From the bedside to the bench and backwards: diagnostic approach and management of Ehlers-Danlos syndrome(s) in Italy

De la génétique à la clinique, approche diagnostique et thérapeutique du syndrome d’Ehlers-Danlos en Italie

M. Castori\textsuperscript{a,*}, M. Colombi\textsuperscript{b}

\textsuperscript{a} Division of Medical Genetics, San Camillo-Forlanini Hospital, Circonvallazione Gianicolense, 87, 00152 Rome, Italy
\textsuperscript{b} Division of Biology and Genetics, Department of Molecular and Translational Medicine, Medical Faculty, University of Brescia, Brescia, Italy

Summary

Ehlers-Danlos syndrome groups together an increasing number of hereditary connective tissue disorders mainly featuring abnormal skin texture, easy bruising, generalized joint hypermobility, and fragility or dysfunctions of internal organs. Diagnosis may be a hard task due to the phenotypic continuity among the different Ehlers-Danlos syndrome types and a variety of Mendelian and non-Mendelian diseases. The training pathways of most medical professionals do not include a practically oriented knowledge of Ehlers-Danlos syndrome and this further hampers prompt recognition and treatment. The multisystem nature of Ehlers-Danlos syndrome depicts a wide range of combining features mostly involving skin and mucosae, osteoarticular, cardiovascular and gastrointestinal systems, and pelvis. More recent evidence suggests a secondary but potentially disabling involvement of the nervous system. The typical Ehlers-Danlos syndrome patient is affected by chronic symptoms which are difficulty managed by standard methods and for which a tailored approach is still lacking. In addition, a few patients are affected by Ehlers-Danlos syndrome variants with extreme vascular fragility and are at risk of potentially life-threatening vascular accidents. These individuals need periodic follow-up focused on the cardiovascular system. Comparably with other European countries, also in Italy general awareness on the protean, clinical manifestations of Ehlers-Danlos syndrome is increasing. Diagnostic and management expertise is still scattered in a few centres without a formal national organization and standardization of the cure. However, dissemination

Résumé

Le syndrome d’Ehlers-Danlos regroupe un nombre croissant d’altérations héréditaires du tissu conjonctif (en particulier une texture anormale de la peau et sa tendance aux ecchymoses), hypermobilité généralisée des articulations et une fragilité ou un mauvais fonctionnement des organes internes. Le diagnostic peut être difficile à cause de la continuité phénotypique des différents types de syndromes d’Ehlers-Danlos et de la variété Mendélienne et non Mendélienne de la maladie. L’enseignement de la plupart des professionnels de la santé ne propose pas une formation qui s’appuie sur la connaissance pratique du syndrome d’Ehlers-Danlos et cela empêche, par la suite, son identification précoce et la mise en place de son traitement. Le caractère multisystémique du syndrome inclut une large palette de signes diversifiés impliquant la peau et les muqueuses, les articulations, les systèmes cardiovasculaire et gastro-intestinal et le bassin. Certaines informations recueillies récemment suggèrent une implication secondaire, mais potentiellement handicapante du système nerveux. Le patient typique du syndrome d’Ehlers-Danlos est affecté par des symptômes chroniques qui sont difficilement maîtrisés par les protocoles habituels et pour lesquels manque encore une approche spécifique. De plus, certains patients sont atteints d’une variante du syndrome qui provoque une fragilité vasculaire extrême, ils risquent potentiellement des accidents vasculaires mortels. Ces derniers nécessitent d’un suivi périodique de leur système cardiovasculaire. En Italie, comme dans les autres pays européens, la prise de conscience des manifestations du syndrome

\* Corresponding author.
e-mail: m.castori@scf.gov.it, marco.castori977@gmail.com (M. Castori).

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of knowledge is improving and many patients are now followed in specialized services coalescing an increasing number of specialists with interest in Ehlers-Danlos syndrome.

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Introduction

Hereditary connective tissue disorders group together an increasing number of genetic conditions due to mutation in one of the various constituents of the connective tissue [1]. They are characterized by marked clinical and genetic heterogeneity and various subtypes can be identified according to the shared clinical issues and involved molecular pathways. Among them, hereditary soft connective tissue diseases (HSCTDs) are emerging as a great biological and medical challenge [2]. They can be delineated as a specific type of systemic hereditary connective tissue disorders, selectively or mostly affecting non-ossified connective tissues mainly in skin, vessels, visceral walls, cardiac valves, tendons, joint capsules, and periarticular and visceral ligaments. Ehlers-Danlos syndrome (EDS) is probably the most common HSCTD and often presents with abnormal skin texture, easy bruising, generalized joint hypermobility (gJHM) and related complications, and fragility or dysfunctions of internal organs and the cardiovascular system [3].

EDS is heterogeneous with various clinical variants, whose phenotypic categories mirror distinct molecular bases. EDS, as a whole, has a prevalence of ~1:5000 in the general population [4] and comprises at least six historically major variants according to the most recent classification (i.e. Villefranche nosology) [5]. Among them, classic EDS (cEDS), vascular EDS (vEDS) and the hypermobility type (EDS-HT) are considered the most common, while kyphoscoliotic, arthralgias and dermatosparaxis types are rarely encountered also in specialized clinics. Many clinicians and researchers agree to consider joint hypermobility syndrome (JHS) clinically indistinguishable from EDS-HT [6]. JHS was originally defined in a rheumatologic setting as clinically separated from other chronic disorders affecting joints in adults [7]. The subsequent observation of various pediatric manifestations [8] and common familial aggregation of JHS [9], as well as clear co-segregation of JHS/EDS-HT in multiple pedigrees [10] supported the inclusion of JHS in the HSCTD category as clinically indistinguishable from EDS-HT (i.e. JHS/EDS-HT) [6]. The conundrum still remains unsolved mostly because EDS-HT and JHS are without known molecular bases.

In Italy, for decades, EDS remained a neglected condition with a single centre in Pavia focused on the biochemical analysis of cultured skin fibroblasts for diagnosis confirmation. Since the second half of the last decade, much more attention was posed on patients with suspected EDS not only for a more stringent phenotype-genotype classification of the affected individuals, but also for their management and follow-up in increasingly specialized centres. The resources are still scarce and only a few Italian professionals reached a real expertise in one or more medical/diagnostic fields related to EDS. Actually, the professionals’ efforts are scattered in a few centres, such as Rome (Medical Genetics at the San Camillo-Forlanini Hospital and Physical Medicine and Rehabilitation at Policlinico Umberto I University Hospital) and Brescia (Department of Molecular and Translational Medicine, University of Brescia and Spedali Civili University Hospital), which work mostly in outpatient settings with very limited facilities for an efficacious long-term improvement of patients’ quality of life. Despite this, the authors of this paper are trying to reach a national shared intent for the eventual improvement of patients’ lives and professionals’ satisfactions.

Nosology and classification

The Villefranche nosology identifies clinical diagnostic criteria for the six historically major variants of EDS [5]. It defines major and supporting minor criteria for all subtypes. The minimum set of criteria that should be met for a clinical diagnosis of any EDS subtype is not clearly defined in the Villefranche nosology, but the presence of at least one major criteria plus a variable number of minor criteria, or two major criteria is usually considered necessary for the clinical suspect of all major EDS subtypes. JHS was not originally included in the Villefranche nosology and is recognized by a different set of criteria, namely Brighton criteria (Table 1) [2], but is actually considered one and the same with EDS-HT. All but JHS/EDS-HT are laboratory diagnoses. In these variants (i.e. cEDS, vEDS, kyphoscoliotic, arthralgias and dermatosparaxis), the clinical diagnosis should be supported by at least one laboratory investigation [11], which is often the identification of the
<table>
<thead>
<tr>
<th>Nosology</th>
<th>Common variant</th>
<th>Inheritance</th>
<th>Major criteria</th>
<th>Minor criteria</th>
<th>Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Classic type</td>
<td></td>
<td>AD</td>
<td>Skin hyperextensibility</td>
<td>Smooth, velvety skin, Molluscoid pseudotumors, Subcutaneous spheroids, Complications of joint hypermobility, Muscle hypotonia, motor delay, Easy bruising, Manifestations of tissue extensibility and fragility, Surgical complications, Positive family history</td>
<td>Laboratory diagnosis By the presence of COL5A1 or COL5A2 mutation after clinical selection (one or more major criteria)</td>
</tr>
<tr>
<td>Hypermobility type</td>
<td>AD (?)</td>
<td></td>
<td>Hyperextensible and/or smooth, velvety skin, Generalized joint hypermobility (e.g. Beighton score ≥ 5/9)</td>
<td>Recurring joint dislocations, Chronic joint/limb pain, Positive family history</td>
<td>Exclusion diagnosis Usually by the presence of both major criteria</td>
</tr>
<tr>
<td>Joint hypermobility</td>
<td>AD (?)</td>
<td></td>
<td>Beighton score ≥ 4/9</td>
<td>Beighton score 1–3, Arthralgia in 1–3 joints, History of joint dislocations, Soft tissue lesions &gt; 3, Marfan-like habitus, Skin striae, hyperextensibility, or scarring, Downsampling palpebral fissures, lid laxity, myopia, History of varicose veins, hernias, visceral prolapse</td>
<td>Exclusion diagnosis By the presence of both major, or 1 major and 2 minor, or 4 minor criteria Criteria major 1 and minor 1 are mutually exclusive as are major 2 and minor 2</td>
</tr>
<tr>
<td>Vascular type</td>
<td></td>
<td>AD</td>
<td>Thin, translucent skin</td>
<td>Acrogeria, Hypermobility of small joints, Tendon and muscle rupture, Talipes equinovarus, Early-onset varicose veins, Arteriovenous, carotid-cavernous sinus fistula, Pneumothorax/pneumohemothorax, Gingival recessions, Positive family history, sudden death in a close relative</td>
<td>Laboratory diagnosis By the presence of COL3A1 mutation after clinical selection (one or more major criteria)</td>
</tr>
<tr>
<td>Kyphoscoliotic type</td>
<td>AR</td>
<td></td>
<td>Generalized joint hypermobility</td>
<td>Tissue fragility, including atrophic scars, Easy bruising, Arterial rupture, Marfanoid habitus, Microcornea, Osteopenia/porosis, Positive family history</td>
<td>Laboratory diagnosis By the presence of PLOD1 mutation after clinical selection (one or more major criteria)</td>
</tr>
<tr>
<td>Arthrochalasis type</td>
<td>AD</td>
<td></td>
<td>Generalized joint hypermobility with recurrent subluxations</td>
<td>Skin hyperextensibility, Tissue fragility, including atrophic scars, Easy bruising, Hypotonia, Kyphoscoliosis, Osteopenia/porosis</td>
<td>Laboratory diagnosis By the presence of COL1A1 or COL1A2 mutation after clinical selection (one or more major criteria)</td>
</tr>
</tbody>
</table>
causative mutation by molecular testing. JHS/EDS-HT are still an exclusion diagnosis, which is reached clinically by the meeting of available diagnostic criteria and the expert-oriented exclusion of partially overlapping conditions/EDS variants. The EDS spectrum is not limited to the six major variants, but also includes an increasing number of rarer clinical and/or molecular subtypes, listed in Table II. Recognition of these extremely rare conditions is still based on the clinician’s intuition and confirmed by molecular investigations performed in a few expert laboratories.

At the time of this writing, a revision of the actual nosology of EDS is ongoing with the involvement of many international experts thanks to the jointed efforts of the Ehlers-Danlos Support UK (EDS UK) and Ehlers-Danlos National Foundation (EDNF).

**Clinical assessment**

The diagnosis of EDS, any subtype, is first based on patients’ and family history, and physical exam. History taking should include a detailed examination of the entire patient’s physiology and clinical history, including pregnancy, delivery, psychomotor development (with emphasis on the progression of psychomotor milestones), sleep quality and diet restrictions. Mucosal, capillary, cutaneous and vascular fragility should be elicited, as well as any gastrointestinal, cardiovascular and genitourinary/pelvic issues. Only a few patients are affected by vEDS (or other EDS variants with vascular fragility) and, then, report acute symptoms due to rupture of vessels and organs; but many individuals present chronic involvement of the cardiovascular, gastrointestinal and urinary systems. Hence, special attention should be put on functional symptoms, such as gastroesophageal reflux, chronic/recurrent gastritis, recurrent unexplained abdominal pain, constipation, chronic diarrhoea, dysphagia/ataypical deglutition, paroxysmal/orthostatic tachycardias, palpitations, atypical chest pain, acrocyanosis/Raynaud phenomenon, chronic fatigue, pollachyuria and stress incontinence, reduced sensation of bladder distension. A list of orthopaedic complications, such as recurrent sprains/strains, dislocations, surgeries and positive investigations for degenerative joint/vertebral disease and entesopathies, should be carried out, as well as a detailed topography of the different pains reported.

Physical examination should be extensive and include a full review of skin and oral cavity findings, anthropometry,
posture of trunk and limbs, and joint mobility. The skin should be reviewed for the entire list of cutaneous manifestations reported in the various EDS subtypes (for a summary see ref. no. 4). A wider spectrum of mucocutaneous manifestations in JHS/EDS-HT has been recently reported [12]. A similar work is ongoing on cEDS (Colombi, manuscript in preparation).

Concerning skin hyperextensibility, a single reproducible method of assessing this feature is described by using two dots applied to the dorsum of hand and an electronic calliper [13], but this is not yet considered a valid substitute of clinical observation. Hence, skin hyperextensibility can be assessed qualitatively by pinching the dermis and stretching the skin (fig. 1). Sites of skin extensibility testing are dorsum of hand, dorsal aspect of the forearm, lateral aspect of the neck or thorax. Presence of skin hyperextensibility can be arbitrarily registered for a stretching above 3 cm [14]. Soft/velvety/doughy skin is an entirely subjective feeling developed during clinical practice and, hence, cannot be standardized. Various types of scars can be found in EDS. Papyraceous scars (i.e. widened scars with atrophy of the underlying dermis and a “cigarette paper” appearance) are typical of cEDS, but may be found also in the vEDS, kyposcoliotic and arthralgias types, as well as a few other rarer variants. Minor abnormalities of scar formation are more ubiquitous in EDS. Atrophic non-papyraceous scars are common in JHS/EDS-HT and, probably, also in other EDS subtypes. More specifically, atrophic non-papyraceous scars are considered those with a resulting atrophic texture but with a minor extend, so that atrophy can be best appreciated by a gentle stretching of the patient’s skin between the observer’s index finger and thumb. Other types of abnormal scars in EDS include widened post-surgical scars, hemosiderotic scars, hypertrophic scars, depressed scars, and autolesionist atrophic scars. Classic EDS is also often characterized by molluscoid pseudotumors (i.e. recurrent, sometime painful swelling at knees and elbows due to accumulation of whitish, filamentous material which may come out after traumas) and subcutaneous spheroids (i.e. small, hard cyst-like and calcified nodules).

Additional cutaneous findings comprise piezogenic papules (mostly at heels), acrogeria, acquired cutis laxa (dorsum of hands, eyelids, etc), keratosis pilaris, focal hyperkeratoses, striae rubrae and distensae. Chronic gingivitis, recurrent minor haemorrhages from gingiva after teeth brushing or, more rarely, spontaneously, and gingival retractions are common, especially in JHS/EDS-HT and vEDS. Severe parodontitis with early tooth loss is typical of the rare EDS parodontitis type, which still remains with unknown molecular basis [15]. Short or hypoplastic lingual frenulum is a well know feature of cEDS and JHS/EDS-HT [12,16–19], although a few studies present contrasting results [20,21]. Similarly to osteogenesis imperfecta (i.e. another well-known hereditary connective tissue disorder but mainly affecting ossifying tissues) [22,23], EDS may present with gray or bluish sclera [12,24]. Their assessment is usually qualitative, although the Munsell color system may be used to establish the intensity. Accordingly, in EDS, the sclerae are lighter than osteogenesis imperfecta [12]. In vEDS, the skin is typically non-hyperelastic, but thin with markedly evident subcutaneous veins, particularly over the sternum (fig. 2). Additional features of vEDS may include acrogeria and a typical triangular face with thin lips and alae nasi [25]. gJHM is a feature of many EDS variants. This term defines the capability of multiple joints to move beyond the limits usually considered “normal” in the general population. At the moment, there is not any consistent tool able to discriminate between gJHM and generalized normal mobility of joints independently from any modifying factor, such as gender, age, habits and training. The 5-point questionnaire has been delineated in order to check for the presence or not of gJHM in an individual who have lost her/his “double-jointness” by the natural progression of age or other acquired influences (table III) [26]. Objectively, gJHM may be assessed by the Beighton score [27]. It is a clinical and

Figure 1. Examples of skin hyperextensibility in Ehlers-Danlos syndrome, on arm (A) and volar aspect of hand (B).
rapid screening tool originally intended for assessing gJHM in African children, which was subsequently introduced as an item in the Villefranche and Brighton criteria for the various EDS variants and JHS [fig. 3]. As repeatedly demonstrated in JHS/EDS-HT, the Beighton score value naturally reduces by age [10,12,28]. At a mean age of 33 years, the Beighton score turns usually below 4 also in the symptomatic individual. Hence, an adequate physical examination should include the assessment of mobility to all joints and groups of joints, especially those not included in the Beighton score. Standards for the evaluation of normal mobility of all joints in adults are available in Clarkson (table IV) [29]. Orthopedic survey should also include the full array of minor structural and postural anomalies/dysmorphisms related to the underlying HSCTD (table V). Given the wide range of (possibly) associated neurological findings in EDS and the partial overlap between EDS and an increasing number of hereditary myopathies with gJHM [30,31], every EDS patient should undergo a general neurological assessment in order to identify those individuals needing a more in-depth, specialistic assessment. The still incompletely defined clinical spectrum of EDS can be actually intended as dichotomic. We actually know that in most EDS subtypes, the co-existence of multiple symptoms is likely the result of pleiotropic manifestations of the same mutated gene affecting the functions and/or development of different structures at the same time. In parallel, there is a growing body of evidence telling us that gJHM may cause, co-exist or amplify a series of orthopaedic and neurodevelopmental attributes that can be considered “secondary” manifestations of the former (fig. 4).

### Differential diagnosis and diagnostic flow-chart

Actually, the most common presentations of EDS include:

- spontaneous, traumatic or iatrogenic soft tissue or internal organ rupture with clinical or intraoperative evidence of softness or fragility of tissues;
- multiple large and middle arteries anomalies or ruptures in the absence of other risk factors;
- skin fragility with propensity to wound formation or excessive bruising;
- a unusual habitus of the Marfanoid or markedly leptosomic types;

### Table III

<table>
<thead>
<tr>
<th>Question</th>
</tr>
</thead>
<tbody>
<tr>
<td>Could you ever place your hands flat on the floor without bending your knees?</td>
</tr>
<tr>
<td>Could you ever bend your thumb to touch your forearm?</td>
</tr>
<tr>
<td>As a child did you amuse your friends by contorting your body into strange shapes OR could you do the splits?</td>
</tr>
<tr>
<td>As a child or teenager did your shoulder or kneecap dislocate on more than one occasion?</td>
</tr>
<tr>
<td>As a child or teenager did you consider yourself double-jointed?</td>
</tr>
</tbody>
</table>

*Modified from Hakim and Graham [36]. For the presence of historical gJHM, one needs to reply positively in at least two questions.*
Beighton score
Degree of mobility by passive maneuvers in 5 joints (or groups of joints)
One point for each hypermobile joint (see points 1→5)
Score range: 0-9
Generalized joint hypermobility: usually, a score ≥ 5

1. Apposition of the thumbs to the flexor aspect of the forearm; one point for each hand
2. Dorsiflexion of the little fingers beyond 90°; one point for each hand
3. Hyperextension of the elbows beyond 10°; one point for each elbow
4. Hyperextension of the knees beyond 10°; one point for each knee
5. Forward flexion of the trunk with knees fully extended so that the palms of the hand rest flat on the floor; one point

Figure 3. Summary for the assessment of the Beighton score in adults and children with suspected generalized joint hypermobility.

Figure 4. Ideogram synthesizing the clinical spectrum of Ehlers-Danlos syndrome by considering generalized joint hypermobility a hallmark for a constitutional fragility of the connective tissue. On the right, a set of parallel manifestations affecting the various organs and structures emerge as the pleiotropic consequences of the same genetic defect. On the left, generalized joint hypermobility appears as pathophysiologically (causally?) linked to a spectrum of orthopedic and neurodevelopmental attributes. EDS: Ehlers-Danlos syndrome; gJHM: generalized joint hypermobility.
multiple orthopedic and/or neurodevelopmental consequences/attributes of gJHM (fig. 5). After the first referral by any one of these features, rapid screening for the remaining and the identification of at least one additional of the above-mentioned issues typically means that the patient is affected by a HSCTD. In any other situations, an accurate evaluation as previously illustrated is needed in order to further substantiate the clinical suspect. In this setting, the differential diagnosis is usually among the three most common forms of EDS (cEDS, JHS/EDS-HT, and vEDS), the other rarer EDS subtypes, Marfan syndrome and Loey-Dietz syndromes. In specific circumstances, differential diagnosis could include a wider range of HSCTDs with the identification of other rare conditions, such as arterial tortuosity syndrome, osteogenesis imperfecta/EDS overlap or the various cutis laxa syndromes. The differential is usually based on clinical grounds and facilitated by a small set of additional investigations, including heart ultrasound with measurements of the aortic diameters, lower spine MRI, full ophthalmological survey and/or selected standard radiographs.

In selected cases with unusually severe gastrointestinal, neurologic or bleeding features, the exclusion of other acquired or hereditary disorders of the gastrointestinal and nervous systems, as well as clotting diseases, is needed. The list may include inflammatory bowel disease and other malabsorption affections of the gut, multiple sclerosis, hereditary or acquired neuropathies and myopathies, von Willebrand factor deficiency and haemophilies. In these cases, the differential diagnosis is wide and often includes other specialist consultations and further investigations. As some EDS subtypes (i.e. cEDS and JHS/EDS-HT) are relatively common conditions, the concurrence of two separate disorders in the same individual may be also possible. JHS/EDS-HT and, perhaps, other EDS types may manifest with a wide range of related comorbidities, which are still under further examinations and, hence, could be interpreted, in the future, as organ-specific manifestations of the same underlying disorder of the connective tissue. JHS/EDS-HT are likely the most common EDS type. An in-depth differential diagnosis of JHS/EDS-HT from other HSCTDs and myopathies with gJHM is recently available in a monographic issue of the American Journal of Medical Genetics Part C Seminars in Medical Genetics [31,32]. After the clinical suspect of a specific EDS or other HSCTDs, or, at least, a specific subgroup of them, the diagnosis usually

#### Table IV

<table>
<thead>
<tr>
<th>Movement</th>
<th>Maximum standard</th>
<th>Preferred tool</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shoulder elevation through flexion</td>
<td>180°</td>
<td>UG</td>
</tr>
<tr>
<td>Elbow extension</td>
<td>190°–195°</td>
<td>UG</td>
</tr>
<tr>
<td>Elbow pronation-supination</td>
<td>170°</td>
<td>UG</td>
</tr>
<tr>
<td>Wrist flexion</td>
<td>80°–85°</td>
<td>UG</td>
</tr>
<tr>
<td>Wrist extension</td>
<td>70°–85°</td>
<td>UG</td>
</tr>
<tr>
<td>Wrist ulnar deviation</td>
<td>25°–30°</td>
<td>UG</td>
</tr>
<tr>
<td>Wrist radial deviation</td>
<td>15°–20°</td>
<td>UG</td>
</tr>
<tr>
<td>2nd finger MCP joint extension</td>
<td>30°–40°</td>
<td>UG</td>
</tr>
<tr>
<td>PIP and DIP joint extension</td>
<td>0°</td>
<td>UG</td>
</tr>
<tr>
<td>Hip abduction with leg extended</td>
<td>45°</td>
<td>UG</td>
</tr>
<tr>
<td>Hip adduction with leg extended</td>
<td>30°</td>
<td>UG</td>
</tr>
<tr>
<td>Knee extension</td>
<td>180°–190°</td>
<td>UG</td>
</tr>
<tr>
<td>Ankle dorsiflexion</td>
<td>20°–30°</td>
<td>UG</td>
</tr>
<tr>
<td>Ankle plantar flexion</td>
<td>30°–50°</td>
<td>UG</td>
</tr>
<tr>
<td>1st toe MTP joint extension</td>
<td>70°</td>
<td>UG</td>
</tr>
<tr>
<td>Mandible depression</td>
<td>35–50 mm</td>
<td>Ruler or FT</td>
</tr>
<tr>
<td>Mandible protrusion</td>
<td>3–7 mm</td>
<td>Ruler</td>
</tr>
<tr>
<td>Mandible lateral deviation</td>
<td>10–15 mm</td>
<td>Ruler</td>
</tr>
<tr>
<td>Neck rotation</td>
<td>11 cm or 3°</td>
<td>Ruler or FT</td>
</tr>
<tr>
<td></td>
<td>80–90°</td>
<td>Ruler or FT</td>
</tr>
<tr>
<td>Neck flexion</td>
<td>45°</td>
<td>UG</td>
</tr>
<tr>
<td>Neck extension</td>
<td>45°</td>
<td>UG</td>
</tr>
<tr>
<td>Neck lateral flexion</td>
<td>45°</td>
<td>UG</td>
</tr>
<tr>
<td>Thoracolumbar spine lateral flexion</td>
<td>35°</td>
<td>UG</td>
</tr>
</tbody>
</table>

DIP: distal interphalangeal; FT: flexible tape; MCP: metacarpophalangeal; MTP: metatarsophalangeal; PIP: proximal interphalangeal; UG: universal goniometer.

a The lower and the upper end fits better for men and women, respectively.

b 80° in supination and 90° in pronation from midposition.

c From the tip of the chin to the lateral aspect of the acromion process.

#### Table V

<table>
<thead>
<tr>
<th>Feature</th>
<th>General and trunk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low body mass index (leptosomic built)</td>
<td>High upper arm span/height ratio (up to true dolichostenomelia)</td>
</tr>
<tr>
<td>Dorsal hyperkyphosis</td>
<td>Lumbar hyperlordosis</td>
</tr>
<tr>
<td>Rotoscoliosis of mild degree</td>
<td>Asymmetry of the thoracic cage</td>
</tr>
<tr>
<td>Limbs</td>
<td></td>
</tr>
<tr>
<td>Long fingers (occasionally, up to true arachnodactyly)</td>
<td>Fixed subluxation of the costochondral and/or sternoclavicular joints</td>
</tr>
<tr>
<td>Fixed subluxation of the first carpometacarpal joint</td>
<td>Cubitus valgus</td>
</tr>
<tr>
<td>Cubitus valgus</td>
<td></td>
</tr>
<tr>
<td>Femur anteverision</td>
<td></td>
</tr>
<tr>
<td>Patella alta or baja</td>
<td></td>
</tr>
<tr>
<td>Genuum valgum</td>
<td></td>
</tr>
<tr>
<td>Flexible flatfoot</td>
<td></td>
</tr>
<tr>
<td>Hallux valgus</td>
<td></td>
</tr>
<tr>
<td>Cranium</td>
<td></td>
</tr>
<tr>
<td>High-arched/narrow palate</td>
<td></td>
</tr>
<tr>
<td>Short/hypoplastic lingual frenulum</td>
<td></td>
</tr>
<tr>
<td>Hypoplastic/dysmorphic uvula</td>
<td></td>
</tr>
<tr>
<td>Dental crowding</td>
<td></td>
</tr>
<tr>
<td>Mild facial asymmetry/deformational plagioccephaly</td>
<td></td>
</tr>
</tbody>
</table>

In selected cases with unusually severe gastrointestinal, neurologic or bleeding features, the exclusion of other acquired or hereditary disorders of the gastrointestinal and nervous systems, as well as clotting diseases, is needed. The list may include inflammatory bowel disease and other malabsorption affections of the gut, multiple sclerosis, hereditary or acquired neuropathies and myopathies, von Willebrand factor deficiency and haemophilies. In these cases, the differential diagnosis is wide and often includes other specialist consultations and further investigations. As some EDS subtypes (i.e. cEDS and JHS/EDS-HT) are relatively common conditions, the concurrence of two separate disorders in the same individual may be also possible. JHS/EDS-HT and, perhaps, other EDS types may manifest with a wide range of related comorbidities, which are still under further examinations and, hence, could be interpreted, in the future, as organ-specific manifestations of the same underlying disorder of the connective tissue. JHS/EDS-HT are likely the most common EDS type. An in-depth differential diagnosis of JHS/EDS-HT from other HSCTDs and myopathies with gJHM is recently available in a monographic issue of the American Journal of Medical Genetics Part C Seminars in Medical Genetics [31,32]. After the clinical suspect of a specific EDS or other HSCTDs, or, at least, a specific subgroup of them, the diagnosis usually
needs confirmation by laboratory tools. At the moment, molecular testing of the gene(s) known as responsible for the selected disease(s) is considered the most reliable and, possibly, the most time- and cost-effective procedure for diagnosis confirmation. Sanger sequencing of one or a very few genes in case of a specific clinical suspect (e.g. cEDS) probably still represents the best laboratory option. In case of a more vague suspect or in presence of overlapping presentations (e.g. the clinical doubt between vEDS and Loeys-Dietz syndromes), the use of gene panels for next generation sequencing able to analyze a great number of genes simultaneously can be considered and could be shortly introduced in the clinical practice also in Italy. It is of utmost importance to consider that, at the time of this writing, JHS/EDS-HT (considered the most common clinical variants of EDS) still remains without a known molecular basis. Hence, in presence of robust clinical evidence for EDS-HT (Villefranche criteria), JHS (Brighton criteria) or an overlapping phenotype (JHS + EDS-HT = both criteria met) further molecular investigations may be considered superfluous, as the diagnosis of these conditions is still clinical and based on expert exclusion of other EDS subtypes. The use of other intermediate laboratory investigations, such as collagen biochemical studies on cultured fibroblasts (skin biopsy) or the dosage of urinary metabolites [11], should be considered only in highly selected cases and, often, as a pre-screening investigation if molecular diagnostics facilities are not available. A possible exception is represented by the use of collagen biochemical studies of cultured fibroblasts in presence of a strong clinical suspect of cEDS after the exclusion of a COL5A1 and COL5A2 mutation or intragenic rearrangement [3,33].

Once fixed a diagnosis of cEDS, JHS/EDS-HT or vEDS, a set of baseline investigations can be identified by recent evidence or reasonable pathophysiological considerations (fig. 4). These investigations are needed in order to establish the general level of well-being of the patient and to identify specific
criticalities which need prevention or treatment to be consid-
ered in the future follow-up. Although available data on the
natural history of the other rarer EDS variants are really scarce
or absent, a similar approach may be temporary applied in
these conditions with minor modifications according to their
known clinical peculiarities.

Management in brief

The management of EDS includes treatment of acute/emer-
gency manifestations (e.g. dislocations and arterial ruptures),
attenuation of chronic symptoms (e.g. pain and fatigue), and
primary and secondary prevention of acute and chronic
complications. Ideally, an ultra-specialized centre for the
diagnosis and management of EDS should include facilities
for the treatment of both acute and chronic complications.
The actual organization of the Italian National Healthcare
System and its regional peculiarities does not fit well with the
interspersed but lifelong disabilities of many EDS patients and
the centralization of the care of all acute and chronic mani-
festations is really a hard task. At the moment, most patients
face acute complications far away from their reference centre
and often meet professionals without a specific background
in the field of HSCTDs. In Italy, dissemination of knowledge
among medical and non-medical professionals at risk of
commonly encountering EDS patients is actually limited to
information sheets given to patients to be used in case of
medical support away from the reference centre, and occa-
sional training courses for a few attendances. In the future, in
Italy, we will need to systematically introduce the study of
HSCTDs during the university training for MDs, physiothera-
pists and nurses, and realize a shared and updated informa-
tion online resource to be consulted by all professionals in
case of necessity.

Follow-up and management of chronic complaints are per-
fomed in specialized centres also in Italy. As above-menti-
ned, there are at least two main services with clinics (partly)
dedicated to EDS or HCTDs in general. More specifically, both
centres are focused on the diagnosis and long-term man-
agement (outpatient) of patients affected by any EDS subtypes
and at any age. In Rome, the twin service at the San Camillo-
Forlanini and Umberto I University Hospital is mostly focused
on the clinical diagnosis, management and treatment of
selected complaints. In Brescia, the activities span the phe-
notypic delineation, and molecular testing and research.
These two centres are actively collaborating at both clinical
and molecular grounds. At the moment, there is not a
consensus on the minimal set of periodic investigations to be
used in the long-term management of the EDS patient, as
well as the optimal investigation flow-chart in case of specific
chronic complications. A list of investigations, commonly or
possibly used in the management of EDS in the Rome and
Brescia centres, is reported in table VI. We still wait for Italian,
European or International guidelines for supporting with
evidence or agreement our proposed outline. Treatment of
chronic manifestations of EDS lacks of high-evidence data on
the efficacy of any specific procedure. Hence, most interven-
tions are based on some pathophysiological hypothesis and/
or the experience of the single professional. The physiother-
apy and occupational therapy requested by the disabled child
or adult with EDS probably represents one of the biggest
problems in Italy. To our knowledge, not any service of the
National Healthcare System has been systematically involved
to the long-term orthopaedic and neurologic disabilities of
EDS. We hope for a future (r)evolution of the rehabilitative
approach to the EDS patient in Italy.

Prevention and treatment

Skin and mucosae

Propensity to skin lesions and capillary ruptures may be
efficaciously contrasted by the use of bandages or hard
protections at sites of major risk for traumas, such as legs,
knees and elbows. In conditions with severe cutaneous fra-
gility, the use of protection for the forehead and scalp can be
also considered. These interventions are usually requested
for the child. Adults usually know their skin fragility and behave
accordingly. In general, daily intake of vitamin C improves
propensity to ecchymoses and minor haemorrhages with a
dose of 500 up to 3000 mg/day (dosage based on age and
severity of propensity). Gingival haemorrhages, inflammation
and retractions may be delayed or prevented by correct but
gentle oral cavity hygiene with soft toothbrushes. Severe
gingival retractions may lead to premature tooth loss and
could need aggressive treatment. In this case, gingival trans-
plantation is possible but surgery requests specific attentions
(reported below). Similarly, also superficial/dermatological
surgery or repair of traumatic wounds should adhere to the
following recommendations. Xerophthalmia with positive
Schirmer test is a known feature of JHS/EDS-HT [34]. Dry
mucosae seem a feature of EDS in general. The use of artificial
tears and vaginal lubrication (especially during sexual inter-
course) is indicated in case of recurrent symptoms. Adequate
daily hydration is a further harmless remedy, which improves
mucosa and other complaints (see below). Vitamin A, E and F,
coenzyme Q10, carnitine are other micronutrients with poten-
tial beneficial effect on skin and mucosal integrity [35]. Vита-
mín A should be used with extreme care due to its teratogenic
potential, especially in fertile women. In patients with marked
skin fragility (i.e. some individuals with cEDS or dermatospa-
raxis), post-traumatic wounds may benefit of prophylactic
application of antiseptics (e.g. argentium sulfadiazine) and deep
wounds may be treated by wound healing agents (e.g.
aqueous extract of Triticum vulgare in form of soaked gauzes
or cream).
### Table VI
Checklist and timetable for useful investigations in Ehlers-Danlos syndromes.

<table>
<thead>
<tr>
<th>Investigation</th>
<th>First execution</th>
<th>Subsequent executions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart ultrasound</td>
<td>Baseline</td>
<td>Every 2–3 years in children and every 3–5 years in adults, if negative</td>
</tr>
<tr>
<td>Bone densitometry</td>
<td>Baseline (also in children)</td>
<td>Every 3–5 years, if negative&lt;br&gt;Every year, if positive but in presence of additional risk factors (e.g. menopause)</td>
</tr>
<tr>
<td>Full ophthalmological survey&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Baseline</td>
<td>Every 2–3 years in children and every 3–5 years in adults, if negative</td>
</tr>
<tr>
<td>Full non-invasive vascular tree assessment&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Baseline (vascular EDS)&lt;sup&gt;c&lt;/sup&gt;</td>
<td>Every 1–2 years, if negative&lt;br&gt;By specialist’s opinion, if positive</td>
</tr>
<tr>
<td>Head-up tilt-test</td>
<td>Orthostatic intolerance or other dysautonomic cardiovascular features</td>
<td>In case of worsening of symptoms despite treatment</td>
</tr>
<tr>
<td>Brain MRI</td>
<td>Disabling occipital/postural headache, seizures, pure X-linked dominant transmission or confirmed FLNA mutation</td>
<td>Not necessary or by specialist’s opinion</td>
</tr>
<tr>
<td>Total spine MRI</td>
<td>Disabling back pain with or without suspected radiculopathy, recurrent orthostatic/postural headache</td>
<td>Not necessary or by specialist’s opinion</td>
</tr>
<tr>
<td>Electromyography</td>
<td>(Proximal) muscle weakness</td>
<td>Not necessary or by specialist’s opinion</td>
</tr>
<tr>
<td>Nerve conduction studies</td>
<td>Distal muscle weakness, distal sensory disturbances, absence of deep tendon reflexes, suspected peripheral or compression neuropathy</td>
<td>Not necessary or by specialist’s opinion</td>
</tr>
<tr>
<td>Pulmonary function tests</td>
<td>Exertional dyspnea, unexplained fatigue</td>
<td>Not necessary or by specialist’s opinion</td>
</tr>
<tr>
<td>Polysomnography</td>
<td>Positive screening for nocturnal airways obstruction</td>
<td>Not necessary or by specialist’s opinion</td>
</tr>
<tr>
<td>Non-invasive GI investigations&lt;sup&gt;d&lt;/sup&gt;</td>
<td>One or more chronic functional GI symptoms</td>
<td>Not necessary or by specialist’s opinion</td>
</tr>
<tr>
<td>Invasive upper GI investigations&lt;sup&gt;e&lt;/sup&gt;</td>
<td>Severe or treatment refractory upper gut symptoms, after specialist’s consultation</td>
<td>By specialist’s opinion</td>
</tr>
<tr>
<td>Other functional GI investigations&lt;sup&gt;f&lt;/sup&gt;</td>
<td>Persistence of GI-related disability, after specialist’s consultation</td>
<td>By specialist’s opinion</td>
</tr>
<tr>
<td>Contrast ultrasound for defecography</td>
<td>Suspected rectocoele, after specialist’s consultation</td>
<td>By specialist’s opinion</td>
</tr>
<tr>
<td>Pelvic MRI</td>
<td>Suspected uterine or multiple organ prolapse, after specialist’s consultation</td>
<td>By specialist’s opinion</td>
</tr>
<tr>
<td>Urologic and urodynamic assessment&lt;sup&gt;g&lt;/sup&gt;</td>
<td>Recurrent urinary tract infections, and/or suspected cystocele or urinary voiding dysfunction, after specialist’s consultation</td>
<td>By specialist’s opinion</td>
</tr>
</tbody>
</table>

EDS: Ehlers-Danlos syndrome; GI: gastrointestinal.

<sup>a</sup>Also including anterior chamber study and Schirmer’s test.

<sup>b</sup>In fully asymptomatic patients, the survey can be performed by Doppler ultrasound of epiaortic vessels, four limbs arteries and abdominal aorta, and intracranial angio-MRI. In presence of doubtful findings, more extensive or invasive investigations, such as total body angio-MRI and angio-CT with slow contrast injection, can be considered.

<sup>c</sup>A similar approach may be extended to all EDS variants with vascular fragility, such as vascular EDS, classic EDS with arterial rupture and kyphoscoliotic EDS.

<sup>d</sup>Including celiac disease autoantibodies screening, Heliocobacter pylori infection screening, hydrogen breath and d-xylose test.

<sup>e</sup>Upper GI endoscopy, esophageal manometry and 24-h pH-metry.

<sup>f</sup>Deglutition study, gastric emptying study, small bowel manometry and colorectal transit study.

<sup>g</sup>Urine analysis, urine culture, kidney and bladder ultrasound for bladder capacity and post-void residue, and uroflowmetry; consider voiding cystourethroscopy in case of recurrent urinary infections.
Table VII
Recommendations for the treatment of pain in Ehlers-Danlos syndromes (particularly, EDS-HT and JHS) available in Italy.

Recommendation

Preventing acute joint and muscle injury/pain
- Regular physical activity
- Avoid smoking and over/underweight
- Stabilize excessively loose joints with soft bracing and/or taping
- Improve ergonomics at home, school and workplace

Treating acute/recurrent joint and muscle pain
- Active rest
- Cold/heat pack application
- Joint stabilization avoiding complete immobilization
- Physical therapy application contrasting muscle spasm
- NSAIDs/paracetamol and/or minor opioids at full dosage

Preventing chronicization of pain
- Optimize treatment of acute/recurrent musculoskeletal pain
- Personalized, long-term physical therapy program based on both passive and active exercises and improving proprioception and muscle tone/strength
- Maintain autonomy/regular physical activity by pacing after periods of immobilization/re-acutization of pain and with the support of an occupational therapist
- Regularly perform activities focused on stress management
- Improve sleep quality
- Request specialized psychological support for improving coping strategies (i.e. cognitive-behavioral therapy)

Treating chronic pain
- As above and
- Personalized painkiller drug schedule, including NSAIDs and/or opioids, as well as other pain modulators in presence of specific pain phenotypes

Consider an integrative (multi-modal) approach including non-traditional medicine resources

Options to consider with caution
- Orthopedic surgery, especially classic interventions on tendons, ligaments and joint capsules
- Generous prescription of periods of inactivity and abstention from regular sport activity
- Use of myorelaxants
- Chronic systemic use of steroids
- Use of antiplatelet drugs, e.g. as acetylsalicylic acid
- Use of antiepileptic drugs

Adapted from Castori et al. [39].
All recommendations presented in this table MUST be considered low-level treatments for EDS. Some patients refer some improving of acute/recurrent musculoskeletal pain by the use of non-traditional resources, such as gentle chiropractic, ultrasound, deep heat, TENS, and epsom/magnesium salt baths (2 cups in warm water for ~ 15 min). Although most of these integrative resources have a few or no major side effects, their use should be considered with caution.

Pain and orthopaedic issues

Musculoskeletal pain is common in EDS, is associated with regular analgesic use, gHM, dislocations, corrective surgery, and is strongly related to functional impairment [36,37]. Great attention has been posed on the nature and evolution of pain in JHS/EDS-HT, the clinical form of EDS in which pain represents a great disability factor together with fatigue [38]. In this condition, pain increases with age in terms of intensity and number of painful foci, with a progressive transition from recurrent “growing pain” in infancy and childhood, to generalized recurrent or chronic musculoskeletal pain in adulthood, to a more severe chronic pain syndrome with central sensitization in the most severely affected individuals [39]. Classically, occasional or even recurrent joint pain may be related to propensity to joint micro- and macrotraumatisms. However, the evolution in pain phenotype implies a more significant involvement of the peripheral and central nervous system, as recently suggested by the preliminary findings of generalized hyperalgesia in adults with JHS/EDS-HT by the Ghent Research Group [40]. Tailored management schedule for pain and orthopaedic injuries is still lacking in EDS. Macrotraumatisms (i.e. dislocations, sprains, strains and acute tenosynovites) should be first treated conservatively according to standard procedures. Orthopaedic surgery needs accurate pros and cons evaluation in relation to procedural risks (see below) and chance of recurrences or loco-regional complications due to laxity of tissues. Consequences of repeated microtraumatisms (i.e. include chronic arthralgias, myalgias and precocious osteoarthritis) may be treated with painkillers (paracetamol, NSAIDs, minor opioids) and a wide range of non-traditional remedies. The efficacy of these treatments usually decreases with the chronicification and evolution of the symptomatology. While painkillers and other resources are effective during the first years after the onset of pain, they are usually useless in more
advanced stages. Chronic/recurrent musculoskeletal pain tends to associate with physical disability, which emerges from the multiplicative effects of behavioral strategies established for contrasting pain and progressive worsening of articular instability, muscle tone and proprioception. The treatment of such a physical disability is complex and often need a multidisciplinary approach, involving physiatrists, orthopaedic surgeons, neurologists or specialists in pain management, physiotherapists and occupational therapists [41]. Table VII summarizes a reasonable approach to the management of pain in EDS, which we follow in Italy. Lower bone mass is a well-known feature of JHS/EDS-HT in adults [42–44] and can be found in other rarer EDS subtypes, such as the osteogenesis imperfecta/EDS overlap due to mutations in COL1A1. As reduced bone mass may predispose to fractures and early joint damage, it should be carefully checked and treated accordingly.

Fatigue and autonomic dysfunction

Though largely ignored in the past, severe fatigue is now considered a common accompanying feature of EDS, particularly JHS/EDS-HT, as it is reported in up to 84% of the patients [45]. Similar results are obtained by other research groups [28,46]. More specifically, the frequency (and, perhaps, severity) of fatigue is influenced by age with a rate of 28% in the first decade of life to 90% in adults over 40 years of age [28]. In JHS/EDS-HT, the impact of fatigue on daily life is often equal or more dramatic than the impact of pain [45]; a fact that underscores the importance of fatigue for both assessment and treatment planning in these patients. A complex presentation of fatigue resembling chronic fatigue syndrome according to Fukuda et al. [47] is reported in most adults with JHS/EDS-HT [48].

Some possible contributors to fatigue-related disability have been investigated in EDS and include sleep disturbances, concentration problems, social functioning, self-efficacy concerning fatigue, and pain severity [45]. A few experimental studies demonstrate that fatigue associates with muscle weakness [49,50], worsens with exercise [51] and affects gait pattern [52]. Recently, dysautonomia has been recognized as one of the most relevant pathogenic factors influencing fatigue onset and evolution. This feature, mostly studied in JHS/EDS-HT, often presents with orthostatic tachycardia syndrome [53] and/or orthostatic intolerance, and seems to relate to an increased sympathetic activity at rest and reduced sympathetic reactivity to stimuli [54]. A summary of the management approach to fatigue for EDS in Italy is presented in Table VIII.

Cardiovascular complications

Mitral or other cardiac valve prolapse/insufficiency is considered a common finding in most EDS subtypes. However, rarely it represents a real clinical problem and does not need specific management in most cases. Classic EDS and JHS/EDS-HT may also present aortic root dilatation (10–13%). At difference with other HSCTDs, such as Marfan syndrome, aortic root dilatation in cEDS and JHS/EDS-HT is a benign trait and is often non-progressive after puberty/adolescence [55–57]. Therefore, pharmacologic prevention of aneurysm rupture is still questioned in cEDS and JHS/EDS-HT. Additional, clinically insignificant cardiac findings include impaired left ventricular relaxation, elongated cardiac silhouette and prominent right coronary artery [57]. In JHS/EDS-HT, electrophysiological studies may often reveal moderate excess in duration of the PR interval and P wave, and various minor conduction defects at standard or 24 h ECG [58].

Table VIII

<table>
<thead>
<tr>
<th>Recommendations for the treatment of fatigue in Ehlers-Danlos syndromes (particularly, EDS-HT and JHS) available in Italy.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Recommendation</strong></td>
</tr>
<tr>
<td><strong>General</strong></td>
</tr>
<tr>
<td>Optimal sleep hygiene (consultable at yoursleep.aasmnet.org/Hygiene.aspx)</td>
</tr>
<tr>
<td>Regular physical exercise</td>
</tr>
<tr>
<td>Weight control (avoid over- and underweight)</td>
</tr>
<tr>
<td>Avoid smoking and alcohol</td>
</tr>
<tr>
<td>Unrefreshing sleep</td>
</tr>
<tr>
<td>Bedtime intake of melatonin (3–5 mg for adults) in case of insomnia</td>
</tr>
<tr>
<td>Bedtime intake of painkillers (e.g. ibuprofen) in case of nocturnal pain</td>
</tr>
<tr>
<td>Pharmacologic and non-pharmacologic treatment of gastroesophageal reflux in case of nocturnal events</td>
</tr>
<tr>
<td>Sleep clinic evaluation in case of persistent poor sleep quality</td>
</tr>
<tr>
<td><strong>Muscle weakness</strong></td>
</tr>
<tr>
<td>I-acetyl-carnitin and coenzyme Q10 daily intake at appropriate dosage</td>
</tr>
<tr>
<td><strong>Orthostatic intolerance</strong></td>
</tr>
<tr>
<td>Generous liquid intake preferring isotonic drinks</td>
</tr>
<tr>
<td>Salt integration to the diet (to avoid in case of systemic hypertension)</td>
</tr>
<tr>
<td>Fragmented meals avoiding refined carbohydrates</td>
</tr>
<tr>
<td>Elastic stockings (and abdominal binders)</td>
</tr>
<tr>
<td>Head-up tilting at night</td>
</tr>
<tr>
<td>Teaching physical counter-maneuvers</td>
</tr>
<tr>
<td>Consider drug use in case of persistence of symptoms and positive autonomic investigations</td>
</tr>
<tr>
<td><strong>Respiratory complaints</strong></td>
</tr>
<tr>
<td>Consider pharmacologic treatment/prevention of pulmonary obstructive disease</td>
</tr>
<tr>
<td><strong>Food intolerances/malabsorption</strong></td>
</tr>
<tr>
<td>Consider appropriate food restrictions in case of confirmed intolerance(s)</td>
</tr>
</tbody>
</table>

Adapted from Castori et al. [59].
All recommendations presented in this table MUST be considered low-level treatments for EDS.
intracranial aneurysms with secondary haemorrhage, spontaneous carotid-cavernous sinus fistula, and cervical artery dissection [59,60]. Carotid-cavernous sinus fistula is actually considered a peculiar feature of vEDS and has been included as a minor criterion in the Villefranche nosology [5]. Vascular complications affecting abdomen and the gastrointestinal tract are reported below. Thoracoabdominal aorta [61], subclavian artery [62] and coronary artery [63] can be commonly affected. Vascular surgery interventions in presence of acute symptoms due to arterial rupture are a hard task in vEDS, because the extreme fragility of the soft tissues and vessels affects surgical outcome and chance of short-term survival. Novel approaches using endovascular therapy with coil embolization proved effective in the treatment of ruptured pseudoaneurysms, visceral aneurysms, and carotid-cavernous fistulas in vEDS. Recent literature shows that elective repair of malformed vessels at risk of rupture may be effective in vEDS [64]. Hence, periodic vascular tree examination can be useful for detecting vascular anomalies treatable electively. A single study demonstrates three-fold reduction of risk in arterial rupture in vEDS by the use of the beta-blocker celioprol [65]. These considerations may be equally applied to other EDS variants with vascular fragility.

**Gastrointestinal and pelvic issues**

Also concerning gastrointestinal and pelvic issues, actual knowledge in EDS chiefly concerns the commonest clinical types, namely cEDS, vEDS and JHS/EDS-HT. More specifically, most papers treat single patients or group of patients with vEDS and JHS/EDS-HT, while only a few works concern cEDS. Although gastrointestinal manifestations are not yet included in any diagnostic set of criteria for the various EDS subtypes, they often have a major role in the quality and quantity of life of many patients, who request expert counselling. The spectrum of gastrointestinal and pelvic manifestations linked to EDS is wide and ranges from: (i) acquired and congenital structural anomalies of the abdominal wall, diaphragm, pelvis and gut, to (ii) chronic functional symptoms and related disability, to (iii) acute presentations due to vascular or hollow organ spontaneous (or iatrogenic) ruptures. While manifestations of (i) and (ii) are typical of JHS/EDS-HT, (iii) is specific of vEDS. Concerning cEDS, accumulated data are too scarce to depict a recurrent GI phenotype. However, cEDS patients seem to present manifestations mostly belonging to acquired and congenital structural anomalies of the abdominal wall, diaphragm, pelvis and gut, although also spontaneous vascular ruptures may rarely occur. In addition, mucosal fragility manifesting as multiple mucosal erosions possibly leading to occult haemorrhages and chronic anaemia is a further possibly underestimated gastrointestinal manifestation of cEDS.

The greatest amount of data concerns JHS/EDS-HT treated as a whole and recently reviewed in Castori et al. [34]. Actual knowledge concerning gastrointestinal and pelvic manifestations of JHS/EDS-HT can be summarized as follows:

- abdominal hernias occur in up to one fifth of the patients, the chance of occurrence increases with age, and their surgical treatment seems effective under standard procedures;
- rectal (and other pelvic) prolapse is observed in more than one tenth of women. It can occur in nulliparous women but its rate is highest in those who underwent episiotomy. As the chance of faecal incontinence as symptomatic surrogate of pelvic dysfunction associates with high-risk deliveries also in the general population, in JHS/EDS-HT pregnant women, it seems reasonable to recommend caesarean section as the first-choice delivery modality in order to prevent long-term disabilities in an affected mother. Treatment of symptomatic pelvic prolapse remains problematic in JHS/EDS-HT. The rate of rectal prolapse in men and children with JHS/EDS-HT remains unknown but is plausibly low;
- ptosis of internal organs, such as stomach, transverse colon and kidney is described in a few clinical reports. Although apparently rare, renal, colonic and gastric ptosis may be underestimated in JHS/EDS-HT. Treatment by organopexy is generally unsuccessful [66–68] and the link between such an anatomic feature and the presumably associated symptoms remains unclear in JHS/EDS-HT. Colonic resection by laparoscopy resulted effective once [69];
- hiatus hernias and intestinal intussusceptions are likely additional structural manifestations of gastrointestinal involvement in JHS/EDS-HT, but available data are too preliminary to affirm a non-casual relationship;
- collectively, the rate of functional gastrointestinal symptoms is high, increases with age and ranges from ~ 1/3 to ~ 3/4 of the patients. Although gastrointestinal manifestations are still not included in the available clinical criteria for JHS/EDS-HT, their frequency and related impact on quality of life suggest consideration of GI involvement as a major feature of this condition;
- in JHS/EDS-HT, functional gastrointestinal features span from mouth to anus and mainly include dysphagia, gastroesophageal reflux, dyspepsia, irritable bowel disease and chronic constipation. The typical adult patient presents with multiple, variably combined symptoms, while (isolated) chronic constipation is the most common manifestation in children;
- functional tests, including oesophageal manometry, 24 h pH-metry, gastric emptying study, small bowel manometry and colorectal transity study, often lead to positive results but should be considered second-line investigations and performed in highly specialized settings, preferably by professionals with experience on JHS/EDS-HT [70]. Swallowing studies could be also considered in patients with upper gastrointestinal complaints but evidence is still lacking;
• first-line investigations, such as upper gastrointestinal endoscopy, could be performed safely, but usually lead to negative or inconsistent results. Colonoscopy should be performed with care due to a possibly increased risk of mucosal bleeding. Colonic redundancy, ptosis and/or hypermobility may be further limitations to colonoscopy [71];
• treatment of functional gastrointestinal complaints in JHS/EDS-HT is problematic due to the absence of tailored strategies and an apparent resistance to pharmacologic treatments at standard dosages/ regimens. The exclusion of common co-morbidities, such as celiac disease, lactose intolerance, small bowel bacterial overgrowth and Helicobacter pylori infection, is reasonable at first examination;
• due to the lack of efficacious treatments and the absence of known precipitating triggers (perhaps, except for inadequate surgical treatment of internal and pelvic organ prolapse(s) as well as traumatic deliveries) patients’ education, also comprising diet and nutritional advice seems at the moment the most effective management tool.

Gastrointestinal involvement in cEDS seems less severe and rarer that in JHS/EDS-HT. Available knowledge is limited to a dozen of case reports. In particular, bowel dilatation with or without malrotation occurred four times [68,72–74], gut diverticula and related complications (i.e. diverticulitis, gut perforation) twice [72,74,75], spontaneous gut perforation (apparently, not secondary to diverticula) twice [73,76], evagination of the diaphragm twice [76,77], multiple mucosal erosions (possibly leading to anaemia) twice [73,74], haemorrhoids once [72], rectal redundancy and inguinal hernia once [78], and lethal haemorrhage due to intra-abdominal vascular fragility once [79]. Management of these complications has been usually carried out following standard approaches. However, surgical and anaesthesiological advice is recommended as follows. No detail is available concerning functional gastrointestinal features in cEDS. The types of gastrointestinal manifestations in vEDS are globally different from cEDS and JHS/EDS-HT, and may represent the reason of ascertainment. In vEDS, internal and vascular organ fragility is extreme and may manifest with spontaneous colonic perforation [80], colonic intramural hematoma [81], splenic rupture [82], hepatic and inferior vena cava rupture [83], and aneurysms at risk of rupture of various intrabdominal vessels, such as splenic [84], ileocolic [85] and mesenterial arteries [86], hepatoportal fistula [87], and retroperitoneal haemorrhage [88]. Many of these reports are described before the publication of the revised Villefranche criteria or concern patients without a formal molecular confirmation. Treatment strategies are reported below.

Surgery and anaesthesia
Surgery is a major issue in most EDS variants. Tissue fragility and hyperextensibility predispose to ruptures of organs and vessels, to visceral ptoses and prolaxes, and increases mobility of the intrabdominal viscera with a theoretically augmented risk of intussusceptions and functional symptoms. In addition, vascular fragility and impaired tissue repair ease intra- and post-operative complications with various degrees among the different types of EDS. Such a risk is the highest in EDS variants with increased vascular fragility (i.e. vEDS, classic EDS with arterial rupture due to mutations in COL1A1 and kyphoscoliotic EDS), but may be encountered with a minor severity in many EDS subtypes. For these reasons, invasive surgery is generally not recommended and should be always postponed except for acute (irreversible) situations or in case of elective surgery with documented or strongly presumed efficacy in EDS. Surgical procedure needs cautions with minimal surgical dissection and use of minimal lateral force during incisions, retraction and suturing [89]. Surgical haemostasis may be difficult and the use of vessel clumping should be avoided or, at least, held lightly due to the risk of tearing [89,90]. Also skin closures after surgery request special precautions. In particular, closures should be performed in two layers (subcutaneous and cutaneous) with minimal tension, sufficient amount of sutures, deep stitches and the support of steristrips, by using proper distance to the incision in order to avoid sutures cutting through the fragile tissue, and without the use of skin clips. Finally, sutures should be left twice as long as normally recommended in order to avoid wound re-opening [91,92]. Additional useful information and details on surgical procedures, particularly concerning gastrointestinal surgery, in EDS are available in Burcharth and Rosenberg [92]. Not only surgery, but also anaesthesia and perioperative management need a tailored approach in EDS. This is mostly influenced by some primary disease features, including vascular, thecal and mucosal fragility, propensity to ecchymoses and the risk of haemorrhage, but also by several common co-morbidities, such as autonomic dysfunction, occipitotransaxial joint instability, spondylitis. A freely downloadable summary of recommendations concerning preoperative evaluation, patient monitoring and positioning, airway management, circulatory and bleeding issues, pharmacology, use of tourniquets, central venous catheterization, obstetrical, regional and local anaesthesia, and other aspects, is available at the OrphanAnesthesia website (http://www.orphananesthesia.eu/en/rare-diseases/published-guidelines/cat_view/61-rare-diseases/60-published-guidelines/89-ehlers-danlos-syndrome.html) or in the work by Wiesmann et al. [93].

Pregnancy and delivery
Fertility is usually unaffected in EDS. First and second trimesters generally proceed without significant increase of complications, except for a single questionnaire study, which highlights a possible excess of spontaneous abortions (57.2%) and ectopic pregnancies (5.1%) in EDS [94]. Curiously, a few reports describe the association between amniotic band
formation/amniotic band-like constrictions in vEDS trice [95-97] and in cEDS once [98]. Disease-related problems may arise in the third trimester, when prognosis generally turns worse in vEDS than in cEDS and JHS/EDS-HT. Pre-term delivery is a relatively common complication in all prevalent forms of EDS, but it occurs relatively earlier in vEDS than other EDSs [99-102]. There is not a consensus on the preferred type of delivery in EDS [100]. In cEDS and JHS/EDS-HT, both vaginal delivery and caesarean section can be performed safely for the mother and baby. However, caesarean section should be preferred in, at least, JHS/EDS-HT, because vaginal delivery with episiotomy seems to be associated with an increased risk of pelvic prolapses [101]. In vEDS, and, likely, in all other EDS types with increased vascular fragility (e.g. cEDS with arterial rupture due to mutations in COL1A1 and kyphoscoliotic EDS), both vaginal delivery and caesarean section have possible life-threatening complications [102]. Vaginal delivery exposes to an increased risk of maternal death for untreated haemorrhages due to uterine or vascular ruptures, and perinatal deaths for irreversible hypoxic-ischemic damage. In turn, caesareans section performed pre-term may prevent uterine rupture during labour, but exposes the mother to surgical risks (see below). Especially in vEDS, delivery needs planning and prevention or early treatment of peri- and postpartum haemorrhages. Too little evidence is available for all other EDS subtypes concerning pregnancy and delivery.

Due to a possibly increased risk of amniotic band formation, invasive prenatal diagnosis could be better performed by chorionic villus sampling than amniocentesis [103,104]. Effective termination of pregnancy may be performed safely before 16 weeks in EDS [105]. Abnormal foetal presentation, transitory neonatal hypotonia, abdominal hernias and congenital dislocations/joint dysplasias are reasonably more common in newborns with EDS [100,106,107]. Congenital skin lacerations and skull fractures may be a neonatal presentation of dermatosparaxis EDS [108].

Genetic counselling

All EDS variants are hereditary disorders. Hence, in all families with at least one affected individual, there is the risk that other family members (born or not yet born) may be affected by the same disorder. Intrafamilial clinical variability is expected for most EDS subtypes. Therefore, the prediction of the eventual severity for an unborn patient found carrier of the causative mutation, as well as of the a posteriori chance that an apparently unaffected/asymptomatic relative of an EDS patient has of being carrier of the trait or at risk of developing future symptoms may be a hard task. Many EDS subtypes show an autosomal dominant pattern, while others are transmitted with an autosomal recessive inheritance. When possible, the identification of the causative mutation(s) eases the identification of non-penetrant carriers of a dominant trait, as well as of a heterozygous carrier of a recessive trait. Molecular results can, therefore, predict the real risk that a carrier has of transmitting the causative mutation. In autosomal dominant trait with negative family history, molecular testing can confirm the de novo nature of the disease. Prognostication of the postnatal phenotype in prenatal diagnosis is still hampered by the limited knowledge concerning clinical variability of each genetic subtype. In general, intrafamilial variability is more marked in dominant traits than in the recessive ones. Given the relatively benign course of many EDS variants and the adult onset of most of the severest complications, families rarely request prenatal diagnosis. More limits characterize the few EDS variants without a known causative gene. This is the case of JHS/EDS-HT and EDS parodontitis type, in which molecular testing is not available and all the above considerations are nearly impossible.

Disclosure of interest

The authors declare that they have no competing interest.

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