Update on Chronic Fatigue Syndrome

Adolescent Rounds
January 22, 2010

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Professor of Pediatrics
Johns Hopkins University

16 year old with fatigue

Healthy and active until 9 mo. before visit
Insidious onset of fatigue
Sleeps 12-14 hrs per night, awakens unrefreshed
Has difficulty getting going in the AM, has to lie down after showering
Has to lie down the day after an active day
Difficulty concentrating
Muscles sore, headaches, dizzy
Unable to attend school

16 Year Old With Fatigue

• On exam: Acrocyanosis. BP 117/81
• Standing test: HR 80 bpm to 121 bpm in 10 min
• Tilt test: Symptoms: fatigue, warmth, LH, nausea, diaphoresis
  Presyncope at 17 minutes
  BP 78/48 HR 70
• Diagnosis: POTS and NMH
• Treatment: Increased salt and fluid intake
  Fludrocortisone, potassium

16 Year Old With CFS: Early Follow-up

• Improvement in all symptoms within 2 weeks
• Began working 2 jobs, feeding livestock at family farm, able to spend time with friends
• Full school attendance since 9/95
• Fatigue only after 45 minutes of swimming
• Repeat standing test: HR 76 to 86 after 10 minutes
Late Follow-up: 1995-2009

- Mild fatigue when allergies active
- Return of impressive fatigue with attempts to wean Florinef, despite good level of exercise and physical conditioning
- Off meds: wellness 50-70/100
- On meds: wellness 85-90/100
- Off Florinef by 2005

Update on CFS

- Definition
- Epidemiology and impact
- Selected research highlights
- Circulatory dysfunction in CFS
- Suggestions for management

Fatigue in CFS

Self-reported persistent or relapsing fatigue lasting 6 or more consecutive months, which:
- Is of new or definite onset (not lifelong)
- Is not the result of ongoing exertion
- Is not substantially alleviated by rest
- Results in substantial reduction in previous levels of occupational, educational, social, or personal activities

Symptom Criteria For CFS

4 of 8 needed for diagnosis

- unrefreshing sleep
- postexertional malaise lasting > 24 hours
- self reported impairment in short-term memory or concentration
- sore throat
- tender cervical or axillary glands
- muscle pain
- multijoint pain without swelling
- headaches of a new type, pattern, severity

Clinical Evaluation

- History, physical, mental status exam
- Labs clinically indicated
- Screening labs:
  - CBC, ESR
  - Chemistries
  - TSH
  - Urinalysis
  - Most would now add celiac screening

CFS Epidemiology

General

Affects previously active individuals

Heterogeneous precipitating & perpetuating factors

Shift in perception of CFS:
No longer considered a single disease
More likely a convergence of co-morbid pathophysiologic influences
Our century’s version of “dropsy”
CFS Epidemiology

**Incidence**
- 400/100,000 adults
- 50-100/100,000 adolescents

**Age**
- Uncommon under 10 years
- Peak prevalence 40-49 years

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**Gender**
- F:M = 1.8:1

**SES**
- Affects all groups

**Genetics**
- Twice as common in MZ as DZ twins
- CFS associated with EDS

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**Clinical Discriminators of Fatigue**

<table>
<thead>
<tr>
<th>Condition</th>
<th>Clinical pearl</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neuromuscular</td>
<td>Weakness</td>
</tr>
<tr>
<td>OSA</td>
<td>Somnolence, ↑bicarb</td>
</tr>
<tr>
<td>Heart/lung disease</td>
<td>SOB, effort intolerance</td>
</tr>
<tr>
<td>Adrenal insufficiency</td>
<td>Bronzing, ↓Na,↑K</td>
</tr>
<tr>
<td>Chiari I</td>
<td>Occipital HA, ↑DTRs</td>
</tr>
</tbody>
</table>

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**Differential Diagnosis Of Acute Fatigue in Older Children and Adolescents**

- Depression, anxiety, and other emotional factors
- Infections (EBV, Chlamydia, HIV, Hepatitis, Lyme disease)
- Anemia
- Pregnancy
- Endocrine disorders (hypothyroidism, adrenal insufficiency, hyperaldosteronism)
- Ehlers-Danlos Syndromes
- Marfan Syndrome
- Neurolologic (Autonomic dysfunction, myasthenia gravis, muscular dystrophy, Charcot-Marie-Tooth, MS)
- GI inflammation (IBD, Celiac disease, eosinophilic gastroenteropathy)
- Ehlers-Danlos or Marfan Syndromes
- Varicose veins
- Immunodeficiency
- Allergy
- Sleep abnormalities
- Obstructive sleep apnea
- Renal failure
- Lung disease (CF, Asthma, hypersensitivity pneumonitis)
- Misc. (congestive heart failure, sleep breathing disturbances, etc.)

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**CFS And Psychiatry**

- Many CFS patients have anxiety or depression, but prevalence estimates vary widely
- Severity usually mild, anhedonia uncommon
- Treating depression and anxiety can improve these symptoms, but usually does not cure CFS
- Common factor may be the exaggerated response to a variety of physical and psychological stressors
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Dubbo study
Hickie I et al. BMJ 2006

- Prospective cohort study
- In SW Australia, 200 km radius with 104,400 residents
- Labs identified all new cases of:
  - Acute EBV DNA virus
  - Q-fever Intracellular bacterium Coxiella Burnetti
  - Ross river virus RNA virus

Of 855 potential participants, 253 followed for 12 months
Post-infective fatigue syndrome present in 22/250 (9%) at 12 months
PIFS predicted by severity of acute illness
Pre-morbid or intercurrent psychiatric disorders had no predictive power

301 adolescents with EBV:
% with CFS over time
Key Etiologic Question

Debate about whether infection acts as a “hit and run” phenomenon, triggering some other physiologic dysfunction but not directly causing symptoms, or whether persistent symptoms are due to active infection.

Other Key Findings

- Immune abnormalities inconsistent & mild, but interferon can cause fatigue syndrome
- HPA axis abnormalities secondary & mild; rare cortisol binding globulin deficiency
- CBT and graded exercise provide modest improvement in function but not cure
- Low rates of spontaneous improvement for those with > 3 yrs of symptoms

Other Key Findings

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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
EDS scar: dehiscence after laparoscopy, requiring revision X 2
EDS: poor healing after 2nd revision of a ganglionectomy, L wrist

How Might Hypermobility Be Associated With CFS?

- Connective tissue laxity in blood vessels promotes excessive pooling during upright posture, leading to OI symptoms
- Hypermobility leads to decreased activity
- Associated with another factor (eg, autonomic dysfunction, panic, biomechanical problems)

Symptoms in 66 consecutive adolescents with CFS

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unrefreshing sleep</td>
<td>97%</td>
</tr>
<tr>
<td>Post-exertional malaise</td>
<td>88%</td>
</tr>
<tr>
<td>Impaired memory/concentration</td>
<td>87%</td>
</tr>
<tr>
<td>Headache</td>
<td>87%</td>
</tr>
<tr>
<td>Myalgia</td>
<td>65%</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>46%</td>
</tr>
<tr>
<td>Sore throat</td>
<td>13%</td>
</tr>
<tr>
<td>Tender glands</td>
<td>2%</td>
</tr>
<tr>
<td>LH several times/wk</td>
<td>33%</td>
</tr>
</tbody>
</table>

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Medical student with chronic fatigue

- Onset of persistent fatigue, unrefreshing sleep, exercise intolerance, myalgias, cognitive difficulties at entry to JHUSOM
- 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. pneumos
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

<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</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Brief sz.</td>
</tr>
</tbody>
</table>

Medical student with chronic fatigue: intermediate follow-up 1 yr later

- 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

Relationship of orthostatic intolerance to chronic fatigue

Can we move fatigue levels from A to B by treating orthostatic intolerance?

Rowell LB
Human Cardiovascular Control, 1993
Symptoms of Orthostatic Intolerance

Lightheadedness  Dyspnea
Syncope        Chest Discomfort
Diminished concentration  Palpitations
Headache      Tremulousness
Blurred vision  Anxiety
Fatigue        Nausea
Exercise intolerance  Nocturia

Orthostatic Intolerance: Behavioral Features

• Orthostatic stress associated with increases in catecholamines (**anxiety**)
• Reduced cerebral blood flow (**inattention**)
• Multi-symptom presentation in autonomic dysfunction (**somatoform disorder**)
• Reduced activity & energy (**depression**)

Common Forms Of Orthostatic Intolerance In Patients With CFS

• Neuromechanically 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
  – orthostatic symptoms

Patterns of response to upright tilt in CFS

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
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
Is neurally mediated hypotension an unrecognised cause of chronic fatigue?

Peter C Rowe, Issam Bou-Holaigah, Jean S Kan, Hugh Calkins

Lancet 1995; 345: 623-24

How Might Orthostatic Intolerance Be Associated With Chronic Fatigue?

- Fainting due to NMH is followed by up to 72 hours of fatigue
- Near-fainting and lightheadedness on a repeated basis throughout the day likely cause fatigue through a similar mechanism
- The more lightheaded and intolerant of orthostatic stress, the more the tendency to lie down—leading to reduced blood volume and worse OI.

Response To Upright Tilt: CFS

<table>
<thead>
<tr>
<th>Abnormal</th>
<th>Normal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage of tilt</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>CFS</td>
<td>16</td>
</tr>
<tr>
<td>CONTROL</td>
<td>0</td>
</tr>
</tbody>
</table>

OR for abnormal tilt in those with CFS: 55 (95% CI, 5.4 - 557)

Adolescents with CFS

<table>
<thead>
<tr>
<th>POTS</th>
<th>NMH</th>
<th>OI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Controls</td>
<td>0</td>
<td>4/13</td>
</tr>
<tr>
<td>Syncope</td>
<td>0</td>
<td>18/26</td>
</tr>
<tr>
<td>CFS</td>
<td>18/26</td>
<td>22/26</td>
</tr>
</tbody>
</table>

Stewart et al, Pediatrics 1999;103:116

Adolescents with CFS

<table>
<thead>
<tr>
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Wyller: controlled comparison

Am J Cardiol 2007;99:997-1001

- 27 with CFS (18 F), 33 controls (19F)
- Mean age 15 yrs (13-18)
- Similar weight, BSA
- Median duration of fatigue 30 mo. (4-132)
- 15 min of HUT to 20 degrees
- HR, BP, stroke index, TPR, end-diastolic volume index, acceleration index
**Wyller: controlled comparison**

*Am J Cardiol 2007;99:997-1001*

<table>
<thead>
<tr>
<th>CFS at rest</th>
<th>CFS during tilt</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Higher TPR†</td>
<td>• Increase in HR†</td>
</tr>
<tr>
<td>• Lower stroke index*</td>
<td>• Increase in DBP‡</td>
</tr>
<tr>
<td>• Lower EDV index*</td>
<td>• Increase in MBP‡</td>
</tr>
<tr>
<td></td>
<td>• Increase in TPR index*</td>
</tr>
<tr>
<td></td>
<td>• Decrease in stroke index*</td>
</tr>
</tbody>
</table>

† P < .001; ‡ P < .01; * P < .05

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**Conclusions**

- Orthostatic intolerance (OI) is strongly associated with CFS
- *All* studies in which the response to upright posture is measured in adolescents with CFS report higher rates of OI
- Upright posture consistently aggravates CFS
- *All* studies that examine HRV in adolescents report a sympathetic predominance of autonomic tone
- Joint hypermobility is a risk factor for CFS and OI
- In a subset with CFS, treatment of OI is associated with improvement in CFS symptoms and function

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**Conclusions**

- Despite the consistency of the physiologic evidence, published reviews on CFS and many national guidelines completely ignore these data, to the detriment of those affected by CFS.
- An increased research focus on cardiovascular problems is likely to advance our scientific understanding of CFS
- Recognition and treatment of orthostatic intolerance has the potential to provide another avenue for a pragmatic, individualized approach to symptoms in those with chronic fatigue syndrome.

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**Treatment of Pediatric CFS**

- Explanation and demystification
- Provide guidance about new treatments
- Help with schooling
  - Letters for accommodations (fluids, extra time, flexibility with assignments)
  - Home and hospital schooling when needed
  - Home tuition when part-time is impossible
**Treatment of Pediatric CFS**

- Regular clinic visits for medical monitoring, symptomatic therapy
  - Sleep disorders
  - Headaches
  - Pain management
    (especially newer agents for FMS)
  - Management of co-morbid anxiety and depression

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**Step 1: Non-pharmacologic measures**

Avoid prolonged quiet sitting & standing  
Support hose; abdominal corsets  
Use postural counter-measures
  - standing with legs crossed
  - squatting
  - knee-chest sitting
  - leaning forward sitting
  - elevate knees when sitting (foot rest)

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**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  
Avoid vasodilators and diuretics

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**Step 1: Non-pharmacologic measures**

Exercise  
Avoid excessive bed rest/sleeping  
For most impaired, start exercise slowly, increase gradually  
Resistance exercises may help

[Inactivity is the enemy]

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**Treatment of Orthostatic Intolerance in CFS**

- Step 1: non pharmacologic measures
- Step 2: treating contributory conditions
- Step 3: medications  
  - Monotherapy
  - Rational polytherapy

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Ref: MacLean AR, Allen EV. Am Heart J 1944; 27:145
Treatment of Orthostatic Intolerance in CFS

- Step 1: non pharmacologic measures
- Step 2: treating contributory conditions
- Step 3: medications
  - Monotherapy
  - Rational polytherapy

**Therapy For Orthostatic Intolerance**

- **↑ blood volume**
  - Sodium (PO & occasionally IV), fludrocortisone, clonidine, OCPs
- **↓ catecholamine release or effect**
  - β-blockers, disopyramide, SSRIs, ACE inh.
- **Vasoconstriction**
  - Midodrine, dexamphetamine, methylphenidate, SSRIs
- **Misc**
  - pyridostigmine bromide

**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
15 year old with fatigue and headaches

- Well until menarche at 12, then onset of HA
- Fatigue, widespread pain, LH began at 14.
- Currently:
  - HA 4-5/10 each AM
  - Widespread pain daily; winces when hugged
  - Fatigue daily; fluctuates in severity; worse with menses, hot environments, sitting in school
  - Tires rapidly when shopping
  - LH on arising, with showers, in hot weather.

GI symptoms

- Reduced appetite, esp. when more tired
- Upper abdominal discomfort
- Burning in the throat with reflux most days
- Heartburn 1-4 times/ mo
- Aphthous ulcers frequently since age 12
- Avoids milk: makes her feel unwell (no infancy problems)

15 year old with fatigue and headaches

- Epigastric pain on abdo palpation
- Diffuse tenderness to palpation of all muscle groups
- SLR restricted to 30 degrees bilat, tight median nerve excursion on PT screening tests
- Supine HR 58, rising to 93 bpm (35 bpm Δ) with 10 min standing test, c/w mild POTS

15 year old with fatigue and headaches

- Rx: Milk-free diet, salt tablets, OCPs
- 2 month F/U: much better energy, LH no longer daily, myalgias much better, fewer HA, abdo pain gone, reflux 50% better
- PE shows marked improvement in ROM
- PLAN: add PPI for remaining reflux, yoga exercises, continuous OCP to reduce menstrual increases in symptoms; continue CBT and efforts to manage pill phobia
15 yr old with headaches and orthostatic intolerance

Energetic and active until June 2005
Developed bitemporal, non-pounding headaches associated with fatigue
Some fluctuation over the next few months
By December 2005, increased frequency, some migraines (left arm and mouth numbness); often felt need to lie down
First syncopal episode in March 2006
Continuous HA, unable to attend school

O/E: nystagmus, positive Romberg
MRI: c/w Chiari malformation
Decompression performed late March 2006
Initial resolution of HA for 3 wks
Then HA returned, associated with vertigo
Vestibular testing normal: vertigo attributed to migraines
No response to trials of Elavil, Topamax, Propranolol, Imitrex, acupuncture, low fat diet

15 yr old with headaches and orthostatic intolerance

July 2007: HA most days, starting mid AM, lasting all day.
Bitemporal, achy, 4-7/10
Worse with warm environment, car and bus
Also reports visual blackouts several times daily
Endorses LH only occasionally, usually with hot baths
Does not feel as sharp mentally; has to re-read texts frequently

Standing test

<table>
<thead>
<tr>
<th></th>
<th>BP</th>
<th>HR</th>
<th>Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Supine</td>
<td>100/56</td>
<td>54</td>
<td>Mild ftg</td>
</tr>
<tr>
<td>2 min</td>
<td>100/64</td>
<td>86</td>
<td>Mild HA, foggy</td>
</tr>
<tr>
<td>8 min</td>
<td>97/53</td>
<td>84</td>
<td>Hot, worse HA, nausea, had to sit (taken sitting)</td>
</tr>
<tr>
<td>9 min</td>
<td>88/40</td>
<td>72</td>
<td></td>
</tr>
<tr>
<td>IMP: mild POTS (32 bpm increase in HR with presyncope); probable NMH</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

15 yr old with headaches and orthostatic intolerance

O/E: Pleasant adolescent in no distress; a bit slow paced in her verbal responses
Exam generally normal.
DTRs 2+, symmetrical
No further nystagmus
Surgical scar well healed, but some neck muscle tightness

Treatments

Salt tabs: fewer HA
Florinef: tolerated low dose of 0.05 mg
Midodrine: good response
PT helpful
[Intolerant of Celexa (worse OI), OCPs (low mood, acne); Stimulants: ineffective]
Pindolol 2.5-5 mg BID helps with stress responsivity
### 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
- Common adverse effects: hypertension, hypokalemia, headache, depression
- Usual dose: 0.05-0.1 mg daily; doses above 0.2 mg daily associated with hypokalemia

### Midodrine
- Alpha-1 agonist with no CNS effects
- Duration of action only 4 hours
- Common adverse effects: scalp tingling, paresthesias, piloerection, hypertension
- Usual dose for adolescents:
  - 2.5 mg q4h while awake for 3 doses
  - 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

### Stimulants
- Vasoconstrictors with CNS effects
- Dosing similar to that for ADHD
- Common adverse effects: insomnia, reduced appetite, moodiness, increased lightheadedness, agitation.
- Usual dose for adolescents:
  - Dexedrine spansules: start at 5 mg qAM, increasing q3-7 days by 5 mg as tolerated to 20-30 mg qAM
  - Ritalin LA: start at 10 mg, increasing q3-7 days by 10 mg as tolerated to 30-50 mg qAM

### Beta blockers
- Interfere with catecholamine-mediated inotropic and chronotropic effects (thus blocking initiation of reflex syncope)
- May prevent epinephrine-induced vasodilation
- Common adverse effects: fatigue, LH, decreased mood, cough/wheeze
- 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)