1. Introduction

The term hydration was coined in 1802 by the French chemist Joseph-Louis Proust and derives from the Greek word ὑδραγωγία, meaning water. Approximately 60% of an adult human’s body weight is water, about 7% - 8% of which is intravascular, constituting the blood volume (Ruth and Wassner, 2006). In medicine, hydration is maintained not only by having sufficient water intake. Intestinal and intravascular fluid volumes are determined by such factors as membrane permeability, hydrostatic and oncotic pressures, and osmotic gradients (Kato and Romero, 2011). The major extracellular osmole is salt, specifically the cation sodium and its accompanying anion, chloride. Sodium can be depleted through diarrhea, emesis, polyuria, or excessive sweating. Sodium balance is influenced by hypothalamic osmoreceptors that control the secretion of antidiuretic hormone and by renal salt excretion. Therefore, sustaining or restoring hydration involves administering not only water, but also providing a balance of electrolytes, principally salt, which accounts for 95% of osmotically active substances in the extracellular compartment.

Patients with autonomic nervous system disorders that impair orthostatic tolerance are often responsive to hydration. These disorders include neurogenic orthostatic hypotension (NOH), postural orthostatic tachycardia syndrome (POTS), vasovagal syncope (VVS), and other disorders of orthostatic intolerance (OI) in which the increase in heart rate is less pronounced. The symptoms that can occur with these disorders can include lightheadedness, syncope, near syncope, brain fog, palpitations, chest pain, and dyspnea. As humans are normally upright when awake, orthostatic disorders can profoundly impair daily function and quality of life. These orthostatic symptoms improve greatly when the intravascular space is fully expanded.

Which methods are best to hydrate patients with orthostatic intolerance is a question that to date lacks robust evidence and, in regard to

**Abbreviations:** ACTH, adrenocorticotropic hormone; CVC, central venous catheter; GI, gastrointestinal; IV, intravenous; NOH, neurogenic orthostatic hypotension; NTS, nucleus tractus solitarii; OI, orthostatic intolerance; ORS, oral rehydration solution; PAC, port-a-cath; PICC, peripherally inserted central catheter; POTS, postural tachycardia syndrome; TC, tunnelled catheter; VVS, vasovagal syncope; WHO, World Health Organization.

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intravenous (IV) hydration for POTS and other forms of orthostatic intolerance, has led to controversy. This review will describe the available hydration modalities and evaluate their pros and cons, drawing from published evidence, autonomic physiology, and our clinical experience.

2. Pathophysiology

Whereas orthostatic disorders have diverse pathophysiologies, they share the problem of ineffective circulating blood volume to sustain perfusion to the brain in the upright posture. Upon standing, the force of gravity causes 400–800 mL of blood volume to shift from the thorax downward to the abdomen and lower extremities. This venous pooling decreases the return of blood to the heart, producing a thoracic blood volume drop of approximately 30%, which decreases stroke volume and cardiac output (Thompson et al., 1988).

The resulting decrease in arterial pressure unloads stretch receptors located in the aortic arch and carotid arteries. These baroreceptors are innervated by afferent fibers traveling in the glossopharyngeal and vagus nerves that exert a tonic inhibitory effect on the nucleus tractus solitarii (NTS) in the medulla oblongata. When the baroreceptors are unloaded by a decrease in arterial pressure, their firing rate decreases, which leads to augmentation of sympathetic outflow from the ventrolateral medulla to vascular smooth muscle with resultant peripheral vasconstriction and increased heart rate (Grubb et al., 2003).

2.1. Neurogenic orthostatic hypotension

In patients with NOH, there is a problem with either the afferent signal from the baroreceptors to the NTS, or the efferent signal from the brain to the peripheral vasculature. The hypoactive sympathetic activity presents with orthostatic hypotension, which is defined as a sustained decrease in systolic blood pressure of ≥20 mmHg or diastolic blood pressure of ≥10 mmHg within 3 min of standing or head-up tilt (Freeman et al., 2011). The symptoms resulting from hypoperfusion to the brain are protean and can include lightheadedness, brain fog, near syncope, or syncope. In addition, decreased perfusion to the muscles of the neck and upper back can cause what has been called “coat hanger pain.”

In addition, patients with autonomic failure are unable to reduce renal sodium excretion in proportion to dietary sodium restriction (Wieling et al., 2002), and the supine hypertension that often accompanies NOH promotes nocturnal sodium excretion (Jordan et al., 1999), for which reasons patients can become sodium-depleted (Wilcox et al., 1988). Causes of NOH include autonomic neuropathies such as diabetic autonomic neuropathy, amyloidosis, autonomic ganglionopathies, and carotid baroreceptor failure following therapeutic radiation to the neck. Alpha synucleinopathies including Parkinson’s disease, Lewy body dementia, multiple system atrophy, and pure autonomic failure frequently cause NOH.

2.2. Postural tachycardia syndrome

As distinguished from NOH, POTS is defined as a sustained increment of heart rate of ≥30 beats/min (≥40 beats/min if under the age of 20 years) within 10 min of standing or head-up tilt in the absence of orthostatic hypotension (Freeman et al., 2011; Raj, 2013). In patients with POTS, intravascular volume is often, but not always, reduced. A radiolabeled serum albumin investigation found that POTS patients had a plasma volume deficit of nearly 13% (Raj et al., 2005). Intravascular hypovolemia may be exaggerated in the upright posture by orthostatic pooling in the abdomen, pelvis, and legs (Jacob et al., 1998). The resulting decrease in blood return to the heart, stroke volume, and cardiac output unloads carotid and aortic baroreceptors, triggering an increase in sympathetic outflow (Charkoudian et al., 2004; Kimmerley and Schoemaker, 2002). The high sympathetic activity leads to a hyperadrenergic state with palpitations, tachycardia, lightheadedness, near syncope, chest pain, dyspnea, as well as noncardiac symptoms affecting the gastrointestinal system, the genitourinary system, and other symptoms of high sympathetic activity including anxiety. The sympathetic activation continues until the patient is supine, or until the patient increases plasma volume by hydration.

Whereas correction of hypovolemia is the most obvious rationale for treating POTS with salt-loading, additional mechanisms may also be relevant. The detection in some patients of antibodies to α1, β1, and β2 adrenergic receptors has led to the suggestion that peripheral adrenergic impairment may cause insufficient vasconstriction (Li et al., 2014; Miller and Raj, 2018), which might be compensated for by expanding intravascular volume. Nitric oxide-dependent vasodilation in POTS (Medow et al., 2005; Stewart et al., 2016) is potentially another target for intravascular volume expansion. Another theory is that central hypovolemia reduces cerebral flow and leads to postural hypocapnic hyperpnea, perpetuating cerebral ischemia (Del Pozzi et al., 2014).

2.3. Vasovagal syncope

Patients with VVS present with episodic orthostatic intolerance characterized by a relatively sudden change in autonomic nervous system activity that leads to a fall in blood pressure and heart rate (Freeman et al., 2011). The resulting decreased cerebral perfusion culminates in transient loss of consciousness and postural tone. These patients do not have orthostatic hypotension, but some of them have low blood volumes (El-Sayed and Hainsworth, 1996), and some may also have chronic OI including POTS. For example, a retrospective survey of 300 patients with POTS found that 18 (6%) also experienced VVS during tilt-table testing (Kanjwal et al., 2011). In a series of 25 patients with chronic OI, 17 (68%) had VVS during tilt-table testing (Goldstein et al., 2003).

3. Hydration

In order to achieve full expansion of intravascular volume, patients with orthostatic disorders must attain hydration. This can be achieved orally, intravenously, or by a combination of the two. Water alone is usually not enough to achieve adequate hydration. Rather, sodium and other electrolytes are necessary for added fluid to remain in the intravascular space. Oral hydration is usually more convenient; however, many of these patients have concurrent gastrointestinal issues or other challenges that limit their ability to achieve adequate hydration by oral means. IV hydration is generally successful, but this also poses logistic challenges as well as potential risks.

3.1. Oral hydration

The standard for treating dehydration from acute diarrhea is World Health Organization (WHO) oral rehydration solution (ORS), which consists of 2.6 g/L sodium chloride, 13.5 g/L glucose, 1.5 g/L potassium chloride, and 2.9 g/L trisodium citrate dihydrate (Bhan et al., 1994). Similar hydration approaches have been extended to the treatment of orthostatic disorders.

3.2. The osmopressor response

A notable exception to the principle that water without salt does not accomplish hydration is bolus water-drinking, which in patients with impaired baroreflex function induces a pressor response through activation of the sympathetic nervous system. Drinking 480–500 mL of plain water elicited a systolic blood pressure increase of 33 mmHg and 37 mmHg in patients with multiple system atrophy and pure autonomic failure, respectively, and the response was sustained for more than an hour (Jordan, 2005). Bolus water-drinking has also been shown to delay or prevent VVS in healthy subjects and to reduce the rise in heart rate and improve orthostatic tolerance in patients with POTS during head-up
are a necessary component of symptom management and are supported peripheral vasculature to restore blood pressure. Hydration measures baroreflex-mediated sympathetic response is inadequate to constrict the by an understanding of the physiology of NOH. With expansion of the intravascular volume, maintaining adequate cerebral perfusion is less dependent on the deficient baroreceptor reflexes and sympathetic adrenergic response.

Whereas sodium restriction is known to worsen orthostatic hypotension (Wilcox et al., 1977), the question of whether or how well salt supplementation improves NOH has not been tested in randomized clinical trials. Nevertheless, strong consensus-based guidelines have consistently recommended oral supplementation of sodium chloride at between 6 g/d and 10 g/d (260–430 mmol/d sodium) (Briggs et al., 2018; Shen et al., 2017; Gibbons et al., 2017; Shibao et al., 2013; Figueiroa and Low, 2010; Low and Fealey, 2008; Lahrnmann et al., 2006; Grubb et al., 2003; Wieling et al., 2002). There is no proven ideal dose of salt, and the right amount likely varies among patients, as people differ in their physiologic sensitivity to salt and in their daily and nightly excretion of salt. 24-hour urine sodium excretion of >170 mmol has been suggested as a marker of adequate sodium supplementation (Figueiroa and Low, 2010).

Salt recommendations for NOH should take into consideration comorbidities such as essential hypertension, renal dysfunction, and congestive heart failure, as these patients are usually older, and their fluid status can be more fragile. A lesser amount of salt may be appropriate in such cases. As at least half of patients with NOH are hypertensive in the supine position, nocturnal and supine blood pressures should also be taken into consideration when choosing among therapeutic options and subsequently when assessing the results of therapy.

An unanswered question is whether salt supplementation should be adjusted for patients with supine hypertension. Salt might be increased to compensate for paradoxically increased renal sodium excretion, or it might be decreased to reduce the potential for end-organ damage (Jordan et al., 2019). The best clinical practice is to individualize therapy and then to reassess.

### 3.4. Oral hydration for orthostatic intolerance

Oral hydration including water and electrolytes is recommended to manage orthostatic intolerance, including POTS, VVS, as well as other forms of OI such as orthostatic intolerance without tachycardia and early and delayed forms of orthostatic hypotension. Patients are encouraged to consume electrolyte beverages to increase osmotic pressure and keep the fluids in the intravascular space. The rationale is expansion of intravascular volume to compensate for intravascular hypovolemia and orthostatic pooling.

Consensus-based guidelines have recommended, in addition to drinking 2 to 3 L of water daily, sodium chloride, 8 g/d to 12 g/d (350–520 mmol/d sodium) (Mar and Raj, 2020; Miller and Raj, 2018; Olshansky et al., 2015; Sheldon et al., 2015; Low et al., 2009; Wieling et al., 2003, 2004; El-Sayed and Hainsworth, 1996; Wen et al., 2020). This is more than the amount recommended for NOH.

In a double blind placebo-controlled study, 70% of 20 patients with recurrent syncope given 120 mmol/d (2.76 g/d) of sodium chloride for 8 weeks showed increased plasma volume and orthostatic tolerance and decreased baroreceptor sensitivity (El-Sayed and Hainsworth, 1996). This salt-loading effect occurred within 3 days (Mitnangi and Hainsworth, 1998) and was seen only in relatively salt-depleted patients who had initial daily sodium excretion of <170 mmol (El-Sayed and Hainsworth, 1996). These findings were confirmed in a larger study of 178 patients with unexplained syncope, 69% of whom experienced improved orthostatic tolerance under conditions of head-up tilt combined with lower body negative pressure following three months of oral salt loading. A small but significant increase in mean arterial pressure was seen (Cooper and Hainsworth, 2002).

In the only prospective study to evaluate a high-sodium diet in treating orthostatic intolerance, 14 female patients with POTS and 13 healthy control subjects were enrolled in a crossover design in which they received either a low-salt diet of 0.6 g/d of sodium chloride or a high-salt diet of 17.6 g/d of sodium chloride over 6 days. As compared to the low-salt diet, the high-salt diet in POTS was associated with a smaller change in upright heart rate (46 beats/min, IQR 32–55 vs 60 beats/min, IQR 55–64, P = 0.001) and increased plasma volume (2.63 L, IQR 2.47–2.96 vs 2.36, IQR 2.16–2.72, P = 0.001). Stopping norepinephrine was decreased (755 pg/mL, IQR 498–919 vs 959, IQR 736–1161, P = 0.017), but the change in norepinephrine from supine to standing did not reach statistical significance. Although not statistically significant, the high-salt diet was associated with a lower symptom burden on the Vanderbilt Orthostatic Symptoms Scale (P = 0.1) (Garland et al., 2021). Whether these results would be sustained over time if a high-salt diet were continued has not been tested.

There have been multiple studies looking at the optimal oral fluid replacement beverages. Studies in the sports medicine literature have compared different methods of oral hydration, and more than just sodium is required to achieve sufficient hydration (McCubbin et al., 2020; Armstrong, 2021). Rehydration solutions need 75 mM of glucose per liter of water for efficient intestinal absorption of sodium (Binder et al., 2014).

### 3.5. Challenges of oral hydration

Oral hydration, because of its simplicity and availability without a prescription, would appear to be an ideal therapy to help improve orthostatic symptoms in NOH or POTS. Unfortunately, there are barriers to oral hydration in some patients. Approximately 69% of patients with POTS have chronic, moderate to severe, associated gastrointestinal (GI) disorders that may limit their ability to ingest fluids and salt. They frequently have concomitant gastroparesis, irritable bowel syndrome, recurrent vomiting, or other disorders making sufficient oral intake difficult or, at times, impossible. A small number of these patients have gastric or jejunal feeding tubes and still may have issues with absorption (Mehr et al., 2018).

Patients with NOH may have issues with oral ingestion related to gastroparesis, other GI disorders, or lack of thirst. The ability to adequately hydrate these patients can be very limited. In addition, some older patients have concomitant systolic or diastolic congestive heart failure or renal failure, which preclude their ability to receive added hydration safely (Camilleri et al., 1985).

### 4. Intravenous hydration

Many patients have difficulty getting adequate hydration orally, especially if they have concurrent GI disorders. IV hydration with normal saline or lactated Ringer’s solution is the easiest way to increase intravascular volume acutely. What is most important in making treatment decisions is to determine whether the increase in intravascular volume translates to clinical improvement in patients.

#### 4.1. Intravenous hydration for orthostatic hypotension

In the patient who presents acutely with orthostatic hypotension, it may not be clear initially whether the cause is neurogenic with
cardiovascular adrenergic failure or dehydration with intravascular volume depletion. If there is a history of poor fluid intake, vomiting, diarrhea, or polyuria, and if the heart rate increases by more than 0.5 beats/min per mmHg of systolic blood pressure fall during standing (Norcliffe-Kaufmann et al., 2018), then a therapeutic IV fluid bolus should be considered, provided there are no signs of congestive heart failure. Orthostatic blood pressure should then be reassessed.

In NOH, as distinguished from dehydration, the systolic drop in blood pressure is typically more pronounced, the heart rate response is reduced, and supine hypertension may be present (Cheshire, 2020). In the autonomic laboratory, NOH can be distinguished from the orthostatic hypotension of acute dehydration by assessing beat-to-beat blood pressure changes to the Valsalva maneuver (Cheshire et al., 2021). There are, to our knowledge, no studies showing benefit of ongoing intravenous hydration in NOH.

4.2. Intravenous hydration for orthostatic intolerance

The goal of IV saline administration in POTS and other forms of OI is to correct underlying hypovolemia and provide a bridge to functional incapacitation and deconditioning to the ability to engage in physical exercise and enter the pathway to recovery (Grubb, 2021; Ruzieh et al., 2017; Takenaka et al., 2002). Several preliminary studies lend support to this approach (Table 1).

4.2.1. POTS

In an early study of 11 patients with orthostatic intolerance who would have met the current definition of POTS, acute plasma volume expansion, not with saline, but with albumin improved symptoms and reduced tachycardia. When tilt-table testing was repeated after a course of oral fludrocortisone, results were normal (Fouda et al., 1986).

In a nonblinded, noncontrolled, observational study, 57 patients with POTS were given intermittent normal saline infusions of 1.5 ± 0.6 L at a mean frequency of every 11.3 ± 8.5 days. Forty-two received fluid peripherally, 12 via a peripherally inserted central catheter, and 3 via subcutaneously implanted ports. Orthostatic tolerance as gauged by an Orthostatic Hypotension Questionnaire and quality of life as measured by SF-36 improved by 3.1 ± 0.3 points (95% CI 2.6–3.7, P < 0.001) and 19.1 ± 2.7 points (95% CI −24.6 to −13.6, P < 0.001), respectively. Patients were followed for 3–12 months, and 93% of patients reported symptomatic improvement. Fifty were successfully weaned from IV fluid in less than 6 months, 44% of them in less than 3 months. Four patients later relapsed. One developed hypertension. No infections or thromboses occurred (Ruzieh et al., 2017). Although this was the largest study to address this question, the study had limitations. It was neither randomized nor blinded, baseline plasma volume was not measured, and a questionnaire designed for orthostatic hypotension may not be ideal for evaluating symptoms of OI in which sympathetic activity is increased rather than decreased.

In a second nonblinded, noncontrolled, observational study of 13 patients with POTS, 1 L of IV saline was more effective than the α1-adrenoceptor agonist midodrine in blunting the heart rate response to head-up tilt. The heart rate increase was 32 ± 5 beats/min before and 14 ± 2 beats/min after the IV saline infusion (t-test P < 0.001). The heart rate increase was 30 ± 5 beats/min before and 26 ± 3 beats/min 2 h after 5 or 10 mg of midodrine (t-test P < 0.05). IV saline also improved orthostatic symptoms as assessed by questionnaire, although the degree of change was not reported (Jacob et al., 1997).

In a third nonblinded, noncontrolled, observational study of 21 patients with POTS, 1 L of IV saline was comparable to 10 mg of midodrine in reducing orthostatic symptoms by approximately one point on a Likert scale, and both interventions were more effective than propranolol, clonidine, or phenoxybarbital. The heart rate increase at 2 min of head-up tilt was 28.1 ± 5 for controls and 23.4 ± 5 for those who received IV saline (t-test P = 0.008). The difference in heart rate change did not reach significance at the immediate or 5-min time points, and longer durations of tilt were not assessed (Gordon et al., 2005).

In a retrospective study of 39 patients that received IV saline infusions of 1–2 L/day administered 3–7 days/week for OI, 79% of the patients had significant improvement in symptoms during 1 week to 3.8 years (average 30 ± 47 weeks) of follow-up. Their cohort included 24 with POTS, 14 with VVS, and 1 with OI without tachycardia. The IV infusions were administered from 1 week to 3.8 years with an average duration of 30 ± 47 weeks. The positive symptomatic response was graded as 2.6 ± 0.7 on a 1–3 scale, and 79% demonstrated improvement in self-reported quality of life. Of 28 patients in the study who had either a peripherally inserted central catheter (PICC) line or port, 3 patients had an upper extremity deep venous thrombosis, and 4 patients had a line infection (Moak et al., 2016). It is important to note that these patients were selected for IV saline infusion because they had failed to respond to more conservative measures, including increased oral fluid intake, added dietary salt of 1–4 g/d, aerobic exercise combined with lower extremity muscle strengthening, and pharmacologic measures. Numerical values were not reported for heart rate.

| Study            | Design                  | N | Diagnosis | Hydration                  | Outcome measure, subjective | Outcome measure, objective | Follow-up | Result, subjective | Result, objective |
|------------------|-------------------------|---|-----------|----------------------------|-----------------------------|-----------------------------|-----------|-------------------|------------------|
| Medow et al., 2019 | Nonblinded, noncontrolled, observational | 10 | POTS       | 1 L normal saline given once | None                        | Time to faint from stepwise lower body negative pressure | 30 min     | None               | Prolonged the time to faint from 18 min to 23 min |
| Ruzieh et al., 2017 | Nonblinded, noncontrolled, observational | 57 | POTS       | 1.5 L normal saline every 11 ± 8.5 days | Orthostatic symptom questionnaire, SF-36 | Unstated | 3–12 months | Symptomatic improvement in 93% | Unstated |
| Moak et al., 2016 | Retrospective            | 39 | POTS, VVS, OI | IV saline 1–2 L/day, 3–7 days/week | Orthostatic symptom questionnaire | Unstated | 30 ± 47 weeks | Symptomatic improvement in 79%, average 2.6 ± 0.7 on a 1–3 Likert scale | Unstated |
| Gordon et al., 2005 | Nonblinded, noncontrolled, observational | 21 | POTS       | 1 L normal saline given once | Orthostatic symptom questionnaire | Heart rate increase during tilt | 10 min     | Symptomatic improvement of 1 point | Heart rate change decreased from 28 to 23 |
| Jacob et al., 1997 | Nonblinded, noncontrolled, observational | 13 | POTS       | 1 L normal saline given once | Orthostatic symptom questionnaire | Heart rate increase during tilt | 2 h        | Symptomatic improvement, degree unstated | Heart rate change decreased from 30 to 26 |
4.2.2. VVS and other forms of OI

In making clinical decisions about which patients with chronic OI might benefit from IV saline infusions, it is of interest to know whether postural tachycardia is a relevant criterion. This cannot be answered by the preceding study, in which the investigators grouped POTS patients together with those with VVS and OI without tachycardia and did not report their responses to IV infusions separately (Moak et al., 2016).

Elsewhere, in a noncontrolled observational study of 65 adolescents with a history of at least one episode of VVS, 12 had reproducible syncope on two consecutive 30-min tilt-table tests. Following a 30-min recovery period, they were given IV infusions of 1 L of normal saline over 20 min and subjected to a third tilt-table test, during which none had syncope (Burklow et al., 1999). The investigators concluded that intravascular volume expansion ameliorated their susceptibility to recurrent syncope.

In a noncontrolled observational study of 101 patients with recurrent presyncope or syncope, 58 had vasovagal syncope, and cardioinhibitory responses to tilt-table testing. Of these, 50 were given IV infusions of 10 mL/kg normal saline and then subjected to a second head-up tilt lasting 30 min, which was normal in 42 patients. Patients responsive to the saline infusion were then treated with oral sodium chloride 0.5–1 g three times daily, and 20 patients who remained symptomatic on oral salt were also given fludrocortisone 0.1–0.2 mg daily. Follow-up data 4 to 40 months later (median 18 months) were available on 35 patients, 26 of whom were asymptomatic, and 9 were improved (Mangru et al., 1996).

4.2.3. Summary

In summary, four noncontrolled observational studies are in agreement in demonstrating that acute intravascular volume loading with normal saline improved heart rates and resulted in clinically meaningful improvement in orthostatic symptoms in patients with POTS (Ruzieh et al., 2017; Jacob et al., 1997; Gordon et al., 2005; Moak et al., 2016). The two studies that included follow-up assessments (Ruzieh et al., 2017; Moak et al., 2016) found that 79%–93% of patients improved during weeks, months, or in some cases years of reassessment.

Additionally, two noncontrolled observational studies of VVS demonstrated that acute intravascular volume loading with normal saline averted presyncope or syncopal responses on a subsequent tilt-table test (Burklow et al., 1999; Mangru et al., 1996). These studies did not assess tilt-table or daily life responses to repeated IV saline infusions, but one of them found that subsequent oral salt supplementation, without or with fludrocortisone, was associated with sustained symptomatic improvement (Mangru et al., 1996).

For all of these syndromes, the question remains open as to whether long-term salt supplementation or periodic intravenous saline infusions leads to lasting clinical improvement.

5. Comparison of oral versus intravenous hydration

Only one study has directly compared IV to oral hydration. The threshold for orthostatic tolerance was assessed in 10 patients with POTS and 15 healthy controls by performing stepwise lower body negative pressure as a stimulus of orthostatic stress. In a nonblinded, observational design, testing was repeated on separate days after subjects drank 1 L of ORS or received 1 L of intravenous normal saline over 30 min. Both oral and intravenous saline administration prolonged the time to faint in POTS patients (P < 0.05 and P < 0.001, respectively). For both groups the transition to loss of consciousness occurred at ~60 mmHg. Neither oral nor intravenous saline improved orthostatic tolerance in the healthy controls (Medow et al., 2019).

6. Complications of IV hydration

Therapeutic IV hydration entails both logistical challenges as well as risk for complications. It may be difficult for patients to travel to an IV infusion center for periodic infusions. Arranging for a home health agency to visit the patient’s home to administer IV fluids becomes expensive and administratively complex. For long-term vascular access, patients have the option of receiving a surgically implanted indwelling central venous catheter (CVC), such as a PICC line, port-a-cath (PAC), or tunneled catheter (TC). However, these catheters are associated with risks for infection, sepsis, thrombosis, pulmonary embolism, or death (Böll et al., 2021; Zaghal et al., 2012; Menéndez et al., 2016; Cheshire, 2016). Central line-associated bloodstream infections are a serious and life-threatening risk.

Although there are no specific studies of implanted CVC specific to autonomic disorders, data from the Strategic HealthCare Programs National Database from April 1999 to September 2000 were analyzed. Event rates were calculated per 1000 catheter days, 50,470 patients representing 2.83 million catheter days (GDs). Tunneled catheters had a complication rate of 1.0 per 1000 catheter days and chest ports had a rate of 0.52. Catheter site infections were 0.26 and bloodstream infections were 0.19/1000 CD (Moureau et al., 2002).

In an observational study of 265 pediatric patients who received PICCs, the incidence of PICC-related thrombosis was 9.03/1000 CD. These comprised 66 isolated superficial venous thromboses, 7 isolated deep venous thromboses, and 15 combined superficial and deep venous thromboses (Menéndez et al., 2016).

7. Improving volume status without salt

Additional approaches to compensate for intravascular hypovolemia in orthostatic disorders include compressive stockings, abdominal binders, and counterpressure maneuvers, which exert their effect by reducing venous pooling (Figuerola and Low, 2010). Additionally, elevating the head of the bed at night will reduce nocturnal sodium diuresis in patients with supine hypertension (Jordan et al., 2019; Ten Harkel et al., 1992; MacLean and Allen, 1940).

A number of off-label pharmacologic strategies are also available to increase blood volume. Fludrocortisone is a synthetic corticosteroid with mineralocorticoid activity that increases renal reabsorption of sodium and water. There is some activity in the GI tract as well. By retaining sodium, fludrocortisone also leads to reciprocal potassium loss through the kidneys, which can cause hypokalemia. Its sodium-retaining effect is transient (Chobanian et al., 1979), and its ongoing effect on blood pressure may be due more to sensitization of vascular α-adrenoceptors to pressor amines (Davies et al., 1978). A Cochrane review of fludrocortisone found the level of evidence for treating orthostatic hypotension to be weak (Veazie et al., 2021). Potential adverse effects related to volume overload include hypertension, hypertensive retinopathy, peripheral edema, cardiomegaly, and congestive heart failure. Mineralocorticoid receptors are present in the heart, and in animal models their activation has been shown to promote hypertension and inflammation (Buonafine et al., 2018) as well as myocardial fibrosis independently of blood pressure elevation (Young et al., 2021). Fludrocortisone also has glucocorticoid activity which can lead to adverse effects related to elevated blood sugar, weight gain, immunosuppression, and osteoporosis. On the positive side, fludrocortisone has been shown to improve nausea in about two-thirds of children with orthostatic intolerance (Fortunato et al., 2011), which may be relevant to their ability to take in oral hydration.

The other medication available to expand volume status is desmopressin, which is a synthetic analogue of vasopressin. This works in the kidneys at the collecting ducts to reabsorb free water. The primary indication for this medication is enuresis. Desmopressin can also increase release of adrenocorticotrophic hormone (ACTH) which can increase sensitivity of α-receptors on blood vessels. This effect is also beneficial in patients with orthostatic disorders whose symptoms improve with vasoconstriction. One of the major adverse effects is hyponatremia, which can cause seizures, and can even be life-threatening. It is critical for the patient to have adequate dietary sodium intake to avoid this complication. In addition, routine monitoring
of electrolytes is important. Desmopressin also stimulates the release of von Willebrand factor which can result in thrombosis.

Vasopressor pharmacologic interventions such as midodrine, droxidopa, and pyridostigmine are frequently used to treat NOH and POTS. These have been reviewed in detail elsewhere (Cheshire, 2019; Miller and Raj, 2018; Wells et al., 2017; Figueroa and Low, 2010).

8. Guidelines for IV hydration

Whereas the current level of evidence is insufficient for dogmatic recommendations regarding IV hydration in orthostatic disorders, a critical review of preliminary data added to clinical knowledge in related conditions allows for the proposal of a set of guidelines to assist with clinical decision-making in difficult cases (Table 2). Prior to considering a program of IV hydration, the healthcare professional should establish an accurate diagnosis by taking a thorough history and performing a careful physical examination that includes, at a minimum, measurement of blood pressure and heart rate in both supine and standing positions (Cheshire, 2020; Freeman et al., 2011). If the clinical diagnosis is unclear, autonomic testing can be helpful to supply objective measures of autonomic function or dysfunction (Cheshire et al., 2021). Symptoms alone are insufficient to diagnose autonomic disorders.

8.1. POTS and chronic OI

The most compelling context for considering an ongoing course of IV hydration is the patient who has severe and incapacitating symptoms of orthostatic intolerance and is unable to attain adequate intravascular volume by oral hydration. The symptoms should be consistently postural, occurring when standing and relieved by sitting, and in the diagnosis of POTS there should be objective evidence of sustained orthostatic tachycardia.

The evidence is less clear for IV hydration in chronic OI without tachycardia and in chronic fatigue in general. Ideally, the decision to employ IV hydration should be based on objective markers of disease, which may be lacking in these patients. There are clearly many patients with chronic orthostatic intolerance who have symptoms indistinguishable from POTS and yet who have normal orthostatic heart rate changes; these patients may have excessive heart rate increases on other days, or their symptoms may be caused by decreased cerebral blood flow independent of arterial pressure measured at the arm (van Campen et al., 2020; Novak, 2018). Transcranial Doppler methodologies that might distinguish these patients are not available in most clinical settings. They are managed in much the same way as POTS, and if their orthostatic intolerance is severe and incapacitating, and if oral hydration is inadequate and pharmacologic interventions have not succeeded, then the argument for considering a trial of IV hydration approaches the strength of the argument for IV hydration in POTS.

8.2. VVS

For VVS, the vast majority of patients recover fully and are encouraged to liberalize oral fluid intake if fatigue persists. In the case of the rare patient with frequent recurrent syncope and the potential for injury, there are no clinical studies to inform the question of whether a long-term commitment to IV hydration would have merit. Whereas acute IV hydration was shown in two studies to prevent or delay the onset of syncope (Burklow et al., 1999; Mangru et al., 1996), it is unclear how well these tilt-table test results can be extrapolated to the conditions of daily life. Before considering a time-limited trial of IV hydration for a patient with recurrent syncope, it would be important to establish with blood pressure measurements a vasodepressor response and distinguish VVS from psychogenic pseudosyncope (Cheshire, 2017).

8.3. NOH

There is no evidence to support ongoing IV hydration for the treatment of NOH. However, for the patient who presents acutely with OH and it is unclear whether the OH is neurogenic or caused by dehydration, a single challenge of IV hydration followed by reassessment of orthostatic blood pressure is often appropriate.

8.4. Goals and risks

Prior to placing an IV access port, the patient should have a trial of outpatient peripheral IV hydration to assess for improvement. If the patient has a qualitatively significant improvement in orthostatic symptoms, consideration for continuing therapy can move forward. The expectation should be stated that IV hydration is intended to be a bridge to other therapy including meeting physical exercise targets and is not meant to be continued indefinitely. It is crucial to explain to the patient the risks for IV therapy including but not limited to site infection, sepsis, deep vein thrombosis, pulmonary embolism, catheter embolism, or death (Table 3). If the patient understands this and is agreeable to assuming these risks, then further discussion may explore options such as intermitent IV hydration with peripheral IV insertions, placement of a PICC line, port, or tunneled catheter.

Patients with IV ports should be carefully instructed in aseptic technique and precautions to minimize the risk of infection. Patients should also be educated to recognize symptoms of central venous thrombosis, such as limb swelling or dilated upper torso veins. Patients undergoing prolonged IV hydration should have their electrolytes monitored periodically to identify and correct imbalances. They should be advised to increase or supplement potassium if hypokalemia occurs. Blood pressure should also be measured periodically to monitor for the possibility of emerging hypertension.

How long IV hydration should be continued depends on the individual patient and the response to therapy. The judicious use of IV hydration is intended to be not a long-term therapy but a short-term bridge

| Table 2 |
| Guidelines for considering intravenous hydration for chronic orthostatic intolerance |
| - Establish an accurate diagnosis of POTS by objective measures |
| - First line of therapy should be oral hydration, electrolytes, and physical exercise |
| - Second line of therapy is to consider pharmacologic measures such as fludrocortisone, beta blockers, midodrine, pyridostigmine, ivabradine |
| - Third line of therapy in refractory and severe cases may be to consider a trial of peripheral IV saline infusion to assess for improvement in orthostatic heart rate as well as symptoms, and as a bridge to exercise |
| - If short-term intravenous hydration produces significant symptomatic improvement, longer term IV hydration may be considered after reviewing with the patient the anticipated benefits of a central venous catheter against the potential risks listed in Table 3. |
| - Establish objective endpoints of therapy |
| - After the catheter is placed, monitor for adverse effects |
| - Reassess periodically and continue IV hydration only if clear functional improvement occurs |
| - Once the patient has significant improvement in symptoms and well being, wean the IV hydration as tolerated to off completely |
| - Remove the central venous catheter 6 to 12 months after the IV hydration has stopped |

| Table 3 |
| Potential complications of ongoing intravenous hydration |
| - Raised blood pressure |
| - Site infection |
| - Sepsis |
| - Endocarditis |
| - Deep vein thrombosis |
| - Pulmonary embolism |
| - Catheter embolism |
| - Death |

[6]
to facilitate engagement in physical exercise as a pathway to recovery.

9. Future directions
At one level of understanding, intravenous saline infusion is a basic clinical response to patients with hypovolemia, which may include some patients with orthostatic disorders who are either chronically or episodically hypovolemic. At another level, anticipated future therapies for orthostatic disorders may be to the current practice of intravascular volume loading as modern hematology is to the ancient practice of blood-letting. Even though orthostatic disorders are extremely common, a detailed understanding of their underlying mechanisms is only beginning to emerge.

Studies to date of intravenous salt-loading in orthostatic disorders have recruited small groups of patients, have varied in their inclusion criteria and outcome measures, and without exception have been noncontrolled. Larger studies are needed to assess the indications, benefits, and ideal treatment conditions for intravenous saline in the full spectrum of orthostatic disorders. Randomized controlled trials are needed, and multicenter trials with explicit and uniform diagnostic criteria would be preferred in order to limit referral bias and yield generalizable results. The selection of patients for future studies should examine comorbidities such as gastrointestinal dysmotility, anxiety, and joint hypermobility that might predict a response to therapy. Studies of OI should evaluate subgroups of patients with and without orthostatic tachycardia, a history of syncope, neuropathic and autoimmune phenotypes.

Baseline intravascular volume status can be reliably estimated by 24-h urine sodium excretion and should be reassessed at intervals following saline infusion to determine the durability of treatment. More precise methods of measuring intravascular volume such as radiolabeled erythrocytes or thermodilution are typically reserved for research settings.

Tilt-table testing should be standardized (Cheshire and Goldstein, 2019) for the assessment of orthostatic intolerance. A suggested approach is to tilt to 70–80 degrees, omit intravenous catheterization (which can induce reflex syncope), omit isoproterenol or nitroglycerin (which can increase heart rate and increase false positive results), utilize beat-to-beat blood pressure and heart rate detection technology (to detect moment-by-moment changes), average heart rate tracings over one-min intervals (to avoid selection bias of peaks), and assess symptoms during the test. There is currently no universal consensus on the ideal duration of head-up tilt, which is typically 10 min for the diagnosis of POTS and 30–60 min for the diagnosis of VVS.

Blood pressure and heart rate responses to head-up tilt are indirect measures of the underlying physiology causing symptoms, and they can be normal in some patients who have symptoms of chronic orthostatic intolerance. Preliminary studies have found reduced or oscillatory patterns of cerebral blood flow in patients with OI (Schnodorf et al., 2001; Low et al., 1999), which suggests that Doppler ultrasound during orthostatic stress might be a useful technique for identifying which patient groups may be responsive to salt-loading. However, the effect of salt supplementation on cerebral blood flow in POTS has not been tested (Williams et al., 2021).

Outcome assessments should include objective measures. These may be the change in heart rate during 10 min of active standing or tilt-table testing, the frequency of self-reported presyncope or syncope, or questionnaires assessing patients’ ability to engage in activities of daily living while standing. Patients receiving ongoing oral salt supplementation or IV saline infusions long-term should be monitored for the emergence of hypertension.

10. Conclusion
Patients with autonomic disorders frequently have orthostatic symptoms that improve by increasing blood volume. This can be accomplished with oral hydration for patients who are able to tolerate drinking large volumes of fluid and supplement electrolytes. For those who cannot tolerate oral hydration, IV hydration has been shown in limited, uncontrolled, observational studies to improve symptoms in appropriately selected patients with POTS and other forms of chronic OI. Long-term outcomes have not been sufficiently studied, and long-term IV central access carries potentially serious risks. It is critical that healthcare professionals who are treating these conditions be aware of the potential complications of therapy.

In general, NOH resulting from degenerative disorders of the autonomic nervous system is irreversible, but many patients without NOH also experience ongoing symptoms of chronic orthostatic intolerance that differ in their physiologic basis. Therefore, more research is needed to find better solutions for managing these disorders. Safer catheters to administer IV fluids could be developed. Perhaps there is a more efficient way to deliver and absorb enteral fluids. Questions of how much salt, by what method of delivery, how frequently and for how long should be subjected to randomized clinical trials. There is a large population of patients who are desperately waiting for more ideal methods for hydration.

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