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# A review of respiratory manifestations and their management in Ehlers-Danlos syndromes and hypermobility spectrum disorders

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## Abstract

**Background:** Ehlers-Danlos Syndromes (EDS) and Hypermobility Spectrum Disorders (HSD) are a heterogeneous group of heritable genetic connective tissue disorders with multiple characteristics including joint hypermobility, tissue fragility, and multiple organ dysfunction. Respiratory manifestations have been described in EDS patients, but have not been systematically characterized. A narrative review was undertaken to describe the respiratory presentations and management strategies of individuals with EDS and HSD. **Methods:** A broad literature search of Medline, Embase, Cochrane Database of Systematic Reviews, and Cochrane CENTRAL was undertaken from inception to November 2020 of all study types, evaluating EDS/ HSD and pulmonary conditions. This narrative review was limited to adult patients and publications in English. **Results:** Respiratory manifestations have generally been described in hypermobile EDS (hEDS), classical and vascular EDS subtypes. Depending on EDS subtype, they may include but are not limited to dyspnea, dysphonia, asthma, sleep apnea, and reduced respiratory muscle function, with hemothorax and pneumothorax often observed with vascular EDS. Respiratory manifestations in HSD have been less frequently characterized in the literature, but exertional dyspnea is the more common symptom described. Respiratory symptoms in EDS can have an adverse impact on quality of life. The respiratory management of EDS patients has followed standard approaches with thoracotomy tubes and pleurodesis for pleural

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manifestations, vocal cord strengthening exercises, continuous positive pressure support for sleep apnea, and exercise training. Reduced respiratory muscle function in hEDS patients responds to inspiratory muscle training. **Conclusion:** Respiratory symptoms and manifestations are described in EDS and HSD, and have generally been managed using conservative non-surgical strategies. Research into the prevalence, incidence and specific respiratory management strategies in EDS and HSD is needed to mitigate some of the associated morbidity.

**Keywords**
Ehlers-Danlos syndrome, respiratory health, dyspnea

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## Introduction

Ehlers-Danlos Syndromes (EDS) encompasses a group of clinically variable disorders of connective tissue. EDS is often characterized by joint hypermobility, abnormal skin texture, and connective tissue fragility. Clinical manifestations vary depending on the subtype of EDS and underlying heritable genetic variation, ranging from subclinical to life-threatening disease.[1] The abnormal collagen synthesis can influence every organ system, with common manifestations including autonomic dysregulation, vascular system and respiratory involvement, joint dislocations, chronic pain, and gastrointestinal disorders.[2]

The nomenclature for EDS has undergone multiple revisions, which is important to highlight given variable overlapping symptoms across the EDS subtypes and evolving literature.[3] In 1999, the Brighton criteria was proposed to diagnose joint hypermobility syndrome (JHS), which includes a constellation of symptoms beyond asymptomatic hypermobile joints such as dizziness, thin skin, digestive problems, and recurrent injuries to account for possible hereditary connective tissue disease related systemic organ manifestations.[4] The International Classification of EDS and related disorders was updated in 2017 to characterize two additional categories including hypermobility spectrum disorder (HSD) and hypermobile EDS (hEDS), based on the recommendations of utilizing Beighton score and connective tissue related systemic manifestations.[5] Updates include hEDS requiring generalized joint hypermobility, systemic involvement, and family history, but having a more narrow diagnostic criteria than HSD.[1,5] HSD was proposed as a distinct subgroup with heritable joint hypermobility and associated comorbidities, but these individuals do not satisfy the 2017 diagnostic criteria for hEDS or other subtypes of EDS.[5] Presently, the most common subtype of EDS is hEDS comprising 80–90% of EDS cases, followed by classical and vascular EDS (vEDS) with known genetic mutations.[5] Given the evolving EDS nomenclature, the prevalence is dependent on the subtype of disease and estimated at 6–10 per 5000 for JHS and EDS cohorts in Sweden (1987–2016)[6] and Wales (1990–2017), respectively.[3]

Of the EDS subtypes, respiratory involvement has often been reported in hEDS, classical, or vEDS, and can be associated with significant morbidity.[7,8] Depending on EDS subtype, respiratory presentations include dyspnea, hoarseness, pneumothorax, hemothorax and associated conditions such as sleep apnea, asthma and emphysema, Table 1. The main respiratory symptom described in HSD has been exterional dyspnea, which is felt to be multifactorial from altered chest proprioception and autonomic dysfunction.[9,10]

Despite the heterogeneity in respiratory symptoms, there have been no reviews on respiratory sequelae within EDS and HSD and the prevalence of manifestations have not been well characterized. Thus, the aim of this narrative review is to provide a synthesis of respiratory presentations and complications within EDS/HSD patients based on a systematic search of the relevant literature. Specifically, we sought to: 1) outline the presentation of common respiratory manifestations such as pneumothorax or hemothorax, respiratory muscle weakness, upper airway symptoms, and sleep apnea; 2) highlight the management of respiratory manifestations in EDS/ HSD patients.

The search was conducted using the following databases: Ovid Medline, Ovid Embase, Cochrane Database of Systematic Reviews (Ovid), and Cochrane Central Register of Control Trials (Ovid).

**Table 1.** Respiratory manifestations based on selected EDS subtypes and HSD.

| EDS Type | Genetic Mutation | Characteristics | Respiratory Presentations, Radiologic and Pathologic Findings | | Prevalence |
|---|---|---|---|---|---|
| **Classical EDS**[7,9,10] | **Major**: COL5A1 (Type V) collagen<br>**Rare**: COL1A1 (Type I collagen) | • Skin hyperextensibility<br>• Soft, doughy skin<br>• Skin fragility<br>• Atrophic scarring<br>• Joint hypermobility<br>• Easy bruising<br>• Molluscoid pseudotumors<br>• Subcutaneous spheroids<br>• Hernia | • Cough<br>• Sputum<br>• Dyspnea<br>• Nocturnal cough or wheeze<br>• Asthmatic symptoms<br>• Bronchitis<br>• Increased lung volumes<br>• Impaired gas transfer | • Pneumonia<br>• Sinusitis<br>• Pleurisy<br>• Hemoptysis<br>• Asthma<br>• Increased tendency to airways collapse<br>• Increased lung compliance | 1/20,000 |
| **Vascular EDS (vEDS)**[7,11–13] | **Major**: COL3A1 (Type 3 Collagen)<br>**Rare**: COL1A1 (Type 1 Collagen) | • Thin translucent skin<br>• Arterial/intestinal/uterine fragility or rupture<br>• Extensive bruising<br>• Facial features (thin vermilion of the lips, small earlobes, prominent eyes)<br>• Aged appearance to the extremities | • Pneumothorax and hemothorax<br>• Emphysematous and bullous lung disease<br>• Hemoptysis<br>• Pulmonary hypertension<br>• Cough<br>• Chest pain | • Diffuse hemorrhage<br>• Hemosiderosis<br>• Fibrosis with calcification organizing hematoma<br>• Cavities, nodules<br>• Pleurisy<br>• Pneumonia<br>• Dyspnea | Between 1/50,000 to 1/250,000 |
| **Hypermobile EDS (hEDS)**[3,7,14,15] | Unknown | • Hyperextensible and/or smooth, velvety skin<br>• Generalized Joint Hypermobility<br>• Musculoskeletal pain<br>• Dislocations | • Reduced inspiratory muscle strength<br>• Dysphonia, hoarseness, weak voice, throat pain, laryngospasm episodes, subglottic stenosis | • Dyspnea<br>• Breathing difficulties<br>• Chest wall deformities<br>• Airway collapse<br>• Restrictive/obstructive patterns | Estimates between 1:5,000 and 1:20,000 |
| **Hypermobility Spectrum Disorder (HSD)**[3,9,16–18] | Unknown | • Dislocation/subluxations<br>• Pain same as hEDS<br>• Disrupted proprioception<br>• Degenerative joint and bone disease<br>• Muscle weakness | • Cough/sputum<br>• Dyspnea<br>• Nocturnal cough or wheeze<br>• Asthmatic symptoms<br>• Bronchitis | • Impaired gas transfer<br>• Increased lung compliance<br>• Increased tendency to airways collapse<br>• Increased lung volumes | Estimate: 1 in 500 |

A research librarian (A.O-C) performed the search using the following key terms: Ehlers-Danlos Syndrome, hypermobility syndrome, hypermobility spectrum disorders, and respiratory tract diseases or respiratory muscles. Searches were executed on March 25, 2020 and updated on November 4, 2020. The references were limited to articles in English with no date limits imposed. The current review identified literature mainly in the form of case series or reports, several cohort studies, and one randomized controlled trial (RCT). Given the change in nomenclature over the years for JHS, EDS-hypermobility, and in March 2017 to hEDS and HSD, these are highlighted in the review when describing respiratory manifestations.

## Respiratory symptoms in EDS and HSD

### *Dyspnea*

Dyspnea is common amongst patients with EDS. In a case series of 20 EDS patients (16 classical/classical-like EDS and 4 vEDS), the investigators observed that patients reported mild to moderate dyspnea, with 70% describing Medical Research Council grade 1 dyspnea, approximately 25% reporting grade 2 or 3 dyspnea, and 5% having variable dyspnea severity attributed to asthma.[7] In 162 EDS patients (unspecified subtypes), there was a greater burden of dyspnea as measured by the St. George's Respiratory Questionnaire (SGRQ) compared to age and sex-matched healthy participants. Compared to healthy controls, there was a six-fold increase in reported dyspnea with walking on a flat level in those with EDS and three-fold in those with HSD.[11] The application of patient-reported instruments for assessment of respiratory symptoms is described in Table 2.

### *Other respiratory symptoms*

EDS and HSD patients often report a higher respiratory symptom burden such as cough, sputum production, and wheeze resembling asthma symptoms (Table 1). In a 2007 cohort study of 162 EDS patients (unspecified subtypes) compared to 221 age and sex-matched healthy controls, EDS participants had a two-fold incidence of cough, 2.5-fold greater production of sputum, and about a three-fold prevalence of increased, intermittent nocturnal cough or wheeze based on the SGRQ.[11] Similarly, cough, sputum production and wheezing were less frequent among those with JHS ($n = 126$) compared to EDS patients, but more pronounced than controls. It is important to highlight that even though EDS patients had symptoms that were three times more likely to be suggestive of chronic bronchitis (cough, sputum production or wheeze), the actual prevalence of chronic bronchitis (cough for $\geq 3$ months most days of the week for 2 consecutive years)[17] was seen only in two individuals.

Cough is multifactorial in EDS. A common contributor to cough in EDS patients is gastroesophageal reflux disease (GERD), which was observed in 69% of patients based on self-report.[18] Given the high prevalence of GERD in those with EDS, it is important to manage GERD in order to minimize risk of aspiration, reduce chronic cough, hoarseness or chest congestion.[19] As in the general population, the other contributor to cough that needs to be considered is post-nasal drip.[20] The management of respiratory symptoms and manifestations in EDS and HSD are described in Table 3.

## Respiratory manifestations

Respiratory manifestations in EDS and HSD can be categorized as involving the upper and lower airways, parenchymal involvement including pneumothorax and hemothorax, and extra-parenchymal manifestations.

### *Asthma*

EDS and HSD are associated with an increased prevalence of atopic diseases, mainly asthma. Based on symptoms and variable airflow obstruction, asthma was observed in 23% of 43 EDS patients (mainly classical EDS) and 37% of 51 JHS patients compared to 14% of controls.[11] Furthermore, the investigators observed that serum immunoglobulin E levels were increased above the upper limit of normal in about a quarter of participants in the EDS group and one-fifth in the JHS group highlighting the atopic nature in these conditions. It has been proposed that asthma, which is a polygenic disease, may have overlapping genes with EDS, with the phenotype modified by genetic and environmental factors.[11]

Standard asthma management should be considered in EDS or HSD patients, including review of symptoms, triggers (i.e. smoking, allergen exposure, etc.), evaluation of comorbidities (i.e. obesity, GERD, etc.), and pharmacotherapy using low dose inhaled corticosteroid and bronchodilators.[35] Morgan et al. observed that EDS and HSD patients with asthma responded to conventional pharmacotherapy suggesting their asthma management could parallel that of the general population.[11] Aerobic physical activity

**Table 2.** Patient-reported respiratory outcome tools used in studies of patients diagnosed with EDS and HSD.

| Tools | Domains | Population | Items/scoring | Minimally importance difference | Recall |
|---|---|---|---|---|---|
| Medical Research Council (MRC) Dyspnoea Scale[20] | Dyspnea | EDS[7] | 5 items. Spectrum of respiratory disability from none (Grade 1) to almost complete incapacity (Grade 5). | Change 1 unit | Everyday activities |
| Borg Rating of Perceived Exertion Scale[21] | Physical Activity Intensity Level | EDS/HSD[22,23] | 15-point scale (minimum 6 – maximum 20) from "not at all" to "very, very hard" exhausted Some studies use modified 10-Borg Dyspnea Scale | Change of 1–2 units in patients undergoing pulmonary rehabilitation or exercise intervention[24] | Current |
| St George's Respiratory Questionnaire[25] | Chronic Airflow Limitation Symptoms, activity impacts | EDS/ HSD[9] | 50 items. Scores span from 0 to 100, with higher scores indicating more limitations. | A mean change score of 4 units is associated with slightly efficacious treatment, 8 units for moderately efficacious change and 12 units for very efficacious treatment in patients with asthma[26] | 3–12 months recall |
| Subjective health complaints inventory (SHC-I)[27] | Somatic and mental health complaints 5 subscales, including: Allergic complaints (asthma, allergies, breathing difficulties, chest pain, and eczema) Colds subscale (colds, flu, coughs, and bronchitis) | EDS[28] | The self-rated levels of affect are graded on a four-point Likert scale: 0 = not bothered, 1 = slightly bothered, 2 = partly bothered, and 3 = severely bothered. The 29 individual complaints are commonly reported on a total score (SHC-total), but can also be grouped into five subscales | | Past 30 days |
| Epworth Sleepiness Scale[20] | Subjective degree of daytime sleepiness | EDS[30,31] | 8 Items. Self-administered questionnaire where respondents rate chance of dozing off on a 4-point scale (0–3). Higher scores indicate more sleepiness (minimum 0 to maximum 24). | Change of 2 to 3 units.[32] | Everyday sleep patterns |

**Table 3.** Management of Common Respiratory Manifestations in EDS and HSD.

| Respiratory manifestations | Management strategies |
|---|---|
| Dyspnea | • Physical activity and exercise, compression vests and garments, and management of dysautonomia |
| Cough | • Management of rhinitis, MCAS, and gastroesophageal reflux disease[18,20] |
| Pneumothorax | • Intrapleural drain, needle aspiration, pleural rubbing, chemical pleurodesis, total pleural covering techniques, and bullectomy[13,21–23] |
| Hemothorax | • Pleural drainage and vascular embolization[25]<br>• Celiprolol to reduce vascular stress in vEDS[26]<br>• Lifestyle changes to minimize risk of trauma, individualized emergency plans, centralized management, and blood pressure control Tranexamic acid (for recurrent hemoptysis)[44]<br>• Annual monitoring of the vascular tree utilizing ultrasound, CT-arteriography and nuclear magnetic resonance[27] |
| Tissue Fragility and Risk | • Avoid use of fluoroquinolones, bronchoscopy, arterial blood gases, and careful discussion regarding surgery |
| Chest Wall Abnormalities | • Physiotherapy, compression vests/garments to improve postural stability |
| Respiratory Muscle Weakness | • Inspiratory muscle training[15] |
| Diaphragmatic Rupture | • Surgical correction of diaphragmatic rupture/reduction of herniation of abdominal contents[28,29]<br>• Aggressive management: oxygenation, ventilation, and fluid resuscitation[30] |
| Lung Herniation | • Thoracic surgical repair of herniation zone[31] |
| Asthma | • Review of symptoms, risk factors and triggers (i.e. smoking, allergens, etc.)<br>• Evaluation of comorbidities (i.e. obesity, GERD, OSA, MCAS, etc.)<br>• Physical activity<br>• Action Plan |
| Mast Cell Activation Syndrome (MCAS) | • Identify potential symptom triggers (i.e. dietary, chemicals, allergens)[32]<br>• Identify other triggers: alcohol, heat, radiocontrast dye, physical stimuli, exercise, and emotional stress<br>• Desensitization therapy and pharmacological therapy (i.e., H1 and H2 antihistamines, sodium cromoglycate, ketotifen, omalizumab and leukotriene receptor blockers) |
| Dysphonia | • Speech therapy[9]<br>• Exercises to strengthen vocal cords |
| Tracheal Stenosis | • Surgical correction[33]<br>• Mechanical dilation[34] |
| Obstructive Sleep Apnea | • Continuous Positive Airway Pressure |
| Hematoma<br>Cavitary Lesions<br>Fibrous Nodules | • Conservative approach with observation |

has also been shown to be beneficial in improving asthma symptoms.[36]

In a subset of EDS patients, asthma may be associated with mast cell activation syndrome (MCAS), but prevalence remains unclear.[32,37] MCAS is characterized by altered mast cell function and release of cell mediators in multiple organ systems.[32] It is important to identify potential symptom triggers (i.e. dietary, chemicals, medications) and environmental modifications undertaken to reduce exposure.[38] Further management strategies can include desensitization and pharmacological therapy such as $H_1$ and $H_2$ antihistamines, sodium cromoglycate, omalizumab and leukotriene receptor antagonists, but therapeutic response can be variable in MCAS.[37]

## *Upper airway manifestations*

Dysphonia is a debilitating manifestation which has been described to be prevalent in EDS.[14] In a case series of 21 hEDS patients, chronic or recurrent dysphonia was present in 8 (38%) patients. Fibroscopy

studies in these 21 hEDS participants demonstrated discoordination or hypotonia of the vocal cords.[14] Furthermore, in a retrospective case series of 9 EDS patients (6 hEDS, 3 classical), patients were found to have painless dysphonia, fluctuating hoarseness, weak voice, dysphagia, recurrent episodes of laryngospasm, and subglottic stenosis.[39] Dysphonia within EDS patients may be partly attributed to laxity, hypotonia, discoordination or decreased movement of the vocal cords, as well as reduced mobility of the cricoarytenoid joint.[14,39,40] In EDS patients with dysphonia, prognosis with the use of speech therapy has shown to improve vocal cord performance using both self- and observer-rated evaluations.[19]

Upper airway collapse and obstruction has been observed in EDS and HSD patients. In a prospective cohort study using a forced expiratory volume in 1 second (FEV1)/Peak Expiratory Flow Rate ratio of 10 or more as a marker of airway collapse, 15% EDS and 20% JHS participants (27 EDS, 30 JHS) met the criteria for upper airway collapse.[11] Possible contributors to airway collapse in the non-asthmatic EDS population may include changes in the airway and in the mechanical properties of the lung parenchyma predisposing to increased distensibility and increased propensity of airways to collapse. Upper airway obstruction can also occur due to hypermobility and displacement of the larynx.[41] Overall, upper airway obstruction can be quite heterogeneous, but the literature describing these presentations remains limited.

Tracheal stenosis has also been observed in individuals with EDS.[33,34] The presentation of an EDS patient with hoarseness may signify an underlying subglottic tracheal stenosis or crico-arytenoid fibrosis necessitating surgical correction.[33] Other management strategies include mechanical dilation, as performed for subglottic tracheal stenosis under general anesthetic with significant improvement in symptoms and pulmonary function.[34]

### *Sleep apnea*

Sleep apnea is increasingly recognized as an underlying comorbidity amongst patients with EDS.[16,42,43] EDS-associated cartilage deficits and increased pharyngeal collapsibility as a consequence of tissue flaccidity have been proposed as risk factors for increased prevalence of obstructive sleep apnea (OSA).[42] A prospective parallel-cohort study of 100 EDS patients matched for age, sex, and body habitus observed that 32% of individuals with EDS patients had OSA (apnea/hypopnea index of $\geq$ 5/h), of which 23% were symptomatic with excessive daytime sleepiness compared to 3% in the control group.[42] OSA in individuals with EDS was associated with higher median excessive daytime sleepiness based on the Epworth Sleepiness Scale Scores and impaired health-related quality of life (HRQL) in all dimensions of the Short-Form 36 compared to non-OSA EDS patients. Furthermore, they observed that OSA severity was associated with increased daytime sleepiness and lower HRQL in EDS participants.

As in the general population, obesity, male sex, and older age are several predictors of OSA among EDS patients.[44] Diagnosis of sleep apnea is best performed with an in-laboratory polysomnogram which allows for assessment of both sleep apnea and sleep-related hypoventilation, which can be a consequence of severe muscle hypotonia described in a few EDS subtypes.[45] Further studies are needed to assess the effectiveness of various therapies for OSA in EDS patients and their safety profile. Although rare, pneumothorax development has been described in case reports with the application of continuous positive airway pressure in EDS and non-EDS patients, which may be attributed to other contributing factors such as diaphragmatic herniation or previous thoracic surgery.[46,47]

## Parenchymal lung involvement

Pneumothorax and hemothorax are common manifestations in vEDS patients. However, other parenchymal involvement in EDS has been observed infrequently and can manifest as emphysematous or bullous changes, fibro-cavitary nodules or hematomas.

### *Hemoptysis, pneumothorax and hemothorax*

Hemoptysis, pneumothorax, and hemothorax are common respiratory complications and are often the initial manifestations in vEDS,[48,49] but not reported in hEDS or HSD. In a case series of 20 vEDS patients, one-quarter had at least one episode of hemoptysis in the absence of any anti-coagulation or coagulopathies.[7] In a multicenter retrospective case series of 96 vEDS patients, the prevalence of pneumothorax or hemothorax was observed to be 18%.[50] The mean age for the first presentation of pneumothorax or hemothorax in vEDS was 30 years old. Pneumothorax or hemothorax preceded the diagnosis of vEDS in the majority of cases (81%) and typically occurred 5 years earlier compared to onset of intestinal

complications, such as perforations, arterial aneurysms or dissections.

The pathophysiology of tissue fragility leading to pneumothorax or hemothorax is mainly a consequence of collagen protein deficiencies and abnormalities, with type I and type III comprising the major collagen proteins in the lungs. Biochemical analysis of lung tissue post-bullectomy in a vEDS patient compared to control lung fibroblasts found lower collagen III levels and less production of type III procollagen relative to type I fibroblasts.[51] These lower levels of type III collagen in the lungs are hypothesized to predispose to increased tissue fragility and risk of pneumothorax.[52] Blood vessel fragility can result in rupture of large arteries and aneurysms, commonly observed in vEDS, which can result in hemothorax or hemoptysis.[12,21]

For pneumothorax management, intrapleural drain, needle aspiration, chemical pleurodesis, total pleural covering techniques, and bullectomy have been utilized in EDS.[13,21–23] Management is often dictated by patient presentation and risk of recurrence. Bullectomy is traditionally performed in patients with large bulla which occupy more than half of the thoracic cavity and have preserved adjacent lung parenchyma.[53,54] In those with recurrent pneumothoraces with bullae, in addition to bullectomy, pleural rubbing and chemical pleurodesis have been utilized with good effect if performed electively, with no further recurrence of pneumothoraces.[13,21–23] In emergency settings, bullectomy should be reserved for those presenting with massive pneumothorax or non-resolving hemoptysis, as the risk of post-operative hemorrhagic complications in vEDS patients is substantially high.[53] Tranexamic acid has been used in vEDS patients presenting with recurrent hemoptysis.[24]

A hemothorax is often a consequence of a spontaneous thoracic artery rupture and can result in significant morbidity and mortality from blood loss.[8,49,55] Pleural drainage and vascular embolization have been undertaken for management of large hemothorax secondary to ruptured arterial aneurysms.[25] In terms of medical management, celiprolol, a β(1)-adrenoceptor antagonist with β(2)-adrenoceptor agonist action, has been shown to prevent major complications in vEDS such as systemic arterial ruptures or dissections in a RCT.[26] The mechanism of action is thought to be a result of increased vasodilation and production of type III collagen, reducing the risk of large arterial ruptures.[56,57] Additional management strategies include lifestyle changes to minimize risk of trauma, maintain good blood pressure control, and development of an individualized emergency treatment plan. Annual monitoring of the vascular tree utilizing ultrasound, CT-arteriography and nuclear magnetic resonance should be considered.[27]

### *Emphysema and bullous disease*

Emphysematous changes (centrilobular, paraseptal, and paracicatricial) and blebs have been described predominantly in vEDS patients.[7,58,59] The pathophysiology of emphysema may be attributed to the fragility of the alveolar wall, which contains type III collagen deficiency, contributing to emphysema and bleb formation.[53]

### *Hematoma, cavitary lesions, and fibrous nodules*

Hematomas, parenchymal cysts, cavitary lesions, and fibrous lung nodules have been described mainly in vEDS patients. In a small case series of nine vEDS patients, Kawabata et al. reported fibrous nodules occurring due to both pleural and other non-alveolar tissue pathology.[58] Pathological evaluation of pulmonary hematomas were seen with no lung tissue in the hematoma, only surrounded by compressed lung parenchyma. It was suspected that these hematomas may show organization, evacuation and extension of fibrosis into the hematoma, leading to shrinkage, cavity formation, and development of fibrous nodules.[12]

## Extra-parenchymal manifestations

Several extra-parenchymal manifestations have been observed in EDS including chest wall abnormalities,[7,60] respiratory muscle weakness,[15] and diaphragmatic herniation,[30,61] and can contribute to respiratory symptoms in EDS patients.

### *Chest wall*

Chest wall abnormalities such as pectus excavatum, straight back syndrome, and thin ribs have been characterized in individuals with EDS.[60] Among 20 EDS patients (16 classical and 4 vEDS), 6 patients were found to have mild pectus excavatum, three had very thin ribs with increased downward slope, four had mild scoliosis, and three had straight back syndrome (characterized by abnormal thoracic kyphosis and extra-parenchymal restriction).[7,60] Other thoracic manifestations include scoliosis, which can result in decreased chest wall compliance, hypoventilation, progressive atelectasis and air trapping, and

associated with respiratory muscle weakness and chronic respiratory failure.[62]

### Respiratory muscle weakness

Respiratory muscle weakness has been investigated mainly in hEDS patients, and may be a factor predisposing to dyspnea. Reychler et al. observed inspiratory muscle strength was reduced in patients with hEDS measured with sniff nasal inspiratory pressures (SNIP: 65 $\pm$ 30% predicted) with a tendency for greater resting lung volumes (TLC 109 $\pm$ 12.2%).[15] These increased lung volumes could be secondary to defects in neuromuscular extracellular matrix or from hypermobility of thoracic joints. Similarly, respiratory muscle weakness is thought to occur in hEDS patients in part due to structural changes in connective tissue surrounding respiratory muscles, which has important consequences on the extra-cellular matrix and possibly increased compliance of muscle-tendons surrounding these muscles.[15]

Inspiratory muscle training (IMT) has been shown to be effective in improving respiratory muscle strength and exercise capacity in hEDS patients. IMT resulted in improved inspiratory muscle strength (SNIP: 13 $\pm$ 8 vs. $-3$ $\pm$ 5 cm $H_2O$, $p < 0.001$), lung function (FEV1%: 8.5 $\pm$ 6.9 vs. $-2.8$ $\pm$ 7.7%, $p = 0.009$), and 6-minute walk distance (65 $\pm$ 69 vs. 8 $\pm$ 17 meters, $p = 0.003$) after 6 weeks of training in a RCT compared to standard of care (no IMT).[15] Even though this was a small RCT that enrolled 20 hEDS participants, it showed promising benefits of IMT in improving muscle strength and exercise capacity. Some important limitations to highlight were that the IMT was unsupervised, maximal inspiratory pressures were not reported, and other forms of concurrent exercise training were not undertaken. Thus, further study is needed to assess whether IMT combined with whole-body exercise training may result in improvements in dyspnea, lung function and exercise capacity beyond hEDS patients, as shown in other respiratory states such as asthma[63] and chronic obstructive pulmonary disease.[64]

### Diaphragmatic rupture and apical herniation

Spontaneous diaphragmatic rupture is a rare surgical emergency and has been described in a few EDS case reports.[28,30] Diaphragmatic rupture potentially occurs due to the weakness and laxity observed in EDS patients.[30] Two separate case reports (hEDS and unspecified subtype) have reported spontanenous diaphragmatic rupture, which can be attributed to pre-existing muscle weakness exacerbated by an increase in intraabdominal coughing in one case[28] and due to prolonged emesis in the second case.[30] Thus, repeated increases in intra-abdominal pressure (i.e. cough, emesis) may increase the risk for diaphragmatic rupture, but it can also occur without any preceding history of trauma in EDS patients.[61] It is imperative that prompt surgical management for diaphragmatic rupture or herniation is initiated with appropriate oxygenation, ventilation, and fluid resuscitation.[30] Surgical correction of diaphragmatic rupture and reduction of herniation of abdominal contents requires a careful approach in EDS patients due to impairments in collagen, which can effect hemostasis and healing.

In addition to diaphragmatic rupture, lung herniation has been described amongst EDS patients requiring surgical correction.[65,66] In a case report, a 49-year-old male patient with EDS (unspecified type) was observed to have spontaneous swelling at the right base of his neck during coughing, which was a large apical lung hernia diagnosed using a recommend approach of airway fluoroscopy and inspiratory computed tomography.[31] This patient underwent a right thoracotomy to repair his right upper lung zone herniation.

## Management and special considerations

### Respiratory investigations

Following a detailed respiratory history and physical examination, pulmonary function, exercise testing, and imaging should be considered. Pulmonary function has demonstrated variable patterns in EDS patients with most individuals having normal lung function, although both increased or reduced flows and lung volumes have been described. In a cohort of 104 outpatients with hEDS, pulmonary function was normal in the majority with an FEV1: 101.7 $\pm$ 16.4% and total lung capacity (TLC) of 109.0 $\pm$ 12.2% predicted.[15] In a cohort study of 162 EDS patients, 52% and 19% patients had significant gas trapping with residual volume (RV) > 150% and RV/TLC > 120%, respectively.[11] In 20 EDS patients (10 classical, 6 classical-like, and 4 vEDS), no consistent spirometry or lung volume abnormalities were observed with increased diffusion capacity observed in 8 (40%) which may be related to hemorrhage or increased pulmonary blood flow, whereas 2 (10%) had a low diffusion capacity.[7] This contrasts with the study by Morgan et al. that found impaired diffusion capacity in over half of the 57 EDS/JHS patients.[11] Pulmonary function abnormalities could be

secondary to increased laxity of connective tissue support, greater compliance of small airways, gas trapping and emphysematous changes that could result in impaired gas transfer.

Chest X-ray and non-contrast computed tomography can be beneficial in identifying parenchymal changes such as emphysematous changes, fibrocavitary nodules, hematomas, and prior pleural involvement.[7,12,58] Echocardiogram may be helpful to rule out any aortic root dilatation, ventricular or valvular dysfunction.[67,68] Six-minute walk and cardiopulmonary exercise testing may help characterize exercise tolerance and autonomic dysfunction.[69,70]

Careful consideration, especially in vEDS, should be undertaken before performing bronchoscopy given increased tendency for bleeding and tissue fragility, but may be useful to document vocal cord function, tracheobronchomalacia and sources of bleeding.[41,53] Furthermore, arterial blood gases are best avoided due to fragile arterial vessel walls.[71]

### *Physiotherapy*

Rehabilitation interventions constitute an essential part of the management of respiratory, musculoskeletal, and functional limitations in the EDS population, and can improve exercise tolerance and physical fitness.[72–74] These programs can restore function and ameliorate symptoms, including improvements in proprioception,[75] strength, and HRQL.

Exercise and rehabilitation professionals are central in providing patient education, coping strategies, and encouraging adherence to exercise. In a 2017 study by Simmons et al,[76] 946 patients with EDS and HSD were asked about their experiences with physiotherapy and beliefs surrounding exercise. Patients who received advice from a physiotherapist were 1.8 times more likely to report higher weekly training volumes compared to those not receiving advice. However, the effects of exercise training on respiratory symptoms have not been well-described, despite the positive effects associated with exercise training on physical function and symptom management.

## Considerations for medical management

### *Use of glucocorticoids*

It is important to avoid prolonged use of oral glucocorticoids for asthma or atopic symptoms given concerns of skin and bone density fragility in EDS. The lowest possible dose of inhaled corticosteroids for asthma management should be utilized, which has been shown to be relatively safe given relative stability of skin and bone collagen synthesis after 1-2 years of use.[77] Thus, the indications for oral and inhaled corticosteroids should be re-evaluated regularly to minimize long-term side effects of corticosteroids in EDS and HSD patients.

### *Avoidance of fluoroquinolones*

Fluoroquinolones are commonly utilized for treatment of community acquired pneumonia, but should be avoided in EDS patients. In 2018, a report by the Federal Drug Agency found that fluoroquinolone use was associated with increased rates of aortic dissections or aneurysms, which can lead to severe hemorrhage or death, especially in vEDS patients.[78] Furthermore, the risk of tendinopathies and tendon ruptures may be increased in EDS patients with fluoroquinolone use. Thus, fluoroquinolones should be avoided in EDS patients unless alternative options are not available.

### *Thoracic surgical interventions*

There have been several case reports describing semi-elective thoracic surgical procedures. The thoracic procedures described include bullectomy and lung transplantation.[54] Surgical options in EDS patients need to be carefully evaluated due to the high risk of post-operative hemorrhagic complications, connective tissue fragility and availability of appropriate expertise, especially in vEDS.[57,79] There have been a few case reports describing surgical bullectomy in the setting of respiratory failure or lung transplantation for emphysema with good functional outcomes 1-year post-transplant.[54,80]

Cardiac dysautonomia is a major feature of EDS and thus requires awareness by the anesthesiology team when planning surgery, as it may dictate strategies on fluid administration and vasopressors intraoperatively.[81] Early mobility in the post-operative period should be reinforced, which can help offset the physical deconditioning that can result from inactivity in the early post-operative period.[82]

## Conclusion

Pulmonary manifestations in EDS may be associated with significant morbidity and mortality. Vascular, classical, and hypermobile subtypes of EDS have

been described contributing to pulmonary manifestations, with fewer reports in the HSD population. A greater clinical awareness of atopy, dyspnea, upper airway symptoms, or critical presentations such as pneumothorax or hemothorax amongst EDS patients by the medical community is important. Further studies exploring respiratory symptoms, daily function, HRQL and therapeutic strategies in EDS and HSD are needed.

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