

Hemostaseology: Differential Diagnosis of Blood Disorders

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Cuts can occur anywhere and any time in daily life—playing sports, working around the home or at work! Fortunately, after a short blood loss, the wound is closed either spontaneously or using only a plaster bandage. But what happens if the apparently minor moment of carelessness suddenly becomes a life-threatening event? What is 'hemophilia' as it is commonly known? This article explains the range of blood disorders, most of which are hereditary and discusses ways to lead an almost incident-free life despite having one.



Definition of Hemostaseology

Within the wider context of the physiology of blood, the science of hemostaseology focuses specifically on **blood clotting events, inhibition of the coagulation pathway, and dissolution of existing blood clots**. Research topics in this area include:

1. The complete clotting process with all the participating coagulating factors, which mutually regulate each other to trigger a coagulation cascade
2. Synthesis of coagulation factors in the vascular endothelium
3. The role of platelets (thrombocytes) in hemostasis (clotting)

Summary: Hemostaseology deals with the complex interactions between blood vessels, coagulation factors, and blood cells. Rudolf Marx, who co-founded this discipline, defined hemostaseology as the 'slowing down and stopping' of the blood.

The process of coagulation is divided into the following three phases: **vasoconstriction, primary hemostasis, and secondary hemostasis**. A detailed description of the

mechanism of the coagulation cascade can be found in the article: [The biochemistry of blood.](#)

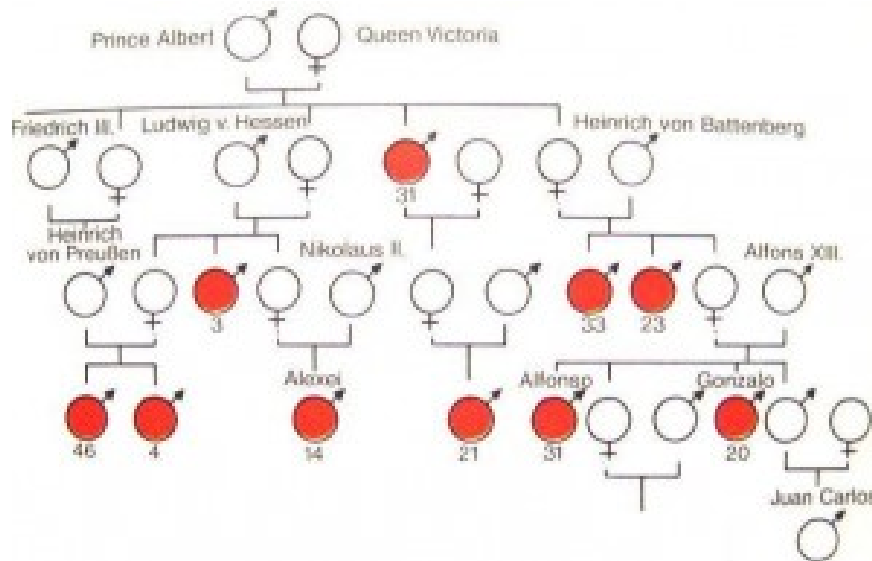


Image: Inheritance of hemophilia. By Caro1409, License: [CC BY-SA 3.0](#)

Definition of Bleeding Disorders

Bleeding and blood coagulation disorders are more commonly known as 'hemophilia'. They alter the **bleeding type pathologically**, i.e., an extended period of time until coagulation occurs, which depends on the severity of the case and is managed therapeutically via medications. Blood coagulation disorders can be hereditary or result from other causes.

Hemophilia Types A and B

Hemophilia is an X-linked recessive **genetic disorder**, which explains why **more males** than females are affected: The defect in female patients is canceled by the presence of a second X chromosome in female genes.

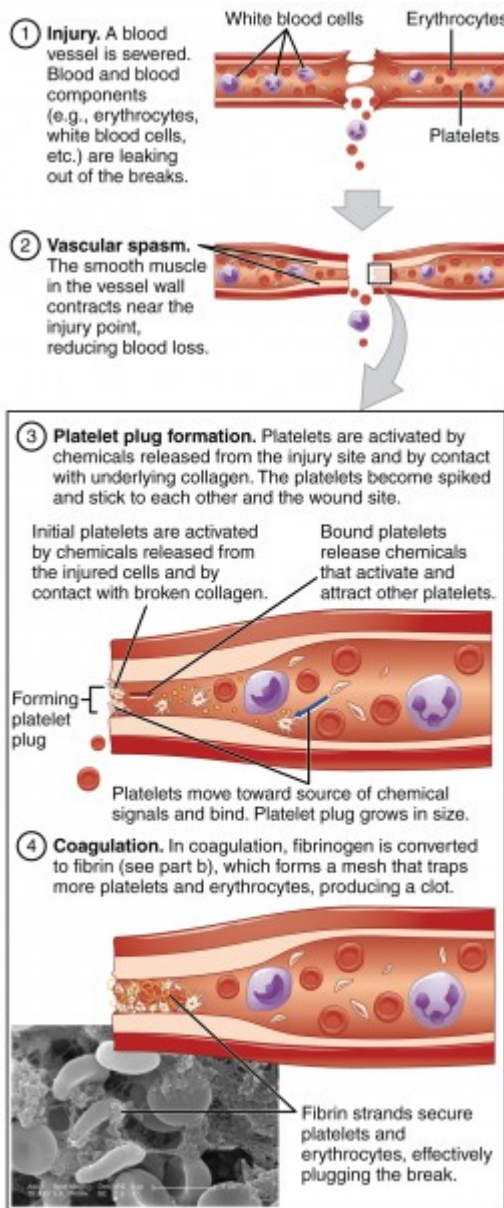
The condition can be distinguished by the lack of a protein, a coagulation factor, which under specific physiological conditions, promotes blood coagulation and thus facilitates wound healing following an injury.

Epidemiology of Hemophilia Types A and B

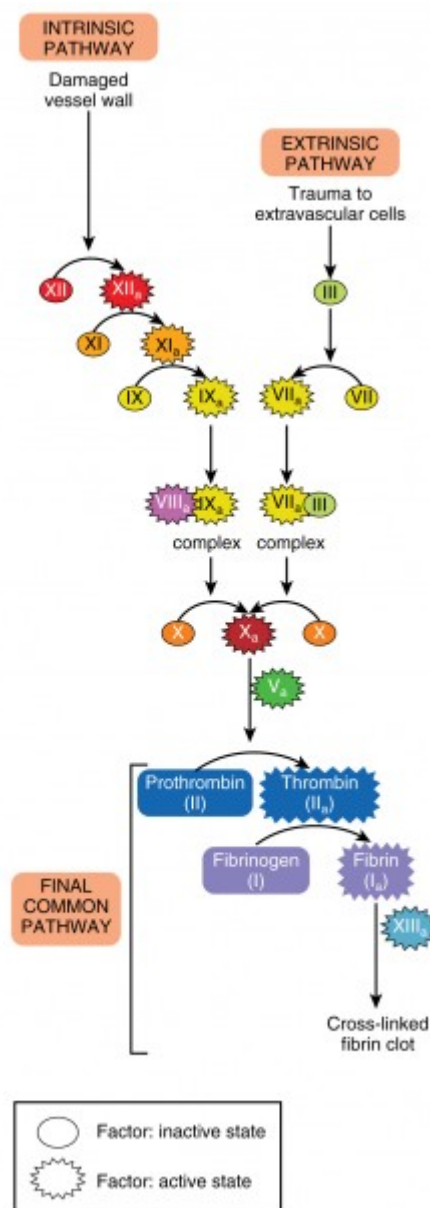
There are two distinct forms of hemophilia, type A and type B. According to the World Federation of Hemophilia, type A affects one person in every 10,000, whereas type B affects only 1 in 50,000 patients. It is estimated that 400,000 people are diagnosed with hemophilia worldwide, which indicates that this disease is a rare hereditary disease.

Hemophilia A, where coagulation factor VIII is missing, accounts for 80% of cases. In the remaining 20% of hemophilia B cases, the coagulation factor IX is the missing factor. The signal cascade of **intrinsic coagulation** is, therefore, not fully functional, suggesting that the formation of a fibrin framework and subsequent clotting is not possible. This phenomenon significantly increases bleeding times and impairs wound healing.

Symptomatically, hemophilia is characterized by spontaneous bleeding in the joints and muscles in the absence of prior injury, which can lead to serious complications and damage such as **arthropathy**, for example.



(a) The general steps of clotting



(b) Fibrin synthesis cascade

Image: Hemostasis. By philschatz, License: [CC BY 4.0](https://creativecommons.org/licenses/by/4.0/)

Treatment of Hemophilia A and B

Substitution Therapy for Hemophilia A and B

As a prophylactic treatment, patients are injected intravenously with **recombinant coagulation factor VIII**.

The manufacture of the protein comprising 2,200 amino acids, is a synthetic challenge for clinical chemists, due to the short shelf life of the protein in the serum. Currently, the coagulation factor is synthesized as a powder and is only combined with the serum and injected as needed.

However, substitution therapy is not completely without complications. First, 30% of all treated patients develop an antibody against the synthetic factor VIII protein. Second, the protein has a short half-life within the body and is, therefore, metabolized relatively quickly.

Research is ongoing to advance the therapy and reduce the need for injections required by patients with particularly severe cases of hemophilia. The latest research results show that the half-life can be extended via **PEGylation** of factor VIII protein by covalently attaching the molecule polyethylene glycol (PEG) to factor VIII protein. The covalent modification increases the overall size of the molecule and obviates the need for filtration and excretion by the [kidneys](#) (**Renal Clearance**).

Gene Therapy for Hemophilia A and B

Further, gene therapy can be used to introduce factor VIII-producing gene via a virus into the [liver](#), where the factor is then synthesized. The virus is a non-pathogenic viral vector, which is used as a gene transporter.

Inhibition of Fibrinolysis in Hemophilia A and B

Further therapy is targeted at the inhibition of fibrinolysis, i.e. the mechanism underlying the dissolution of blood clots is designed to physiologically counteract thrombosis in the body. In this case, **antifibrinolytics** are prescribed in order to inhibit the fibrinolysis-activating plasminogen and also plasmin. These findings suggest the possibility of a patient with hemophilia leading active, risk-free, and almost unimpaired life.

Von Willebrand Disease

[Von Willebrand Disease](#) is named after the Finnish doctor, Erik von Willebrand. He examined a family that lived on the Aaland Islands in the Baltic Sea, manifesting severe bleeding episodes. He jokingly referred to the island as 'nosebleed' island.

The result of his examination led him to document a new clinical picture, which clearly distinguished the entity from hemophilia. Initially designated as 'pseudohemophilia', the clinical condition was more commonly known as 'von Willebrand Disease'.

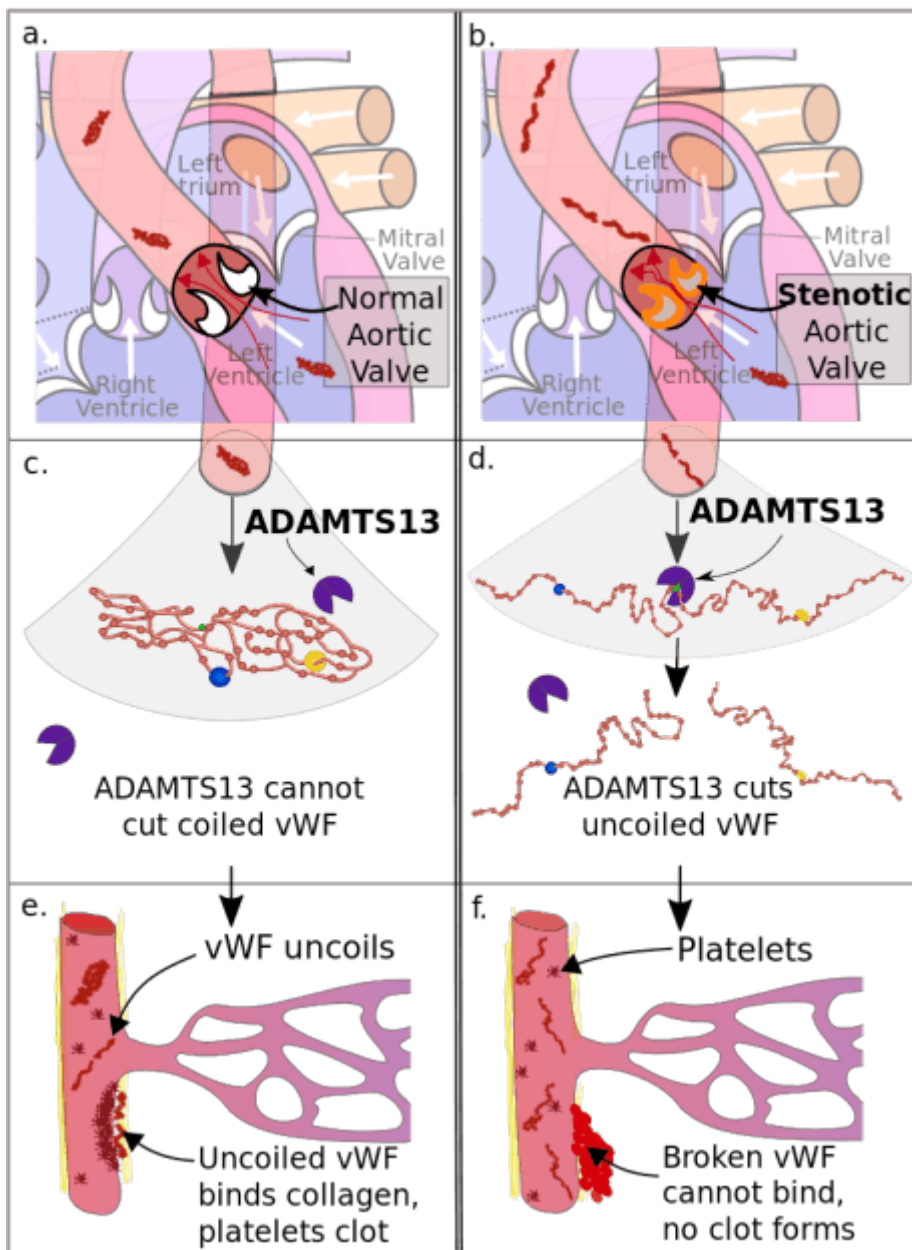


Image: The pathophysiology of acquired von Willebrand's Disease type 2A (vWD-2A) from an aortic stenosis (Heyde's Syndrome). By Michael D. Dacre, License: [CC BY-SA 4.0](https://creativecommons.org/licenses/by-sa/4.0/)

- a. Von Willebrand factor (VWF) fits through a normal aortic valve and remains in a folded, high molecular weight form.
- b. VWF passes through a stenotic aortic valve and unravels under the high load.
- c. The coiled VWF is unaffected by the catabolic enzyme ADAMTS-13 and enters the circulatory system through the aorta.
- d. The unraveled active VWF is split into 2 components by ADAMTS-13 and is rendered inactive.
- e. In small, damaged arterioles under increased strain, the VWF unravels and becomes active. It binds to the collagen on the contralateral damaged wall of the arteriole. Platelets bind to VWF and release a cytokine signal, which activates other clotting factors, leading to the binding of additional thrombocytes resulting in clot formation and bleeding cessation.
- f. The split, inactive VWF cannot bind the collagen, and the high blood flow prevents platelet binding.

Etiology of von Willebrand Disease

Causative Factors

The underlying etiology of the disease relates to the insufficiency of a von Willebrand Factor (VWF) that is involved in **primary hemostasis**. VWF is responsible for the association of thrombocytes with the sub-endothelial tissue of the ruptured, damaged blood vessel. Furthermore, the proteolytic degradation of VWF is prevented by pairing with factor VIII, which acts as a complex in the intrinsic clotting system.

VWF is synthesized in the endothelial cells of the blood vessels. Von Willebrand disease is hereditary similar to hemophilia A and B. The genes are inherited both in an **autosomal dominant** and **recessive manner**.

Diagnosis of von Willebrand Disease

Tests to diagnose von Willebrand Disease **are based on activated Partial Thromboplastin Time (aPTT)** as well as the normal **bleeding time** required for the first signs of coagulation.

Symptoms of von Willebrand Disease

Patients with von Willebrand disease manifests significantly longer bleeding times until the start of coagulation compared with normal bleeding time, due to inadequate vasoconstriction as well as insufficient factor VIII levels in secondary hemostasis. The following symptoms are pathognomonic for the disease in descending order of prevalence:

- Tendency towards bruising
- Frequent secondary bleeding in dental treatments or during operations and heavy menstrual bleeding
- Bleeding times lasting around 10-15 minutes

Therapy for von Willebrand Disease

Three Types of Therapy

Von Willebrand Disease can be subdivided into 3 types, each with its own form of treatment.

1. Type 1 therapy: DDAVP, Factor VIII/VWF concentrate, estrogen treatment in women
2. Type 2 therapy: factor VIII concentrate
3. Type 3 therapy: factor VIII / VWF concentrate

DDAVP is a synthetically manufactured protein and is structurally related to the body's own peptide hormone vasopressin (also known as antidiuretic hormone or ADH). It binds to the V2 receptors and triggers the release of von Willebrand Factor and therefore prescribed as an **anti-hemorrhagic** drug.

As well as being prescribed in tablet form, a nasal spray is also offered. Due to its low molecular mass, the hormone can easily pass through the nasal mucosa into the bloodstream. The tablet form remains the most reliable method of administration.

Treatment with **estrogen** in women reduces the severity of menstrual bleeding. The contraceptive pill that is prescribed by a doctor is usually sufficient for this purpose.

Naturally, patients with von Willebrand disease also suffer from fevers or headaches.

Note: Maximum caution is recommended when taking medications for headaches, fever or similar symptoms! Drugs such as aspirin, acetylsalicylic acid (ASA), Alka-Seltzer and other ASA-based drugs as well as the combination of ASA with paracetamol or tablets containing ASA and caffeine have a 'blood-thinning' effect and prolong the bleeding time in the case of injury.

Vascular Diseases

Vascular diseases may be hereditary or acquired. The next section covers three clinical conditions: **allergic purpura**, **Ehlers-Danlos Syndrome (EDS)** and **hemorrhagic telangiectasia**.

Allergic Purpura

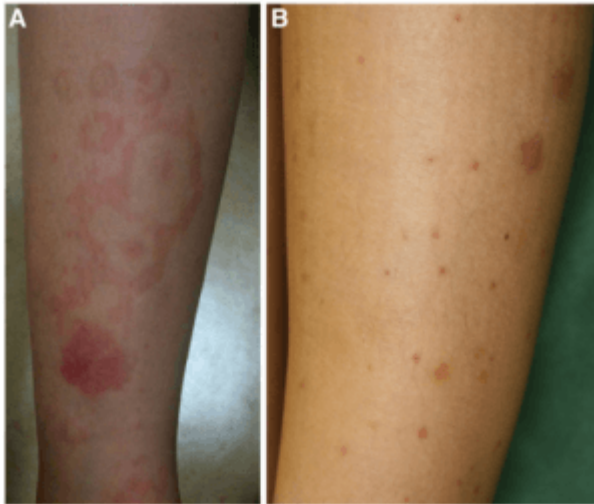


Image: Allergic Purpura (A) Erythema multiforme. Multiple papular, macular and target lesions of the right lower leg 6 days before admission. (B) Henoch-Schönlein purpura. Purpuric rash over the right lower leg was observed on admission. By Openi, License: [CC BY 2.0](https://creativecommons.org/licenses/by/2.0/)

Definition of Allergic Purpura

Purpura is an **autoimmune disease** that is defined by minor capillary bleeding in the skin, subcutaneous tissue or the mucous membranes. The extent of bleeding can be small (**ecchymosis**), large (**bruises**), or associated with tiny spots (**petechiae**).

Etiology of Allergic Purpura

This disease is triggered by inflammation of blood vessels often as a result of, or in conjunction with cold or flu. **IgA antibodies** in the blood attach themselves to vessel walls to trigger an autoimmune response. The inflammation partly destroys the vessels in some places, leading to leakage of the vessels. Blood no longer flows completely through the capillaries, but escapes the vessel and distributes itself in the surrounding connective tissue.

Diagnosis of Allergic Purpura



Image: Eruption of the first necrotic purpura on the feet (A), elbows (B) and knees (C). By Openi, License: [CC BY 2.0](https://creativecommons.org/licenses/by/2.0/)

Allergic purpura is diagnosed by analyzing the immune complexes for IgA antibodies in the blood or through a tissue **biopsy**. In a biopsy, a tissue sample of the skin is obtained and the characteristic changes caused by purpura are analyzed under a microscope. In advanced stages of this disease, increased plasma protein levels can be detected in the urine (**proteinuria**), which suggests deteriorating kidney function and the spread of inflammation to the kidneys.

Treatment for Allergic Purpura

Allergic purpura is treated with either corticosteroids or immunoglobulin to reduce the inflammation. In most cases, no therapy is necessary and the inflammation resolves spontaneously.

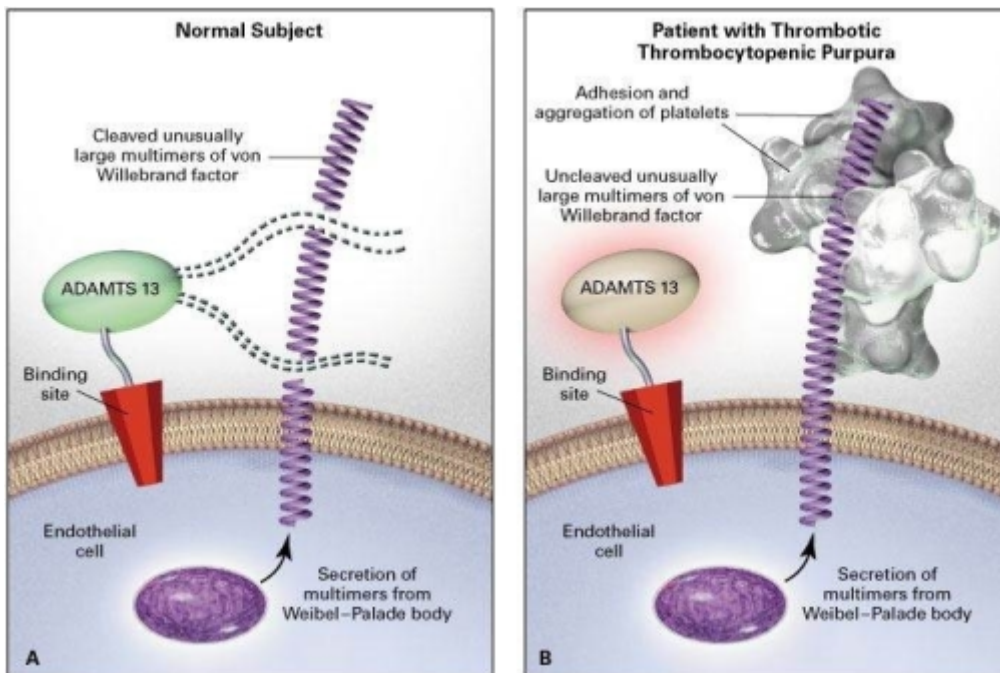


Image: Thrombotic purpura. By Openi, License: [CC BY 3.0](https://creativecommons.org/licenses/by/3.0/)

Ehlers-Danlos Syndrome

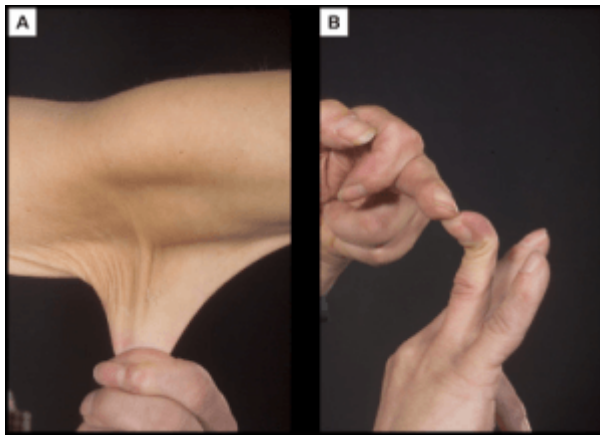


Image: (A) Prominent hyperextensible skin (B) hypermobile joints.
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Definition of Ehlers-Danlos Syndrome

Ehlers-Danlos syndrome (EDS) is a hereditary disease characterized by a weakness of the connective tissue.

The primary etiology of this disease involves defective collagen synthesis, which interferes with cohesion and elasticity. This disease is also known as '**Cutis hyperelastica**'.

Symptoms of Ehlers-Danlos Syndrome

Patients are affected by EDS to different extents. The possible symptoms include minor anomalies, such as bruises, agonizing pains, minor encumbrances, and reduced life expectancy. Blood vessels become extraordinarily flexible, thinner than average, easily damaged, and tend to form hematomas. The blood vessels leak and rupture easily.

Epidemiology of Ehlers-Danlos Syndrome

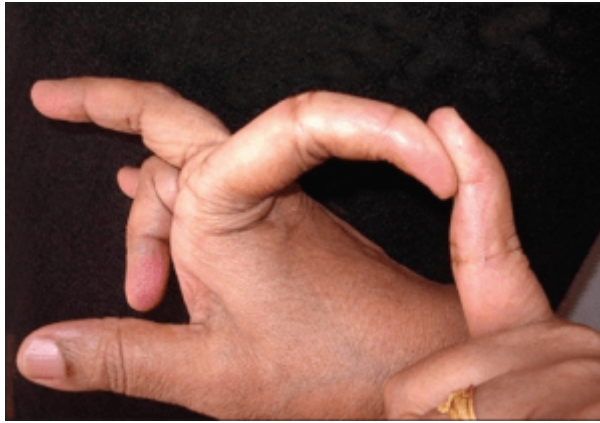
In Germany, around 1 in 10,000 people are affected and the figures are similar worldwide. The disease is therefore considered quite rare.

Clinical Diagnosis of Ehlers-Danlos Syndrome

Patients often exhibit a long history of suffering due to a lack of knowledge of this syndrome even today. Doctors with poor insight suspected that the patients were falsifying symptoms. Other serious misdiagnoses include the assumption that hematomas, bruises, and injuries in children with EDS were due to abuse.

The 6 distinct types and features of EDS include:

1. **Classical Type:** hematomas, abnormal wound healing, hyperkinesia of the joints, easily damaged blood vessels
2. **Hypermobility Type:** very pronounced motility of the joints
3. **Vascular Type:** thin skin, pronounced hematoma formation, and defective internal organs and blood vessels.
4. **Kyphoscoliosis Type:** defective eyes, moderate to severe abnormal wound healing, hyperkinesia of the joints.
5. **Arthrochalasia Type:** thin skin, hip dislocation, pronounced hyperkinesia of the joints
6. **Dermatosparaxis Type:** very loose skin, internal organs also affected



[Image](#): Hyper extensibility of the fingers in proband's sister. By Openi, License: [CC BY 2.0](#)

Treatments for Ehlers-Danlos Syndrome

The disease is incurable and often progresses unpredictably. If joints are badly affected, sporting activities may have to be avoided, especially in children. A sports program that reflects the joint load can be used to cope with the daily needs.

Joint hypermobility, which is often of interest or amusement for the general public, is a source of chronic and in many cases, continually worsening pain. Treatment usually entails **pain management therapy**. In addition to medications used to alleviate pain, **psychological therapy** is used to address chronic pain-related symptoms of depression, anger, and fear.

In general, currently, no complete cure is available for EDS, and only symptomatic treatment is available. Children can wear custom-made neoprene protective bandages to prevent impact and bruising to affected parts of the body such as the shins, knees or elbows. Physiotherapy should also be undertaken. Pain management therapies can be utilized to alleviate painful symptoms.

Hemorrhagic Telangiectasia

Definition of Hemorrhagic Telangiectasia

Hereditary hemorrhagic telangiectasia (HHT or Osler-Weber-Rendu syndrome) is an **autosomal dominant** hereditary condition affecting blood vessels. In this autosomal dominant inheritance, if one of the partners is affected, half of their children on average is also affected, regardless of gender.

Etiology of Hemorrhagic Telangiectasia

HHT is characterized by a pathological widening of the blood vessels, which are very fragile and bleed easily.

Symptoms of Hemorrhagic Telangiectasia

HHT can be recognized macroscopically by prominent and protruding capillaries on the facial surface. The nose is frequently affected area, resulting in **nosebleeds**. Telangiectasia in the gastrointestinal tract is often the cause of frequent and recurring bleeding.

[Blood vessel](#) widening within the [lungs](#), brain or liver is rarely detected initially but can become life-threatening in case of sudden bleeding. Investigations revealed at least 3 mutant genes contributing to the clinical condition: **endoglin**, a TGF β 1 receptor on chromosome 9q, and **ALK1 gene** located on chromosome 12q.

Thrombocytopenia

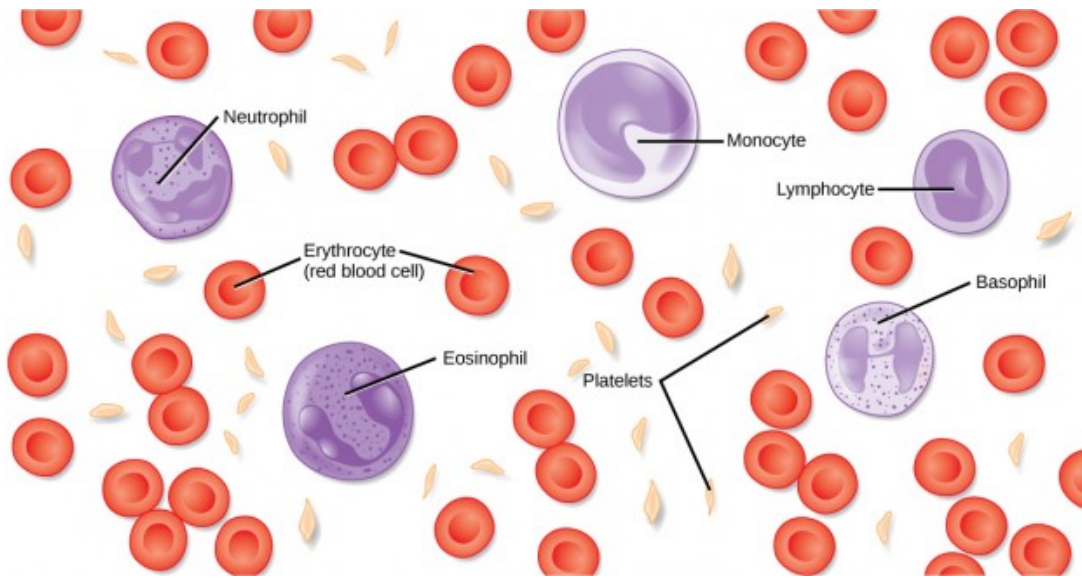


Image: The cells and cellular components of human blood are shown. By philschatz, License: [CC BY 4.0](https://creativecommons.org/licenses/by/4.0/)

Diagnosis of Thrombocytopenia

The diagnosis of **thrombocytopenia** is established by the presence of **fewer than 150,000 thrombocytes per μl of blood**.

Clinical Diagnosis of Thrombocytopenia

Thrombocytopenia is clinically diagnosed by blood counts less than $80,000/\mu\text{l}$, which increases the risk of prolonged bleeding in the absence of functional defects in the thrombocytes (thrombocytopathy).

Etiology of Thrombocytopenia

Thrombocytes are responsible for primary hemostasis in primary wound closure. Bleeding time can be significantly prolonged after injury due to defective or absent thrombocytes. Hematomas are common, as are nosebleeds and bleeding gums. A wide spectrum of etiological factors are listed below:

Formation defects	Congenital (Wiskott-Aldrich syndrome, TAR syndrome, Fanconi anemia) Acquired (aplastic anemia, bone marrow disease, Vitamin B12- or folic acid deficiency)
Shortened life expectancy	Antibody response (transfusion incident, hemolytic disease of the newborn, idiopathic thrombocytopenic purpura) Coagulation (heparin-induced thrombocytopenia type II)
Distribution anomalies	Splenomegaly, hypothermic anesthesia
Laboratory phenomenon	Pseudothrombocytopenia

Furthermore, the status of thrombocytes is negatively affected by chemotherapy, radiotherapy, HIV-AIDS as well as leukemia.

Treatment of Thrombocytopenia

Thrombocytopenia is treated via transfusion of platelet concentrate. Prior to operative procedures, thrombocyte counts should be elevated to at least $50,000/\mu\text{l}$ to minimize the

risk of heavy blood loss. Thrombocyte concentrates are either harvested from whole blood or via apheresis directly from the blood donor.

References

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