Managing Orthostatic Intolerance

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Moderated by Kim McCleary

September 1, 2010

Hosted by
the CFIDS Association of America
Thank you for joining us!

- 13th CFIDS Association webinar of 2010 series
- Dr. Rowe and Kim are in different locations
- 270 people preregistered to participate
- Questions submitted with registration helped shape discussion topics
- Time for Q&A after presentation – type them as you think of them
- Recording will be posted online within a couple of days
- Dr. Rowe is not able to address individuals’ questions about their symptoms, test results or therapy
What we learned from registrants:

- 50% have been diagnosed with orthostatic intolerance (OI)
- 30% have symptoms of OI but have not had testing
- 60% indicate that OI has a significant impact on daily life
- Only 5% indicate that it has little or no effect
- 60% have participated in another Association webinar

- Lots of questions submitted in advance!
Peter M. Rowe, MD

Johns Hopkins University School of Medicine
Baltimore, Maryland

Sunshine Natural Wellbeing Foundation
Professor of Chronic Fatigue and Related Disorders

Specializes in pediatric and adolescent medicine

With colleague Hugh Calkins, credited with identifying link between CFS and OI
Managing Orthostatic Intolerance

CFIDS Association Webinar
1 September 2010

Peter C. Rowe, MD

Sunshine Natural Wellbeing Foundation Professor of Chronic Fatigue and Related Disorders

Johns Hopkins University School of Medicine
Baltimore, USA
Managing Orthostatic Intolerance

• Introduction to the problem
• Definition and overview of the physiology
• Common forms of OI in CFS
• Treatment of OI
  – Non-pharmacologic measures
  – Treating contributory conditions
  – Medications
15 year old with fatigue

Insidious onset of fatigue and lightheadedness at age 13
Awakens unrefreshed after 10 hours of sleep.
Tired all the time, worse by noon after being in school,
with shopping and any physical activity
Headaches, generalized achiness by school day’s end
Shoulders sore; worse low back and knee pain with sitting
Concentration off, easily distracted
Home schooling due to fatigue in the last 18 months
15 year old with fatigue

Lightheaded every time he stands
No syncope, but some presyncope
Since onset of fatigue, craves salt: keeps salt shaker in bedroom, licks it out of his hand
PMH: allergic rhinitis
FH: 2 sibs, several maternal relatives flexible
Prior work-up:

WBC 6.6, Hgb 14.1, Plt 335
Chemistry panel normal
TSH 2.06
ESR 3, CRP < 1
Urinalysis normal
Cardiac eval (with ECG and echo) normal
Brain MRI normal
Exam

Mature, pleasant adolescent.
Ht 50\textsuperscript{th} %, Wt 75\textsuperscript{th} %
BP 120/80, HR 80 bpm
General exam notable for:
- Blue sclera
- Beighton score 7/9
- Subluxes shoulders at will
**POTS**

**BP / HR**

- **HR**
- **BP**

- 51 bpm Δ

**Supine**

**Standing**

**Supine**

**min**
15 Year Old with Fatigue

**Diagnoses:** Joint hypermobility
Orthostatic intolerance (POTS)
(HR Δ 51 bpm [62 → 113])
Allergic rhinitis
CFS

**Treatment:** Fexofenadine 180 mg qD
Fludrocortisone 0.1 mg daily
KCl 10 mEq qD
15 Year Old With CFS: Early Follow-up

- Less congested
- Within a week of reaching the full 0.1 mg daily dose of fludrocortisone, noted improvement in all symptoms:
  - No LH, no HA, normal energy
  - No post-exertional worsening of malaise
  - Wellness: 90s
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Orthostatic Intolerance

The term “orthostatic intolerance” refers to a group of clinical conditions in which symptoms worsen with quiet upright posture and are ameliorated (although not necessarily abolished) by recumbency.

Low PA
Rowell LB
Human Cardiovascular Control, 1993
Symptoms of Orthostatic Intolerance

Lightheadedness
Syncope
Diminished concentration
Headache
Blurred vision
Fatigue
Exercise intolerance

Dyspnea
Chest Discomfort
Palpitations
Tremulousness
Anxiety
Nausea
Nocturia
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• Illustrative case discussions
Common Forms Of Orthostatic Intolerance In Patients With CFS

• Neurally mediated hypotension
  – during orthostatic testing, 25 mm Hg drop in systolic BP, with no associated increase in HR
  – reproduction of typical orthostatic symptoms

• Postural tachycardia syndrome
  – 30 bpm increase in HR (or HR ≥ 120) in the first 10 minutes of orthostatic testing
  – reproduction of typical orthostatic symptoms
↑ pooling, ↓ vasoconstriction  
↓ intra-vascular volume

Standing/ Tilt test  
↑ sympatho-adrenal response

↓ NE/Epi  
↑ NE/Epi

NMH  POTS
Neurally Mediated Hypotension

*also known as*

Vasovagal syncope
Neurocardiogenic syncope
Vasodepressor syncope
Neurally mediated syncope
Neurally Mediated Hypotension

- The most common cause of recurrent syncope
- More common in women, the young, those with low normal or low BP
- Common following infection
- Family members often affected
- Routine physical and lab tests normal
- Hypotension not detected unless orthostatic stress is prolonged
- Fatigue common for hours after syncope
NMH

BP / HR

HR
BP

Standing
Supine

HR Δ 27 bpm

Supine
Standing
Supine

min

-4 -2 0 2 4 6 8 10

0 50 100

NMH

HR
BP

Supine
Standing
Supine
Catecholamines during upright tilt in syncope patients and controls

Postural Tachycardia Syndrome (POTS)

- Common disorder, F > M
- Insidious vs. onset after infection, surgery, trauma
- Heterogeneous pathophysiology
  - Hyperadrenergic and dysautonomic/neuropathic forms
  - Some classify into low-, normal-, and high-flow POTS
  - Subsets with hypovolemia, elevated PRA/Aldosterone ratios, AChR ab positive, NET deficiency
- Fatigue, exercise intolerance, palpitations common; often disabling symptoms
Standing
Supine
Supine

BP / HR

HR ∆ 66 bpm

-5 0 5 10 15 min

Supine Standing Supine

POTS

HR
BP
Dependent acrocyanosis
Joint hypermobility

Orthostatic Intolerance

CFS
Insights on OI 1995-2010

- OI is strongly associated with CFS
- Upright posture aggravates CFS symptoms, often before HR/BP changes of POTS & NMH appear
- Treatment of OI can improve CFS symptoms
- OI can be the primary abnormality, or it can be a consequence of a variety of other problems (e.g. deconditioning, an underlying infection)
- Therefore, it is important to evaluate patients carefully for the non-cardiovascular problems
- POTS and NMH can occur in the same person, and are not mutually exclusive
- Treatment of POTS and NMH overlap
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  – Medications
• Illustrative case discussions
Step 1: Non-pharmacologic measures

Where possible, avoid factors that precipitate symptoms
Precipitating Factors For NMH & POTS

• Increased pooling/decreased volume
  Prolonged sitting or standing
  Warm environment
  Sodium depletion
  Prolonged bed rest
  Varicose veins
  High carbohydrate meals
  Diuretics, vasodilators, alpha-blockers
  Alcohol
Precipitating Factors For NMH & POTS

- Increased catecholamines
  Stress
  Exercise
  Pain
  Hypoglycemia
  Albuterol
  Epinephrine
Step 1: Non-pharmacologic measures

- Raising the head of the bed has an anti-diuretic effect and preserves blood volume at night

MacLean AR, Allen EV. Am Heart J 1944; 27:145
Step 1: Non-pharmacologic measures

Compression garments
  – Support hose
    (waist high > thigh high > knee high)
  – Body shaper garments
  – Abdominal binders
Pilot data on the utility of compression garments

5 patients with CFS and OI were studied while taking their usual medications, with the exception of no beta-blockers, stimulants, midodrine, pyridostigmine bromide on the day of the test.

Two 5-minute standing tests were performed, in random order, separated by 15 minutes, one with a compression suit on, the other without.
Step 1: Non-pharmacologic measures

Use postural counter-measures
- standing with legs crossed
- squatting
- knee-chest sitting
- leaning forward sitting
- elevate knees when sitting (foot rest)
- clench fists when standing up
[Use the muscles as a pump]
Step 1: Non-pharmacologic measures

Fluids: Minimally 2 L per day
Drink at least every 2 hours
Need access to fluids at school
Avoid sleeping > 12 hrs/day

Salt: Increase according to taste
Supplement with salt tablets
Heart rate and BP responses to head-up tilt before (—) and after (----) intravenous saline

Step 1: Non-pharmacologic measures

Exercise

Avoid excessive bed rest/sleeping
For most impaired, start exercise slowly, increase gradually
Recumbent exercise may help at outset
Manual forms of PT may be a bridge to better tolerance of exercise

[Inactivity is the enemy]
FIG. 39.3. Percent change in plasma volume with data from studies that utilized horizontal bed rest with no remedial procedures. [From Greenleaf et al. (130) with permission.]
Treatment of Orthostatic Intolerance in CFS

• Step 1: non pharmacologic measures

• Step 2: treating contributory conditions

• Step 3: medications
  – Monotherapy
  – Rational polytherapy
Treatment of Orthostatic Intolerance in CFS

• Step 1: non pharmacologic measures
• Step 2: treating contributory conditions
• Step 3: medications
  – Monotherapy
  – Rational polytherapy
Pool pooling, vasoconstriction.

↓ intra-vascular volume

Vasoconstrictors

Volume expanders

Standing

↑ sympatho-adrenal response

↓ NE/Epi

↑ NE/Epi

NMH

POTS

Reduce catecholamine release/effect
Therapy For Orthostatic Intolerance

• \(\uparrow\) **blood volume**
  Sodium (PO & occasionally IV),
  fludrocortisone, clonidine, OCPs

• \(\downarrow\) **catecholamine release or effect**
  \(\beta\)-blockers, disopyramide, SSRIs, ACE inh.

• **Vasoconstriction**
  Midodrine, dexedrine, methylphenidate, SSRIs, SNRIs, aescin (horse chestnut seed extract); L-DOPS (Droxidopa) in trials

• **Misc:** pyridostigmine bromide
Fludrocortisone

- A synthetic mineralocorticoid used for several decades for the treatment of adrenal insufficiency and autonomic dysfunction
- Promotes reabsorption of sodium in distal tubule
- Pharmacologic effects: volume expansion, improved small vessel response to catecholamines
- Most common adverse effects: headache, swelling, hypertension, hypokalemia, depression
- Usual dose: 0.1 mg daily; doses above 0.2 mg daily often associated with hypokalemia
- Potassium chloride supplements recommended at initiation of therapy
Bou-Holaigah I, Rowe PC, Kan JS, Calkins H.
Fludrocortisone RCT design

Week | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11
--- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | ---
Assessments | X | X | X | X

T | Fludro | T | Off meds | T | Placebo

T |
## Results: primary outcomes

<table>
<thead>
<tr>
<th>Improvement in Wellness</th>
<th>Placebo</th>
<th>Fludro</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-point</td>
<td>34%</td>
<td>28%</td>
<td>.52</td>
</tr>
<tr>
<td>10-point</td>
<td>12%</td>
<td>18%</td>
<td>.58</td>
</tr>
<tr>
<td>15-point</td>
<td>10%</td>
<td>14%</td>
<td>.76</td>
</tr>
<tr>
<td>20-point</td>
<td>6%</td>
<td>10%</td>
<td>.72</td>
</tr>
<tr>
<td>Mean change</td>
<td>2.7 (10.0)</td>
<td>3.8 (11.5)</td>
<td>.71</td>
</tr>
</tbody>
</table>
Fludrocortisone Trial Limitations

- Patients did not increase intake of sodium
- Fludrocortisone dose limited to 0.1 mg/d to avoid unmasking treatment assignment
- Patients with prolonged CFS may respond differently; 71% in this study had CFS > 3 years
- Insufficient power to exclude true improvements in young patients and those with CFS < 3 years
- No patients < 18 enrolled
- No ability to account for “background noise” of other medical problems
Midodrine

• Alpha-1 agonist vasoconstrictor; no CNS effect
• Duration of action only 4 hours
• Common adverse effects: scalp tingling, paresthesias, piloerection, hypertension
• Usual dose for adolescents/adults:
  – 2.5 mg q4h while awake for 3 days
  – Increase by 2.5 mg per dose q3-7 days until desired effect or to max of 10 mg per dose
  – 4th dose OK if > 2 hours before bed; some need 10-15 mg/dose
Number of symptom free days during midodrine (treatment) or placebo study periods.

10/16 vs. 2/16 normal HUT after 1 mo., and more symptom free days (P< .0001)

Ward C R et al. Heart 1998;79:45-49
Stimulants

• Vasoconstrictors with CNS effects
• Dosing similar to that for ADHD
• Most common adverse effects: insomnia, reduced appetite, moodiness, increased lightheadedness, agitation.
• Usual dose for adolescents:
  – Dextroamphetamine SR: start at 5 mg qAM, raise every 3-7 days by 5 mg as tolerated to 20-30 mg/day
  – Methylphenidate SR: start at 10 mg, increasing every 3-7 days by 10 mg as tolerated to 30-50 mg/day
Stimulants: references

Beta blockers

- Interfere with catecholamine-mediated increases in heart rate (for POTS) and force of heart contraction (to block initiation of NMH reflex)
- May prevent epinephrine-induced vasodilation
- Most common adverse effects: fatigue, LH, decreased mood, cough/wheeze in asthmatics
- Usual dose for adolescents:
  - Atenolol 25 mg, increasing q3-7 days by 12.5 mg to 1 mg/kg (resting HR should be no lower than 50 bpm)
  - “Less is more” (Raj S, Circulation, 2009)
Clonidine

• Alpha-2 adrenergic receptor antagonist. Reduces sympathetic nervous system outflow; can lead to an expansion of blood volume in those with orthostatic intolerance.
• Second line treatment for ADHD; can improve sleep when taken at night.
• Most common side effects: worse fatigue and lightheadedness (due to the anti-hypertensive effect), and dry mouth. Must wean off slowly to avoid rebound hypertension.
• Usual dose for adolescents: 0.05 mg at night for 3-7 days, then increase to 0.1 mg at night.
SSRI/SNRI

- Inhibit the reuptake of serotonin (+/- norepinephrine) at nerve terminals, leaving more serotonin (+/- NE) available as a neurotransmitter.
- Serotonin can have a vasoconstricting effect on blood vessels. One RCT shows efficacy for paroxetine in NMH.
- Especially helpful in patients with co-morbid anxiety or depressed mood, or pain (duloxetine/Cymbalta)
- Adverse effects: occasionally worse lightheadedness or worse fatigue; bruising, sweating, reduced libido, diarrhea or nausea, or insomnia.
- Increased risk of suicide in the early phase of treatment, lower risk of suicide later in those with severe depression
Pyridostigmine bromide

- Acetylcholinesterase inhibitor
- Improves cardiovagal tone, lowering HR; other mechanisms may also play a role
- Typical doses:
  - Start with 30 mg twice/day- three times/day
  - Increase gradually to 60 mg 2-3 times daily
- Adverse effects: usually well tolerated, but can cause nervousness, muscle cramps or twitching, nausea, vomiting, diarrhea, stomach cramps, increased saliva, anxiety, and watering eyes.
Pyridostigmine in OI

**FIGURE 1.** Heart rate in the supine position (*light bars*) and during head-up tilt (*dark bars*) before and after pyridostigmine.
How to select initial therapy?

Algorithm vs. individualized approaches
Postural Orthostatic Tachycardia Syndrome
An Approach to Treatment

↑ hydration: >2 L/day
↑ salt intake: >200 mEq/day
Support stockings: 30 mm Hg
(Poor adherence in teenagers)

Non-pharmacologic
(all patients)

Family education
Psychophysiological therapy
Exercise – aerobic and lower extremity strengthening: ≥5x/week

Pharmacologic
(case by case)

1st line:
Beta blocker
↓ heart rate, block peripheral vasodilation
Metoprolol 12.5-50 mg 2-3x daily

1st or 2nd line:
Alpha agonist
Peripheral vasoconstriction
Midodrine 2.5-12.5 mg 1-3x daily

2nd line/adjunct:
Mineralocorticoid
↑ salt retention and plasma volume
Fludrocortisone 0.05-0.2 mg 1-2x daily

3rd line:
SSRIs/SSNRIs
Improves serotonin regulation
eg, citalopram, fluoxetine, venlafaxine

Rarely used:
Alternate medications (pyridostigmine, EPO, ddAVP, clonidine, methylphenidate)

Titrate all meds to effect and tolerance.

Individualized approach

- **SBP < 110**: fludrocortisone, midodrine
- **Increased HR at baseline or when upright**: β-blocker

Modified from Bloomfield, Am J Cardiol 1999;84:33Q-39Q

- **Based on other clinical clues**
  - Increased salt appetite: fludrocortisone
  - HA: β-blocker
  - Dysmenorrhea/worse fatigue with menses: OCP, Depo
  - Anxiety/low mood: SSRI, SNRI
  - Myalgias prominent: SNRI
  - FH of ADHD: stimulant
  - Hypermobility: stimulant, midodrine
Management of orthostatic intolerance

• requires careful attention by the patient and the practitioner to the factors that provoke symptoms
• requires a willingness to try several medications before a good fit is achieved
• requires a realization that meds often can treat symptoms but do not necessarily cure OI
• management of OI is one part of a comprehensive program of care
Association Between CFS, Orthostatic Intolerance and Ehlers-Danlos Syndrome/Joint Hypermobility Syndrome
Medical student with chronic fatigue

- Onset of persistent fatigue, unrefreshing sleep, exercise intolerance, myalgias, cognitive difficulties at entry to SOM
- PMH: onset of fatigue and syncope at age 11; initially averaged 2 episodes of syncope per yr, usually after standing or after showers
- Frequent knee dislocations, 4 spont. pneumothoraces
Medical student with chronic fatigue

• LH several times/day; 2 episodes of presyncope/week
• Typically with only 10-15 seconds of warning
• Worse fatigue after syncopal episodes
• Symptoms thought due to atypical depression, although mood reported as OK. Worse syncope on sertraline 150 mg/day.
• Had to repeat year 1
Medical student with chronic fatigue

<table>
<thead>
<tr>
<th>Tilt test</th>
<th>HR</th>
<th>BP</th>
<th>Sx</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>74</td>
<td>112/70</td>
<td>None</td>
</tr>
<tr>
<td>Immed tilt</td>
<td>83</td>
<td>115/75</td>
<td>LH, pale</td>
</tr>
<tr>
<td>5 min</td>
<td>52</td>
<td>50/---</td>
<td>Syncope, Brief sz.</td>
</tr>
</tbody>
</table>
Medical student with chronic fatigue

- Syncope resolved with increased salt, fluids, midodrine
- Joint hypermobility and skin laxity noted
- Echo: aortic root normal, mild MVP
- Dx: Ehlers-Danlos syndrome
- Persistent non-cyclic pelvic heaviness and low back pain with standing; concerned about ability to tolerate surgical clerkship
Pelvic Congestion Syndrome

- Pelvic heaviness or pain with long periods of standing
- Worse at end of the day, during menses
- Other symptoms: fatigue, dyspareunia, bladder urgency
- Strong association with varicose ovarian veins
- 89% have > 80% relief after embolization of ovarian vein varicosities
Medical student with chronic fatigue

- Improved pelvic pain and orthostatic symptoms after embolization of ovarian vein varices
- No further syncope
- Now able to stand for 7 hrs during surgical clerkship
- Wants to be a surgeon
Ehlers-Danlos Syndrome

- Heterogeneous disorder of connective tissue
- Prevalence unknown, perhaps 1 per 5000
- Characterized by varying degrees of:
  - Skin hyperextensibility
  - Joint hypermobility
  - Cutaneous scarring
- Early varicose veins, easy bruising
- Easy fatigability and widespread pain common, of unclear etiology
Beighton score: On each side, 1 point for $> 90^\circ$ hyperextensibility of 5th finger, 1 point for thumb to forearm, and 1 for $> 10^\circ$ hyperextensibility at elbow.

Fig. V-1 Passive hyperextension of the little finger beyond 10 degrees. This index was used by Ellis and Bundick (1956) in their large scale survey of the variations in joint mobility and skin extensibility which occurred in individuals of differing sex, age and race. (Fig. V-1 from Beighton, P. (1968) Brit. med. J. 3, 409.)

Fig. V-2 Passive apposition of the thumb to the forearm.

Fig. V-3 Hyperextension of the elbow joint beyond 10 degrees.
Beighton score:

on each side, 1 point for $>10^\circ$ hyperextensibility at knees; 1 point for palms to floor

Hypermobility present if Beighton score is 4 or higher
CFS Associated With EDS and Orthostatic Intolerance

Among 100 adolescents in the CFS clinic at JHH over a 1 year period, we identified 12 with EDS (P < 0.01)

6 classical-type, 6 hypermobile-type EDS

EDS In CFS Patients With Orthostatic Intolerance

Fatigue present for median of 37 mo before EDS recognized (range 12-62)
5 had at least 3 episodes of syncope
7 had lightheadedness, but no syncope
NMH in 9/12, POTS in 10/12

Joint Hypermobility In Children With CFS

Study question: do children with CFS have a higher prevalence of joint hypermobility?

Beighton scores obtained in 58 new & 58 established CFS patients, and in 58 controls

Median Beighton scores higher in CFS (4 vs. 1)
Beighton score ≥ 4 higher in CFS (60% vs. 24%)

Beighton Joint Hypermobility Scores in 58 Adolescents With CFS And 58 Healthy Controls

How Might Hypermobility Be Associated With OI and CFS?

Working hypothesis:

Connective tissue laxity in blood vessels allows increased vascular compliance, promotes excessive pooling during upright posture, leading to diminished blood return to the heart, and thus to OI symptoms

Dysautonomia in JHS

• Subjects:
  – 48 consecutive patients with joint hypermobility syndrome referred to rheumatology division
  – 30 healthy controls

• Methods
  – Questionnaire of symptoms
  – Autonomic testing in a subset

Gazit et al. Am J Med
2003;115:33-40
Dysautonomia in JHS: Results

- Symptoms of OI more common in patients
  - LH, syncope, palpitations, fatigue, impaired concentration, dyspnea, tremulousness, nocturia

- OI more common
  - 78% of JHS vs. 10% of controls had OI
  - Standing tolerance 14.5 (6) vs. 19 (3.5) min, [P = .004]

Dysautonomia in JHS

Dose to increase HR 15 bpm

Dose to increase SBP 15 mm Hg
Unanswered Questions

1. What are the risk factors for fatigue in JHS/EDS?
2. What is the prevalence of OI in EDS patients?
3. What is the prevalence of CFS or fibromyalgia symptoms in JHS/EDS?
4. Do therapies directed at OI & related co-morbidities in JHS and EDS improve QOL?
Upcoming Webinars:

• Thurs., Sept. 16: **CFS & the Viral Connection**
  Anthony L. Komaroff, MD, Harvard Medical School

• Tues., Oct. 5: **Expanding Research**
  Suzanne D. Vernon, PhD, CFIDS Association

• Thurs., Oct. 21: **Co-Morbid Conditions – The Alphabet Soup of CFS**
  Morris Papernik, MD, Hartford Hospital, Hartford, CT
For more information:

- CFIDS Association website: [www.cfids.org](http://www.cfids.org)
- Facebook: [www.facebook.com/cfidsassn](http://www.facebook.com/cfidsassn)
The CFIDS Association of America

Our Mission:
For CFS to be widely understood, diagnosable, curable and preventable.

Our Strategy:
To stimulate research aimed at the early detection, objective diagnosis and effective treatment of CFS through expanded public, private and commercial investment.

Our Core Values:
To lead with integrity, innovation and purpose.