Beighton score

Beighton’s modification of the Carter and Wilkinson scoring system. Give yourself 1 point for each of the manoeuvres you can do, up to a maximum of 9 points.

1. Can you put your hands flat on the floor with your knees straight? ........................................ 1
2. Can you bend your elbow backwards? .................................................................................. 1 1
3. Can you bend your knee backwards? .................................................................................... 1 1
4. Can you bend your thumb back on to the front of your forearm? ..................................... 1 1
5. Can you bend your little finger up at 90° (right angles) to the back of your hand? ........ 1 1

Source: Arthritis Research UK
Classic EDS: molecular basis

Type V collagen deficiency

- Member of the fibrillar collagens
- Present in collagen type I-rich tissues (skin, tendon, bone)
- Key role in type I collagen fibrillogenesis via huge N-propeptide
Classic EDS-like EDS: Tenascin-X deficiency

- Complete deficiency of tenascin-X causes an AR condition with great similarity to classic EDS, with:
  - Hyperelastic skin, tissue fragility
  - Hypermobile joints, joint pain, (sub)luxations
  - Easy bruising
  - No atrophic scarring

Classic EDS-like EDS: Tenascin-X deficiency

- Caused by truncating mutations or large deletions in both alleles of the TNX-B gene
- Tenascin-X interacts with collagen and other ECM molecules

ECM: Extracellular matrix.
Case History

- male, aged 24 years
- Born with unilateral clubfoot, surgically corrected
- Multiple ‘spontaneous’ ecchymoses since early age, but no wound healing problems, hyperlaxity confined to the small joints
- No specific medical problems up to age 24 years
- At age 24: hospitalisation after sudden collapse due to spontaneous bilateral rupture of two intercostal arteries
- Angiography reveals presence of multiple aneurysms of A. carotis and A. renalis
- Genetic consultation: diagnosis of EDS, type III collagen defect
Vascular Ehlers–Danlos syndrome (vEDS)

• **Disease prevalence:** 1:200,000–1:50,000

• **Major diagnostic criteria:**
  › Thin translucent skin
  › Arterial / intestinal / uterine fragility or rupture
  › Extensive bruising
  › Characteristic facial appearance

• **Minor diagnostic criteria:**
  › Acrogeria
  › Hypermobility of small joints
  › Tendon and muscle rupture
  › Talipes equinovarus
  › Early-onset varicose veins
  › Arteriovenous, carotid-cavernous fistel
  › Pneumothorax / pneumo-haemothorax
  › Gingival recession
  › Positive family history, sudden death in a close relative

![Thin, translucent skin](image1)

![Acrogeria](image2)
vEDS: facial characteristics

Characteristic face

Consent from patients received.
vEDS: natural history

- Life span significantly reduced, death mainly in 3rd or 4th life decade
- Most deaths result from arterial rupture/dissection
  - Abdominal > thoracic > cerebral
  - Aorta often involved
  - Not always preceded by dilatation
- Bowel rupture (sigmoid): 20–25% of all complications
- Pregnancy-related complications are rare, but life-threatening

Clinical characteristics of 100 vEDS patients

- Total number of major complications: n= 129 in 60 patients
  - 7% first major complication by age 20 yrs
  - 75% first for major complication by age 40 yrs
  - Majority (35/60) experienced more than 1 complication

- Arterial complications: 82%
- Gastro-intestinal complications: 15%
- Pregnancy-related complications
  34 reported pregnancies in 21 women: major complications in 5/34 pregnancies
- Organ ruptures: 3% (spleen, liver)
vEDS: molecular basis

Majority are substitutions for glycine residue within triple helical domain

Wide range of COL3A1 mutations throughout the gene

Type III collagen defect
Case History

- Male, 56 yrs
- Bilateral clubfeet
- Easy bruising
- Varicose veins at young age
- Repetitive dislocations at age 25 yrs
- Joint hyperlaxity of small joints
- Limited extension of elbows
- Soft skin, mildly dilated scars
- 51 yr: diagnosis MVP, surgery at age 56 yrs, mild dilatation proximal aorta

- **COL3A1, FBN1, TGFBR1, TGFBR2, ACTA2, Smad3,**: negative

- **TBFB2 mutation**
Diagnostic evaluation

• Clinical Hx
• Clinical examination
  ‣ Skin
  ‣ Joint hyperlaxity (Beighton score)
  ‣ Skeletal manifestations
  ‣ Craniofacial features
  ‣ Echocardiography
  ‣ CT/MRA: Arterial tortuosity, arterial aneurysms
  ‣ Ophthalmologic examination
  ‣ Skeletal X-rays

  ‣ Family history (three generations)
Diagnostic evaluation: arterial fragility

• If clinical suspicion of vascular EDS → sequencing of COL3A1 gene (genomic DNA)

• If negative: consider other EDS-subtypes…
  ▶ Classic EDS: COL5A1, COL5A2
  ▶ Cardiac-vascular-like EDS (R-to-C): COL1A1
  ▶ EDS kyphoscoliotic type: PLOD1

• … or other heritable disorders of connective tissue
  ▶ Especially in presence of aortic dilatation and/or arterial tortuosity
    → Consider FTAA
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<th>NGS panel</th>
<th>Genes</th>
<th>TAT (months)</th>
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<td>FBN1, TGFBR1/2, ACTA2, TGBF2, SMAD3, COL3A1</td>
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<td>MYH11, MLCK, SLC2A10, NOTCH1, FBN2<em>², ADAMTS10, FBLN4, FLNA, ELN</em>³</td>
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<td>EDS panel 1</td>
<td>COL3A1, COL5A1, COL5A2, ADAMTS2</td>
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<tr>
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<td>PLOD1, ZNF469, PRDM5, CHST14, SLC39A13, FKB14, B4GALT7</td>
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<td>LEPRE1, PP1B, CRTAP, SP7, PLOD2, FKB10, BMP1, SERPINH1, SERPINF1</td>
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<tr>
<td>Stickler panel 1</td>
<td>COL2A1, COL11A1, COL11A2</td>
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<tr>
<td>PXE panel 1</td>
<td>ABCC6, ENPP1, GGCX, VEGFA</td>
<td>3</td>
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Patients with EDS require a **multi-disciplinary approach** with:

- Genetic counselling
- Cardiovascular work-up
- Physiotherapy
- Orthopaedic surgeon
- Pain management
- Psychological support
- …
Skin Care:
• Avoid undue trauma to the skin
• Children should wear protective bandages and paths
• Dermal wounds should be closed without tension
• Cutaneous stitches should be left in place twice as long as usual
• Fixation of skin adjacent to stitches with adhesive tape to prevent stretching of the scar
Joint Protection

• In children with hypotonia and delayed motor development: physiotherapeutic programme
• Avoid excessive or repetitive heavy lifting that produces undue strain to the joints
• Avoid “showing off” joint hyperlaxity, and excessive stretching of the already hypermobile joints
• Provide assisting devices, such as ring splints and braces
• Delay surgery in favour of physical therapy and bracing
EDS: general management guidelines

• **Pain management** should be tailored to the individual’s subjective symptoms

• **Cognitive behavioural therapy** can be beneficial

• **Psychological follow-up** to explore coping strategies and recognise depression

• Follow-up and monitoring of **pregnancy** is recommended
EDS: general management of bleeding and bruising

- **Control the risk for bruising** by avoidance of contact sports and heavy exercises and by wearing protective pads and bandages.

- **Control the risk of vascular damage** by avoidance of risk factors for atherosclerotic cardiovascular disease (smoking, hypertension, obesity, etc.).

- **Supplementation of ascorbic acid** (cofactor for cross-linking of collagen fibrils).
EDS: general management of bleeding and bruising

- Vasopressin analogue **DDAVP** has been reported to reduce bleeding tendency temporarily in subjects undergoing dental or surgical procedures.

- Case report of successful use of **recombinant factor VIIa** in a patient with vascular EDS with continued bleeding\(^1\).

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**DDAVP:** Desmopressin.

EDS: preventive measures in vascular EDS

• **Avoid drugs that interfere with haemostatic process:** aspirin (acetylsalicylic acid), non-steroidal anti-inflammatory drugs, anticoagulant drugs (oral vitamin K antagonists, heparin, low molecular weight heparin, oral thrombin inhibitors)

• **Avoid invasive vascular procedures** (catheterisation, arteriography)

• **Avoid surgical intervention**, if possible
Beta-blockers in treatment of vascular EDS

• **Purpose:** to test the ability of celiprolol, a β1-adrenoceptor antagonist with a β2-adrenoceptor agonist action, of preventing arterial dissections and ruptures of vEDS in a multicentre, prospective, randomised, open, blinded endpoints trial

• **Design:** 53 patients with clinical vEDS (33 patients COL3A1 mutation positive), randomised to celiprolol (n=25) or no treatment (n=28); uptitration from 100 to 400mg, 5 years treatment

• Primary endpoints: arterial events (rupture or dissection, fatal or not)
• Secondary endpoints: intestinal/uterine rupture, major clinical event related to vEDS

Beta-blockers in treatment of vascular EDS

- Mean duration of follow-up: 47 months
- Primary endpoints: 5 patients in celiprolol (20%) and 14 patients in control group (50%)
- Primary and secondary endpoints: 6 celiprolol (24%) and 17 control group (61%)
- Study was ended prematurely since significant differences between the two groups were reached after 64 months
- Treatment was well-tolerated and target dose of 400 mg was reached in all but 2 patients
- Results were nearly identical in COL3A1 mutation positive group
- Conclusion: Treatment with celiprolol compared to no treatment reduced by threefold arterial events such as rupture or dissection in vEDS patients

Key messages

1. EDS is a **multisystemic** disorder
2. EDS is a clinically recognisable but **underdiagnosed** disorder!
3. EDS is clinically and genetically very heterogeneous
4. Diagnosis of **correct EDS subtype** may require combination of clinical, biochemical and molecular studies
5. EDS has a serious impact on **Quality of Life**, morbidity and mortality
6. Management and therapy → comprehensive and **multidisciplinary**
7. Genetic counselling is mandatory
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