Pediatric Disorders of Orthostatic Intolerance

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abstract

Orthostatic intolerance (OI), having difficulty tolerating an upright posture because of symptoms or signs that abate when returned to supine, is common in pediatrics. For example, ~40% of people faint during their lives, half of whom faint during adolescence, and the peak age for first faint is 15 years. Because of this, we describe the most common forms of OI in pediatrics and distinguish between chronic and acute OI. These common forms of OI include initial orthostatic hypotension (which is a frequently seen benign condition in youngsters), true orthostatic hypotension (both neurogenic and nonneurogenic), vasovagal syncope, and postural tachycardia syndrome. We also describe the influences of chronic bed rest and rapid weight loss as aggravating factors and causes of OI. Presenting signs and symptoms are discussed as well as patient evaluation and testing modalities. Putative causes of OI, such as gravitational and exercise deconditioning, immune-mediated disease, mast cell activation, and central hypovolemia, are described as well as frequent comorbidities, such as joint hypermobility, anxiety, and gastrointestinal issues. The medical management of OI is considered, which includes both nonpharmacologic and pharmacologic approaches. Finally, we discuss the prognosis and long-term implications of OI and indicate future directions for research and patient management.

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Consensus guidelines define orthostatic disorders in adults on the basis of expert opinion and randomized controlled studies.[1–3] These conclusions incompletely extend to children, for whom large trials and even small controlled studies are sparse. Pediatric orthostatic intolerance (OI) has drawn increasing attention in recent publications from different groups with different perspectives.[4–7] The high and possibly increasing prevalence of orthostatic disorders in teenagers prompted the American Autonomic Society to convene member experts to draft an evidence-based State of the Art document. This document is intended to provide common ground on which to build a better understanding of pathophysiology and treatment.

THE CHALLENGE OF ORTHOSTASIS (STANDING UPRIGHT)

Humans are bipedal. While upright, our brain is above our heart, whereas 70% of our blood volume is below the heart. If not for autonomic and cardiovascular compensatory mechanisms, hypotension and loss of consciousness would ensue after orthostasis.

Orthostatic Intolerance

OI can be defined as having difficulty tolerating the upright posture because of symptoms that abate

when returned to supine. Typical symptoms include a sense of impending loss of consciousness, cognitive deficits (memory loss and decreased reasoning and concentration), visual difficulties, lightheadedness, headache, fatigue, weakness, nausea, abdominal discomfort, tremulousness, exercise intolerance, and reported signs such as pallor, diaphoresis, tachycardia, bradycardia, or hypotension.

This definition encompasses all forms of orthostatic disorders, such as postural faint and orthostatic hypotension (OH), but not others, such as a broken leg or overt muscle disease. The definition is sufficiently broad to encompass postural vertigo, balance issues, and positional headache.

Chronic OI is defined as OI that is present for at least 3 months, although symptoms may wax and wane. An example is postural tachycardia syndrome (POTS).

Acute and subacute OI are defined as OI that has been present for <1 week and <3 months, respectively, or is restricted to recurrent episodes, such as with postural vasovagal syncope (VVS).

Some OI represents an extension of normal physiology, such as transient lightheadedness immediately on standing. Some consider infrequent VVS to be a normal response to central hypovolemia because its lifetime incidence approaches 40%, and it can be universally induced with sufficient orthostatic provocation.[2] However, OI that importantly diminishes quality of life deserves treatment.

In what follows, we more specifically define individual entities comprising OI and discuss how best to test for and diagnose OI. We review the epidemiology, predisposing factors, putative causes, and frequent comorbidities of OI and focus on POTS. We discuss management, prognosis, and future directions for research and therapy.

INDIVIDUAL ENTITIES

Initial Orthostatic Hypotension

On standing, there is symptomatic hypotension because of the caudal transference of blood because of gravity and a time delay in sympathetic activation.[8] Blood pressure (BP) can decrease by >30%, reaching a nadir at 10 to 15 seconds after standing. Lightheadedness and reflex tachycardia occur. BP is restored within 30 seconds, but cerebral blood flow and heart rate (HR) take longer.[9–11] Clinically significant initial orthostatic hypotension (IOH) is defined as a decrease in systolic BP of >40 mm Hg or a decrease in diastolic BP of >20 mm Hg.[10] The fall in BP is enhanced by the duration of the previous supine position. A history of transient lightheadedness dissipating in <1 minute should be considered as IOH.[7,10,12] Syncope is uncommonly reported with IOH. Countermeasures to obviate symptoms include active contraction of lower-body muscles or recumbence.[9,10] IOH is the most common form of OI.[9,12,13] A representative standing test in which IOH is experienced is shown in Fig 1.

OH is defined by the steady decrease in BP exceeding 20 mm Hg systolic or 10 mm Hg diastolic within 3 minutes of standing from supine.[1,7,14] The associated compromise in brain blood flow may cause syncope. OH may be nonneurogenic from severe central hypovolemia or pharmaceutical vasodilation.[15] There is supine tachycardia, which increases markedly when upright. OH may be neurogenic (nOH) because of an inadequate release of norepinephrine from sympathetic neurons.[1] nOH results from primary autonomic failure or secondary autonomic failure, as in diabetes and amyloidosis.[14,16–18] nOH is uncommon in pediatrics but occurs in familial dysautonomia and autoimmune disorders.[18,19] There may be little postural HR increase in adults because of frequent, associated cardiac denervation.[1,18] In contrast, children typically mount a compensatory tachycardia, suggesting intact cardiac parasympathetic efferents.[6] A representative tilt table test in which OH is experienced is shown in Fig 2.

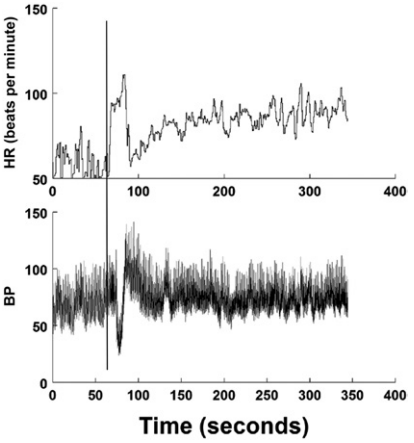

FIGURE 1
A standing test of IOH is shown. The upper panel shows HR in beats per minute, and the lower panel shows BP in mm Hg. The vertical line indicates standing. BP decreases, and HR increases briefly. Hypotension resolves within 30 seconds. HR stabilizes gradually to its upright, steady-state value.

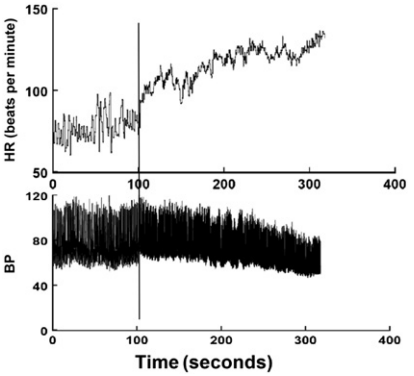

FIGURE 2
A tilt table test shows true OH. The upper panel shows HR in beats per minute, and the lower panel shows BP in mm Hg. The vertical line indicates tilt. There is a monotonic decrease in BP and a compensatory increase in HR, which can often exceed 40 beats per minute in youngsters.

Postural Vasovagal Syncope

Syncope is defined by a transient loss of consciousness and postural tone because of global cerebral hypoperfusion characterized by rapid onset, short duration (<2 minutes), and spontaneous recovery.[20] Postural VVS is syncope occurring after several (>3) minutes upright. Characteristic history features environmental precipitating factors, a prodrome of lightheadedness, diaphoresis, warmth, nausea, hyperventilation, pallor, and a postdrome of fatigue and headache.[2,21–23] Cardiac causes for syncope must be ruled out.[7,24] Hypotension and bradycardia typically occur together. Postural VVS is aborted by lying down; consciousness returns within seconds. VVS is also provoked by noxious stimuli, such as venipuncture or emotional stress.[2,21–23] The most common age of onset is 15 years. VVS occurs twice as often in female adolescents, with sex ratios equalizing later in life.[25] Athletic youngsters have an increased prevalence of VVS. Postexercise VVS can occur in patients with postural VVS. Low-serum iron and/or ferritin can contribute to the occurrence of VVS.[26,27] VVS can be induced in healthy volunteers in the laboratory but is only clinically important in daily life. Reflex syncope occurs in OH and situational variants, such as deglutition, defecation, micturition, and cough syncope, but rarely from IOH.[6,7] Asystolic or convulsive syncope may occur in VVS without prodrome and with tonic posturing after loss of consciousness. Physical injury is common in these patients because of falls and other related trauma. In adults, pacing has been used to prevent these injuries. In patients with presumptive VVS, competing diagnoses include epilepsy and pseudosyncope. A representative tilt table test in which VVS is experienced is shown in Fig 3.

POTS is defined by daily symptoms of chronic OI combined with sustained, excessive upright tachycardia in the absence of postural hypotension. The origins of POTS are heterogeneous. Most cases are in girls (>80%).[7,28,29] Symptoms are initiated by an upright posture and abate when supine (ie, they must be postural to be POTS).[30] Excessive upright tachycardia is defined in adults as an average sustained increase in HR of >30 beats per minute or to an HR of >120 beats per minute within 10 minutes of standing or upright tilt. Excessive upright tachycardia is defined in adolescents 18 years or younger by an increase in HR of >40 beats per minute.[29] By definition, sustained hypotension must be absent. POTS does not cause a transient loss of consciousness, per se, although VVS may also occur in some patients.[7] A secondary form of POTS can occur with any central hypovolemic state, such as dehydration or hemorrhage, and can progress to OH.[28] Excessive tachycardia also occurs in young VVS patients preceding syncope, but sustained hypotension precludes POTS. POTS can be evoked by excessive upright sympathetic activation or excessive parasympathetic withdrawal. When a cause is identified (eg, Addison disease), some discard the POTS label in favor of the disease name, whereas others prefer to call it secondary POTS. Regardless, POTS is a syndrome, and evaluations for underlying causes, such as dehydration, anemia, hyperthyroidism, and autonomic neuropathies, are necessary in all cases. A representative tilt table test in a patient with POTS is shown in Fig 4.

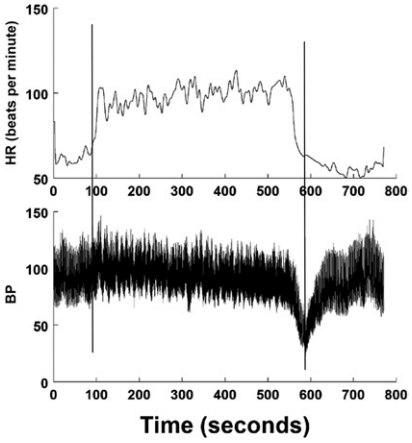

FIGURE 3
A tilt test shows VVS. The upper panel shows HR in beats per minute, and the lower panel shows BP in mm Hg. Vertical lines indicate the start and end of tilt. On tilt, BP is initially stable then slowly falls because HR rises often by >40 beats per minute. BP then falls rapidly, followed by HR (hypotension bradycardia).

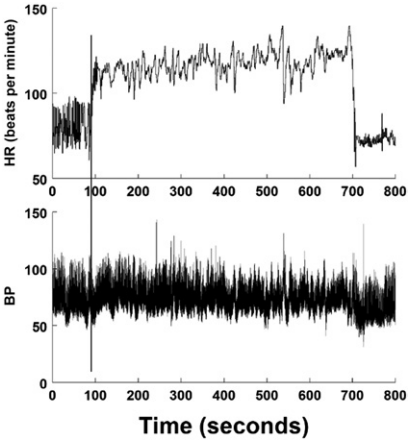

FIGURE 4
A tilt test shows POTS. The upper panel shows HR in beats per minute, and the lower panel shows BP in mm Hg. Vertical lines indicate the start and end of tilt. On tilt, BP is initially stable, with a small downward drift during tilt. There is excessive tachycardia but no hypotension.

Prolonged bed rest (>23 hours) induces gravitational deconditioning with concomitant physiologic findings and is distinct from exercise deconditioning; these include a markedly reduced blood volume, blood volume redistribution, trophic cardiac atrophy, baroreflex changes, reduced vasoconstriction to pressor drugs, skeletal muscle atrophy with loss of the skeletal muscle pump, and osteoporosis. The earliest changes are detectable within 24 hours. In a bed-rested patient, OI may take the form of POTS, OH, or VVS, and bed rest worsens these states if they are already present.[7,31–35]

Hypocaloric Weight Loss

A study of healthy volunteers showed a deterioration of orthostatic

tolerance with weight loss of 1% to 4%, which is likely because of a reduced blood volume, the modulation of autonomic function, altered baroreflex function, and altered vascular smooth muscle tone and responsiveness.[36] This is potentiated by bed rest.[36] OI resembling POTS or OH occurs in anorectic states and during starvation and may precede the well-known terminal bradycardia.[37]

TESTING FOR OI

Symptoms of OI must be present to merit testing. Autonomic and vasoactive drugs should be stopped for at least 5 half-lives before testing.

Upright tilt table testing is the de facto standard for orthostatic stress tests. The use of the tilt table at angles between 60° and 70° dates to 1930, but its use to diagnose VVS is more recent.[38,39] Tilt testing limits the effects of the skeletal muscle pump. Diagnostic criteria for POTS were also developed by using tilt table testing. The standardization of tilt table testing for the diagnosis of VVS has been problematic. The so-called Italian protocol (20 minutes upright followed by sublingual nitroglycerin as pharmacological potentiation) is now commonly used.[40,41] Tilt angles of 60° to 70° are advocated because angles of 80° to 90° increase the incidence of false-positive test results.[42]

Although a 10-minute tilt is standard for POTS, a 5-minute tilt may suffice. There is little consensus on the duration of the supine period preceding the tilt, although it affects results. Extending the tilt past 10 minutes reduces the accuracy of the POTS diagnosis, although it may provide additional information about the nature of OI and the diagnosis of syncope.[43] OH can be reliably diagnosed by tilt or standing for 3 minutes.[1]

TABLE 1 Predominant Presenting Symptoms of OI

Affected System	Symptoms Present While Upright
General	Fatigue, heat intolerance, weakness, temperature regulation difficulties
Cardiovascular	Lightheadedness, tachycardia, chest pain, palpitations, exercise intolerance, syncope, acrocyanosis, diaphoresis, pallor, flushing
Gastrointestinal	Nausea, abdominal pain, dysmotility
Respiratory	Dyspnea, hyperpnea
Neurologic	Headaches, paresthesias, balance problems
Neuropsychological	Memory and attention issues (brain fog)

Standing is arguably the most physiologic orthostatic test, although it is difficult to standardize. There is little consensus regarding how long a patient should stand, whether movement should be allowed or restricted, and how long a patient should be supine before standing. Validation of a standing test for POTS exists for adults but not yet for children, for whom the tilt table is standard.[43] Standing is validated in pediatric patients to diagnose OH and IOH.[1,10]

MONITORING DURING ORTHOSTATIC TESTING

The minimum requirement is an intermittent measurement of HR and BP. Current US *Current Procedural Terminology* codes require the measurement of beat-to-beat electrocardiogram and BP.[9,12,13] Automated autonomic testing is not validated and is not recommended for diagnoses.[44] Other monitoring uses nasal capnography, EEG, cerebral blood flow, or cerebral oximetry. Research measurements include regional blood flow and blood volume, pneumotachography, microneurography, and combined modalities.

PREVALENCE AND PHENOTYPE OF PEDIATRIC POTS

The prevalence of POTS is not well established.[45] Its incidence in pediatrics is not known because screening for OI is not routine. OI affects a broad range of organ systems. Examples of common signs and symptoms are shown in Table 1. Onset may be gradual or acute and often occurs after an infection, immunization, surgery, sepsis, or head trauma.[46–49] Infectious diseases exacerbate preexisting OI.[50,51]

DEMOGRAPHIC CHARACTERISTICS

Girls represent >80% of patients.[51] BMI is reduced in patients with POTS and hypovolemia.[52] Onset is often near puberty, but younger patients have been identified less frequently.[48,53] Literature on racial differences is limited: orthostatic tolerance characterizes African Americans, and most reported patients with POTS are white.[53–55] Family members of patients with POTS often describe similar symptoms.[56] Many young patients with POTS were formerly high achievers.[5,53] Yet, with the onset of symptoms, children experienced reduced participation in school, social life, sports, and recreational activities. Psychiatric comorbidities in these patients are also common.

PREDISPOSING AND CONTRIBUTING FACTORS AND PUTATIVE CAUSES OF POTS

Up to 50% of case patients have antecedent symptoms that suggest a viral infection with a prolonged course (eg, infectious mononucleosis).[57] Others have previous stressors, such as pregnancy, injury, or surgery; the remainder of patients develop symptoms insidiously.[58] Inflammatory or autoimmune mechanisms may also be responsible. Patients with prolonged illness may

confine themselves to bed, making matters worse.[53]

Central hypovolemia reduces cardiac venous return, resulting in a compensatory tachycardia. Hypovolemia may be absolute or distributive and accompanies exercise deconditioning and chronic fatigue.[59,60] Exercise deconditioning is a result rather than the cause of POTS, and some patients with POTS have normal to supranormal cardiovascular responses to exercise, with a normal stroke volume in 30% of patients.[61,62] However, exercise deconditioning can worsen POTS by further reducing blood or plasma volume, heart size, and stroke volume.[61]

Gravitational deconditioning occurs during microgravity and chronic bed rest and emulates the pathophysiology of POTS.[63] Plasma volume decreases by ~15% within several days, red cell mass declines, and blood flow and blood volume redistribute abnormally from skin and splanchnic reservoirs, reducing cardiac filling, particularly when upright and during exercise.[28,51,64–68] Muscle atrophy increases leg venous pooling, contributing to acrocyanosis, impaired vasoconstriction, and loss of the skeletal muscle pump.[31,58,68–70] The cardiovascular effects of prolonged bed rest contribute to the pivotal pathophysiology of POTS (central hypovolemia) and potentiate OI and POTS.[71] Measures that preserve peak oxygen uptake during exercise do not necessarily reduce OI, supporting the suggestion that POTS and deconditioning each represent separate downstream effects of an inciting cause.[63] POTS symptoms are often improved by physical activity, but not all patients with POTS are exercise deconditioned.

Immune Mechanisms

The idea of a limited autonomic neuropathy underlying POTS was suggested in its original description.[30] Evidence of partial autonomic denervation, suggestive of a limited autonomic neuropathy in some patients with POTS with a female predominance and preceding viral syndrome with subacute symptom onset, supports an underlying immune system–related cause.[56,72,73] This is further supported by the detection of nicotinic ganglionic acetylcholine receptor autoantibodies in a small percentage of patients with OI.[47] Recent reports postulate that autoantibodies cross-react with a wide range of cardiac proteins and α- and β-adrenergic receptors in many adult patients with OI, although these findings have thus far not been reproduced.[74,75] A study in which evaluate the sera of patients with POTS found organ-specific autoantibodies, particularly thyroid-specific, to be more common in patients with POTS.[76] The preliminary nature of these findings prohibits any generalizable recommendations for immunomodulatory or immunosuppressive treatments at this time.

Mast Cell Activation Disorders

POTS was found in patients with mast cell activation disorders (MCADs) 1 decade ago.[77] MCADs and POTS are increasingly found together.[78] MCADs are symptomatically similar to attenuated mastocytosis, but they are unassociated with increased mast cell numbers. Instead, there is an excessive release of biologically active materials from otherwise normally growing mast cells.[79,80] In MCADs, mast cells release histamine, prostaglandins, and leukotrienes, often without a recognizable allergen. Symptoms may be episodic and associated with facial flushing or chronic with fatigue, dizziness, and abdominal discomfort, often posturally induced. Symptomatic flares of MCADs may result in elevated serum tryptase levels. Patients with chronic MCADs may exhibit excessive amounts of urinary N-methylhistamine, leukotriene E4, or 11-β-prostaglandin F2 α.[79] Initial treatment targets the chemical being excessively released (aspirin or ibuprofen for 11-β-prostaglandin F2 α, montelukast for leukotriene E4, and antihistamines for histamine).[79,80] Many patients require a combination of H_1 and H_2 antihistamines, antileukotrienes, anti-inflammatory agents, and a mast cell stabilizer (Cromolyn). β-blockers, often used for POTS, may worsen MCAD symptoms.

COMORBIDITIES IN PEDIATRIC OI

Several conditions are associated with pediatric OI, including joint hypermobility, functional gastrointestinal disorders (functional abdominal pain, nausea, and cyclic vomiting syndrome), chronic fatigue syndrome, headache, sleep disorders, cognitive dysfunction (brain fog), anxiety, and depression. Comorbidity does not signify direct causation.[81] Most researchers evaluate comorbidities in POTS; few address OH and VVS.

Joint hypermobility is associated with POTS, syncope, presyncope, fatigue, heat intolerance, and abnormal autonomic testing scores.[82–85] Chronic pain and joint hypermobility are equally present in patients with POTS versus those without.[81]

Functional gastrointestinal disorders are associated with autonomic dysfunction.[86–88] POTS is associated with upper-gastrointestinal symptoms and antroduodenal dysmotility, which exacerbate with standing[89] and may improve when OI is treated.[90] Both delayed and rapid gastric emptying have been reported.[89–92]

OI has been identified in both younger and older case patients with cyclic vomiting syndrome,[93] with POTS present in 35% of adults.[93–95]

Symptoms and patterns of orthostatic HR and BP changes occur

in adolescents with chronic fatigue syndrome and overlap with those of POTS.[96–99]

Headache, including migraine, is commonly reported in POTS and VVS.[100,101] The association between headaches and OI has been primarily documented in adults. A few studies that include children have shown similar associations.[102–104] In a study of adolescent headache patients in a tertiary-care setting, 53% had POTS.[105] Although headache can be a symptom of OI, the relationship is unclear. The treatment of POTS has been found to be only partially effective in relieving headache.[106]

Sleep disorders, such as problematic sleep onset, maintenance, duration, quality, and daytime sleepiness, are consistently reported.[5,53,57,107,108] However, sleep studies in adults have shown little differences in sleep characteristics among POTS patients and controls.[109–112]

Cognitive symptoms or brain fog, which is described as having difficulty with attention, concentration, and memory, are commonly reported in POTS. Triggers include prolonged concentration and sleep disorders.[108] Cognitive performance during tilt testing is impaired because of an entrainment of cerebral blood flow by BP that reduces neurovascular coupling, the link between an increase in neural activity in response to a neural activation task, and the resulting increase in cerebral blood flow.[113,114] Increased depression and heightened anxiety in patients with POTS negatively impact attention and short-term memory.[115]

Depression, anxiety, and pain catastrophizing are common in pediatric POTS and VVS, in which they can mirror parental psychiatric symptoms.[5,53,116–119] These types of studies are often associative and are complicated by an overlap of psychiatric symptoms with those of OI. Therefore, further research is needed to elucidate the moderating effects of sleep, cognitive, psychiatric, and social-interactional factors on pediatric OI symptoms.

MANAGEMENT

Although pharmacologic and nonpharmacologic interventions have not been compared, it is the opinion of the authors that nonpharmacologic interventions are more important to long-term outcomes, and they are therefore presented first.

Nonpharmacologic Management

Fluids and Exercise

Cell dehydration causes adverse responses, including exaggerated cortisol response to exercise, decreased sympathetic nervous activity, and impaired cognitive and physical performance.[120–123] Adequate daily water intake is defined by the National Academy of Medicine (formerly the Institute of Medicine) as 3.7 L for men and 3.0 L for women; however, euhydration is difficult to assess.[124]

Bed rest emulates POTS with decreased stroke volume and increased HR to orthostasis, which occur in response to central hypovolemia.[125] Vigorous salt and water loading eliminates OH after bed rest.[126] Symptom severity negatively correlates with urinary sodium excretion.[127] Intravenous saline and salt improve symptoms in adolescents.[108] Large amounts of dietary salt improve symptoms in adults.[128] Some patients with POTS have deficits in plasma and blood volume without increased plasma renin or aldosterone but with increased angiotensin-II.[129,130]

Target salt and water intakes of 2.5 to 3 L daily in adolescent girls and 3.0 to 3.5 L daily in adolescent boys are recommended, which should be accompanied by >8 g sodium chloride daily. Glucose polymers (eg, maltodextrins) in commercial sports drinks are preferred.[131,132] A goal is to achieve urine osmolality of <300 mmol/L or urine sodium >200 mmol per 24 hours. Intravenous hydration may be used acutely (eg, for gastrointestinal so-called influenza) but is strongly discouraged on a chronic basis.

Exercise Training

Four trials in young adults using HR as the target for exercise training showed efficacy in POTS. Exercise can expand blood volume by 20% to 25%.[133,134] One approach aims for 60% to 70% of a subject's HR achieved during maximal exercise testing beginning with semirecumbent exercise; there are 5 minutes of warm-up to achieve target, 15 minutes at target, then 5 minutes of cool down. As exercise tolerance improves, add 5 minutes per session at target until one can complete 30 minutes at the target HR.

Alternative nutritional, psychological, and multidisciplinary therapies have been employed without an evidence base. These have included biofeedback; acupressure and acupuncture; craniosacral therapy; increased fiber intake; gluten avoidance; a diet of avoiding fermentable oligosaccharides, disaccharides, monosaccharides and polyols; and probiotics.

Cognitive behavioral therapy and intensive multidisciplinary rehabilitative programs for individuals with OI, particularly POTS, report improvement in functional outcomes.[135] Further research is needed to evaluate the benefits and durability of treatment.

Pharmacologic Management

Studies of pharmacologic interventions in OI are mostly retrospective or single-dose trials. Even documented therapies vary with provider, involve off-label use, and can produce variable clinical responses because of individual differences in drug sensitivity,

TABLE 2 Medications

Medication	Dose	Side Effects	Comments
Circulatory support			
Fludrocortisone	0.1–0.2 mg qAM	Peripheral edema, acne, headache, hypokalemia, hypomagnesemia	Monitor basic metabolic panel and magnesium at higher doses[90,136]
Midodrine	2.5–10 mg TID q4h	Tingling, goosebumps, headache, hypertension	Check supine BP 30–60 min after a dose[137–140]
Desmopressin	0.1–0.4 mg BID	Hyponatremia, headache[141]	—
Octreotide	25–100 μg subcutaneously BID	Injection site discomfort, diarrhea, thyroid derangement	Decreased gastrointestinal transit time may be beneficial for some patients[138,142,143]
Erythropoietin	10 000–20 000 IU subcutaneously weekly	Hypertension, arthralgias	Ensure hematocrit <50%, ensure adequate iron intake[144,145]
Acute normal saline infusion	1–2 L intravenous every 5–7 d	Repeated phlebotomy can lead to scarring of veins	Intermittent rescue use may be beneficial in acute management[146]
Ivabradine	2.5–10 mg BID	Bradycardia without hypotension	Inhibits I_f sinoatrial node, FDA approved for adult CHF. Small trials showed benefit in POTS[147,148]
Autonomic modulation			
Metoprolol succinate	12.5–100 mg daily	Lightheadedness, decreased exercise tolerance, fatigue, worsening asthma, depression	Nighttime dosing may decrease lightheadedness[139,149]
Metoprolol tartrate	12.5–50 mg BID		
Atenolol	12.5–50 mg BID	Same as metoprolol succinate	—
Nebivolol	2.5–10 mg daily	Same as metoprolol succinate	Fewer overall side effects because of decreased blood–brain barrier penetration
Propranolol	—	Same as metoprolol succinate	—
Citalopram	10–40 mg daily	Nausea, headache, fatigue, increased appetite, suicidal ideation requiring early and frequent monitoring	Causes central sympathetic modulation, reduces abnormal autonomic response[150]
Escitalopram	5–20 mg daily	Same as citalopram	—
Sertraline	25–200 mg daily	Same as citalopram	—
Clonidine	0.1–0.3 mg transdermal every 7 d	Contact dermatitis with adhesive, fatigue, dry mouth, headache	Centrally acting α-agonist, may also be used for insomnia[151,152]
Pyridostigmine	30–120 mg BID to TID	Abdominal pain, muscle twitch, decreased intestinal transit time	May also be helpful for early satiety and constipation[153–155]

BID, twice daily; CHF, congestive heart failure; FDA, Food and Drug Administration; I_f, sinus node inward "funny" pacemaker channel; q4h, every 4 hours; qAM, every morning; TID, thrice daily; —, not applicable.

metabolism, or tolerance to adverse effects.

Key therapies provide circulatory and autonomic support (Table 2), including efforts to increase blood volume. However, we strongly discourage the chronic use of central lines or ports because of the risk of infection, endocarditis, and thrombosis. An enteral intake of fluids and sodium is always preferred.

Another common approach targets the treatment of specific symptoms. Often, drugs are employed that successfully improve similar symptoms in other diseases. These can include fatigue, cognitive dysfunction, insomnia, chronic pain, gastrointestinal symptoms, and headaches. Further discussion of specific therapies is beyond the scope of this review.

PROGNOSIS

Patients with VVS improve in their 20s, but symptoms often recur in middle age.[25] Recurrent syncope among children and adolescents can negatively affect health-related quality of life.[156,157]

Little is known about the long-term prognoses for pediatric patients with POTS. Heterogeneous pathophysiology leads to a common phenotype, but prognosis depends on the underlying etiology.[30,72,129,158] Comorbidities and treatments can influence short- and long-term outcomes. A survey from a single tertiary center conducted by using a mailed questionnaire suggests a good overall prognosis among adolescent patients with POTS, with 86% reporting symptom improvement or resolution at 5.4 years after diagnosis.[159] Another center showed improvements among young adult patients with POTS (aged 20–33 years) over a mean follow-up period of 92 ±41 months.[160]

FUTURE DIRECTIONS AND RESEARCH

Despite an evolving consensus of clinical phenotypes and medical management of OI, underlying mechanisms remain poorly understood. To establish evidence-based diagnostic and treatment strategies, diverse research findings must be integrated to generate hypotheses, develop prognostic and natural history studies, and improve patient care. Uniform, multicenter databases and clinical registries will be important in reaching this goal. This

concept has been put into practice in adult patients with POTS.[161]

Among the challenges in characterizing pediatric patients with OI is defining a consistent method of performing orthostatic stress testing, including a proposed validation of practical standing tests. Also, recent work shows the utility of measuring serum and urinary biomarkers because they relate to different OI phenotypes or because they predict treatment response.[161,162]

Large prospective randomized controlled studies are needed to determine the impact of treatment strategies ranging from pharmacological regimens, salt and water requirements, and exercise. A better understanding of the effects of treatments on neurocognitive, autonomic, and cardiovascular signs and symptoms underscores the need to incorporate well-trained neuroscientists, psychologists, immunologists, and physiologists in research and therapy. Studies relating diagnostic tools such as functional brain imaging to objectively document neurocognitive assessments may be critical in this regard.

ABBREVIATIONS

BP: blood pressure
HR: heart rate
IOH: initial orthostatic hypotension
MCAD: mast cell activation disorder
nOH: neurogenic orthostatic hypotension
OH: orthostatic hypotension
OI: orthostatic intolerance
POTS: postural tachycardia syndrome
VVS: vasovagal syncope

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