce symptom progression with upright activity. Stabilization may particularly reduce symptoms sustained as a consequence of motion/vibration in cars or other transport. Use less than 4 hours per day so as to not lead to weakening of cervical musculature (can utilize soft cervical collars, hard cervical collars without traction).[37,60]
- Cervical traction may be achieved via direct supine manual manipulation from a skilled physical therapist, by utilizing supine cervical traction devices, or by off-label utilization of adjustable cervical collars that can maintain neutral cervical positioning during traction in an upright position (Aspen Vista MultiPost Therapy Collar, Minerva, etc.).
  - Traction may be used diagnostically or therapeutically to attempt to reduce myriad symptoms of ME/CFS, especially symptoms of dysautonomia, cognitive dysfunction, sensory sensitivity, and headaches. Traction could exacerbate symptoms of a concurrent tethered cord.[37,60,159]
  - **Medical professionals should perform all physical manipulations, as patients should never attempt these techniques independently. Only seek treatment from qualified practitioners with appropriate training and expertise in these specific approaches.**

Interventional Options (if very severe):

- Surgical cervical stabilization (CCI/AAI fusion surgeries) ONLY as a last resort for severe or rapidly progressing symptoms otherwise resistant to conservative therapies.[37,60,68]
- Note: PRP (platelet-rich plasma) and Prolotherapy have been proposed as procedures that may improve ligament laxity, but currently do not have established or peer-reviewed evidence supporting their use.[37]

12.2 Acquired/Occult Tethered Cord Syndrome (TCS)

What is Tethered Cord Syndrome (TCS)?

TCS occurs when the spinal cord is abnormally tethered to the surrounding tissue, leading to neurological and autonomic dysfunction. It is increasingly recognized in ME/CFS, Long COVID, and connective tissue disease (like hEDS) as a contributor to worsening central and peripheral nervous system dysfunction and pain.[37,60,68,159]

Key Symptoms of Tethered Cord Syndrome

Neurological & Autonomic Dysfunction

- Bladder dysfunction (urinary hesitancy, urgency, incontinence, retention, bladder spasm)[37,60,159]
- Lower body weakness, leg heaviness, gait disturbances[37,60,159]
- Low back pain, sacral or coccyx pain[37,60,159]
- Sciatica-like symptoms, numbness in legs or feet[37,60,159]

Key Clinical Clues:

- Symptom relief (pain, urinary symptoms, sensory symptoms) in fetal position or knee-to-chest posture, which reduces tension on the tethered base of the spinal cord.[37,60]
- Symptom exacerbation with cervical traction as a result of increased tension on the tethered base of the spinal cord.[37,60,]
- Heal/Toe Walk Screen
  - Walk 20 feet on your heels then walk 20 feet on your toes twice per day for 10 days.
  - Note how you feel particularly in your lower back, legs, and bladder.
  - Log date, time, low back symptoms, leg symptoms, bladder symptoms.
  - If you start having worsening symptoms you do not need to complete the full 10 days.[37,60]

Diagnostic Workup[37,60,159]

Imaging Tests:

- **MRI of the lumbar spine, both supine and prone** (look for a low-lying conus medullaris, thickened filum terminale, lack of cord movement from supine to prone)[37]
- **Supine vs. standing MRI** (some tethered cords only show in standing position)[37]
- **Urodynamics testing** (assesses bladder dysfunction)[37]

Treatment Approaches[37,60,159]

Conservative Management:

- Pelvic floor therapy (for bladder symptoms, pain relief)
- Bracing, core strengthening exercises (avoid flexion-based activities)
- Neuropathic pain management (LDN, gabapentin, amitriptyline, duloxetine)

Surgical Consideration:[37,60,159]

- Filum terminale release surgery (**for severe cases with confirmed imaging abnormalities**)[37]

12.3 Venous Congestion Syndromes & Structural Vascular Compression

Overview

Impaired venous drainage is increasingly recognized as a contributing factor in some patients with ME/CFS and Long COVID. Venous congestion can be localized to specific vascular territories (e.g., jugular, pelvic) and may result from anatomical compression, poor tone, or altered autonomic regulation.[186,189] Celiac artery and/or plexus compression or dysfunction (also known as median arcuate ligament syndrome or MALS) may also trigger severe postprandial pain and digestive complications and is most often discovered in those with connective tissue diseases as well.[153]

Venous congestion may involve:

Head and Neck:

- Jugular vein compression
  - Extrinsic, (Eagle syndrome, etc.)[186]
  - Positional (cervical flexion, extension, rotation) or postural[165]
- Intracranial vascular stenosis or positional pressure gradient changes[69]
- Thoracic Outlet Syndrome (TOS) with venous involvement[110]

Abdominal/Pelvic:

- Pelvic Venous Congestion Syndromes, such as:
  - May-Thurner Syndrome (MTS) – compression of the left iliac vein by the right iliac artery[34,121]
  - Nutcracker Syndrome – compression of the left renal vein[137]
  - Pelvic Congestion Syndrome (PCS) – varicosities and venous insufficiency in the pelvic region

Symptoms can be diverse and overlap with other syndromes. Clues that suggest venous congestion (or MALS) may be contributing include:

- Head and neck pressure, especially with Valsalva or exertion[9,186]
- Increased intracranial pressure signs (pulsatile tinnitus, positional headaches, brain fog, vision changes)[69,70]
- Pelvic pain or fullness, especially worse with prolonged standing or menstruation[121,137]
- Unexplained leg swelling, heaviness, or varicosities[34,121]
- Persistent flank pain (and possibly hematuria) in the absence of renal etiology[137]
- Post prandial abdominal pain (especially with MALS)[153]

Evaluation & Workup (high level overview)

Venous congestion syndromes and arterial compression syndromes (MALS) are often missed due to lack of awareness or nonspecific symptoms. Further evaluation could include:[37,42,121]

- **MR Venogram or CT Venogram of the Head and Neck:**
  - Assess intracerebral and jugular vasculature for compression, stenosis[9]
- **MR Angiogram/Venogram, CT Angiogram/Venogram or Ultrasound of Upper Extremity:**
  - Asses for thoracic outlet syndrome[110]
- **Abdominal/Pelvic MR Venogram, CT Venogram, or Venous Ultrasound:**
  - Assess for May-Thurner's, Nutcracker's, other pelvic venous congestion[121,137]
- **Arteriography or Duplex Arterial Ultrasound:**
  - Median Arcuate Ligament Syndrome (MALS)/Celiac Artery/Plexus Compression Syndrome[153]
- **Referral to interventional radiology or vascular surgery**

Management Overview[17,37,60,98,110,156,165,185]

Management depends on symptom severity, suspected pathology, anatomical and imaging findings, and patient preference. Interventions may include:

- **Non-invasive support:**
  - Compression garments (graded, abdominal and lower body)
  - Elevation of legs or recumbency to reduce pooling
  - Avoid positioning that exacerbates symptoms
- **Medications** (guided by a vascular specialist):
  - Venoactive agents or vasoconstrictors (e.g., midodrine)
  - Anticoagulation if thrombosis is present or suspected.
  - Symptom-targeted medications (pain control, etc.)

- **Interventional options** (typically in severe or refractory cases):
  - **Venous stenting** (for May-Thurners, pelvic venous congestion, or Nutcracker)[98]
  - **Surgical decompression** (for MALS or thoracic outlet or jugular venous compression)[98,153,186]
  - **Renal autotransplant** (for Nutcracker's)[137]
  - **Embolization of pelvic varices** (for Pelvic Congestion Syndrome)

12.4 Clinical Pearls[27,37,60,165]

- Patients with connective tissue disorders like hEDS/HSD may be more prone to vascular compression due to increased tissue laxity and other genetic factors.
- Postural and positional symptom patterns are often key in suspecting venous congestion.
- Treating orthostatic intolerance, MCAS, sleep dysfunction, and PEM may improve the body's tolerance to venous congestion even before pursuing structural interventions.
- Collaboration with interventional radiologists, vascular surgeons, and pelvic floor physical therapists may be necessary for comprehensive care.

CHAPTER 13: PEDIATRIC AND YOUNG ADULTS

Introduction

While ME/CFS and Long COVID are often thought of as adult conditions, a growing number of children and adolescents are being diagnosed—many following viral infections such as SARS-CoV-2.[62,105,141] Pediatric patients often present with the same hallmark features as adults, including PEM, orthostatic intolerance, cognitive dysfunction, and sleep disturbances, but they may describe their experiences differently or struggle to articulate what they are feeling.[78,81,82,148] Clinicians should recognize that ME/CFS and related post-infectious syndromes can affect children at all developmental stages, and adapt management approaches to meet age-specific needs.[12,78,148]

This section provides guidance on recognizing PEM in pediatric patients, pacing strategies tailored to age and developmental level, and communication approaches that empower both the child and family to participate in care planning.[148]

13.1 Recognizing Post-Exertional Malaise (PEM) in Children

PEM is a required feature for ME/CFS diagnosis and a frequent symptom in Long COVID[12,26,72] In pediatric patients, it manifests as a delayed and prolonged worsening of symptoms—including fatigue, pain, brain fog, dizziness, and sensory sensitivity—following physical, cognitive, emotional, or sensory exertion.[78,82,148] Unlike typical fatigue, PEM is not resolved with sleep and may worsen over hours or days.[32,148,182]

PEM typically begins 12-48 hours after exertion, though some children may experience more immediate effects.[32,148] The delay between activity and symptom exacerbation makes it particularly challenging to identify cause-and-effect relationships. PEM episodes may last from 24 hours to several days, with some children requiring a week or longer to return to their baseline functioning level.[32,148,182]

PEM may present as:

- Sudden need to lie down or rest after mild activity.[32,148]
- Regression in developmental or academic skills during or after illness episodes.[78,148]
- Complaints of flu-like symptoms or “not feeling right” after engaging in previously tolerable tasks.[32,148]
- Emotional dysregulation or behavioral shifts when energy thresholds are exceeded.[78,148]

Recognition Challenges: Children often lack the vocabulary or self-awareness to identify and articulate PEM.[78,148] They may not connect their symptoms to activities from previous days, instead describing immediate feelings such as "my body hurts" or "I'm too tired." Parents, caregivers, and teachers are frequently the first to notice patterns of post-exertional symptom exacerbation.[129,130,148] Clinicians should specifically ask about delayed symptom onset when interviewing families and consider having caregivers track activities and symptoms to identify correlations.[148]

Common Triggers of PEM:[32,78,148,160]

- Physical activity (e.g., walking, playing)
- Cognitive activity (e.g., homework, reading)
- Emotional stress or excitement
- Orthostatic stress (e.g., prolonged sitting or standing)
- Environmental or sensory exposure (e.g., noise, light, temperature)

Pacing and Energy Management for Children

The concept of the "energy envelope" can help children and families understand the importance of staying within personal energy limits.[79,148] Pacing strategies should be tailored by developmental stage and family dynamics. The "5 Ps" framework is a helpful guide:[79,148]

1. Pace – Encourage rest before, during, and after activities to prevent PEM.[79,182]
2. Plan – Space out tasks and use timers to help the child stop before symptoms worsen.[79,148]
3. Prioritize – Choose meaningful activities, understanding that energy is finite.[79,148]
4. Position – Reclining or lying down can reduce orthostatic load and energy use.[148,174]
5. Prevent – Use preemptive rest strategies before known stressors (e.g. appointments, school days).[79,182]

Children may benefit from visual tools, like energy charts or "battery meters," and routines that balance activity with restorative breaks.[79,148] Heart rate monitoring may be appropriate for older children or teens who are developmentally able to participate.[148]

The Bateman Horne Center has created a short, animated video describing PEM and pacing through the analogy of apps on your phone. This may be a helpful and engaging tool to share with patients and their families when introducing the concepts of pacing and PEM.[12]

[Life with a Low Battery: Living with ME/CFS]

13.2 Age-Specific Adaptations

Young Children (Ages 4–8):

- Use visual aids (e.g., magnets, stickers) to teach pacing concepts.[13,148]
- Create comfort spaces with soft lighting and soothing items.[148]
- Offer simple explanations: “Your body needs extra rest to feel better.”[13,148]

School-Age Children (Ages 9–12):

- Introduce tracking tools they can help complete.[148]
- Use analogies (e.g., “energy bank”) to teach pacing.[79,148]
- Encourage participation in building their own crash kits.[148]

Teenagers (Ages 13+):[148]

- Support autonomy in managing symptoms and developing pacing strategies.
- Introduce digital tools for tracking PEM, heart rate, and symptom trends.
- Offer validation around the emotional and social challenges of chronic illness.
- Encourage safe social connections that honor the teen’s energy limitations.
- Involve teens in care planning and medical appointments to build confidence in self-advocacy.

- Consider hormonal cycles in menstruating teens: Many teens who menstruate experience a worsening of PEM, orthostatic intolerance, and mast cell activation symptoms in the days leading up to and during their cycle.[148]
  - Encourage tracking symptoms in relation to the menstrual cycle to identify patterns.
  - During this time, proactively reduce activity demands and increase support (e.g., schedule rest days, reduce school workload, allow for more reclined rest).
  - Ensure additional autonomic and mast cell support is considered, such as increased hydration, electrolytes, compression garments, or antihistamines, as appropriate.
  - Educate the teen and family that these symptom flares are physiologic and not a sign of regression or personal failure.

13.3 Crash Management

When a child or teen experiences a PEM crash, the focus should be on **rest, reducing stimulation, and supporting comfort**.[32,148] Crashes are not behavioral or psychological events—they are *physiological* responses to overexertion and can be physically and cognitively debilitating.[32,148,182]

During a Crash:

- Cancel or reschedule any non-essential activities or medical appointments.[79,148]
- Avoid introducing new medications or therapies.[148]
- Create a low-stimulation environment (dark, quiet, cool room).[148]
- Allow flexible routines—let the child lead their recovery pace.[79,148]
- Offer physical comfort: soft bedding, easy-to-digest snacks, electrolyte-rich fluids.[148]
- Normalize the need for full rest—this is not avoidance; it's active healing.[79,148,183]
- Limit screen time and interaction, even if the child is "tired but wired."[148]

Minimize Social Demands:[148]

- Reduce expectations for social engagement and communication.
- Create a 'social buffer zone' with family members taking turns providing brief, necessary care.
- Explain to siblings, friends, and extended family that the child needs sensory rest, including social interaction.
- Offer simple ways for the child to signal when they need complete solitude or when they're open to quiet company.
- Reassure the child that stepping back from social interaction is a necessary part of their medical care, not a rejection of loved ones.

Prepare a Crash Support Kit (for home or school):

- Electrolyte drink or oral rehydration solution
- Earplugs or noise-canceling headphones
- Eye mask or sunglasses
- Weighted blanket (if soothing)
- Simple comfort items (stuffed animal, fidget, low-effort distractions)
- Medication list and pre-approved supports for symptoms like nausea, pain, or dysautonomia

13.4 Communication Strategies for Families and Providers[32,78,148]

Clear and validating communication helps children and teens feel understood, safe, and empowered in managing a complex, unpredictable illness.

What Children and Teens May Say:

- "I don't feel right, but I don't know how to explain it."
- "I'm not tired like sleepy—I'm tired like sick."
- "I want to do things, but my body won't let me."

What Children and Teens May NOT Say

- Children experiencing PEM may become non-communicative or minimally responsive.
  - This withdrawal is a physiological response, not defiance or rudeness.
- Parents should interpret quietness, one-word answers, or inability to engage as signs that the child needs immediate rest.
  - These communication changes often signal that the child has exceeded their energy threshold.

What Parents Can Say to Others:

- "My child has a medical condition that causes delayed symptom crashes after activity."
- "We need to pace and limit stimulation to prevent worsening."
- "We'd love to participate but need to modify how we show up."

What Parents Can Say to Child:

- Avoid expressing disappointment when the child cannot participate in activities.
- Instead of "I'm sad you can't go to the party," try "I understand your body needs rest today."
- Normalize the experience: "Your body is telling you what it needs, and that's okay."
- Help children separate their self-worth from their illness: "This doesn't define you."
- Create alternative ways to celebrate or participate that respect energy limitations.
- Acknowledge grief and frustration while reinforcing that the illness is not their fault.
- Consider age-appropriate support groups or connecting with other affected children.

What Providers Can Model:[130,131,148]

- Acknowledge the real and disabling nature of PEM and validate the child's experience.
- Encourage the child's voice in appointments (as developmentally appropriate).
- Help families explain the illness to schools, caregivers, or extended family.
- Provide written notes for accommodations, rest periods, and schedule flexibility.

Communication Within the Family:

- Create a judgment-free space for children to express symptom changes and limitations.
- Develop simple check-in systems: "On a scale of 1-5, how is your energy today?"
- Acknowledge siblings' feelings while educating them about their brother/sister's condition.
- Hold family meetings to adjust expectations and responsibilities during difficult periods.
- Use hopeful but realistic language about the future: "We're learning what helps your body feel better."

CHAPTER 13: PEDIATRIC AND YOUNG ADULTS

13.5 School Considerations

Children and teens with ME/CFS or Long COVID often face significant barriers to attending and participating in school.[36,44,129] Symptoms such as PEM, orthostatic intolerance, cognitive dysfunction ("brain fog"), pain, and sleep disruption make sustained academic activity difficult and can vary day to day.[129,130,148]

Clinicians can support families by validating these challenges **and advocating for appropriate accommodations and alternative education plans** that support the child's health without jeopardizing their educational access.[129,130,131]

Common School Challenges

- **Unpredictable attendance:** Symptoms fluctuate, making consistent participation difficult.[36,44,129]
- **Cognitive dysfunction:** Trouble focusing, retaining information, reading, or processing complex ideas[78,129,147]
- **PEM triggers at school:** Noise, lighting, social interaction, or sitting upright too long[78,129,148]
- **Orthostatic intolerance:** Difficulty sitting at a desk or walking between classes[148,160]
- **Fatigue:** Inability to sustain energy throughout a full school day[129,148]

Helpful School Accommodations

Providers can recommend a **504 Plan or IEP** (depending on individual needs)[30,130], which may include:

Area	Examples of Support[129,130]
Attendance	Part-time or reduced hours, flexible scheduling, asynchronous participation
Learning Environment	Remote learning options, home or hospital-based instruction, quiet rest space at school
Cognitive Support	Extra time on tests and assignments, reduced workload, breaks during instruction
Physical Support	Elevator access, shortened walking distances, seating accommodations, use of a recliner or cot
Sensory Support	Sunglasses or ear defenders, reduced lighting, low-stimulation classroom
Activity Modification	Exemption from PE, pacing breaks, opportunity to leave class early to avoid crowds
Communication Tools	Voice-to-text apps, audio lessons, visual schedules

13.6 Tips for Providers[129,130,131,148]

- Offer clear documentation that outlines **fluctuating symptoms** and the **need for flexibility.**
- Include statements about **PEM and post-activity crashes**, not just fatigue.
- Reassure school teams that **education is still possible**—just on the student's timeline.
- Suggest that schools **assign a point-person** (e.g., a counselor or nurse) who can check in regularly.
- Encourage use of a **daily energy tracker or pacing log** (if appropriate for the child's age).

CHAPTER 14: SEVERE AND VERY SEVERE CONSIDERATIONS

Caring for Patients with Severe and Very Severe ME/CFS

Introduction

Severe and very severe ME/CFS represents one of the most profound states of disability found in medicine. These patients are often completely housebound or bedbound, often unable to tolerate light, sound, movement, or touch.[40,64,119] Many require assistance with basic activities of daily living (ADLs) such as toileting, feeding, or even turning over in bed. Some rely on tube feeding or are confined to a dark, quiet room, completely isolated from the world.[64,119]

Despite the extreme nature of their debility, patients with severe and very severe ME/CFS remain largely invisible to the medical system. They are often neglected, mischaracterized, or even disbelieved—leading to catastrophic gaps in care.[64,90,119] Yet these patients still deserve—and urgently require—compassionate, informed medical support.

Providing care for this population demands a paradigm shift: a commitment to honor their experience, recognize the distinct biological basis of their illness, and adapt to their profound needs.[90,119] Effective care requires building a collaborative network among primary care providers, home health teams, and family or caregiver supports. Together, these partnerships can help overcome the systemic barriers that have long left these patients unseen, ensuring they receive the respectful, accessible, and individualized care they deserve.[90,119]

14.1 Clinical Characteristics of Severe and Very Severe ME/CFS

Severe ME/CFS patients often present with:

- **Profound physical weakness:** Many are unable to sit upright, eat without assistance, or communicate beyond minimal efforts.[64,119]
- **Extreme sensory sensitivity:** Light, sound, touch, temperature changes, and even movement in the room may trigger worsening symptoms.[64,119]
- **Severe cognitive dysfunction:** Speech, memory, and processing abilities may be markedly impaired.[64,147]
- **Severe PEM:** Even small physical, cognitive, or emotional exertion can trigger deep PEM lasting weeks or months.[32,64,119]
- **Severe gastrointestinal dysfunction:** Early satiety, gastroparesis, or hypersensitivities may necessitate tube feeding.[64,119]
- **Profound orthostatic intolerance:** Inability to tolerate upright posture, sometimes even with slight head elevation.[64,175]
- **Multiple comorbidities:** Including mast cell activation syndrome, POTS, hypermobility spectrum disorders, and others. [64,92,93,119]

Spectrum of Severity:

- **Severe ME/CFS**: Housebound, may tolerate short conversations or brief seated activities with rest.[64,119]
- **Very Severe ME/CFS**: Totally bedbound, may be unable to speak, tolerate light, or eat solid foods; complete care required.[64,119]

14.2 The Critical Role of Compassionate, Patient-Centered Care

Because these patients cannot typically attend office visits, clinicians must think beyond traditional models of care.[90,119]

Key Principles:

- **Meet the patient where they are:** Home-based care or telehealth are critical when possible.[90,119]
- **Honor patient expertise:** Many patients and their caregivers have become experts in their own illness through necessity.[64,90]
- **Minimize sensory exposures:** Reduce light, sound, touch, fragrance, and movement in clinical encounters.[64,119]
- **Use patient and caregiver input**: Leverage the caregiver's observations to minimize energy expenditure for the patient.[64,90]
- **Respect energy limitations:** Keep interactions short, allow for pre-visit planning, and limit physical examinations to essentials.[119]

Inaction or avoidance of severely affected patients reinforces harm. Care must be proactive, even if interventions are limited.[90,119]

14.3 Practical Clinical Recommendations

Diagnosis and Assessment:

- **Confirm diagnosis through history**, using 2015 National Academies of Medicine (formerly the Institute of Medicine) criteria.[72] The Canadian Consensus Criteria (CCC)[25] and the International Consensus Criteria (ICC)[26] provide a more detailed description of severe illness presentation.
- **Assess basic and instrumental ADLs** to understand care needs. Consider ME/CFS and PEM informed occupational therapists (OT).[64,119]
- **Document limitations** carefully and fully to support disability documentation.[119]
- **Screen gently for comorbidities**: POTS, MCAS, gastroparesis, cervical instability, and others.[119]
- **Carefully consider the implications** of PEM when selecting tests.[32,119]

Management Strategies:

- **Prioritize energy conservation**: Implement strict pacing and minimize all exertion. Suggest the use of communication cards where the patient can point to their needs rather than vocalize. Bateman Horne Center's ME/CFS Crash Survival Guidebook contains tools for communication, PEM supports, etc.[12,64,119]
- **Nutrition and hydration support**: Maintain oral intake when possible, use feeding tubes or IV hydration when necessary.[64,119]
- **Medication strategies**:
  - Use low and slow dosing ("start low, go slow").[119]
  - Treat sleep dysfunction, orthostatic intolerance, pain, and MCAS when possible.[119]
- **Physical therapy adapted for severe ME**: Employ passive range-of-motion **only if tolerated**; **aggressive or graded rehab is contraindicated.**[119,183]

- **Mental health support:** Utilize trauma-informed counseling for coping with isolation and debility, not to psychologize the disease itself.[119]
- **Advanced planning:** Encourage completion of advanced directives, home safety plans, and caregiver support systems.[119]

Critical Caveat:

Patients with severe ME/CFS are extremely sensitive to interventions. Even seemingly benign activities—turning a patient, assisting with toileting—can trigger catastrophic PEM and deterioration. All care must proceed with extreme caution and respect for patient signals.[32,64,119]

14.4 Addressing Systemic Barriers

Severe ME/CFS exposes profound gaps in the healthcare system:

- **Lack of provider education:** Many clinicians have never been taught about severe ME/CFS.[64,119]
- **Home health misunderstandings:** Severe patients are sometimes mischaracterized as "neglect cases" when their appearance reflects disease burden.[64,90,119]
- **Lack of appropriate services:** Few home health or hospice organizations are equipped to support these patients safely.[90,119]

Provider Role:[90,119]

- Advocate for home-based medical services when possible.
- Hospice services may be medically necessary for this patient population. Accommodations, disability supports, and home-based services require the medical practitioner to orchestrate and proactively trigger these supports.
- Educate home health providers and social workers about the realities of ME/CFS.
- Document functional impairments precisely to support access to services.

An Important Distinction:

- **Signs of profound debility are not evidence of neglect.** Malnutrition, immobility, or minimal interaction may reflect the disease's severity, not caregiver failure. Providers must recognize this distinction to protect patients and caregivers alike.[64,90,119]

14.5. Dignity[64,90,119,185]

While full recovery is rare, skilled supportive care can improve quality of life, reduce suffering, and prevent deterioration.

Small gains matter.

- Preserve oral nutrition.
- Reduce sensory triggers.
- Manage pain.
- Empower patients with control over their environment and care decisions.

These interventions restore dignity, even in the face of overwhelming illness.

Providers can make an extraordinary difference by bearing witness, offering care, and refusing to abandon those most vulnerable.

14.6 Supporting the Caregiver[90,119]

Caring for someone with severe or very severe ME/CFS is an all-consuming responsibility that can place extraordinary emotional, physical, and financial strain on caregivers. As clinicians, it is essential to recognize the caregiver's critical role—not only in facilitating patient care but in observing subtle changes, advocating for appropriate interventions, and maintaining continuity between medical visits.

Healthcare professionals can play a meaningful role by:

- Acknowledging caregiver expertise and the intensity of their responsibilities.
- Including caregivers in care planning, while respecting the patient's autonomy.
- Monitoring for caregiver burnout or grief.
- Offering guidance and referrals to appropriate mental health, respite, or social services.

This Guide includes a dedicated *Caregiving* chapter with communication strategies, documentation tips, and practical recommendations to support care partners. Clinicians are encouraged to review that section in tandem with this chapter. Additionally, the following resources may be shared directly with caregivers:

Recommended Resources for Supporting Caregivers of Patients with Severe ME/CFS:

1. How to be a Demanding Diplomat as an ME/CFS Caregiver
2. Caregiver Mental Health handout
3. Severe ME/CFS Caregiver Webinar
    a. Caregiver Resource Guide
    b. Transcript
    c. Recording

Closing Reflection

Caring for patients with severe and very severe ME/CFS requires deliberate coordination between primary care providers, home health professionals, and family caregivers. Building effective partnerships across disciplines ensures that patient needs are met with minimal disruption to their fragile baseline. By prioritizing collaboration, adapting care delivery to patient tolerance, and maintaining respect for the complex biology underlying this illness, we can provide comprehensive, compassionate care that these patients urgently deserve.[64,90,119]

Additional Provider Resources

1. Montoya et al., "Caring for the Patient with Severe or Very Severe ME/CFS," Healthcare (2021) https://pubmed.ncbi.nlm.nih.gov/34683011/
2. MDPI Healthcare: ME/CFS- The Severe and Very Severely Affected Special Issue
3. CDC Clinical Care Guidance – "Severely Affected Patients" https://www.cdc.gov/me-cfs/healthcare-providers/clinical-care-patients-mecfs/severely-affected-patients.html
4. Dialogues for a Neglected Illness – Educational film series on Severe ME/CFS https://www.dialogues-mecfs.co.uk/films/severeme/
5. Identifying and Managing Suicidality in ME/CFS – Bateman Horne Center *https://batemanhornecenter.org/wp-content/uploads/filebase/providers/Identifying-Managing-Suicidality-in-MECFS.pdf*
6. van Campen et al., "Reductions in Cerebral Blood Flow Can Be Provoked by Sitting in Severe ME/CFS," Healthcare (2020) https://www.mdpi.com/2227-9032/8/4/394

CHAPTER 15: ALLIED PROFESSIONALS (PHYSICAL THERAPY, OCCUPATIONAL THERAPY, SPEECH THERAPY)

Introduction

Rehabilitation professionals, including Occupational Therapists (OTs), Physical Therapists (PTs), and Speech Language Pathologists (SLPs), play a vital and often overlooked role in supporting patients with infection-associated chronic conditions like ME/CFS.[12,183]

Although rehabilitation treatments do not cure ME/CFS, they are essential for helping patients learn how to effectively manage their chronic condition.[183]

The primary goals of rehabilitation are to enhance the patient's:[12,183]

- Quality of life.
- Ability to engage in meaningful daily activities.
- Autonomy in managing their health.
- Access to healthcare services, social resources, and financial support.
- Knowledge and understanding of their condition.
- Education and support for caregivers, family, and friends.

⚠ Clinical Disclaimer:

Rehabilitation protocols that involve progressive increases in exertion—such as the Levine or CHOP protocols—are not suitable for patients experiencing post-exertional malaise (PEM).[89,135,183] Conventional therapeutic approaches like graded exercise therapy (GET)[181] and graded activity therapy (GAT) have been shown to be harmful to individuals with ME/CFS or Long COVID with PEM.[89,135,183] Patients with PEM should not be encouraged to gradually increase physical or cognitive activities—such as riding a stationary bike or performing progressively more demanding word recall tasks—as these methods can be ineffective and potentially detrimental.[183,184] Instead, therapists must tailor their care plans to prioritize activity pacing, ensuring they accommodate the specific needs of people with ME/CFS and Long COVID with PEM, and avoid any strategies that rely on graded exertion.[61,182,183]

15.1 Therapists Treating Individuals with ME/CFS Should:[12,32,79,89,92,183]

- Offer telehealth options and flexible scheduling to accommodate the patient's needs.
- Provide a quiet, private space with the option to lie down, dim lights, and minimize stressors.
- Assess whether therapy is safe and appropriate for the patient.
- Listen to and validate the patient's experience.
- Monitor the patient closely during sessions and allow for rest breaks or accommodations to minimize discomfort and exertion.
- Screen for post-exertional malaise (PEM).
- Screen for comorbid conditions (e.g., autonomic dysfunction, orthostatic intolerance, mast cell-related issues, biomechanical conditions).
- Determine if additional medical evaluations, imaging, or referrals to outside providers are needed.
- Assess the patient's functional capacity and ability to perform activities of daily living (ADLs).
- Identify the necessary accommodations, assistive devices, mobility aids, and support systems.
- Tailor care to the patient's tolerance level, using symptom-guided approaches.
- Instruct the patient on activity pacing and energy conservation techniques.
- Prioritize improving the patient's quality of life above all other goals.

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Each rehabilitation professional has a distinct but complementary role in the delivery of care as outlined below:

Allied Health Care Providers: Specialty care for PEM			
	Occupational Therapy	**Physical Therapy**	**Speech Language Pathology**
Scope of Practice	Activity of Daily Living (ADL) Specialists: Diagnose and address limitations in daily living tasks and life roles (occupations).	Movement Specialists: Diagnose and manage movement dysfunction to optimize physical function and support ADLs.	Communication Specialists: Diagnose and treat disorders of communication and cognition, as well as voice, speech, and swallow dysfunction.
Role in Care	• Screen for Post-Exertional Malaise (PEM). • Focus on function in daily life, self-care, work, and leisure activities. • Educate on the use of adaptive equipment, environmental and activity modifications, and symptom management. • Teach activity pacing and energy conservation strategies. • Assess activity stressors as they relate to symptom responses. • Suggest adaptive equipment and activity or environmental modifications. • Help with ADLs/occupations. • Suggest sensory modifications to reduce symptom triggers. • Educate and support caregivers and family members. • Assist with disability documentation and accommodations related to functional performance and occupational impairments.	• Screen for Post-Exertional Malaise (PEM). • Focus on physical function, mobility, strength, and balance. • Educate on symptom management, lifestyle changes, and ME/CFS-appropriate exercises. • Teach activity pacing and energy conservation strategies. • Recommend adaptive equipment and modifications to activities or environments. • Suggest sensory environment adjustments to reduce symptom triggers. • Support patients with activities of daily living (ADLs). • Provide manual (hands-on) treatments such as lymphatic massage or joint mobilizations. • Educate caregivers on safe movement and positioning. • Assist with disability documentation and accommodations related to physical and mobility impairments.	• Screen for Post-Exertional Malaise (PEM). • Focus on cognitive-communication and swallowing function. • Educate in compensatory strategies to support swallow function • Teach energy conservation and cognitive pacing strategies. • Instruct in compensatory strategies for memory, processing, and executive function. • Instruct in strategies to support verbal and written expression and comprehension. • Educate caregivers on communication strategies and cognitive supports. • Assist with disability documentation and accommodations related to cognitive or communication impairments.

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15.2 Benefits of Rehabilitation for ME/CFS[12,130,183]

- **Extended Patient Interaction:** Rehabilitation providers typically have longer and more frequent appointments, giving them greater insight into the patient's needs, limitations, and responses to treatment.
- **Specialized Focus:** With a problem-solving approach, rehab professionals focus on improving daily functioning by helping patients adapt to the challenges of living with a chronic condition.
- **Patient Education:** Longer sessions allow rehab providers to spend more time educating patients about managing their condition and optimizing daily activities.
- **Disability Support:** Rehabilitation professionals assist with disability documentation by carefully noting impairments and limitations that affect participation in daily living and work activities.
- **Comorbidity Screening:** Frequent and prolonged contact enables rehab providers to identify potential comorbid conditions that may require further medical evaluation.
- **Ongoing Monitoring:** Rehab providers can regularly update referring medical providers about the patient's status and response to treatments, supporting timely adjustments to care plans.

15.3 Example Physician Referrals for Patients with Suspected PEM[32,183]

Referral to Occupational Therapy: Refer for evaluation and treatment of functional limitations related to suspected post-exertional malaise (PEM). Please assess activities of daily living (ADLs), recommend adaptive strategies, and provide education on pacing, energy conservation, and symptom management. Screen for comorbid conditions and assist with disability documentation as needed. Offer telehealth options if able and appropriate.

Referral to Physical Therapy: Refer for evaluation and treatment of physical and functional limitations related to suspected post-exertional malaise (PEM). Please evaluate for safe mobility, suggest appropriate mobility aids, teach energy conservation and activity pacing techniques, and modify physical tasks to minimize exertional stress. Do not prescribe graded exercise or activity. Minimize or avoid exertion-based testing that could contribute to PEM. Offer telehealth options if able and appropriate.

Referral to Speech Language Pathology (SLP): Refer for evaluation and treatment of cognitive-communication and swallowing function in the context of suspected post-exertional malaise (PEM). Please assess for cognitive fatigue, memory, and word retrieval difficulties, teach cognitive pacing strategies, recommend communication supports, and assist with documentation for accommodations as needed. Communicate any safety concerns in the referral specific to swallow (aspiration risk, malnutrition/dehydration risk, etc.). Offer telehealth options if able and appropriate.

When making referrals, it is important to include any comorbid conditions or considerations that may be relevant to the patient's care. These can include, but are not limited to, craniocervical instability,[37,60] mast cell hyper-reactivity,[92,180] orthostatic intolerance,[106,149] post-exertional malaise,[32] sensory processing disorder, autism, or a history of trauma. Including these details will help ensure a comprehensive and coordinated approach to the patient's treatment.

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Rehabilitation Resources:

- Rehab Professional Resources (BHC)
- How the Basics of PT & OT Can Help People with ME/CFS (BHC)
- Educational Videos About Graded Exercise and Pacing (Workwell Foundation)
- Educational Handouts on ME/CFS (Workwell Foundation)
- Opposition to Graded Exercise Therapy Letter (Workwell Foundation)
- Using Exercise Therapy for Long COVID Without Screening for Post-Exertional Symptom Exacerbation Potentially Increases the Risks for Patients Who Suffer from it
- Wright J Astill SL, Sivan M: The Relationship between Physical Activity and Long COVID: A Cross-Sectional Study. Int. J. Environ. Res. Public Health 2022;19,5093. doi.org/10.3390/ijerph19095093
- Greenhalgh T., Sivan M., Perlowski A., Nikolich J. Ž. (2024). Long COVID: a clinical update. The Lancet. ISSN 0140-6736. https://pubmed.ncbi.nlm.nih.gov/39096925/ Rehabilitation would normally include pacing strategies

CHAPTER 16: BEHAVIORAL HEALTH

Introduction

Behavioral health support is an important component of multidisciplinary care for individuals with ME/CFS, Long COVID, and other infection-associated chronic conditions (IACCs).[3,8,16] These illnesses are multisystem, physiological in nature, and often characterized by post-exertional malaise (PEM), dysautonomia, mast cell activation, and neuroinflammation.[10,12,124,139]

Historically, patients have been told their symptoms are "all in their head"—an assertion rooted in the absence of biomarkers and limited medical understanding rather than evidence.[8,12,95] This misattribution has caused long-standing harm. Individuals have been misdiagnosed with conversion disorder, somatic symptom disorder, factitious disorder, obsessive-compulsive disorder and treatment-resistant depression.[8,12,95] Many have been prescribed psychiatric medications that worsened their autonomic symptoms or subjected to behavioral therapies like graded exercise therapy (GET) or cognitive behavioral therapy (CBT) under the false assumption that these illnesses stemmed from maladaptive beliefs or behaviors.[89,135,181]

When referring a patient for behavioral health support, it is critical that providers select specialists who understand the physiological basis of ME/CFS and Long COVID, or who are willing to engage in learning. It is equally important to maintain collaborative oversight to ensure that psychological interventions do not inadvertently worsen physical health.[8,12,16]

While some patients do experience grief, anxiety, or depression, these often emerge as natural responses to profound physical impairment, loss of identity, chronic medical trauma and ongoing medical uncertainty—not as root causes of their condition.[8,16] Behavioral health providers have a meaningful role to play when they approach care with humility, physiological literacy, and trauma-informed collaboration.

16.1 Shifting the Narrative: Recognizing Historical Harm

- A significant proportion of patients report delayed diagnosis, dismissal, or psychiatric mislabeling prior to receiving appropriate medical care.[8,39] It benefits behavioral health providers to assume patients seeking care have likely received some manner of this mistreatment.
- CBT and GET have historically been promoted as curative treatments for ME/CFS and, more recently, Long COVID—but mounting evidence has shown these interventions may trigger PEM, increase symptom burden, and contribute to physical and psychological harm.[89,135,181,183]
- Prevalence data suggest that the majority of psychiatric symptoms in this population are secondary—not pre-existing—and stem from the medical trauma, isolation, and uncertainty of living with a misunderstood condition.[5,16]

"We must move away from a default psychiatric framing and toward a nuanced understanding of how immune, autonomic, and neurological dysfunctions shape mood and behavior." — Paige Zuckerman, CMHC

16.2 Understanding Symptom Expression

Behavioral symptoms in this population may not follow conventional psychiatric patterns.
Providers should ask: Is this truly a mental health disorder—or a physiological manifestation of autonomic dysfunction, mast cell activation, neuroinflammation, or PEM?[1,5,10,32]

Common psychological or behavioral symptoms and potential physiological roots:[1,5,8,10,12,16,32,93]

Symptom	Potential Physiological Driver
Panic attacks, heart racing, dizziness	Orthostatic intolerance, POTS
Emotional lability, irritability	Mast cell activation, hormonal shifts, HPA-axis dysregulation, PEM
Memory lapses, word-finding difficulty	Neuroinflammation, PEM, MCAS, OI
Social withdrawal, anhedonia	PEM recovery, overstimulation
Depression or grief	Loss of identity, future uncertainty, prolonged illness course

It is critical to validate these symptoms while avoiding psychiatric pathologization.[8,12]

16.3 Best Practices in Behavioral Health Support.[8,12,16,32,79]

Effective approaches include:

- **Supportive psychotherapy** to help patients navigate grief, identity shifts, and life restructuring.
- **Acceptance and Commitment Therapy (ACT)** or **mindfulness-based strategies** for emotion regulation and grounding.
- **Somatic-based therapies** (e.g., sensorimotor psychotherapy, trauma-informed yoga, NSDR) if well tolerated and adapted to avoid PEM.
- **Pacing-informed adaptations** to session length, frequency, and sensory input.

Cautions in Therapy:

- **EMDR** can be effective, but may be too activating if conducted traditionally (e.g., with eye movements). Some patients tolerate **bilateral tactile stimulation** (tappers or auditory tones) better than visual or vestibular methods. Sessions may need to be shortened and spaced out, with frequent opportunities for pause and symptom scaling. Additionally, clinicians may need to prepare for a more protracted treatment time frame apropos to pacing.
- **Talk therapy** may induce PEM if cognitive load is too high. Encourage low-stimulation environments, reclined positioning, adaptive telehealth options, and protected rest periods post-session.
- Always screen for PEM risk post-therapy, and adjust treatment plan and modalities accordingly.

16.4 Medication Considerations[12,107,185]

- Medications that worsen orthostatic symptoms, mast cell activation, or cognitive impairment should be prescribed cautiously. These include certain SSRIs, SNRIs, or antipsychotics.
- Start with low doses and titrate slowly.
- Consider mitochondrial or neuroinflammatory support agents (e.g., low-dose naltrexone, magnesium, omega-3s) in collaboration with the medical team.

16.5 Collaborative, Trauma-Informed Care[8,12,32,39,89]

- Acknowledge and address **medical trauma** in care plans. Many patients have been undermined, interrogated, disbelieved, or harmed by the healthcare system.
- Use **neutral, supportive language:** "This is a real, multisystem condition," "You deserve care," and "Let's work together to manage what's happening in your body."
- Communicate with the behavioral health provider about:
  - The primary physiological diagnosis.
  - The presence of PEM and autonomic dysfunction.
  - The need to avoid interventions that could excessively exacerbate physiological symptoms.
- Monitor for inappropriate psychiatric relabeling (e.g., functional neurological disorder, somatization, conversion) by any member of the care team and intervene early if necessary.
- Educate family members and caregivers about PEM, sensory sensitivities, and how to support without overwhelming.

Closing Note

Behavioral health support should never be positioned as a substitute for comprehensive medical care.[8,12] However, when offered thoughtfully—grounded in an understanding of PEM, autonomic dysfunction, and the lived experiences of people with ME/CFS, Long COVID, and IACCs—it can be a critical part of healing, stabilizing and improving a patient's quality of life.[12,16]

Medical providers and behavioral health specialists each have distinct and complementary roles to play. Working collaboratively, they can ensure that the physiological aspects of the illness are recognized and addressed while also supporting patients in navigating grief, identity shifts, emotional distress, and daily coping.[12,16] Clear communication, shared understanding of the disease, and trauma-informed principles strengthen this partnership.

By approaching care with humility, clinical vigilance, and deep respect for the realities of these conditions, providers across disciplines can help restore trust, reduce harm, and offer patients a more integrated, compassionate path forward.[8,12]

CHAPTER 17: CAREGIVING

Introduction

Caring for someone with ME/CFS, Long COVID, or other IACCs can be life-altering. For family members, partners, friends, or professionals, the caregiving role often involves navigating a long course of uncertainty, advocating for needs that are frequently misunderstood, and adjusting daily life to support a loved one with limited capacity. As symptoms intensify or the illness progresses, caregivers may find themselves overwhelmed, isolated, or unsure how to help.

Clinicians play a vital role not only in validating the caregiver's experience, but also in guiding them toward sustainable, compassionate care. This chapter offers practical strategies for supporting caregivers—including tools to help them believe and understand their loved one's condition, access appropriate in-home services, adapt living environments to avoid symptom exacerbation, and preserve the integrity of the relationship. When providers acknowledge and support the caregiver's journey, they help lay the foundation for more effective, person-centered care.

17.1 Understanding the Caregiver's Role and Needs

Caregivers of people with ME/CFS and related conditions often assume responsibilities that span far beyond typical support roles. They may coordinate appointments, track medications and symptoms, manage daily activities, advocate within healthcare or educational systems, and provide emotional support—all while witnessing their loved one struggle with unpredictable and often severe symptoms. Many caregivers express grief over lost routines, social connections, or changes in identity and roles within the family.

Healthcare providers can help by recognizing and affirming the emotional and logistical complexity of caregiving. Listening without judgment, offering education about the disease, and validating both the caregiver's and the patient's experiences are essential steps. When providers signal belief in the patient's condition, they empower the caregiver to do the same with confidence—strengthening trust and improving care.

Caregivers also need tools to navigate their own well-being. Providers should screen for caregiver stress, depression, and burnout, and when possible, direct them to respite services, counseling, or community-based resources. This proactive support not only protects the caregiver's health, but also contributes to greater stability and continuity in care for the patient.

17.2 Creating a Supportive Home Environment

For caregivers, adapting the home environment is an important part of supporting their loved one's stability and dignity. These changes do not need to be costly or complex, but they do require awareness and intentionality. Providers can help by discussing the specific sensitivities associated with ME/CFS and encouraging caregivers to explore environmental modifications such as:

- **Minimizing sensory input**: Use blackout curtains, soft lighting, and noise-dampening tools (e.g., earplugs, white noise machines) to reduce visual and auditory overstimulation.
- **Supporting orthostatic intolerance**: Encourage use of mobility aids, adjustable beds, shower chairs, and flexible rest spaces that allow patients to recline or lie flat throughout the day.

- **Reducing physical exertion:** Simplify layout and access to key items in the home to reduce the need for movement. Assistive tools (grabbers, wheelchairs, or stools in the kitchen) can preserve energy.
- **Improving air quality and temperature regulation**: Patients with ME/CFS may have poor temperature tolerance and sensitivities to odors or chemicals. HEPA filters, scent-free products, and layered clothing or blankets can help.

These modifications can also be a tangible way for caregivers to stay engaged and feel effective in their role. Providers can support this process by offering documentation for accommodations, connecting families with occupational therapists, or supplying pacing and PEM prevention handouts that guide home-based care.

17.3 Preserving Relationships and Emotional Connection

The relational impact of ME/CFS can be profound. Roles within a household shift, routines are disrupted, and the emotional toll on both the patient and the caregiver can leave each feeling isolated or misunderstood. Maintaining emotional connection and a sense of partnership is essential—not only for quality of life, but also for long-term caregiving sustainability.

Providers have a critical role in naming these challenges openly and supporting both members of the caregiving dyad. One of the most effective ways to foster emotional connection is to ensure caregivers have access to in-home services and respite support, which allow them to preserve some of their prior roles—as a partner, parent, sibling, or friend.

When caregivers have structured time away or professional help with physically and mentally taxing aspects of care, they can:

- Spend more meaningful, present time with their loved one, engaging in ways that feel emotionally nourishing rather than purely task-based.
- Protect their own health and energy, which helps prevent resentment and burnout.
- Reconnect with their own identity, support networks, and hobbies, allowing them to bring a fuller self into the caregiving relationship.

Meanwhile, the person with ME/CFS often reports less guilt or fear of being a burden when their caregiver is supported. This shift can reduce emotional strain and enhance the quality of shared moments. Providers can facilitate this dynamic by:

- Proactively offering documentation and language for in-home care services (e.g., home health, personal care aides, or respite programs).
- Helping caregivers navigate Medicaid waivers, local disability services, or community-based home and community support options.
- Reinforcing to both the patient and the caregiver that asking for help is not a failure—it is a strategic way to preserve connection and prevent crisis.

By validating the relational strain and offering concrete tools to address it, providers help preserve the bond between patient and caregiver—a bond that often becomes a source of resilience and strength.

17.4 Supporting the Caregiver Over Time: Routine Check-Ins

The role of caregiver to someone with ME/CFS or Long COVID is often sustained over years and may involve periods of increased severity, new medical challenges, and evolving needs. As such, caregivers require **ongoing support**, not just at the time of diagnosis or initial role transition.

Providers are uniquely positioned to monitor the health and well-being of the caregiver as part of a comprehensive care model. This can include:

- **Brief, routine check-ins** during appointments to ask how the caregiver is doing, what supports are in place, and whether they are receiving care for their own medical, emotional, or social needs.
- **Referrals to counseling**, caregiver support groups, or primary care if signs of burnout, depression, or chronic stress are evident.
- **Normalizing** caregiver strain and reinforcing that caring for themselves is not selfish, but essential to their ability to continue caring for someone else.
- **Offering proactive resources,** including printouts, service lists, or care planning tools, that caregivers can review outside the visit when time and energy allow.

These small but intentional gestures can reduce isolation, validate the caregiver's experience, and build trust with both members of the care dyad. They also reinforce the idea that care is not only about symptom management—it is about **sustaining a system of support** around the person living with ME/CFS.

Recommended Resources for Supporting Caregivers of Patients with Severe ME/CFS:

- How to be a Demanding Diplomat as an ME/CFS Caregiver
- Caregiver Mental Health handout
- Severe ME/CFS Caregiver Webinar
  - Caregiver Resource Guide
  - Transcript
  - Recording
- Caregiver Wisdom webpage (rich with resources and monthly online support groups)

Conclusion

Caring for someone with ME/CFS or Long COVID requires a deep emotional, physical, and logistical commitment—and providers play a critical role in sustaining that care. By validating the caregiver's experience, offering practical tools, facilitating access to services, and making time for ongoing check-ins, clinicians can help maintain not only the well-being of the caregiver, but the stability and connection of the entire care partnership. Supporting the caregiver is not a separate task—it is a central part of whole-person, relationship-centered care.

CHAPTER 18: DISABILITY AND ACCOMMODATIONS

Introduction

Patients with ME/CFS, Long COVID, and infection-associated chronic conditions (IACCs) often experience substantial functional impairment that significantly limits their ability to engage in daily activities, maintain employment, or attend school. These impairments are frequently not captured by standard diagnostic tests, contributing to underrecognition of the illness and delays in obtaining appropriate support. Clinicians have a critical role in identifying, documenting, and advocating for these impairments to support accommodation requests and disability claims.

18.1 Essential Documentation Elements

Accurate and specific clinical documentation is essential when supporting requests for disability accommodations or benefits. The following elements should be included in your records:

1. Detailed Symptom Course & Fluctuations

- Document severity and unpredictability (e.g., good days vs. bad days).
  - *Example: "Patient experiences 3–4 bad days per week. On bad days, they are primarily confined to bed, require caregiver assistance for meals, and need support for basic mobility such as using the bathroom."*
- Include descriptions of post-exertional malaise (PEM) triggered by activity:
  - *Example: "Following attendance at her daughter's graduation, the patient spent the entire next day bedridden recovering from PEM."*

2. Functional Impairment Metrics

- Use metrics like Hours of Upright Activity (HUA), the Good Day/Bad Day Questionnaire, and objective orthostatic intolerance testing.
  - *Example: "Patient is only able to tolerate 4 hours with feet on the ground on good days and less than 1 hour with feet on the ground on bad days. Patient is able to perform 2-3 of the following simple tasks on good days: grooming, preparing a simple meal, and riding in the car to go to a doctor's appointment. On bad days, the patient is not able to do these simple tasks and is primarily confined to bed requiring assistance to get food and drinks and go to the bathroom."*

3. Impact on Activities of Daily Living (ADLs)

- Specify lost abilities (e.g., unable to cook, dress without rest breaks).
- Consider using FUNCAP Questionnaires which are structured tools designed to assess functional capacity and disability across multiple domains, helping to capture the impact of PEM on daily life and support needs.
- Consider occupational therapy home evaluation.
  - *Example: "Patient requires assistance from caregivers with basic ADLs including dressing, meal prep, and bathing. Patient is only able to tolerate bathing once/week and cannot sit upright for more than 10 minutes at a time."*

4. Orthostatic Testing Results

- Include objective data from 10-Minute NASA Lean Test or Tilt Table Test findings that support autonomic impairment.
  - *Example: "Patient experienced tachycardia and syncope after 4 minutes of standing during 10-Minute NLT."*
  - *Example: "While the patient's HR and BP were within a normal range during the 10-Minute NASA Lean Test, the patient had obvious signs and symptoms of cerebral hypoperfusion including cognitive impairments (specifically, the inability to follow basic commands and answer questions) and acrocyanosis of hands and feet that were partially relieved with abdominal compression and lying down with legs elevated for 10 minutes."*

5. Cognitive or Neurocognitive Testing Data

- Consider speech therapy evaluation.
- Consider neurocognitive evaluation.
- Deficits in cognition, communication, and language along with physical symptoms can justify workplace accommodations and disability.
- Specify communication deficits (e.g., delayed response time, increasing requests for repetition/clarification, word finding delays, lack of clarity or linear thought process, difficulty maintaining topic, prolonged reading time).
- Note any other communication symptoms (e.g., speech or voice changes) or physical symptoms including headache, eye strain, sensory intolerance, dizziness, etc.
- Document how long until symptomatic and whether you think a cognitive component of the appointment affected the patient (e.g., screen use, reading, answering questions, etc.)
- Document delayed symptoms (e.g., whether patient experienced PEM after session and how long it took to resolve)
    - *Example: "In both this session and the previous one, the patient was unable to continue beyond 35 minutes of therapy, which included reading, education, and collaborative discussion. They reported symptoms of lightheadedness, eye strain, increased sensitivity to sound, and cognitive fog. Clinically, they demonstrated slowed and halting speech, frequent word-finding difficulties, tangential and incomplete thought processes, and diminished comprehension. At present, they continue to exhibit low tolerance for brief periods of cognitively demanding activities, even while seated."*

6. Trialed & Failed Treatments

- Document attempts to manage symptoms, showing that impairment persists despite interventions.
    - *Example: "Patient's symptoms have improved since implementing activity pacing strategies and starting cromolyn sodium and ivabradine, but the patient is still only able to sit upright for 4 hours/day and requires assistance with ADLs."*

18.2 Referral for Specialized Cognitive Assessment

Formal neurocognitive evaluation remains the gold standard for documenting cognitive impairment in ME/CFS and Long COVID.

When referring for evaluation:

- Seek clinicians familiar with ME/CFS/Long COVID.
- Request:
    - Shorter sessions
    - Built-in rest breaks
    - Option to break testing into two days (to capture PEM)
        - Documentation of delayed symptom exacerbation is important to capture PEM and to identify how long it takes to resolve.
- These evaluations are especially useful for:
    - Disability claims
    - Academic/workplace accommodations
    - Differential diagnosis
    - Atypical or disproportionate cognitive symptom presentations

18.3 Supporting Disability Applications

- **Cardiopulmonary Exercise Testing (CPET)**
  - 2-Day Cardiopulmonary Exercise Test (CPET) shows reduced aerobic capacity and anaerobic threshold (useful for SSDI cases but may induce severe PEM). Use with caution and implement pre/post supports. See PEM chapter for more insights.
- **Medical-Legal Language for Documentation**
  - Avoid vague terms like "chronic fatigue." Instead, use:
    - "*Patient meets the diagnostic criteria for ME/CFS, as defined by the IOM (2015), with disabling post-exertional malaise (PEM), autonomic dysfunction, and cognitive impairment.*"
    - "*Functional impairment is equivalent to severe heart failure or advanced multiple sclerosis.*"
  - Accurately describe the patient's physical and cognitive presentation in visits, either telehealth or in-person.
  - Avoid vague descriptors like "healthy appearing," as they can misrepresent the patient's condition. Instead, provide objective observations such as cognitive changes, physical posture (e.g., efforts to elevate legs, reclining during the visit), autonomic indicators (e.g., changes in pupil size), and any other relevant clinical signs noted during the encounter.

Disability Resources:

- ME/CFS Clinician Coalition Resources
- *Documenting Disability in ME/CFS* (Podell, Dimmock, Comerford, 2019)
- Medically Documenting Disability in ME/CFS Cases (Frontiers in Pediatrics, 2019)
- Disability in ME/CFS (National Academy of Medicine Report, Appendix C.)
- Providing Medical Evidence for Individuals with ME/CFS (SSA)
- Evaluating Disability for Patients with Fibromyalgia (SSA)
- Guidance on "Long COVID" as a Disability Under the ADA, Section 504, and Section 1557

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18.4 Workplace Accommodations

People with ME/CFS or Long COVID may hesitate to request accommodations due to fear of job loss or stigma. Clinicians can help patients understand their rights and identify practical supports.

Provider Role

- Offer documentation that educates without disclosing unnecessary details that could endanger job security.
- Encourage communication with employers about accommodations early.

Accommodations

- **Emergency Contact/Support During Symptom Exacerbations**
  - During episodes of PEM or autonomic dysfunction (POTS/OI), employees may struggle to effectively communicate their needs and may require extra assistance in managing symptoms or arranging transportation home. To prepare for such situations, employees should designate a support person who can notify their employer if they are unable to communicate their need to miss work or leave.
- **Communication with Employer**
  - Employees should inform the employer as early as possible about the need for accommodations, and seek to understand what options are available and the process for putting them in place.
- **Common Accommodations**
  - Work attendance flexibility
    - Remote or hybrid work options
    - Flexible work schedules
    - Allow the employee to leave early or arrive later, when necessary.
    - Allow the option to participate remotely in meetings.
    - Allow frequent or extended rest breaks when needed.
    - Allow employee to work when they have the most energy.
  - Task flexibility
    - Allow flexible deadlines.
    - Provide alternative tasks if possible.
  - Physical
    - Allow assistive devices and mobility aids.
    - Provide accessible bathrooms and allow frequent bathroom breaks.
    - Photosensitivity
      - Allow sunglasses or blue-light-blocking glasses.
      - Provide screen protectors that reduce blue light or glare.
      - Allow adjustment of computer display settings.
      - Ability to dim or adjust lighting
      - Allow camera to be off in meetings.

        - Sounds Sensitivity
            - Provide a quiet workspace.
            - Allow earplugs or noise-cancelling headphones.
        - Provide a talk-to-text software option instead of typing.
        - Offer ergonomic workstation setup.
        - Allow access to food/drinks during work.
    - Cognitive
        - Offer monotasking vs multitasking.
        - Provide task reminders.
        - Provide written instructions.
        - Limit distractions/interruptions.
        - Provide a quiet workspace with minimal sensory or socializing.
        - Record meetings and provide transcripts after.
        - Offer screen reader software.
    - Orthostatic intolerance
        - Offer the option to lie down with legs elevated.
        - Offer the option to sit, ideally with legs elevated, or use of a zero-gravity chair.
        - Offer computer displays that can change positions.
    - Allergies and chemical sensitivities
        - No-fragrance office policies
        - Nontoxic, unscented, or zero-fragrance cleaning products
        - Allergy- and sensitivity-friendly food options
        - Allow air purifiers.
        - Change air filters regularly.
        - Allow employee to wear a mask at work.
    - Accessibility
        - Disability placard for parking
        - Private, disability-accessible office space
        - Support with transportation to work
        - Allow employee to record meetings or have someone else take notes for them.
        - Provide rest areas in the office.
        - Allow the use of assistive devices or mobility aids.
        - Allow the use of assistive technology.

- **Collaboration with Rehabilitation Providers (OT, PT, SLP)**
    - If you feel uncomfortable or inadequate in knowing what accommodations to suggest, referral to rehabilitation providers may be helpful.

Work Accommodation Resources

- Recommendations for ME/CFS from US Job Accommodations Network (JAN)

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18.5 School Accommodations

School personnel need to be informed early and reminded often that ME/CFS symptoms can be unpredictable and fluctuate rapidly. Educating staff on the role they play in a student's well-being is essential, as they may not realize how accommodations and consistent follow-through can influence health outcomes. Because students with ME/CFS or Long COVID may be unaware of their options or unsure how to navigate the process, helping them identify and implement accommodations can make a meaningful, though often unseen, difference in their ability to engage and recover.

Provider Role

- Educate schools about symptom fluctuation and the impact of PEM, POTS, etc.
- Write letters supporting accommodations.
- Recommend inclusion of PEM management guidance for teachers, school nurses, etc.

Common Accommodations

- **Emergency Contact/Support During Symptom Exacerbations:**
  - During episodes of PEM or autonomic dysfunction, students may struggle to effectively communicate their needs and might require extra assistance in managing symptoms or arranging transportation home. To prepare for such situations, students should designate a support person who can notify their teachers or school personnel if they are unable to communicate their need to miss class or leave early.
  - Parents should provide resources for staff to know how to help them during these episodes.
- **Communication with School**
  - Students and their parents should promptly notify the school about the need for accommodations in order to explore available options and understand the steps required to implement them.
  - Students and their parents should meet with academic advisors and teachers early on to discuss what the student can realistically achieve with the support of accommodations.
- **Common Accommodations**
  - Attendance flexibility
    - Allow the student to miss class or leave class early.
    - Allow the option to participate remotely.
    - Allow the student to change positions (e.g., option to lie down with legs elevated).
  - Assignment flexibility
    - Allow flexible deadlines.
    - Provide alternative assignments (mastery over quantity).
  - Examination flexibility
    - Schedule examination when the student has more energy during the day.
    - Allow student to take part of the exam on one day and complete it on a different day.
    - Allow a private, quiet space with minimal distractions to complete the exam.
    - Allow rest breaks during the exam and the option for the student to lie down or go to the bathroom when needed.
    - Allow the student to have food and drinks during exams.
    - Allow alternative testing methods (e.g., verbal vs written).

    - Accessibility
        - Disability placard for parking
        - Private, disability-accessible dorm rooms
        - Support with transportation to classes
        - Allow student to record lectures or have someone else take notes for them.
        - Provide quiet, low sensory rest areas on campus.
        - Allow the student to leave class to go to the bathroom or access food/drink when needed.
        - Allow the use of assistive devices or mobility aids.

- **Collaboration with Rehabilitation Providers (OT, PT, SLP)**
    - If you feel uncomfortable or are unsure what accommodations to suggest, a referral to rehabilitation providers may be helpful.

School Accommodation Resources

- Environmental Accommodations for University Students Affected by ME/CFS
- Open Medicine Foundation School Fact Sheet (OMF)
- Recommendations for ME/CFS from US Job Accommodations Network (JAN)
- Meeting the Educational Needs of Young, ME/CFS Patients
- ME/CFS in Children: Information for Teachers and Schools (CDC)

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ME/CFS AND LONG COVID MEDICATION REFERENCE GUIDE

Important Clinical Notes

- **Start Low, Go Slow:** All medications should be started at low doses and titrated slowly
- **Medication Sensitivity:** Many ME/CFS and Long COVID patients have heightened sensitivity to medications
- **Monitor Regularly:** Watch closely for side effects and therapeutic benefit
- **Excipient Reactions:** Some reactions may be due to inactive ingredients rather than the medication itself
- **PEM Caution:** New medications can trigger PEM in sensitive or severely affected patients
- **Timing Consideration:** Avoid starting new medications during PEM episodes

Sleep Medications

Medication	Dosage	Notes
Trazodone	12.5-150 mg Q HS	For sleep initiation
Mirtazapine (Remeron)	7.5-15 mg Q HS	For sleep maintenance
Amitriptyline	10-100 mg Q HS	For pain modulation and sleep
Nortriptyline	10-50 mg Q HS	For pain modulation and sleep
Melatonin	0.5-3 mg Q HS	Low doses recommended; higher doses may be stimulating
Doxepin	3 mg Q HS	Dosage for insomnia lower than that for depression
Hydroxyzine	12.5-50 mg Q HS	For sleep and anxiety

Orthostatic Intolerance/POTS Medications

Medication	Dosage	Notes
Fludrocortisone	0.1-0.2 mg QD	Monitor electrolytes
Midodrine	2.5-10 mg TID	Avoid within 4 hours of bedtime
Droxidopa (Northera)	100-300 mg TID	Avoid within 4 hours of bedtime
Pyridostigmine (Mestinon)	15-120 mg TID or 180 mg-360 mg ER QD	Start low, increase gradually, may change to ER formulation if tolerance issues with short-acting
Ivabradine	2.5-7.5 mg BID	Selective heart rate reduction
Propranolol	10 mg TID or 60-160 mg ER	Beta-blocker
Atenolol	12.5-100 mg QD-BID	Beta-blocker

Orthostatic Intolerance/POTS Medications Continued

Medication	Dosage	Notes
Metoprolol ER	12.5-100 mg QD	Beta-blocker
Desmopressin	0.1-0.2 mg QD-BID	Hyponatremia possible, electrolyte monitoring needed
Atomoxetine (Strattera)	10-25 mg QD-BID	Off-label SNRI for neurogenic orthostatic hypotension, up titrate slowly
Methyldopa	125-250 mg BID	For POTS and autonomic dysfunction

Autonomic Dysfunction

Medication	Dosage	Notes
Clonidine	0.05-0.3 mg QD to TID, or long-acting patch	Alpha-adrenergic blocker for sleep/sympathetic overdrive
Prazosin	1-5 mg qHS up to BID	Alpha-adrenergic blocker for sleep/sympathetic overdrive
Guanfacine ER	1-4 mg QD	Alpha-adrenergic blocker; also for cognitive support

Pain Management

Medication	Dosage	Notes
Low-Dose Naltrexone (LDN)	0.5-4.5 mg Q HS	For neuroinflammation and pain; may cause vivid dreams. AM dosing if this occurs
Gabapentin	100-300 mg up to TID	For neuropathic pain
Pregabalin	75-150 mg QD-BID	For neuropathic pain
Duloxetine	40-120 mg QD	SNRI for pain
Milnacipran	12.5 to 50 mg BID	SNRI for pain
Cyclobenzaprine	5-10 mg Q 8 hrs	Muscle relaxant
Tizanidine	2-8 mg Q 8-12 hrs	Muscle relaxant, can increase HR
Amitriptyline	10-25 mg Q HS	For pain and sleep
Nortriptyline	10-25 mg Q HS	For neuropathic pain and sleep

Mast Cell Activation Syndrome (MCAS)

Medication	Dosage	Notes
Cromolyn Sodium	100-200 mg QID	Mast cell stabilizer; liquid and compounded forms
Gastrocrom (liquid Cromolyn)	1-5ml (up-titrate slowly to 5ml 3-4x/day; 15 minutes before meals and medications	Mast cell stabilizer; liquid
Ketotifen	1-2 mg Q HS	Mast cell stabilizer, H1 blocker
Famotidine	20-40 mg BID	H2 blocker
Cetirizine	10 mg BID	H1 blocker
Diphenhydramine	10-50 mg up to q 6 hours	H1 blocker
Hydroxyzine	10-25 mg up to q 6 hours	H1 blocker
Levocetirizine	5 mg BID	H1 blocker
Fexofenadine	180 mg BID	H1 blocker
Loratadine	10 mg BID	H1 blocker
Famotidine	20-40 mg BID	H2 blocker
Cimetidine	300-400 mg BID	H2 blocker
Montelukast	10 mg QD	Leukotriene blocker
Zafirlukast	20mg BID	Leukotriene blocker
Omalizumab (Xolair)	300 mg SQ once - twice a month	Anti-IgE biologic
Imatinib	100-200 mg QD	C-Kit Tyrosine-Kinase Inhibitor

GI Dysmotility

Medication	Dosage	Notes
Metoclopramide	2.5-5 mg BID	Black box warning for higher doses; limit to 12 weeks continuous use
Prucalopride (Motegrity)	1-2 mg QD	For constipation
Linaclotide	145-290 mcg QD	For constipation
Lubiprostone	8-24 mcg BID with food	For constipation
Loperamide	2-4 mg PRN (max 16 mg/day)	For diarrhea
Cholestyramine	4 g BID	For diarrhea; separate from other medications

PEM Support

Medication	Dosage	Notes
Dextromethorphan (DM)	15 mg soft capsule Q 4-6 hours, up to TID	For PEM episodes
IV Saline	1-1.5L up to every other day	For PEM episodes

Additional prescribing recommendations are available on the U.S. ME/CFS Clinician Coalition website.

- Treatment Recommendations

Supplements

Medication	Dosage	Notes
Magnesium Glycinate	400-800 mg at bedtime	For muscle relaxation and constipation
Omega-3 fatty acids	Not specified	Anti-inflammatory; for cognitive support
Curcumin	Not specified	Anti-inflammatory
NAC (N-Acetyl Cysteine)	600-1200mg QD	For cognitive support
CoQ10	100-300 mg QD	Mitochondrial support
Alpha-lipoic acid	600-1800 mg QD	For SFPN and mitochondrial support
Quercetin	500 to 1000mg	Mast cell stabilizer
Luteolin	100-300 mg QD	Mast cell stabilizer
Phosphatidylserine	100-300 mg QD	For cognitive support
Phosphatidylcholine	1200 mg QD	For cognitive support
Diamine Oxidase (DAO)	Take 30 minutes before meals	For histamine intolerance

Dietary Recommendations

Intervention	Details	Notes
Sodium Intake	4 grams/day (unless contraindicated)	For orthostatic intolerance
Fluid Intake	2-3L/day	For orthostatic intolerance
Low-FODMAP Diet	As tolerated	For GI symptoms
Low-histamine Diet	As tolerated	For MCAS symptoms

ASSISTIVE COGNITIVE STRATEGIES

Attention

- Work in a distraction-free environment such as a private office
- Limit background stimuli (e.g., avoid listening to music, having the television on in the background)
- Manage interruptions (e.g., set phone to Do Not Disturb, instruct others not to interrupt during focus time)
- Focus on only one task at a time
  - If you must be interrupted, switch tasks completely and complete the new one before returning to the first
- Pace yourself so that you are working when you feel your best, and plan to take rest breaks before you feel significantly fatigued

Memory

- Externalize memory by:
  - Keeping a daily prioritized "to do" list
  - Using a calendar in a highly visible area, and refer to it often
  - Have designated locations for frequently used items (e.g., keys, wallet, phone) and do not deviate from that spot
  - Take notes on important conversations
  - Use reminder apps or alarms
- Ask friends and family to give cues (e.g., "what are we doing today"?) instead of immediately providing the answer
  - This approach can help strengthen memory
- Use reflective listening (e.g., repeating what others have said) to make sure you understand and improve learning
- Use internal memory strategies such as:
  - Repetition of information
  - Visual imagery (e.g., learning the name of a friend as "Smiling Susan" or "Mustache Mike")

Executive Function

- Keep an organized, decluttered space
- Establish regular, structured routines for recurring tasks
- Break larger tasks down into smaller ones
- Narrate what you are doing to yourself
  - Regularly remind yourself of the end goal
  - Evaluate whether you are still on track
  - Adjust approach as needed

RESOURCES

Diagnostic & Treatment Resources

National Academy of Medicine 2015 Diagnostic and Treatment Guidelines

- Guide for Clinicians
- Full Report

U.S. ME/CFS Clinician Coalition

- Testing Recommendations for Suspected ME/CFS (2021)
- ME/CFS Treatment Recommendations (2021)
- Basics of Diagnosis & Treatment (2020)

Mayo Clinic Proceedings

- Myalgic Encephalomyelitis/Chronic Fatigue Syndrome: Essentials of Diagnosis and Management (2021)
- Diagnosis and Management of Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (2023)

Disability & Accommodation Resources

Disability Resources:

- ME/CFS Clinician Coalition Resources
- Documenting Disability in ME/CFS (Podell, Dimmock, Comerford, 2019)
- Medically Documenting Disability in ME/CFS Cases (Frontiers in Pediatrics, 2019)
- Disability in ME/CFS (National Academy of Medicine Report, Appendix C.)
- Providing Medical Evidence for Individuals with ME/CFS (SSA)
- Evaluating Disability for Patients with Fibromyalgia (SSA)
- Guidance on "Long COVID" as a Disability Under the ADA, Section 504, and Section 1557

Work Accommodation Resources:

- Recommendations for ME/CFS from US Job Accommodations Network (JAN)

School Accommodation Resources:

- Environmental Accommodations for University Students Affected by ME/CFS
- Open Medicine Foundation School Fact Sheet (OMF)
- Recommendations for ME/CFS from US Job Accommodations Network (JAN)
- Meeting the Educational Needs of Young, ME/CFS Patients
- ME/CFS in Children: Information for Teachers and Schools (CDC)

RESOURCES

Forms

- Good Day/Bad Day Questionnaire: (captures function on baseline/good days and PEM/crashed/bad days and hours of upright activity (HUA)
- 10-Minute NASA Lean Test or Tilt Table Test: in-office passive standing test to assess for orthostatic intolerance
- PROMIS Fatigue and Cognitive Function Questionnaires (4 or 7)
- SF-36 [RAND-36] Functional Assessment Scale– Measures health-related quality of life and daily limitations.
- **FUNCAP** – Assists in documenting support needs and loss of independence across multiple domains.
- FUNCAP55: more detailed
- FUNCAP27: shorter
- MCAS 24-Hour Urine Collection Guide (Handout)
- 10-Minute NASA Lean Test Instructions (Handout)
- Orthostatic Intolerance & Dysautonomia Educational (Handout)

Continuing Medical Education

- CME Michigan State Medical Society Grand Rounds: Post-Exertional Malaise
- Long COVID & Post-Infectious Syndrome ECHO series: See PEM lecture with respective slides

Patient Education

- Patient Education Modules by Bateman Horne Center and Emerge Australia: A step-by-step series designed to help patients understand their experience with PEM, recognize personal triggers and early warning signs, and develop individualized pacing strategies.
- Life with a Low Battery: Living with ME/CFS
- The Basics: ME/CFS
- The Basics: Post-Exertional Malaise (PEM)
- The Basics: Orthostatic Intolerance (OI)
- The Basics Playlist

Provider Education VIDEOS

Provider education videos can be found on the Bateman Horne Center YouTube channel.

- Clinical Care Guide: Managing ME/CFS, Long COVID, and IACCs play list.

RESOURCES

Rehabilitation Resources:

- Rehab Professional Resources (BHC)
- How the Basics of PT & OT Can Help People with ME/CFS (BHC)
- Educational Videos About Graded Exercise and Pacing (Workwell Foundation)
- Educational Handouts on ME/CFS (Workwell Foundation)
- Opposition to Graded Exercise Therapy Letter (Workwell Foundation)
- Using Exercise Therapy for Long COVID Without Screening for Post-Exertional Symptom Exacerbation Potentially Increases the Risks for Patients Who Suffer from it