Long COVID & Fatiguing Illness Recovery Program ECHO

Thursday, May 12, 2022
History of ME/CFS
myalgic encephalomyelitis/chronic fatigue syndrome

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Bateman Horne Center (BHC)

BHC is a 501(c)3 non-profit organization with a mission to improve lives through direct clinical care, facilitation of research, and dissemination of educational resources.

This specifically/exclusively includes the lives of people with:

- myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS)
- fibromyalgia (FM)
- post-viral syndromes and
- related comorbid conditions (small fiber neuropathy, mast cell activation syndrome, hypermobile EDS, postural orthostatic tachycardia syndrome/POTS)
May 12th

International
ME/CFS and FM Awareness Day

https://www.nih.gov/research-training/medical-research-initiatives/mecfs/me-cfs-fibromyalgia-international-awareness-day
What is ME/CFS?
myalgic encephalomyelitis/chronic fatigue syndrome

• A chronic, complex, debilitating, multi-system illness involving:
  • **Brain** (neuroinflammation, abnormal stress response system, HPA-axis dysregulation)
  • **Peripheral nervous system** (especially small fiber nerves involving pain, sensation, and ANS function)
  • **Immune system** (impaired NK Cell fxn, abnormal T-cells, cytokines, autoimmune conditions, immune activation, mast cell activation)
  • **Circulatory system** (orthostatic intolerance, perfusion abnormalities)
  • **Impaired cellular metabolism**

• Often a post-viral or post-infectious syndrome, but diagnosis is typically made so late (if ever) that evidence of the acute infection has been lost, or diagnostic studies of common potential pathogens were not done at illness onset.

• Immune triggers may also be associated with onset of ME/CFS

US ME/CFS Clinician Coalition website: [https://mecfscliniciancoalition.org/](https://mecfscliniciancoalition.org/)

*Inflammation correlates with symptoms in chronic fatigue syndrome. Komaroff AL. Proc Natl Acad Sci USA. 2017 Aug 22; 114(34): 8914-8916. Published online 2017 Aug 15. doi: 10.1073/pnas.1712475114 PM CID: PMC5576849*
ME/CFS can be triggered by a variety of pathogens

- Many viruses can cause a post-viral syndrome and have been associated with the onset of ME/CFS, including Epstein-Barr Virus, CMV and other herpesviruses, Parvovirus B19, West Nile Virus, enteroviruses, coronaviruses (SARS CoV1, MERS, SARS CoV-2) and other non-viral pathogens as well (giardia, Q-fever/Coxiella burnetii, Lyme/Borrelia burgdorferi, and more).

- ME/CFS may be caused by the body’s complex reactions to certain acute infections, or viral reactivation, in combination with an abnormal chronic immune/inflammatory response. Genetic predisposition may play a role.

- People with ME/CFS share the same core symptoms but heterogeneity exists, likely due to the systems affected, disease duration and the development of comorbid conditions. This heterogeneous illness has been challenging to study.

- Post acute sequelae of COVID (Long COVID) may change that!

- ICD-10 G93.3 Post-viral syndrome, myalgic encephalomyelitis.
ME/CFS historical background

ME/CFS is not a new illness. Post-infectious illnesses of this nature and severity have been world-wide and multicultural.

Comparable illnesses have been documented for centuries (but historical comparisons are problematic).
ME/CFS historical background

• Illnesses like ME/CFS have historically been described many ways.

• Initial descriptions included “epidemic neuromyasthenia,” and later, “benign myalgic encephalomyelitis” first used in the 1950s. The syndrome usually applied to epidemic outbreaks, but sporadic cases were identified as well.

• In 1970, two psychiatrists in the UK reviewed 15 outbreaks and concluded these “were psychosocial phenomena caused by...mass hysteria...and conclusions were based on the higher prevalence in females and the lack of physical signs. They recommended the name “myalgia nervosa” reminiscent of the term neurasthenia from the 19th century.

• These ideas were refuted for decades by a dedicated physician, Dr. Melvin Ramsay, who eventually published the first definition of Myalgic Encephalomyelitis in 1986.
ME/CFS historical background

- The term **Chronic Fatigue Syndrome (CFS)** was first published in 1988 to replace the misnomer “**Chronic EBV.**” The paper described a post-infection or post-viral syndrome and proposed a research case definition.

- It was revised in 1994 but proved too broad, encompassing many other causes of “chronic fatigue” (including fibromyalgia and some mental health conditions).

- Very descriptive **clinical criteria** for ME/CFS were published in 2003 by expert clinical consensus, eventually called the “**Canadian Consensus Criteria,**” but the publication wasn’t widely accessible to practicing clinicians. These criteria were revised, updated and published in 2011 as the “**International Consensus Criteria**” for ME. Both are widely used outside the U.S.

- Many other definitions and criteria have been published as well.

ME/CFS historical background

- After an evidence-based review the Institute of Medicine/IOM (now the National Academy of Medicine/NAM) proposed clinical diagnostic criteria in 2015 based on the common core symptoms of ME/CFS*.

- The IOM/NAM report is readily available: https://pubmed.ncbi.nlm.nih.gov/25695122/

*The term Systemic Exertion Intolerance Disease (SEID) was suggested but not adopted
ME/CFS “Key Facts” of the 2015 NAM report

- 836,000 to 2.5 million Americans affected, and many more worldwide.
- Women > men. Most patients currently diagnosed are Caucasian, but some studies suggest it is more common in minority groups.
- 25% bed-bound or house-bound at some point of illness.
- 75% are unable to work or attend school. Symptoms can persist for years, and most never regain pre-illness level of health or functioning.
- Loss of productivity and medical costs contribute to a total economic burden of $17-24 billion annually in the U.S. [this has recently been revised to $36-51 billion]


2015 ME/CFS Clinical Diagnostic Criteria:
(IOM/NAM)

CORE criteria **required** for diagnosis

1) **Impairment of normal function accompanied by fatigue, >6 months duration**
2) **PEM: post exertional malaise***
3) **Unrefreshing [dysregulated] sleep***
4) Plus at least one of the following:
   - **Cognitive impairment***
   - **Orthostatic intolerance** (autonomic nervous system dysregulation)

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

Additional *common but variable* and not “CORE” features of illness in the ME/CFS population:

- **Chronic pain** (headache, muscle and joint aches, hyperalgesia, central sensitivity, tingling, burning...)
- **Immune/inflammatory manifestations** (allergy, inflammation, immunodeficiency, chemical sensitivities)
- **Infection manifestations** (viral or atypical infections, sore throat, tender lymph nodes, low grade fevers)
- **Neuroendocrine manifestations** (HPA-axis dysregulation, impaired stress response)

SF-36 scores for patients in the CDC multisite clinical assessment of ME/CFS (MCAM)

Clinical tips...IMPAIRED FUNCTION with fatigue

We use simple **tools to communicate impaired function**

**HUA: Hours of “Upright” Activity:**
Report the # of hours spent with **feet-on-floor in 24 hours:** sitting, standing, walking

*Must ask the question clearly to be sure time spent sitting is considered in the total.*
Clinical tips...IMPAIRED FUNCTION with fatigue

Typical HUA*

**Hours of Upright Activity in 24 hours**

- Normal healthy folks: HUA 13-17
- Chronic Illness (MS, RA, CHF, COPD, FM): HUA 9-12
- ME/CFS: HUA 0-8

Observational clinic data from BHC
**Clinical tips…IMPAIRED FUNCTION with fatigue**

**Good Day/Bad Day Questionnaires**

1) Average number of **GOOD_____** **BAD______** days per MONTH

2) Average **hours of UPRIGHT activity (HUA)** on a **GOOD_______** **BAD_______** day:
   - *Sitting, standing, walking --- activities with FEET ON FLOOR*
   
   (Hours of upright activity + Hours of non-upright activity = 24 hours)

3) **Give examples** of activities/tasks you **CAN** do on a:
   - **GOOD day**__________________________________________
   - **BAD day**__________________________________________

4) **Give examples** of activities/tasks you **CAN NOT** do on a:
   - **GOOD day**__________________________________________
   - **BAD day**__________________________________________

“Unraveling the complexity of chronic pain and fatigue”
https://www.youtube.com/watch?v=7HJG-WlnxSg&t=69s
Clinical tips...IMPAIRED FUNCTION with fatigue

**Good Day/Bad Day** Questionnaire Example

- **On GOOD days**, 4-5/mo, he can manage 8 HUA*
  - **Can**: read (<30 min), watch TV, listen to music, cook a meal, shower, walk one block, drive short distances
  - **Cannot**: walk more than 3 blocks, work, complete household chores exceeding 15 minutes, drive >30 minutes

- **On BAD days**, 25-26/mo, he tolerates only 2 HUA*
  - **Can**: recline on the couch, microwave prepared food, have a short conversation (<5 min)
  - **Cannot**: read, listen to music, work, do household chores, take a shower, exercise, drive

*HUA= Hours of Upright Activity (seated with feet on floor, standing, walking)

“Unraveling the complexity of chronic pain and fatigue”
https://www.youtube.com/watch?v=7HJG-WlnxSg&t=69s
What causes...IMPAIRED FUNCTION with fatigue?

• **Impaired cellular metabolism**--- reduced ATP, reduced levels of many molecules, oxidative stress.
• **Post exertional malaise (PEM)**--- the consequences of exceeding physiologic capacity
• **Orthostatic Intolerance**
• **Cognitive impairment** and cognitive fatigability

*This is an important research question*


[https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8180841/#b0005](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8180841/#b0005)
POST-EXERTIONAL MALAISE (PEM)

PEM is a distinctive exacerbation of the patient’s symptoms and a further reduction in functioning after physical, cognitive, orthostatic, emotional, or sensory stressors.

- It is supported objectively by abnormal **cardiopulmonary exercise testing (CPET)** showing low anaerobic threshold, impaired aerobic metabolism, and inability to replicate the test results on serial days.

**PEM:** Two Day CPET Test confirmed

Test 1 = dark grey bars  Test 2= light grey bars

22 ME/CFS subjects

PEM and Invasive CPET (iCPET)

• Invasive CPET studies of people with ME/CFS and OI/POTS have demonstrated "biologically plausible contributors to ME/CFS exertional intolerance."

• 1516 upright invasive iCPETs were performed to investigate exertional intolerance.

• Two types of peripheral neurovascular dysregulation were identified:
  • reduced cardiac output from impaired venous return
  • impaired peripheral oxygen extraction

• They note the overlap of ME/CFS, POTS and FM, and suggest that in patients with small-fiber pathology, neuropathic dysregulation causing microvascular dilation may limit exertion by shunting oxygenated blood from capillary beds and reducing cardiac return.

• Similar findings are being seen in Long COVID

Also read: [https://consultqd.clevelandclinic.org/unexplained-dyspnea-could-it-be-due-to-a-chronically-low-preload-state/](https://consultqd.clevelandclinic.org/unexplained-dyspnea-could-it-be-due-to-a-chronically-low-preload-state/)
PEM take-home messages

• While we may not completely understand it, **exceeding energy capacity results in illness pathology—post-exertional malaise (PEM)**. The severity and duration of PEM are relative to the energy expenditure.
  • A loose analogy is using HgA1C to measure the extent of glucose exertions in diabetes

• Energy expenditures include **all types of physiologic stress—physical activity, orthostatic stress, cognitive work, emotional exchanges**, responding to **environmental stress and sensory input**, etc.

• The threshold for triggering PEM varies day to day, at stages of illness, and from person to person with ME/CFS.

• In absence of a primary treatment for ME/CFS, the mainstay of treatment is **prevention of illness exacerbation** by carefully “**pacing**” activities to avoid significant PEM. *It isn’t easy.*

• The better one prevents PEM, the more likely one is to stabilize and/or improve. The opposite is also true. Pushing into PEM may result in severe crashes and overall decline, sometimes permanently.
UNREFRESHING SLEEP--- known physiology

- Sleep is variably disturbed and thus “unrefreshing”.
- **Nocturnal autonomic dysregulation** has been demonstrated as *reduced heart rate variability* from *increased sympathetic activity* relative to parasympathetic activity.
- **HPA-axis dysregulation** with *flattened* AM cortisol levels and throughout the day, rather than normal circadian changes, may play a role as well.
UNREFRESHING SLEEP---sleep studies

Polysomnography (PSG):

• PSG is non-diagnostic but usually abnormal in ME/CFS*
  • Increased alpha waves (dozing, light sleep)
  • Decreased delta waves (slow wave, deep sleep)
  • Fragmentation
  • Delayed onset

Abnormal sleep architecture may be a major presenting disturbance of ME/CFS

• Sleep Structure and sleepiness in chronic fatigue syndrome with or without coexisting fibromyalgia. Arthritis Research & Therapy 10(3):R56. Togo 2008
• Are patients with chronic fatigue syndrome just “tired” or also “sleepy”? Neu et al 2009. Journal of Sleep Research 17(4):427-431
Cognitive Impairment:

- **Slowed information processing speed** is the most common cognitive deficit.
- Other abnormalities include **decreased working memory and attention**.
- Defects worsen when patients face deadlines, unrelenting demands, and multiple simultaneous tasks.
Total errors on PASAT testing (Paced Auditory Serial Addition Task)

Total errors represent both incorrect responses and missed responses (i.e. errors of omission). There was a significant Group by Time Interaction ($F = 8.4, p = 0.007$).

Cognitive scores: IMPROVE with each attempt in healthy controls and WORSEN with each attempt in ME/CFS

Research contributions from:

- Neurocognitive testing---deficits in attention, memory, and reaction time
- Spinal fluid studies---increased WBC, abnormal proteins
- MRI, fMRI, PET scans---hypoperfusion, glial cell activation, white matter changes
- Spectral analysis of EEG data can distinguish ME/CFS from HC and MD
- Neuroendocrine studies---abnormalities of the HPA-axis

Inflammation correlates with symptoms in chronic fatigue syndrome. Komaroff AL. Proc Natl Acad Sci USA. 2017 Aug 22; 114(34): 8914-8916. Published online 2017 Aug 15. doi: 10.1073/pnas.1712475114 PM CID: PMC5576849

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5576849/
ORTHOSTATIC INTOLERANCE

Orthostatic intolerance is the development of symptoms in **upright posture** that are relieved or partially relieved by **reclining**.
ORTHOSTATIC INTOLERANCE

Orthostatic Intolerance from Autonomic N.S. dysfunction:

1) **Cerebral under-perfusion symptoms and signs**
   - Lightheadedness, fainting, impaired cognition, disorientation, headaches, visual changes, unusual neurologic symptoms, exhaustion

2) **Peripheral cardiovascular symptoms and signs**
   - Sympathetic nervous system activation---palpitations, nausea, abdominal and chest discomfort, facial pallor, cold hands and feet, anxiousness, shortness of breath, sweating, tremor...

Worsened by heat, dehydration, prolonged sitting or standing, deconditioning and weakness, medications, and worsens during or immediately after exercise.

Chapter 4, pg 107; Chap 6, pg 185.

Beyond Myalgic Encephalomyelitis: Redefining an Illness.
Institute of Medicine. Washington (DC):
Orthostatic intolerance and reduced cerebral blood flow are core manifestations of ME/CFS but BP & HR may not tell the whole story.


Can orthostatic intolerance testing be done by primary care providers? The 10 min stand/lean test can!

Head Up Tilt Table Testing
The Gold Standard
ORTHOSTATIC INTOLERANCE

A standardized clinic-based approach: the 10 min NASA Lean Test

Hyatt, K. H., Jacobson, L. B., & Schneider, V. S. (1975). Comparison of 70 degrees tilt, LBNP, and passive standing as measures of orthostatic tolerance. Aviation, Space, and Environmental Medicine, 46(6), 801-808.
ORTHOSTATIC INTOLERANCE: 10 min NASA Lean

37-year-old disabled professional woman with ME/CFS
2-4 HUA/d. Sitting: BP 112/75. P-77

Lying down resting for 10-15 min:
Supine: BP 99/68 P-68

Standing relaxed with shoulders against wall, feet 6” from the wall.
Standing at 0 minutes: BP 99/72 P-90
Standing at 1 minute: BP 90/74 P-100 mild weakness, heavy feeling in legs
Standing at 2 minutes: BP 101/74 P-94 dependent rubor, facial pallor
Standing at 3 minutes: BP 104/84 P-111 hands tingling
Standing at 5 minutes: unable to measure
Standing at 6 minutes: BP 88/62 P-132 palpitations
Standing at 7 minutes: BP 94/64 P-115 palpitations, increased nausea
Standing at 8 minutes: did not register on B/P cuff

Tingling in face increased, tingling all over, sees “spots”, muted sounds, legs gave way, vision blacking out. Assisted gently to the floor and legs elevated.

HR 68 → 132 (+64 bpm) just before near-syncope.

The 10 min NASA Lean test can diagnose OI, OH, POTS, orthostatic syncope

Selected common CO-MORBID CONDITIONS of interest in ME/CFS patients

I’m defining a **co-morbid condition** as a known condition that can occur alone but also commonly occurs as a part of the ME/CFS clinical presentation.

Co-occurrence with ME/CFS generally makes a co-morbid condition much more difficult to treat. But still a worthy treatment target.
Selected common CO-MORBID CONDITIONS of interest in ME/CFS patients

- Fibromyalgia/pain amplification, central sensitivity
- Small fiber poly neuropathies (SFPN) and peripheral neuropathies
- Viral reactivation (VZV, HSV, HHV-6, EBV, CMV, etc.)
- Chronic sleep disorders (“primary” and secondary)
- Postural orthostatic tachycardia syndrome (POTS), orthostatic hypotension, other manifestations of dysautonomia
- Allergies, chemical sensitivities, mast-cell activation syndrome (MCAS), food intolerances
- Autoimmune thyroid disease, subclinical hypothyroidism, euthyroid-sick syndrome
- Celiac disease and gluten intolerance, IBS, gastroparesis, SIBO (small intestine bacterial overgrowth)
- Sjogren syndrome/sicca syndrome (dry eyes and dry mouth)
- Hypermobility and Ehlers Danlos Syndrome (the common type with no genetic markers)
- Craniocervical instability syndromes (high cord or brain stem compression syndromes)

These are conditions we can diagnose and manage with standard of care.
Managing ME/CFS (and Long COVID)

• Provide understanding and support.
• Teach “pacing” and activity management to prevent or reduce PEM.
• Identify and treat “comorbid conditions” but remember that it generally won’t be a magic bullet for the whole illness.
• **Address severe symptoms** sensibly, especially those that are “stressors”
  - Pain and headaches
  - Sleep disturbances
  - Orthostatic intolerance
  - Cognitive impairment
  - Anxiety, grief/loss (especially in the first 1-2 years of illness)
• Help patients build a “toolbox” of rescue medications and strategies to manage symptom flares and maintain some physical conditioning.
• Remember that any other medical problem can occur in someone with ME/CFS.
Useful links


US ME/CFS Clinician Coalition website: https://mecfscliniciancoalition.org/

Bateman Horne Center website and YouTube videos
BHC Quick videos
• What is ME/CFS? [5 min] https://www.youtube.com/watch?v=vQWVZdGm508&t=20s
• Orthostatic Intolerance, Part 1. Diagnosis [6 min] https://www.youtube.com/watch?v=X3Ym8rnYk_4&t=1s
• Orthostatic Intolerance, Part 2. Management [5 ½ min] https://www.youtube.com/watch?v=GlkS4w3tlg8&t=1s

CDC: https://www.cdc.gov/me-cfs/index.html
NIH: https://www.nih.gov/research-training/medical-research-initiatives/mecfs