ORTHOSTATIC HYPOTENSION

Differential Diagnosis

**Differential Diagnosis of Orthostatic Hypotension**

<table>
<thead>
<tr>
<th>Autonomic dysfunction</th>
<th>Vasodilator excess</th>
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<tbody>
<tr>
<td>Baroreceptor failure (common in the elderly)</td>
<td>Mastocytosis (histamine, prostaglandin D2)</td>
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<tr>
<td>Bradberry-Eggleston syndrome (pure autonomic failure)</td>
<td>Hyperbradykininism</td>
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<tr>
<td>Shy-Drager syndrome (multiple system atrophy)</td>
<td>Carotid syndrome (bradykinin)</td>
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<td>Autonomic failure with Parkinson’s disease</td>
<td>Hypermagnesemia</td>
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<tr>
<td>Riley-Day syndrome (familial dysautonomia)</td>
<td>Paroxysmal autonomic syncope</td>
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<td>Dopamine-β-hydroxylase deficiency</td>
<td>Glossopharyngeal syncope</td>
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<tr>
<td>Acute pandysautonomia</td>
<td>Micturition syncope</td>
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<tr>
<td>Diabetes mellitus</td>
<td>Carotid sinus syndrome</td>
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<tr>
<td>Amyloidosis</td>
<td>Swallow syncope</td>
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<tr>
<td>Porphyria</td>
<td>Cough syncope</td>
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<tr>
<td>Paraneoplastic autonomic neuropathy</td>
<td>Bezold–Jarisch reflex activation</td>
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<tr>
<td>Acute inflammatory neuropathy</td>
<td>Miscellaneous</td>
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<td>Hereditary sensory</td>
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**Hypovolemia**

<table>
<thead>
<tr>
<th>Hemorrhage or plasma loss</th>
<th>Drugs and toxins</th>
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<tbody>
<tr>
<td>Overdiuresis</td>
<td>Alcohol</td>
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<tr>
<td>Overdialysis</td>
<td>Stroke-Adams attacks</td>
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<tr>
<td>Endocrine disorders</td>
<td>Mitral valve prolapse syndrome</td>
</tr>
<tr>
<td>Primary adrenal insufficiency</td>
<td>Hypokinesia, weightlessness, bed rest</td>
</tr>
<tr>
<td>Hypoaldosteronism</td>
<td>Vascular insufficiency</td>
</tr>
<tr>
<td>Pheochromocytoma</td>
<td>Varicose veins</td>
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<tr>
<td>Renovascular hypertension</td>
<td>Absent venous valves</td>
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**Treatment** (primarily directed to autonomic dysfunction)

- If underlying cause is hypovolemia, treat with volume replacement.

**NONPHARMACOLOGIC TREATMENT**

(effective for mild to moderate orthostatic hypotension)

**Remove offending medications**

- diuretics
- antihypertensives (B-blockers)
- antianginal drugs
- antidepressants

Some geriatric patients actually have supine hypertension and may present with symptoms of orthostatic hypotension (syncope or presyncope) shortly after starting meds for HTN.

**Patient education and physical maneuvers**

- Rise slowly in stages, from supine to seated to standing. Be particularly careful in the morning when orthostatic tolerance is lowest.
- Avoiding straining, coughing, and walking in hot weather (reduced venous return).
- Custom-fitted elastic stockings – apply graded pressure to the lower extremities and lower abdomen which decreases peripheral blood pooling. Stockings must extend to waist since most pooling occurs in splanchnic circulation.
- Exercise may be beneficial especially if cardiovascular deconditioning rather than chronic autonomic failure is the cause.
- Tensing the legs by crossing them while actively standing on both legs. Squatting. Both increase venous return.

**Increase salt and water intake**

Autonomic insufficiency can lead to increased urinary sodium and water excretion

- High-sodium containing foods, salt tablets, drinking water with meals.
- Minimizing alcohol intake

**PHARMACOLOGIC TREATMENT**

Goal is to treat symptoms not numbers!

**FLUDROCORTISONE ACETATE**

- synthetic mineralocorticoid, works by increasing blood volume
- **first line** for most patients with orthostatic hypotension.
- Long acting, well-tolerated by most with chronic autonomic failure.
- Enhances sensitivity of blood vessels to catecholamines and enhanced norepinephrine release. Increases BP by increasing PVR.
- Monitor patients for pedal edema, CHF or worsening of supine hypertension. May require K+ supplements.

**SECOND LINE AGENTS**

**Sympathomimetic agents**
- May be added if the patient remains symptomatic on fludrocortisone. Alpha agonist usually has synergistic effects and allows for lower dosage of both agents.
- Pressor agents may be used alone in those unable to tolerate fludrocortisone.
- Alpha-1 adrenoreceptor agonists:
  - Ephedrine, pseudoephedrine (tid dosing) (direct and indirect effects)
  - methylphenidate, dextroamphetamine sulphate (indirect effects only)
  - No longer used because intolerable CNS side effects
  - Vasoconstrictor effect of indirect agonists is due to the release of norepinephrine from postganglionic neurons. These meds most likely only those with partial or incomplete lesions.
- Phenylephrine and midodrine (direct effects only)
  - Peripheral selective alpha-1-adrenergic agonists.
  - For chronic orthostatic hypotension
  - Pressor effect due to both arterial and venous constriction.
  - Side effects: pilomotor reactions, pruritus, supine hypertension, gastrointestinal complaints, and urinary retention. Does not cross the bbb therefore no anxiety, tremor, tachycardia as seen with adrenergic agents that cross the bbb.
  - Contraindicated in patients with organic heart disease, uncontrolled hypertension, or urinary retention.

**SUPPLEMENTARY AGENTS**
- Prostaglandin synthetase inhibitors (ie, NSAIDs), caffeine and erythropoietin may be used in combination with first or second line agents
  - NSAIDs limit the vasodilating effects of circulating prostaglandins. May enhance vascular sensitivity to norepinephrine.
  - Caffeine has a pressor effect due to blockade of vasodilating adenosine receptors (100-250 mg tid)
  - Erythropoietin improves orthostatic tolerance in patients with anemia that may be associated with autonomic failure. A trial of erythropoietin should be used in all patients with orthostatic hypotension and anemia who have low serum erythropoietin concentrations.

**THIRD LINE AND EXPERIMENTAL AGENTS**
- **Vasopressin analogues**
  V1 (vasoconstricting) and V2 (collecting tubules) receptor agonists.
  Action may be enhanced by supersensitivity to vasopressin in patients with autonomic failure because of reduced postural release of vasopressin.
  - Desmopressin acts on V2 receptors, prevents nocturia and overnight weight loss and reduces the morning OH in patients with autonomic failure. Stop dDAVP if hyponatremia develops.
  - Lysine-vasopressin nasal spray, intramuscular triglycyl-lysine vasopressin act on VI receptors direct vasopressor effect, thereby improving symptoms of orthostatic hypotension. No RCTs done as of yet.
- **Clonidine**
  Normally a centrally-acting alpha-2 adrenergic agonist which produces a peripheral sympatholytic effect that decreases blood pressure. But patients with autonomic failure have little or no central sympathetic efferent activity therefore the effect of clonidine on postsynaptic alpha-2 vascular adrenoreceptors may predominate. This results in increased BP (through arterial constriction)
- **Yohimbine**
  Central acting selective alpha-2 antagonist. Increases sympathetic nervous system efferent output by blocking central and/or presynaptic alpha-2 receptors. Produces a modest pressor effect. Side effects: anxiety, tremor, palpitations, diarrhea, and supine hypertension.
- **Dihydroergotamine**
  An ergot alkaloid, interacts with alpha-adrenergic receptors. Selective vasoconstrictor effect. Increases venous return without producing a significant increase in peripheral vascular resistance. Low oral bioavailability.
- **B-blockers**
  B-blockers (non-selective, with intrinsic sympathomimetic activity) ex. pindolol and xamoterolol. Work by blockade of vasodilating B2 receptors. This leads to unapposed A-adrenoreceptor vasoconstriction. Side-effects CHF and fatigue.
- **Dihydroxyphenylserine**
synthetic, norepinephrine precursors
To treat neurogenic orthostatic hypotension.

- **Dopamine antagonists**
  - metoclopramide and domperidone
  - for chronic orthostatic hypotension.
  - Inhibit the vasodilating and natriuretic effect of dopamine and increase noradrenaline release by blocking receptors for dopamine which exhibits inhibitory control of noradrenaline.
  - EPS and tardive dyskinesia limits their long-term use.

- **Monoamine oxidase inhibitors**
Combination therapy: Tyramine (which releases norepinephrine) from neuronal storage pools) plus a monoamine oxidase inhibitor (which prevents breakdown of norepinephrine).
Limited use because: severe supine hypertension, unpredictable response, may improve BP numbers but not symptoms.

- **Ambulatory norepinephrine infusion**
For patients with refractory orthostatic hypotension due to primary autonomic failure

  - **Treatment of orthostatic hypotension with supine hypertension**
    - Nonpharmacologic measures + drugs only to increase BP sufficient to allow the patient to ambulate.
    - Avoid lying down, and rest in a seated position during the day.
    - Should sleep in a semisitting position.
    - Can treat supine hypertension with nitro patch at night only.