

Bleeding Disorders 2025

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**CONTINUING MEDICAL EDUCATION
DEPARTMENT OF MEDICINE**

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- Boston University Medical School
- Medicine Residency (Chief Resident) BUMC
- Hematology/Oncology Fellowship at BIDMC
- Assistant Professor of Medicine at HMS

Clinical focus

Thrombosis/Hemostasis

– Platelet Disorders

Research focus

– Platelets in Disease

Disclosures

- *Nothing to Disclose*

Key Objectives

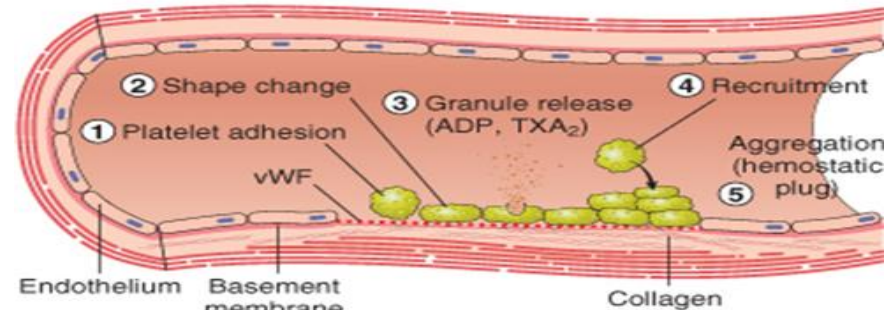
Use 4 case vignettes to:

- Highlight diagnosis and management of 4 key bleeding disorders
- Understand the key steps in Hemostasis

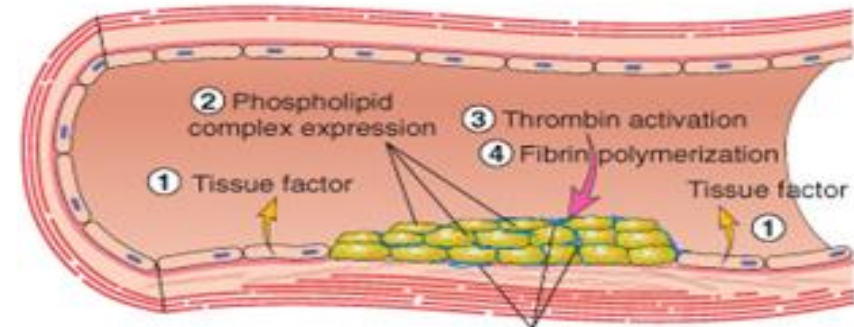
A. VASOCONSTRICTION



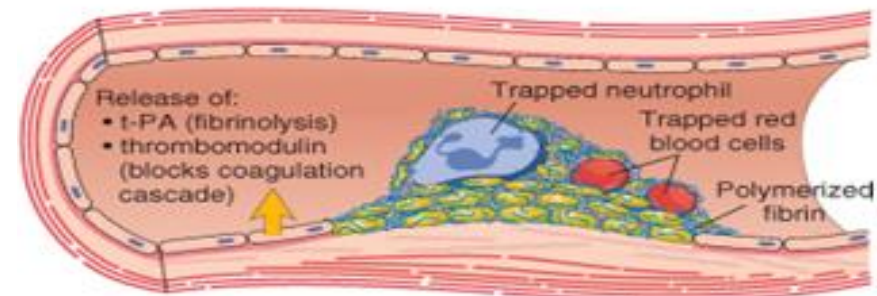
B. PRIMARY HEMOSTASIS



C. SECONDARY HEMOSTASIS



D. THROMBUS AND ANTITHROMBOTIC EVENTS



<http://medicinembbs.blogspot.com/2011/02/normal-hemostasis.html>

Case 1

- A 32 yo woman, pregnant with her first child, is visiting friends and unexpectedly goes into labor.
- She tells the covering obstetrician at your hospital that she has von Willebrand's Disease and wants to know if it is okay for her to have an epidural.
- You are asked to see her and provide advice re the advisability of an epidural and possible treatment for the von Willebrand's disease.

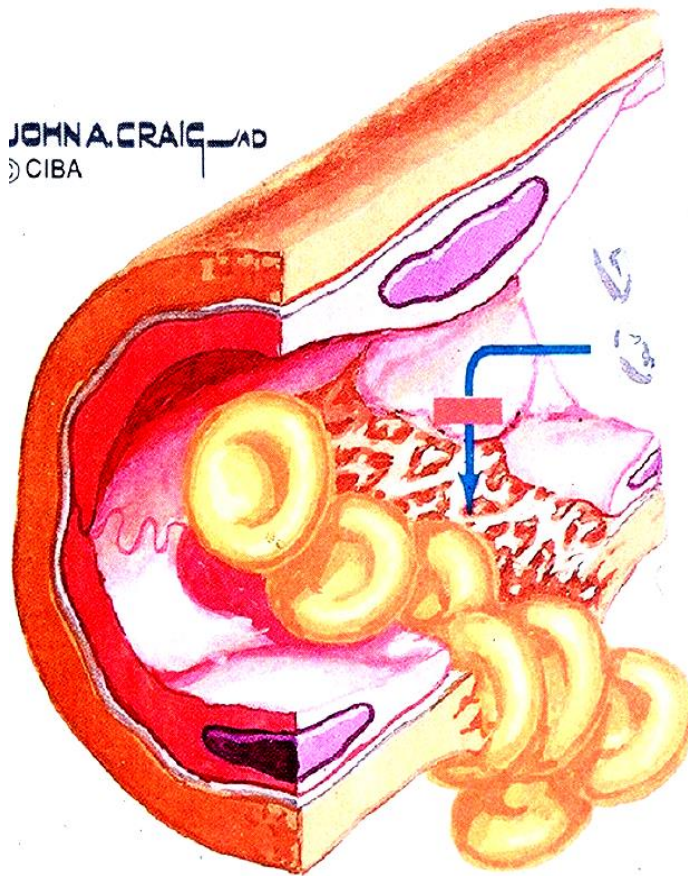
Laboratory results

- Chemistries including BUN, creatinine and glucose are normal
- CBC:
 - Hb is 12.3 gm/dl
 - Hct 35.5%
 - WBC 9500
 - Platelet count 450,000
 - Differential is reported as normal
- Coagulation Parameters:
 - PT 11.5 seconds (INR 1.1)
 - PTT 28 seconds (nl < 35)

Your consultation

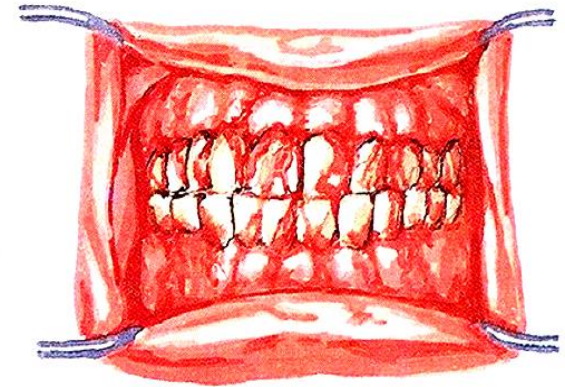
- She tells you that she has had occasional nosebleeds since she was a child and has had menorrhagia, also she bled a lot when she had her wisdom teeth extracted.
- She is usually treated with the intravenous or intranasal administration of ddavp for bleeding or before surgeries.
- Her mother and one sister have similar symptoms and respond to the same medication regimen.
- You try but are not able to reach her primary hematologist.

von Willebrand's Disease: VIII:vWF Abnormalities

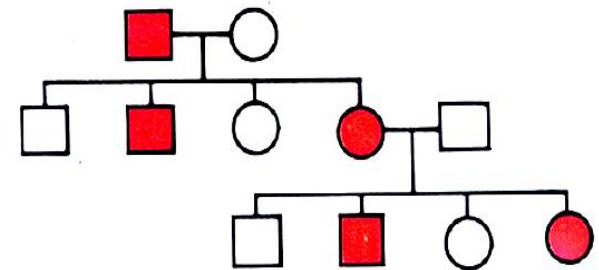


Reduced quantities or abnormal forms of subendothelial VIII:vWF decrease platelet adherence at sites of vascular injury

Inadequate platelet plug causes excessive blood loss and prolongs bleeding time



Spontaneous mucosal bleeding



Autosomal dominant inheritance pattern

Coagulation in Pregnancy

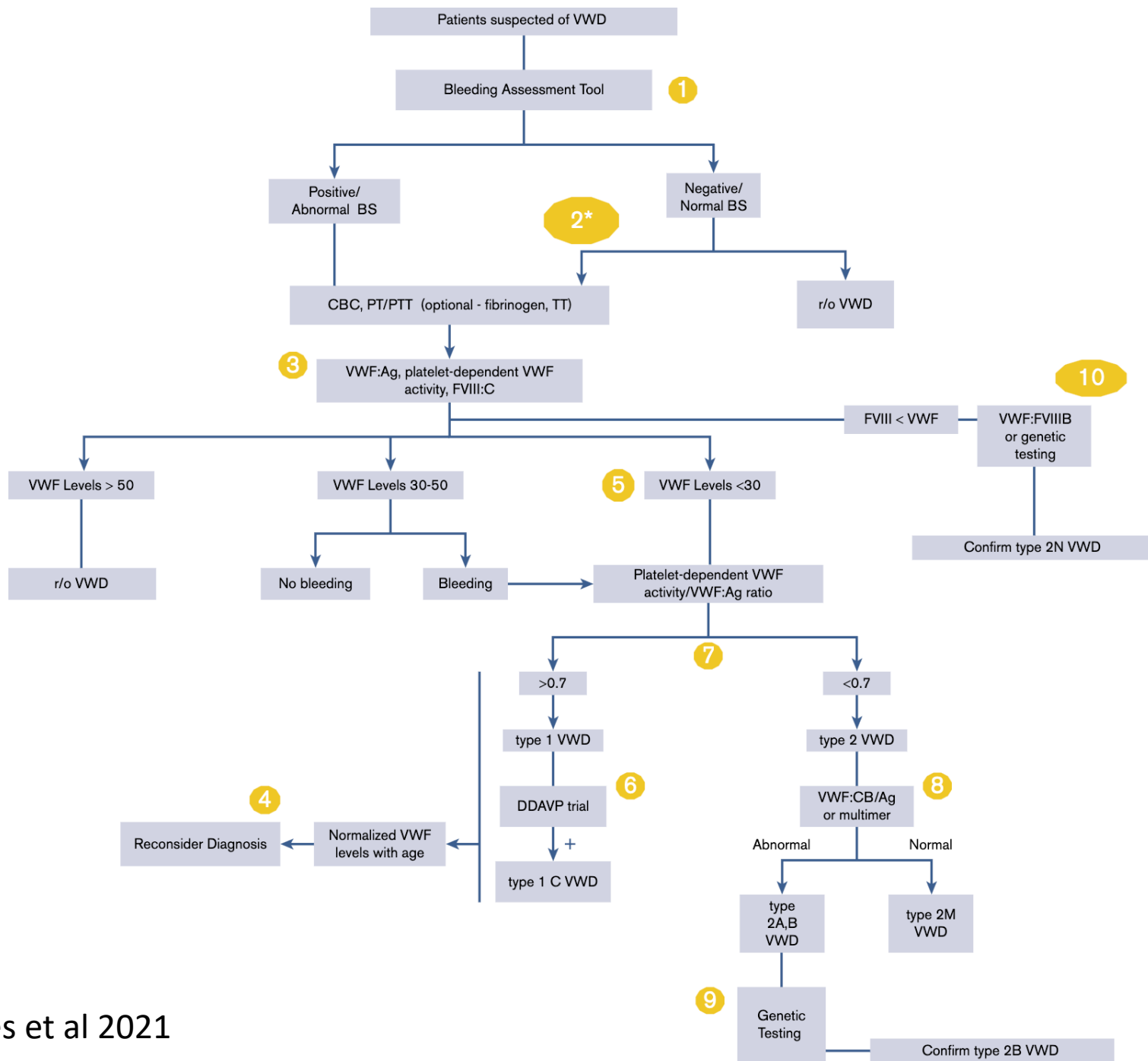
Increase	Decrease
<ul style="list-style-type: none">•Fibrinogen•vWF•VIII•VII•X•IX•XII	<ul style="list-style-type: none">•Protein S•Acquired resistance to activated protein C•Fibrinolysis (inhibition)•Platelet Count

vWD

- Most common inherited hemostatic disorder, prevalence up to 1%
- Mucocutaneous bleeding
 - Epistaxis
 - Easy bruising
 - GI bleeding
 - Post-op
 - Surgery--immediately
 - Dental procedures
- Women's health issue
 - 75% women with vWD have menorrhagia
 - often dx with first menstrual period or PPH

vWF: Laboratory Evaluation

- aPTT
 - FVIII:C
 - vWF:Ag
 - vWF:RCo Ristocetin cofactor activity
 - Multimer gel electrophoresis



vWD

- Mild vWD can be difficult to diagnose
- Levels vary and are affected by:
 - Blood type
 - Estrogen
 - Inflammation
 - Stress
 - Smoking

vWD: Classification

- **Type I:** autosomal dominant, **quantitative** decrease in vWF and ***concordant*** decrease in all functions
 - 70-80% of vWD cases
- **Type III:** homozygous recessive, almost no detectable vWF
 - Very Rare

vWD: Classification

Type II: *Qualitative Abnormalities*

A: decreased large mw multimers

10-15% of VWD

B: gain of function mutations, increased binding to GPIb

M: loss of function mutations, decreased binding to GPIb

N: loss of function mutations, decreased FVIII binding

vWD and Pregnancy

- Antigen levels increase with increased estrogen
- Function does not change
- Increased risk of post-partum hemorrhage
 - Levels return to baseline over 7-21 days
 - 20-25% patients with vWD have delayed PPH
 - Mean onset 15.7 ± 5.2 days

What happens next?

- Your patient delivers a baby boy without any bleeding issues
- You reach primary hematologist and learn that she indeed has Type I vWD.
- Labs prior to pregnancy vWF Ag 30%, activity 35%, VIII activity 45%

What happens next (Cont.)?

- Values two weeks before delivery vWF Ag 105%, activity 120%, VIII activity 150%
- 48 hours after delivery she has developed uterine hemorrhage.

vWD: NHLBI Guidelines

- “We suggest that VWF ristocetin cofactor activity and factor VIII levels of at least **50 IU/dL** be achieved before delivery and maintained for three to five days afterward ([Grade 2C](#)).”

vWD: Treatment

DDAVP

- Release of stored vWF from Weibel-Palade bodies
- Onset of action within 30 mins
- Watch for Tachyphylaxis with repeated dosing
- Side effects include:
 - Headache, HTN, flushing, N/V, hyponatremia and seizures, uterine contractions
- Pre-procedure DDAVP challenge test to monitor response

vWD: Treatment

vWF containing concentrates

- plasma derived pathogen-inactivated.
- Dose by FVIII or vWF levels.
 - Humate-P
 - Alphanate
- Transexamic Acid to augment

Case 2

- 23 year old female who presents with bleeding after wisdom tooth removal. Patient has been referred to ED from dental clinic after the dentist could not control the bleeding.
- Pt. has no history of epistaxis, gingival bleeding but does report that at onset of menses her period was very heavy prompting her to regulate menses with OCPs.

Case 2 Cont.

- No history of any other tooth extractions or surgical procedures.
- Family Hx: Mother with von Willebrand disease per report of patient. No other bleeding history in the Family.

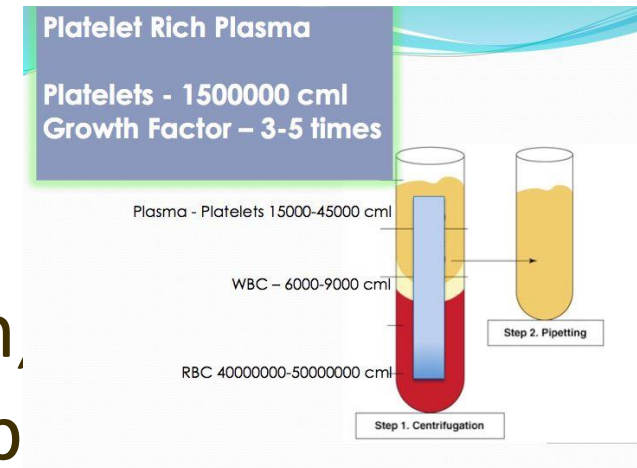
- WBC 8.6
- Hct 38
- Plt 235, normal appearance on smear
- PT 1.1
- PTT 32.5
- Fibrinogen 365
- von Willebrand Panel is normal
- Platelet Aggregation studies: Abnormal

Platelet Aggregation Studies

- Absent platelet aggregation in response to multiple agonists:
 - ADP
 - Thrombin
 - Collagen
 - Arachadonic Acid
- Normal Aggregation to Ristocetin

Platelet Aggregation Studies

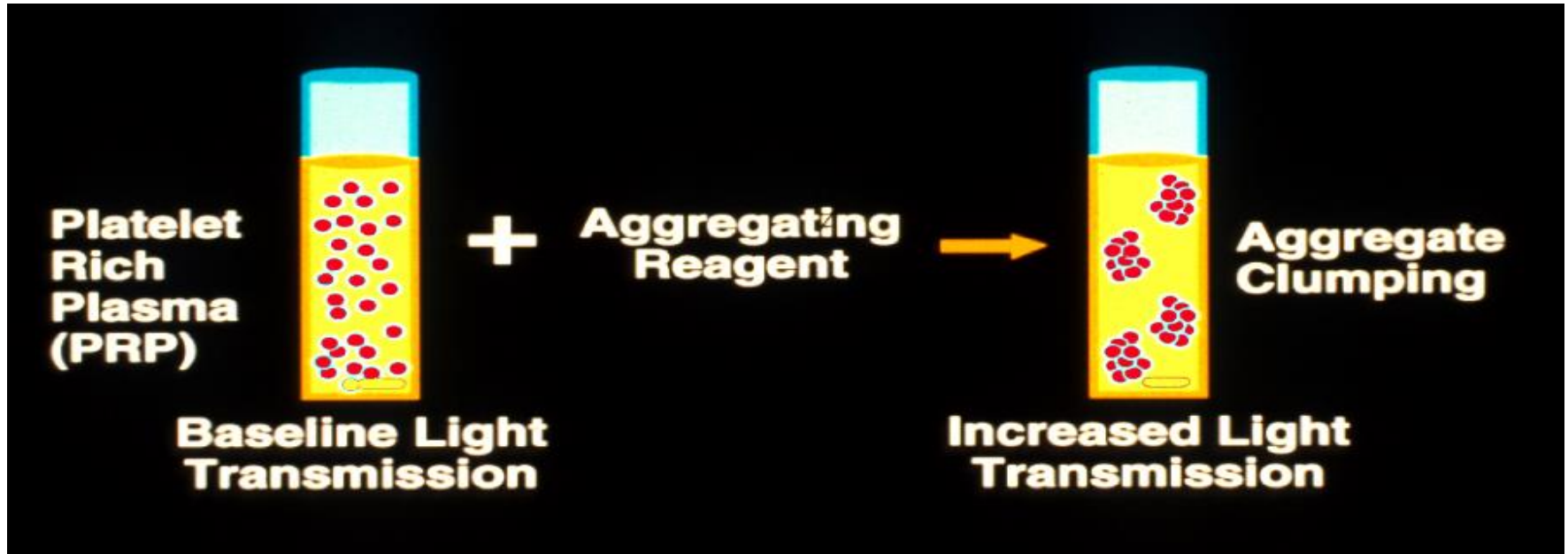
- Aggregation
 - Light transmission aggregometry using Chrono-Log instrument
 - ADP, arachidonic acid, collagen, epinephrine, ristocetin
- ATP secretion
 - Luciferin-Luciferase assay
 - ADP, arachidonic acid, collagen, epinephrine, ristocetin, thromb



Problems with Platelet Aggregation Studies

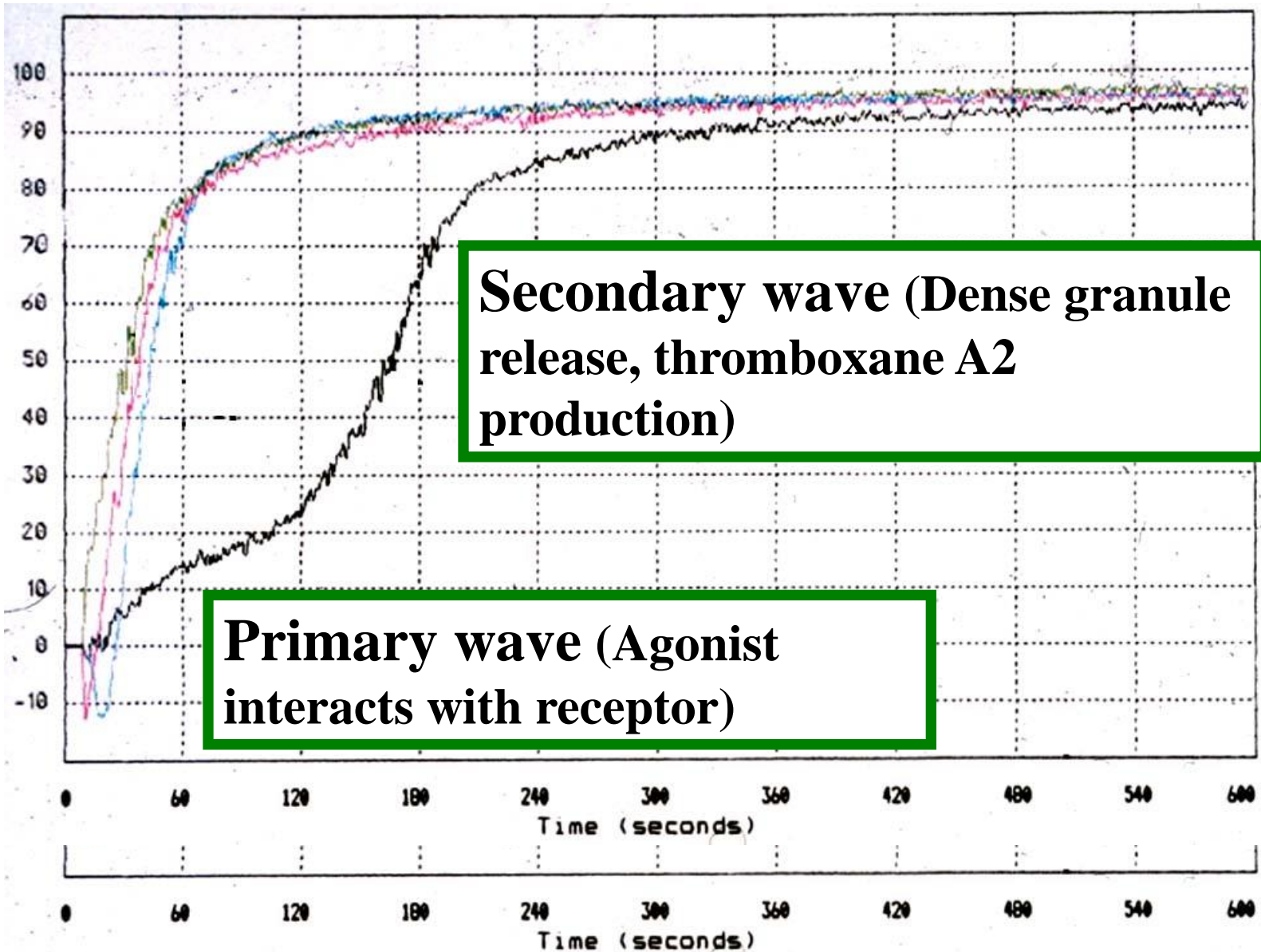
- Numerous variables affect aggregation:
 - Anticoagulant (sodium citrate best)
 - Plt count in PRP
 - Plt size distribution
 - Time of day
 - Temporal relation to meals and physical activity

Aggregometry

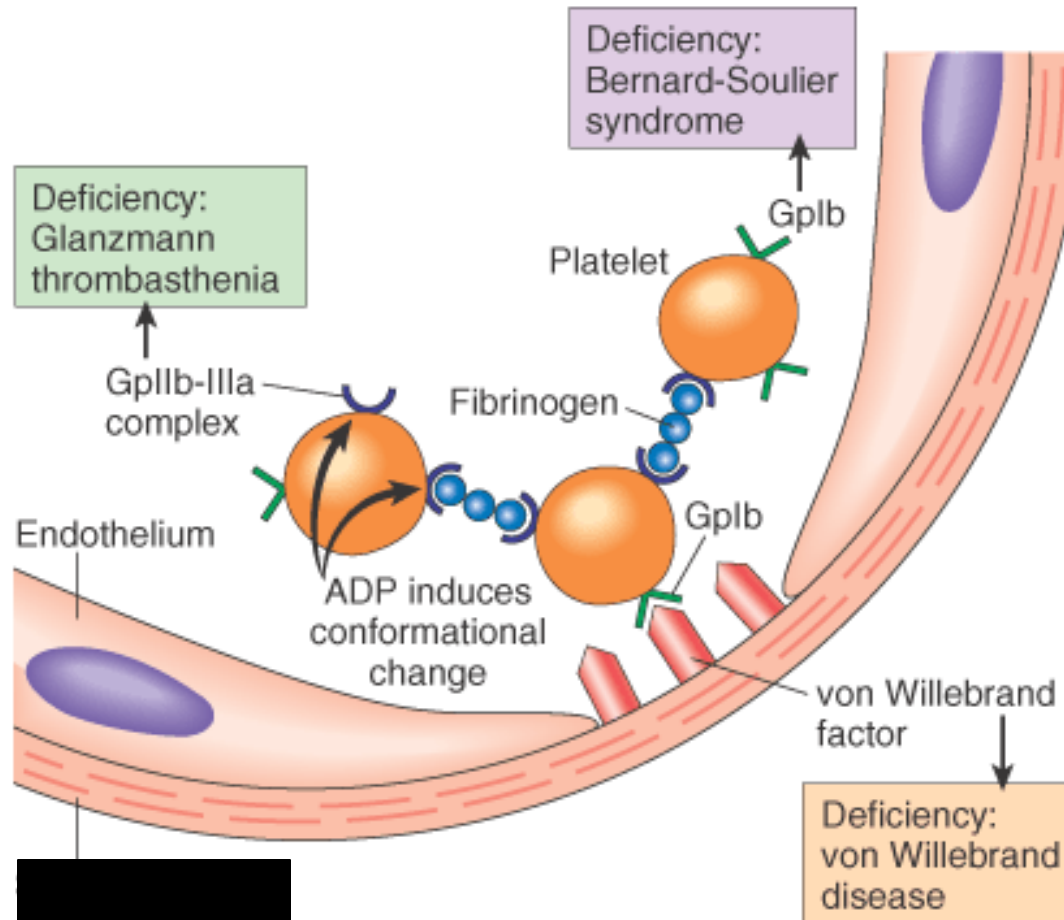


- Platelets shift from disc-like to a rounded form with pseudopods transiently decreasing light transmission.
- Then they aggregate into clumps, increasing light transmission.

The Aggregometer Tracings



Disorders in Platelet Aggregation



Diagnosis: Glanzmann Thrombasthenia

- Platelet count and morphology is normal
- Bleeding time prolonged
- The hallmark of the disease is severely reduced or absent platelet aggregation in response to multiple agonists
 - ADP, thrombin, or collagen
 - Normal response to Ristocetin
- Flow cytometry: decreased mAb expression of CD41 (GPIIb) and CD61 (GPIIIa)

Management

- Platelet transfusions
 - Caution for development of platelet antibodies
- Supportive care: ddavp and transexamic acid
- Factor VIIa

Case 3

- 75 y.o. female comes to you for pre-op clearance for cardiac surgery.
- She is referred to your clinic for a prolonged PTT.
- She has not seen a physician in 40 years.
- No bleeding history per the patient

Laboratory testing

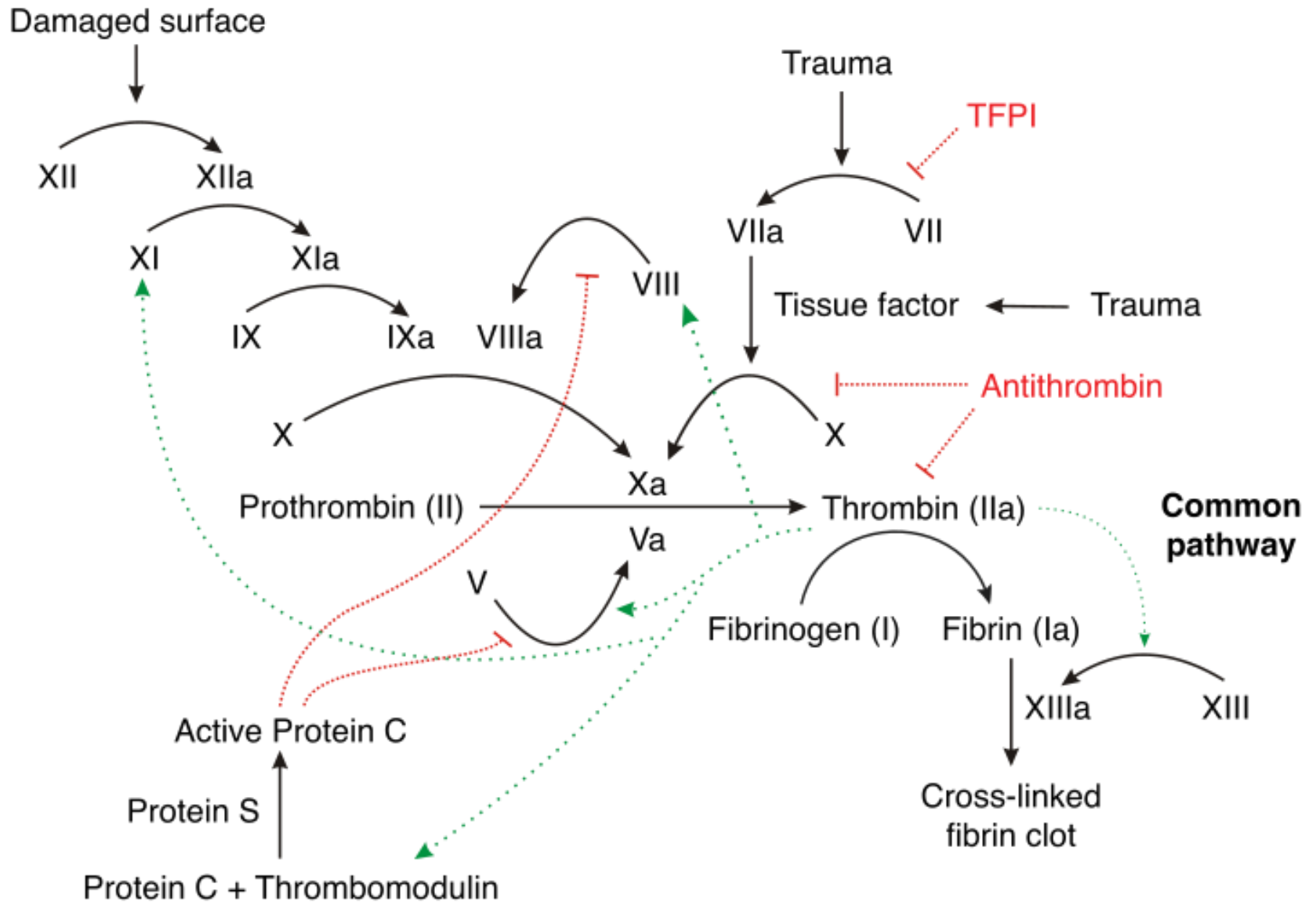
- Factor XIII screen is normal
- Factor VIII level is 102%
- Factor IX level is 89%
- Factor XI level is 22%

Factor XI Deficiency

- Rare bleeding disorder
- Inherited as Autosomal Recessive
- Prolongs the PTT
- Characterized by variable bleeding history
- Incidence is 1 in 450 in the Ashkenazi Jewish population and 1 in a million in non-Jewish population.

Contact activation (intrinsic) pathway

Tissue factor (extrinsic) pathway



Factor XI deficiency

- Bleeding manifestations do not correlate with factor XI levels
- Most bleeding episodes in patients with severe deficiency are injury-related
- Spontaneous bleeding is rare
- May be associated with bleeding after surgery or trauma
- Up to 33% of patients with severe deficiency develop inhibitors after replacement therapy

Treatment for Factor XI Deficiency

- 10-20 ml fresh frozen plasma/kg, then 5-10 ml/kg every 24 hours as necessary
- Antifibrinolytic therapy
- Patients with inhibitors have been treated successfully with plasma, prothrombin complex concentrates, and recombinant activated factor VII
- Note: factor XI concentrates available in Europe

Case 4

- 44 y.o. female comes into clinic for bleeding evaluation prior to planned knee surgery.
- History of heavy menses and bleeding with wisdom teeth extraction and during childbirth.
- Mother also had history of bleeding with procedures

Labs

- WBC 6.7
- Hct 38.7
- Platelet Count 287
- PT 18.0
- INR 1.5
- PTT 37.9
- Fibrinogen 67

Types of Fibrinogen Abnormalities

Quantitative

- Afibrinogenemia: Absence of circulating fibrinogen
- Hypofibrinogenemia: Reduced levels of circulating fibrinogen

Qualitative

- Dysfibrinogenemia: Dysfunctional fibrinogen
- Hypodysfibrinogenemia: Reduced levels and dysfunctional

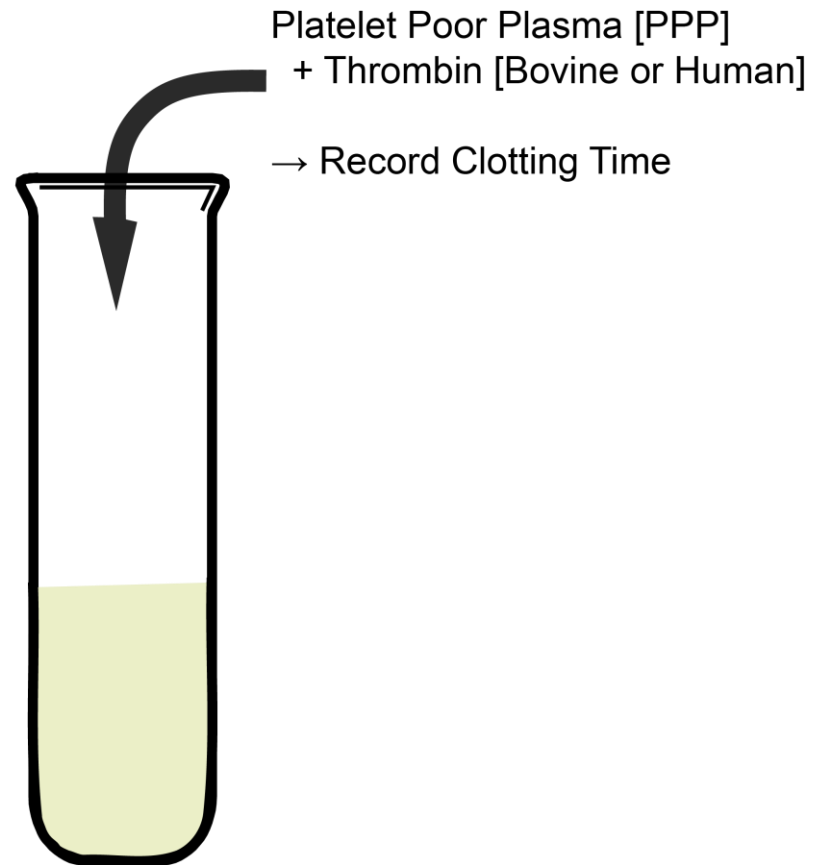
Acquired Abnormalities

- Liver Disease
 - Dysfibrinogenemia
 - Due to increased sialic acid residues that results in delayed fibrin aggregation
 - Hypofibrinogenemia
- DIC
 - Increased levels of fibrin degradation
- Hemophagocytic lymphohistiocytosis
 - Hypofibrinogenemia due to liver issues

Diagnostic Approach

- Personal and Family History of Bleeding
- Coagulation testing:
 - PT/aPTT
 - Thrombin time
 - Fibrinogen level:
 - Functional Fibrinogen and Fibrinogen Antigen
- Reptilase Time
- Mixing Study (corrects with afibrinogenemia or hypofibrinogenemia but not dysfibrinogenemia)

Thrombin Time [TT]



Reptilase Time

- Reptilase is a thrombin-like enzyme from snake venom.
- Catalyzes conversion of fibrinogen to fibrin
- Unlike Thrombin, the enzyme cleaves only fibrinopeptide A from fibrinogen
- Unaffected by Heparin

Distinguishing the Fibrinogen Disorders

Deficiency	TT	PT	PTT	Fibrinogen	Fibrinogen Ag
Afibrinogenemia	Increased	Increased	Increased	None	None
Hypofibrinogenemia	Increased	Increased	Increased (depends on level)	Decreased	Decreased
Dysfibrinogenemia	Increased	Increased	Increased	Low to normal	Low to Normal

Laboratory Testing

- Thrombin Time 32.5
- Reptilase Time >100
- Fibrinogen Antigen 63

Management

Acute Bleeding

- Increase fibrinogen level to 150-200mg/dL
 - Fibrinogen Concentrates
 - Plasma Products (Cyroprecipitate or Fresh Frozen Plasma)

Prophylaxis

- Not usually required unless afibrinogenemia or severe hypofibrinogenemia

Summary

- In bleeding disorders think about primary and secondary hemostasis to understand etiology.

Primary: Platelets disorder and vWD

Secondary: Coagulation Factors and
Fibrinogen/Fibrinolysis

History is Key for diagnosis and management.

Board Review Questions

Question 1

- You are asked to see a 37 yo woman with history of vWD for consultation planning to have elective knee surgery?”
- Pt. has never had any other surgeries. She had frequent epistaxis as a child and heavy menses.
- FH: Mother has hx vWD but died young (trauma). 5 uncles, one with bleeding disorder.

Question 1

- F VIII:C 27
- vWF:ag 89
- vWF:RCo 75
- PTT 46 sec

- What type of vWD does this patient have?

Question 1

- A. Types I vWD. Treat with ddavp prior to surgery.
- B. She does not have vWD because her VWF:ag and :Rco are normal.
- C. You need more info. She could have type 2N or be a hemophilia A carrier.

2N vs. Hemophilia A carrier

- 2N should be considered in AR inheritance with disproportionately low FVIII:C levels compared with VWF levels.
- To prove 2N, a FVIII-VWF binding assay is required.
- VWF gene mutation screening: R854Q at amino-terminus of VWF subunit is most frequent

Question 1

- A. Types I vWD. Treat with ddavp at delivery and postpartum.
- B. She does not have vWD because her VWFAg and Rco are normal.
- C. You need more info. She could have type 2N or be a hemophilia A carrier.

Question 2

- 38 y.o. Female is seen in the ER for bleeding gums after a dental procedure. She tells you that she has essential thrombocytosis and takes daily hydroxyurea and aspirin.
- A CBC is drawn and her platelet count is $1600 \times 10^9/\text{L}$ million.

The ER team asks why this patient is bleeding

Possible Answers

- A. The patient is on aspirin and bleeding due to its anti-platelet effects.
- B. The patient has developed an acquired von willebrand disease.
- C. This is a laboratory error and the platelet count should be repeated.

Question 2

- This patient has developed an acquired von willebrand disease in the setting of thrombocytosis.
- Diagnosis is confirmed by von Willebrand panel demonstrates low ristocetin cofactor activity with normal antigen levels.
- Aspirin should be used cautiously in patients with platelets $>1000 \times 10^9/L$

Case 2: Answer

- A. The patient is on aspirin and bleeding due to its anti-platelet effects.
- B. The patient has developed an acquired von willebrand disease.
- C. This is a laboratory error and the platelet count should be repeated.

References

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