# Chronic Illness Patterns After Immune Insult

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February 25, 2022

# BATEMAN HORNE CENTER

BHC is a 501(c)3 non-profit, interdisciplinary Center of Excellence where **clinical care**, **research**, and **education** meet to collectively advance the diagnosis and treatment of:

- **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)**

# Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS)

- A chronic, debilitating, multisystem illness characterized by central and peripheral **nervous system** impairment, **immune system** dysfunction, and impaired cellular metabolism (**energy metabolism**)(1).
- The **cause** of ME/CFS remains unknown but symptoms may be triggered by an infection which leads to a **post-viral or post-infection syndrome**.
- Other triggers, however, have been associated with illness onset, including "**immunization**, anesthetics, physical trauma, exposure to environmental pollutants, chemicals and heavy metals…"(2).

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1. Advances in Understanding the Pathophysiology of Chronic Fatigue Syndrome. Komaroff AL. JAMA. 2019 Aug 13;322(6):499-500. doi: 10.1001/jama.2019.8312. PMID: 31276153

2. Beyond Myalgic Encephalomyelitis/Chronic Fatigue Syndrome: Redefining an Illness. Introduction, second paragraph. IOM/NAM. Washington (DC): National Academies Press (US); 2015 Feb 10

# ME/CFS CAN BE TRIGGERED BY A VARIETY OF PATHOGENS

- Infections associated with onset of ME/CFS include **Epstein-Barr Virus, other herpesviruses, Parvovirus B19, West Nile Virus, enteroviruses, coronaviruses including SARS-CoV-2, and non-viral pathogens as well** *(e.g. giardia).*

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

***By the time the diagnosis is made, there is generally***

***no definitive evidence left of the trigger.***



Advances in Understanding the Pathophysiology of Chronic Fatigue Syndrome. Komaroff AL. JAMA. 2019 Aug 13;322(6):499-500. doi: 10.1001/jama.2019.8312. PMID: 31276153

# 2015 IOM/NAM ME/CFS CLINICAL DIAGNOSTIC CRITERIA

**The CORE criteria** (required for diagnosis) ***Must be moderate-severe and present >50% of time**

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**

**Additional common but not CORE 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**



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 distinguished from other types of chronic fatigue by the degree of impairment/debilitation and the development of post-exertional malaise (PEM).

PEM is illness relapse or worsening triggered by activity or stressors. These can be physical, cognitive, sensory, emotional or even being in upright posture.

**Illness severity and functional capacity ranges from:**

Mild impairment but difficulty maintaining a normal schedule of work, school or family, and low tolerance for exercise



Bedridden, barely able to speak or move

# There are no “specific” diagnostic tests for ME/CFS

- In recent years there has been an increasing awareness of **comorbid conditions** that contribute to the presenting symptoms of ME/CFS.

- I am defining a **comorbid condition** as a diagnosis that can “stand alone” without ME/CFS but seems to commonly occur with ME/CFS.

*(and if comorbid with ME/CFS, the condition may be much more difficult to treat than when it stands alone)*

# SELECTED COMMON CO-MORBID CONDITIONS OF INTEREST IN ME/CFS & LONG COVID PATIENTS

- Small fiber poly neuropathies (SFPN, SFN) and peripheral neuropathies
- Postural orthostatic tachycardia syndrome (POTS), orthostatic hypotension, other types of dysautonomia
- Allergies, chemical sensitivities, mast-cell activation syndrome (MCAS), food intolerances
- Viral reactivation (herpesviruses: VZV, HSV, HHV-6, EBV, CMV…)
- Autoimmune conditions (thyroid, Celiac disease, Sjogren syndrome/sicca syndrome, other targets of autoantibodies)
- Fibromyalgia/pain amplification, central sensitivity
- Chronic sleep disorders and dysregulated sleep
- IBS, gastroparesis, SIBO (small intestine bacterial overgrowth)

# Small Fiber Neuropathy (SFN)/Small Fiber Polyneuropathy (SFPN)

Small nerve fibers (also called C-fibers) are tiny, bare (unmyelinated)

- **sensory nerves** to the skin, heart, organs (pain, pressure, temperature, light, sound…)
- **autonomic nervous system nerves** that activate "involuntary" muscles (*smooth muscle)* that constrict/dilate blood vessels, contract/relax the gut or bladder, etc.

**Pain symptoms** from SFN may be:

- **cold-like pain, tingling or a pins and needles**
- **burning pain**
- **transient electric shock–like pain**

SFN pain may worsen during periods of rest and at night

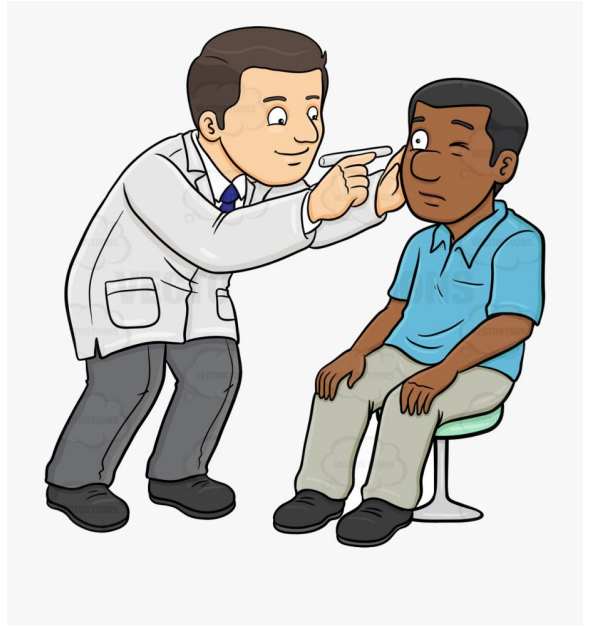


Pain. 2013 Nov;154(11):2310-6. doi: 10.1016/j.pain.2013.06.001. Epub 2013 Jun 5.
Objective evidence that small-fiber polyneuropathy underlies some illnesses currently labeled as fibromyalgia.
Oaklander AL, Herzog ZD, Downs HM, Klein MM.

# SFN MAY CAUSE

## AUTONOMIC DYSFUNCTION AND MULTISYSTEM ILLNESS SYMPTOMS

- dry eyes, dry mouth
- postural lightheadedness (orthostatic intolerance), fainting
- abnormal sweating
- nausea, vomiting, diarrhea, constipation, low appetite
- difficulty with urinary frequency, nocturia, and/or voiding



Physical examination, even a standard neurologic exam, plus EMG and nerve conduction tests may be normal!

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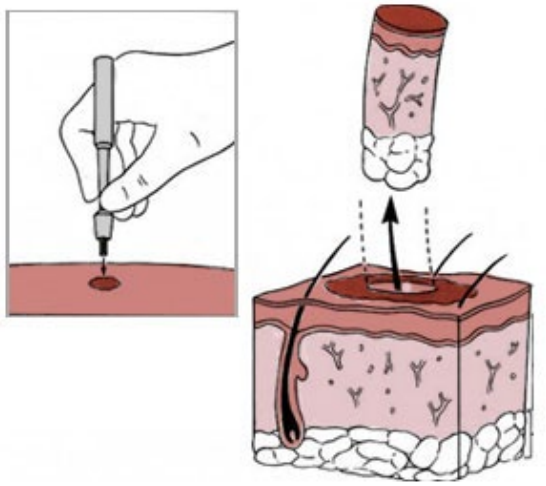
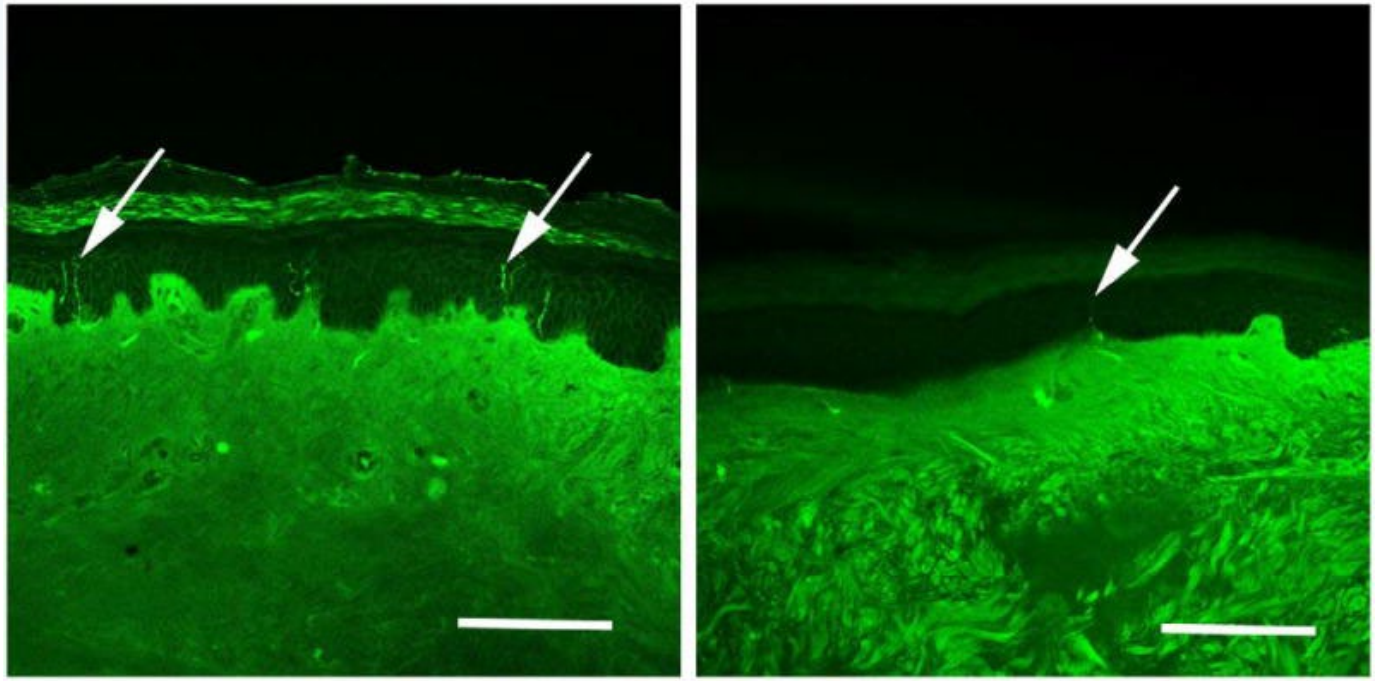
# SFN: SKIN BIOPSY IS THE MOST DEFINITIVE TEST



- Must be sent to a high-quality lab with appropriate expertise.
- The sensitivity (78%–92%) and specificity (65%–90%) of skin biopsy for diagnosing a small fiber neuropathy is relatively good in research publications, but not always practical or available in a clinical setting.

Figure 2



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# SFN (SMALL FIBER NEUROPATHY)

- Underdiagnosed due to lack of objective markers and variable presentation; not length dependent (like a peripheral neuropathy)

- Many potential causes including genetic predisposition, viral infections, immune conditions, toxic exposures, etc.

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Scientific Advances in and Clinical Approaches to Small-Fiber Polyneuropathy: A Review. **Oaklander AL**, Nolano M.JAMA Neurol. 2019 Sep 9. doi: 10.1001/jamaneurol.2019.2917. PMID: 31498378

# Case Example
# Fall 2019: ME/CFS with SFN

61 yr. old female physician working 70 hours/week, happy and exercising.

Prior medical history: severe EBV mono/hepatitis at age 20 with 2+ years of recovery

In the fall of 2019:

- **Aug:** After 1 wk. on hospital service developed **a cold and sinusitis** which lingered 7 wks. Kept pushing to complete her work. 2 antibiotic courses.
- **Sept**: Progressively unable to examine or interview patients due to fatigue and cognitive impairment; took "brief" medical leave but never returned.
- **Oct:** Difficulty reading, focusing eyes, headaches and dizziness.
- **Nov**: Could longer walk outside of her home; mostly homebound. Internal medicine and rheumatology consults.
- **Dec:** A **mild viral cold** led to severe shortness of breath and a 5-day hospital admission. Cardiac, pulmonary, neurological and infectious disease consultations. Extensive workup NEG.

# Case Example
# Fall 2019:  ME/CFS with SFN

January 2020:

- Meets ME/CFS criteria
- Typical questionnaire scores for ME/CFS
- Orthostatic Intolerance Questionnaire(OIQ) 65/100  (0-10 in healthy controls )
- I sent instructions for the **10 Minute NASA Lean Test** and recommended a **skin biopsy** for SFN

# Case: ME/CFS & SFPN
# NASA LEAN TEST→ Diagnosis of POTS and OH

Supine 122/79 82

122/75 85

Standing BP and HR per minute

- 0-"Too thready" 100
- 1- 108/80 126
- 2- 98/75 132
- 3- 120/60 132
- 4- 108/80 132
- 5- 120/84 132
- 6- 112/72 140
- 7- 102/? 140
- 8- 102/? 136
- 9- 102/? 132
- 10- 92/? 124

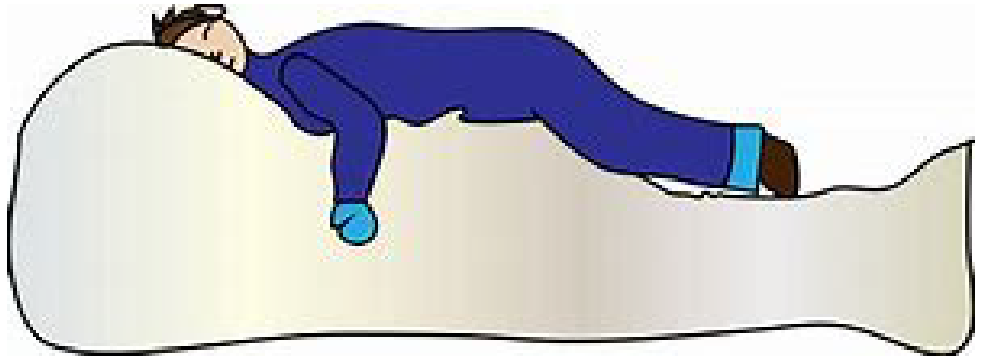
- HR increased from 85 bpm supine to 140 bpm at 6 minutes standing. (+55)
- **Postural Orthostatic Tachycardia Syndrome (POTS)**

- SBP decreased from 122 to 98 at 2 min. (-24)
- **Orthostatic Hypotension (OH)**

- **Skin biopsy confirmed small fiber polyneuropathy (SFPN)**

# What is Orthostatic Intolerance (OI)?

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



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# Orthostatic Intolerance (OI) symptoms

**Orthostatic Intolerance/Autonomic N.S. Dysfunction symptoms**

1) **Reduced brain blood flow** symptoms and signs
   - lightheadedness, fainting, impaired cognition, disorientation, headaches, visual changes, unusual neurologic symptoms, exhaustion

2) **Reduced body blood flow** symptoms and signs
   - Sympathetic nervous system activation---palpitations, nausea, abdominal and chest discomfort, pale appearance, 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**



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

# Defined Syndromes of Chronic Orthostatic Intolerance/OI

- **Orthostatic hypotension**: a BP reduction of at least 20 systolic or 10 diastolic within the first 3 min of upright posture (standing, leaning, Tilt Table).
- **Postural Orthostatic Tachycardia Syndrome (POTS)**: the reproduction of orthostatic symptoms together with a +**30 bpm** increase in HR, from supine to 10 min upright, or a standing HR of ≥120. Age 12-19 heart rate increase must be +**40 bpm.**
- **Neurally Mediated Hypotension/Syncope:** synonymous with vasovagal fainting, neurocardiogenic fainting. Sudden fainting during quiet upright posture.



Freeman R et al., Consensus statement on the definition of orthostatic hypotension, neurally mediated syncope and the postural tachycardia syndrome. Clin Auton Res. 2011 Apr;21(2):69-72.

# A way to identify impaired function due to OI: Assess HUA

## HUA: Hours of "Upright" Activity:

The #hours spent with **feet-on-floor** in 24 hours (i.e. sitting, standing, walking)

*Be sure to include time spent sitting with **feet on the floor**.*

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Thanks, and credit to David Bell MD

# Typical HUA* in 24 hours:

- Normal healthy folks: HUA 14-17 hrs.
- Chronic illness/FM: HUA 10-12 hrs.
- ME/CFS: HUA 0- 8 hrs.

HUA=Hours of Upright Activity

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*based on BHC clinical data

# Evaluate for Orthostatic Intolerance: 10-Minute NASA Lean Test

HR and BP after 10-15 minutes of quiet supine rest

HR and BP every 1-2 minutes for 10 minutes while standing/leaning in upright posture

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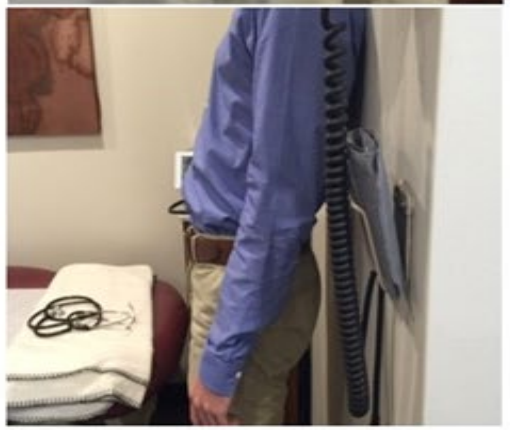
# The 10 min NASA Lean Test
# (A standardized passive lean test)

**10 minutes NASA Lean Test**

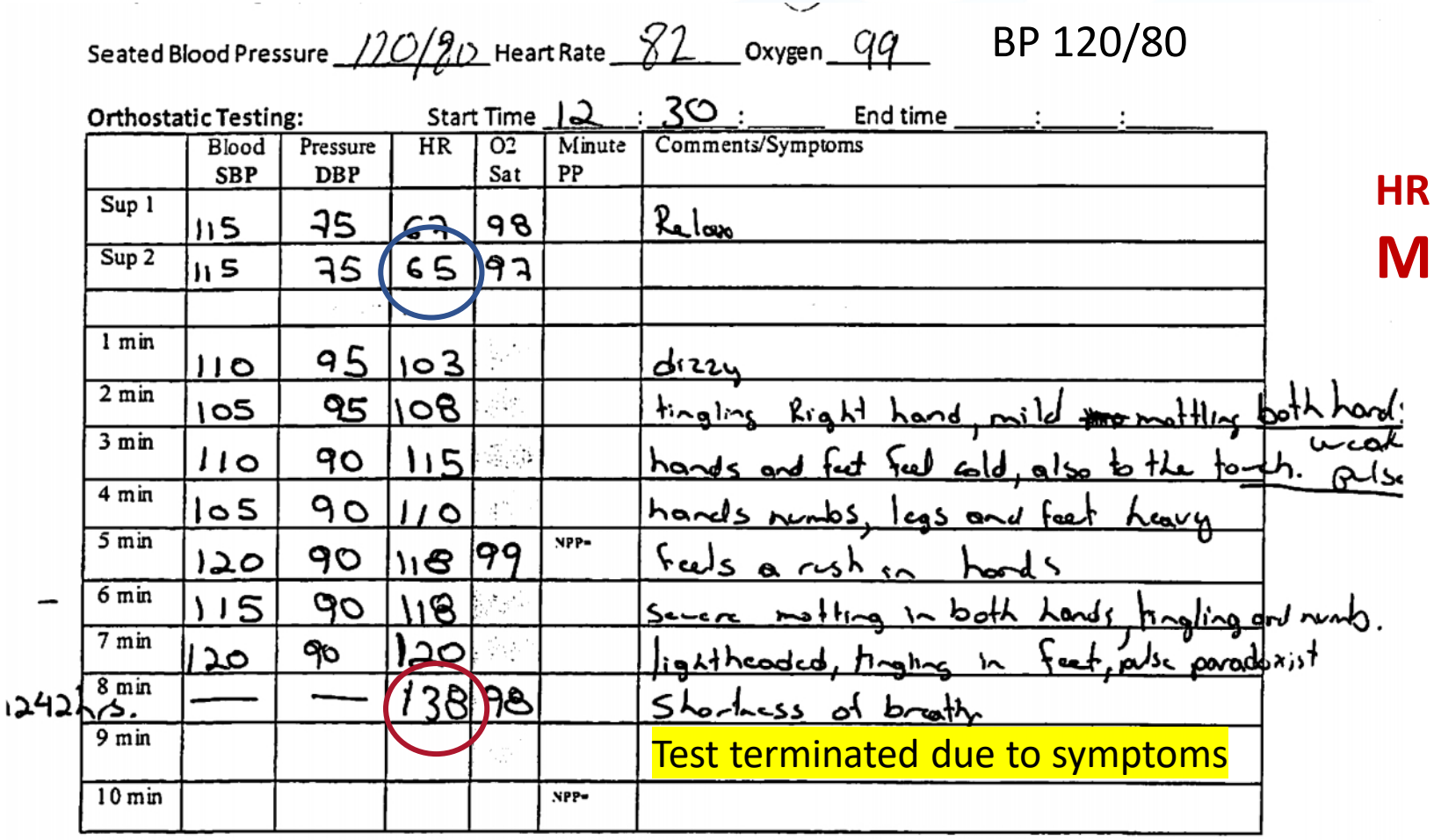
**Orthostatic Vital Signs/The NASA 10-minute Lean Test**

| | Blood Pressure (BP) | | Pulse | Comments |
|---|---|---|---|---|
| | Systolic | Diastolic | | |
| Supine 1 minute | | | | |
| Supine 2 minute | | | | |
| | | | | |
| Standing 0 minute | | | | |
| Standing 1 minute | | | | |
| Standing 2 minute | | | | |
| Standing 3 minute | | | | |
| Standing 4 minute | | | | |
| Standing 5 minute | | | | |
| Standing 6 minute | | | | |
| Standing 7 minute | | | | |
| Standing 8 minute | | | | |
| Standing 9 minute | | | | |
| Standing 10 minute | | | | |



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.

# Male teacher, age 45, Long COVID and (POTS) postural orthostatic tachycardia syndrome*



Seated Blood Pressure 120/80 Heart Rate 82 Oxygen 99

BP 120/80

Orthostatic Testing: Start Time 12 : 30 : End time : :

| | Blood Pressure SBP | DBP | HR | O2 Sat | Minute PP | Comments/Symptoms |
|---|---|---|---|---|---|---|
| Sup 1 | 115 | 75 | 67 | 98 | | Relax |
| Sup 2 | 115 | 75 | 65 | 97 | | |
| | | | | | | |
| 1 min | 110 | 95 | 103 | | | dizzy |
| 2 min | 105 | 95 | 108 | | | tingling Right hand, mild ~~mo~~ mottling both hands |
| 3 min | 110 | 90 | 115 | | | hands and feet feel cold, also to the touch. weak pulse |
| 4 min | 105 | 90 | 110 | | | hands numbs, legs and feet heavy |
| 5 min | 120 | 90 | 118 | 99 | NPP= | feels a rush in hands |
| 6 min | 115 | 90 | 118 | | | severe motting in both hands, tingling and numb. |
| 7 min | 120 | 90 | 120 | | | lightheaded, tingling in feet, pulse paradoxist |
| 8 min | — | — | 138 | 98 | | Shortness of breath |
| 9 min | | | | | | Test terminated due to symptoms |
| 10 min | | | | | NPP= | |

1242 hrs.

**HR 65 bpm → 138 bpm= +73 bpm**

**Meets criteria for POTS**

*A diagnosis of POTS requires an increase of HR >30 bpm for adults and 40 bpm up to age 18

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# Interventions for OI

## Recognize and <u>avoid</u> the common factors that aggravate OI

- Heat, getting overheated
- Dehydration
- Prolonged standing in place
- Prolonged sitting with feet on floor
- Prolonged bedrest (confuses the ANS)
- Muscle atrophy and weakness
  - Abdomen/core, upper and lower legs
- Medications that cause/worsen OI
- PEM

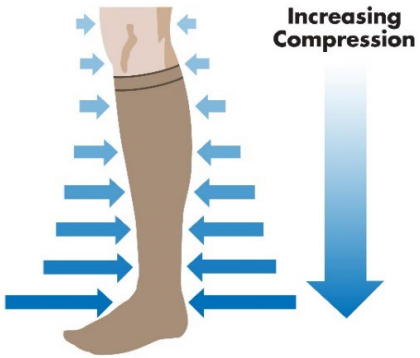
# Interventions for OI

## Increase volume in the blood vessels

- Consume extra **water/fluids** to expand blood volume (2-4 liters)
- Increased **salt intake** helps retain water in the circulation and tissues
- **fludrocortisone 0.1 mg** once daily
- **Rapid water ingestion** (16 oz) helps reduce OI within 20 minutes (chugging)
- **IV normal saline.** Can be very helpful as “rescue” and support, especially when ill, dehydrated, or having medical procedures such as colonoscopy.

## External compression or internal constriction of blood vessels

- Compression socks, pants, sleeves, abdominal binder
- **Midodrine 5-10 mg every 4-5 hr.**, a peripheral alpha-1 receptor agonist



# Interventions for OI

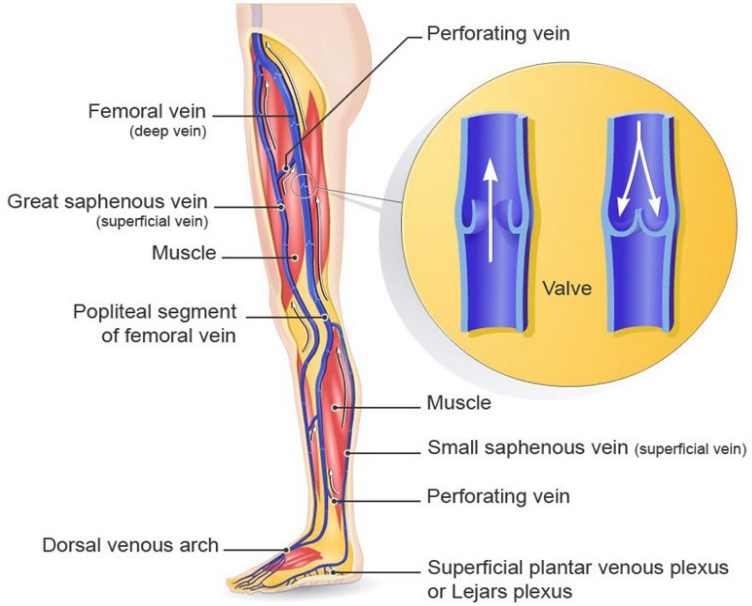
**Additional ways to alter autonomic nervous system function and control the rapid heart rate response** if indicated and helpful**:**

**Ex: Low dose beta blockers:** Propranolol 10 mg bid (2x/day) to tid (3x/day), metoprolol succinate 12.5-25mg

**Ex: Pyridostigmine*** Raises acetylcholine, the neurotransmitter of most of the parasympathetic nerves, and a few sympathetic nerves.

- Improved venous return and decreased pre-load failure
- Reduces AV shunting and opens capillaries at tissue level
- Increased parasympathetic activity and GI motility

**Strengthen and use the muscular "pumps" for better venous return.** Muscular pumps = leg and abdominal muscles

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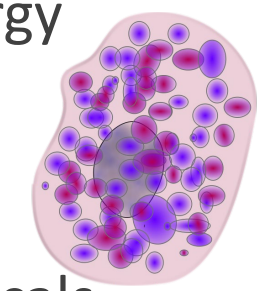
*Raj SR, Black BK, Biaggioni I, Harris PA, Robertson D. Acetylcholinesterase inhibition improves tachycardia in postural tachycardia syndrome. Circulation. 2005 May 31;111(21):2734-40. Epub 2005 May 23.

# WHAT IS MAST CELL ACTIVATION SYNDROME?

Mast cell activation syndrome (MCAS) is an illness characterized by repeated allergy reactions affecting several body systems. In MCAS, mast cells release too many chemical agents…



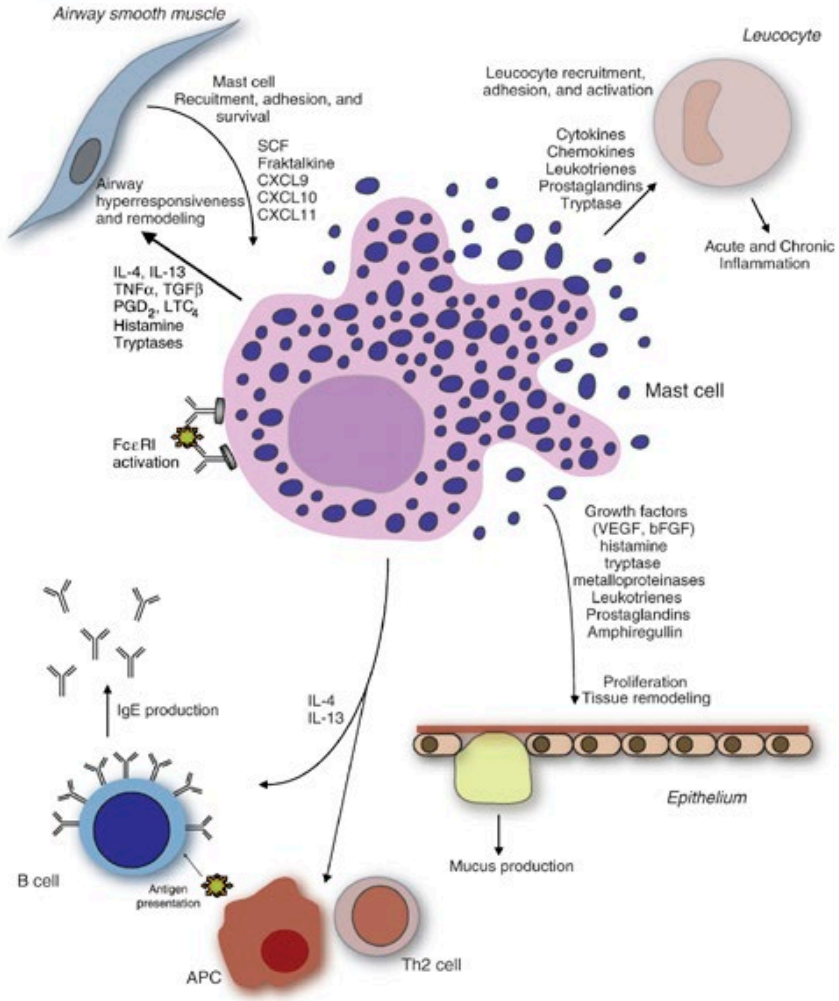
- **Mast cells** are present throughout most of our body and secrete various chemicals.
- Symptoms include episodes of abdominal pain, cramping, diarrhea, flushing, itching, wheezing, coughing, lightheadedness and rapid pulse and low blood pressure.
- The exact cause of MCAS is unknown but may reflect underlying chronic inflammation.
- Diagnosis is based on the symptoms, clinical exam, and specific laboratory testing.



https://rarediseases.info.nih.gov/diseases/12981/mast-cell-activation-syndrome

# Mast Cell Activation/Hypersensitivity

- Mast Cells are a type of **white blood cell** found in connective tissues all through the body, especially under the skin, near blood vessels and lymph vessels, in nerves, and in the lungs.
- When mast cells are “activated,” they release inflammatory chemicals known as cytokines, with histamine and leukotrienes being the most famous of these.
- Activated mast cells may also send distress signals, through the nervous system and immune system, to other areas of the body, alerting other mast cells to activate as well.




Clinical & Experimental Allergy, Volume: 38, Issue: 1, Pages: 4-18, First published: 21 November 2007, DOI: (10.1111/j.1365-2222.2007.02886.x)

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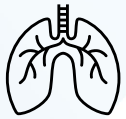
“Mast Cell Activation Syndrome: AAAAI.” *The American Academy of Allergy, Asthma, &Immunology*, www.aaaai.org/conditions-and-treatments/related conditions/mcas

Mast Cell Activation Syndrome: A review. Frieri M., Patel R., Celestin J. Curr Allergy Asthma Rep. 2013 Feb;13(1):27-32. doi: 10.1007/s11882-012-0322-z.

# CLINICAL CRITERIA FOR MAST CELL ACTIVATION SYNDROME

**1)** Episodic symptoms consistent with mast cell mediator release affecting **two or more organ systems** evidenced as follows:

- Skin: urticaria (hives), angioedema (sudden swelling), flushing, dermatographia 
- Gastrointestinal: nausea, vomiting, diarrhea, abdominal cramping 
- Cardiovascular: hypotensive syncope (fainting), tachycardia 
- Respiratory: wheezing 
- Naso-ocular: conjunctival injection, pruritus(itching), nasal stuffiness 

# CLINICAL CRITERIA FOR MAST CELL ACTIVATION SYNDROME

**2) Improved symptoms after treatment** with:

- H1 and H2 histamine receptor antagonist (blocker) medications
- Anti-leukotriene medications
- Mast cell stabilizer medications

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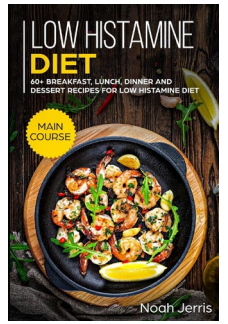
Mast cell activation disease: a concise practical guide for diagnostic workup and therapeutic options. Gerhard J Molderings et al…Afrin. Journal of Hematology & Oncology 20114:10. https://doi.org/10.1186/1756-8722-4-10©. 2011

# Mast Cell Activation Treatments

- Low Histamine Diet
- H1 Blockade
- H2 Blockade
- Leukotriene Blockade (montelukast)
- Mast Cell Stabilizers
  - Liquid cromolyn/Gastrocrom (1 ml or 20 mg up to 5 ml or 100 mg 15 minutes before meals and medications)
  - Compounded cromolyn sodium (200 mg po (by mouth) tid (3x/day) to qid (4x/day)
  - Compounded ketotifen (1 mg po bid)
  - OTC Quercetin
- Anti-IgE biologics (omalizumab/Xolair)







**REMEMBER: Empiric trials of therapy when a clinical suspicion for MCAS can also be diagnostic!**

# CLINICAL CRITERIA FOR MAST CELL ACTIVATION SYNDROME

**3) Evidence of an elevation in a validated urinary or serum marker of mast cell activation:**

- Total serum **tryptase** (very specific for mast cells)
- Elevated serum **histamine**
- Biopsy tissue (i.e. GI tissue) with staining positive for mast cells (CD 117 staining)
- 24-hour urine levels of:
  - **N-methylhistamine**
  - **11B -Prostaglandin F2α** (11B-PGF2α)
  - **Leukotriene E4 (LTE4)**

**REMEMBER: Empiric trials of therapy when a clinical suspicion for MCAS can also be diagnostic!**

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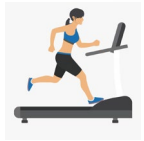
# Mast Cell Activation/Hypersensitivity Triggers

**Figure 1. Some *Potential* Mast Cell Triggers[2-5]**

- Heat, cold or sudden temperature changes
- Stress: emotional, physical, including *pain*, or environmental (i.e., weather changes, pollution, pollen, pet dander, etc.)



- Exercise

- Fatigue

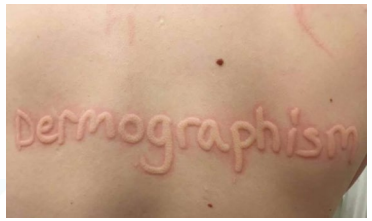

- Food or beverages, including alcohol

- Drugs (opioids, NSAIDs, antibiotics and some local anesthetics) and contrast dyes

- Natural odors, chemical odors, perfumes and scents

- Venoms (bee, wasp, mixed vespids, spiders, fire ants, jelly fish, snakes, biting insects, such as flies, mosquitos and fleas, etc.)

- Infections (viral, bacterial or fungal)




- Mechanical irritation, friction, vibration

- Sun/sunlight

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RESEARCH | CLINICAL CARE | EDUCATION

"Symptoms and Triggers of Mast Cell Activation - TMS - The Mastocytosis Society." *The Mastocytosis Society*, 29 July 2019, tmsforacure.org/symptoms/symptoms-and-triggers-of-mast-cell-activation/.

# A TIME-TESTED GENERAL TREATMENT APPROACH

1) **Identify and treat all identifiable medical conditions (co-morbid or underlying).**
2) **Learn how to "pace" activity to prevent, and reduce severity/duration of "Post Exertional Malaise" (PEM).**
3) **Address the major aspects of illness:**
   - **Mental health:** reduce grief/despair/anxiety. Seek insight.
   - **Orthostatic intolerance (OI):** if present (good literature available).
   - **Pain:** when pain is a stressor.
   - **Sleep:** when corrupted and non-restorative.
   - **Fitness:** as compatible with illness manifestations. **PACING** trumps FITNESS.

# RESOURCES

- **Mast Cell Activation Syndrome (MCAS):**

https://www.aaaai.org/Conditions-Treatments/Related-Conditions/mcas

- **OI/POTS:** http://dysautonomiainternational.org/
- **BHC YouTube site education videos:** https://www.youtube.com/user/OFFERUtah
- **BHC website:** https://batemanhornecenter.org/