European Reference Network
for rare or low prevalence complex diseases

Network Vascular Diseases (VASCERN)

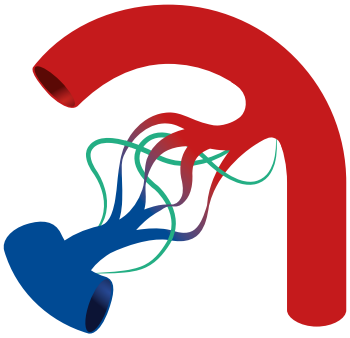
VASCERN DO'S AND DON'TS FACTSHEETS FOR RARE VASCULAR DISEASE PATIENTS FACING FREQUENT SITUATIONS

Marfan syndrome and related disorders (HTAD-WG)

Vascular Ehlers-Danlos syndrome (MSA-WG)

Hereditary Haemorrhagic Telangiectasia (HHT-WG)

Pediatric and Primary Lymphedema (PPL-WG)



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Co-funded by the Health Programme of the European Union

VASCERN

VASCERN, the European Reference Network on Rare Multisystemic Vascular Diseases, is dedicated to gathering the best expertise in Europe in order to provide accessible cross-border healthcare to patients with rare vascular diseases (an estimated 1.3 million concerned). These include arterial disease (affecting aorta to small arteries), arterio-venous anomalies, venous malformations, and lymphatic diseases.

VASCERN currently consists of 31 highly specialised multidisciplinary Healthcare Providers (HCPs) from 11 EU Member States and of various European Patient Organisations and is coordinated in Paris, France.

Through our 5 Rare Disease Working Groups (RDWGs) as well as several thematic WGs and the ePAG – European Patient Advocacy Group, we aim to improve care, promote best practices and guidelines, reinforce research, empower patients, provide training for healthcare professionals and realise the full potential of European cooperation for specialised healthcare by exploiting the latest innovations in medical science and health technologies.

More information available at: **https://vascern.eu**
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Marfan syndrome and related disorders

Abbreviations

HTAD-WG: Heritable Thoracic Aortic Diseases Working Group

MFS: Marfan syndrome

IVF: In vitro fertilization

ßblockers: beta-blockers

Introduction

These factsheets are based on existing French factsheets which have been reviewed and adjusted by the experts of the VASCERN HTAD-WG.

The HTAD-WG agrees with the recommendations but wishes to emphasize that these are recommendations made by consensus at expert level. We would recommend that these factsheets be used as a guide to implement locally agreed policies.

These factsheets are meant for patients as well as for caregivers. Implementing these recommendations should go hand in hand with strategies to educate patients about medical situations where specific care is required and about relevant symptoms and how to act when they occur.

Pregnancy, delivery and postpartum care

1.1 Before Pregnancy

WHAT IS RECOMMENDED

- Address the issue of pregnancy in both male and female Marfan syndrome (MFS) patients of childbearing age in a systematic manner to inform them of the options of prenatal/pre-implantation diagnostics. Inform women as well about specific management and care recommendations - also include the optimal conditions of follow-up and a written delivery plan.
- As soon as a pregnancy is being considered by someone suspected of having MFS, refer him and/or her to a specialized centre, if this has not already been done, for a full assessment and pre-pregnancy counselling.
- Plan the pregnancy in collaboration with the specialized centre.
- Assess the risk of aortic dissection before pregnancy by measuring the aortic diameter.
- <40 mm: pregnancy allowed.
- 40-45 mm: pregnancy allowed on a case by case basis.
- >45 mm: contra-indication for pregnancy with limited evidence. This aortic diameter may warrant prior surgery.
- No data is available on the effect of hormonal procedures (IVF). The same thresholds as for pregnancy (contra-indicated when ARD >45 mm) should be used.

Pregnancy, delivery and postpartum care

1.2 During Pregnancy

The risk of aortic dissection is increased during pregnancy, delivery and the postpartum period

WHAT IS RECOMMENDED

- Treatment with βblockers throughout the entire pregnancy and in the postpartum period. Check the type of βblocker: atenolol is the least favourable; propranolol, metoprolol and labetalol are preferred.
- Monitor the aortic diameters (including abdominal diameters) by ultrasound at least twice during pregnancy: 20-24w and 32-36w. More examinations may be considered if the aortic diameter is above 40 mm or when increased growth is noted.
- Monitor blood pressure on a regular basis (target <130/80 mm Hg).
- Foetal growth should be monitored carefully to assess the effect of βblockers.

WHAT YOU SHOULD NOT DO

- Prohibit pregnancy for all women with Marfan Syndrome.
- Stop treatment with beta-blockers during the pregnancy or at delivery.

Pregnancy, delivery and postpartum care

1.3 Delivery

WHAT IS RECOMMENDED

- Assess the risk of aortic dissection before delivery based on the aortic diameter.
- <40mm: vaginal delivery. Shorten the duration of stage 2 of labour with vacuum extractors, etc.
- 40-45 mm: delivery on a case by case basis (contact the expert centre).
- >45 mm: Caesarean section and plan the delivery by limiting the duration of the third trimester, the period of maximum risk.
- A tailored delivery should be formalized. Different factors should be taken into account: distance of home to hospital, aortic diameter, etc… Labour should be limited to a minimum.
- Adequate epidural anesthesia should be performed with caution, considering dural leakage and in some cases dose adjustment.

WHAT YOU SHOULD NOT DO

- Administer an epidural without first checking the condition of the spine (scoliosis, spondylolisthesis, dural ectasia).
- Stop treatment with βblockers.
- Prescribe beta-mimetics.

Pregnancy, delivery and postpartum care

1.4 Postpartum care

WHAT IS RECOMMENDED

- Cardiac ultrasound in the mother within 48 hours postpartum and after 6 weeks.
- Depending on the heart rate of the baby at birth, additional monitoring can be decided by the paediatrician.

Breastfeeding

- Breastfeeding is not contraindicated.

Physical activity

Sports can be of great value considering body weight, blood pressure and fitness of the patient. Many symptoms like aches, pains and migraines may benefit from exercise. Sports can also be dangerous if they are accompanied by a significant increase in arterial blood pressure or if there is a risk of impact (to the eye in particular).

WHAT IS RECOMMENDED

- Endurance sports such as swimming, walking, running, and cycling.
- The physical activity level should be adjusted by the cardiologist based on the evaluation of aortic dimensions and valvular function, both in children and adults.

WHAT YOU SHOULD NOT DO

- Abrupt, isometric exercises, such as weightlifting, football, basketball, handball, and tennis.
- Expose oneself to the risk of bodily collisions which could increase the likelihood of ectopia lentis.

Anaesthesia

General anaesthesia does not pose any particular problems, apart from an interaction with βblocker treatment or anticoagulants (www.orphananesthesia.eu).

WHAT YOU SHOULD NOT DO

- Expose the patient to blood pressure fluctuations.

Antiplatelet agents and anticoagulants

WHAT IS RECOMMENDED

- Indications and contraindications for antiplatelet and anticoagulant treatments are identical in Marfan and non-Marfan patients.

WHAT YOU SHOULD NOT DO

- Modify the prescription of antiplatelet agents or anticoagulants as a result of a diagnosis with Marfan Syndrome.

Stroke

The incidence of stroke is not increased in patients with Marfan Syndrome.

WHAT IS RECOMMENDED

- Rule out aortic dissection with extension to the supra-aortic trunks.
- Management and treatment are identical for Marfan and non-Marfan patients.

WHAT YOU SHOULD NOT DO

- Stop treatment with βblockers.
- Delay management and treatment as a result of a diagnosis of Marfan Syndrome.

Orthopaedic surgery

WHAT YOU SHOULD NOT DO

- Stop βblockers - expose the patient to blood pressure fluctuations.

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Colonoscopy, gastroscopy and laparoscopy

No particular issues except in cases with dissection of the descending aorta.

WHAT IS RECOMMENDED

- A high degree of caution in cases with dissection of the descending aorta due to the high risk of blood pressure variations.

WHAT YOU SHOULD NOT DO

- Expose the patient to blood pressure fluctuations.

Retinal detachment

There are no specific issues with management and treatment even though patients have a higher incidence of retinal detachment.

Aortic dissection

WHAT IS RECOMMENDED

- Consider aortic dissection if chest pain/back pain/abdominal pain is present in a patient with Marfan syndrome or a Marfan-related syndrome.
- Treat the dissection as an emergency, following the same protocols as with a non-Marfan patient.

WHAT YOU SHOULD NOT DO

- Use a stent as a first option in the presence of a dissection of the descending aorta.

Extra-aortic peripheral arterial dissection

WHAT IS RECOMMENDED

- Ensure that there is no evidence of aortic dissection.

Pulmonary embolism

Thrombolysis is not contraindicated.

Fibroscopy

No specific recommendations.

Glaucoma

Glaucoma is potentially related to lens dislocation.
Check the position of the lens.

Spontaneous haemoperitoneum

WHAT IS RECOMMENDED

- Rule out aortic dissection.

Infiltrations

No particular issues except in cases of anticoagulant treatment.

Contraindicated medications

There are no specific contraindications to Bromocriptin, or any other drug, in patients with Marfan syndrome

WHAT IS RECOMMENDED

- QT prolongation should be checked on the electrocardiography prior to proposing QT prolonging drugs.

Odontology/Dentistry

No specific issues with management and treatment, even though patients have a very narrow jaw.

WHAT IS RECOMMENDED

- Regular monitoring.
- Early orthodontic follow-up due to dental misalignments.
- The prevention of endocarditis, as in the general population (only in the case of a history of valve surgery or if previous history of endocarditis).

Pneumothorax

No particular issues except in cases of anticoagulant treatment.

WHAT IS RECOMMENDED

- Indications and treatments are identical for Marfan and non-Marfan patients.
- Perform aortic imaging if there is the slightest suspicion of aortic dissection.

WHAT YOU SHOULD NOT DO

- Stop treatment with βblockers.
- Delay care as a result of the diagnosis of Marfan syndrome.

Acute coronary syndrome

WHAT IS RECOMMENDED

- A coronary dissection may be seen in syndromes related to Marfan Syndrome, and this diagnosis should be considered in a young person.
- Ensure that there is no aortic dissection.

Abdominal/gastrointestinal/ gynaecological emergencies

No particular issues except in cases of anticoagulant treatment.

WHAT IS RECOMMENDED

- Rule out aortic dissection if there is the slightest doubt or in the event of unexplained pain.
- Indications and treatments are identical in Marfan and non-Marfan patients.

WHAT YOU SHOULD NOT DO

- Administer a spinal anaesthetic without first checking the condition of the spine (scoliosis, spondylolisthesis, dural ectasia).
- Stop treatment with βblockers.
- Delay treatment as a result of the diagnosis of Marfan Syndrome.

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Marfan syndrome and related disorders

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Vascular Ehlers-Danlos syndrome

Abbreviations

CTA: Computed tomography angiography
EDS: Ehlers-Danlos syndrome
GPIIβ/IIIα: Glycoprotein II beta/III alpha
LOVD: Leiden Open Variation Database
MRA: Magnetic Resonance Angiography
MSA-WG: Medium-Sized Arteries Working Group
SVI: Superficial venous insufficiency
vEDS: Vascular Ehlers-Danlos syndrome

Introduction

Vascular EDS (OMIM #130050) is a rare disorder that results from heterozygosity for mutations in COL3A1 which encodes the pro-alpha1 chains of the type III procollagen homotrimer. The condition is dominantly inherited but asymptomatic parental mosaicism can result in sib recurrence to normal parents. Arterial fragility, bowel rupture, and pregnancy complications are the major clinical complications and may limit survival to about 50 years.

Molecular diagnostic testing is therefore a key factor in identifying patients for appropriate management. More than 600 COL3A1 genetic variants are registered in the EDS database of the LOVD system, a large majority of them being private (http://www.lovd.nl/). This genetic testing requires having access to a genetic laboratory with experience to test and interpret COL3A1 variants, since not all variants are pathogenic and since those leading to haploinsufficiency result in a better prognosis than those with missense variants at a glycine residue or splice-site variants (Frank et al, 2015).

Clinical evaluation is usually undertaken in expert centres with the involvement of a multidisciplinary team familiar with the clinical features of this condition in probands and their first degree relatives. This rare disease suffers from lack of recognition since the main clinical diagnostic criteria for vEDS are nonspecific (hematomas, skin transparency, arterial events) and it is their association that is suggestive.

Major and minor clinical diagnostic criteria of the 2017 International classification of EDS illustrate the variety of physical signs that may constitute the clinical phenotype, adding to the diversity of arterial and visceral events during the natural course of the disease.

Because of the number of affected tissues, clinical evaluation often involves: cardiologists, clinical geneticists, vascular and interventional radiologists, ophthalmologists, orthopaedicians, physiotherapists, bowel surgeons, and vascular, endovascular and cardiac surgeons. Regular MDT meetings with multiprofessional team involvement will also aid in coordinating care of these patients. Appropriate transition of care of patients from paediatric to adult care is also essential in the care of these patients.

Genetic counselling, pre-pregnancy counselling and management during pregnancy by specialist fetal maternal teams will also be an essential part of the care of pregnant women with this disorder. Provision of appropriate counselling for family planning will also be necessary as pregnancy is associated with death in about 5% of women.

Treatment is largely mechanical, surveillance is not universally adopted, and treatment with antihypertensive agents may provide a measure of protection from arterial rupture. Medical therapy with celiprolol (particular beta-blocker) has shown its efficacy in reducing morbid cardiovascular events in a small group of patients, but there are still unmet medical needs. The need for detailed studies of natural history and mechanistic evaluation of arterial rupture are clear and probably the only way to identify helpful interventions.

Factsheets

These factsheets are based on existing French factsheets which have been reviewed and revised by the VASCERN MSA-WG members.

The MSA-WG wishes to emphasize that these are recommendations made by consensus at expert level. We would recommend that these factsheets be used as a guide to implement locally agreed policies.

These factsheets are meant for patients as well as for caregivers. Implementing these recommendations should go hand in hand with strategies to educate patients about medical situations where specific care is required and about relevant symptoms & how to act when they occur.

Complications in vEDS

Major life limiting complications are due to the increased risk of arterial ruptures. In these cases, urgent repair by any possible means is required. Locations that are commonly symptomatic are iliac and femoral arteries, mesenteric and celiac vessels, renal arteries, aorta (any location), and peripheral arteries of the limbs.

Peripheral arterial dissection

Peripheral arterial dissections, especially those of the medium-sized arteries, are the most frequent complication of vascular Ehlers-Danlos syndrome. They are spontaneous and must be suspected in the presence of an unexplained pain syndrome.

WHAT IS RECOMMENDED

- Call the national centre of reference or the regional centre of competence to seek advice due to the seriousness of the risk of dissection.
- Quickly implement all necessary actions in order to confirm the diagnosis of vascular Ehlers-Danlos Syndrome.
- Preference should be given to non-invasive examinations (such as MRA or CTA) and medical/conservative treatment whenever possible.
- When an arteriography is necessary (rupture, perforation), particular precaution should be taken when the guide is being moved upwards (due to risk of dissection/arterial perforation) and enhanced monitoring of the femoral insertion point is necessary.
- Arterial ruptures should be treated in preference by embolization.
- A protocol of permissive hypotension is recommended without compromise to organ function.
- Caution with use of inotropes is recommended.
- Caution with use of indwelling catheters is advised.

WHAT YOU SHOULD NOT DO

- The insertion of stents (except in the case of a life-threatening emergency) should be avoided.
- Consider surgical treatment, other than as a last resort.
- Systematically initiate treatment with anticoagulation and/or antiplatelet agents.

Abdominal emergencies

Vascular Ehlers-Danlos syndrome predisposes young adults to a high risk of digestive tract events which can be life-threatening. Bowel rupture is uncommon in early childhood, has been described in late childhood, and continues to be a risk into adulthood. Bowel rupture ultimately affects about 25–30% of individuals but rarely leads to death.

The main abdominal emergencies are (in order of severity):

- spontaneous arterial rupture in the peritoneal and/or retroperitoneal cavity,
- spontaneous digestive tract perforation, most often of the sigmoid colon, but also of the rest of the colon, the small intestine, and even the stomach,
- spontaneous rupture of an intra-abdominal organ (spleen, liver).

WHAT IS RECOMMENDED

- Perform an emergency angiography scan in the presence of an acute abdominal syndrome.
- In the event of colonic perforation, a wide colonic resection is the preferred method of treatment (Hartmann type for sigmoid colon).
- In cases of arterial rupture, percutaneous embolization should be preferred over open surgery.
- The use of stents should be limited to life-threatening emergencies, and embolization preferred whenever possible.
- In cases of spontaneous perforation of the digestive tract in a young adult or a child, a diagnosis of vascular Ehlers-Danlos syndrome should be automatically considered.
- A protocol of permissive hypotension is recommended without compromise to organ function.
- Caution with use of inotropes is recommended.
- Caution with use of indwelling catheters is advised.

Abdominal emergencies

WHAT YOU SHOULD NOT DO

- Attempt a minimal repair of a spontaneous perforation of the digestive tract.
- Perform a postoperative follow-up colonoscopy in the event of perforation of the digestive tract.
- Perform open surgery as first-line treatment in cases with arterial rupture.
- Any invasive or semi-invasive examination, particularly when the expected diagnostic rewards are minimal.

Haemoperitoneum

Haemoperitoneum is the cardinal indicator of acute bleeding in the abdominal cavity and requires emergency care.

WHAT IS RECOMMENDED

- Perform an emergency abdominal angiography scan to look for an arterial rupture, a digestive tract perforation or an intra-abdominal organ rupture.
- In the event of an arterial rupture, selective embolization should be preferred over open surgery.
- A protocol of permissive hypotension is recommended without compromise to organ function.
- Caution with use of inotropes is recommended.
- Caution with use of indwelling catheters is advised.

WHAT YOU SHOULD NOT DO

- Anticoagulant and antiplatelet treatments are associated with the occurrence of haemoperitoneum, in particular in the post-operative digestive period. In order to limit the risk of complications, these treatments should be taken for the shortest duration possible.
- Avoid unnecessary arterial puncture.

Arterial revascularisation

Arterial events (dissections, aneurysms) are the most frequent complications of vascular Ehlers-Danlos syndrome. Most often, the arterial events are treated medically and therefore do not require intervention, such as surgery.

WHAT IS RECOMMENDED

- Give preference to medical management and treatment for arterial events whenever possible.
- In the event of arterial rupture, emergency arteriography with embolization should be preferred, ideally in a specialised centre with prior experience in dealing with patients with vascular EDS.
- A protocol of permissive hypotension is recommended without compromise to organ function.
- Caution with use of inotropes is recommended.
- Caution with use of indwelling catheters is advised.

WHAT YOU SHOULD NOT DO

- Treat an arterial rupture by surgical means in an emergency context, except in the case of salvage surgery. In this case, special precautions with vascular clamping and sutures are required.
- In the event of an emergency surgical procedure, simple procedures (ligatures) are to be preferred over complex vascular reconstruction.

Aortic dissection

Taking into account the arterial fragility which is characteristic of the disease, the occurrence of a dissection and, rarely, the rupture of the aorta are the possible complications. However, these arterial accidents occur in the abdominal aorta more often than the thoracic aorta.

WHAT IS RECOMMENDED

- If an acute chest and/or abdominal pain syndrome is present, it is imperative to urgently check for the presence of a dissection or rupture of the aorta.
- Give preference to non-invasive examinations (such as MRA or CTA) and medical treatment whenever possible.
- For type A aortic dissections, surgical treatment is indicated as the primary option.
- A protocol of permissive hypotension is recommended without compromise to organ function.
- Caution with use of inotropes is recommended.
- Caution with use of indwelling catheters is advised.

WHAT YOU SHOULD NOT DO

- Use a stent as a first option in the presence of a dissection of the descending aorta; unless there is no other therapeutic alternative.

Acute coronary syndrome

There does appear to be a slightly increased risk of acute coronary syndrome in vascular Ehlers-Danlos syndrome. Given the arterial fragility, dissection of a coronary artery may result in an acute coronary syndrome (non-atheromatous).

WHAT IS RECOMMENDED

- Rule out an aortic dissection in the presence of an acute coronary syndrome in a patient with vascular Ehlers-Danlos syndrome.
- Give preference to non-invasive examinations (coronary scan) and medical treatment whenever possible.
- When a coronary angiography is necessary, particular caution should be taken when moving the guide upwards (due to risk of dissection/arterial perforation) and enhanced monitoring of the femoral insertion point is necessary.

WHAT YOU SHOULD NOT DO

- Use fibrinolytic or anti GPIIβ/IIIα agents as first-line treatments.
- Insertion of stents requiring dual or prolonged antiplatelet therapy should be avoided whenever possible.
- Radial coronary angiography (risk of dissection and ischemia of the hand).

Carotid-cavernous fistulas

Carotid-cavernous fistula is a possible complication of vascular Ehlers-Danlos syndrome. It affects around 10-15% of patients with the syndrome, and consists of a rupture of the intracranial carotid artery into the main collection site of venous blood in the brain. Its spontaneous character is pathognomonic for vascular EDS.

WHAT IS RECOMMENDED

- The appearance of a pulsating murmur in the auscultation of the skull or the eye will suggest the presence of a carotid-cavernous fistula. This suspicion is increased when the eye on the same side as the murmur becomes red and/ or painful. Swelling around the eye may also be present.
- If a carotid-cavernous fistula is suspected, an angiography /cerebral MRI scan is recommended.
- Management and care in a neurovascular unit is required. Therapeutic occlusion of the fistula is often necessary, in spite of the inherent risk of the procedure. This procedure must be carried out in a specialist centre with the greatest possible level of experience.
- Blood pressure in particular should be closely monitored. Maintain a blood pressure target <130/80 mmHg. A protocol of permissive hypotension is recommended without compromise to organ function.
- Caution with use of inotropes is recommended.
- Caution with use of indwelling catheters is advised.

WHAT YOU SHOULD NOT DO

- Delay imaging procedures which alone determine the diagnosis.
- Delay embolization when it is absolutely necessary, as it is a source of significant functional sequelae.

Pneumothorax

Pneumothorax is frequently associated with vascular Ehlers-Danlos syndrome and is the most frequent respiratory manifestation of the disease. It can occur from adolescence onwards and sometimes precedes genetic diagnosis. Treatment usually involves the insertion of a chest tube (complete pneumothorax).

WHAT IS RECOMMENDED

- In the event of a failure to remove the chest tube, a mechanical pleurodesis should be discussed at the time of the first occurrence.

WHAT YOU SHOULD NOT DO

- Pleurodesis in the event of first episode without a failure to remove the chest tube.
- Pleurodesis in cases of partial or prophylactic pneumothorax with asymptomatic bullous lesions in a patient without pneumothorax.

Stroke

Due to the vascular fragility which is characteristic of vascular Ehlers-Danlos syndrome, the cerebral arteries are often affected by complications, most commonly at the cervical level. The latter often present in the form of spontaneous dissections, which can obstruct the affected artery to varying degrees.

WHAT IS RECOMMENDED

- In the event of clinical signs that may suggest a stroke, urgently carry out an imaging scan of the brain and of the cerebral arteries (angiography scan or MRI).
- Discuss with the referring team any indication of revascularisation (thrombolysis, salvage arteriography), arteriography presents a particular risk.
- Search specifically for a carotid-cavernous fistula in the event of pulsatile tinnitus, associated or not with exophthalmos.

WHAT YOU SHOULD NOT DO

- An angioplasty (salvage) with stenting at the level of the arteries of the supra-aortic trunks.

Pregnancy, Delivery and Postpartum care

Pregnancy

Pregnancy presents a particular risk in female patients with vascular Ehlers-Danlos syndrome. It is associated with an increased risk of pregnancy-related complications, directly related to the tissue fragility which is characteristic of the disease. Complications occur in about half the pregnancies and include premature rupture of membranes with preterm delivery, rare uterine rupture during labor, severe perineal tears, and antepartum and post-partum hemorrhage.

WHAT IS RECOMMENDED

- Discuss any planned pregnancy with the medical and obstetrics referral team prior to conception,
- The occurrence of arterial or digestive system incidents may contraindicate a pregnancy.
- Discuss and suggest the possibility of performing prenatal diagnosis.
- Perform a complete arterial lesion assessment before or in early pregnancy.
- Arrange for increased monitoring of the uterine cervix, especially from the 28th week onwards.
- Maintain treatment with celiprolol, or introduce it if the pregnancy started without treatment.

WHAT YOU SHOULD NOT DO

- Interrupt treatment with beta-blockers during pregnancy and the peripartum period.

Delivery

There are no formal recommendations regarding the best method of delivery for patients with vascular Ehlers-Danlos syndrome. A caesarean section between 35 and 37 weeks of gestation is the approach adopted by the reference centre for rare vascular diseases, especially for primiparous patients with a known diagnosis.

WHAT IS RECOMMENDED

- Schedule the delivery due to the elevated risk of maternal complications.
- Always recommend carrying out a caesarean section between 35 and 37 weeks of gestation.
- Plan for the birth to take place in a level 3 maternity unit.

WHAT YOU SHOULD NOT DO

- Delivery at home or in a level 1-2 maternity unit.
- Vaginal delivery without prior multidisciplinary consultation.

Breastfeeding

Vascular Ehlers-Danlos syndrome in itself is not a contraindication to breastfeeding. Nonetheless, the beta-blocker treatment prescribed to prevent the vascular complications of the disease in the mother is not generally recommended during breastfeeding as it is transmitted to the newborn through breast milk.

WHAT IS RECOMMENDED

- Discuss breastfeeding on a case-by-case basis with the attending obstetric and paediatric teams.

WHAT YOU SHOULD NOT DO

- Interrupt the mother's beta-blocker treatment with celiprolol in order to allow for breastfeeding.
- Consider breastfeeding when the newborn has displayed side-effects of beta-blocker use (including bradycardia, respiratory distress and/or hypoglycemia).
- Consider breastfeeding when maternal complications, related to vascular Ehlers-Danlos syndrome, have been reported in the peripartum period.

Invasive investigations and treatment of common medical emergencies in vEDS

Colonoscopy

Colonoscopy is an invasive examination of the colon frequently performed in routine medical practice. Patients with vascular Ehlers-Danlos syndrome have a fragility of the colon which can make this examination dangerous. It is therefore in principle avoided, in order to prevent potentially serious complications.

WHAT IS RECOMMENDED

- Colonoscopy screening for common diseases of the colon should be avoided.
- Colonic video capsule should be the preferred examination whenever possible over invasive exploration of the colon.

WHAT YOU SHOULD NOT DO

- Perform a colonoscopy after an episode of spontaneous perforation of the colon, particularly in a patient who has previously experienced a colonic perforation.

Pulmonary embolism

There is no particular risk of pulmonary embolism associated with vascular Ehlers-Danlos syndrome.

WHAT IS RECOMMENDED

- Follow standard treatment protocols for pulmonary embolisms (anticoagulant treatment).

WHAT YOU SHOULD NOT DO

- Fibrinolysis should be avoided whenever possible due to the increased risk of haemorrhage over the course of the disease.

Venous Thrombosis

There is no particular risk of venous thrombosis associated with vascular Ehlers-Danlos syndrome. In contrast, superficial venous insufficiency (SVI) of the lower limbs is common (varicose veins), which may be a risk factor for venous thrombosis. SVI in vEDS is characterized by its onset of venous disease before the age of 20 years and the early presence of significant (>3 mm) varicose veins.

WHAT IS RECOMMENDED

- Carry out a venous assessment if there are functional or physical symptoms of superficial venous insufficiency of the lower limbs.

WHAT YOU SHOULD NOT DO

- Treat saphenous insufficiency by vein stripping (risk of arterial or femoral venous rupture).

Antiplatelet agents and anticoagulants

The fragility of patients with vascular Ehlers-Danlos syndrome is not conducive to the prescription of antiplatelet and anticoagulant treatments.

WHAT IS RECOMMENDED

- Discuss the prescription of antiplatelet agents / anticoagulants on a case-by-case basis.
- In all cases limit the prescription to the minimum duration necessary.
- Limit the prescription of NSAIDs and if they are necessary use only on an infrequent basis.

WHAT YOU SHOULD NOT DO

- Continue antiplatelet / anticoagulant treatment over the long term, unless otherwise indicated.
- Combine anticoagulants with antiplatelets, and/or several antiplatelet agents.

Exercise

Most of the usual aspects of daily living and recreational activities are not restricted in vEDS. The major concerns associated with high level sports activities are the risk of vascular rupture with the trauma of collisions and the change in blood pressure during these activities.

WHAT IS RECOMMENDED

- Mild to moderate aerobic physical activity, where there is the capacity to converse with partner, is thought to be beneficial.
- Use of equipment such as stationary bicycles, elliptical trainers or well cushioned treadmills could be encouraged.
- Light weights to retain tone and strength and good breath control while using weights.

WHAT YOU SHOULD NOT DO

- Collision sports and isometric activities are generally discouraged.
- Running on hard surfaces and for long distances may exacerbate foot, ankle, knee, and hip pain.
- Activities with rapid acceleration/deceleration should be discouraged as these may increase the risk of vessel dissection.

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Vascular Ehlers-Danlos syndrome (vEDS)

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Hereditary Haemorrhagic Telangiectasia

Abbreviations

HHT: Hereditary Haemorrhagic Telangiectasia

HHT-WG: Hereditary Haemorrhagic Telangiectasia Working Group

APA: Antiplatelet agent

ENT doctor: Ear, Nose, and Throat doctor

AVM: Arteriovenous malformation

VM: Vascular malformation

SaO2: Oxygen saturation

Introduction

These factsheets are based on existing French factsheets which have been reviewed and adjusted by the experts of the VASCERN HHT-WG.

The HHT-WG agrees with the recommendations but wishes to emphasize that these are recommendations made by consensus at expert level. We would recommend that these factsheets be used as a guide to implement locally agreed policies.

These factsheets are meant for patients as well as for caregivers. Implementing these recommendations should go hand in hand with strategies to educate patients about medical situations where specific care is required and about relevant symptoms and how to act when they occur.

Physical activity

WHAT IS RECOMMENDED

- There are no physical activity or sport restrictions, except in the event of acute hypoxia.

WHAT YOU SHOULD NOT DO

- Scuba diving with a diving tank in patients with pulmonary arteriovenous malformations, even if embolised (risk of air embolism).

Breast feeding

WHAT IS RECOMMENDED

- Breastfeeding is not contraindicated in women with hereditary haemorrhagic telangiectasia.

WHAT YOU SHOULD NOT DO

- No specific recommendations.

Contraindicated medications

No medication is formally contraindicated.

WHAT IS RECOMMENDED

- Always discuss the risks and benefits with the centre of reference or competence responsible for the care of the patient.
- Adapt the treatment to the patient's clinical condition (epistaxis, gastrointestinal bleeding).

WHAT YOU SHOULD NOT DO

- Prescribe antiplatelet agents (APAs) or anticoagulants without having weighed the potential risks and benefits.

Antiplatelet agents (APA) and anticoagulants

WHAT IS RECOMMENDED

- Discuss the risks and benefits with the centre of reference or expertise responsible for the patient.
- Adapt the treatment to the patient's clinical condition (epistaxis, gastrointestinal bleeding).
- After an ischemic stroke secondary to pulmonary arteriovenous malformations, there is no indication to continue this type of treatment (APA or anticoagulant) if all pulmonary arteriovenous malformations have been treated satisfactorily.

WHAT YOU SHOULD NOT DO

- Prescribe APAs or anticoagulants without having weighed the risks and benefits.

Deep-vein thrombosis, pulmonary embolism
(or venous thromboembolic disease)

No medication is formally contraindicated.

WHAT IS RECOMMENDED

- Follow the standard treatment for thrombosis and/or pulmonary embolism (anticoagulant treatment) having weighed the potential risks and benefits.
- Adapt the treatment to the patient's clinical condition (epistaxis, gastrointestinal bleeding, blood count).
- In the event of increased epistaxis while taking anticoagulation treatment, arrange for a consultation with an ENT doctor who has knowledge of the disease in order to consider appropriate treatment.
- Outside of an emergency situation, and depending on anti-coagulant tolerance, discuss alternative treatments (thrombectomy, cava filter) with the centre of reference or competence.

WHAT YOU SHOULD NOT DO

- Avoid treating vascular thromboembolic disease because of hereditary haemorrhagic telangiectasia.

Haemorrhagic stroke

WHAT IS RECOMMENDED

- Emergency management and treatment (as in non-HHT patients).
- Look for underlying brain AVMs to prevent recurrence.
- If the patient's clinical condition requires the insertion of a nasogastric tube, it should be soft, of small diameter (unless clinical circumstances demand a large bore tube), and put in place with extreme caution due to the risk of triggering a severe episode of epistaxis related to the presence of mucous telangiectases.

WHAT YOU SHOULD NOT DO

- No specific contraindications.

Brain abscesses

A brain abscess is a classic complication of hereditary haemorrhagic telangiectasia. It is related to the right-to-left shunt secondary to pulmonary arteriovenous malformations.

WHAT IS RECOMMENDED

- Emergency management and treatment (as in non-HHT patients).
- Perform a chest CT scan without injection, or contrast echocardiogram to identify pulmonary arteriovenous malformations (the most common cause of brain abscess in hereditary haemorrhagic telangiectasia), and treat the pulmonary arteriovenous malformations to reduce the risk of recurrence.
- If the patient's clinical condition requires the insertion of a nasogastric tube, this should be soft, of small diameter (unless clinical circumstances demand a large bore tube), and put in place with extreme caution due to the risk of triggering a severe episode of epistaxis related to the presence of mucous telangiectases.

WHAT YOU SHOULD NOT DO

- No specific contraindications.

Heart failure

Heart failure in Hereditary Haemorrhagic telangiectasia may be related to the evolution of hepatic AVMs that can entail cardiac chronic overload: both hepatic and cardiac hemodynamics must be investigated.
Medical treatment will be adapted to each particular case: treatment of heart failure, correction of anemia, management of arrhythmia.

WHAT IS RECOMMENDED

- Measure cardiac output and the cardiac index, the filling pressures and the presence or absence of pulmonary hypertension (often post-capillary).
- Search for hepatic arteriovenous malformations (Doppler ultrasound and/or hepatic scan).
- Refer the patient to a centre of reference.
- Correct the anaemia.

WHAT YOU SHOULD NOT DO

- Overlook cardiac evaluation (including echocardiography) if severe liver VMs are present.
- Treat pulmonary hypertension secondary to liver VMs with high output cardiac failure, with vasodilators.

Kidney failure

WHAT IS RECOMMENDED

- No contraindications to kidney biopsy puncture after exclusion of kidney AVMs by doppler sonography.

WHAT YOU SHOULD NOT DO

- No specific contraindications.

Care for patient with multiple traumatic injuries

It is always necessary to contraindicate nasal manipulations (nasal intubation, aspirations, etc.) due to the significant risk of triggering sometimes very severe episodes of epistaxis linked to mucous telangiectases.
Apart from the risk of bleeding related to the presence of mucous telangiectases (nasal, gastrointestinal), there are no coagulation anomalies associated with hereditary haemorrhagic telangiectasia and no surgical bleeding risk connected with this pathology.

WHAT IS RECOMMENDED

- Check that there is no low SaO2 that could be related to the presence of undiagnosed pulmonary AVMs, which would warrant treatment.

WHAT YOU SHOULD NOT DO

- Intubate or aspirate through the nose: risk of severe epistaxis.

Bronchoscopies

Be aware that coughing may be tolerated less well than in other patients due to the risk of haemoptysis from tube abrasion.

WHAT IS RECOMMENDED

- Follow the standard fibroscopy technique.
- In case of biopsy, perform with antibiotic prophylaxis if pulmonary AVMs are present, or if pulmonary status is unknown.

WHAT YOU SHOULD NOT DO

- Nasal manipulations during anaesthesia (nasal intubation, aspirations, etc.) due to the significant risk of triggering sometimes very severe episodes of epistaxis linked to mucous telangiectases.

Aortic dissection

Before any surgery it is always necessary to contraindicate nasal manipulations (nasal intubation, aspirations, etc.) due to the significant risk of triggering sometimes very severe episodes of epistaxis linked to mucous telangiectases.

Apart from the risk of bleeding related to the presence of mucous telangiectases (nasal, gastrointestinal), there are no coagulation anomalies associated with hereditary haemorrhagic telangiectasia and no surgical bleeding risk connected with this pathology.

WHAT IS RECOMMENDED

- Emergency management and treatment (as in non-HHT patients).
- Follow standard treatment protocols for this pathology.
- If the patient's clinical condition requires the insertion of a nasogastric tube, this should be soft, of small diameter (unless clinical circumstances demand a large bore tube), and put in place with extreme caution due to the risk of triggering a severe episode of epistaxis related to the presence of mucous telangiectases.

WHAT YOU SHOULD NOT DO

- Intubate or aspirate through the nose: risk of severe epistaxis.

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Pediatric and Primary Lymphedema

Abbreviations

NSAIDs: Nonsteroidal Anti-Inflammatory Drugs

PPL-WG: Pediatric and Primary Lymphedema Working Group

BMI: Body Mass Index

Introduction

These factsheets have been written and reviewed by the experts of the VASCERN PPL-WG. The PPL-WG agrees with the recommendations but wishes to emphasize that these are recommendations made by consensus at expert level. We would recommend that these factsheets be used as a guide to implement locally agreed policies.

These factsheets are meant for patients as well as for caregivers. Implementing these recommendations should go hand in hand with strategies to educate patients about medical situations where specific care is required and about relevant symptoms and how to act when they occur.

Diagnosing Primary Lymphedema

WHAT IS RECOMMENDED

- Consider the diagnosis in any newborn or child with swelling of one or more limbs, chylothoraces/pleural effusions or ascites, for which no other obvious explanation is present.
- Refer children suspected of having lymphedema to an expert centre for inter(multi)- disciplinary analysis (follow the guidelines).
- Include parents in the diagnostic process if the lymphedema is present in a child.
- Refer adults with lymphedema to an expert clinic for inter(multi)-disciplinary analysis if lymphedema is present in one or more limbs and no obvious other explanation is present, especially if other congenital anomalies or disorders are present.

WHAT YOU SHOULD NOT DO

- Perform routine genetic testing, lymphoscintigraphy and blood examinations without dedicated lympho-vascular expertise.

Inter/(Multi)-disciplinary treatment

There exist various non-surgical treatment options for lymphedema and a few surgical options. These can be divided into reconstructive and reductive methods. All surgical treatments should be performed in a dedicated expert center with interdisciplinary cooperation and embedded in a non-operative treatment protocol.

WHAT IS RECOMMENDED

- After confirming the diagnosis of primary lymphedema, an interdisciplinary treatment protocol should be created for the individual patient.
- Treatment of lymphedema is divided into 2 stages: initial and maintenance treatment phases: ensure that the patient (or the parents) is aware of this.
- The treatment protocol is monitored by the lymphedema therapists.
- Compression technology is the cornerstone in both stages of treatment.
- Swelling of the toes can be treated with compression and podiatry.
- The patient and/or the parents should pay attention to skin care, toenail problems and be vigilant for signs of cellulitis.
- Monitoring of the patient's weight and volume / circumference, with clinimetrics and photography, are part of the treatment.

WHAT YOU SHOULD NOT DO

- Wait and see without follow-up.
- Surgery for lymphedema without an interdisciplinary team approach.
- Reconstructive surgery in patients with primary lymphedema.

Follow-up for patients with primary lymphedema

WHAT IS RECOMMENDED

- Children and adults with primary lymphedema should be followed regularly in an expert centre for individuals with primary lymphedema.
- Follow-up for children and adults with primary lymphedema should be provided using the standard practice, but this standard practice may need to be adapted depending on the nature of the primary lymphedema, due to potential differences in their response to management and the possible development of other associated health problems.
- The expert centres should organize a network of care and work with the local healthcare provider and have an open door policy.
- Patients should be pro-active and be encouraged to monitor their own lymphedema (self-management).

WHAT YOU SHOULD NOT DO

- Fail to follow-up the patient.

Physical activity and lymphedema

Physical activity is very important in the management of lymphedema. During the maintenance phase, exercise in combination with compression is recommended. No type of physical activity is contraindicated in children with lymphedema. Regular physical activity is beneficial for both the affected limb and for general health.

An increase in limb volume during exercise is normal and transient and should not result in the cessation of physical activity.

WHAT IS RECOMMENDED

- There are no physical activity or sport restrictions. Let the children play.
- Physical activities in combination with compression will stimulate lymph flow and reduce swelling.
- Exercise is important to reduce weight (if they are overweight) or keep weight under control.
- Exercise is important to prevent muscle wasting.
- Wear compression garments during exercise if tolerated. If not tolerated, remove compression garments during exercise but put them back on afterwards or wear a lighter compression garment during exercise.
- Be aware of the daily recommended physical activity level for adults (10,000-15,000 steps a day).

WHAT YOU SHOULD NOT DO

- Take more rest than usual as part of lymphedema treatment.
- Sleep in a chair / recliner chair with legs downwards.
- Perform activities that may harm the skin without proper protection.
- Refrain from physical activity because of lymphedema.
- Restrict physical activities associated with daily life.

Weight and lymphedema

Obesity is the most important risk factor for the worsening of lymphedema. Weight loss to the normal range of weight and BMI will result in a reduced severity of the lymphedema.

WHAT IS RECOMMENDED

- Have a normal healthy diet.
- If intestinal lymphangiectasia, chylothoraces, chylous reflux and/or chylous ascites are present, a medium chain triglyceride (MCT), high protein diet should be considered.
- Aim for a healthy weight (BMI 19-24).
- Measure weight every 3-6 months.

WHAT YOU SHOULD NOT DO

- Allow obesity to develop (BMI > 29).

Cellulitis/erysipelas

Children and adults with lymphatic impairment have a much higher risk of developing cellulitis/erysipelas.
The clinical signs of erysipelas are: high fever (39-40˚C) of sudden onset, with rigors, a 'flu-like' or unwell feeling, followed by redness, warmth, and increased volume of the affected limb. Sometimes additional treatment is necessary, depending on the diagnosis.

WHAT IS RECOMMENDED

- Awareness of the first signs and symptoms of cellulitis.
- Prompt treatment of cellulitis / erysipelas with systemic antibiotics.
- Consider hospitalization in case of a young child and/or marked illness.
- Proper skincare and good compression treatment.
- Prompt treatment of interdigital fungal infections (Athletes foot) and eczema.
- Take preventive measures such as good hygiene following injury or insect bite: clean with soap and water and disinfect using topical antiseptic cream.
- Provide antibiotics for the patient to use if they feel that they are starting to develop cellulitis.
- Consider preventive long-term use of antibiotics in children/adults with recurrent cellulitis (2≥ episodes per year).

WHAT YOU SHOULD NOT DO

- Ignore the increased swelling.
- Stop wearing garments or low-stretch bandages. The patient may need to take off their compression materials for the first 2 days because of pain and/or discomfort in the acute phase, but they should be reintroduced as soon as possible or the lymphedema will deteriorate.
- Take antibiotics without clear signs of cellulitis/erysipelas.

Genetic testing for Primary Lymphedema

Genetic testing is a specialised test, which can clarify a genetic cause of primary lymphedema. The indication for testing and the type of test may vary.

WHAT IS RECOMMENDED

- Every family with one or more children or adults with primary lymphedema should be referred for genetic counseling.
- Gene testing should be performed only in the context of evaluation by a inter(multi)disciplinary clinic, in which a clinical geneticist participates.

WHAT YOU SHOULD NOT DO

- Perform routine genetic testing without expertise in lympho-vascular medicine or clinical genetics and without patient consent.

Pregnancy and Lymphedema

Pregnancy can increase lymphatic filtration and may result in aggravation of the lymphedema. However, this is usually reversible.

Consider the risk of an offspring or sibling of an affected individual inheriting the same condition.

WHAT IS RECOMMENDED

- Standard monitoring of pregnancy and focus on lymphedema.
- Contact the patient's center of expertise for genetic counseling for risk of lymphatic problems in the fetus and the option of prenatal diagnosis.
- More frequent assessments by the lymphedema therapists. They may need extra help with bandaging or compression garment fitting.
- Continue compression and bandage treatment as long as possible but adapt to the patient's needs (e.g. use thigh length stockings instead of tights).
- Encourage control of the weight gain.
- In the event of a sudden increase in volume, a venous Doppler ultrasound of the lower limbs is indicated to exclude an underlying deep vein thrombosis (rare).
- Consider the guidance of an obstetrician during pregnancy, including advice for delivery.
- If the patient is on prophylactic antibiotics, ensure that they are not harmful to the fetus.

WHAT YOU SHOULD NOT DO

- Stop all compression treatments.
- Ignore a sudden increase in swelling.
- Start anticoagulants because of the lymphedema swelling alone.

Compression treatment

Compression technology is the cornerstone in lymphedema treatment. There are dedicated modalities for both the initial and maintenance treatment phases. Combinations of various products can be very helpful to the patient.

WHAT IS RECOMMENDED

- Measure the affected limb to provide 'made to measure' garments.
- Use various compression technologies and teach the patient how to use them.
- Application of compression by the patient or the parent can be learned easily in most cases.
- Compression treatment is always individualized for each patient.
- Wear flat-knitted garments (Circular knit garments are often ineffective).
- Dedicated use of various compression technologies is possible for all ages.

WHAT YOU SHOULD NOT DO

- Ignore the lymphedema.
- Withdraw compression without proper monitoring.

Medication and lymphedema

No medication is formally contraindicated. However, some medications may aggravate the lymphedema so consider alternative treatments when available.

WHAT IS RECOMMENDED

- Consider the risks and benefits when medication is provided which can lead to more swelling. (eg calcium channel blockers).
- Be aware that the following drugs may aggravate the swelling: calcium channel blockers, corticosteroids, NSAIDs, sex hormones and related compounds, pregabalin, docetaxel, zoledronic acid, and sirolimus.
- In case of doubt: contact the centre of expertise responsible for the care of the patient.

WHAT YOU SHOULD NOT DO

- Ignore any increase in the degree of swelling.
- Ignore a worsening of the fit of the compression garment.
- Use diuretics to treat the lymphedema.

Operative intervention in a lymphedematous limb

Sometimes an operation is indicated in a patient with lymphedema. Precautions should be considered especially when a operation is performed on a lymphedematous limb, even for conditions which are not directly related to the lymphedema (e.g. varicose veins, hydrocele).

WHAT IS RECOMMENDED

- Discuss the risks and benefits with the centre of expertise responsible for the patient.
- Consider consultation with a specialist in lymphatic diseases prior to non-lymphatic surgery.
- Choose the direction of the incision to minimize the damage to the lymph vessels (e.g. hydrocele operation by a midline scrotal incision instead of a groin incision).
- Post-operatively, ensure proper compression treatment with bandages if there is a hematoma or extra swelling.
- If there is no extra swelling, continue wearing compression garments.
- A team of specialists in lymphatic diseases should perform surgery for lymphedema.
- Measure the swelling/volume /circumference pre-and post-operatively.

WHAT YOU SHOULD NOT DO

- Discontinue the routine lymphedema treatment (e.g. compression garments) when the patient undergoes surgery.
- In general, operations for lymphedema are not indicated for patients under the age of 18 years.

Anesthesia

Anesthesia does not pose a particular problem in patients with lymphedema.

WHAT IS RECOMMENDED

- No specific recommendations related to the management of a patient with lymphedema.
- If necessary, blood samples, infusions and blood pressure can be performed on the affected limb. However due to the volume of the limb, which can make these procedures more difficult, the use of an unaffected limb is preferred if possible.

WHAT YOU SHOULD NOT DO

- No specific recommendations.

Care for patient with traumatic injuries

WHAT IS RECOMMENDED

- Consider extra compression to the swelling of the limb (including the fingers/toes).
- Monitor the swelling.
- Be aware of the increased risk of cellulitis and consider antibiotic prophylaxis.

WHAT YOU SHOULD NOT DO

- Forget the routine lymphedema treatment (e.g. compression garments).

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