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# Postural orthostatic tachycardia syndrome (POTS): Priorities for POTS care and research from a 2019 National Institutes of Health Expert Consensus Meeting – Part 2

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ABSTRACT

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The National Institutes of Health hosted a workshop in 2019 to build consensus around the current state of understanding of the pathophysiology of postural orthostatic tachycardia syndrome (POTS) and to identify knowledge gaps that must be addressed to enhance clinical care of POTS patients through research. This second (of two) articles summarizes current knowledge gaps, and outlines the clinical and research priorities for POTS.

POTS is a complex, multi-system, chronic disorder of the autonomic nervous system characterized by orthostatic intolerance and orthostatic tachycardia without hypotension. Patients often experience a host of other related disabling symptoms. The functional and economic impacts of this disorder are significant. The pathophysiology remains incompletely understood.

Beyond the significant gaps in understanding the disorder itself, there is a paucity of evidence to guide treatment which can contribute to suboptimal care for this patient population. The vast majority of physicians have minimal to no familiarity or training in the assessment and management of POTS.

Funding for POTS research remains very low relative to the size of the patient population and impact of the syndrome. In addition to efforts to improve awareness and physician education, an investment in research infrastructure including the development of standardized disease-specific evaluation tools and outcome measures is needed to facilitate effective collaborative research. A national POTS research consortium could facilitate well-controlled multidisciplinary clinical research studies and therapeutic trials. These priorities will require a substantial increase in the number of research investigators and the amount of research funding in this area.

## 1. Background

Postural orthostatic tachycardia syndrome predominantly affects adolescent or young adult women and can be severely debilitating (Bagai et al., 2011). While POTS may be recognized clinically, using a consensus clinical definition, the epidemiology and pathophysiology of the disorder is not fully understood (Raj and Robertson, 2018). The syndrome is heterogeneous in terms of associated clinical features and etiology, and the clinical assessment of patients and treatment approaches are not standardized.

A major limitation is the lack of comprehensive epidemiological data to establish the prevalence of POTS. Experts have estimated that 500,000 to 3,000,000 Americans could be affected (Lei et al., 2019; Mar and Raj, 2020). However, these estimates are not based on population studies but rather on experience from autonomic centers. One study in China reported 6.8% of adolescents met clinical criteria for POTS (Lin et al., 2014), and another study found that 10% of male Austrian military recruits met the criteria for POTS (Winker, 2004), but these findings cannot be applied broadly to other populations. The true prevalence remains unknown. Challenges in determining actual prevalence include physician differences in applying consensus diagnostic criteria and lack of a specific ICD-10 diagnosis code for POTS, although a specific code should be available in ICD-11 (World Health Organization, 2021). Nevertheless, it is clear that POTS is one of the most common forms of autonomic dysfunction. The associated loss of productivity and associated healthcare costs are likely substantial (Bourne et al., 2021).

In 2018, the US Congress encouraged the National Heart, Lung, and Blood Institute (NHLBI) and the National Institute of Neurological Disorders and Stroke (NINDS) to host a symposium of leading POTS experts (U.S. Senate Committee on Appropriations, 2018). The purpose of the symposium was to gather information for a report that Congress directed the NIH to prepare, which was to reflect the POTS expert participant findings on:

(1) the current state of POTS research;
(2) priority areas of focus for future POTS research through 2025;
(3) ongoing and upcoming efforts by NIH to advance the scientific understanding of POTS; and
(4) an estimate of the level of funding that would be needed to achieve the above stated objectives.

On July 29, 2019, a workshop was convened at the NIH Intramural Campus in Bethesda, Maryland comprising a broad representation of clinicians and researchers in the field. The NIH prepared a report for Congress (National Heart, Lung and Blood Institute and National Institute for Neurological Disorders and Stroke, 2019), but this report did not adequately reflect the perspectives of the POTS expert participants, as directed by Congress. Therefore, the POTS expert workshop participants prepared two independent manuscripts to address questions posed by Congress. The first manuscript reviews the current state of the science and clinical care for POTS. This second manuscript addresses the knowledge gaps, clinical care needs and research priorities for POTS going forward. It is our hope that these manuscripts will help raise awareness, inform federal decision-making with regards to POTS research and advance POTS clinical care.

Clinical care for patients with POTS is currently suboptimal due to significant gaps in knowledge. There is a general lack of awareness and recognition of the disorder in the medical community, uncertainty about the scope of the clinical presentation and diagnostic criteria, and incomplete understanding of the underlying pathophysiology. Advancement of the field is limited by the relative paucity of active NIH-funded research in this area.

## 2. Clinician education and awareness

While descriptions can be found as early as the 1800s (DaCosta, 1871) and a modern definition was created in 1993 (Schondorf and Low, 1993), a majority of clinicians remain unaware of POTS and how to diagnose it. Meaningful discussions of autonomic disorders, including POTS, are not included in most medical school curricula, or even in residency/fellowship training in relevant specialties such as pediatrics, internal medicine, family medicine, cardiology, gastroenterology and neurology. This lack of physician education contributes to diagnostic delays. On average, POTS patients wait over four years for a POTS diagnosis from symptom onset, with 75% of patients experiencing one or more misdiagnoses based on an online patient survey with self-reported, physician-diagnosed POTS (Shaw et al., 2019). Patients see an average of seven physicians for their symptoms prior to a POTS diagnosis (Shaw et al., 2019).

Even when a diagnosis of POTS is made, physicians are often unable or unwilling to coordinate care. The number of physicians familiar with the care of POTS is insufficient for the existing patient volume, and there appears to be an increase in POTS cases, as some individuals with COVID-19 are developing post-viral POTS (Goldstein, 2020; Kanjwal et al., 2020; Miglis et al., 2020). Although POTS patient symptoms cross over into multiple specialties, multidisciplinary integrated clinical care is rarely available, even at academic centers. Strategic efforts to increase clinician education are needed in multiple disciplines to reduce diagnostic delays and improve access to high-quality care after diagnosis.

## 3. Diagnostic criteria and clinical measures

The POTS diagnostic criteria have evolved slightly since the first modern definition in 1993 (Schondorf and Low, 1993). In 2011, the

American Autonomic Society and American Academy of Neurology published a consensus statement on the definition of POTS, including diagnostic criteria (Freeman et al., 2011). In 2015, the Heart Rhythm Society, in collaboration with experts from many other professional societies, published a consensus statement that included criteria fairly similar to the 2011 consensus (Sheldon et al., 2015). All of these diagnostic criteria focus on the heart rate and fail to capture the variety of other symptoms that are a part of this syndrome. More recently, the Canadian Cardiovascular Society and ad-hoc groups have proposed criteria that acknowledge the chronic and multi-system nature of the disorder of POTS (Olshansky et al., 2020; Raj et al., 2020). It remains to be seen whether modifications in diagnostic criteria will improve specificity, precision or patient care.

Beyond the diagnostic criteria, there is a need for disease-specific clinical measures that capture the severity and distribution of POTS symptoms. Currently, clinicians and researchers depend on clinical rating scales that are either non-specific (such as generic scales of disability) or those that were developed to evaluate patients with autonomic failure (such as the Composite Autonomic Symptom Score [COMPASS]) (Rea et al., 2017; Sletten et al., 2012). These scores may fail to capture important aspects of the POTS clinical phenotype. The Vanderbilt Orthostatic Symptoms Score (Raj et al., 2009) is designed to capture acute orthostatic symptom burden in POTS, but not the daily impact of living with POTS. There is a need for both a POTS-specific patient-reported outcome measure and a physician-rated clinical rating score that includes objective clinical data. These tools should ideally be valid for use in both adult and pediatric patients.

## 4. Clinical care

Although POTS is defined by criteria involving cardiovascular parameters, associated symptoms of dysautonomia are much more diverse. The clinical presentation of POTS is heterogeneous both in terms of symptoms and pathophysiology (Benarroch, 2012). As a result, POTS patients often interact with multiple different medical specialties, further complicating their care. POTS patients may undergo numerous, and in some cases, unnecessary and expensive diagnostic evaluations. Given these factors, there is a critical need for an efficient, cost-effective, multidisciplinary approach, with emphasis on the "medical home" (Jackson et al., 2013). Importantly, such an approach has the potential to improve efficiency of clinical care, patient experience, and lower medical costs (Williams et al., 2012). The clinical care for POTS patients can be improved through a multidisciplinary structured approach that includes both algorithmic and individualized components.

A diagnostic algorithm should include recommendations and guidelines for the rational use of diagnostic testing, including serological, imaging and physiological (autonomic and cardiovascular) testing where appropriate. Treatment algorithms should be individualized based on the symptom profile and diagnostic categorization. Treatment guidelines should be based on best available scientific evidence with plans for regular revisions of consensus recommendations as clinical trials are completed. The lack of research funding has hampered efforts to develop evidence-based diagnostic algorithms and treatment guidelines.

There are currently very few dedicated specialty clinics for POTS, and even fewer multidisciplinary programs. While only a subset of patients will require care at formalized POTS specialty centers, such centers would be important for establishing best practices, developing educational materials and providing up-to-date guidance to primary care providers. In most cases, a primary care provider with sufficient knowledge can coordinate care and integrate input from other providers, including subspecialists as needed. Given the paucity and unequal geographic distribution of dedicated specialty centers, it will be important to create virtual regional and national "POTS networks." Such networks could facilitate learning, collaboration, and exchange of knowledge, as well as support primary providers in creating local multidisciplinary care teams. Current technology, including web-based resources, telemedicine, and electronic medical records systems, could be leveraged to accomplish this goal.

## 5. Pathophysiology of POTS

The pathophysiological mechanisms of POTS remain poorly understood. Prior studies have categorized POTS patients into various subtypes (including neuropathic (Garland et al., 2007), hyperadrenergic (Shibao et al., 2005), and hypovolemic (Raj et al., 2005)). However, the clinical relevance of these subtypes is unknown due to lack of uniform phenotyping, and the fact that patients may present with multiple overlapping features. It remains uncertain if these represent different underlying diseases or if they are different manifestations of a common underlying disease. The reasons underlying the overwhelming female predominance seen in POTS are not understood. There is a lack of robust long-term outcome data about the natural history of POTS across the lifespan of the patients. In addition, prognostication in POTS remains difficult due to the lack of specific outcome measures for this condition, and the lack of common data elements shared by investigators. Since POTS is clearly heterogeneous, advancements will require careful investigations of several different, but interacting, mechanisms which are described in the accompanying manuscript (Vernino et al., 2021).

There is currently no accepted animal model of POTS, so our understanding of this condition depends on clinical research. In any case, traditional small animal models are unlikely to prove useful insights, given that the core feature of POTS is orthostatic intolerance and bipedal standing is fairly unique to humans. Further, the constellation of associated symptoms (such as cognitive impairment and gastrointestinal complaints) would be difficult to capture in model systems. Human research itself can be challenging in a diverse disorder like POTS. Careful assessment, measurement, and control of confounding variables (including but not limited to age, sex, body weight, plasma volume, cardiovascular fitness, temperature, and medications) must be part of pathophysiological studies. All investigations should include comparisons to matched healthy controls.

Several areas of pathophysiological research are currently important and active. First is the role of genetic factors in defining the risk and determining the manifestation of POTS. A monogenetic cause is unlikely, but a familial tendency exists (Boris et al., 2020b; Posey et al., 2017). The associations of POTS with migraine headache, the hypermobile form of Ehlers-Danlos syndrome (hEDS) (De Wandele et al., 2014) and the hypermobility spectrum disorder, allergic disorders like mast cell activation syndrome (MCAS) (Shibao et al., 2005), and autoimmune disorders have been clearly described. The disorder, therefore, occurs in a broader clinical context, and the contribution of these associations to disease risk, pathophysiology or treatment requires further study.

Recently, initial efforts by several groups have led to the identification of autoantibodies against G-protein coupled receptors (GPCRs) in POTS. These include autoantibodies that modulate the function of adrenergic and muscarinic receptors relevant to autonomic function (Fedorowski et al., 2017; Gunning et al., 2019; Li et al., 2019). These autoantibodies have been proposed to be a unifying mechanistic explanation for the cardiovascular changes in POTS, but the role of these antibodies remains unclear. Low titers of autoantibodies against these and other GPCRs may be found in healthy controls and have been well described in patients with a variety of other conditions including cardiomyopathy and asthma, as well as autoimmune conditions like systemic lupus erythematosus and Sjögren disease. While it is possible that POTS could be an antibody-mediated autoimmune disorder in some cases, the presence of these antibodies may also represent dysregulation of a physiological network of GPCR autoantibodies (Cabral-Marques et al., 2018) which is not specific to POTS. This dysregulation could contribute to the perpetuation of the POTS phenotype, or could actually represent an immune-mediated adaptation (or maladaptation) to other

primary physiological changes.

Future autoantibody studies will need to be confirmed on larger cohorts across multiple institutions, with harmonization of analysis and assay techniques. The antibody studies also need to be carefully controlled with contemporaneous matched healthy controls and appropriate disease controls including patients with other types of dysautonomia, hypovolemia or cardiovascular deconditioning.

Prior studies have documented small fiber neuropathy in approximately half of POTS patients (Billig et al., 2020; Gibbons et al., 2013; Peltier et al., 2010), and there is some evidence that small fiber neuropathy in POTS may correlate to reduced cardiac innervation (Haensch et al., 2014). Additional characterization of neuropathology is needed in POTS, including further exploration of cardiac, vascular and gastrointestinal innervation. There has been no research exploring neuropathological findings in children and adolescents with POTS.

Since POTS is a syndrome, a more precise disease definition will require not only greater mechanistic understanding and clinical phenotyping, but also biomarkers to gauge disease activity and responsiveness to therapy. Symptom severity correlates poorly with the magnitude of postural tachycardia (Boris et al., 2020a; Parsaik et al., 2013), and therefore more specific markers of disease activity and severity are needed. The ideal biomarker must be both sensitive and specific, reproducible, cost-effective, readily available, and able to serve as a therapy-responsive progression marker (FDA-NIH Biomarker Working Group, 2016). Development of improved disease and pathophysiological biomarkers could include biospecimens, imaging modalities, neuropsychological assessments, and physiological autonomic measures. Thus far, despite significant cognitive symptoms, brain imaging and assessment of functional brain connectivity have not been investigated in POTS. This clinical phenotyping should be part of a large collaborative natural history study.

## 6. Clinical trials

To date, there have been very few clinical interventional trials evaluating treatment for POTS (Wells et al., 2018). Among published treatment studies, the majority are uncontrolled case series. A number of the published randomized interventional studies consist of acute interventions aimed at demonstrating short term improvement of tachycardia and orthostatic tolerance.

Early efforts in POTS clinical trials should focus on establishing evidence to guide best practices in POTS treatment. This would include interventional trials and comparative studies on symptomatic therapies, such as beta blockers, fludrocortisone, stimulants, and other therapies currently in use. Such studies should be of sufficient length to establish efficacy and tolerability for chronic use. Studies should also address the non-cardiovascular symptoms and disorders seen in POTS patients. Clinical research studies in POTS should endeavor to capture the entire age spectrum of POTS patients whenever safe and ethical to do so. At the same time, they should take into account pathophysiological subtypes that may respond differentially to target therapies. Randomized controlled trials of disease modifying therapies, such as immunotherapy, vagus nerve stimulation, and exercise, are also needed to determine the benefits of such interventions and provide a justification for health care coverage for such treatment.

## 7. Research infrastructure

An organized research infrastructure promotes collaboration and accelerates the pace of research, but the lack of investment in POTS has led to the lack of such a resource. There are very few academic centers engaged in POTS research, and those that do often focus on other autonomic disorders and lack dedicated resources for POTS research. There are no shared databases or specimen repositories to date and collaborative research between centers is uncommon. Currently, there is no national or international disease registry for POTS which limits assessment of the natural history of the disease, and potential phenoconversion between pathophysiological subtypes. The lack of a fundamental research infrastructure limits our ability to adequately plan clinical trials.

The creation of a national consortium of POTS centers would be a first step toward such a research infrastructure. Participating centers would adopt the use of common disease-specific measures and diagnostic criteria and incorporate those into clinical care and research activities. Common database elements would be a resource for investigating pathophysiology. A common (or distributed) biospecimen repository in the setting of a POTS research consortium is critical. Biospecimens could include samples for immune modulation, hormonal fluid biomarkers in blood (e.g. plasma catecholamines, renin-angiotensin-aldosterone measures, and growth/sex hormone), and RNA & DNA samples.

The community of clinicians and researchers interested in POTS is committed to working together and to promoting high quality research. The creation of a POTS research consortium is a high priority suitable for NIH support.

## 8. Research funding

Given the large number of individuals impacted by this condition and the associated morbidity, there is a remarkable dearth of funding for POTS research. A detailed review of the National Institutes of Health's RePORTER database identified that NIH spent an average of $1.5M on POTS research funding per year over the past five years (Table 1 and Supplementary data tables) (National Institutes of Health, 2020a). The estimated prevalence and disease burden of POTS is similar to multiple sclerosis (Wallin et al., 2019). By comparison of Fiscal Year 2020 NIH funding, NIH invested substantially more for other disorders that affect young women with similar prevalence ($118M for multiple sclerosis research and $127M for lupus research (Wallin et al., 2019)). Over the long term, this disparity in research investment may explain, in part, why numerous FDA-approved treatments are now available for multiple sclerosis while there are no FDA-approved treatments for POTS. There are several major challenges in securing NIH funding for POTS research. The first is the relative paucity of investigators submitting applications. The second is the relative lack of a defined funding pathway at NIH. Since POTS is a clinical syndrome that is multidimensional, POTS research does not currently have an NIH disease designation, nor a clear home in one of the NIH Institutes, nor a trans-institutional working group, such as has existed for chronic fatigue syndrome/myalgic encephalomyelitis (National Institutes of Health, 2020b). Fortunately, NIH plans to develop a POTS-specific category under its research, condition and disease categorization (RCDC) system which will allow for better tracking and reporting POTS research. A third challenge is that POTS is a disorder with diverse manifestations and heterogeneous pathophysiology. Funding mechanisms through NIH work best for applications focused on testing a specific pathophysiological hypothesis rather than those focused on characterizing a larger syndrome. A RFA designed to support a deeper comprehensive understanding of POTS would be a helpful first step.

**Table 1**
Annual NIH spending on POTS research.

| Fiscal year | NIH POTS funding |
|---|---|
| 2015 | $1,295,326 |
| 2016 | $1,012,514 |
| 2017 | $1,597,904 |
| 2018 | $1,812,492 |
| 2019 | $1,787,429 |
| 2020 | $1,200,055 |

Source: NIH RePORTER Database, available at https://projectreporter.nih.gov/reporter.cfm. Accessed January 24, 2021. See Supplementary materials.

In 2018, Congress asked NIH to prepare a report identifying the funding needed to support "priority areas of focus for future POTS research through 2025" and "ongoing and upcoming efforts by NIH to advance the scientific understanding of POTS" (U.S. Senate Committee on Appropriations, 2018). The report was to reflect the perspectives of the "leading external researchers and stakeholders," but the NIH report submitted to Congress in January 2020 failed to do so.

As the leading researchers, clinicians and stakeholders invited by NIH to attend the June 2019 POTS Research meeting, we estimate the need for at least $10 M per year in additional extramural NIH funding for the next five years to achieve the priority areas of focus for future POTS research identified in this manuscript (Table 2), in addition to any administrative or intramural funding needed by NIH.

## 9. Summary

Our understanding of POTS is limited, leading to challenges in providing optimal care for this large group of patients. A symposium of POTS experts met in 2019 to identify priorities for POTS clinical care and research; recommendations are summarized in Table 2. Given the number of Americans affected by POTS and the negative impact on their productivity and quality of life, a larger and intentional investment in POTS research is needed as well as concerted efforts to educate physicians and standardize diagnosis and treatment. This is not purely an American issue. We would advocate for a similar increase in funding from the Medical Research Council in the United Kingdom, the National Health and Medical Research Council in Australia, the Canadian Institutes of Health Research in Canada, and other leading research agencies worldwide.

Information about POTS must be incorporated actively in medical education for patients, caregivers, medical students, medical residents and practicing physicians. Development of standards of care models for POTS based on outcomes data are needed to improve quality of care and access to care while reducing the cost of care for this common disorder.

The first steps should be the creation of a multicenter research consortium with a biospecimen repository and well annotated patient registries. The creation of a set of POTS-specific common data elements, including quantitative clinical outcome measures, will enhance the value of these other research investments. Clinical research focused on pathophysiology should integrate data from multiple modalities including cardiovascular and autonomic physiology, immunology, genetics, neurohormonal axis and psychology. Such research on etiology will allow better assignment of clinical subtype, and point toward promising therapeutic options.

Ultimately, large, prospective, well-designed and appropriately powered clinical treatment trials are needed to advance the quality of care for POTS. POTS clinical trials should focus on long-term restoration of quality of life and function, rather than only short-term amelioration of tachycardia.

**Table 2**
Recommended priorities for POTS clinical care and research.

*Clinical care priorities*
- Improve POTS education and awareness for medical providers
- Develop standard algorithms for diagnosis and treatment
- Establish diagnostic criteria to help identify POTS subtypes and tailor therapy
- Engage multidisciplinary networks of care

*Research priorities*
- Better define the role of genetic and associated disease factors
- Define the natural history of the disease
- Investigate the role of autoimmunity and autoantibodies in POTS
- Create a national/international consortium of academic centers
- Develop POTS-specific rating scales and outcome measures as standardized common data elements
- Create common data elements and definitions for use across both clinical and research approaches
- Conduct properly-controlled and randomized clinical research trials

The NIH (and other agencies funding research) can help by clearly recognizing POTS as an important disorder affecting many Americans, and by better defining which NIH center and study sections are responsible. The NIH issued a Notice of Special Interest to "Stimulate Research on the Diagnosis, Treatment, and Mechanistic Understanding of Postural Orthostatic Tachycardia Syndrome (POTS)" on March 26, 2021 (Notice Number NOT-HL-21-008). This is an important first step that should be accompanied by an intentional targeted increase in funding for POTS research. The scientific and academic medical community for its part must commit to developing high quality, impactful research proposals.

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## Appendix A. Supplementary data

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