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CLINICAL PRACTICE UPDATES

AGA Clinical Practice Update on GI Manifestations and Autonomic or Immune Dysfunction in Hypermobile Ehlers-Danlos Syndrome: Expert Review

Qasim Aziz,[1] Lucinda A. Harris,[2] Brent P. Goodman,[3] Magnus Simrén,[4] and Andrea Shin[5]

[1]Blizard Institute, Wingate Institute of Neurogastroenterology, Centre for Neuroscience, Surgery and Trauma, Barts and the London School of Medicine and Dentistry, Queen Mary University, London, United Kingdom; [2]Division of Gastroenterology and Hepatology, Mayo Clinic, Scottsdale, Arizona; [3]Department of Neurology, Mayo Clinic, Scottsdale, Arizona; [4]Department of Molecular and Clinical Medicine, Institute of Medicine, Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden; and [5]Vatche and Tamar Manoukian Division of Digestive Diseases, University of California, Los Angeles, Los Angeles, California

DESCRIPTION: **The purpose of this Clinical Practice Update Expert Review is to describe key principles in the evaluation and management of patients with disorders of gut-brain interaction (DGBI) and hypermobile Ehlers-Danlos syndrome (hEDS) or hypermobility spectrum disorders (HSDs) with coexisting postural orthostatic tachycardia syndrome (POTS) and/or mast cell activation syndrome (MCAS).**

METHODS: **This expert review was commissioned and approved by the American Gastroenterological Association (AGA) Institute Clinical Practice Updates Committee and the AGA Governing Board to provide timely guidance on a topic of high clinical importance to the AGA membership, and underwent internal peer review by the Clinical Practice Updates Committee and external peer review through standard procedures of *Clinical Gastroenterology and Hepatology*. These Best Practice Advice statements were drawn from a review of the published literature and from expert opinion. Because systematic reviews were not performed, these Best Practice Advice statements do not carry formal ratings regarding the quality of evidence or strength of the presented considerations.**

BEST PRACTICE ADVICE 1: **Clinicians should be aware of the observed associations between hEDS or HSDs and POTS and/or MCAS and their overlapping gastrointestinal (GI) manifestations; while theoretical explanations exist, experimental evidence of the biological mechanisms that explain relationships is limited and evolving.**

BEST PRACTICE ADVICE 2: **Testing for POTS/MCAS should be targeted to patients presenting with clinical manifestations of POTS/MCAS, but universal testing for POTS/MCAS in all patients with hEDS/HSDs is not supported by the current evidence.**

BEST PRACTICE ADVICE 3: **Gastroenterologists seeing patients with DGBI should inquire about joint hypermobility and strongly consider incorporating the Beighton score for assessing joint hypermobility into their practice as a screening tool; if the screen is positive, gastroenterologists may consider applying 2017 diagnostic criteria to diagnose hEDS (https://www.ehlers-danlos.com/wp-content/uploads/2017/05/hEDS-Dx-Criteria-checklist-1.pdf) or offer appropriate referral to a specialist where resources are available.**

BEST PRACTICE ADVICE 4: **Testing for POTS through postural vital signs (eg, symptomatic increase in heart rate of 30 beats/min or more with 10 minutes of standing during an active stand or head-up tilt table test in the absence of orthostasis) and referral to specialty practices (eg, cardiology or neurology)**

Abbreviations used in this paper: AGA, American Gastroenterological Association; DGBI, disorders of gut-brain interaction; EDS, Ehlers-Danlos syndrome; GI, gastrointestinal; hEDS, hypermobile Ehlers-Danlos syndrome; HSD, hypermobility spectrum disorder; IBS, irritable bowel syndrome; MCAS, mast cell activation syndrome; POTS, postural orthostatic tachycardia syndrome.

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for autonomic testing should be considered in patients with hEDS/HSDs and refractory GI symptoms who also report orthostatic intolerance after exclusion of medication side effects and appropriate lifestyle or behavioral modifications (eg, adequate hydration and physical exercise) have been attempted but is not required for all patients with hEDS/HSDs who report GI symptoms alone.

BEST PRACTICE ADVICE 5: In patients presenting to gastroenterology providers, testing for mast cell disorders including MCAS should be considered in patients with hEDS/HSDs and DGBI who also present with episodic symptoms that suggest a more generalized mast cell disorder (eg, visceral and somatic pain, pruritus, flushing, sweating, urticaria, angioedema, wheezing, tachycardia, abdominal cramping, vomiting, nausea, diarrhea, urogynecological and neurological complaints) involving 2 or more physiological systems (eg, cutaneous, GI, cardiac, respiratory, and neuropsychiatric), but current data do not support the use of these tests for routine evaluation of GI symptoms in all patients with hEDS/HSDs without clinical or laboratory evidence of a primary or secondary mast cell disorder.

BEST PRACTICE ADVICE 6: If MCAS is suspected, diagnostic testing with serum tryptase levels collected at baseline and 1–4 hours following symptom flares may be considered by the gastroenterologist; increases of 20% above baseline plus 2 ng/mL are necessary to demonstrate evidence of mast cell activation.

BEST PRACTICE ADVICE 7: If a diagnosis of MCAS is supported through clinical and/or laboratory features, patients should be referred to an allergy specialist or mast cell disease research center where additional testing (eg, urinary *N*-methylhistamine, leukotriene E4, 11β-prostaglandin F2) may be performed.

BEST PRACTICE ADVICE 8: Diagnostic evaluation of GI symptoms consistent with DGBI in patients with hEDS/HSDs and comorbid POTS and/or MCAS should follow a similar approach to the evaluation of DGBI as in the general population including the use of a positive symptom-based diagnostic strategy and limited noninvasive testing.

BEST PRACTICE ADVICE 9: Testing for celiac disease may be considered earlier in the diagnostic evaluation of patients with hEDS/HSDs who report a variety of GI symptoms and not only limited to those with diarrhea. There is insufficient research to support routine testing for disaccharidase deficiencies or other diet-mediated mechanisms as causes of GI symptoms in hEDS/HSDs.

BEST PRACTICE ADVICE 10: Diagnostic testing for functional defecation disorders with anorectal manometry, balloon expulsion test, or defecography should be considered in patients with hEDS/HSDs and lower GI symptoms such as incomplete evacuation given the high prevalence of pelvic floor dysfunction, especially rectal hyposensitivity, in this population.

BEST PRACTICE ADVICE 11: In patients with hEDS/HSDs and comorbid POTS who report chronic upper GI symptoms, timely diagnostic testing of gastric motor functions (eg, measurement of gastric emptying and/or accommodation) should be considered after appropriate exclusion of anatomical and structural diseases, as abnormal gastric emptying may be more common than in the general population.

BEST PRACTICE ADVICE 12: Medical management of GI symptoms in hEDS/HSDs and POTS/MCAS should focus on treating the most prominent GI symptoms and abnormal GI function test results. In addition to general DGBIs and GI motility disorder treatment, management should also include treating any symptoms attributable to POTS and/or MCAS.

BEST PRACTICE ADVICE 13: Treatment of POTS may include increasing fluid and salt intake, exercise training, and use of compression garments. Special pharmacological treatments for volume expansion, heart rate control, and vasoconstriction with integrated care from multiple specialties (eg, cardiology, neurology) should be considered in patients who do not respond to conservative lifestyle measures.

BEST PRACTICE ADVICE 14: When MCAS is suspected, patients can benefit from treatment with histamine receptor antagonists and/or mast cell stabilizers, in addition to avoiding triggers such as certain foods, alcohol, strong smells, temperature changes, mechanical stimuli (eg, friction), emotional distress (eg, pollen, mold), or specific medications (eg, opioids, nonsteroidal anti-inflammatory agents, iodinated contrast).

BEST PRACTICE ADVICE 15: **Besides general nutritional support, special diets including a gastroparesis diet (ie, small particle diet) and various elimination diets (eg, low fermentable carbohydrates, gluten- or dairy-free, low-histamine diets) can be considered for improving GI symptoms. Dietary interventions should be delivered with appropriate nutritional counseling or guidance to avoid the pitfalls of restrictive eating.**

BEST PRACTICE ADVICE 16: **Management of chronic GI symptoms in patients with hEDS/HSDs who do not exhibit symptoms consistent with POTS or MCAS should align with existing approaches to management of DGBI and GI motility disorders in the general population, including integrated multidisciplinary care involving multiple specialties, where appropriate (eg, cardiology, rheumatology, dietician, psychology).**

Keywords: Disorders of Gut-Brain Interaction; Motility Disorders; Functional Gastrointestinal Disorders; POTS; Mast Cell Activation; Joint Hypermobility.

Introduction

Hypermobile Ehlers-Danlos syndrome (hEDS) is a syndrome belonging to a cluster of inherited disorders of connective tissue characterized by features such as musculoskeletal symptoms, joint hypermobility, and tissue fragility.[1] hEDS is the most common among the various EDS subtypes, accounting for 80%–90% of patients with EDS,[2,3] and is further recognized as part of a larger group of hypermobility spectrum disorders (HSDs) that encompass common features of pain and joint hypermobility, but do not satisfy diagnostic criteria for hEDS. Gastrointestinal (GI) symptoms are frequently reported[4–7] in patients with hEDS/HSDs and are associated with impaired quality of life and increased healthcare utilization.[5,6,8–10] In one cross-sectional survey study of over 600 individuals with hEDS/HDS, almost all (98%) patients met diagnostic criteria for disorders of gut brain interaction (DGBI).[5]

There is a growing body of literature[11–13] describing a link between hEDS/HSDs and other poorly understood disorders such as postural orthostatic tachycardia syndrome (POTS) and mast cell activation syndrome (MCAS). However, data are limited to observational studies lacking rigorous diagnostic criteria for hEDS/HSDs, POTS, or MCAS.[14] Concurrently, clinical gastroenterologists are encountering an increasing number of patients with chronic GI symptoms who also appear to experience comorbid hEDS/HSDs, POTS, and/or MCAS.[15,16] Recognizing and treating GI symptoms in patients with hEDS/HSDs and comorbid POTS or MCAS present major challenges for clinicians, who often feel under equipped to address their needs. Poor understanding of these overlapping syndromes can lead to nonstandardized approaches to diagnostic evaluation and management. Until sufficient data are available to develop evidence-based recommendations, clinicians require rational guidance on best practices for identifying, evaluating, and treating patients with GI symptoms or DGBIs presenting with hEDS/HSDs and comorbid POTS or MCAS.

Pathophysiology

Limited Evidence on the Biological Link Between hEDS/HSDs, POTS, and MCAS

Theoretically, a mechanistic link exists between hEDS/HSDs, POTS, and MCAS. Skin biopsies in hEDS/HSDs and classical EDS patients show collagen fibril structure, which appears to trigger fibroblasts dysfunction within the connective tissue with altered adhesion and cytoskeletal response. An important parameter controlled by connective tissue microstructure is mechanical stiffness. There is evidence that in hEDS, the connective tissue is softer and less stiff than in control subjects. Mast cells are derived from multipotential hematopoietic stem cells, differentiate into mast cell progenitors, and migrate into connective tissue and mucosa, where they proliferate into mast cells containing granules of histamine, heparin, and various cytokines among other proinflammatory molecules that are released into surrounding tissues when mast cells degranulate. Early or too much degranulation can lead to mast cell activation disorders causing multisystemic symptoms commonly involving skin and soft tissue, gastrointestinal tract, respiratory tract, and cardiovascular system. MCAS is a subtype of mast cell activation disorder characterized by mast cell activation caused by triggers such as food, heat, emotion, and mechanical stimuli, due to abnormal sensitivity of mast cells without mast cell proliferation. Symptoms typically occur in 2 or more systems of the body, for example the GI tract, skin, cardiac, and/or nervous system.[9,10,17,18]

POTS is a form of dysautonomia characterized by impaired autonomic responses leading to clinical symptoms of orthostatic intolerance. The autonomic nervous system consists of the parasympathetic and sympathetic nervous system, which innervate every organ in the body and integrate control of heart rate, blood pressure, and body temperature. When dysfunction occurs, defects may occur at various levels from peripheral nerves, autonomic ganglia, the spinal cord, and/or the brain, resulting in cardiac, respiratory, alimentary, urinary,

reproductive, ocular, and sudomotor defects. Different POTS phenotypes include hypovolemic, neuropathic, and primary hyperadrenergic POTS, which represent different pathophysiological perturbations leading to chronic orthostatic intolerance. Patients with hEDS/HSDs commonly experience symptoms of autonomic dysregulation and orthostatic intolerance. Although the mechanistic basis of this association is not fully understood and may be confounded by other factors such as medications (eg, stimulants or other centrally acting agents), it is theorized that vascular laxity and/or peripheral neuropathy could play a role,[19] and newer evidence has implicated possible autoimmune etiologies.[20]

It has been reported that patients with hEDS/HSDs may have a higher incidence of MCAS and POTS compared with the general population. In one prospective study of 139 patients with MCAS and refractory GI symptoms, 23.7% had EDS, 25.2% had POTS, and 15.1% had both.[21] In a small study, one-third of POTS patients reported having a diagnosis of irritable bowel syndrome (IBS).[22] In a survey study of 616 hEDS/HSDs patients, 37.5% reported a diagnosis of POTS.[23] In another recent study investigating hEDS/HSDs, over 60% had at least 1 GI symptom; those with concomitant POTS were more likely to have fibromyalgia, IBS, gastroesophageal reflux disease, or dysmotility.[24] However, in these studies the diagnosis of hEDS/HSDs is often not based on the 2017 criteria, and MCAS and POTS are not always categorically established. Hence, the nature and extent of the link between these 3 conditions require further investigation.

Best Practice Advice 1. Clinicians should be aware of the observed associations between hEDS or HSDs and POTS and/or MCAS and their overlapping GI manifestations; while theoretical explanations exist, experimental evidence of the biological mechanisms that explain relationships is limited and evolving.

Best Practice Advice 2. Testing for POTS/MCAS should be targeted to patients presenting with clinical manifestations of POTS/MCAS, but universal testing for POTS/MCAS in all patients with hEDS/HSDs is not supported by the current evidence.

Mechanisms of DGBI Symptoms in hEDS/HSDs, POTS, and/or MCAS

Many of the mechanisms (eg, altered motility, visceral hypersensitivity, immune activation, altered secretion, and disordered central processing) that have been described[25–27] in common DGBI are likely to contribute to GI symptoms in patients with hEDS/HSDs, POTS, and/or MCAS. Some evidence suggests that patients with hEDS/HSDs, POTS, or MCAS may be uniquely predisposed to altered sensorimotor functions and central processing. Pasricha et al[20] recently demonstrated a possible role for autoimmune dysfunction in the common pathogenesis of these conditions. In hEDS/HSDs, changes in collagen structure or extracellular matrix molecules may lead to changes in intestinal motility, tone, sensation, and/or permeability.[28] However, data supporting these hypotheses are limited and often inconsistent. Retrospective studies have reported a high prevalence of abnormal gastrointestinal transit and structural or functional pelvic floor abnormalities in patients with EDS.[29,30] Others have reported changes in motility using a water challenge magnetic resonance imaging protocol in patients with hEDS compared with control subjects but no differences in gastric emptying or accommodation.[31] Similarly, Carbone et al[28] demonstrated that joint hypermobility syndrome in functional dyspepsia was less likely to be associated with impaired gastric accommodation and nutrient tolerance. Some studies of anorectal physiology have also suggested that rates of functional or structural pathology and impaired motility may not necessarily differ between tertiary referral patients with and without hEDS/HSDs.[32,33] In general, prospective studies investigating changes in GI physiology in hEDS/HSDs are lacking.

Although research is limited, a few studies have also suggested that the pathophysiology of GI symptoms in patients with dysautonomia including POTS may also involve GI motor dysfunction and visceral sensitization.[34] In one study of 163 patients, two-thirds of patients with POTS and GI symptoms had evidence of abnormal gastric emptying.[35] Another retrospective study demonstrated an increased prevalence of delayed small bowel transit and hypocontractility patterns among patients with POTS based on wireless motility capsule testing.[36] Others have described impaired gastric myoelectrical activity and central sensitization[37] in POTS as a potential mechanism for DGBI symptoms. In a recent study of both retrospective and prospective cohorts, Pasricha et al[20] demonstrated that patients with HSDs were more likely to have autoimmunity, severe dysautonomia, and GI dysfunction than those without.

Meanwhile, low-grade inflammation, barrier dysfunction, and visceral hypersensitivity may be relevant in patients with MCAS who exhibit DGBI symptoms.[38–41] Recently, Aguilera-Lizarraga et al[42] demonstrated mast cell activation in response to local IgE antibodies against dietary antigens leading to visceral sensitization. Results suggest that mast cells may modulate nociception in common DGBIs such as IBS and functional dyspepsia.[43,44]

Clinical Features and Risk Factors

When to Suspect hEDS/HSDs, POTS, and/or MCAS in Patients With DGBIs

In 2017, an international consensus guideline defined hEDS/HDS according to 3 major criteria.[1] The first criterion uses the Beighton score to assess for generalized hypermobility (Figure 1). The second assesses for the presence of at least 2 of the following features: other manifestations of a connective tissue disorder (eg, soft,

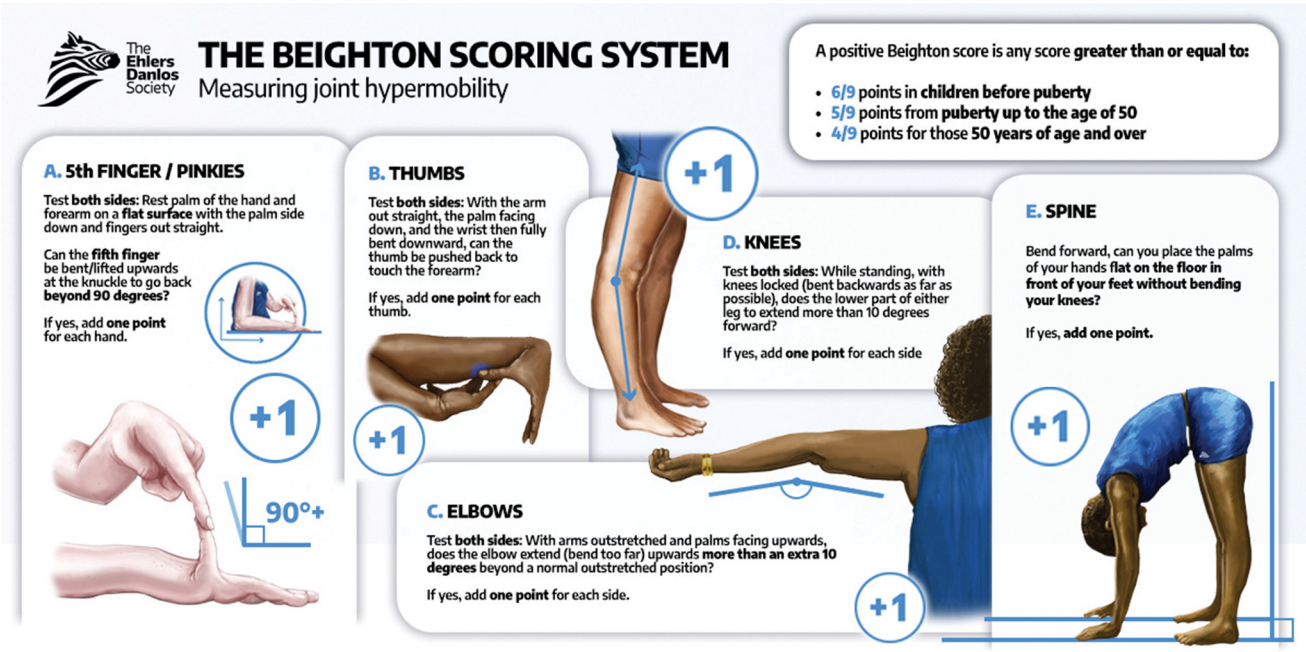

Figure 1. How to assess for joint hypermobility using the Beighton score. Reproduced with kind permission from the Ehlers-Danlos Society.

velvety skin, striae, or pelvic organ or rectal prolapse in children, men, or nulliparous women), family history, and musculoskeletal complications such as joint instability or widespread pain. The third criterion requires patients to have the absence of unusual skin fragility, which should prompt exclusion of other forms of EDS, other heritable and acquired connective tissue disorders, and other joint disorders involving hypotonia and/or connective tissue laxity.

Clinically, POTS is defined in adults as an increase in heart rate of ≥30 beats/min within 10 minutes of upright posture (≥40 beats/min in adolescents 12–19 years of age) with an absence of orthostatic hypotension.[45,46] Symptoms of orthostatic intolerance should be present for at least 6 months and should not be explained by causes such as dehydration, medications, diet, primary anxiety disorder, eating disorders, or other medical conditions. Other symptoms include palpitations, tremulousness, lightheadedness, fatigue, blurred vision, and generalized weakness. Cognitive and bladder dysfunction and GI symptoms that may be attributable to visceral hypersensitivity and/or dysmotility are not uncommon.[47] Nausea, abdominal pain, vomiting, diarrhea, bloating, and severe constipation may be common in POTS, of which nausea, pain, and early satiety are the most predictive of abnormal GI motility.[48]

MCAS is part of a much debated global classification that is divided into primary, secondary, and idiopathic types (Table 1).[17] Generation of vasoactive and inflammatory mediators including histamine along with other cytokines and chemokines produces allergic reactions and a variety of other symptoms including fatigue, tinnitus, conjunctivitis, headaches including migraines, brain fog, palpitations, flushing, pruritus, urticaria, myalgias, and lymphadenopathy. GI symptoms of MCAS often overlap with DGBIs (eg, nausea, vomiting, heartburn, dysphagia, abdominal pain, atypical chest pain, bowel dysfunction).

Best Practice Advice 3. Gastroenterologists seeing patients with DGBI should inquire about joint hypermobility and strongly consider incorporating the Beighton score for assessing joint hypermobility into their practice as a screening tool; if the screen is positive, gastroenterologists should consider applying 2017 diagnostic criteria to diagnose hEDS (https://www.ehlers-danlos.com/wp-content/uploads/2017/05/hEDS-Dx-Criteria-checklist-1.pdf) or offer appropriate referral to a specialist where resources are available.

Prior Infection as a Risk Factor for Dysautonomia

Up to 40% of patients with POTS may self-report a viral upper respiratory or GI infection as the precipitating event to their symptoms.[49] More recently, an association between both acute and long COVID-19 and POTS has been described.[50–52] The possibility of an immunologic cause to POTS is also supported by an increased prevalence of autoimmune disease in POTS patients, increased likelihood of autoimmune disease in family members, and a greater than expected frequency of nonspecific autoantibodies (eg, cardiovascular G protein–coupled membrane receptors, ganglionic

Table 1. MCAS Classification and Consensus Guidelines

Type of MCAS	Main Diagnostic Features
Primary	**Clonal** MCAS: most MCs display CD25 and *KIT* D816V8[a] mutation is detected A) With confirmed CM or SM[b] B) With only 2 minor SM criteria[b]
Secondary	**IgE mediated**, or related to another hypersensitivity reaction or immunologic disorder inducing MCAS, but with the absence of a neoplastic mast cells or *KIT* D816V8 mutation
Idiopathic	Criteria for MCAS are met but there is absence of clonal MCs or IgE-mediated allergy
Consensus Guideline for MCAS	
A) Typical clinical signs of severe, recurrent (episodic) systemic (at least 2 organ systems) MC activation are present (often in the form of anaphylaxis)	
B) Involvement of MCs is documented by biochemical studies: **increase in serum tryptase level** as the preferred marker from individual's baseline to plus 20% + 2 ng/mL[c]	
C) Response of symptoms to therapy with MC-stabilizing agents, drugs directed against MC mediator production, or drugs blocking mediator release or effects of MC-derived mediators[d]	

Modified from supplemental content from Valent et al.[17]
CM, cutaneous mastocytosis; MC, mast cell; MCAS, mast cell activation syndrome; SM, systemic mastocytosis.
[a]Rarely, other *KIT* mutations are found.
[b]Most of the patients experience CM or SM. However, in some cases, only 2 minor SM criteria are detected and criteria for SM and CM are not fulfilled.
[c]Other markers have been proposed but are less specific (eg, histamine and histamine metabolites, prostaglandin D2, and leukotriene C4 metabolites).
[d]For example, histamine blocking agents, mast cell stabilizers, etc.

acetylcholine receptors, antinuclear antibody, Sjogren's antibodies) and antibodies to norepinephrine, acetylcholine, and angiotensin II.[53] Evidence also exists that the COVID 19 virus exhibits neuronal tropism and may induce GI dysmotility via COVID-induced angiotensin converting enzyme 2 depletion.[54] A recent study demonstrated differences in the gut microbiome between control subjects and patients with POTS or post-COVID syndrome as well as associations of microbiota composition with IBS symptoms.[55] Because disorders like gastroparesis, functional dyspepsia, and IBS may also be associated with prior infection, history of an infectious insult may prompt further consideration for POTS/MCAS.

Diagnostic Evaluation

The diagnostic evaluation of GI symptoms or DGBI in patients with hEDS/HSDs with POTS and/or MCAS should largely follow recommendations proposed for the general population. This strategy includes the use of a positive symptom-based strategy, limited noninvasive testing,[26,56–58] and careful attention to individual factors (eg, diet, lifestyle, psychological distress) and drugs (eg, opioids) that may underlie chronic GI symptoms[58] with some special considerations. Studies have reported that the risk of celiac disease is elevated in patients with hEDS/HSDs and/or POTS[59] compared with the general population,[60] to suggest that serological testing for celiac disease followed by endoscopic biopsies could be considered earlier in individuals with hEDS/HSDs who report a variety of GI symptoms and not only limited to those with diarrhea. With the exception of individuals with vascular EDS, rates of endoscopy-related complications such as perforation do not appear to be increased among adults with hEDS/HSDs.[61] Age- and indication-appropriate endoscopic evaluation should be performed. For individuals with chronic pain, use of opioid medications should be avoided. For those who are already prescribed opioids, these agents should be managed through a careful multidisciplinary approach, with facilitation of opioid cessation where possible, as summarized by others.[62]

Although food-related symptoms including exacerbation of dysautonomia and orthostatic intolerance have been described in patients with EDS and HSDs,[63] it is theorized symptoms are related to physiologic responses such as splanchnic vasodilation. There is insufficient research on the prevalence of specific food-mediated mechanisms of GI symptoms such as disaccharidase deficiencies in hEDS/HSDs to support the routine testing for carbohydrate maldigestion or malabsorption. Aguilera-Lizarraga et al[42] recently described mast cell-dependent mechanisms of abdominal pain in response to dietary antigens. While it is conceivable that mast cell dysfunction may underlie GI symptoms, including visceral hypersensitivity in hEDS/HSDs, validated clinical tests for mast cell–mediated mechanisms of abdominal pain are lacking. There is limited evidence to guide the use of MCAS-specific tests such as serum tryptase levels or mast cell staining on endoscopic biopsies for the evaluation of isolated GI symptoms without evidence of a generalized mast cell disorder.

DGBI may exist along a continuum with other disorders of altered GI sensorimotor functions that may be particularly relevant in patients with hEDS/HSDs, POTS, and/or MCAS. Retrospective studies have reported GI dysmotility to be relatively common in patients with hEDS/HSD,[24,29] and enrichment of EDS gene variants has been described in patients in idiopathic gastroparesis.[64] However, reports are inconsistent, and others have failed to demonstrate a clear increase in the risk of abnormal GI sensorimotor function among patients with hEDS/HSDs.[28,32,33,65] Currently, the use of GI motility testing is guided by symptoms and responses to first-line treatments (reviewed in Fox et al).[66] Based on the available data, there is no clear evidence to warrant an alternative approach to motility testing in hEDS/HSDs. However, it may be reasonable to consider earlier testing of gastric motor functions with investigations to assess gastric emptying or accommodation in patients with coexisting POTS because underlying autonomic dysfunction may predispose to gastroparesis[67] or perturbations in GI motility. Additionally, diagnostic testing for with anorectal manometry, balloon expulsion test, or defecography in those with difficult bowel evacuation should be considered given the high prevalence of pelvic floor dysfunction in this patient population.

Evaluation for POTS and/or MCAS may also be performed in patients with the appropriate clinical history. When POTS is suspected, clinicians should assess for signs of exaggerated orthostatic tachycardia using postural vital signs and consider referral for autonomic function testing including tilt table or sudomotor testing in addition to expanded laboratory testing with autoantibodies if POTS is confirmed (reviewed in Goodman).[68]

For those patients who are suspected to experience MCAS as a cause of GI symptoms and nonspecific symptoms spanning other organ systems or consistent with allergy (eg, pruritus, wheezing, flushing, urticaria, nasal congestion, headache, hypotension),[69] diagnostic testing with tryptase[70] levels collected at baseline and during symptomatic periods can be performed to assess for increases in total serum tryptase of 20% plus 2 ng/mL.[2] Some have proposed counting mast cells per high power field from intestinal biopsies.[71] However, the threshold distinguishing normal from abnormal mast cell counts is debated, and therefore CD-117 immunohistochemical staining has been thought to be a much more sensitive marker in the second portion of the duodenum or ileum. Consensus for these guidelines, even among allergists, is controversial. If symptoms of mast cell activation are present, clinicians can consider getting a baseline tryptase. Once a diagnosis of MCAS is supported through clinical and laboratory findings, referral to an allergy specialist or mast cell disease research center should be made where additional testing (eg, urinary *N*-methylhistamine, leukotriene E4, 11β-prostaglandin F2) may be performed.

Best Practice Advice 4. Testing for POTS through postural vital signs (eg, symptomatic increase in heart rate of 30 beats/min or more with 10 minutes of standing during an active stand or head-up tilt table test in the absence of orthostasis) and referral to specialty practices (eg, cardiology or neurology) for autonomic testing should be considered in patients with hEDS/HSDs and refractory GI symptoms who also report orthostatic intolerance after exclusion of medication side effects and appropriate lifestyle or behavioral modifications (eg, adequate hydration and physical exercise) have been attempted but is not required for all patients with hEDS/HSDs who report GI symptoms alone.

Best Practice Advice 5. In patients presenting to gastroenterology providers, testing for mast cell disorders including MCAS should be considered in patients with hEDS/HSDs and DGBI who also present with episodic symptoms that suggest a more generalized mast cell disorder (eg, visceral and somatic pain, pruritus, flushing, sweating, urticaria angioedema, wheezing, tachycardia, abdominal cramping, vomiting, nausea, diarrhea, urogynecological and neurological complaints) involving 2 or more physiological systems (eg, cutaneous, GI, cardiac, respiratory, and neuropsychiatric), but current data do not support the use of these tests for routine evaluation of GI symptoms in all patients with hEDS/HSDs without clinical or laboratory evidence of a primary or secondary mast cell disorder.

Best Practice Advice 6. If MCAS is suspected, diagnostic testing with serum tryptase levels collected at baseline and 1–4 hours following symptom flares may be considered by the gastroenterologist; increases of 20% above baseline plus 2 ng/mL are necessary to demonstrate evidence of mast cell activation.

Best Practice Advice 7. If a diagnosis of MCAS is supported through clinical and/or laboratory features, patients should be referred to an allergy specialist or mast cell disease research center where additional testing (eg, urinary *N*-methylhistamine, leukotriene E4, 11β-prostaglandin F2) may be performed.

Best Practice Advice 8. Diagnostic evaluation of GI symptoms consistent with DGBI in patients with hEDS/HSDs and comorbid POTS and/or MCAS should follow a similar approach to the evaluation of DGBI as in the general population including the use of a positive symptom-based diagnostic strategy and limited noninvasive testing.

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Best Practice Advice 11. In patients with hEDS/HSDs and comorbid POTS who report chronic upper GI symptoms, timely diagnostic testing of gastric motor functions (eg, measurement of gastric emptying and/or accommodation) should be considered after appropriate exclusion of anatomical and structural diseases, as abnormal gastric emptying may be more common than in the general population.

Management

Because GI symptoms are prevalent in these 3 conditions individually,[6,22,24,29] and even more so when they overlap,[23,24] it is unfortunate that few clinical trials can guide management of GI symptoms in hEDS/HSDs, POTS, or MCAS. Instead, management of GI symptoms in patients with these disorders largely follows general treatment principles for DGBI, with the addition of specific treatments for the orthostatic symptoms in POTS,[16] and for symptoms suggestive of mast cell activation.[18] In general, management should largely be supportive and symptom focused, and follow the principles of integrated or multidisciplinary care that focus on the multisystemic nature of these conditions,[2,7] including avoidance or cessation of opioids in patients with pain-predominant features[62] and psychological support with use brain-gut behavioral therapies, as some studies have demonstrated increased rates of anxiety and vulnerabilities to psychological distress in patients with hypermobility, which may be mediated by autonomic dysfunction.[72]

Management of GI symptoms (Table 2) focuses on treating the most prominent symptoms and abnormal results of GI function tests (eg, gastric emptying), and is to a large extent similar to management of DGBIs and GI motility disorders.[26,57,73–76] Nausea and/or vomiting can be treated with antiemetics (eg, ondansetron, promethazine, prochlorperazine, aprepitant) and prokinetics (eg, metoclopramide, domperidone, erythromycin, prucalopride). Abdominal pain is frequent, and treatments including acid-suppressive drugs (proton pump inhibitors, H_2 receptor antagonists), antispasmodics (eg, hyoscyamine, dicyclomine, peppermint oil), and neuromodulators (tricyclic antidepressants, selective serotonin reuptake inhibitors, serotonin and norepinephrine reuptake inhibitors, pregabalin, gabapentin) can be considered, depending on the location, type, and frequency of symptoms. Caution with opiates is advocated, and opiates should not be used specifically to treat abdominal pain. For constipation, osmotic or stimulant laxatives, a chloride channel activator (lubiprostone), guanylate cyclase-C agonists (linaclotide, plecanatide), 5-HT_4 receptor agonist (prucalopride), and a sodium hydrogen exchanger (tenapanor) can be trialed. Diarrheal symptoms can be treated with antidiarrheals (loperamide), bile acid sequestrants (cholestyramine, colestipol, colesevelam), a mixed opioid receptor agonist/antagonist (eluxadoline), 5-HT_3 receptor antagonists (alosetron, ondansetron), or cholinesterase inhibitors (pyridostigmine). Patients whose symptoms worsen with stress and struggle with maladaptive coping behaviors can benefit early referral for brain gut hypnotherapy that target emotional, cognitive, behavioral, or autonomic aspects mediating dysregulation of the gut-brain axis.[77] In addition, as pelvic floor symptoms are common in hEDS/HSDs,[6] clinicians should focus on treating these symptoms according to the general treatment principles for anorectal disorders.[27]

Treatment of orthostatic symptoms associated with POTS, which may include GI symptoms, includes increased fluid (2 L/d) and salt intake (10 g/d), exercise training, and use of compression garments. More severely affected individuals may require pharmacological treatment (eg, fludrocortisone, midodrine, beta-blockers)[15,16] with integrated care involving multiple specialties (eg, cardiology, neurology). When MCAS is suspected due to the presence of allergic reactions and other characteristic symptoms (eg, fatigue, tinnitus, conjunctivitis, headaches including migraines, brain fog, palpitations, flushing, pruritus, urticaria, myalgias, lymphadenopathy), patients may benefit from treatment with nonsedating H_1 histamine and H_2 histamine receptor antagonists as first-line choices, with oral cromolyn mast cell stabilizers and/or leukotriene receptor antagonist as second line options.[18,69,78] Some have estimated response rates to antimediator treatment in patients with MCAS of 75% and 82% for symptoms such as diarrhea and abdominal pain, respectively.[79] However, reliable estimates from well-designed randomized trials are lacking, and recommendations for MCAS treatment are currently based on expert opinion.[69] The role of immunotherapy[20] remains under active study (Table 2).

Because undernutrition and dehydration might be a problem in a proportion of patients with these conditions, special attention to nutrition and hydration is needed, and frequently a dietitian should be involved. It is vital to screen for weight loss and disordered eating.[80] Besides general nutritional support, special diets targeting symptom improvement are frequently used, even though studies supporting their efficacy in these patient groups are lacking. A gastroparesis or small particle diet[81] with modified food composition, consistency, and volume[82] can be advised if upper GI symptoms such as nausea and vomiting predominate. If lower GI symptoms predominate, dietary advice used for IBS and other bowel disorders may be used,[83] including a diet low in poorly absorbed fermentable carbohydrates[84] or wheat- or gluten-free diets,[85] but their efficacy in hEDS/HSDs, POTS, and MCAS requires further study. In patients with severe symptoms and weight loss or dehydration despite optimal medical management, parenteral fluid and/or enteral or parenteral nutrition is sometimes necessary as a stabilizing measure and should be administered through a multidisciplinary model.[86] For patients with MCAS, attempts to reduce exposure to triggers is suggested as patients may have physical sensitivities (tem-

Table 2. Treatment Considerations for Patients With Hypermobile Ehlers-Danlos Syndrome or Hypermobility Spectrum Disorder With POTS and/or MCAS

Symptom	Treatment
POTS symptoms	**Lifestyle** (exercise, dietary fluid/salt, salt tablets, acute/chronic intravenous hydration [rare], compression garment) **Blood volume expanders** (fludrocortisone, desmopressin, erythropoietin) **Heart rate lowering agents** (propranolol, ivabradine) **Central nervous system sympatholytics** (clonidine, methyldopa) **Other** (midodrine, pyridostigmine, droxidopa, modafinil)
Diarrhea	**Dietary modification** (low FODMAP, gluten free, soluble fiber) **Microbiome modification** (rifaximin, *Bifidobacterium infantis* 35624) **Antidiarrheals** (loperamide, diphenoxylate) **Bile acid sequestrants** (cholestyramine, colesevelam, colestipol) **μ- and κ-opioid receptor antagonist and δ-receptor antagonist** (eluxadoline)[a] **5-HT$_3$ receptor antagonist:** alosetron (female patients only)
Constipation	**Fiber supplements** (psyllium, methyl cellulose) **Osmotic laxatives** (PEG 3350, lactulose, and milk of magnesia) **Stimulant laxatives** (bisacodyl and senna) **Chloride channel activator** (lubiprostone) **Guanylate cyclase-C agonist** (linaclotide and plecanatide) **5-HT$_4$ agonist** (prucalopride) **Sodium hydrogen exchanger 3 inhibitor** (tenapanor)
Nausea/vomiting	**Antiemetics** (ondansetron, prochlorperazine, promethazine, aprepitant, off-label use of carbidopa)[b] **Prokinetics** (metoclopramide, domperidone, pyridostigmine and off-label use of prucalopride) **Complementary medicine therapies** (aromatherapies, ginger tea, STW5)
Abdominal pain	**Acid Suppression** (H_2 receptor antagonist, proton pump inhibitors) **Antispasmodics** (dicyclomine, hyoscyamine and peppermint oil) **Neuromodulators** (TCA, SSRI, SNRI, neuroleptics, anticonvulsants) **Psychological therapies** (cognitive behavioral therapy, hypnotherapy, relaxation therapies)
Autoimmunity	**Corticosteroids or immunoglobulins**[20,c]
MCAS	**H$_2$ receptor antagonist** (famotidine, nizatidine, ranitidine) **Second-generation H$_1$ antagonist** (cetirizine, levocetirizine, fexofenadine, loratadine) **Mast cell stabilizer** (cromolyn sodium, ketotifen[d]) **Leukotriene receptor antagonist** (montelukast)

MCAS, mast cell activation syndrome; POTS, postural orthostatic tachycardia syndrome; SNRI, serotonin and norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant.
[a]Contraindicated in patients having ≥3 alcoholic beverages per day, postcholecystectomy, and moderate-to-severe hepatic insufficiency.
[b]Patients often require multiple therapeutic agents, and care should be taken to monitor for QT prolongation on the electrocardiogram.
[c]Gastroenterology providers may need to refer to allergy and immunology or mast cell specialists for the management of these medications.
[d]Not approved by the Food and Drug Administration but can be compounded.

perature, ultraviolet radiation, etc.), antigenic sensitivities (pollen, mold, etc.), and food/alcohol intolerances. Diets low in histamine, gluten, and dairy have been recommended based on clinical experience,[18] but formal studies are absent.

Best Practice Advice 12. Medical management of GI symptoms in hEDS/HSDs and POTS/MCAS should focus on treating the most prominent GI symptoms and abnormal GI function test results. In addition to general DGBI and GI motility disorder treatment, management should also include treating any symptoms attributable to POTS and/or MCAS.

Best Practice Advice 13. Treatment of POTS may include increasing fluid and salt intake, exercise training, and use of compression garments. Special pharmacological treatments for volume expansion, heart rate control, and vasoconstriction with integrated care from multiple specialties (eg, cardiology, neurology) should be considered in patients who do not respond to conservative lifestyle measures.

Best Practice Advice 14. When MCAS is suspected, patients can benefit from treatment with histamine receptor antagonists and/or mast cell stabilizers, in addition to avoiding triggers such as certain foods, alcohol, strong smells, temperature changes, mechanical stimuli (eg, friction), emotional distress (eg, pollen, mold), or specific medications (eg, opioids, nonsteroidal anti-inflammatory agents, iodinated contrast).

Best Practice Advice 15. Besides general nutritional support, special diets including a gastroparesis diet and various elimination diets (eg, low fermentable carbohydrates, gluten- or dairy-free, low-histamine diets) can be considered for improving GI symptoms. Dietary interventions should be delivered with appropriate nutritional

counseling or guidance to avoid the pitfalls of overly restrictive eating.

Summary and Future Directions

Accumulating evidence suggests DGBI or GI motility disorders, hEDS/HSDs, POTS, and MCAS may be linked, but the mechanisms explaining their associations are not fully understood. Gastroenterology providers should be aware of the features of hEDS/HSDs, POTS, and MCAS to recognize the full complexity of patients presenting with multisystemic symptoms, offer informed counseling, and guide patients away from unreliable sources or fragmented care to foster therapeutic relationships and evidence-based care. Early diagnostic testing of gastric motor or anorectal functions, treatment of POTS symptoms, use of histamine receptor antagonists, and/or referral to an allergy specialist or mast cell research center may be considered in some. However, the overall approach should follow general recommendations for management of DGBI and GI motility disorders. Further work will be necessary to identify the biological mechanisms connecting these disorders, develop new diagnostic tools, and identify novel therapeutics such as immunotherapy to optimize care and improve long-term outcomes.

Best Practice Advice 16. Management of chronic GI symptoms in patients with hEDS/HSDs who do not exhibit symptoms consistent with POTS or MCAS should align with existing approaches to management of DGBI and GI motility disorders in the general population, including integrated multidisciplinary care involving multiple specialties, where appropriate (eg, cardiology, rheumatology, dietician, psychology).

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Correspondence
Address correspondence to: Lucinda A Harris, MS, MD, Department of Medicine, Division of Gastroenterology and Hepatology, Mayo Clinic School of Medicine, 13400 East Shea Boulevard, Scottsdale, Arizona 85259. e-mail: harris.lucinda@mayo.edu.

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