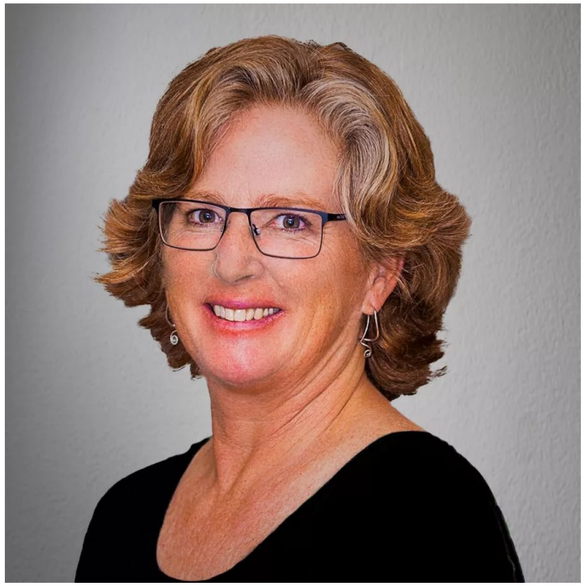
A Practical Approach to Complex Long COVID & ME/CFS Patient Cases



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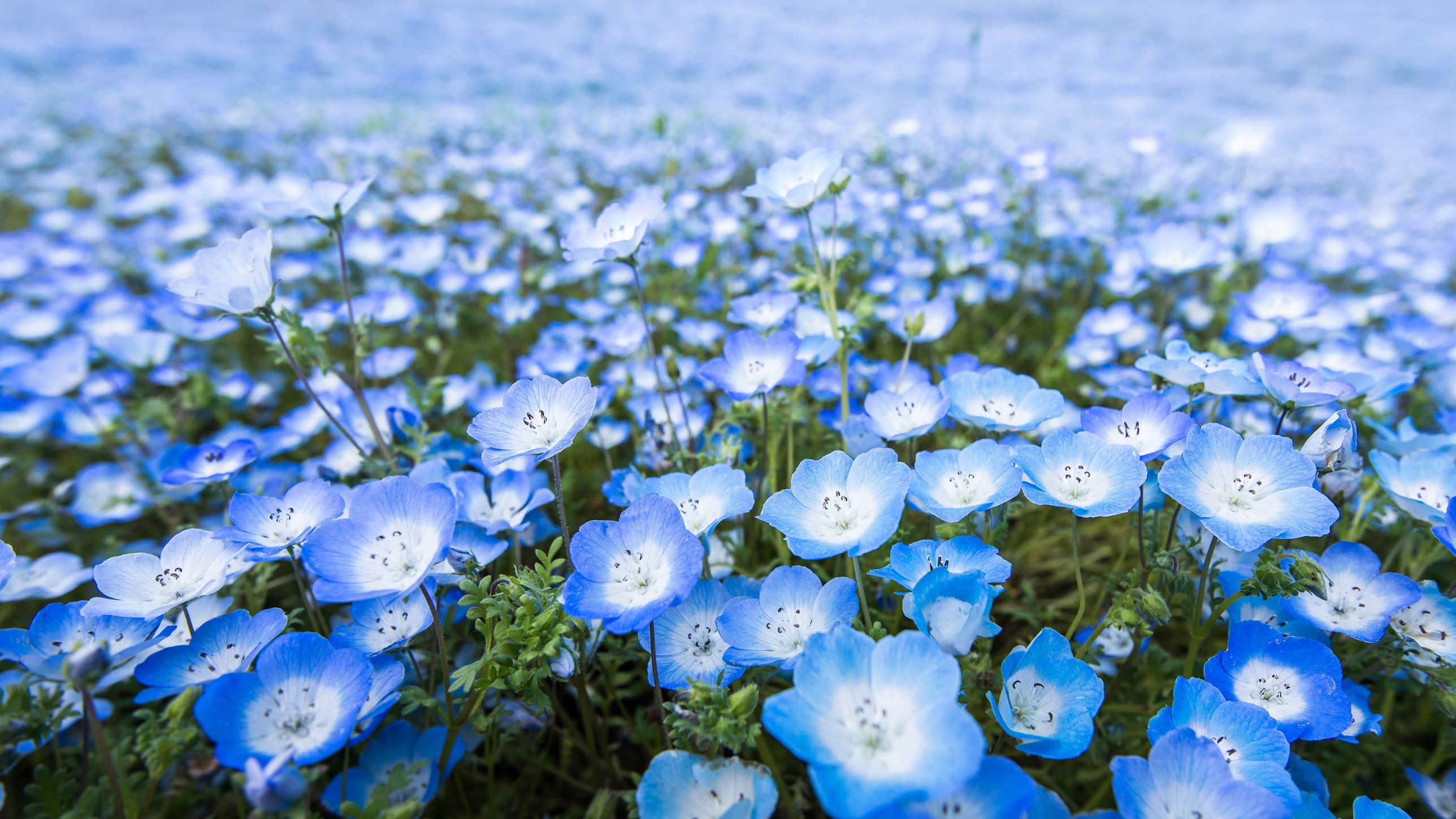
RESEARCH | CLINICAL CARE | EDUCATION

Objectives

- Define a complex Long COVID ME/CFS patient.
- Demonstrate the commonalities and differences between complex Long COVID ME/CFS patients.
- Discuss assessment and treatment approaches for complex Long COVID ME/CFS patients.
- Develop strategies for caring for complex Long COVID ME/CFS patients.

Disclaimer

Patient cases shared in this session are intended solely for educational purposes. Some cases represent composite scenarios that illustrate key aspects of disease presentation, rather than the experience of a specific individual. In instances where individual patient information or video content is shared, the patients have provided full consent and authorized the use of their content and discussion of their case in this setting.



What is a complex Long COVID ME/CFS patient?

- Multiple Comorbid Conditions
  - Meet ME/CFS criteria and have significant PEM
  - Dysautonomia
  - MCAS
  - Hypermobility/Connective Tissue Disorders
    - CCI/AAI
    - Tethered cord symptoms
    - Symptomatic intracranial pressure fluctuations
    - Venous compression/congestion syndromes
- Multi-drug sensitivities "paradoxical reactions"
- Seemingly treatment resistant
- Repeat COVID infections
- Evidence of prior tendency to ME/CFS per patient history
- Prior health conditions
  - Diabetes
  - Asthma/COPD/allergies
  - Autoimmune illnesses

Comorbidity triad of POTS, MCAS and hypermobility is common in our most complex patients.

Selected common comorbid conditions of interest in ME/CFS patients

Common Comorbid Conditions

**Content is the property of the U.S. ME/CFS Clinician Coalition.*

The following reflects the 2020 U.S. ME/CFS Clinician Coalition's Guidelines: Basics of Diagnosis and Treatment.

In the past, a diagnosis of ME/CFS was made by first excluding all other possible conditions. However, the 2015 National Academy of Medicine report established ME/CFS as a positive diagnosis that can coexist with other conditions, including those in the differential diagnosis. Recognizing comorbid conditions early, and treating them appropriately, may improve the patient's health, function, and quality of life.

Autonomic Dysfunction • Postural Orthostatic Tachycardia Syndrome (POTS) • Neurally Mediated Hypotension (NMH) • Orthostatic Hypotension (OH)	**Rheumatological Disorders** • Fibromyalgia (FM) • Ehlers-Danlos Syndrome (EDS) • Temporomandibular Joint Dysfunction (TMJ, TMD) • Sicca Syndrome (dry eyes/mouth)	**Neurological Disorders** • Sensory Hypersensitivities (light, sounds, touch, odors or chemicals) • Poor Balance • Migraine Headaches • Peripheral Neuropathy • Small Fiber Neuropathy
Immunological Disorders • New or worsened allergies • Mast Cell Activation Syndrome (MCAS) • Multiple Chemical Sensitivities • Chronic Infections & immunodeficiencies	**Gastrointestinal Disorders** • Food Allergy & Intolerances, including to milk protein • Gut motility issues • Celiac Disease • Irritable Bowel Syndrome • Small Intestinal Bacterial Overgrown (SIBO)	**Endocrine/Metabolic Disorders** • Hypothyroidism • Hypothalamus-Pituitary-Adrenal Axis dysregulation (low normal or flattened cortisol curve) • Metabolic Syndrome
Sleep Disorders • Sleep Apnea • Restless Leg Syndrome (RLS) • 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.		

Patient Case #1 – 35 yro woman LC ME/CFS

- Hx of EBV → OI
- 2015 – Severe Vestibular Neuritis → intermittent POTS and PEM
- 2022 first COVID infection → severe dysautonomia, took 1 yr to recover
- Sept 2023 – 2nd COVID infection → severe dysautonomia/POTS and disequilibrium → bedbound
- Nov 2023 – Pt at BHC
  - ME/CFS very severe 75-100% of the time
  - OIQ 91/100,
  - NLT → low resting BP,+43bpm, PP/SBP <25%
  - DANA Brain vital – unable to calculate
  - MCAS screen mild
  - Other diagnostics essentially nl
- Intermittent MCAS symptoms with PEM
- Later found to have hypermobility, CCI/AAI, possible TC, and possible right IJV compression

- **Why is this patient considered complex?**
  - Prior ME/CFS and POTS with viral etiology
  - Repeated COVID infections with severe Long COVID symptoms
  - Medication sensitivity
  - Complexity triad of POTS, MCAS, hypermobility

Treatment Focus

- **Pacing and reduction of PEM** – Top priority
- **Dysautonomia and OI** – vascular volume support, compression, vagal nerve stimulation techniques
- Optimized **sleep**
- **MCAS** never fully took hold. However, pt is on daily quercetin as a precaution
- **Hypermobility** – Core strengthening, isometric neck exercises, management of the above issues.

Present condition

❖ Doing very well. Back to baseline prior to 2nd COVID infection. Has more tools to manage their dysautonomia and PEM avoidance.

❖Early and aggressive intervention greatly improved her chances of not becoming severely ill.

Patient Case #2 – 19 yro woman with LC ME/CFS

- Assumed 1st COVID infection Sept 2020 - Healthy prior except for post-prandial abd. pain and IBS symptoms.
- 2nd COVID infection March 2021 → worsened dysautonomia → POTS. Needed academic accommodations.
- BHC pt March 2022
  - Met ME/CFS criteria –severe to very severe 75-100% of the time.
  - NLT + 37bpm, PP/SBP 16%, sign symptoms
  - MCAS screen minimal but GI hx is suspect
  - Other complaints – joint pain
  - FmHx connective tissue disorder
  - Rheumatology Dx'd with UCTD
  - Initially treatment resistant to POTS management MCAS
  - Developed more pronounced MCAS months later.
  - Referred to allergy/immunology due to angioedema and low C1 esterase.
  - Dx'd with MCAS, treated aggressively
  - Somewhat treatment resistant
  - Positive eval for hypermobility and EDS via PT, genetic testing
  - Diagnosed with Celiac Compression/Median Arterial Ligament Syndrome.

- **Why is this patient considered complex?**
  - Possible MCAS prior to COVID
  - Undifferentiated connective tissue disease and FMHX of connective tissue disorder.
  - Repeat COVID infections
  - Medication sensitivity
  - Treatment resistant
  - Developed triad of POTS, MCAS, and hypermobility/EDS

Treatment Focus

- **Pacing and reduction of PEM** – Top priority
- **Dysautonomia**
  - Vascular volume and vascular support
    - Counseled on aggressive oral hydration and sodium supplementation. IV hydration not that beneficial.
    - Vascular compression, fludrocortisone, midodrine
  - HR control and Sympathetic OD
    - Managed with Beta Blockers
    - Effects – mild to mod improvement in upright tolerance, less emotional, less cognitive impairment. Improvement in HRV and RHR. But not responding as much as expected.
- **MCAS** therapy per allergy/immunology - MCAS becomes a primary driver of her illness
  - Slowly enhanced her MCAS regimen to include full dose cromolyn, ketotifen, H1/H2 blockers, leukotriene receptor antagonists. Omalizumab has been recommended but has not been started yet.
- **Hypermobile** evaluation by PT positive.
  - PT – Isometric neck exercises, recumbent core strengthening, joint strengthening
  - Aggressive management of Dysautonomia and MCAS to reduce inflammation
- Celiac Artery Compression – Not sure if and how this plays a role in her illness. Surgery will provide some answers.

Patient Case #3 - 31 yro woman w/ LC ME/CFS

- Initial COVID infection 11/2020.
- Presented at BHC 12/2021 with diagnosis of POTS per HUTT (increase HR of 48bpm) and 6 months pregnant w/EDD 3/2022.
  - PMH: Endometriosis, Menorrhagia, Migraines, IDA
  - Eval by cardiology, neurology, and GI
  - Treating POTS with aggressive H20 and dietary sodium and PRN propranolol, compression clothing.
  - Iron supplementation

- BHC work up
  - Met 2015 IOM criteria for ME/CFS with moderate to severe symptoms 50-75% of the time.
  - OI was 75-100% of the time.
  - 10-min NLT positive for OI but not POTS. HR increase of 22bpm. PP/SBP <25%, symptoms of venous pooling, head pressure/headache, SOB, increased restlessness.
  - Lab evaluation prior had been extensive. I added ID eval for prior viral infections.
  - Pushed more aggressive sodium supplementation with electrolyte powders in addition to dietary. This helped.
  - Educated on pacing and PEM.
  - Was doing fairly well secondary to expanded vascular volume from pregnancy.

Patient case #3 (cont.)

- Post-partum
  - Did well for the first 2 months but then started experiencing more “bone crushing fatigue”, dysautonomia, WSP, headaches - different from her prior migraines.
  - Repeat NLT not that different from the previous except for more pronounced increase of her DBP w/ standing than before.
  - Nursing her infant so medication options were very limited. Focused oral hydration/sodium and compression.
  - MCAS symptom screen was more positive now w/elevated histamine level. RX liquid cromolyn but she did not start it. Discussed low inflammatory/histamine diet and avoiding triggers as much as possible.

- **Lost to f/u for 14 months but pt reported she managed okay. Periods of PEM with recovery to baseline.**

Patient Case #3 (cont.)

- Returned to BHC 11/2023 with worsening and persistent PEM, brain fog, dysautonomia, labile BP/HR, MCAS, sleep disturbances, WSP/FM, increased menorrhagia with worsening IDA.
  - Cardiology managing the IDA and iron infusions x3.
  - Self-referred to allergist/immunologist who she had seen the week prior, labs pending.
  - Self-referred to geneticist for hypermobile EDS evaluation.
  - Repeat COVID infection 6/2024.

Why is this patient considered complex?

- PMHx of endometriosis, connective tissue disorder
- Repeated COVID infections
- Co-morbid conditions of ME/CFS, POTS, MCAS, CTD/Hypermobility

Treatment Focus

- **Pacing and PEM avoidance** was top priority.
- **Dysautonomia** -Focused on managing dysautonomia and OI
  - OI - NLT more stable, +17 bpm, BP stable, PP/SBP < 25% (mild), symptoms of venous pooling, lightheaded.
  - Dysautonomia – poor sleep, anxiety, tremors, sensory sensitivity
  - Vascular volume support, vasoconstriction, HR control
  - Sleep management
- Diagnosed with **MCAS** per allergist and started on MCAS regimen – H1/H2 blocker and mast cell stabilizers.
- **Classical EDS** suspected per geneticist, genetic testing pending
- Pt focused on MCAS but not pacing → severe PEM November 2024, nearly bed bound.
  - Severe PEM management of IV fluids, controlling dysautonomia w/benzodiazepine, beta blockers, dextromethorphan, vagal nerve stimulation techniques, and aggressive rest and pacing.
  - Pt began to appreciate pacing and PEM as the foundation of management.
  - Took 1 month to stabilize, has gained control and function over the last 4 months with careful PEM avoidance and management of co-morbid conditions.

Adapting your approach to care

- Strategic and flexible approach
- Partnership with the patient
  - Patients know a lot about their illness. Listen, learn and collaborate with them.
- Expectations of cure vs management of a chronic illness – clinician and patient.
  - Despite no cure, there are intervention options that can make an impact
  - Set realistic treatment goals
  - Expect setbacks – this is not a linear illness
- Medication strategies
  - Trial and pivot vs trial and error
    - Start one medication/intervention at a time
    - Start very low dose
    - Consider compounded formulations – removes excipients and enables very low doses
    - If something doesn't work, try it again later

Adapting your approach to care

- Treatment comfort zone
  - Be willing to try interventions but stay within your comfort zone.
    - Do risk/benefit analysis
    - Attend CMEs like this one to expand your knowledge and comfort zone.
    - Stay current on emerging research utilizing ME/CFS forums both lived experience and clinician driven.
- Frequent visits will be required
  - Every 2-4 weeks to start
  - Comprehensive vs targeted visits
  - Utilize Telehealth for some visits
- Empower the patient with knowledge, resources, tools
- Assess needs for academic and work accommodations, and disability resources
  - Chart with these in mind
- Assess needs for and access to social services, mental health services, and community support.

IOM (NAM) 2015 ME/CFS Clinical Diagnostic Criteria

The IOM (now the National Academy of Medicine (NAM)) *demoted the term fatigue* and placed **impairment of function and PEM** as the leading diagnostic features.

Major Criteria (required for diagnosis):

1. **Impairment of normal function, accompanied by fatigue, persisting >6 months**
2. **PEM: post-exertional malaise***
3. **Unrefreshing sleep***
4. **Plus at least one of the following:**
   - Cognitive impairment*
   - Orthostatic intolerance (ANS dysfunction)

***Must be moderate-severe and present >50% of time**

Additional Common Features of Illness in the ME/CFS population:

- **Chronic pain** (headache, muscle and joint aches, hyperalgesia, central sensitivity)
- **Immune/inflammatory manifestations** (allergy, inflammation, chemical sensitivities)
- **Infection manifestations** (viral or atypical infections, sore throat, tender lymph nodes, low grade fevers)
- **Neuroendocrine manifestations –** HPA Axis dysregulation

Beyond Myalgic Encephalomyelitis: Redefining an Illness. Institute of Medicine. Washington (DC): National Academies Press (US); 2015 Feb 10. ISBN-13: 978-0-309-31689-7ISBN-10: 0-309-31689-8

- **ME/CFS is a clinical diagnosis, PEM is a unique symptom of ME/CFS**
- **Assess and reassess for PEM symptoms**. PEM Symptoms can provide clues to other comorbidities that may be playing a role in their LC ME/CFS and may help appreciate the significance of those co-morbidities and how to treat them.

Questionnaires – to assess for ME/CFS and function

- **Good Day/Bad Day Questionnaire** (captures function on baseline/good days and PEM/crashed/bad days and hours of upright activity (HUA))
  - https://batemanhornecenter.org/wp-content/uploads/filebase/education/top_resources/Good-Day-Bad-Day-Questionnaire-Fillable-V3-6_6_2022.pdf
- **DePaul Symptom Questionnaire for PEM** (identifies presence and severity of PEM). Only validated questionnaire to screen for PEM. Helps to assess frequency and severity of PEM once ME/CFS diagnosis has been made. Primarily used in research.
  - https://csh.depaul.edu/about/centers-and-institutes/ccr/myalgic-encephalomyelitis-cfs/Pages/measures.aspx
- **SF-36 Functional Assessment Scale** (health-related quality of life measure)
  - https://www.rand.org/health-care/surveys_tools/mos/36-item-short-form/survey-instrument.html

Dysautonomia – often the low hanging fruit

ASSESS

- Listen for history that suggests dysautonomia and orthostatic intolerance
- 10-Minute NASA Lean Test
- Orthostatic Intolerance Questionnaire
- COMPASS 31questionnaire – dysautonomia symptoms
- Cognitive function
- Heart Rate Variability and Resting Heart Rate trends
- Sleep - Deep sleep trends, types and causes of sleep disruption

TREAT

- Vascular volume support and vascular compression
- Heart Rate and BP Management
- Improve cardiac out-put and cerebral perfusion
- Disrupted sleep – autonomic dysfunction, neuroinflammation, pain, MCAS
- Vagal nerve stimulation - mediation, resonant breathing, neuroplasticity programs
  - These vagal nerve stimulation techniques can help activate the vagus nerve, which in turn may counteract the 'fight or flight' response driven by the sympathetic nervous system.

Mast Cell Activation Syndrome (MCAS)

ASSESS

- Listen for symptoms of and screen patients for MCAS
  - Symptom screen – multi-system involvement
  - Laboratory evaluation – low sensitivity so frequently negative
- Have a low threshold for suspicion for MCAS
- Reassess frequently – this can begin to emerge, especially after PEM
- Listen for MCAS symptoms as part of their PEM symptoms

TREAT

- Educate patient to avoid triggers
- Try empiric therapy – often diagnostic
- Start one therapy at a time. Comprehensive MCAS therapy is a significant medication burden but often necessary.
- Consider use of compounded medications as much as possible – reduces excipient reactions.
- Establish strategies for MCAS flares
- Involve a trusted allergist/immunologist as needed

Pain

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.

Presentation

- Widespread body pain, diffuse and moves – think FM
- Nerve pain – burning, tingling, numbness – think SFPN/FM
- Joint pain, subluxations, dislocations – think hypermobility
- Treatment resistant/intermittent pressure headaches – think hypermobility, venous congestion syndromes.

ASSESS

- Fibromyalgia
  - 2016 ACR Fibromyalgia Questionnaire
  - Tender point +11/18 required
- Small Fiber Polyneuropathy – primarily a clinical diagnosis but can get skin bx, QSART test
- Hypermobility/CTD
- Imaging and other diagnostics as appropriate for the pain presentations

Pain (cont.)

TREAT

- Pain reduction interventions
  - Treat what can drive pain
    - Pacing and PEM avoidance is key!
    - Improve autonomic function – fluids, compression, dysautonomia treatment
    - Manage MCAS – antihistamines, mast cell stabilizers
    - Optimizing sleep – Low dose TCAs, melatonin, dysautonomia treatment,
  - Address central sensitization – LDN, TCAs, SNRIs, antiseizure agents/GABA analogs – gabapentin & pregabalin
  - Utilize standard pain medications
  - Refer to pain management as appropriate

Hypermobility/Connective Tissue Disorder

Presentation

- Musculoskeletal Manifestations – joint pain, subluxations, dislocations, overuse injuries
- Autonomic Dysfunction & Dysautonomia
- MCAS
- Frequent headaches – base of skull, pressure, positional, worse with PEM, unresponsive to usual h/a medications

ASSESS

- Beighton Score assesses for hypermobility
- Brighton Criteria – Used to diagnose hEDS
- Five-point questionnaire for joint hypermobility
- Genetic testing for CTD – no genetic markers for hEDS but testing will eval for other genetic variations.
- Brain, spinal, and venous imaging as indicated

TREAT

- Aggressive management of PEM, Dysautonomia and MCAS to reduce inflammation
- Pain management
- Have PT evaluate to aid in diagnosis and management
- Refer to orthopedics, neurology, vascular and/or neurosurgery as indicated

Referrals

- Identify trusted referral sources for these patients.
- Be clear as to why you are referring. Many specialists will deny referrals if they think you want them to manage LC or ME/CFS.
  - Ask for evaluation of specific issues
  - Rule out possible concerns
  - Specific testing or treatments
- Most common referrals we make
  - **Physical Therapy –** make sure PT understands about PEM or they can do more harm than good.
    - Reconditioning with PEM in mind
    - Hypermobility evaluation and management
    - Provide strategies for pacing and exertional recovery
    - Pelvic Floor PT can help with core strengthening and urogyn/tethered cord issues
  - **Occupational Therapy –** can be immensely helpful with more severely ill patients and with pacing within the home, life, etc.
  - **Speech Therapy –** Communication Specialists can diagnose and treat disorders of communication and cognition, as well as voice, speech, and swallow dysfunction. Can help with cognitive processing and memory.
  - **Allergy/Immunology –** Evaluate for and manage more complex immune issues, prescribe omalizumab for MCAS.
  - **Neurocognitive Specialist** for cognitive testing – primarily for disability but also in helping with cognitive processing and memory.

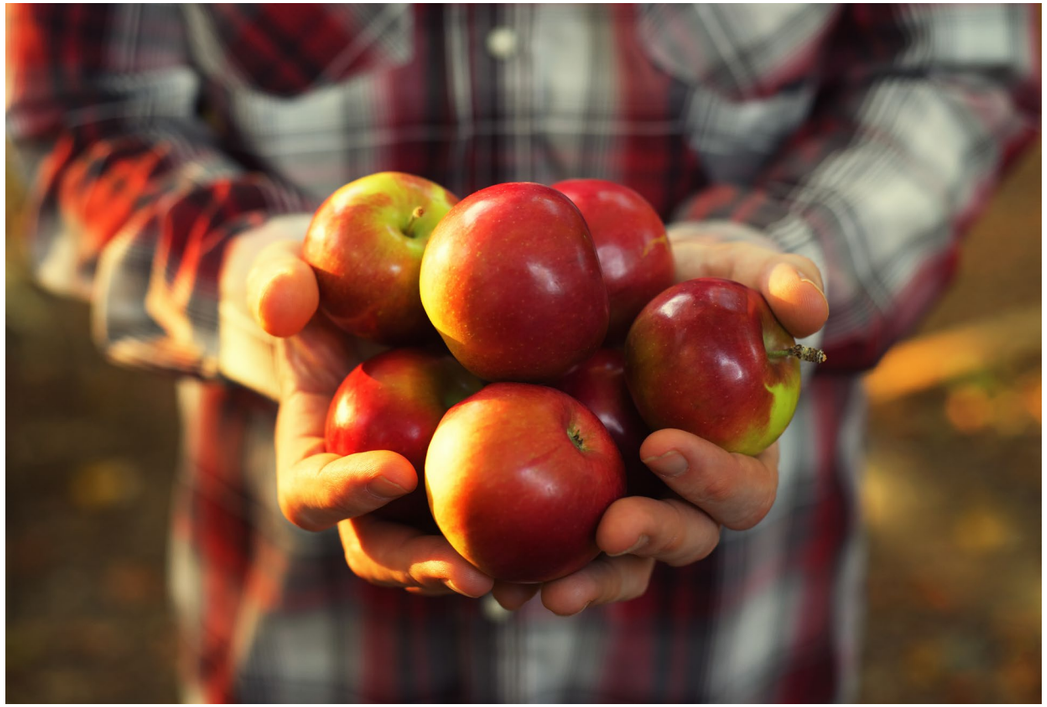
Referrals (cont.)

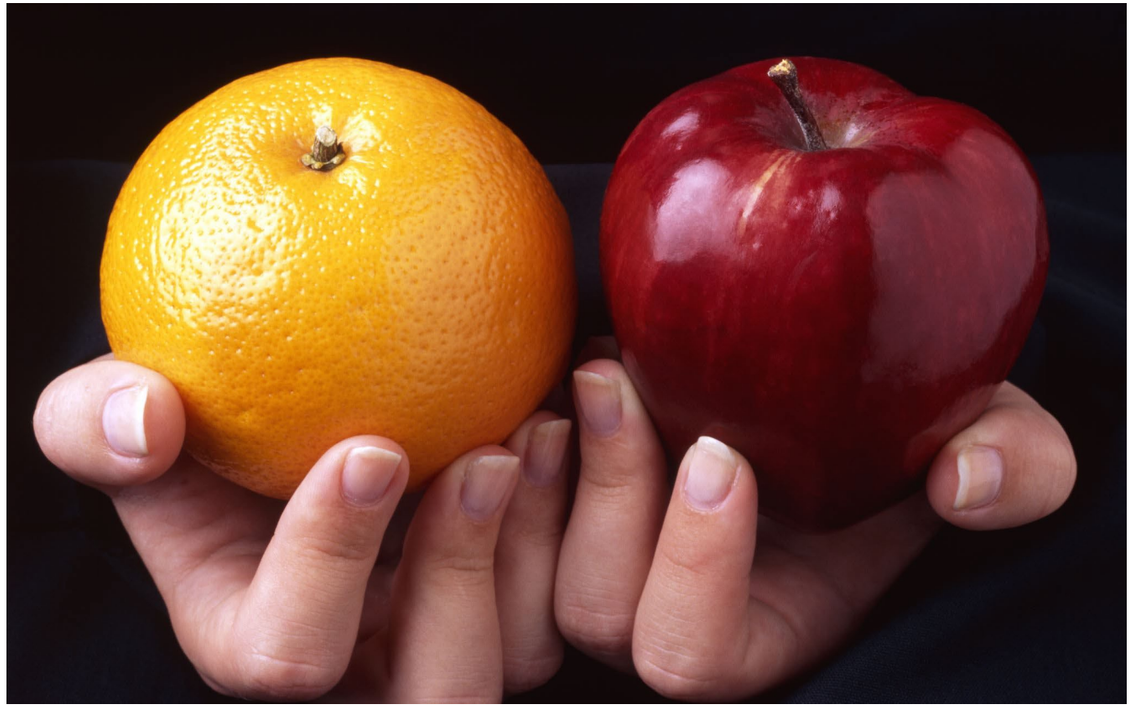
- **Neurology** – advanced w/u for unusual neurological findings, may be helpful in evaluation and treatment of increased intracranial pressure and head/neck venous congestion syndromes, other headache management.
- **Pain Specialist** – pain management interventions, Stellate Ganglion Blocks
- **Behavioral and Mental Health** –can be particularly helpful with processing medical and grief trauma, along challenges associated with chronic illness and chronic pain.
- **Cardiology** – for more advanced w/u, certain prescriptions

❖ Other less common referrals

- Pulmonology, Rheumatology, Gastroenterology, other specialties – for more advanced w/u, evaluation of non-related conditions.

Same and Different





THANK YOU!