Autoimmunity and postural orthostatic tachycardia syndrome: Implications in diagnosis and management

ABSTRACT

Postural orthostatic tachycardia syndrome (POTS)—sustained tachycardia upon standing without orthostatic hypotension—can be diagnosed clinically without an extensive diagnostic evaluation unless certain atypical features suggest an alternative diagnosis. A unifying pathophysiologic mechanism has not been identified, although several have been proposed. Similarities between POTS and various autoimmune disorders suggest an immune mechanism in a subset of patients. However, no causative antibody has been identified, and associated antibodies are rarely clinically relevant. Moreover, immunotherapies are not currently recommended for POTS, although clinical trials are underway to clarify their utility.

KEY POINTS

POTS is a heterogeneous syndrome defined by orthostatic intolerance and can be diagnosed clinically without extensive testing.

Various mechanisms may be involved in POTS, but the initial treatment approach remains the same.

Atypical features are important to recognize and may suggest an alternative diagnosis.

Antibody testing is recommended only when considering an alternative diagnosis.

POTs is a chronic syndrome defined by a sustained increase in heart rate of at least 30 beats per minute (bpm) within 10 minutes of standing in adults (or ≥ 40 bpm in patients ages 12 to 19) without accompanying orthostatic hypotension, which is defined as a fall in systolic blood pressure of 20 mm Hg or greater or a fall in diastolic blood pressure of 10 mm Hg or greater (Table 1).1,2,4,5 In many patients, the absolute heart rate while upright remains above 120 bpm.
POTS symptoms can be grouped broadly as either cardiovascular or noncardiovascular (Table 2).1 Orthostatic intolerance is a defining feature of the condition, with symptoms that get worse upon standing and improve with supine posture.5 Additional cardiovascular symptoms include palpitations, dizziness, lightheadedness, and presyncope or syncope. Noncardiovascular symptoms can involve many organ systems and include fatigue, generalized weakness, neuropathic pain, cognitive difficulty, nausea, and bladder dysfunction (Table 3).1,5–7

The onset is typically subacute and often follows a trigger such as infection, surgery, trauma, or childbirth.6 Heat, fever, dehydration, morning hours, strong emotion, and menstruation have been known to exacerbate symptoms.1 The typical age at onset is between 15 and 45, and at least 80% of patients are women.1,2,6

A typical presentation of POTS is in a young active woman with a subacute onset of lightheadedness, dizziness, and presyncope provoked by standing, often following a viral illness, surgical procedure, trauma, or prolonged period of inactivity. The patient may report that symptoms are worse in warm weather or morning hours, or when feeling particularly stressed or anxious.1

### VARIOUS MECHANISMS MAY BE INVOLVED

A unifying pathophysiology of POTS has not been determined, although various mechanisms may be involved. These include abnormally increased sympathetic nervous system activity and circulating catecholamines resulting in a hyperadrenergic state (“hyperadrenergic POTS”), peripheral sympathetic denervation leading to venous pooling and volume dysregulation (“neuropathic POTS”), low blood volume (absolute hypovolemia), and an underlying immune dysregulation (discussed in further detail below).1–3

These varying mechanisms may coexist within an individual patient, resulting in a heterogeneous symptom presentation, ultimately defined by orthostatic intolerance.5

### BARRIERS TO A TIMELY DIAGNOSIS

POTS can be diagnosed clinically by the general practitioner without extensive testing.8 However, lack of familiarity with the condition, its nonspecific symptoms indirectly related to orthostatic intolerance, and the overlap of symptoms with those of similar conditions often result in unnecessary referrals, excessive testing, and a delay in diagnosis, as concern about missing an alternative diagnosis often adds to the diagnostic challenge.9,10

Using the clinical history alone, POTS can be challenging to differentiate from other causes of orthostatic intolerance such as chronic fatigue syndrome and inappropriate sinus tachycardia.10 Fortunately, objective testing can help to identify POTS, and the initial management strategies are often similar.10 Further information on differentiating POTS from other causes of orthostatic intolerance can be found elsewhere.5

Comorbid psychiatric conditions such as untreated major depression can complicate the evaluation but are important to recognize and address in equal measure to improve clinical response to treatment.11

### APPROACH TO POTS DIAGNOSIS AND MANAGEMENT

The diagnostic evaluation of POTS starts with a focused history centering on symptom onset and progression, comorbid conditions, precipitating and

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**TABLE 1**

**Diagnostic criteria for postural orthostatic tachycardia syndrome**

All of the following criteria are necessary:

- A sustained increase in heart rate by ≥ 30 beats per minute within 10 minutes of standing or head-up tilt in adults (or ≥ 40 beats per minute for patients ages 12–19) without orthostatic hypotension (a fall in systolic blood pressure ≥ 20 mm Hg or diastolic blood pressure ≥ 10 mm Hg)
- Associated symptoms of orthostatic intolerance that are worse with standing (light-headedness, fatigue, palpitations, tremulousness, blurred vision, syncope) and improve with recumbency
- Symptom duration of at least 3 months
- Absence of other conditions to explain sinus tachycardia (prolonged bed rest, medications, hyperthyroidism, anorexia nervosa, anemia, pain, fever, infection, dehydration)

Based on information in reference 1, 2, 4, and 5
exacerbating factors, and positional dependence. Other topics and investigations include the following:

**Diet**, including meal size and frequency and the volume of salt and water intake, is important in looking for symptom triggers and developing treatment strategies. Reducing the size of meals reduces the likelihood of postprandial hypotension, with less blood flow routed away from the brain to the gastrointestinal system.

**Exercise tolerance** (length and type of exercise) can be used to assess the severity of symptoms and evaluate treatment efficacy over time.

**Medications** with side effects that mimic POTS symptoms include diuretics, vasodilators, antipsychotics, anticholinergics, nonstimulant medications for attention deficit hyperactivity disorder (eg, atomoxetine), and oral contraceptive pills with antimineralocorticoid action (eg, those that contain drospirenone).

A detailed autonomic review of systems (Table 4) should be performed to accurately describe symptoms and screen for features that may indicate an alternative diagnosis (Table 5).

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**TABLE 2**

**Clinical presentation and associated symptoms in postural orthostatic tachycardia syndrome**

<table>
<thead>
<tr>
<th>Cardiovascular symptoms</th>
<th>Orthostatic intolerance, orthostatic tachycardia, palpitations, dizziness, lightheadedness, presyncope, syncope, exercise intolerance, dyspnea, chest pain, acrocyanosis, Raynaud phenomenon, venous pooling, limb edema</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Noncardiovascular symptoms</strong></td>
<td><strong>Deconditioning, fatigue, heat intolerance, fever</strong></td>
</tr>
<tr>
<td><strong>General</strong></td>
<td>Headache, migraine, cognitive impairment, “brain fog,” difficulty concentrating, tremulousness, photophobia, phonophobia, blurred vision, neuropathic pain, sleep disorder, involuntary movements</td>
</tr>
<tr>
<td><strong>Nervous system</strong></td>
<td>Muscle fatigue, weakness, pain</td>
</tr>
<tr>
<td><strong>Gastrointestinal</strong></td>
<td>Nausea, bloating, dysmotility, gastroparesis, diarrhea, constipation, pain, weight loss, irritable bowel syndrome</td>
</tr>
<tr>
<td><strong>Respiratory</strong></td>
<td>Shortness of breath, hyperventilation, bronchial asthma</td>
</tr>
<tr>
<td><strong>Urogenital</strong></td>
<td>Bladder dysfunction, polyuria, nocturia, urgency, frequency</td>
</tr>
<tr>
<td><strong>Skin</strong></td>
<td>Rash, erythema, petechiae, telangiectasias, diaphoresis, flushing, pallor, dry eyes, dry mouth, sudomotor dysregulation (hyperhidrosis, hypohidrosis, anhidrosis)</td>
</tr>
<tr>
<td><strong>Psychiatric</strong></td>
<td>Anxiety, depression, panic attacks, suicidal ideation, somatic hypervigilance, catastrophizing personality</td>
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Based on information in reference 1.

The physical examination should include a complete cardiac and neurologic assessment. Look for clues pointing to diseases that can produce a POTS-like phenotype, such as:

- **Thyroid dysfunction** (exophthalmos, goiter, hair-thinning, nail discoloration)
- **Anemia** (pallor, jaundice, cool or discolored extremities)
- **Connective tissue disorders** such as Ehlers-Danlos syndrome (joint hypermobility).

**An active stand** test can be performed in the office by measuring heart rate and blood pressure in the supine position and again 1, 3, 5, and 10 minutes after standing, although the changes occur within the first 5 minutes in most patients with POTS.

**Basic laboratory testing** should include a complete blood cell count, electrolytes, and thyroid function testing. A 12-lead electrocardiogram is recommended to assess for an underlying arrhythmia.

**Further investigation**, including ancillary cardiovascular testing (echocardiography, external electrocardiographic loop monitoring), is not recommended as part of the routine evaluation.
unless there is strong suspicion for structural heart disease or symptomatic arrhythmia contributing to exercise intolerance.4 Similarly, tilt-table testing is not required for diagnosis but can be useful when a patient is unable to perform an active stand test or when other conditions such as neurocardiogenic (vasovagal) syncope or peripheral autonomic neuropathy are suspected.7,16

Further autonomic testing such as quantitative sudomotor axonal reflex testing, skin biopsy to evaluate epidermal nerve fiber density, thermoregulatory sweat testing, or other autonomic cardiovascular evaluation (eg, Valsalva maneuver, deep-breathing test) is unnecessary for the initial diagnosis. These tests may be pursued by a specialist primarily to understand the underlying pathophysiology of a particular patient who has had no improvement with initial conventional therapy, and when symptoms raise suspicion for an autonomic neuropathy.5

Nonpharmacologic treatments first

Once the diagnosis of POTS is established, initial treatment is aimed at reducing symptoms, improving quality of life, and educating the patient. Nonpharmacologic strategies should be the first intervention and include the following:

- **Volume expansion** by increasing oral intake of water to 2 to 3 L/day and salt to 10 to 12 g/day (regular intravenous fluid infusions are not recommended and are potentially harmful2)
- **Compression garments** including abdominal and thigh compression and full abdominal and leg compression17
- **Sleeping with the head of the bed elevated 4 to 6 inches**
- **Removing exacerbating factors** such as large meals and medications2,5,8
- **A graded exercise program** featuring endurance reconditioning and lower-body resistance training can be highly beneficial18
- **Behavioral and cognitive therapy** should also be considered for patients with significant anxiety, somatic hypervigilance, or catastrophizing behaviors.8 An in-depth discussion of treatment for patients with severe or refractory symptoms is beyond the scope of this article but can be found elsewhere.19

### RED FLAGS AND MIMICS: WHEN TO BROADEN THE DYSAUTONOMIA WORKUP

In evaluating a putative POTS diagnosis, it is important to recognize certain red-flag features that may suggest an alternative diagnosis. When these features are present, a more thorough workup should be considered.

**Evolving symptoms**, with widespread dysautonomia that is highly debilitating and rapidly progresses over days to weeks, should raise concern for an alternative diagnosis.14,20

A history of autoimmune disease or malignancy may further raise suspicion for an alternative diagnosis, especially if the initial presentation occurs after age 65.20

**Red-flag autonomic symptoms** are often widespread and severe, involving the sympathetic, parasympathetic, and enteric nervous systems. Signs and symptoms that should raise suspicion include pupillary dysfunction, hyperhidrosis or anhidrosis, urinary retention, sexual dysfunction, and severe gastrointestinal dysmotility.14 The coexistence of these symptoms should raise suspicion for an alternative diagnosis, especially when disabling and severe.

**Extra-autonomic features** that should also raise concern for alternative diagnoses include involvement of the central nervous system (cerebral cortex, brainstem, cerebellum, spinal cord) or endocrinopathies (amenorrhea, syndrome of inappropriate antidiuretic hormone secretion, adrenal insufficiency, panhypopituitarism).14

If red flags are present

When red-flag features are present, systemic testing, neurologic testing, or both may be warranted. In these cases, testing for specific antibodies that could account for the clinical presentation is advised.

For example, a combination of sicca symptoms, impaired pupillary reflex, urinary retention, and gastroparesis should raise suspicion for a severe form of immune-mediated dysautonomia termed autoimmune autonomic ganglionopathy.20 This clinical picture war-

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**TABLE 3**

<table>
<thead>
<tr>
<th>Commonly reported symptoms in patients with postural orthostatic tachycardia syndrome</th>
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<tbody>
<tr>
<td>Light-headedness or dizziness</td>
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<tr>
<td>Palpitations</td>
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<tr>
<td>Fatigue</td>
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<tr>
<td>Headache</td>
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<tr>
<td>Breathing difficulty</td>
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<tr>
<td>Tremulousness</td>
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Based on information in references 1, 5, 6, and 7.
rants testing for the alpha-3 ganglionic acetylcholine receptor (gAChR) antibody.20

A limited form of autoimmune autonomic ganglionopathy that predominantly affects the gastrointestinal system is termed autoimmune gastrointestinal dysmotility syndrome.21 Patients with this form develop severe subacute multilevel gastrointestinal dysmotility, sometimes presenting with intestinal pseudo-obstruction, and are often found to be gAChR antibody-positive.21

Alternatively, predominant sicca symptoms in the setting of dysautonomia with or without sensory abnormalities may warrant testing for Sjögren syndrome A and B (SSA and SSB) antibodies.22,23

Patients who present with dysautonomia in the setting of symmetric proximal weakness that improves with exercise should raise suspicion for Lambert-Eaton myasthenic syndrome and should undergo testing for P/Q-type and N-type voltage-gated calcium channel antibodies.20

Other antibody-associated (often paraneoplastic) neurologic disorders exist that can present with pervasive dysautonomia, often in the setting of severe nervous system dysfunction. They are beyond the scope of this review, but include disorders associated with antineuronal nuclear antibody type 1 (ANNA-1, Anti-Hu), anti-dipeptidyl-peptidase-like protein-6, anti-contactin-associated protein-like 2 antibody, and anti-collapsin response mediator protein 5.20,24

They are rare and should not be tested for regularly unless clinically indicated, to avoid exposing patients to unnecessary and potentially harmful interventions.

The overlap of signs and symptoms among several of these autoimmune conditions and POTS has raised the possibility of an underlying autoimmune mechanism in the disease itself. The following section focuses on this topic in greater detail.

### THE ROLE OF AUTOIMMUNITY IN POTS

The role of the immune system in POTS has attracted much interest in recent years. While a clear autoimmune etiology has not been identified, the shared clinical features between POTS and various autoimmune conditions suggest several immune-mediated mechanisms. These shared features have also given rise to further investigation into possible diagnostic and management avenues within the field.

### Clinical similarities between POTS and autoimmune conditions

Most patients with POTS are young women, with recent estimates suggesting a 94% female predominance.25 Symptom onset is frequently preceded by an acute stimulus such as a viral infection, vaccination, physical trauma, surgery, or pregnancy, suggesting an immune-mediated process may be at play.25 Furthermore, many patients with POTS have associated generalized symptoms including fatigue, malaise, sleep disruption, headache, and gastrointestinal symptoms, features often observed in chronic autoimmune disease.25

From 16% to 20% of patients with POTS have a coexisting autoimmune disease, and many have a family history of one.9,26,27 In a large community-based survey, the most common coexisting autoimmune conditions were Hashimoto thyroiditis (present in 6%), celiac disease (3%), Sjögren syndrome (3%), rheumatoid arthritis (2%), and systemic lupus erythematosus (2%).9

Furthermore, many patients with POTS have various autoantibodies, suggesting an autoimmune link. However, many of these antibodies are discovered incidentally at low titers and have unclear clinical significance.26,28,29 One study found that 25 (25%) of 100 patients with POTS had antinuclear antibodies, indicating a possible autoimmune etiology.
significantly more than in the general population (16%, $P < .05$). Similarly, the prevalence of anti-phospholipid antibodies in the patients with POTS was 7%, compared with 1% in the general population ($P < .001$). Thyroid-specific antibodies have also been found in up to 33% of patients with POTS, again with unclear significance. Neurologic autoantibodies directed at voltage-gated potassium channels and glutamic acid decarboxylase 65 may also be incidentally discovered but are nonspecific, and can also be seen in patients with nonimmune neurologic diseases as well as in healthy controls.

While the prevalence of antibody positivity in patients with POTS may suggest an autoimmune association, the presence of these antibodies shows no clear difference in the severity of POTS symptoms or response to therapy. In clinical practice, checking for these antibodies is not recommended in patients with an otherwise typical POTS presentation without additional features of an underlying secondary disease process.

Molecular mechanisms proposed
The molecular mechanisms linking POTS and autoimmunity remain poorly understood. One theory suggests a state of sympathetic overdrive and reduction of cardiovagal tone resulting in an elevation in the cytokine interleukin 6 inducing systemic inflammation. The elevation in interleukin 6 may act centrally to upregulate further sympathetic activity, resulting in a chronic hyperadrenergic state leading to cardiovascular deconditioning. This proinflammatory state may explain several systemic features associated with POTS including sleep disturbance, cognitive impairment, and hyperalgesia. Additionally, elevated cytokines may be important mediators of vasodilation and vascular permeability.

Others have suggested the possibility of a circulating autoantibody with a direct pathological mechanism affecting the autonomic nervous system.

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**TABLE 5**

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<thead>
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<th>Red-flag features suggesting an alternative diagnosis</th>
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<tr>
<td><strong>Onset</strong></td>
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<tr>
<td>Widespread autonomic involvement</td>
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<tr>
<td>Functional decline</td>
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<tr>
<td>Signs and symptoms</td>
</tr>
<tr>
<td>Relevant personal or family history</td>
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<tr>
<td>Central nervous system dysfunction</td>
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<tr>
<td>Endocrinopathy</td>
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Based on information in reference 14.
POTENTIAL AUTOANTIBODY TARGETS IN POTS

Thus far, several possible autoantibody targets have been studied in POTS.

The gAChR antibody, initially identified as the pathogenic antibody in autoimmune autonomic ganglionopathy, has been suggested as a possible culprit, as it can be detected in low titers in up to 25% of patients with POTS. However, it can be nonspecific, as low-titer positivity (≤ 0.05 nmol/L) has been noted in healthy controls and in various other autoimmune-mediated conditions, without clear clinical relevance. McKeon et al found that, of 155 patients who tested positive for gAChR antibody after being referred because of neurologic symptoms, 31% did not have autoimmune disease, 37% had low titers (≤ 0.09 nmol/L), 55% had medium titers (0.10–0.99 nmol/L), and 8% had high titers (≥ 1.00 nmol/L). While the antibody has been speculated to play a role in sympathetic denervation in POTS, no clear clinical difference between seropositive and seronegative patients has been shown.

Thus, it is always important to interpret antibody testing results within the clinical context, regardless of the titer level. Ultimately, testing for gAChR antibody in a patient with a classic POTS presentation without additional red flags has little clinical utility and may confound the clinical picture if the result is positive.

G-protein coupled receptor (GPCR) antibodies, which target adrenergic receptors, are another class of antibodies that may be detected in patients with POTS. Notably, GPCR antibodies have also been detected in patients with Sjögren syndrome, orthostatic hypotension, malignant hypertension, and preeclampsia, as well as in patients with POTS-like conditions such as inappropriate sinus tachycardia, complex regional pain syndrome, and chronic fatigue syndrome, and are thus nonspecific. Specific antibodies in this class include those directed against alpha-1 adrenergic receptor, beta-1 adrenergic receptor, and beta-2 adrenergic receptor and are thought to inhibit norepinephrine action peripherally, resulting in increased heart rate and orthostatic intolerance.

Angiotensin II T1 receptor antibodies have similarly been detected in patients with POTS and may act by disrupting systemic vasoconstriction in response to upright posture.

Muscarinic receptor antibodies. Recent evidence has also suggested activity of muscarinic receptor antibodies (M1, M2) in contributing to POTS pathophysiology.

Testing for these antibodies is currently considered experimental and thus is not available commercially. Furthermore, a recent study investigating the presence of GPCR antibodies in POTS patients compared with healthy controls showed no significant difference in antibody (adrenergic, muscarinic, and angiotensin II) concentrations by enzyme-linked immunosorbent assay testing. While the presence of these antibodies raises the possibility of an autoimmune link, they do not appear to be directly pathogenic, and testing for them does not currently offer clear clinical utility in POTS.

POTENTIAL USE OF IMMUNOTHERAPY IN POTS

Given the possibility of an immune-mediated mechanism underlying POTS, researchers have begun to investigate the efficacy of immunotherapies in its treatment, but as yet, no prospective trials have been completed.

In a case series from Rodriguez et al, 6 patients with a clinical diagnosis of POTS and a positive GPCR antibody test were treated with intravenous immunoglobulin intermittently over 6 months. The patients were all young women (ages 23–31), had refractory POTS symptoms despite first-line treatment, and had tested positive for the alpha-1 adrenergic receptor antibody. Response to treatment was measured with a subjective symptom-based survey and with objective testing including a tilt-table test. The subjective and objective results appeared to be positive after 6 months of therapy, although notably, treatment tolerance was poor, with 2 patients requiring hospitalization. Also, all the patients were pretreated with intravenous fluids in addition to receiving intravenous immunoglobulin, likely resulting in a significant volume repletion that may have contributed to the overall treatment effect. This is an important confounder in assessing the use of intravenous immunoglobulin in the treatment of POTS.

Currently, a double-blind randomized control trial is investigating the feasibility, tolerability, and potential benefit of intravenous immunoglobulin treatment in POTS. The study plans to enroll 32 participants with POTS who have moderate to severe symptoms and clinical or laboratory features of autoimmunity including a serum autoantibody (antineuclear antibody, gAChR antibody, extractable nuclear antigen, antiphospholipid antibody, or tissue transglutaminase immunoglobulin A), a personal or family history of autoimmune disease, evidence of small-fiber neuropathy, or history of acute to subacute onset of symptoms.
With an expected completion date in late 2023, this study will help to further clarify a clinical question that at this time remains uncertain. Until then, there is not enough rigorous evidence to suggest a benefit of immunotherapy in the treatment of POTS.

**TAKE-HOME POINTS**

Although the etiology and pathophysiologic mechanisms underlying POTS remain uncertain, a clinical diagnosis can be made with a focused history, examination, and basic diagnostic evaluation.

Initial treatment strategies are simple and include optimizing fluid intake, compression stockings, avoiding known triggers, exercise to improve stamina, and cognitive behavioral therapy to reduce hypervigilance.

Autoimmunity may play a role in the pathogenesis of POTS in some patients. However, if the initial clinical presentation is consistent with POTS and no major red-flag features are evident, further antibody testing is not recommended because it will not change management. Although several antibodies are being investigated that may be associated with POTS, a single causative antibody has not been identified. If red flags are present, a targeted autoimmune investigation should be considered to exclude diagnostic mimics.

There are not enough data currently to warrant treating POTS with immunosuppressive therapies. Important clinical trials are underway to explore this treatment approach further.

**REFERENCES**


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