

Table E1. Demographic and laboratory characteristics of interviewed patients.

| Subject characteristics | | N=26 |
|---|-------------------|----------------------|
| Median Age (range) | | 52 (17-76) |
| Gender (M/F) | | 13/13 |
| Race/Ethnicity | | |
| | White | 20 (73%) |
| | African American | 3 (12%) |
| | Asian | 2 (8%) |
| | Hispanic | 1 (4%) |
| HES subtype* | | |
| | Idiopathic (IHES) | 18 (69%) |
| | Myeloid (MHES) | 6 (23%) |
| | Lymphoid (LHES) | 2 (8%) |
| Organ involvement* | | |
| | Dermatologic | 17 (65%) |
| | Pulmonary | 16 (62%) |
| | Gastrointestinal | 15 (58%) |
| | Sinus | 12 (46%) |
| | Neurologic | 7 (27%) |
| | Cardiac | 5 (19%) |
| No. organs involved* | | |
| | 1 | 3 (12%) |
| | 2 | 9 (35%) |
| | ≥3 | 18 (69%) |
| Median peak eosinophils (cells/μL) (Range) | | 7515 (1000-28130) |
| Most recent (median) eosinophils (cells/μL) prior to interview (Range) | | 433 (0-4930) |
| Therapy at time of interview | | |
| | Prednisone | 21 (81%) |
| | Hydroxyurea | 3 (12%) |
| | Interferon-alpha | 3 (12%) |
| | Other** | 6 (23%) |
| | Any | 24 (92%) |

*based on physician assessment or chart review, **benralizumab (n=2), rituximab (n=1), dexamipexole (n=1), mycophenolate (n=1), methotrexate (n=1)

Table E2. Frequency of HES signs and symptoms by number of articles reporting.

| | | | |
|-------------------------|----|------------------------|---|
| Angioedema | 12 | Myalgia | 4 |
| Cough | 12 | Thrombocytopenia | 4 |
| Fatigue | 10 | Weakness | 3 |
| Anemia | 9 | Asthma | 3 |
| Urticaria | 9 | Sweats | 3 |
| Dyspnea | 9 | Anorexia | 3 |
| Splenomegaly | 9 | Cognitive changes | 2 |
| Skin lesions | 8 | Erythema | 1 |
| Weight loss | 8 | Papules | 1 |
| Fever | 7 | Heart murmur | 1 |
| Heart failure | 6 | Pleural effusion | 1 |
| Hepatomegaly | 6 | Arthritis | 1 |
| Thrombi | 5 | Wheezing | 1 |
| Diarrhea | 5 | Mitral regurgitation | 1 |
| Abdominal pain | 5 | Myocardial infarction | 1 |
| Endomyocardial fibrosis | 5 | Low exercise tolerance | 1 |
| Nausea/vomiting | 4 | Peripheral neuropathy | 1 |
| Arthralgia | 4 | Hydrothorax | 1 |
| Rash | 4 | Colitis | 1 |
| Chest pain | 4 | Ascites | 1 |
| Malaise | 4 | | |

Table E3. HES symptom checklist used for semi-structured interview.

General Symptoms

- Fatigue/tiredness
- Swelling under the skin (angioedema)
- General feelings of discomfort (malaise)
- Fever
- Weakness
- Lymph node enlargement
- Chills or sweats
- Weight loss
- Weight gain

Skin

- Rashes
- Hives
- Raised bumps (papules)
- Raised flat lesions (plaques)
- Itching
- Tightness of the skin
- Redness of skin
- Hair loss
- Ulcers of the mouth
- Ulcers of the genital area
- Blisters (vesicles)

Pulmonary

- Wheezing
- Shortness of breath
- Cough

Sinus

- Sinus pain
- Stuffy nose
- Sore throat
- Polyps
- Inability to smell

Cardiovascular

- Chest pain
- Swelling in your legs
- Heart palpitations

Neurologic

- Headache
- Dizziness
- Tingling in extremities
- Numbness in your hands or feet
- Loss of motor control of falling
- Weakness in your arms or legs
- Changes in your behavior
- Difficulty concentrating
- Memory problems
- Problems with speech
- Problems with vision

Musculoskeletal

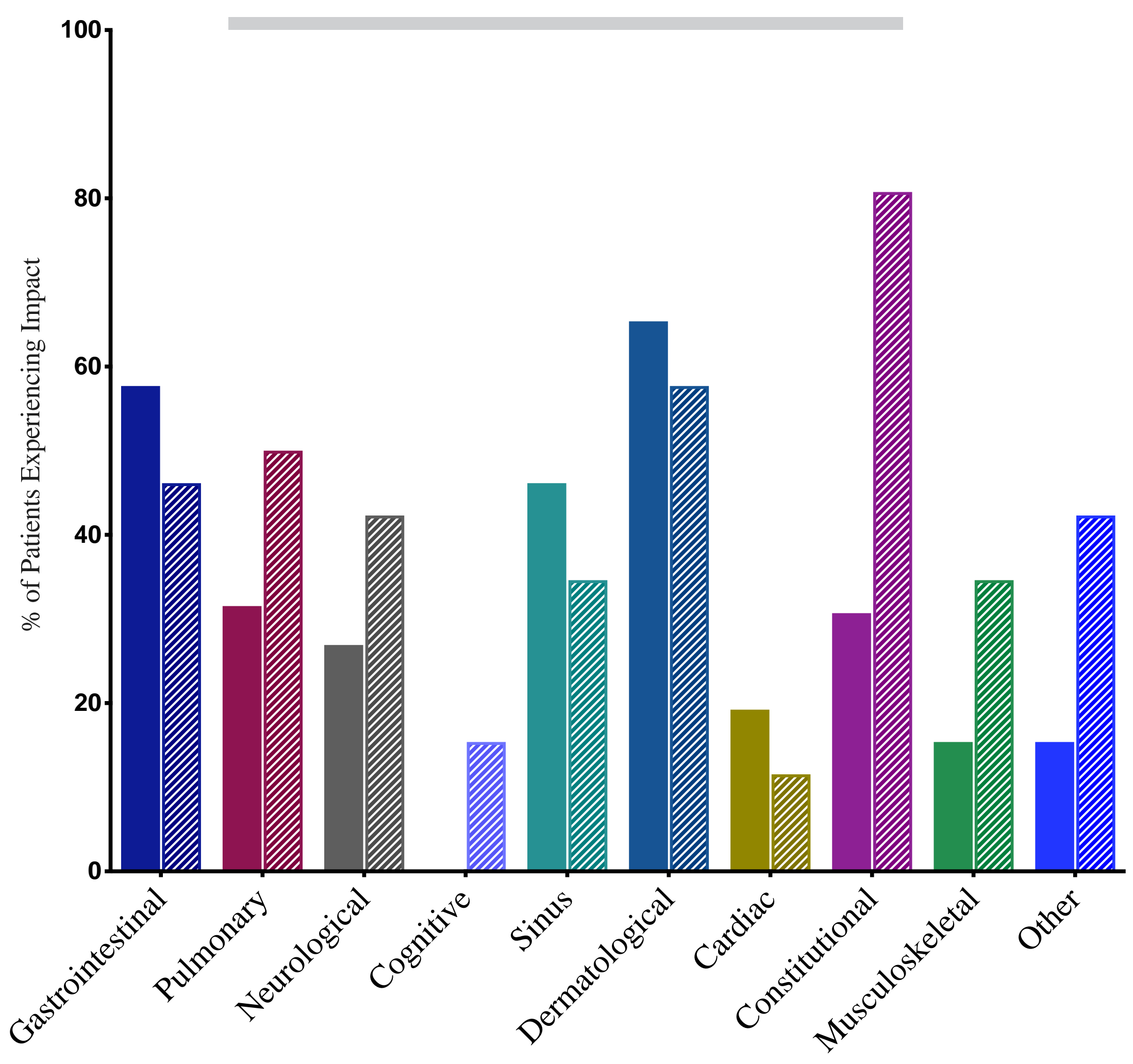
- Muscle spasms
- Muscle pain
- Joint pain
- Joint swelling

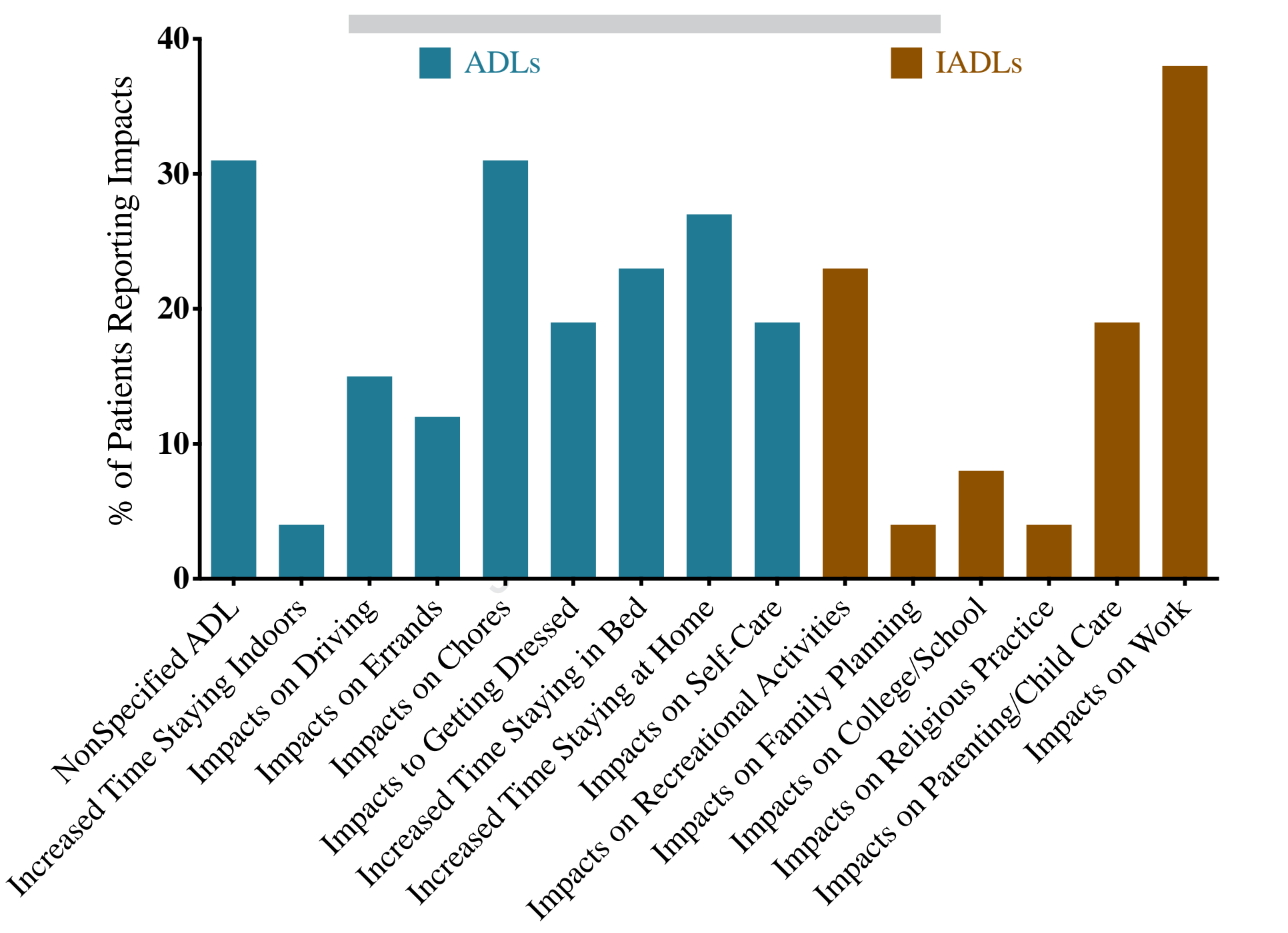
Gastrointestinal

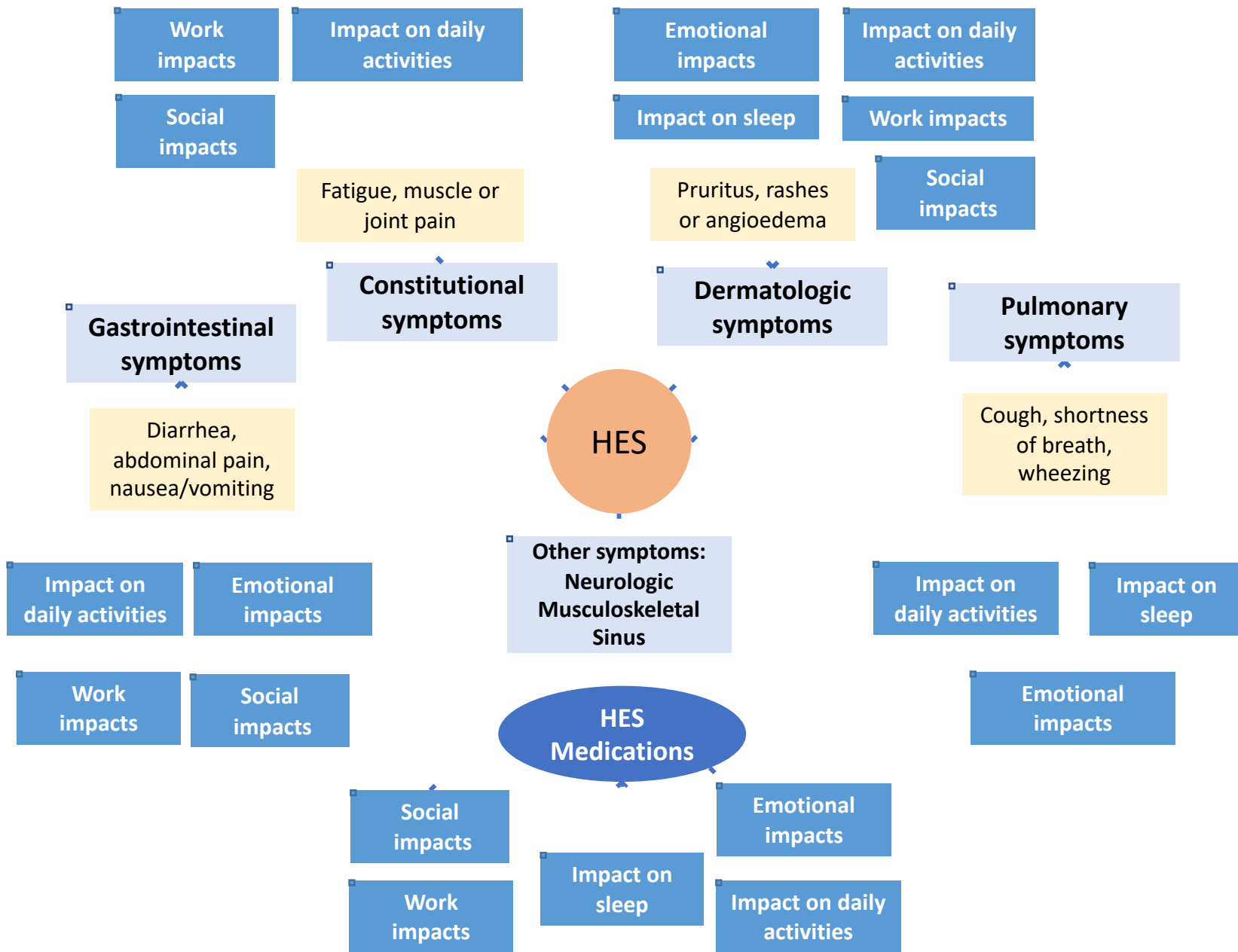
- Nausea
- Vomiting
- Lack of appetite
- Difficulty swallowing or food getting stuck
- Diarrhea
- Pain in your abdomen
- Bloating of the abdomen after food
- Constipation
- Yellow skin
- Gallbladder pain

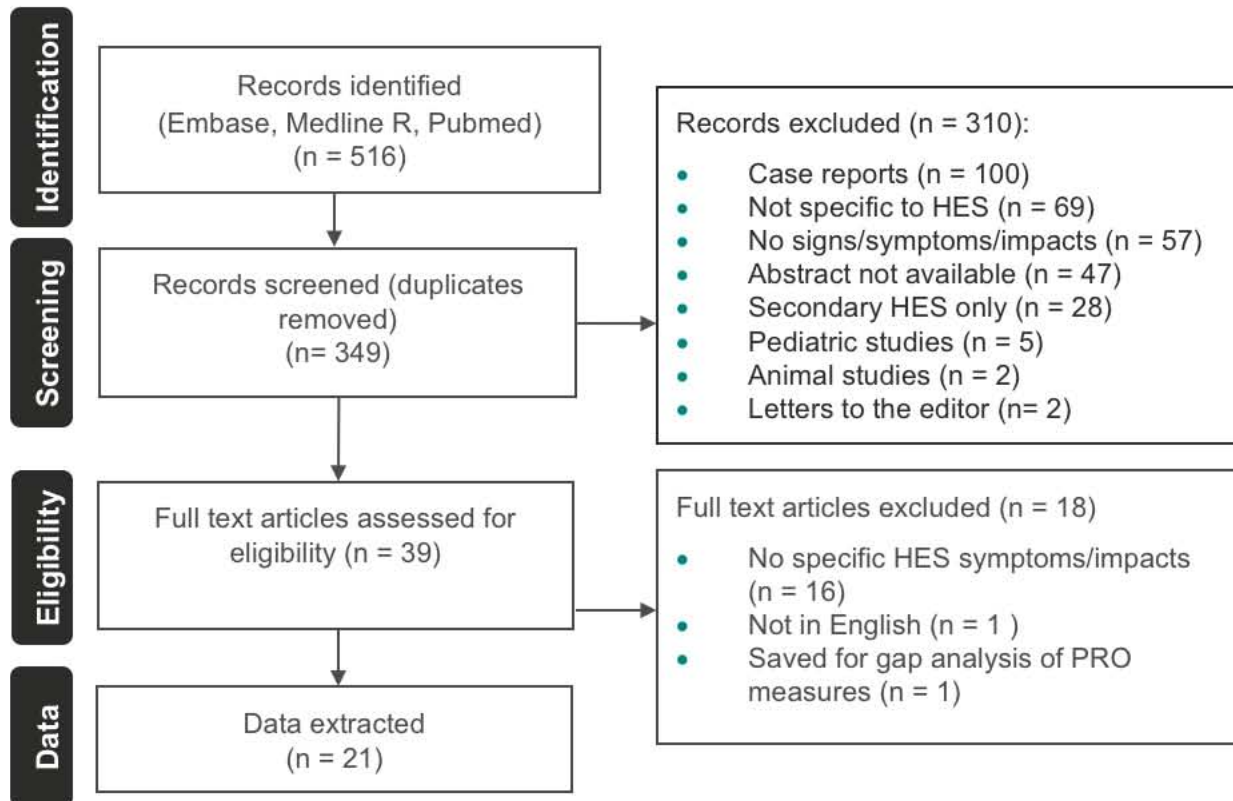
Other

- Eye redness
- Ear pain
- Raynaud's Syndrome









Online Repository Methods

Literature Review

A literature search was conducted using Medline, Embase, and PubMed databases to identify English language publications describing the clinical manifestations of HES (**Figure E4**). Data extracted from 22 articles described a number of symptoms, but none reported disease symptoms and impacts from the patient's perspective. Information from the literature review (**Table E2**), three clinical studies of mepolizumab in HES (NCT00086658; NCT00097370; NCT00244686; **Table E2**), and expert feedback (including from authors PK and AK) were used to create a draft conceptual model of key concepts related to HES disease activity (**Figure E3**).

Patient Selection

Patients were recruited from an IRB-approved study of eosinophilia (NCT00001406). All patients signed informed consent and agreed to audio-recording of the interview prior to being interviewed. Patients 12 years or older, with clinically confirmed HES, defined as an blood absolute eosinophil count (AEC) $\geq 1.5 \times 10^9/L$ with signs and symptoms of organ or tissue involvement attributable to the eosinophilia (1), were identified by retrospective chart review. Inclusion criteria required symptoms of HES starting at least 12 months prior to the interview, a diagnosis of HES for at least 6 months, and at least one disease exacerbation in the prior 12 months requiring a change in HES medication. Patients with mutations in platelet-derived growth factor receptor alpha (*PDGFRA*) or HES secondary to a known treatable cause, such as parasitic infection or malignancy, were excluded. Demographics (age, gender, race, state of residence), HES subtype, organ system involvement, and clinical manifestations were collected to ensure adequate geographic representation across the USA, as well as representation of the

various HES subtypes. The treating clinician completed a form describing the patient's organ system involvement, medications and comorbid conditions prior to the interview.

Interview Process

Concept elicitation interviews were conducted using a semi-structured interview guide to obtain a comprehensive understanding of the symptoms and impacts of HES on the daily lives of patients. Interviews were conducted by phone or in person by a single interviewer (NK) and lasted approximately 60 minutes. A 60-symptom checklist (**Table E3**), based on a draft conceptual model, was reviewed with the patient to ensure that the interview covered key symptoms and impacts. Recorded interviews were transcribed and reviewed for accuracy by the interviewer.

A qualitative analysis of the interview data was performed using a thematic analytic approach (2) by applying codes to the interview transcripts to identify emergent themes and concepts in real-time. Transcribed interviews were analyzed using a qualitative analysis software tool, MAXQDA (VERBI Software, Berlin, Germany) and assessed on an ongoing basis for concept saturation, defined as the point when additional interviews no longer yielded new information. Symptom codes most consistent with treatment-related adverse events were removed from the analysis after adjudication by the treating physician.

Subject characteristics

A total of 26 HES patients were interviewed. Demographic and clinical characteristics are presented in Table 1. Half of the patients were female, and most were white (n=19, 73%). The

median age was 54 (range 17-76 years). Based on chart review, 23 patients (88%) had involvement of more than one organ system (median 3, range 1-5). Dermatologic manifestations were most common (n=17, 65%), followed by pulmonary (n=16, 62%) and GI (n=15, 58%) involvement. Other involved organ systems included sinus (n=12, 46%), neurologic (n=7, 27%) and cardiac (n=5, 19%). All HES subtypes were included in the cohort. Peak absolute eosinophil count (AEC), defined as a patient's highest documented AEC, ranged from 1.0 to $28.13 \times 10^9/L$ with a geometric mean (GM) of $10.26 \times 10^9/L$. At the time of the interview, the majority (n=18; 69%) of patients had $AEC < 1.0 \times 10^9/L$ and 24 (92.3%) were on therapy, including prednisone (n=22, 85%; 1-30 mg daily), interferon- γ (n=3), hydroxyurea (n=4). Eight patients (31%) were on more than 1 therapy.

Patient-reported symptoms

Patients reported a wide variety of symptoms (**Figure 1**), and most experienced multiple HES symptoms over the course of their disease (median 12, SD 8.3). However, not all symptoms were present at the time of interview or were equally bothersome. The most commonly reported symptom was fatigue (n=17, 65%), followed by itching (n=13, 50%) and shortness of breath (n=10, 38%) (Figure 1). Shortness of breath was described as “scary,” “disturbing,” “causing suffering,” and resulting in limitations in activities ranging from having a conversation to exercising. Other common symptoms (present in >20% of patients) included abdominal pain, diarrhea, muscle pain, sinus congestion or rhinorrhea, chills or sweats, cough and wheezing. The most bothersome symptoms to patients varied considerably and depended on the organs affected; for example, most patients with dermatological involvement (n=17) reported itching as their most bothersome symptom, whereas those with GI involvement (n=12) more frequently reported

abdominal pain. Physicians noted GI, cardiac, and sinus symptoms more than patients complained of symptoms referable to those organ systems. Conversely, patients often reported pulmonary, constitutional, musculoskeletal and neurologic/cognitive symptoms in the absence of documented objective evidence of eosinophilic organ involvement (**Figure E1**).

Classification of patient-reported symptoms into organ system categories was difficult because many symptoms crossed categories. Constitutional symptoms (symptoms that could not be clearly attributed to a specific organ system, e.g., fatigue) were most commonly reported, followed closely by dermatologic, pulmonary and GI symptoms (**Figure E1**). Sinus (n=9), neurologic (n=8) and musculoskeletal (n=7) symptoms were also described.

Constitutional Symptoms

A variety of constitutional symptoms were reported. These included fatigue (n=17) which was described frequently as a “full body” sensation akin to “having the flu” or being “run over by a truck” accompanied by lack of desire to be active (n=6) or decrease or stopping physical activity (n=6). Four patients described this as the most bothersome symptom of their HES. Other constitutional symptoms included chills and sweats (n=7) and generalized weakness (n=6). In general, constitutional symptoms were experienced almost daily and tended to vary with medication use and disease activity.

Dermatologic Symptoms

Fifteen of the 26 patients described at least one dermatological symptom, with a majority (n=9, 60%) reporting more than one dermatological symptom. There was considerable variation in the

descriptions of specific dermatologic symptoms between patients. The most commonly reported, and impactful symptom in this domain was pruritus, with 50% of patients reporting itching, although the duration and magnitude of pruritus varied among individuals. Descriptions of rashes included “affecting the entire body” or large parts of the body (n=5), “redness” or “splotches and blotches” (n=6), “raised bumps” (n=3), “dry, flaky” appearance (n=4), associated with a “hot” or “burning” sensation (n=3), and complications from scratching (“pain,” “bleeding”, or “scarring”; n=3) were noted. The impacts of dermatological symptoms included sleep difficulties (n=5), psychological or emotional impacts such as embarrassment or feeling depressed (n=4), difficulty in walking or moving (n=3), concentrating (n=2), social or relationship problems (n=3), and limiting clothing choice (n=1).

Pulmonary Symptoms

At least one pulmonary symptom was reported by 13 patients (50%), 10 of whom had clinically-confirmed pulmonary involvement. Pulmonary symptoms included shortness of breath (n=10), coughing (n=8), and wheeze (n=8). Ten patients had more than one symptom. Patients reported pulmonary symptoms to be very bothersome, especially cough and wheeze, and these symptoms had a range of impacts on daily life and emotional function. Patients reported difficulty with physical activity (n=4), increased fatigue or weakness (n=3), sleep disruption (n=4), emotional impacts such as feeling scared or worried (n=4) and reduced ability to do daily household (n=4) or self-care activities (n=2).

Gastrointestinal Symptoms

Twelve patients, all with clinically confirmed GI involvement, reported at least one GI symptom. Abdominal pain (n=8), diarrhea (n=5) and bloating (n=5) were most common, and most patients reported multiple GI symptoms. Daily occurrence of these symptoms was typical. Some patients described daily abdominal pain (n = 5) either when experiencing an episode of symptomatic HES or upon eating. Two patients were hospitalized for abdominal pain. Three of the 5 patients experienced daily diarrhea with one patient reporting “constant” diarrhea over the preceding 3 years. Patients described their GI-related symptoms as very bothersome. Impacts included difficulty in eating, being confined to home or bed, and being unable to work or participate in social activities. Patients described an emotional burden associated with GI symptoms in terms of “annoyance”, “frustration,” and associated feelings of depression and isolation.

Sinus

Nine patients reported sinus or nasal symptoms including congestion (n=7), pain or pressure (n=4) with 3 patients reporting daily symptoms. Symptoms were described as moderately bothersome and impacts included loss of smell (n=3), taste (n=2) or hearing (n=2) as well as emotional, work, or social effects (n=3).

Neurologic

Four patients experienced neuropathy described as “numbness”, “tingling”, or “nerve pain or sensitivity”. Only one patient had persistent symptoms whereas others reported intermittent symptoms and 2 patients reported symptoms as bothersome. Impacts included affecting activity or sleep (n=2), work (n=1), and ability to walk (n=1).

Musculoskeletal

Patients reported symptoms of joint and muscle aches and pains (n=7), with three patients reporting these symptoms as very bothersome and affecting physical (n=3) or sexual activity (n=1), sleep (n=2) and affecting mood (n=2).

Other

A few patients reported symptoms that either crossed domains or were not specifically associated with an organ system. Examples include non-cardiac swelling (n=6) and eye problems such as “redness” or “irritation” that were described as an allergy symptom (n=4).

Effect of HES symptoms on activities of daily living

A total of 19 patients (73%) reported that HES symptoms impacted their activities of daily living (ADLs), including their ability to get out of bed (n=6), perform chores (n=8), leave the house (n=7) or care for themselves (n=5) (**Figure E2**). Ten patients (38%) reported an impact on their Instrumental ADLs (IADLs) including ability to work or having to reduce work hours (n=5) (**Figure E2**). Nine patients had to stop working temporarily or permanently due to their symptoms. HES affected all areas of patient functioning, with >80% of patients reporting an effect on their physical, emotional and social functioning (**Figure 2**). The most common functional impacts were on social activities (n=18, 69%), sleep (n=17, 65%) and walking (n=15, 58%).

Relationship of symptoms to treatment

According to chart review, all 26 patients had received glucocorticoids at some point during their disease course. During the interviews, the majority (n=25) reported being treated with prednisone

(currently or in the past), and of these 21 reported at least one symptom that they attributed to glucocorticoid therapy (e.g., weight gain). Twelve patients reported that they could easily distinguish glucocorticoid-related symptoms from the symptoms of their disease; whereas, 6 found it difficult to differentiate, and 3 did not comment.

Characterization of HES Disease Exacerbations

To better understand how patients identify HES exacerbations, patients were asked about the events that cause them to seek medical attention and/or lead to a change in therapy. No consistent term was used to characterize exacerbation episodes; some patients (n=12) used the term “flare” or “flare-up,” and a handful used the term “episode” (n=4). Several reported that symptom exacerbations occurred only in the setting of a prednisone taper. Some patients reported close monitoring of their blood eosinophil counts by their physician because of prior organ damage, with medication changes being initiated based on laboratory results irrespective of perceived changes in symptoms.

Figure Legends:

Figure E1. Documented organ system involvement as compared to reported symptoms in HES patients. Solid bars- patients with documented symptoms or organ-involvement in the medical record; Hashed bars- patients self-reporting symptoms in a given category.

Figure E2. Patient reported impact of HES on activities of daily living (ADLs) and instrumental ADLs (IADLs).

Figure E3. Draft Conceptual Model of symptoms and the impact of medications in HES.

Figure E4. Literature review of manifestations of HES

Bibliography

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