Intro to Bleeding and Coagulation:

Coagulopathy, bleeding disorders, procoagulants

Courtney Fitzgerald
MSN, APRN, FNP-BC, OCN

Memorial Cancer Institute

Coagulopathy

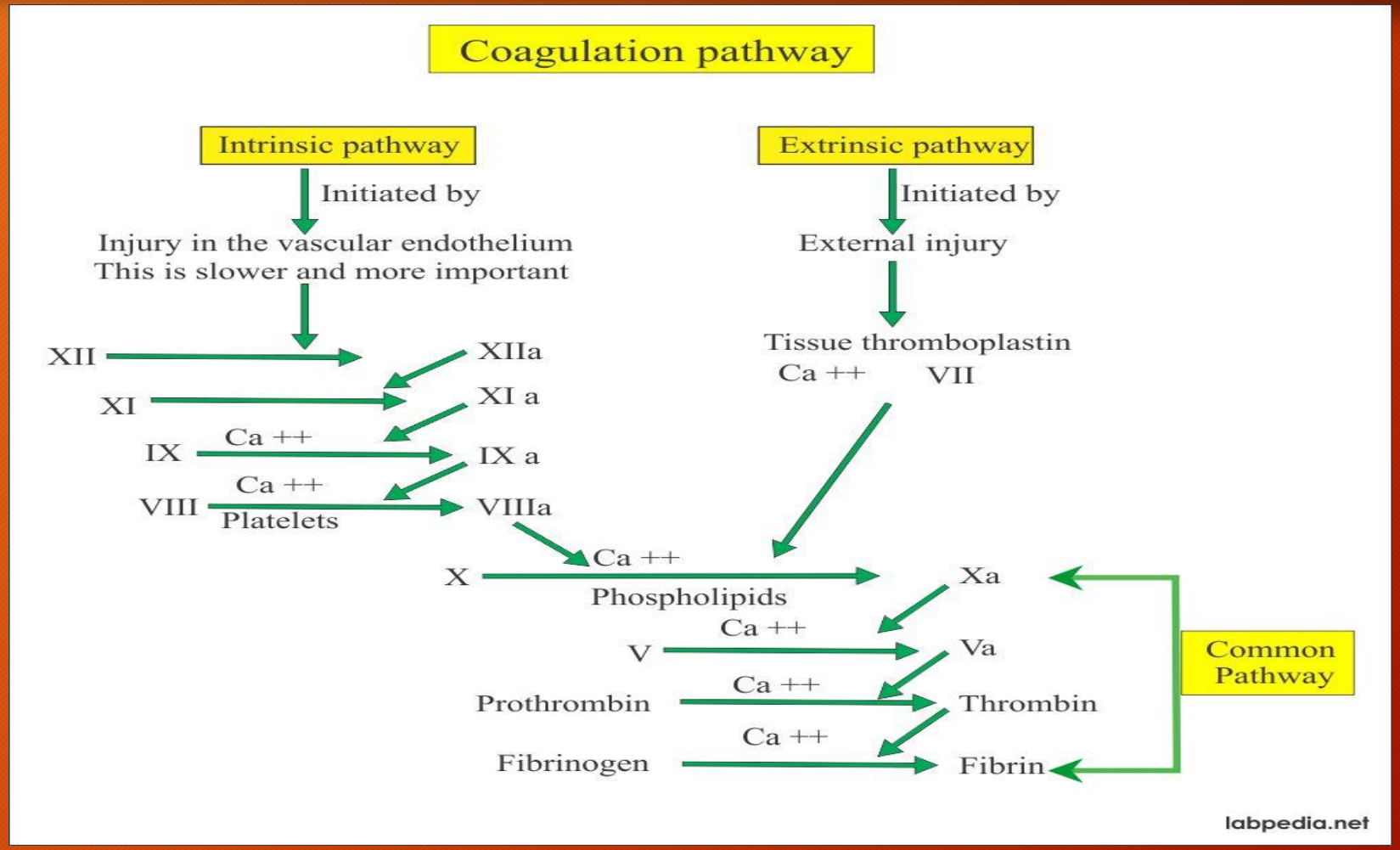
- **Definition - A disease or condition affecting the blood's ability to coagulate**
- **Cause - Reduced or absent levels of coagulation proteins and related molecules, decreased platelet function, or disruption of vasculature**
  - Genetic disorders - such as hemophilia and von Willebrand's disease, can cause a reduction in clotting factors.
  - Acquired factors- such as anticoagulant medicines (blood thinners), the continued use of antibiotics, liver disease or disseminated intravascular coagulation
  - Surgery or Trauma

Top doctors, medical dictionary, coagulopathy. 8-18-21

Coagulation Factors

Clotting Factors:	*Synonyms:*
Fibrinogen	Factor I
Prothrombin	Factor II
Thromboplastin	Factor III (tissue factor)
Calcium	Factor IV
Factor V	Proaccelerin; labile factor
Factor VII	SPCA; stable factor
Factor VIII	AntiHemophilic factor A
Factor IX	AntiHemophilic factor B
Factor X	Stuart factor
Factor XI	plasma thromboplastin antecedent
Factor XII	Hageman factor

Coagulation Cascade



Coagulopathy Symptoms

The most common symptoms of coagulopathy are:

- Bruising that occurs for no apparent reason.
- Hemarthrosis (bleeding into a joint cavity)
- Hemorrhage after childbirth.
- Hemothorax (accumulation of blood in the pleural cavity)
- Very heavy menstrual flow
- Epistaxis (loss of blood through the nose)
- Rectal bleeding
- Hematuria (blood in the urine)
- Blood in the sperm
- Thrombocytopenia
- Priapism (persistent involuntary and painful erection of the penis)
- Gingival bleeding / Bloody gums
- Joint pain and swelling

Coagulopathy Tests

- ✓Complete blood count (CBC).
- ✓Partial thromboplastin time (PTT) test, also called an activated PTT (aPTT)
- ✓Prothrombin time (PT)
- ✓Mixing tests
- ✓Von Willebrand factor (vWF)
- ✓Clotting factor tests, also called factor assays or a coagulation panel
- ✓Bethesda test
- ✓Factor XIII antigen and activity assays
- ✓Genetic testing

Bleeding Disorders

ACQUIRED

- Disseminated intravascular coagulation (DIC)
- Liver disease-associated bleeding
- Vitamin K deficiency bleeding
- Von Willebrand disease and hemophilia
- Factor deficiencies
- Arteriovenous malformations

INHEREITED

- Combined deficiency of the vitamin K-dependent clotting factors (VKCFDs),.
- Hemophilia A
- Hemophilia B
- Hemophilia C
- Von Willebrand disease (VWD)
- Other inherited bleeding disorders include other factor deficiencies, such as I, II, V, V + VIII, VII, X, XI, or XIII deficiencies.
- Hereditary hemorrhagic telangiectasia

https://www.nhlbi.nih.gov/health-topics/bleeding-disorders

Acquired Bleeding Disorders

- Disseminated intravascular coagulation (DIC)
- Liver disease-associated bleeding
- Vitamin K deficiency bleeding
- Von Willebrand disease and hemophilias
- TTP and other rarer types of acquired bleeding disorders include deficiencies of certain factors, such as factor I, II, and V, that are named for the clotting factor causing the problem.
- Arteriovenous malformation can form in the brain or elsewhere in the body and lead to bleeding. These tangles may form before birth or later in life.

https://www.nhlbi.nih.gov/health-topics/bleeding-disorders

Inherited Bleeding Disorders

- Hemophilia A
- Hemophilia B
- Hemophilia C
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- Other inherited bleeding disorders include other factor deficiencies, such as I, II, V, V + VIII, VII, X, XI, or XIII deficiencies.
- Hereditary hemorrhagic telangiectasia

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Types of Hemophilia

A	B	C
Most Common (Severe)	2nd most common (Moderate)	Mild
Also known as Factor VIII deficiency or classic hemophilia	Originally named “Christmas Disease” Factor IX deficiency	Deficiency of Factor XI
X-linked gene	X-linked gene	Autosomal

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Causes

GENETICS

- Bleeding disorders can be caused by genes that are passed down from the patient's parents. Their genes provide instructions for how each clotting factor is made. If there is a mutation in the gene, then the clotting factor may be made incorrectly or not at all.

OTHER CAUSES

- Medical conditions
- Procedures
- Medicines

https://www.nhlbi.nih.gov/health-topics/bleeding-disorders

Medications and other substances that may increase the risk of bleeding or bruising

Drug class or substance	Mechanism
Anticoagulants	Interfere with clot formation (secondary hemostasis)
Antiplatelet agents, including NSAIDs	Interfere with platelet function (primary hemostasis)
Glucocorticoids	Interfere with vascular integrity
Antibiotics	Cause vitamin K deficiency, especially with longer use Some interfere with platelet function
SSRIs	Interfere with platelet function (primary hemostasis)
Alcohol	Complications of liver disease may affect clot formation and may cause thrombocytopenia May cause thrombocytopenia due to direct marrow toxicity
Vitamin E	Interferes with vitamin K metabolism in some individuals
Garlic	Interferes with platelet function in some individuals
Gingko biloba	Unknown

Laboratory diagnosis of abnormal fibrinolysis

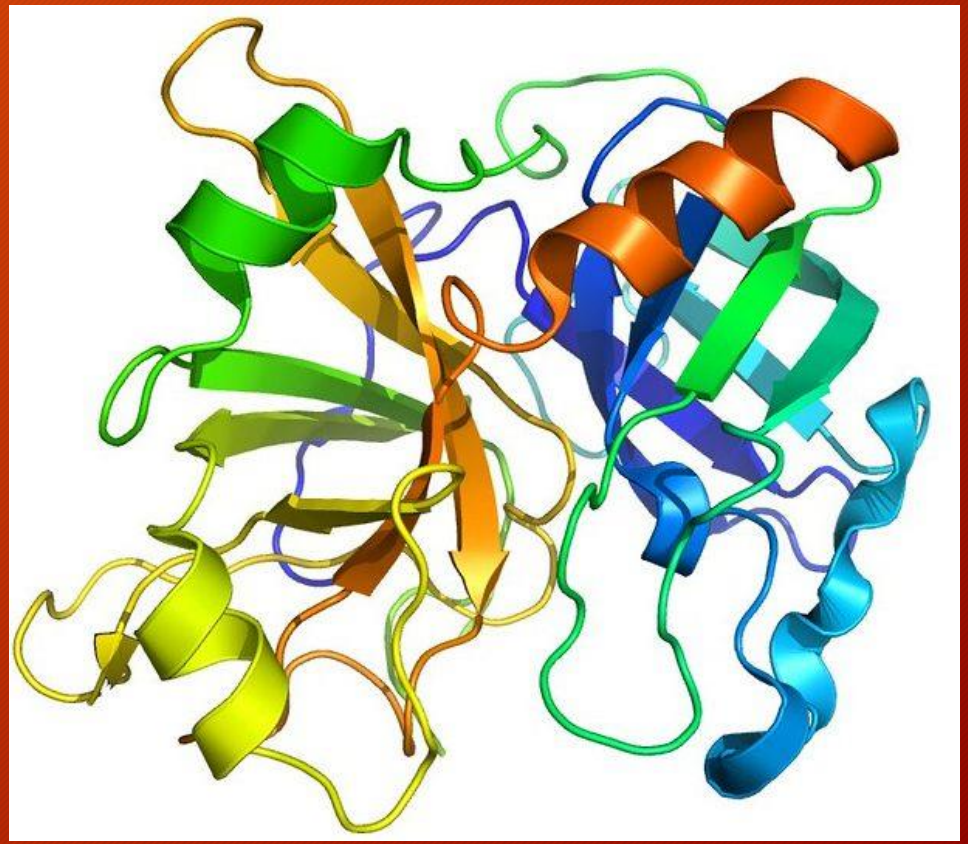
Test	Primary hyperfibrinolysis	DIC	TTP
CBC and blood smear	Normal	Thrombocytopenia, MAHA	Thrombocytopenia, MAHA
PT and aPTT	Normal or prolonged	Prolonged	Normal
Fibrinogen	Decreased	Decreased	Normal
D-dimer or FDP*	Increased	Increased	Normal
Antithrombin	Normal	Decreased	Normal
Euglobulin clot lysis time	Shortened	Shortened	Normal
ADAMTS13 activity	Normal	Normal or mildly reduced¶	Severely deficient (usually <10%)Δ

Procoagulant

Definition: relating to or denoting substances that promote the conversion in the blood of the inactive protein prothrombin to the clotting enzyme thrombin.

The precursor of various blood factors necessary for coagulation. An agent that promotes blood coagulation

Procoagulant and anticoagulant proteins have important roles in the regulation of fibrin formation during secondary hemostasis.



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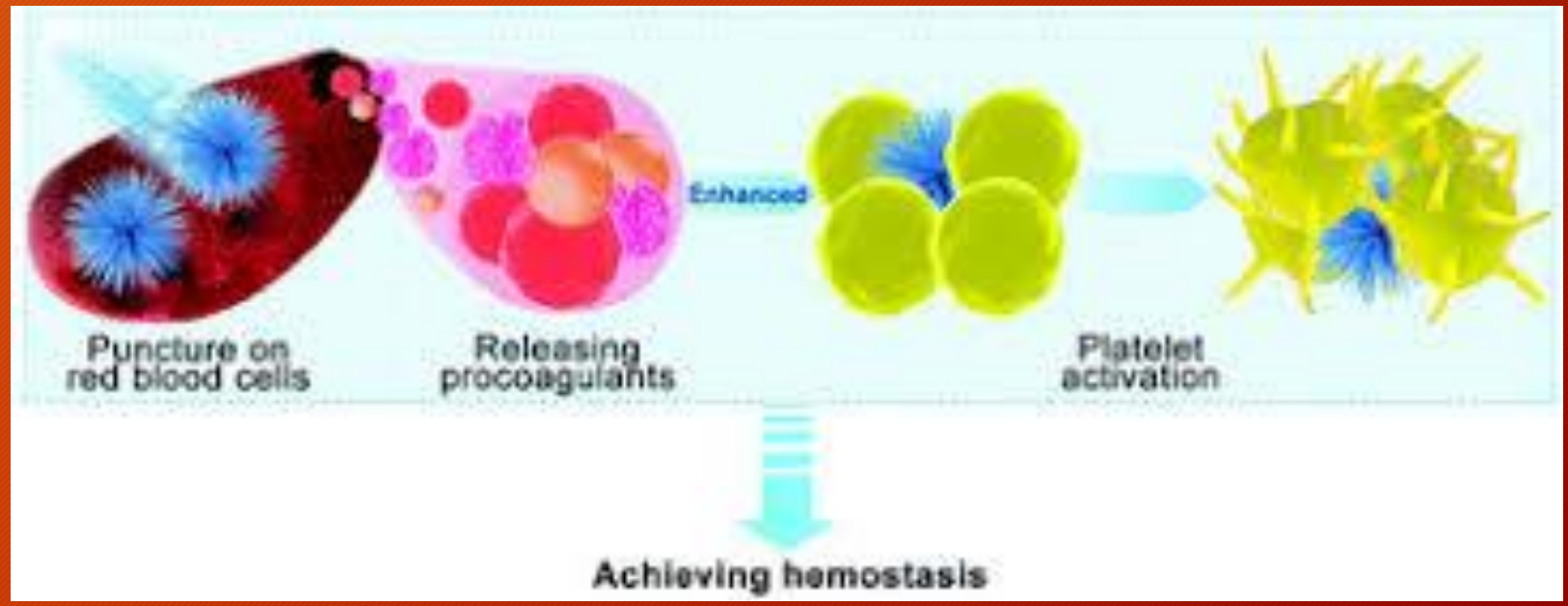
Procoagulants

Examples:

- Plasminogen activator inhibitor
- Tissue Factors
- vonWillibrand Factor



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Cancer Procoagulants

- Cancer procoagulant — Cancer procoagulant (CP) is a calcium-dependent cysteine protease that has been found in malignant and fetal tissue, but not normally differentiated tissue.
- It activates factor X directly, independent of the tissue factor/factor VIIa complex
- Cancer procoagulant has been reported to be present in extracts of cells obtained from patients with acute promyelocytic leukemia, malignant melanoma, and cancers of the colon, breast, lung, and kidney

Treatments

Varies – depending on the cause:

- FFP (Fresh Frozen Plasma)
- PCC (prothrombin complex concentrate)
- Platelets
- Vitamin K supplement, to treat vitamin K deficiency bleeding
- Antifibrinolytic agents, such as tranexamic acid, to treat bleeding after childbirth or during procedures such as those involving dental work

Treatments cont.

- Birth control pills to treat heavy menstrual bleeding for women with von Willebrand disease
- Desmopressin (DDAVP), a human-made hormone, to treat minor bleeding in hemophilia or VWD.
- Immunosuppressive medicines, such as prednisone, to block production of antibodies in acquired bleeding disorders

Lethagen S. Desmopressin (DDAVP) and hemostasis. Ann Hematol. 1994 Oct;69(4):173-80. doi: 10.1007/BF02215950. PMID: 7948303.
Massimo Franchini, Giuseppe Lippi; Acquired factor VIII inhibitors. Blood 2008; 112 (2): 250–255. doi: https://doi.org/10.1182/blood-2008-03-143586

Hemophilia Management:

The aim is to correct factor VIII activity to 100% for severe and to 30-50% for minor hemorrhage.

Enhanced factor VIII levels are maintained for 7-10 days for severe bleeds and for 1-3 days for minor bleeds.

Desmopressin and aminocaproic acid may be used to boost factor VIII activity and reduce factor VIII administration requirements.

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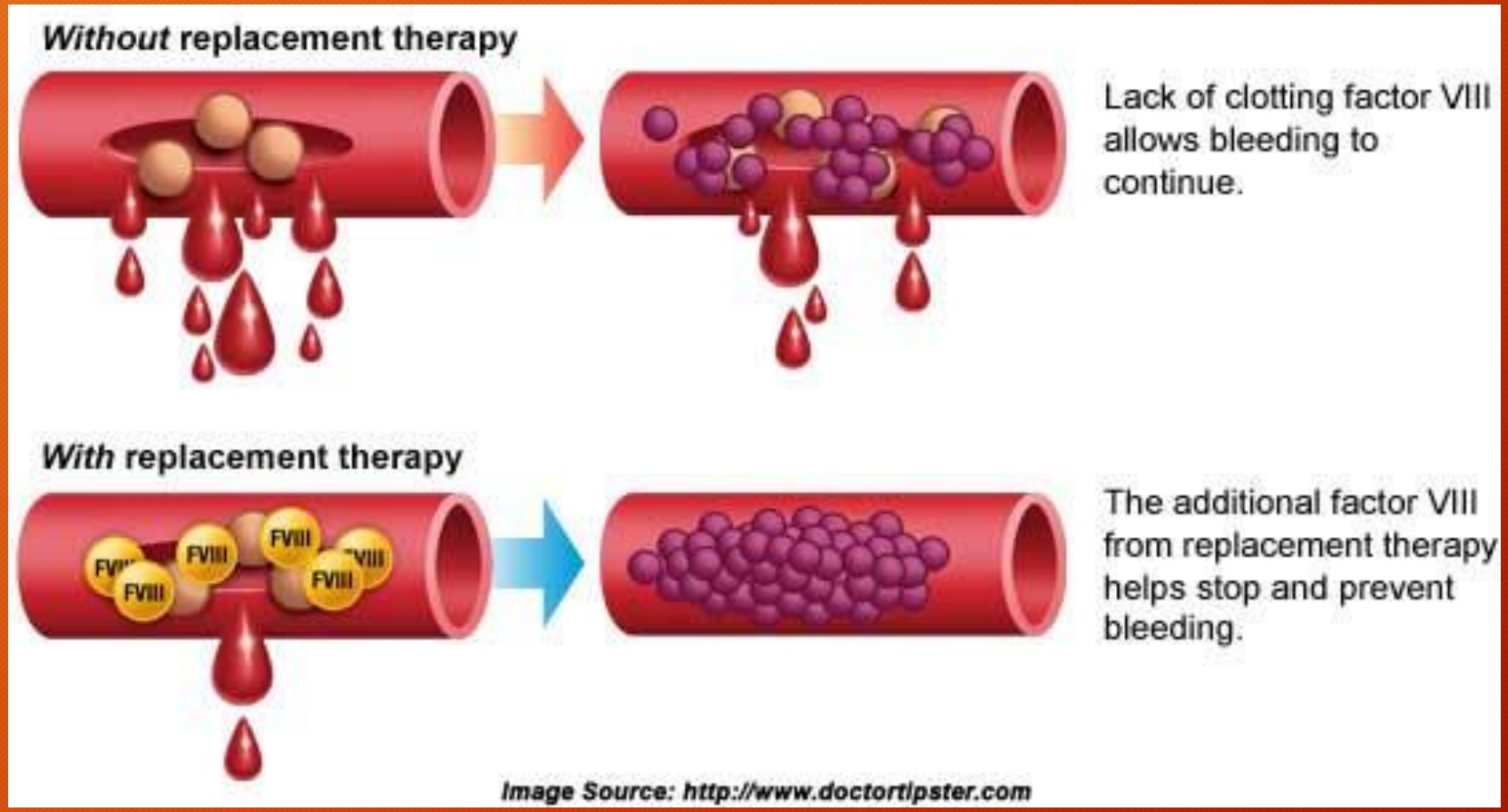
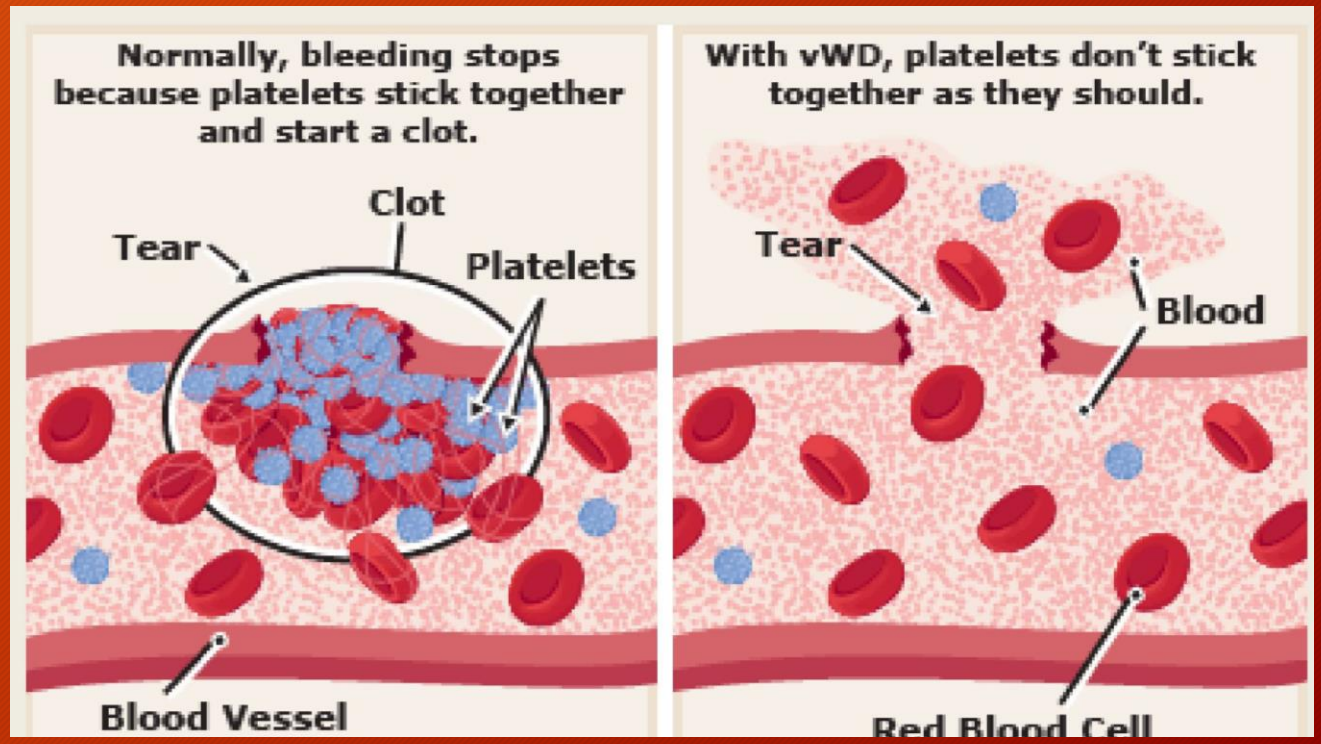

Without replacement therapy
Lack of clotting factor VIII allows bleeding to continue.
With replacement therapy
FVIII
FVIII
FVIII
FVIII
FVIII
The additional factor VIII from replacement therapy helps stop and prevent bleeding.
Image Source: http://www.doctortipster.com

Von Willebrand disease

- Most common hereditary coagulation abnormality in humans
- Arises from a qualitative or quantitative deficiency of von Willebrand factor (vWF) (a protein required form

vWD Type 1	vWD Type 2 (broken down into subtypes 2A,2B,2M,2N)	vWD Type 3
Partial quantitative deficiency	Qualitative defects	Virtually complete deficiency of vWF



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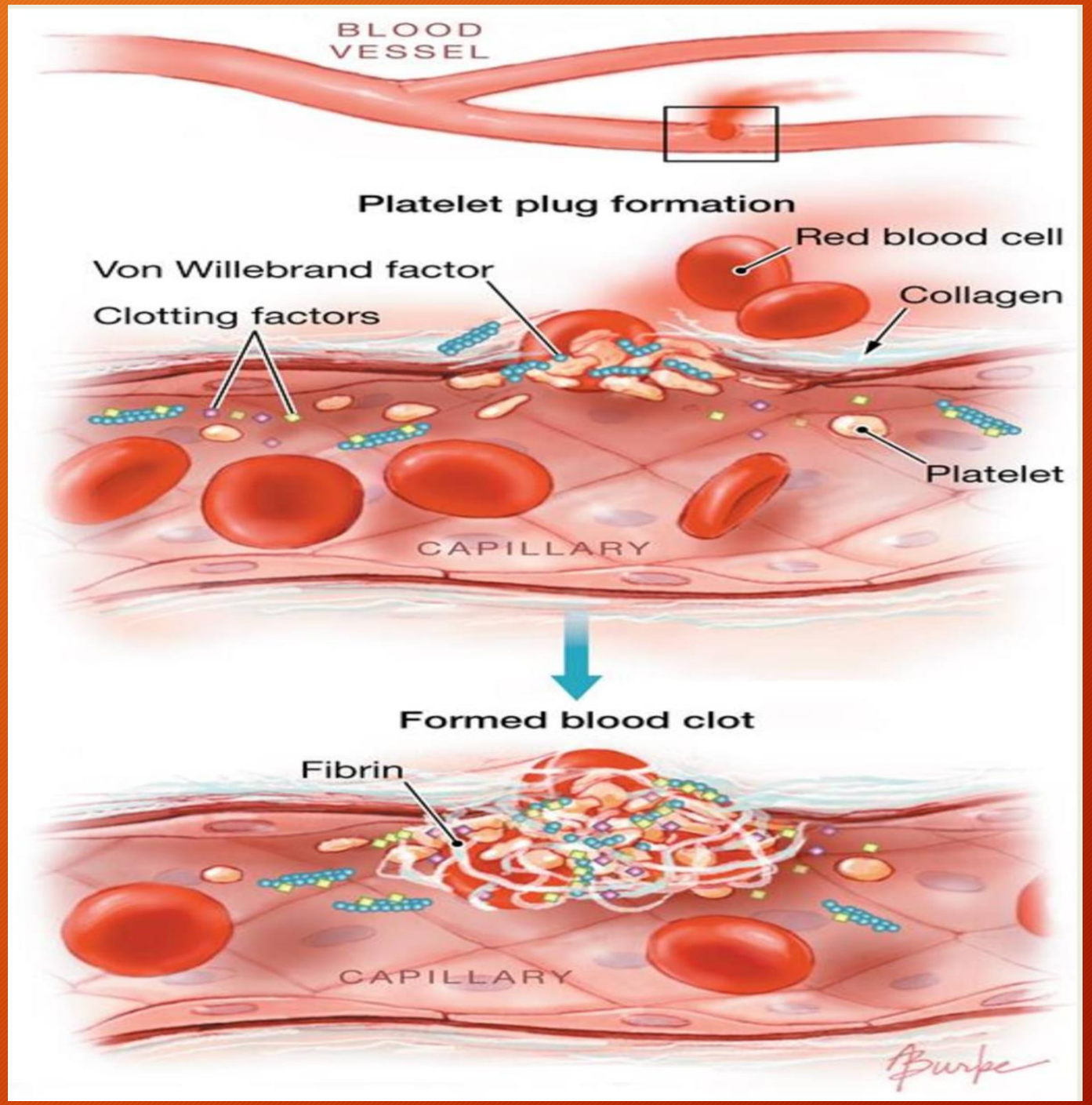
BLOOD VESSEL
Platelet plug formation
Red blood cell
Von Willebrand factor
Collagen
Clotting factors
Platelet
CAPILLARY
Formed blood clot
Fibrin
CAPILLARY

Prothrombin complex concentrate

- Prothrombin Complex Concentrate (PCC) is a combination of blood clotting factors II, VII, IX and X with Protein C and Protein S. It is a human derived pooled plasma product.
- For urgent reversal of acquired coagulation factor deficiency induced by vitamin K antagonist (VKA, e.g., warfarin) therapy in adult patients with acute major bleeding

- Common side effects of Prothrombin Complex Concentrate include headache, nausea, vomiting, joint pain, low blood pressure (hypotension), and low levels of iron in the blood (anemia). The dose is individualized based on the patient's current pre-dose International Normalized Ratio (INR) value, and body weight.

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NDC 63833-386-02
500 U
Prothrombin Complex Concentrate (Human)
One single-use vial containing 400 – 620 units of lyophilized Factor IX concentrate for reconstitution. Also contains Factors II, VII, X and proteins C and S.
For Intravenous Administration Only
℞ only
EXP: AUG. 03,2019
LOT: J0660111A
Prothrombin Complex Concentr
For Intravenous Administration Only

QUESTIONS?

References

Top doctors, medical dictionary, coagulopathy. 8-18-21 https://www.topdoctors.co.uk/medical-dictionary/autoimmune-coagulation-disorders#

Massimo Franchini, Giuseppe Lippi; Acquired factor VIII inhibitors. Blood 2008; 112 (2): 250–255. doi: https://doi.org/10.1182/blood-2008-03-143586

Labpedia.net.

Basic physiology.com