Hypermobile Ehlers-Danlos Syndrome (hEDS)

A Patient Guide for Immunologists & Allergists

WHAT IS hEDS? hEDS is a heritable disorder of connective tissue, the structural 'glue' of the body, causing joint instability, skin fragility, and systemic effects. Severity varies widely, from mild laxity and intermittent bracing to wheelchair use and complex multisystem involvement.

~1 in 500 people affected	Avg. 10+ years to diagnosis	3:1 to 4:1 diagnosed are female	No cure: management-focused

HOW HEDS AFFECTS THE BODY — SYSTEMIC INVOLVEMENT:

Patient has checked applicable symptoms

Neurological

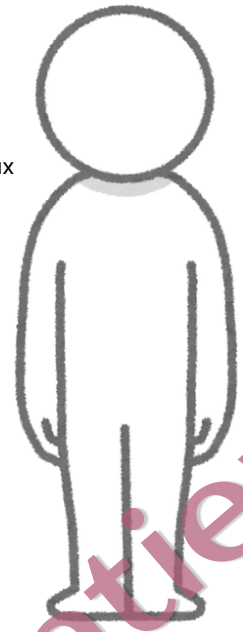
- ☐ Migraines & headaches
- ☐ Brain fog/cognitive fatigue
- ☐ Small fiber neuropathy
- ☐ Proprioception deficits
- ☐ Anxiety/depression (often neurological in origin)

Gastrointestinal

- ☐ IBS
- ☐ Gastroparesis/ delayed emptying
- ☐ GERD & acid reflux
- ☐ Food intolerances

Cardiovascular

- ☐ POTS — heart rate spikes on standing
- ☐ Blood pooling & dizziness
- ☐ Palpitations



Dermatological

- ☐ Soft, velvety, hyperextensible skin
- ☐ Stretch marks without weight change
- ☐ Easy bruising
- ☐ Poor wound healing

Immune / MCAS

- ☐ MCAS — mast cell overactivation
- ☐ Flushing, hives, itching
- ☐ GI distress & food reactions
- ☐ Chemical/environmental sensitivity

Genitourinary

- ☐ Pelvic floor dysfunction
- ☐ Bladder urgency/frequency
- ☐ Chronic pelvic pain
- ☐ Menstrual irregularities

Musculoskeletal

- ☐ Joint hypermobility & instability
- ☐ Subluxations & dislocations
- ☐ Chronic widespread pain
- ☐ Muscle fatigue & weakness
- ☐ Cervical instability (may contribute to headache, cranial nerve symptoms, or myelopathy)

Fatigue & Sleep

- ☐ Profound fatigue
- ☐ Non-restorative sleep
- ☐ Post-exertional malaise
- ☐ Chronic widespread pain at rest

DO

- Evaluate MCAS as a legitimate and common hEDS comorbidity
- Consider a clinical trial of mast cell–targeted therapy when symptoms are consistent with MCAS
- Assess for histamine intolerance and MCAS
- Recognize that negative standard allergy testing does not rule out MCAS
- Screen for triggers: foods, medications, temp, stress, and environmental exposures
- Coordinate with gastroenterology, rheumatology, and primary care

DON'T

- Dismiss MCAS because tryptase is normal: it frequently is in MCAS
- Treat allergic symptoms in isolation without considering hEDS as the underlying condition
- Assume negative skin prick or IgE testing closes the case
- Attribute multi-system allergic symptoms solely to anxiety
- Overlook food reactions and GI symptoms as MCAS manifestations
- Assume drug-seeking behavior

ORDER / REFER

- Serum tryptase (baseline and during reaction if possible)
- 24-hour urine prostaglandin D2 and histamine
- Plasma histamine levels
- Serum chromogranin A (rule out carcinoid; elevated in MCAS when tryptase is normal)
- Trial of H1/H2 antihistamines and/or mast cell stabilizers
- GI evaluation if food reactions and motility symptoms are present
- Rheumatology if hEDS not yet formally diagnosed

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The hEDS Trifecta: Frequently Co-Occurring Conditions

hEDS	POTS	MCAS
Joint instability Structurally abnormal connective tissue Systemic symptoms	Heart rate spikes on standing Dizziness & fatigue Brain fog & cognitive dysfunction Exercise intolerance	Mast cell overactivation Flushing, hives, itching GI distress & food reactions Chemical/environmental sensitivity

Why Immunology Matters for hEDS: MCAS diagnostic criteria remain debated. However, when a patient presents with multi-system allergic-type symptoms, negative standard allergy testing, and a known hEDS diagnosis, a clinical trial of mast cell-targeted treatment is reasonable and supported by emerging literature, even when tryptase is normal. Mast cells are found throughout connective tissue; their dysfunction in hEDS is biologically plausible and increasingly recognized. Immunologists are often the first to validate what patients have been told is "just anxiety," and a positive response to treatment is itself diagnostically meaningful.

Anaphylaxis and hEDS: A Higher-Risk Population Patients with MCAS in the context of hEDS are at elevated risk for anaphylaxis and may react to medications, contrast dye, anesthesia, and other triggers that would not cause reactions in typical patients. Epinephrine auto-injector prescribing should be a low threshold decision in this population. Pre-medication protocols before procedures are worth discussing proactively.

COMMON MISDIAGNOSES IN hEDS PATIENTS PRESENTING TO ALLERGY & IMMUNOLOGY

Often Diagnosed As	Consider Instead/Also	Key Differentiator
Allergic reaction (IgE-mediated)	MCAS in the context of hEDS	Normal skin prick and IgE testing; episodic multisystem symptoms; responds to H1/H2 antihistamines and mast cell stabilizers rather than allergen avoidance alone
Idiopathic urticaria or angioedema	MCAS with hEDS	Recurrent episodes without identifiable allergen; mast cell mediator testing more informative than standard allergy panel
Anxiety disorder	hEDS with MCAS and dysautonomia	Flushing, palpitations, GI distress, and feeling of impending doom are mast cell and autonomic in origin, not primary psychiatric
Food allergy (multiple)	MCAS with histamine intolerance	Reactions are dose-dependent and inconsistent rather than reliably allergen-specific; histamine load and mast cell burden drive symptoms
Chronic sinusitis or nasal polyps	MCAS with upper airway involvement	Mast cell infiltration drives mucosal inflammation; symptoms extend beyond the airway and do not respond fully to standard allergy treatment
Psychosomatic or functional symptoms	hEDS with MCAS and normal labs	Normal tryptase does not rule out MCAS; clinical diagnosis supported by response to treatment

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The Clinical Trial Approach to MCAS Diagnosis Because MCAS diagnostic criteria remain contested and mediator testing is unreliable in isolation, a positive response to a structured treatment trial (H1 blocker, H2 blocker, mast cell stabilizer) is itself diagnostically meaningful. A trial is low-risk, low-cost, and often the clearest path to confirmation. This reframes the diagnostic uncertainty in a way that gives the provider a concrete next step.

MY CURRENT MEDICATIONS & SUPPLEMENTS	WHAT HELPS:
	WHAT MAKES IT WORSE:

WHAT I NEED FROM TODAY'S APPOINTMENT
My primary concern today:
Questions I have:
Medication changes:
Referrals needed:
Other:

CURRENT SYMPTOM SEVERITY:
Joint Pain and Instability Pain Severity:
Fatigue Severity:
GI Symptoms Type, Frequency, and Severity:
Heart rate and Dizziness Triggers and Frequency:
Additional Symptoms:

Sources: Afrin et al. 2017 (JAMA) | Valla et al. 2017 (JAMA) | Genetics in Medicine Open 2025 | ehlers-danlos.com | Kushnir & Chang 2020 (Clin Rev Allergy Immunol) | Afrin 2021 (Am J Med Genet C)

This document was created to provide a focused reference on MCAS and histamine intolerance for providers less familiar with their overlap with hEDS. It is evidence-based and designed to support clinical evaluation rather than direct it.

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MANKOSKI PAIN SCALE

Use this scale when rating your pain severity in CURRENT SYMPTOM SEVERITY

#	What the pain is like	Typical treatment	In my own words
0	No pain.	*No medication needed.*	*"I feel completely normal."*
1	Very minor annoyance -- occasional minor twinges.	*No medication needed.*	*"Hardly notice it."*
2	Minor annoyance -- occasional strong twinges.	*No medication needed.*	*"Annoying but manageable."*
3	Annoying enough to be distracting.	*Mild OTC painkillers may help.*	*"Hard to ignore; affects my focus."*
4	Can be ignored if very focused, but still distracting.	*Mild OTC painkillers relieve pain for 3-4 hours.*	*"Getting in the way of tasks."*
5	Can't be ignored for more than 30 minutes.	*Mild OTC painkillers reduce pain for 3-4 hours.*	*"Stops me mid-task."*
6	Can't be ignored. Can still go to work and participate in social activities.	*Stronger prescription pain relief needed; works 3-4 hours.*	*"Present all the time. I push through."*
7	Difficult to concentrate; interferes with sleep. Can still function with effort.	*Stronger painkillers only partially effective.*	*"Hard to function. Sleep is disrupted."*
8	Physical activity severely limited. Can read/converse with effort. Nausea possible.	*Strongest painkillers minimally effective.*	*"Mostly bed-bound. May feel nauseated."*
9	Unable to speak. Crying out or moaning uncontrollably. Near delirium.	*Strongest painkillers only partially effective.*	*"Cannot communicate. Losing control."*
10	Unconscious. Pain causes passing out.	*Strongest painkillers only partially effective.*	*"Passed out or on the verge of it."*

Mankoski Pain Scale developed by Andrea Mankoski, 1995. Adapted for patient communication. Not a clinical diagnostic tool.

IMPORTANT NOTE FOR HEDS PATIENTS & PROVIDERS:

People with hEDS often have an altered pain baseline due to central sensitization -- a process in which the nervous system becomes increasingly sensitized to pain signals over time.

A "5" for this patient may be what others feel as a "8."
Please do not compare severity numbers to those of patients without chronic illness.

This scale helps us communicate:
it is not a measure of tolerance, willpower, or how "bad" things really are.