University of Basrah
Al-Zahraa Medical College

Ministry of Higher education
and Scientific Research

Block: Child Health.

Lecture: Haemostasis

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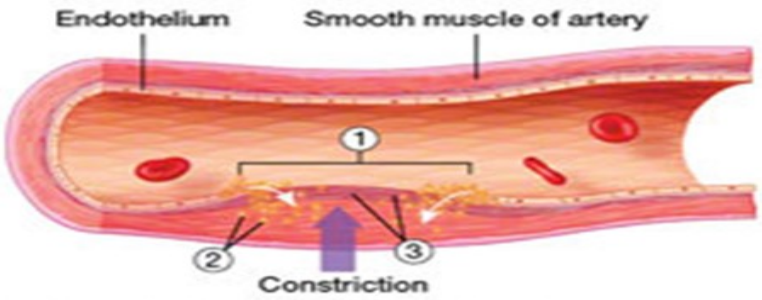
Nelson Textbook of Pediatrics, 21th edition.
Nelson Essentials of Pediatrics, 7th Edition 2015
Pediatric Decision-Making Strategies
Illustrated Textbook of Pediatrics
Short Atlas in Pediatrics

Hemostasis is the biological process that limits hemorrhage after blood vessel injury

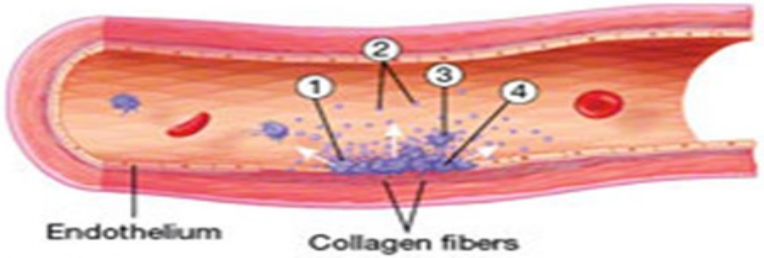
- Primary hemostasis
- Secondary hemostasis

The main components of the hemostatic process are the **vessel wall**, **platelets**, **coagulation factors**, **anticoagulant proteins**, and **fibrinolytic system**



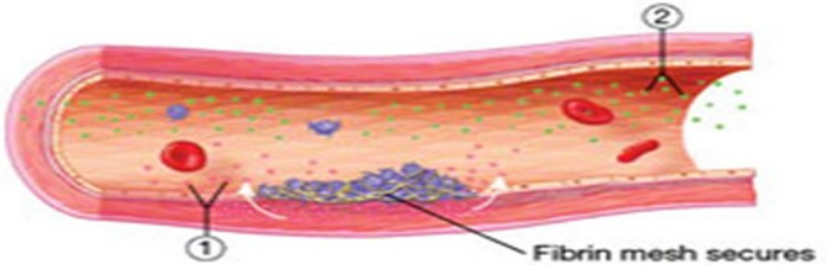
A. Vessel wall injury and constriction

1. Site of injury
2. Endothelin released causes constriction
3. Collagen fibers exposed



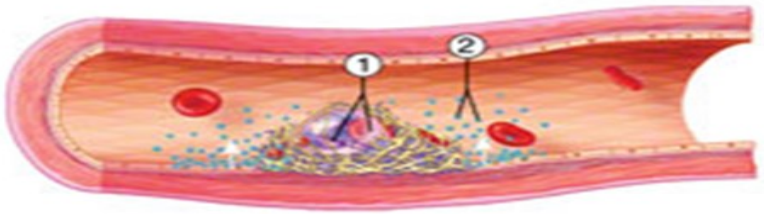
B. Platelet aggregation

1. Platelet adhesion
2. Chemicals released by platelets
3. Platelets aggregate
4. Platelets cluster to repair wall



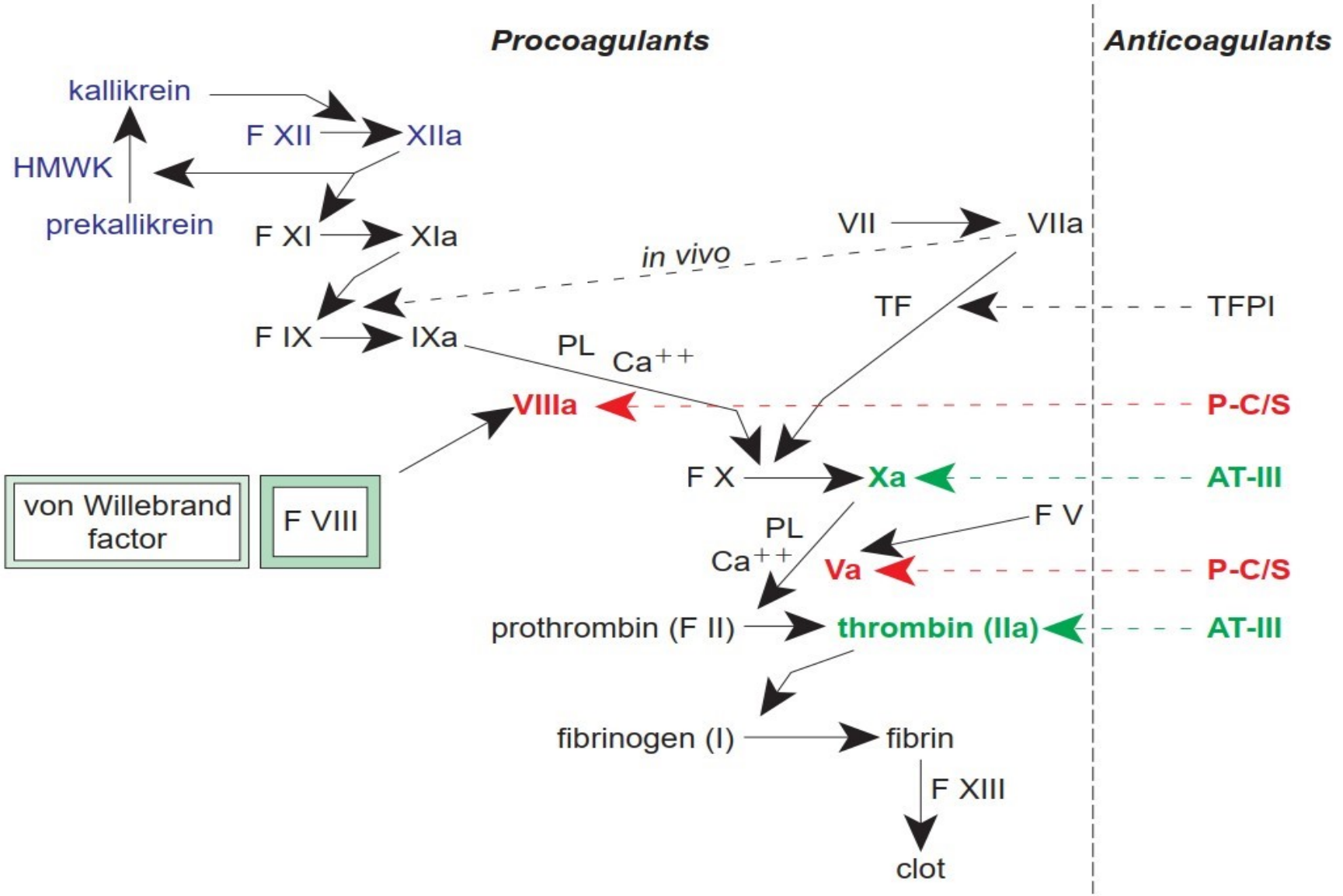
C. Platelet plug formation

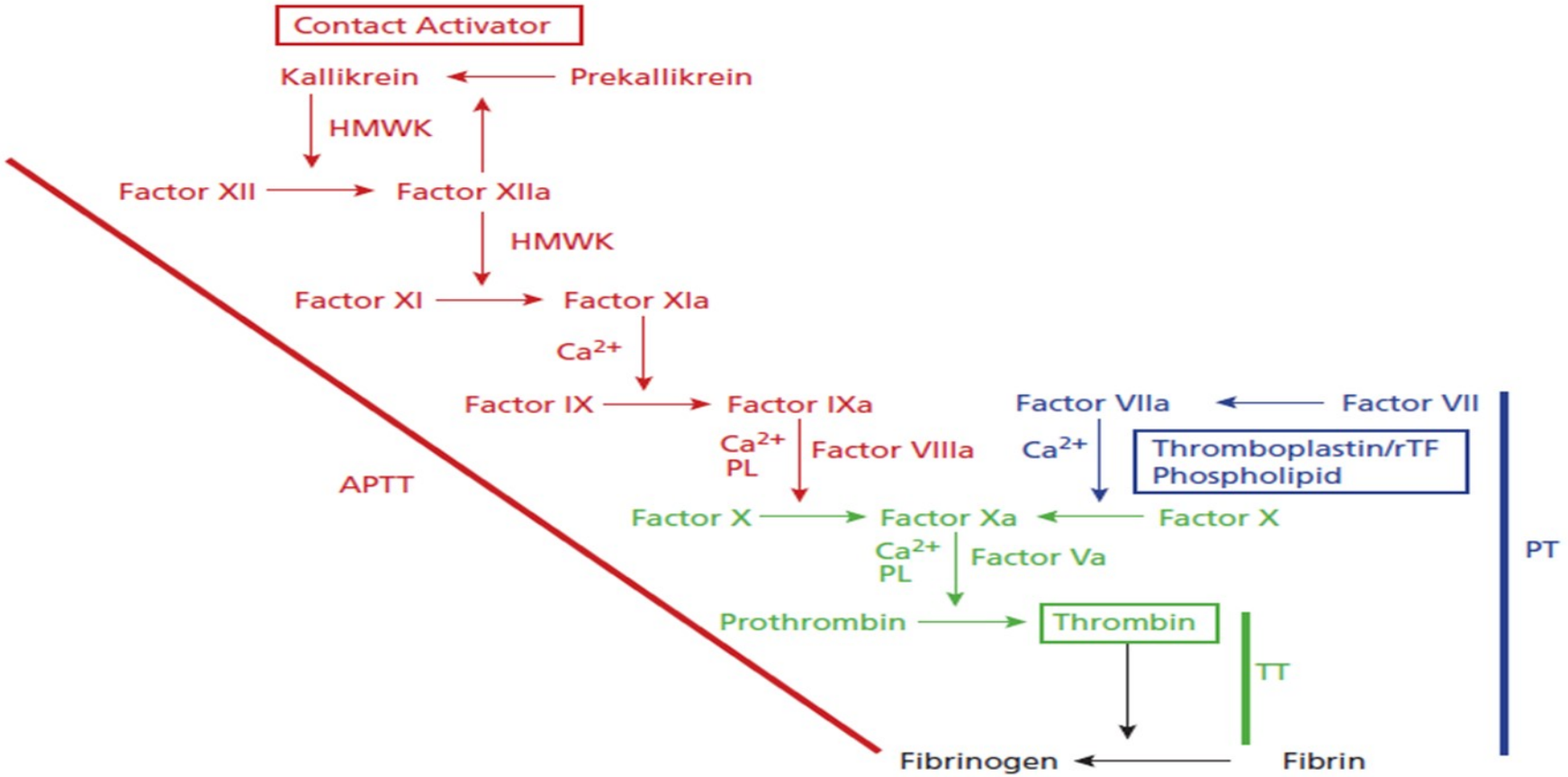
1. Tissue factor released
2. Clotting factors released



D. Blood clot formation

1. Red and white blood cells are trapped in mesh
2. Release of coagulation inhibitors and other chemicals


Procoagulants
Anticoagulants
kallikrein
F XII
XIIa
HMWK
prekallikrein
F XI
XIa
VII
VIIa
in vivo
TF
TFPI
F IX
IXa
PL
Ca++
VIIIa
P-C/S
F X
Xa
AT-III
von Willebrand factor
F VIII
F V
PL
Ca++
Va
P-C/S
prothrombin (F II)
thrombin (IIa)
AT-III
fibrinogen (I)
fibrin
F XIII
clot



The coagulation cascade. The traditional concept of blood coagulation with separate intrinsic (red) and extrinsic (blue) pathways converging on the common pathway (green) with the generation of FXa.

PT= Prothrombin Time (10-12s)

APTT= Activated Partial Thromboplastin Time (26-40s)

TT= Thrombin Time (15-19s)

ISOLATED PROLONGED PT	ISOLATED PROLONGED aPTT	PROLONGED PT AND aPTT	CAUSES OF BLEEDING WITHOUT PT/aPTT PROLONGATION
FVII deficiency	Hemophilia A (FVIII deficiency)	Disseminated intravascular coagulation	FXIII deficiency
Mild common pathway factor deficiency (II, V, and X), fibrinogen deficiency	Hemophilia B (FIX deficiency)	Dilutional coagulopathy	von Willebrand disease
Early vitamin K deficiency	Hemophilia C (FXI deficiency)	Liver synthetic dysfunction	Platelet dysfunction
Early liver synthetic dysfunction	von Willebrand disease	Marked vitamin K deficiency	Mild deficiency of FVIII, FIX, and FXI
Direct Xa inhibitor	Acquired FVIII, FIX, or FXI inhibitors	Common pathway factor deficiency (FII, FV, and FX), severe fibrinogen deficiency	α_2-antiplasmin deficiency and other causes of hyperfibrinolysis
—	Heparin	Warfarin or direct thrombin inhibitor, DOAC (not always)	Collagen vascular diseases (i.e., Ehlers-Danlos syndrome)
—	—	Increased tissue factor pathway inhibitor, FV Amsterdam or East Texas bleeding disorder	DOAC

Hereditary Clotting Factor Deficiencies (Bleeding Disorders)

- Hemophilia A (factor VIII deficiency) and hemophilia B (factor IX deficiency) are the **most common** and serious **congenital coagulation** factor deficiencies.
- Hemophilia C is the bleeding disorder associated with reduced levels of factor XI.
- Reduced levels of the contact factors (factor XII, high-molecular-weight kininogen, and prekallikrein) are associated with significant prolongation of activated partial thromboplastin time, but are not associated with hemorrhage

Factor VIII or Factor IX Deficiency (Hemophilia A or B)

Pathophysiology

- Factors VIII and IX participate in a complex required for the activation of factor X. Together with phospholipid and calcium, they form the “tenase,” or factor X–activating complex.

Clinical manifestations

- Neither factor VIII nor factor IX crosses the placenta; bleeding symptoms may be present from birth or may occur in the fetus.
- Only **2%** of neonates with hemophilia sustain **intracranial hemorrhages**, and
- **30%** of male infants with hemophilia bleed with **circumcision**.
- Thus, in the absence of a positive family history (hemophilia has a high rate of **spontaneous mutation**), hemophilia may go undiagnosed in the newborn.

Classification

- **Severe** hemophilia is characterized as having **<1%** activity of the specific clotting factor, and bleeding is often **spontaneous**.
- Patients with **moderate** hemophilia have factor levels of **1-5%** and usually require **mild** trauma to induce bleeding.
- Individuals with **mild** hemophilia have levels **>5%**, may go many years before the condition is diagnosed, and frequently require **significant** trauma to cause bleeding.

The hemostatic level for factor VIII is >30-40%, and for factor IX, it is >25-30%. The lower limit of levels for factors VIII and IX in normal individuals is approximately 50%

Laboratory findings and diagnosis

- The laboratory screening test that is affected by a reduced level of factor VIII or factor IX is **PTT**. In severe hemophilia, the PTT value is usually 2-3 times the upper limit of normal.
- Results of the **other screening tests** of the hemostatic mechanism (platelet count, bleeding time, prothrombin time, and thrombin time) are **normal**.
- Unless the patient has an inhibitor to factor VIII or IX, the **mixing** of normal plasma with patient plasma results in **correction of PTT** value.
- The **specific assay** for factors VIII and IX will **confirm** the diagnosis of hemophilia.

Treatment

- Early, appropriate therapy is the hallmark of excellent hemophilia care.

- When mild to moderate bleeding occurs, values of factor VIII or factor IX must be raised to hemostatic levels, in the 35-50% range.

- For life threatening or major hemorrhages, the dose should aim to achieve levels of 100% activity

Prophylaxis

- Many patients are now given lifelong prophylaxis to prevent spontaneous joint bleeding.

- The National Hemophilia Foundation recommends that prophylaxis be considered optimal therapy for children with severe hemophilia.

VON WILLEBRAND DISEASE

- von Willebrand disease (VWD) is the **most common inherited bleeding disorder**, with an estimated prevalence cited at 1 : 100 to 1 : 10,000 depending on the criteria used for diagnosis.

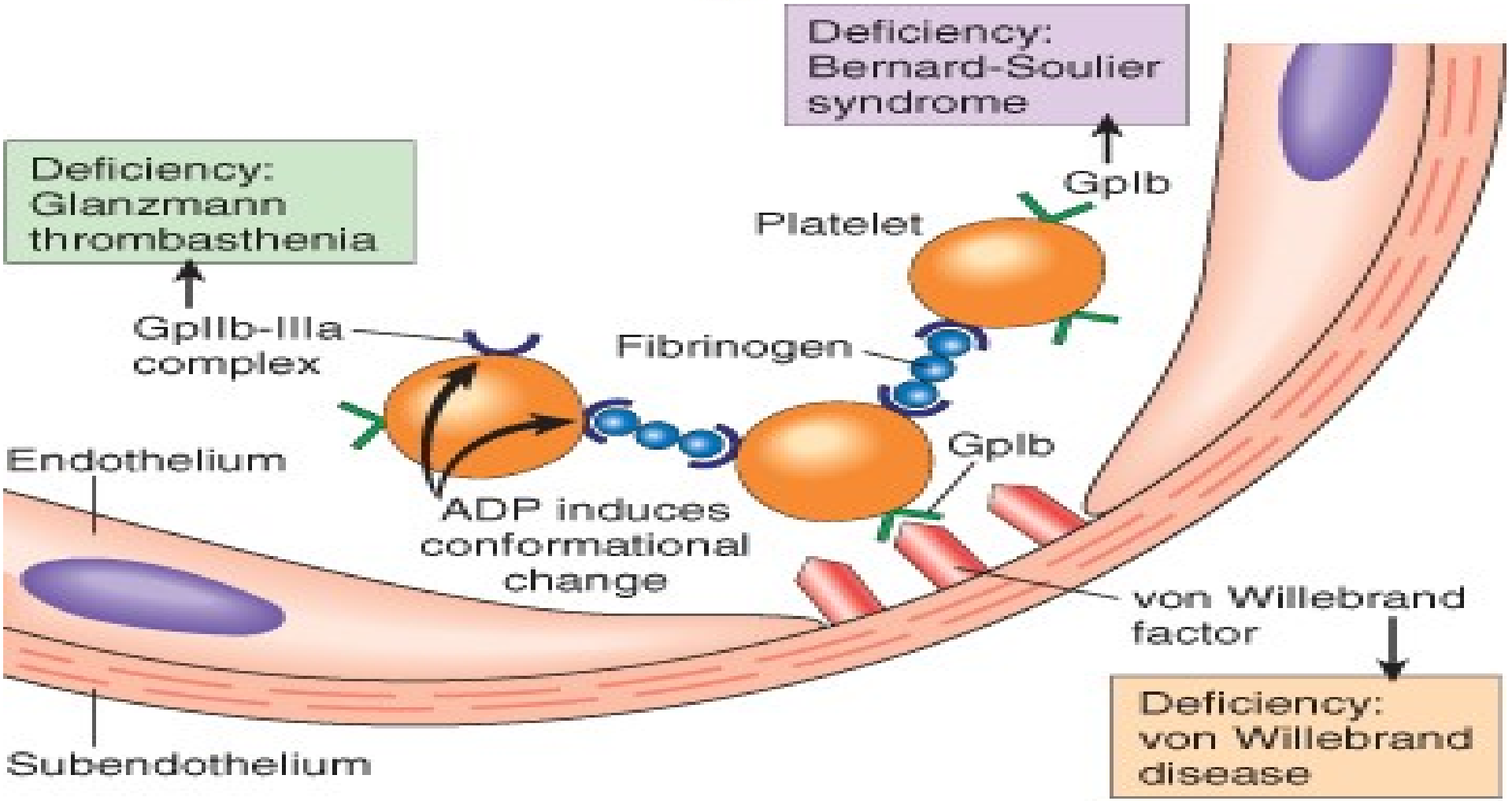
- Patients with VWD typically present with mucosal bleeding.

Pathophysiology

- VWD is caused by a defect in von Willebrand factor

- VWF has several functions in coagulation.
  First, VWF serves to **tether platelets** to injured sub-endothelium via binding sites for platelets and for collagen.
  Second, VWF serves as a **carrier** protein for factor VIII (FVIII), protecting FVIII from degradation in plasma.

- VWF is stored in endothelial cells and in platelet Weibel-Palade bodies and circulates as a large multimeric glycoprotein.



Classification

VWD may be caused by **quantitative** or **qualitative** defects in VWF.

- **Mild** to moderate **quantitative** defects are classified as **type 1** VWD,
- While **severe quantitative** defects, in which there is no detectable VWF protein, are classified as **type 3** VWD.
- The **qualitative** defects are grouped together as **type 2** VWD.

VWF levels can be influenced by external factors.

- Blood type has long been known to affect VWF, with lower VWF levels seen in people with blood group O.
- Stress, exercise, and pregnancy all increase VWF levels; therefore, a single normal VWF level does not necessarily rule out the presence of VWD.
- Certain diseases, such as hypothyroidism, and medications, such as valproic acid, can lower VWF levels in affected patients.

Repeat testing may be required to **rule out** or **confirm** a diagnosis of VWD

Type 1 VWD is by far the most common type, accounting for **60-80%** of all VWD patients. Typical symptoms include mucosal bleeding, such as epistaxis and menorrhagia as well as easy bruising and potentially surgical bleeding. Guidelines use a VWF level, as measured by the VWF antigen assay (VWF : Ag), of **<30 IU/dL** for diagnosis of VWD

Type 3 VWD is the most severe form and presents with symptoms similar to those seen in mild hemophilia. In type 3 VWD, the VWF protein is completely absent.

Type 2A VWD is characterized by a **defect in VWF multimerization** and decreased VWF activity in terms of platelet binding. It is the most common of the type 2 variants, accounting for approximately 10% of VWD cases.

Type 2B VWD results from **gain-of-function** mutations that increase the ability of VWF to bind platelets. This leads to increased clearance of both VWF and platelets from circulation and results in the loss of high-molecular-weight multimers and decreased VWF activity, similar to that seen in type 2A VWD

Platelet-type, pseudo-VWD occurs when a mutation in platelet GPIb causes spontaneous binding to VWF and also presents with decreased VWF activity, loss of high-molecular-weight multimers, and thrombocytopenia similar to type 2B VWD.

Type 2M VWD includes those patients with decreased VWF activity but normal (or near-normal) multimer distribution. This is generally caused by a defect in the ability of VWF to bind platelet GPIb, but this category also includes patients with defects in VWF-collagen interactions.

Type 2N VWD is characterized by a defect in the ability of VWF to bind FVIII. Some patients with type 2N VWD may be misdiagnosed as mild hemophilia, therefore a high index of suspicion for this diagnosis is required in patients with low FVIII and an absent family history of FVIII deficiency

TEST	ABBREVIATION	PURPOSE
VWF antigen	VWF:Ag	Measures total amount of VWF protein present
VWF activity	VWF:RCo	Assess interaction of VWF and platelets as mediated by ristocetin
VWF activity/antigen ratio	VWF:RCo/VWF:Ag	A decreased ratio (<0.7) is found in type 2A, type 2B, and type 2M VWD
Factor VIII activity	FVIII	Measures circulating FVIII, which will be very low in type 2N and type 3 VWD
Multimer distribution	VWF multimers	Allows visualization of VWF multimers, used to identify high-molecular-weight multimers, which will be absent in types 2A and 2B VWD

	TYPE 1	TYPE 3	TYPE 2A	TYPE 2B*	TYPE 2M	TYPE 2N
VWF:Ag	↓	Absent	↓	↓	↓	Normal or ↓
VWF:RCo	↓	Absent	↓↓	↓↓	↓↓	Normal or ↓
FVIII	Normal	↓↓	Normal or ↓	Normal or ↓	Normal or ↓	↓↓
Multimer distribution	Normal	Absent	Loss of HMWM	Loss of HMWM	Normal	Normal

TREATMENT	VWD TYPES	ADMINISTRATION
Desmopressin*	Type 1 VWD Some type 2 VWD (use with caution)	IV or IN
von Willebrand factor concentrates‡	Type 3 VWD Type 2 VWD Severe type 1 VWD (or type 1 clearance defects)	IV
Antifibrinolytics	Mucosal bleeding, all types of VWD	PO or IV

Idiopathic (Autoimmune) Thrombocytopenic Purpura

The **most common** cause of **acute** onset of thrombocytopenia in an otherwise **well child** is (autoimmune) idiopathic thrombocytopenic purpura (ITP).

Epidemiology

- In a small number of children, estimated at 1 in 20,000,
- A recent history of viral illness is described in 50-65% of cases of childhood ITP.

Clinical manifestations

- The classic presentation of ITP is a **previously healthy 1-4 year** old child who has **sudden onset** of generalized petechiae and purpura. The parents often state that the child was fine yesterday and now is covered with bruises and purple dots.
- There may be bleeding from the **gums** and mucous membranes, particularly with profound thrombocytopenia (platelet count <10 × 10^9/L).
- There is a history of a **preceding viral** infection 1-4 week before the onset of thrombocytopenia.
- Splenomegaly, lymphadenopathy, bone pain, and pallor are rare.

Clinical manifestations

- Classification system has been proposed from the United Kingdom to characterize the severity of bleeding in ITP on the basis of symptoms and signs, but not platelet count:

1. **No symptoms**
2. **Mild** symptoms: bruising and petechiae, occasional minor epistaxis, very little interference with daily living
3. **Moderate**: more severe skin and mucosal lesions, more troublesome epistaxis and menorrhagia
4. **Severe**: bleeding episodes—menorrhagia, epistaxis, melena requiring transfusion or hospitalization, symptoms interfering seriously with the quality

Laboratory findings

- In acute ITP, the hemoglobin value, white blood cell count, and differential count should be normal. Hemoglobin may be decreased if there have been profuse nosebleeds or menorrhagia.
- Bone marrow examination shows normal granulocytic and erythrocytic series, with characteristically normal or increased numbers of megakaryocytes. Some of the megakaryocytes may appear to be immature and are reflective of increased platelet turnover.
- Indications for bone marrow aspiration/biopsy include an abnormal WBC count or differential or unexplained anemia as well as findings on history and physical examination suggestive of a bone marrow failure syndrome or malignancy.

Treatment

There are no data showing that treatment affects either short- or long term clinical outcome of ITP.

1. No therapy other than education and counseling of the family and patient for patients with minimal, mild, and moderate symptoms, as defined earlier.
2. A single dose of IVIG [intravenous immunoglobulin] (0.8-1.0 g/kg) or a short course of corticosteroids should be used as first-line treatment.
3. Intravenous anti-D therapy. For Rh-positive patients, at a dose of 50-75 µg/kg causes a rise in platelet count to >20 × 10^9/L in 80-90% of patients within 48-72 Hrs.

THANK YOU