Vascular Ehlers-Danlos Syndrome
An Overview Part II:
Adult Presentation and management

Sherene Shalhub MD MPH FACS
Associate Professor of Surgery
Division of Vascular Surgery, Department of Surgery
University of Washington School of Medicine
Vascular Ehlers-Danlos Syndrome in Adults
Part I: An Overview

• Pathology and features of vEDS in adults
• Why Accurate Diagnosis of vEDS Matters
• Management principles in vEDS
• Screening for arterial pathology in vEDS

• Aortic and arterial repair will be discussed in a separate webinar
## Diagnostic Criteria for Vascular Ehlers–Danlos Syndromes

<table>
<thead>
<tr>
<th>Major criteria</th>
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<tbody>
<tr>
<td>1. Family history of vEDS with documented causative variant in \textit{COL3A1}</td>
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<td>2. Arterial rupture at a young age</td>
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<td>3. Spontaneous sigmoid colon perforation in the absence of known bowel pathology</td>
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<td>4. Uterine rupture during the third trimester in the absence of risk factors</td>
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<td>5. Carotid-cavernous sinus fistula (CCSF) in the absence of trauma</td>
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<table>
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<th>Minor criteria</th>
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<tr>
<td>1. Bruising unrelated to identified trauma</td>
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<td>2. Thin, translucent skin with increased venous visibility</td>
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<td>3. Characteristic facial appearance</td>
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<td>4. Spontaneous pneumothorax</td>
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<td>5. Acrogeria</td>
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<td>6. Talipes equinovarus</td>
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<td>7. Congenital hip dislocation</td>
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<td>8. Hypermobility of small joints</td>
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<td>9. Tendon and muscle rupture</td>
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<tr>
<td>10. Keratoconus</td>
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<tr>
<td>11. Gingival recession and gingival Fragility</td>
</tr>
<tr>
<td>12. Early onset varicose veins</td>
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*The 2017 International Classification of the Ehlers–Danlos Syndromes*  
*Malfait et al, American Journal of Medical Genetics Part C (Seminars in Medical Genetics) 175C:8–26 (2017)*
COL3A1 encodes procollagen for type III collagen (skin, hollow organs, uterus, arteries)

Pathology:
- Pneumothorax/Hemothorax
- Bowel Perforation
- Aortic/Arterial events
  - Dissection/Aneurysms
  - Ruptures
  - Arteriovenous Fistulae

Control

p.Gly373Arg

Smith LT. J Invest Derm, 1997
Spontaneous Pneumothorax/Hemothorax

occurs when air or blood leaks into the space between the lung and chest wall

Wikiversity Journal of Medicine. DOI:10.15347/wjm/2014.010. ISSN 20018762.)
Pneumothorax occurs at a significantly younger age compared to arterial ruptures in individuals with vEDS.

**RESEARCH ARTICLE**

*Spontaneous pneumothorax and hemothorax frequently precede the arterial and intestinal complications of vascular Ehlers–Danlos syndrome*

Sherene Shalhub, Enid Neptune, Desiree E. Sanchez, Anahita Dua, Nelson Arellano, Nazli B. McDonnell, Dianna M. Milewicz

First published: 22 February 2019 | [https://doi.org/10.1002/ajmg.a.61094](https://doi.org/10.1002/ajmg.a.61094)
Spontaneous Gastrointestinal Perforation

- Abdominal pain
- Tender abdomen
- Pain with walking (Peritoneal signs)

The most frequent site of perforation:
- Colon (sigmoid)
- Small bowel
- Upper rectum
- Stomach

Re-perforation rate considerably higher in the “partial colectomy with anastomosis” group than in the Hartmann group.
Arterial and Aortic Pathology in vEDS

The spectrum, management and clinical outcome of Ehlers-Danlos syndrome type IV: A 30-year experience

Gustavo S. Oderich, MD, Jean M. Panneton, MD, Thomas C. Bower, MD, Noralane M. Lindor, MD, Kenneth J. Cherry, Jr, MD, Audra A. Noel, MD, Manju Kalra, MBBS, Timothy Sullivan, MD, and Peter Gloviczki, MD, Rochester, Minn; and Norfolk, Va

Arterial and Aortic Pathology in vEDS: Aneurysms

Dilatation of the artery to more than 1.5 times the size of the normal.

Usually asymptomatic

Ruptured Aneurysm
Cause internal bleeding. Presents with Sudden onset severe pain
Arterial and Aortic Pathology in vEDS: Dissection

- False Lumen
- Blood in wall of artery
- Blood in True Lumen
- Intimal Flap

Aortic dissection

Type B Aortic dissection

Celiac artery dissection

External iliac artery dissection
Carotid Cavernous Fistula

- Abnormal communication between the carotid artery and cavernous sinus
  - Bulging eye, which may pulsate
  - Red eye
  - Abnormal eye movement
  - Pain

Adham et al, Orphanet Journal of Rare Diseases, 2018
Facial Features

- N=68
- 61% had facial features
  - Prominent eyes
  - Thin lips and philtrum
  - Thin, pinched nose
  - Hollow cheeks
  - Attached ear lobes

Skin: Visible veins
soft velvety skin
Why Accurate Diagnosis of vEDS Matters

1. Overlapping features with other syndromes
Vascular Ehlers-Danlos Syndrome

Marfan Syndrome

Loeys Dietz Syndrome

Shalhub, Genetic considerations in patients with aortic disease

Endovascular Aortic Repair, Oderich ed, 2017
Why Accurate Diagnosis of vEDS Matters

1. Overlapping features with other syndromes
2. Genotype-Phenotype correlation
Single functional copy of a gene

50% of normal type III collagen
Why Accurate Diagnosis of vEDS Matters

1. Overlapping features with other syndromes
2. Genotype-Phenotype correlation
3. Knowing the diagnosis improves outcomes
   - Aggressive risk factor modification:
     - Smoking cessation
     - Exercise recommendations
     - Assessment and treatment for hypertension
   - Tailor operative techniques
A multi-institutional experience in the aortic and arterial pathology in individuals with genetically confirmed Vascular Ehlers Danlos Syndrome

Molecular diagnosis in vascular Ehlers-Danlos syndrome predicts pattern of arterial involvement and outcomes

Sherene Shalhub, MD, MPH, a James H. Black III, MD, b Alana C. Cecchi, MS, c Zhi Xu, PhD, d
Ben F. Griswold, BS, e Hazim J. Safi, MD, f Dianna M. Milewicz, MD, PhD, f and
Nazli B. McDonnell, MD, PhD, f Seattle, Wash; Baltimore, Md; and Houston, Tex

N=68


Arterial pathology in vEDS individuals is related to the underlying COL3A1 mutation type (Haploinsufficiency vs. other subtypes)

Haploinsufficiency: milder phenotype, more aortic pathology

Patients with an established preoperative diagnosis treated in an elective setting have significantly improved outcomes compared with patients who undergo emergency repair and when the diagnosis is not known
Why Accurate Diagnosis of vEDS Matters

1. Overlapping features with other syndromes
2. Knowing the diagnosis improves outcomes
3. Knowing the diagnosis improves outcomes
   • Aggressive risk factor modification:
     • Smoking cessation
     • Exercise recommendations
     • Assessment and treatment for hypertension
   • Tailor operative techniques
4. Multidisciplinary care (Care Team)
Why Accurate Diagnosis of vEDS Matters

1. Overlapping features with other syndromes
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3. Knowing the diagnosis improves outcomes:
   • Aggressive risk factor modification:
     • Smoking cessation
     • Exercise recommendations
     • Assessment and treatment for hypertension
   • Tailor operative techniques
4. Multidisciplinary care (Care Team)
5. Research implications
Effect of celiprolol on prevention of cardiovascular events in vascular Ehlers-Danlos syndrome: a prospective randomised, open, blinded-endpoints trial

*Kim-Thi Thi Ong, Jérôme Perdu, Julie De Baecker, Erwan Bozec, Patrick Collignon, Joseph Emmerich, Anne-Laure Fauret, Jean-Noël Fiesinger, Dominique Perarnau, Gabrielle Georgesco, Jean-Sebastien Huot, Anne Delafosse, Henri Plouchna, Xavier Jeunemaitre, Stéphane Lavaut, Pierre Boitouyrie*

87 eligible individuals

- 18 previously treated with β blockers included in follow-up cohort
- 16 excluded (12 refused to participate, 4 unable to move)

53 randomised
- 33 mutated
- 18 not mutated
- 2 unidentified

25 allocated to 100 mg celiprolol, titrated to 200 mg, 300 mg, and 400 mg twice a day
- 13 mutated
- 11 not mutated
- 1 unidentified

28 allocated to no β blockers (control group)
- 20 mutated
- 7 not mutated
- 1 unidentified

0 lost to follow-up, 1 death

Celiprolol BID to a maximum of 400 mg per day

- Male, 31 Control: Death or iliac artery rupture within 4 months of enrollment. Underwent open abdominal aortic repair then died from type A dissection
- Male, 28 Control: Hypogastric artery rupture
- Female, 51 Control: Spontaneous cerebral hematoma
- Female, 38 Control: Spontaneous hematoma of psoas muscle with blood suffusion
- Male, 25 Control: Carotid dissection
- Male, 28 Control: Death or aortic dissection
- Female, 24 Control: Carotid dissection
- Female, 34 Control: Carotid-cavernous sinus fistula
- Female, 31 Control: Carotid-cavernous sinus fistula
- Female, 42 Control: Primitive iliac artery dissection
- Male, 45 Control: Sudden death after acute lumbar pain
- Male, 19 Celiprolol: Sudden death after acute chest pain radiating to the right arm
- Male, 19 Celiprolol: Hemoptysis (recurrent)
# Effect of celiprolol on prevention of cardiovascular events in vascular Ehlers-Danlos syndrome: a prospective randomised, open, blinded-endpoints trial

*Lancet, 2010*

Kim-Thi Thang Ong, Jérôme Perdu, Julie De Backer, Erwan Bozec, Patrick Collignon, Joseph Emmerich, Anne-Laure Fauret, Jean-Noël Fiesinger, Dominique P Germain, Gabriella Georgecco, Jean-Sebastien Huot, Anne DePape, Henri Plauchu, Xavier Jeunemaître, Stéphane Laurent, Pierre Boutouyrie

- **87 individuals screened (2003-2006)**
- **53 randomized (33 with confirmed mutation)**
- **Celiprolol group**
  - 13 with confirmed mutation
  - 1 death (8%)
- **Control group**
  - 20 with confirmed mutation
  - 3 deaths (15%)

| Male, 31 | Control | Death or iliac artery rupture within 4 months of enrollment. Underwent open abdominal aortic repair then died from type A dissection |
| Male, 28 | Control | Hypogastric artery rupture |
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| Female, 42 | Control | Primitive iliac artery dissection |
| Male, 45 | Control | Sudden death after acute lumbar pain |
| Male, 19 | Celiprolol | Sudden death after acute chest pain radiating to the right arm |
| Male, 19 | Celiprolol | Hemoptysis (recurrent) |

Celiprolol BID to a maximum of 400 mg per day

- **87 individuals screened (2003-2006)**
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- **Control group**
  - 20 with confirmed mutation
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vEDS Management Principles

Aggressive risk factor modification
• Smoking cessation
• Assessment and treatment for hypertension
• Daily walking
• Screening program

Medical Management
• Beta blockers (Celiprolol data)
• Vitamin C (Anecdotal)
• Aspirin (aneurysms/dissections)
• Doxycycline (Aneurysm data)
• Anti-inflammatory diet

Aortic and arterial repair will be discussed in a separate webinar
Mild aerobic exercise blocks elastin fiber fragmentation and aortic dilatation in a mouse model of Marfan syndrome associated aortic aneurysm

Mild aerobic exercise at 55% intensity (55% VO2max)
Fluoroquinolones

Avelox (moxifloxacin)
Baxdela (delafloxacin)
Cipro (ciprofloxacin)
Factive (gemifloxacin)
Levaquin (levofloxacin)
Generic ofloxacin

FDA Drug Safety Communication: FDA updates warnings for oral and injectable fluoroquinolone antibiotics due to disabling side effects

This information is an update to the FDA Drug Safety Communication: FDA advises restricting fluoroquinolone antibiotic use for certain uncomplicated infections; warns about disabling side effects that can occur together issued on May 12, 2016
Screening for arterial pathology in vEDS

- Vascular Surveillance
- Goal: discover asymptomatic aneurysms/dissections
- Can also be used for diagnostic purposes

- Duplex Ultrasound
- Computed Tomography (CT)
- Magnetic Resonance Imaging
Duplex Ultrasonography

- No radiation
- Works anywhere except the chest
Computerized Axial Tomography (CT)

- CT scan, CAT scan

- What does it entail?
  - Radiation exposure
  - Starting an IV
  - Contrast (also called dye)
  - Computer – imaging reconstruction

- Oral vs. IV contrast
- CT angiogram (CTA)
Magnetic Resonance (MR) Imaging

What does it entail?

• uses strong magnetic fields & radio waves

• Starting an IV

• May need sedation

• Contrast (also called dye)

• Computer – imaging reconstruction

• Limitations
Summary of vEDS Management Principles

• Accurate diagnosis of vEDS is an imperative (genetic testing)

• Management principles: Holistic care
  • Creating a care team
  • Risk factor modification
  • Medical management
  • Screening

• The future in translational vEDS research:
  • A comprehensive knowledge of the natural history
  • Accurate and detailed phenotypes description and knowledge of the genotype
  • Patient input into research priorities
Vascular Ehlers-Danlos Syndrome Collaborative (2018)
| **Virtual Research Network (VRN)** | • Group of 300+ stakeholders, assembled via remote outreach through existing relationships and networks of Collaborative members  
• Responsible for responding to surveys from Collaborative and assisting with data collection and outreach |
| **Stakeholder Group** | • Group of 25 people (patients, families, clinicians, and researchers) who meet monthly via teleconference  
• Responsible for giving feedback on survey materials, outreach plans, and contributing meaningfully to major decisions |
| **Advisory Group** | • Five core leaders (includes a patient partner, a family member, a researcher, and a clinician), meets monthly via teleconference and leads stakeholder group meetings  
• Responsible for strategic planning, event planning, and preparing funding applications on behalf of Collaborative |