แนวทางในการดูแลผู้ป่วยที่มีภาวะเลือดออกง่าย
Approach to bleeding disorders

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มหาวิทยาลัยขอนแก่น

Objectives

- Understanding mechanism of hemostasis
- Understanding clinical manifestations of bleeding disorders
- Investigate proper according to bleeding disorders
- Differentiate primary and secondary hemostasis

Major components of hemostasis

- Vasoconstriction
- Platelet activation

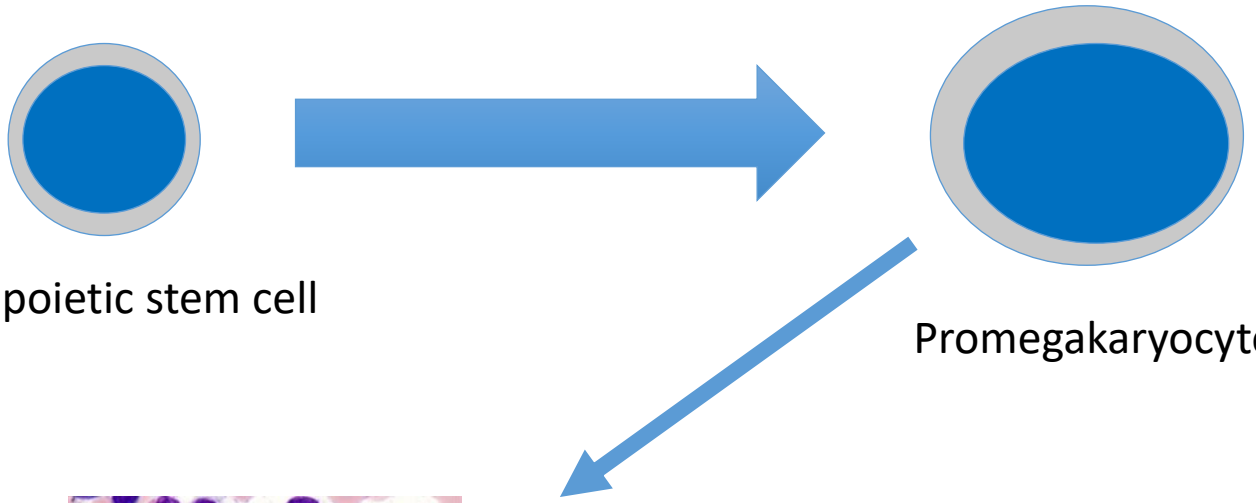
} Primary hemostasis

- Coagulation cascade/antithrombotic control mechanisms
- Fibrinolysis

↓

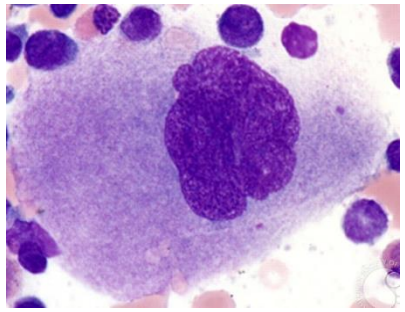
Secondary hemostasis

Primary hemostasis

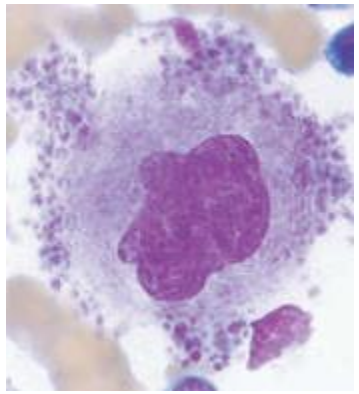


Hematopoietic stem cell

Promegakaryocyte

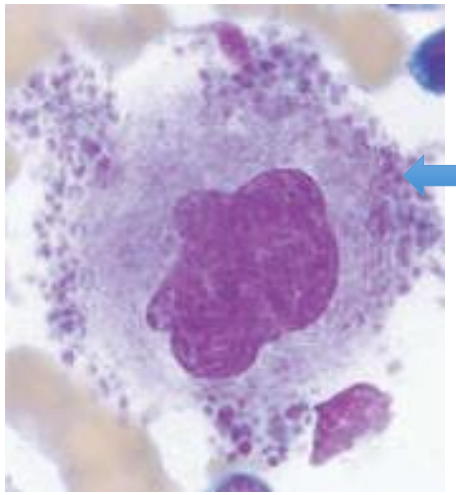


Megakaryocyte



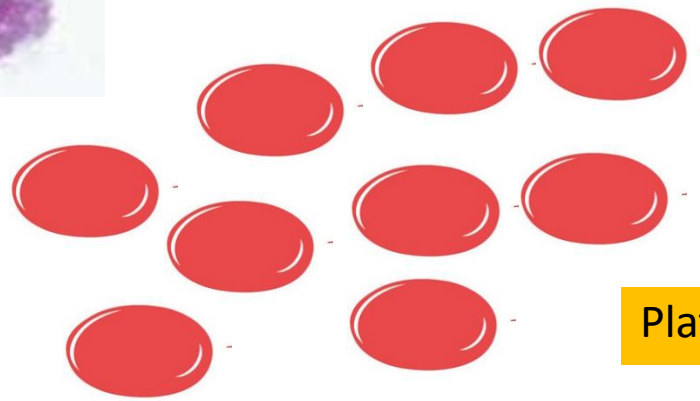
Platelet

Primary hemostasis



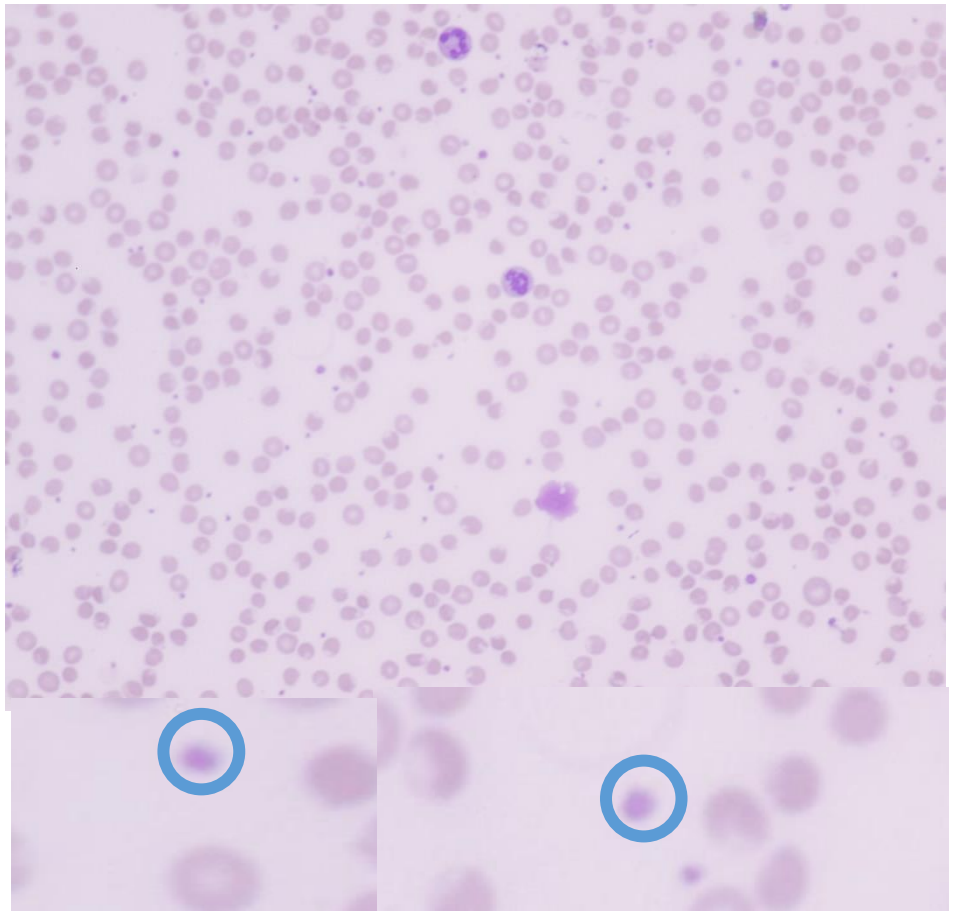
Megakaryocyte are giant cells with Multiple copies of DNA in the nucleus

The edges of megakaryocyte break off to form cells fragment called platelets



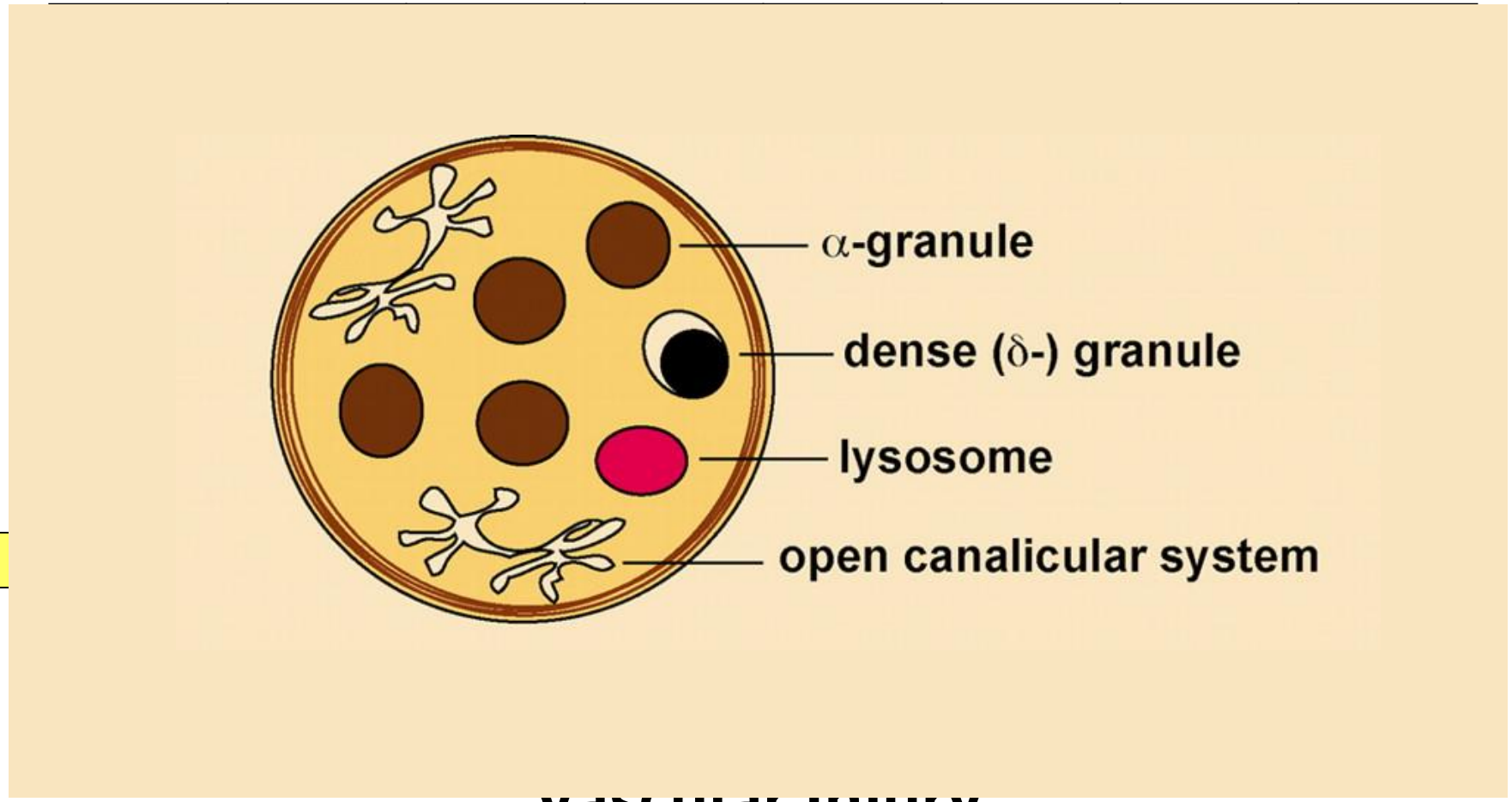
Platelets

Primary hemostasis



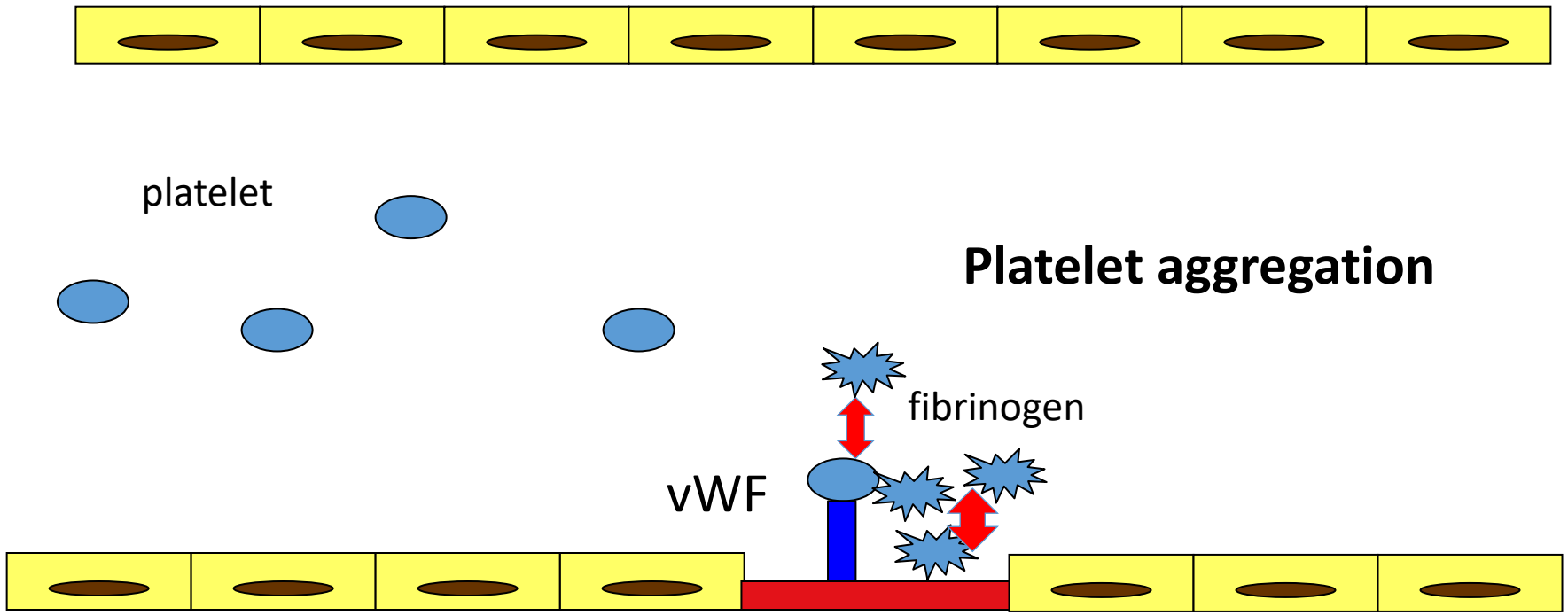
- Platelet number 150,000 – 450,000/mm^3
- size 7.2 -11.1 fL
- 14 times smaller than RBC
- Azurophilic Abundant granule
- lifespan 5 to 9 days
- megakaryocyte → 5,000 -10,000 plts
- 1 x 10^{11} platelets /day
- destroyed by phagocytosis in spleen, Kupffer cells in liver
- A reserve of platelets : spleen

Major components of hemostasis



vascular injury

Major components of hemostasis

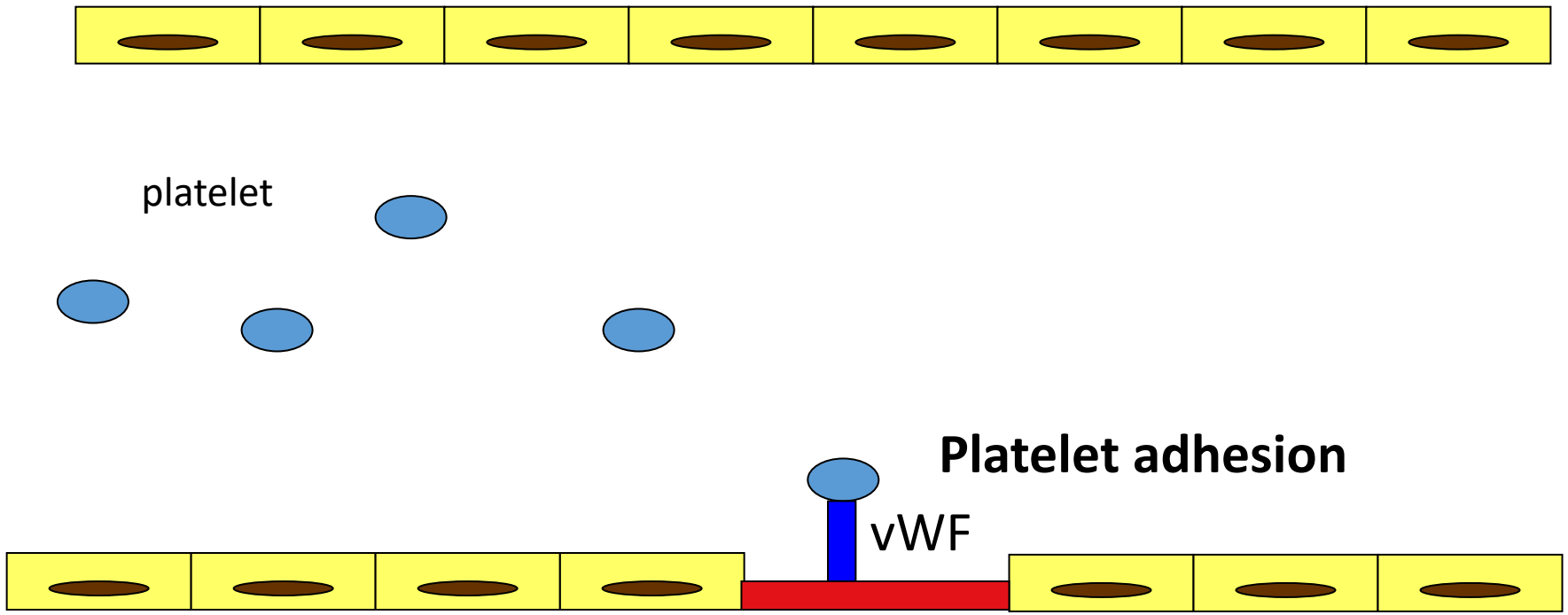


Function of Platelets: Response to Vascular Injury

Function of Platelets

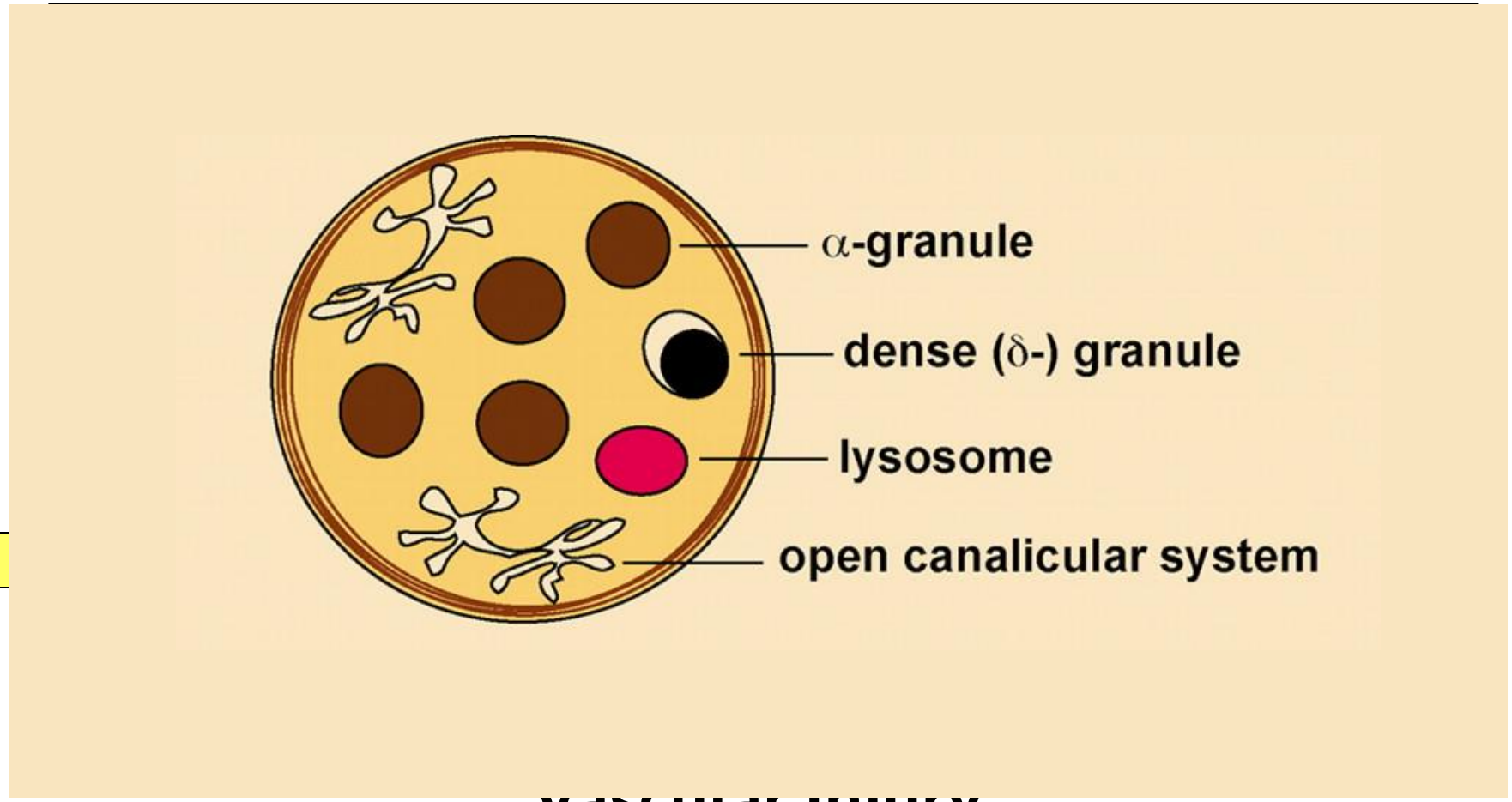
- Platelet adhesion
- Platelet activation
- Platelet secretion
- Platelet aggregation

Major components of hemostasis



Function of Platelets: Response to Vascular Injury

Major components of hemostasis

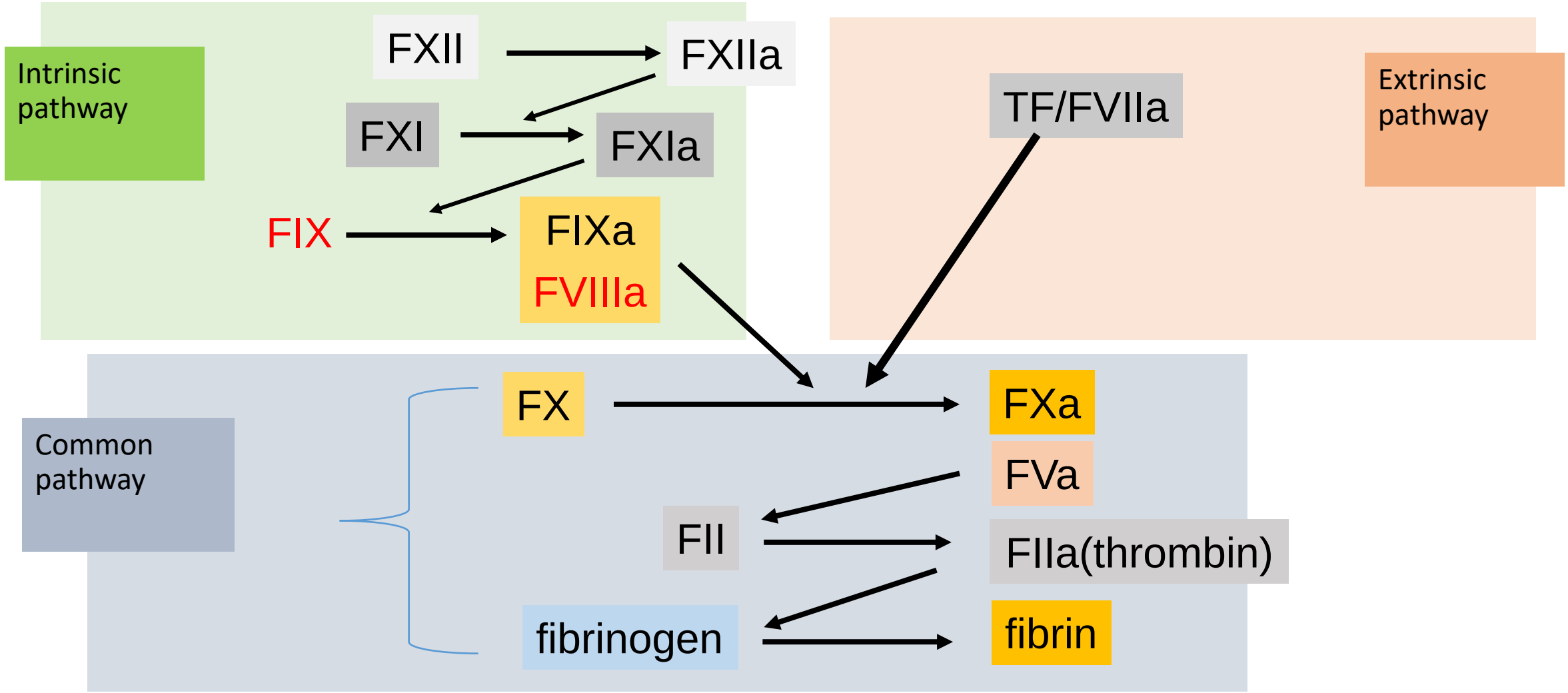


vascular injury

Introduction to coagulation system

- Procoagulant: Factor I – Factor XIII ไม่มี Factor VI
- Anticoagulant: antithrombin III, Protein C, Protein S and heparin cofactor II
- Fibrinolysis: plasminogen

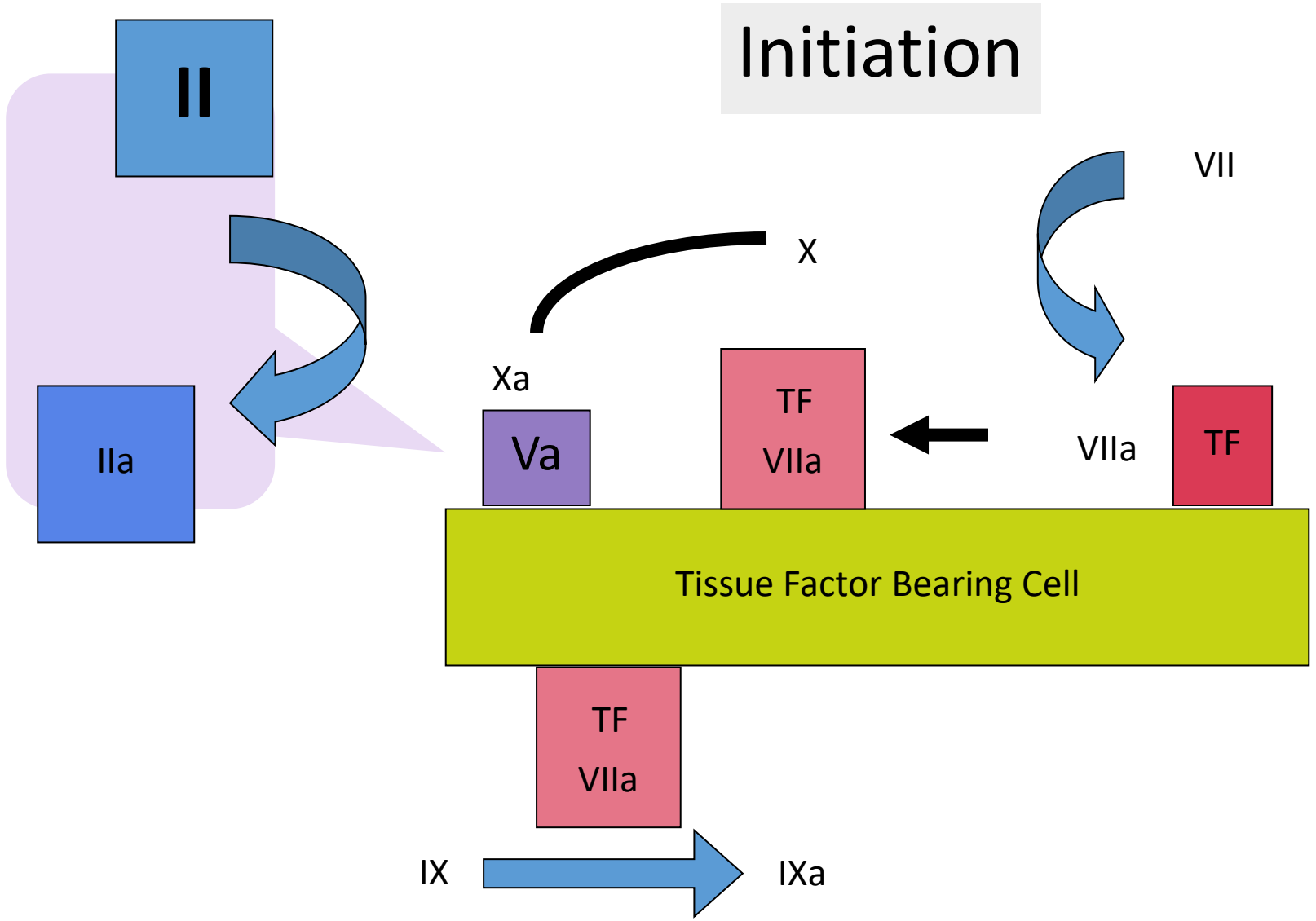
Process of secondary hemostasis: Cascade or Waterfall Model



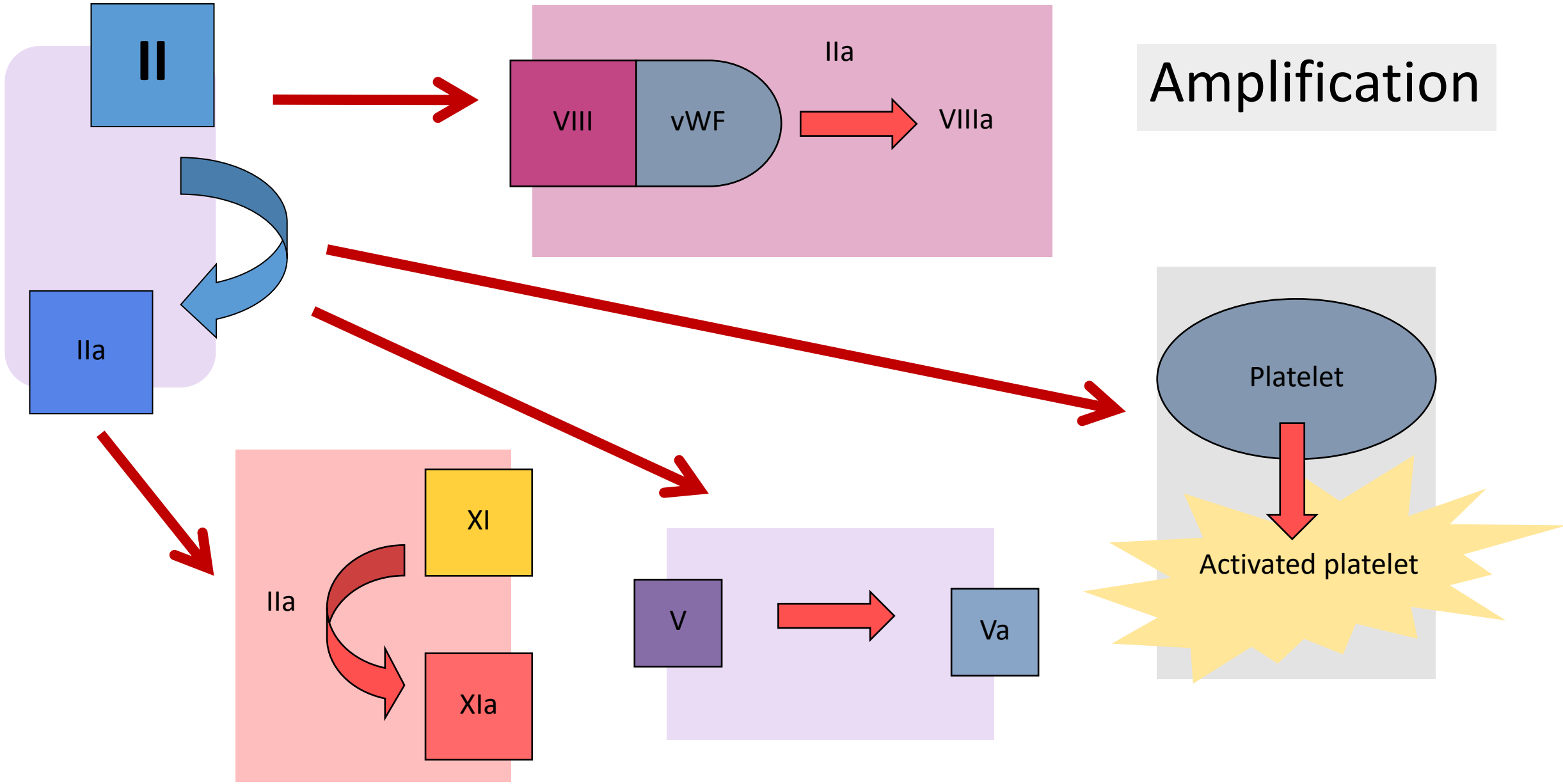
Process of secondary hemostasis: A Cell-based Model of Hemostasis

- Coagulation occurs not as a “cascade”, but in three overlapping stages.
- ***Initiation:***
  - occurs on a tissue factor bearing cell
- ***Amplification:***
  - platelets and cofactors are activated to set the stage for large scale thrombin generation
- ***Propagation:***
  - large amount of thrombin are generated on the platelet surface

Thromb Haemost. 2001 85:958



Modified from Lichtman MA, Kipps TJ, Seligsohn U, Kaushansky K, Prchal JT: William Hematology, 8th edition: http://ww.accessmedicine.com



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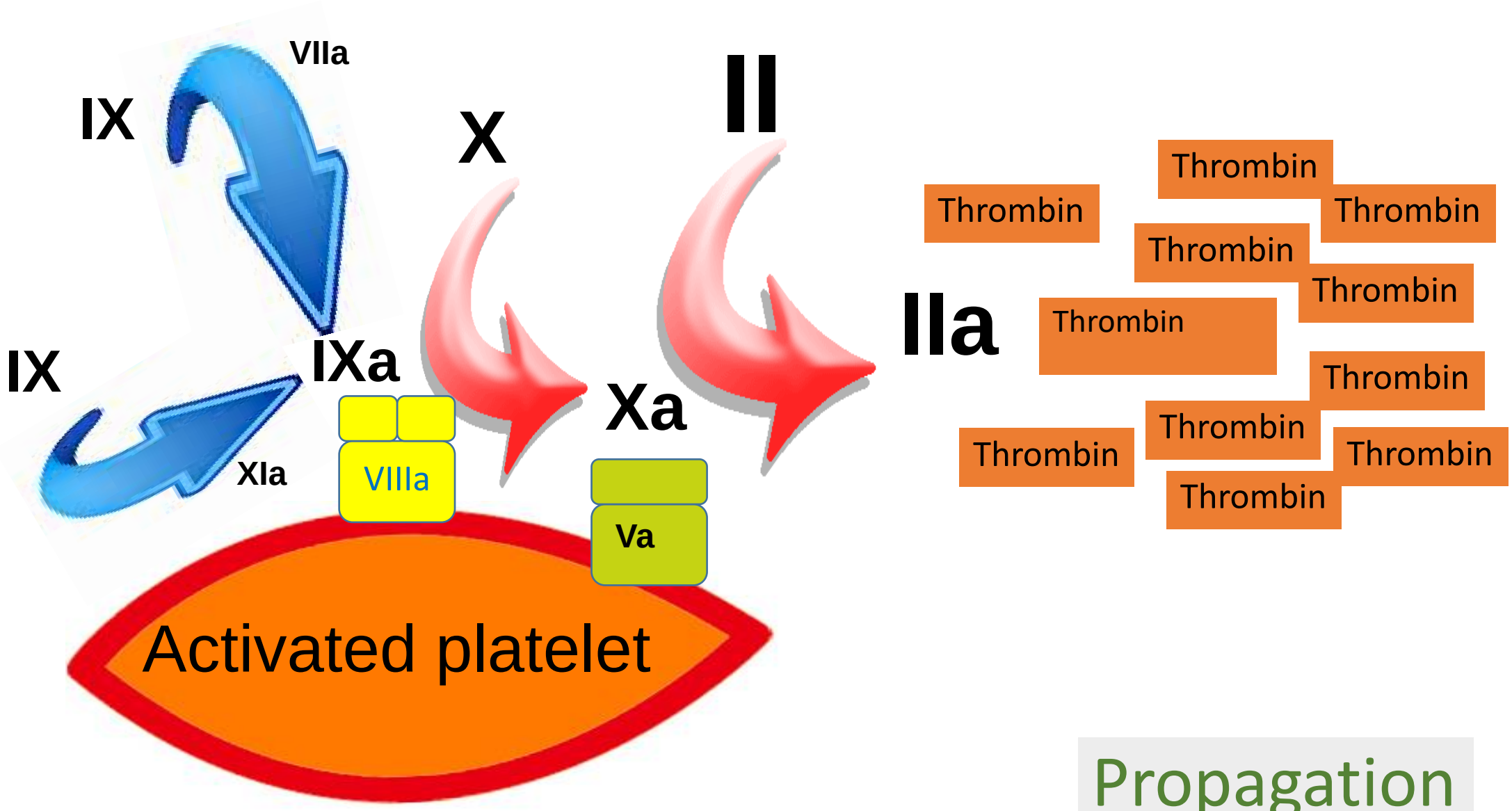
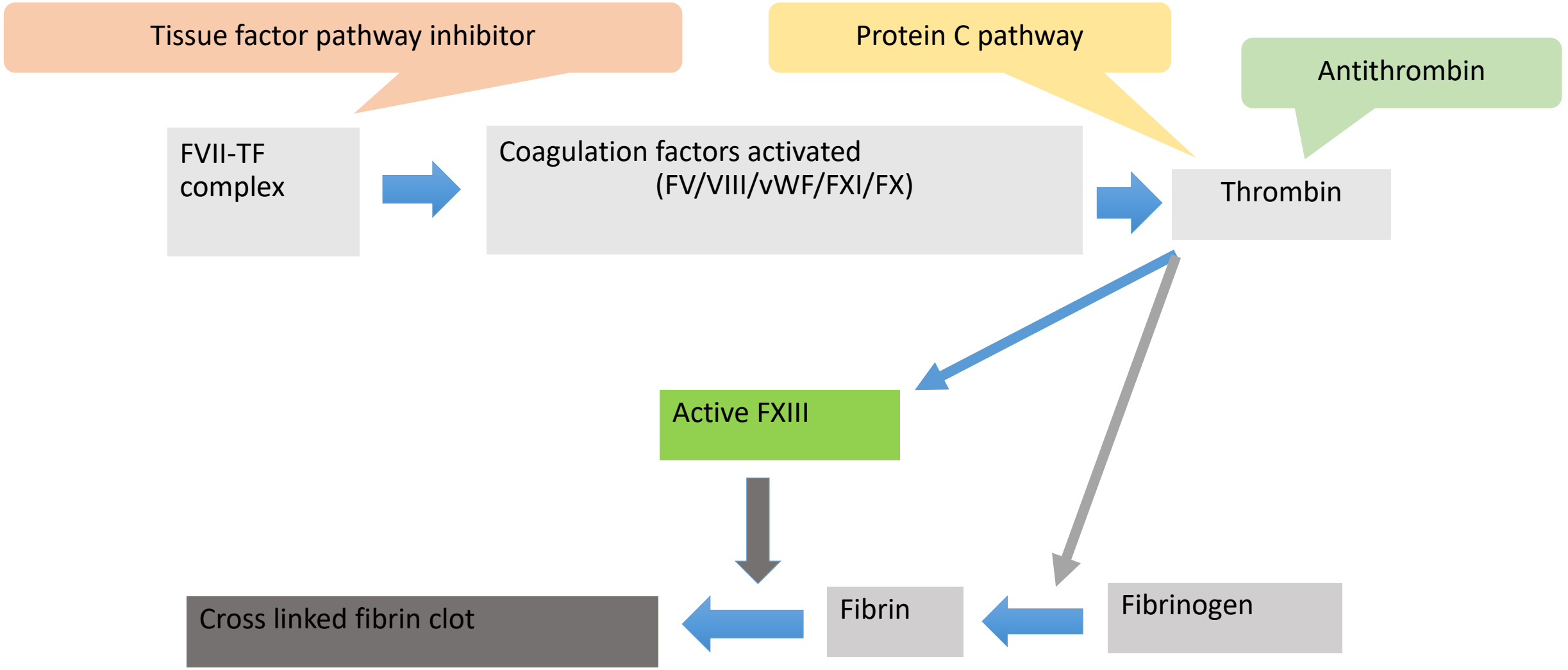


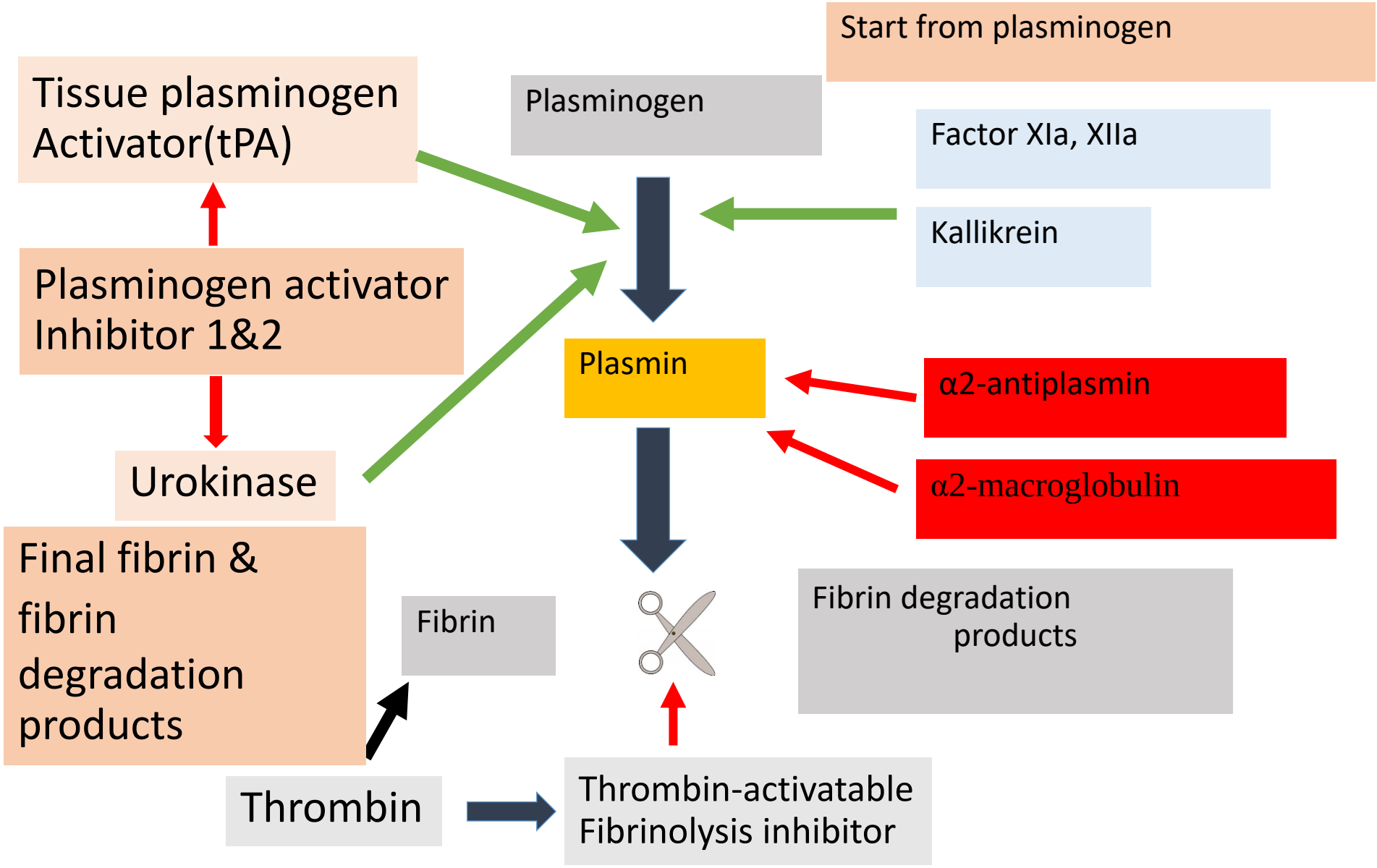
Propagation

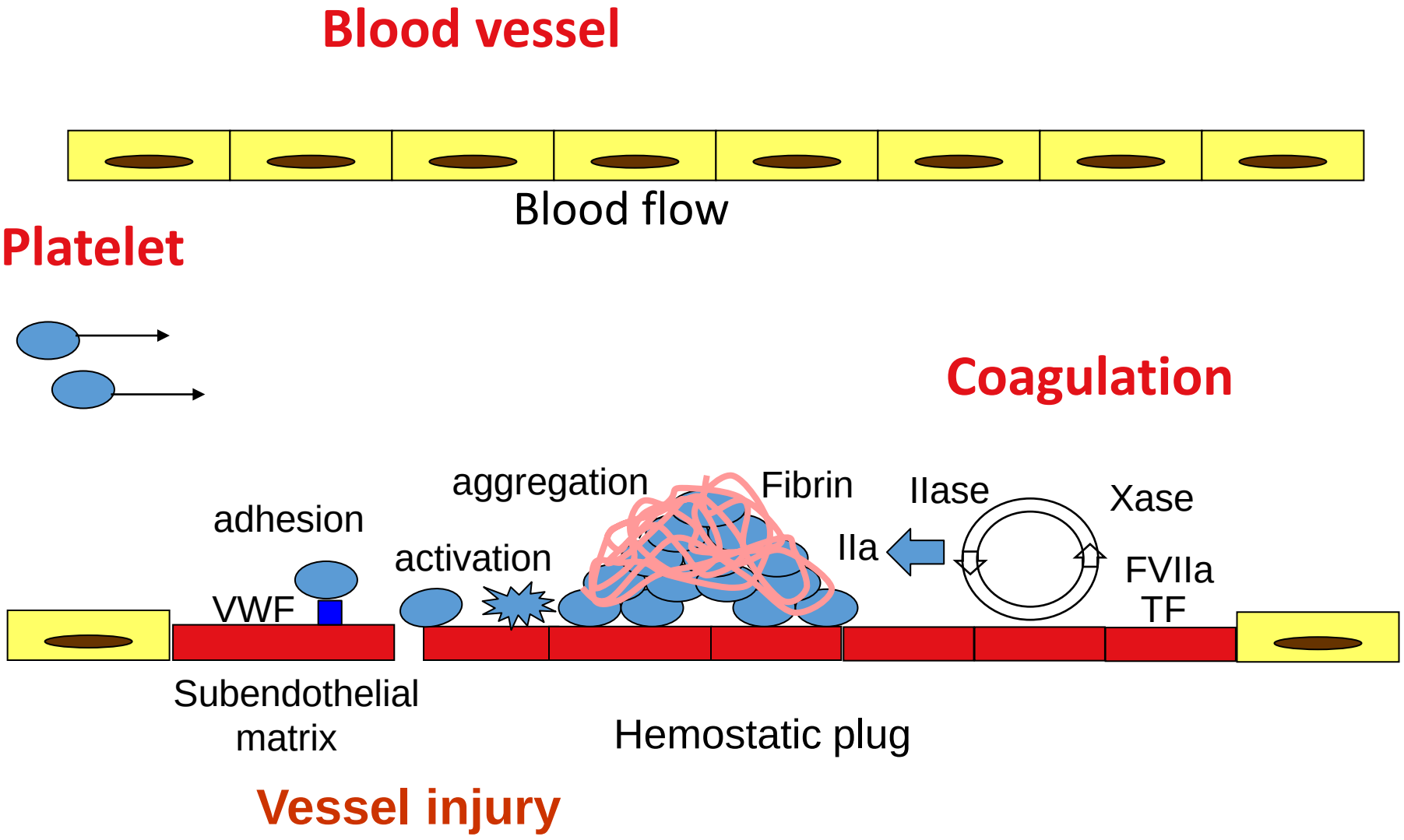
Modified from Lichtman MA, Kipps TJ, Seligsohn U, Kaushansky K, Prchal JT: William Hematology, 8th edition: http://ww.accessmedicine.com



Fibrin clot formation

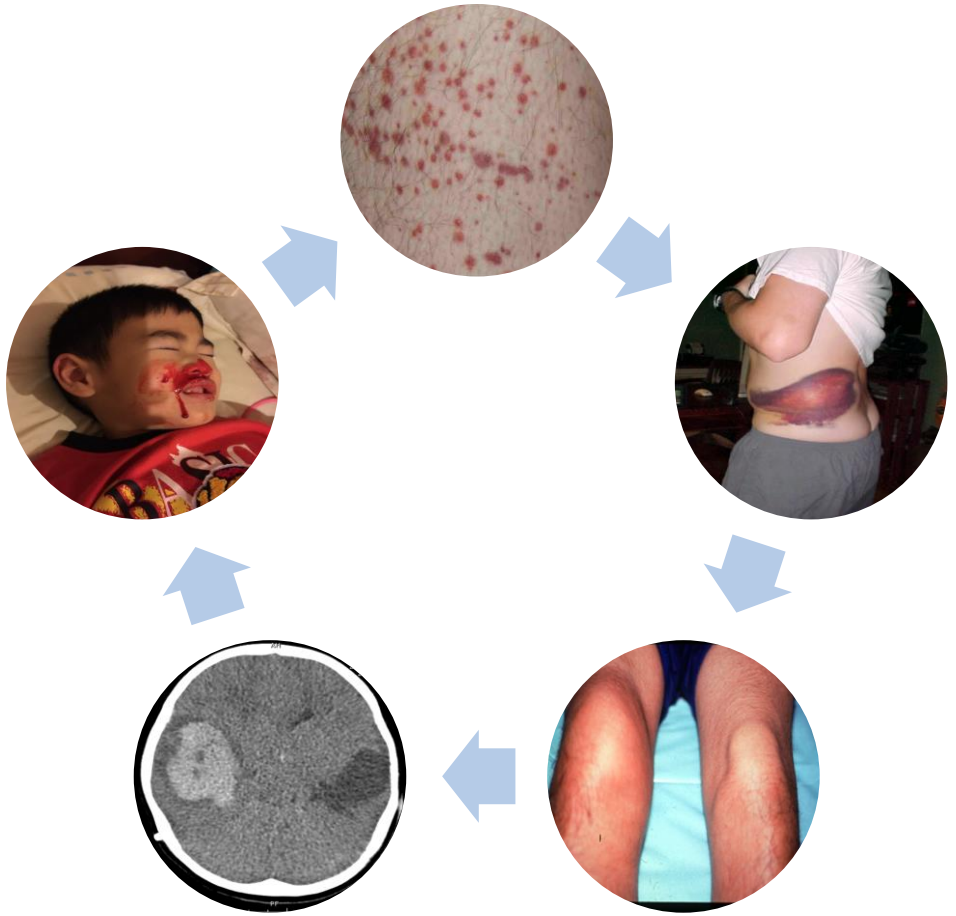
Modified from Image from Thrombotic abnormalities in diabetes


Start from plasminogen
Tissue plasminogen Activator(tPA)
Plasminogen
Factor XIa, XIIa
Kallikrein
Plasminogen activator Inhibitor 1&2
Plasmin
α2-antiplasmin
α2-macroglobulin
Urokinase
Final fibrin & fibrin degradation products
Fibrin
Fibrin degradation products
Thrombin
Thrombin-activatable Fibrinolysis inhibitor



The mechanism of hemostasis

Clinical presentations of bleeding disorders



Evaluation of patients with bleeding

- The evaluation of a child presenting with bleeding should include a comprehensive medical and bleeding history, a complete family history
- In children with severe bleeding disorders, the bleeding history is usually clear. However, children presenting with mild/moderate bleeding symptoms may be difficult
- The use of standardized scores to quantitate bleeding symptoms is recommended
- The mean bleeding score in healthy children was 0.5, and a bleeding score of ≥ 2 was defined as abnormal

Pediatric Bleeding Questionnaire (PBQ) Scoring Key

Date: Patient name: Patient number:

Symptom \ Score	-1	0	1	2	3	4
Epistaxis	-	No or trivial (≤5 per year)	>5 per year OR >10 minutes duration	Consultation only	Packing, cauterization or antifibrinolytics	Blood transfusion, replacement therapy or desmopressin
Cutaneous	-	No or trivial (≤1cm)	>1cm AND no trauma	Consultation only	-	-
Minor wounds	-	No or trivial (≤5 per year)	>5 per year OR >5 minutes duration	Consultation only or Steri-strips	Surgical hemostasis or antifibrinolytics	Blood transfusion, replacement therapy or desmopressin
Oral cavity	-	No	Reported at least once	Consultation only	Surgical hemostasis or antifibrinolytics	Blood transfusion, replacement therapy or desmopressin
Gastrointestinal tract	-	No	Identified cause	Consultation or spontaneous	Surgical hemostasis, antifibrinolytics, blood transfusion, replacement therapy or desmopressin	-
Tooth extraction	No bleeding in at least 2 extractions	None done or no bleeding in 1 extraction	Reported, no consultation	Consultation only	Resuturing, repacking or antifibrinolytics	Blood transfusion, replacement therapy or desmopressin
Surgery	No bleeding in at least 2 surgeries	None done or no bleeding in 1	Reported, no consultation	Consultation only	Surgical hemostasis or antifibrinolytics	Blood transfusion, replacement therapy or desmopressin
Menorrhagia	-	No	Reported or consultation only	Antifibrinolytics or contraceptive pill use	D&C or iron therapy	Blood transfusion, replacement therapy, desmopressin or hysterectomy
Post-partum	No bleeding in at least 2 deliveries	No deliveries or no bleeding in 1 delivery	Reported or consultation only	D&C, iron therapy or antifibrinolytics	Blood transfusion, replacement therapy or desmopressin	-
Muscle hematoma	-	Never	Post-trauma, no therapy	Spontaneous, no therapy	Spontaneous or traumatic, requiring replacement therapy or desmopressin	Spontaneous or traumatic, requiring surgical intervention or blood transfusion
Hemarthrosis	-	Never	Post-trauma, no therapy	Spontaneous, no therapy	Spontaneous or traumatic, requiring replacement therapy or desmopressin	Spontaneous or traumatic, requiring surgical intervention or blood transfusion
Central nervous system	-	Never	-	-	Subdural, any intervention	Intracerebral, any intervention
Other Post-circumcision Umbilical stump Cephalohematoma Macroscopic hematuria Post-venepuncture Conjunctival hemorrage	-	No	Reported	Consultation only	Surgical hemostasis, antifibrinolytics or iron therapy	Blood transfusion, replacement therapy or desmopressin

Total Bleeding Score _____

Symptom	−1	0	1	2	3	4
Epistaxis	—	no or trivial (≤5 per year)	>5 per year or >10 min duration	consultation only	packing, cauterization or antifibrinolytics	blood transfusion, replacement therapy or desmopressin
Cutaneous	—	no or trivial (≤1 cm)	>1 cm and no trauma	consultation only	—	—
Minor wounds	—	no or trivial (≤5 per year)	>5 per year or >5 min duration	consultation only or steri-strips	surgical hemostasis or antifibrinolytics	blood transfusion, replacement therapy or desmopressin
Oral cavity	—	no	reported at least one	consultation only	surgical hemostasis or antifibrinolytics	blood transfusion, replacement therapy or desmopressin
Gastrointestinal tract	—	no	identified cause	consultation or	surgical hemostasis,	—
Tooth extracti						eplacement essin
Surgery						eplacement essin
Menorrhagia						eplacement sin or
Postpartum						
Muscle hemat						matic, tervention or
Hemarthrosis			no therapy	therapy	traumatic, requiring desmopressin or replacement therapy	matic, requiring surgical intervention or blood transfusion
Central nervous system	—	never	—	—	subdural, any intervention	intracerebral, any intervention
Other: postcircumcision umbilical stump cephalohematoma macroscopic hematuria postvenipuncture conjunctival hemorrhage	—	no	reported	consultation only	surgical hemostasis, antifibrinolytics or iron therapy	blood transfusion, replacement therapy or desmopressin

Pediatric bleeding questionnaire scoring key

provides a summative score for 13 bleeding symptoms: epistaxis, cutaneous bleeding, bleeding from minor wounds, oral cavity bleeding, gastrointestinal bleeding, bleeding post-tooth extraction, postsurgical bleeding, menorrhagia, postpartum hemorrhage, musclehematoma, hemarthrosis, central nervous system bleeding and ‘other’, pediatric-specific bleeding symptoms (postcircumcision bleeding, umbilical stump bleeding, ephalohematoma, macroscopic hematuria, postvenipuncture bleeding, conjunctival hemorrhage)

Scoring Keys in Thai Language

แนวทางในการให้คะแนนแบบสอบถามอาการเลือดออกในเด็ก (PBQ) [ร่วมกับการให้คะแนนที่แตกต่างไปใน ISTH-BAT ในส่วนที่แรเงา]

คะแนน / อาการ	-1	0	1	2	3	4
เลือดกำเดาไหล	-	ไม่มี หรือ เล็กน้อย (≤5 ครั้งต่อปี)	> 5 ครั้งต่อปี หรือระยะเวลาที่เลือดออก >10 นาที	ขอคำปรึกษาทางการแพทย์เท่านั้น	รักษาด้วยการอัดผ้าก๊อซเข้าโพรงจมูก, การจี้ไฟฟ้า หรือยาต้านการสลายลิ่มเลือด	รักษาด้วยการให้เลือด การให้ส่วนประกอบของเลือดทดแทน หรือยา ประเภทกระตุ้น
เลือดออกที่ผิวหนัง	-	ไม่มี หรือ เล็กน้อย (≤1 ซม.)	> 1 ซม. และ ไม่ได้รับอุบัติเหตุ สำหรับรอยช้ำ≥5 ตำแหน่ง (> 1 ซม.) บริเวณนอกร่มผ้า	ขอคำปรึกษาทางการแพทย์เท่านั้น	- เลือดออกที่ผิวหนังเป็นบริเวณกว้าง	- ก้อนเลือดที่เกิดขึ้นเอง และต้องการการรักษาด้วยการให้เลือด
เลือดออกจากแผลที่ไม่รุนแรง	-	ไม่มี หรือ เล็กน้อย (≤5 ครั้งต่อปี)	> 5 ครั้งต่อปี หรือ ระยะเวลาที่เลือดออก >5 นาที >5 ครั้งต่อปี หรือ >10 นาที	ขอคำปรึกษาทางการแพทย์เท่านั้น หรือ รักษาด้วยการแปะแผ่นปิดแผลที่ผ่านการฆ่าเชื้อ ขอคำปรึกษาทางการแพทย์เท่านั้น	รักษาด้วยการเย็บแผล หรือยาต้านการสลายลิ่มเลือด	รักษาด้วยการให้เลือด การให้ส่วนประกอบของเลือดทดแทน หรือยา ประเภทกระตุ้น
เลือดออกในช่องปาก	-	ไม่มี	เคยมีเลือดออกอย่างน้อยหนึ่งครั้ง มีอาการ	ขอคำปรึกษาทางการแพทย์เท่านั้น	รักษาด้วยการเย็บแผล เพื่อห้ามเลือดหรือยาต้านการสลายลิ่มเลือด	รักษาด้วยการให้เลือด การให้ส่วนประกอบของเลือดทดแทน หรือยา ประเภทกระตุ้น
เลือดออกในทางเดินอาหาร	-	ไม่มี	ตรวจพบสาเหตุ มีอาการ (ไม่เกี่ยวกับแผลในทางเดินอาหาร, ความดันในเลือดสำพอร์ทอลสูง, ริดสีดวงทวาร, หลอดเลือดมิลปกติในทางเดินอาหาร)	ขอคำปรึกษาทางการแพทย์หรือเลือดออกเอง ขอคำปรึกษาทางการแพทย์เท่านั้น	รักษาด้วยการฉ่ำสัด, ยาต้านการสลายลิ่มเลือด, การให้เลือด การให้ส่วนประกอบของเลือดทดแทน หรือยา ประเภทกระตุ้น รักษาด้วยการเย็บแผล แผลเพื่อห้ามเลือดหรือยาต้านการสลายลิ่มเลือด	- รักษาด้วยการให้เลือด การให้ส่วนประกอบของเลือดทดแทน หรือยา ประเภทกระตุ้น

Clinical distinction of platelet disorders from coagulation disorders

	Platelet defects	Coagulation defects
Petechiae	common	uncommon
Ecchymoses	small	large
Excessive bleeding after minor trauma or with menstruation	common	uncommon
Bleeding during or after surgery	usually immediate	may be immediate or delayed
Spontaneous hemarthroses and soft tissue hematomas	rare	common in severe disorders

Conclusions

- The pediatric BQ may help discriminate a significant bleeding history from otherwise trivial bleeding and may be integrated into the primary care algorithm for evaluating children suspected of having VWD
- The score cut-off of ≥3 included 100% of patients with VWD and approximately 80% of patients with platelet disorders
- Characteristic of bleeding symptoms is helpful for consideration of laboratory for diagnosis of bleeding disorders

Laboratory for hemostasis

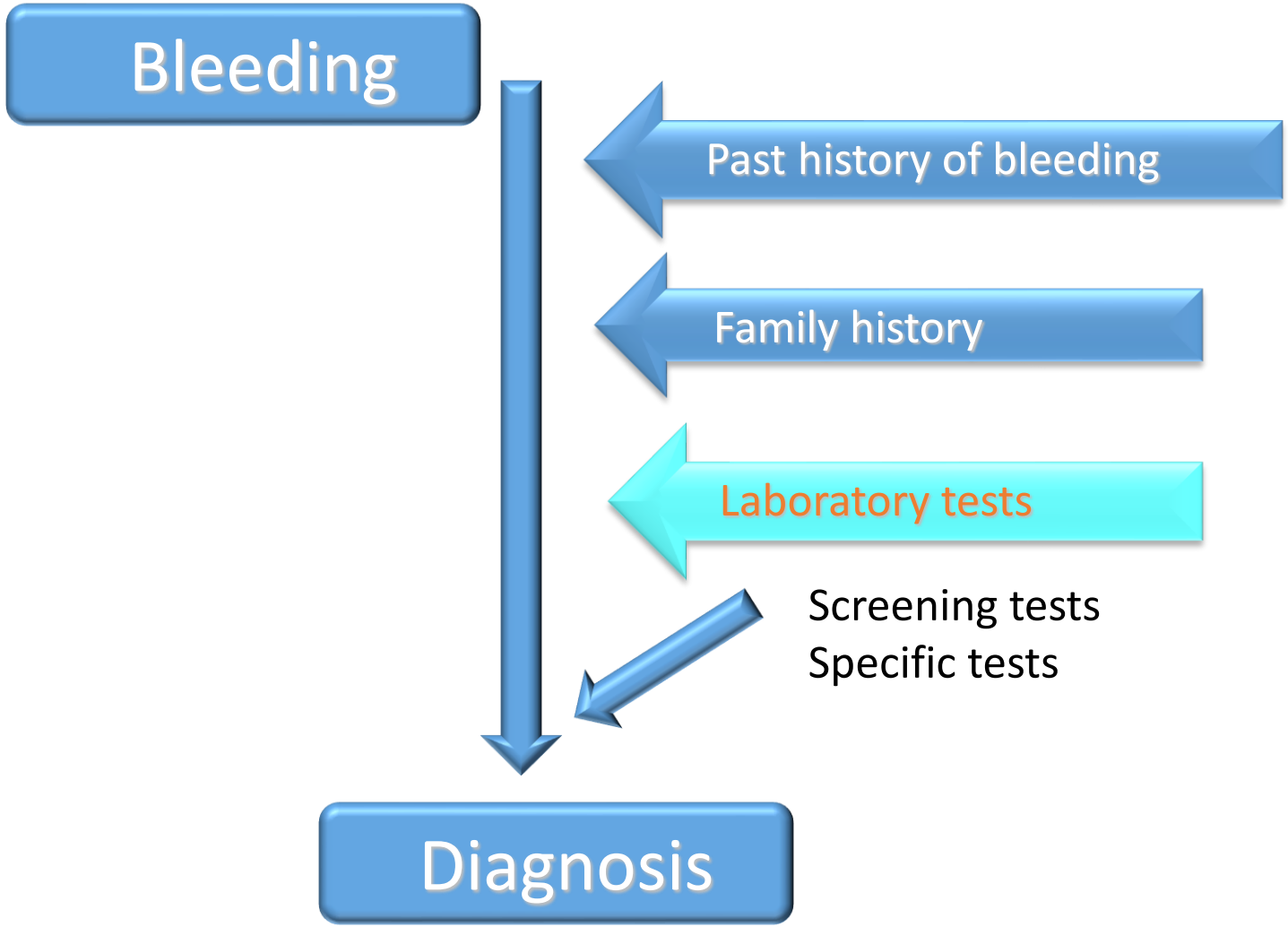
Assessment of bleeding symptoms

- Careful and full clinical bleeding history and examination;

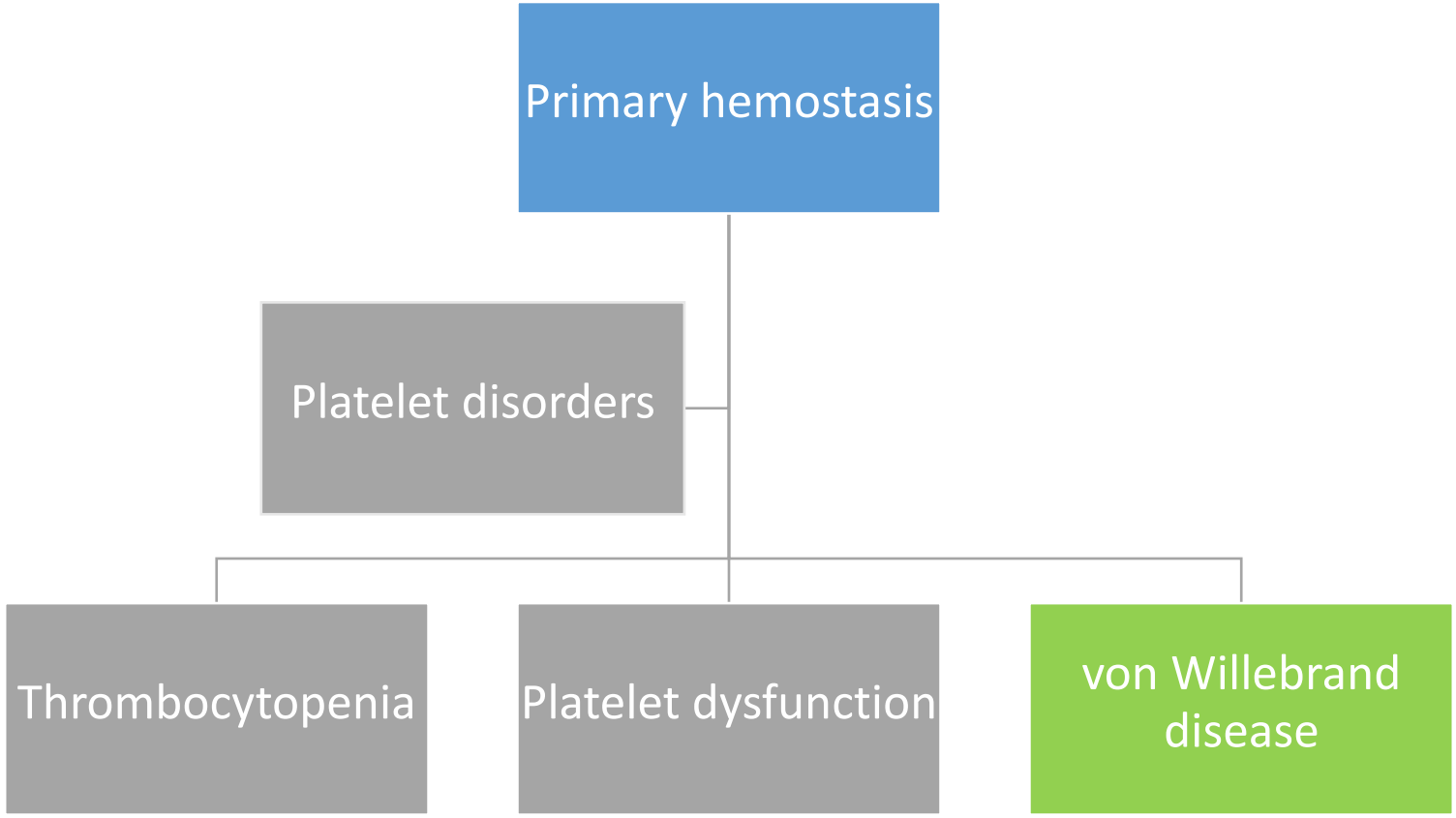
Bleeding history: site of bleeding, duration, surgery, family history, systemic illness and drugs

- Appropriate laboratory investigations

Assessment of bleeding symptoms



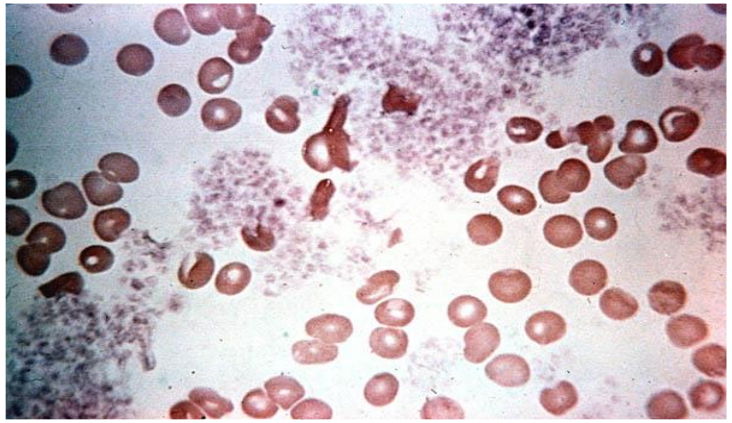
Primary Hemostasis



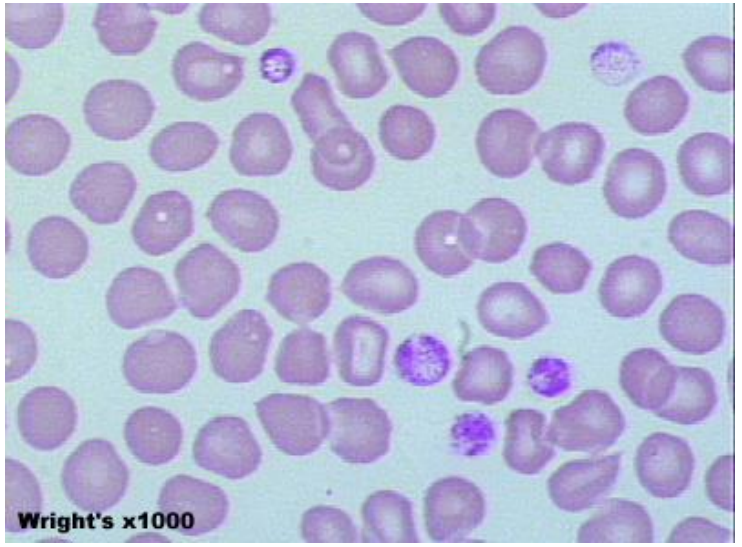
Complete Blood Count

- **Platelet count, size and morphology**
- **Leukocyte morphology**
- **Other cytopenias**

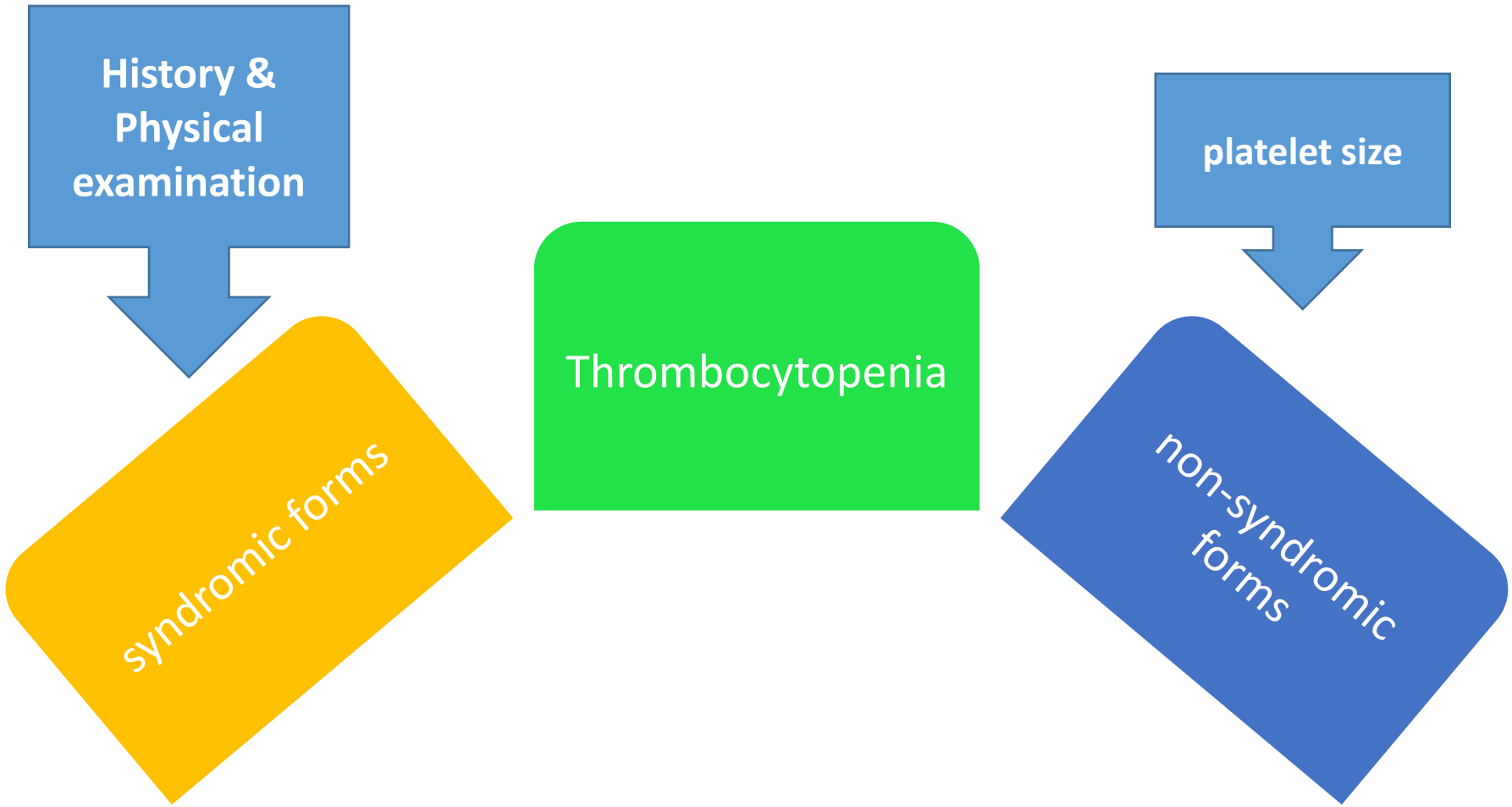
Thrombocytopenia

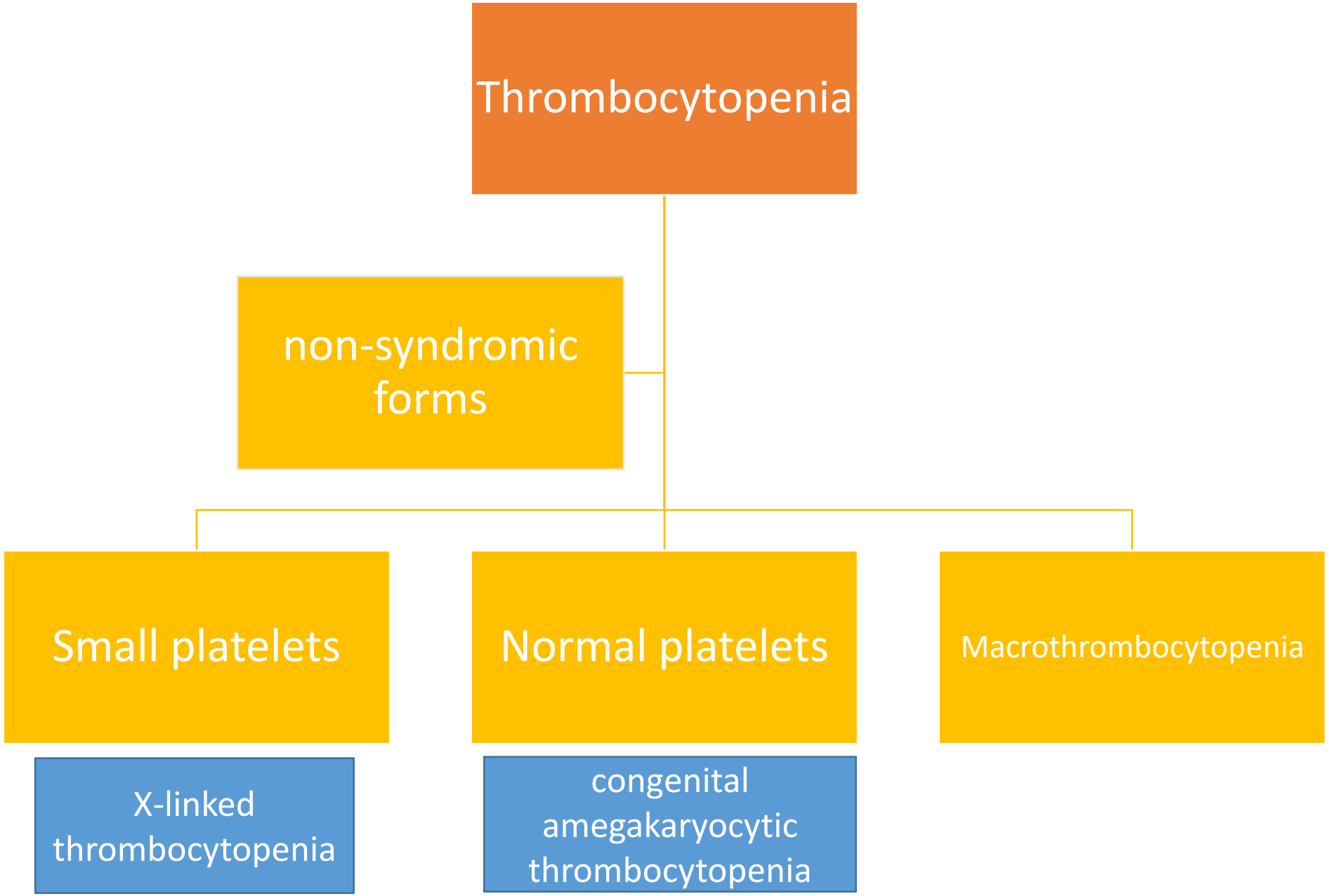


Pseudothrombocytopenia



Giant platelet


History & Physical examination
platelet size
Thrombocytopenia
syndromic forms
non-syndromic forms


Thrombocytopenia
non-syndromic forms
Small platelets
Normal platelets
Macrothrombocytopenia
X-linked thrombocytopenia
congenital amegakaryocytic thrombocytopenia

Bleeding time

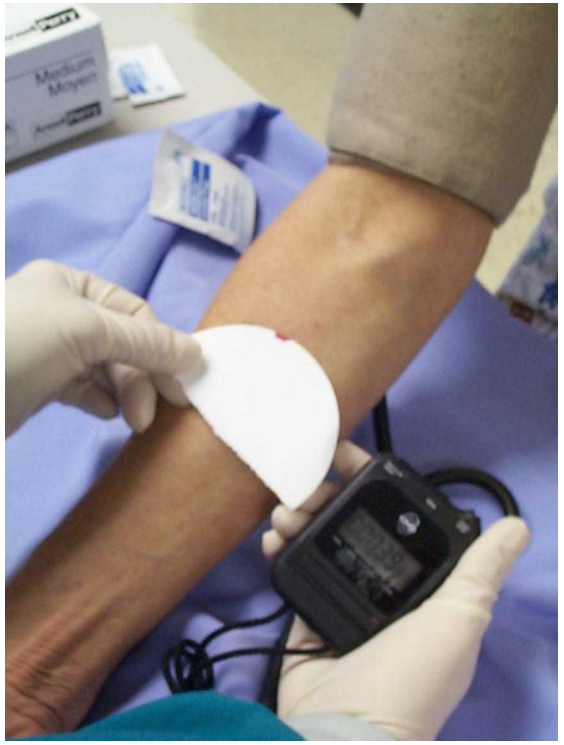


Image from Bleeding Time Test Procedure. Contra Costa Medical Career College Online

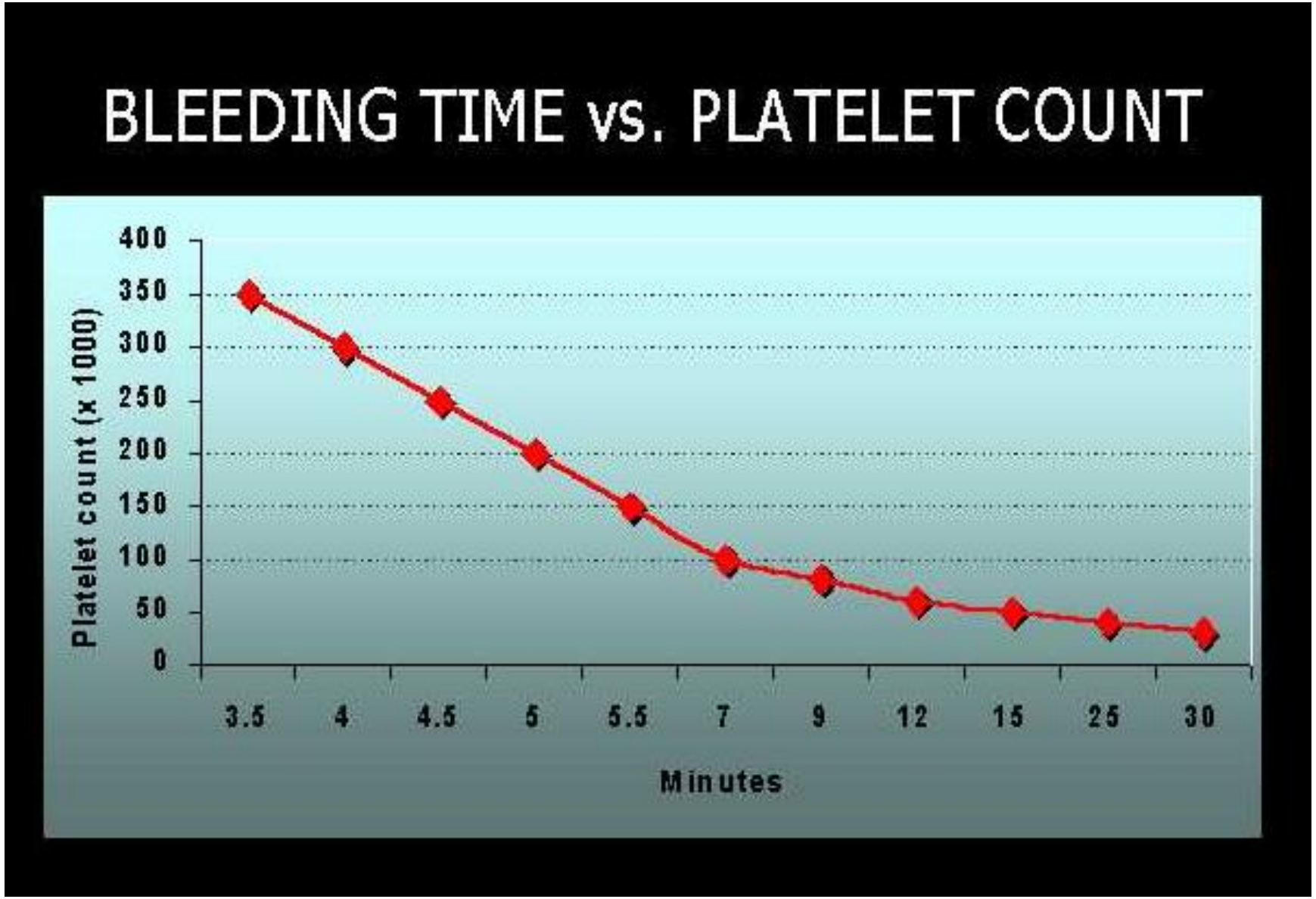
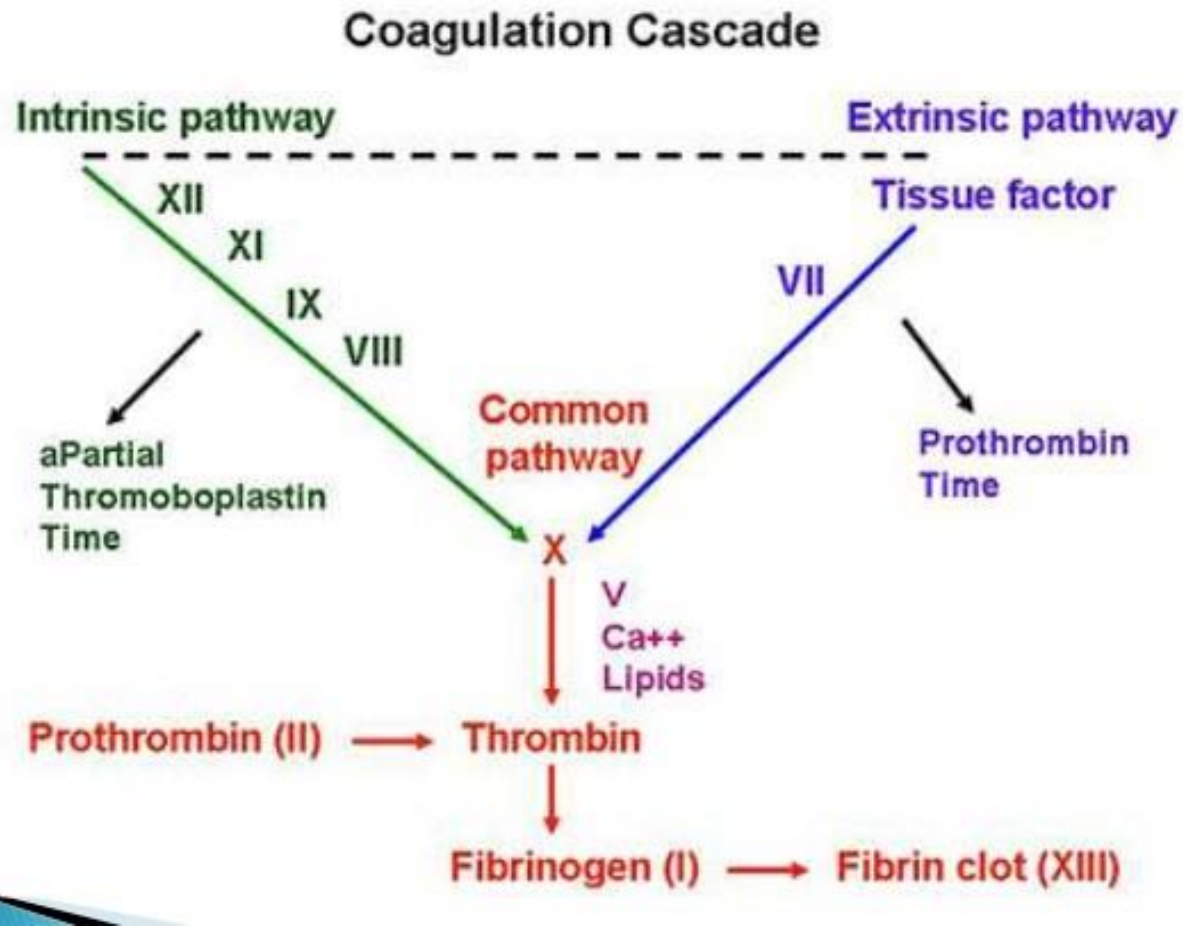
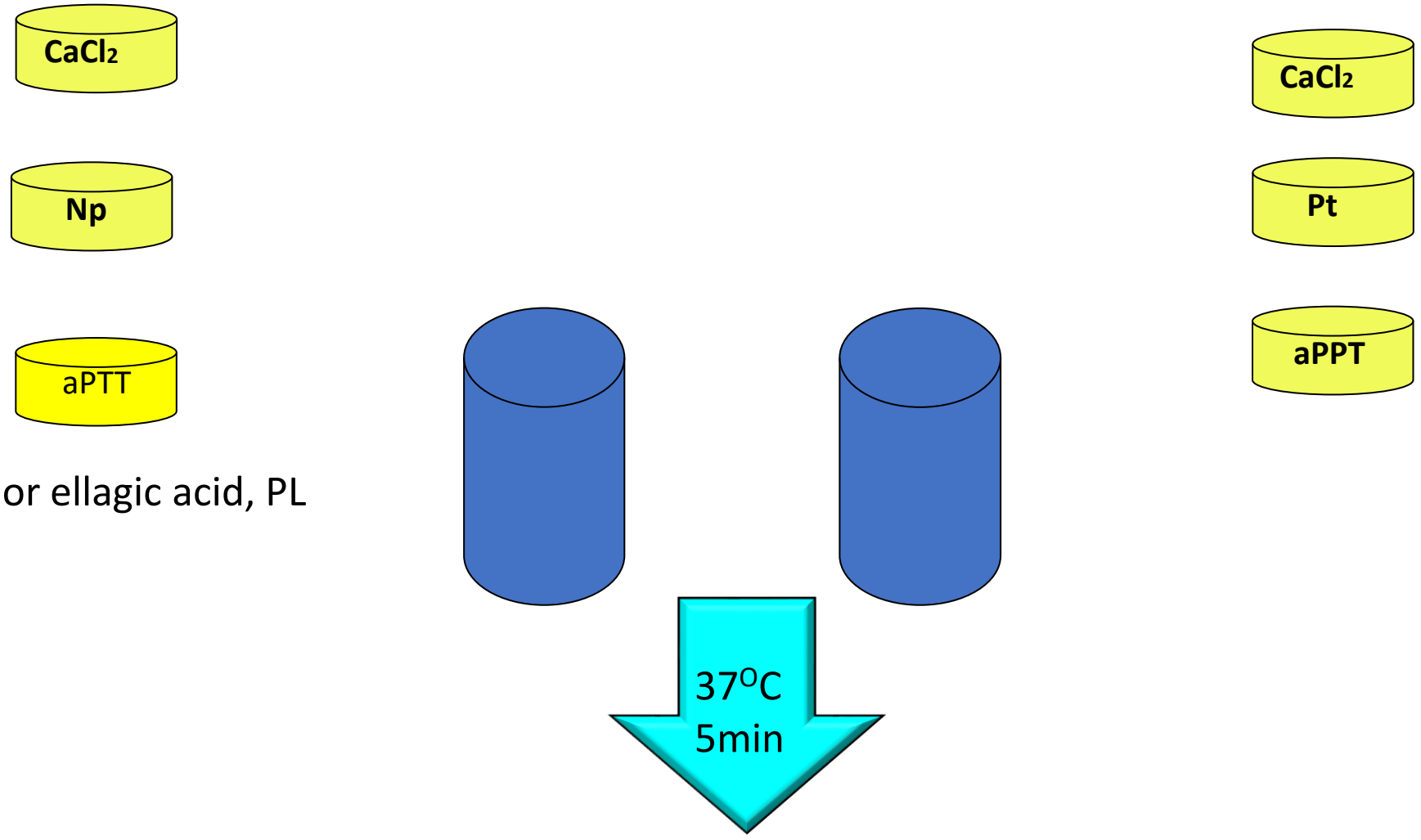


Image from Bleeding Disordersby Dr. Farjah H.AlGahtani powerpoint

Secondary Hemostasis

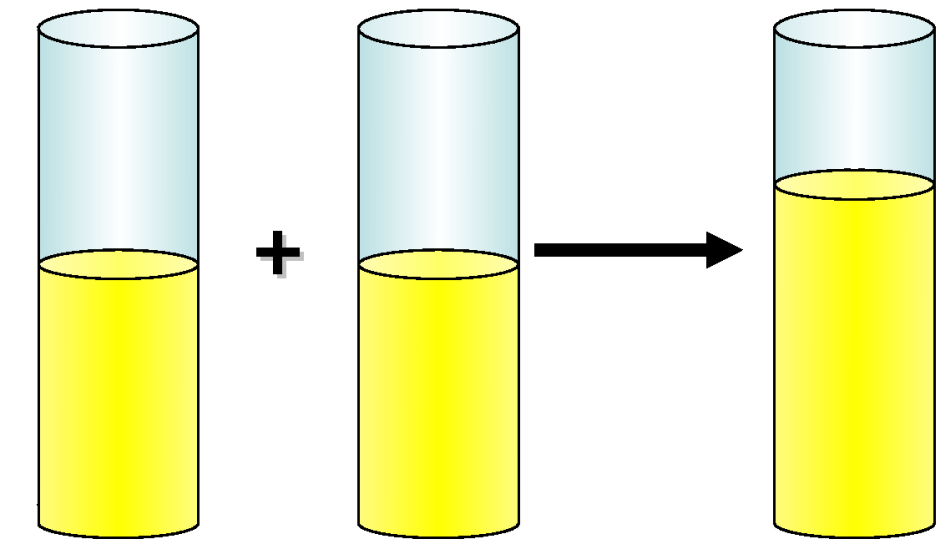

Coagulation Cascade
Intrinsic pathway
Extrinsic pathway
XII
XI
IX
VIII
Tissue factor
VII
aPartial
Thromoboplastin
Time
Common
pathway
Prothrombin
Time
X
V
Ca++
Lipids
Prothrombin (II)
Thrombin
Fibrinogen (I)
Fibrin clot (XIII)

activated partial thromboplastin time (aPTT)



PT	aPTT	TT	Results
prolonged	normal	normal	FVII deficiency
normal	Prolonged	normal	FVIII, IX, XI, XII, von Willebrand disease
prolonged	prolonged	normal	FII, VII, IX, X
prolonged	prolonged	prolonged	Fibrinogen

Basic Mixing Study Concept



Sample + npp → Mixture

Results

1. Correct
2. Fail to Correct

npp = normal pooled plasma

	1:1 Mixing Study Results	
	Not incubated	*Incubated*
Factor deficiency	Correction	Correction
Immediate acting inhibitor	No correction	No correction
Time/temperature dependent inhibitor	Correction (**Falsely**)	No correction

Table adapted from McKenzie, S.,, *Clinical l Laboratory Hematology,* 2004, p. 790.

Primary Haemostatic Defects

<u>Vascular defects</u>

- Vitamin C deficiency
- Vasculitis
- Henoch Scholein purpura
- Hemorrhagic telangiectasia

- **Platelet function disorders**
  I. **Acquired**
  II. **Hereditary**

- **Thrombocytopenia**
  I. **Decreased production**
  II. **Platelet consumption**
  III. **Platelet destruction**

Secondary Haemostatic Defects

Congenital

- Haemophilia
- Congenital FVII, XI, XIII deficiency

Acquired

- Disseminated intravascular coagulopathy
- Vitamin K deficiency

Summary

- ระบบการห้ามเลือดเกิดขึ้นไปพร้อมๆกันทั้งระบบห้ามเลือดแบบปฐมภูมิและทุติยภูมิ
- อาการเลือดออกง่ายช่วยในการวินิจฉัยแยกโรคระหว่างระบบห้ามเลือดแบบปฐมภูมิและทุติยภูมิ
- การส่งตรวจทางห้องปฏิบัติการควรส่งตรวจตามการวินิจฉัยแยกโรคระหว่างระบบห้ามเลือดแบบปฐมภูมิและทุตยภูมิ

HAEMOPHILIA

Background

- An X-linked congenial bleeding disorder
- A deficiency of coagulation factor VIII or FIX related to mutations of the clotting factor gene
- HA is more common than HB, representing 80-85% of the total

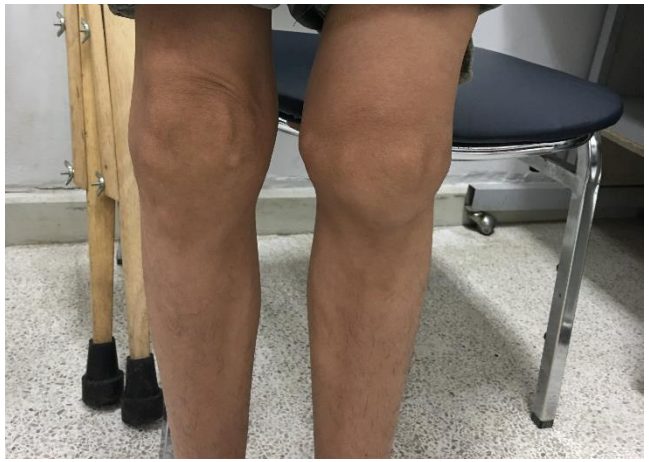
Background

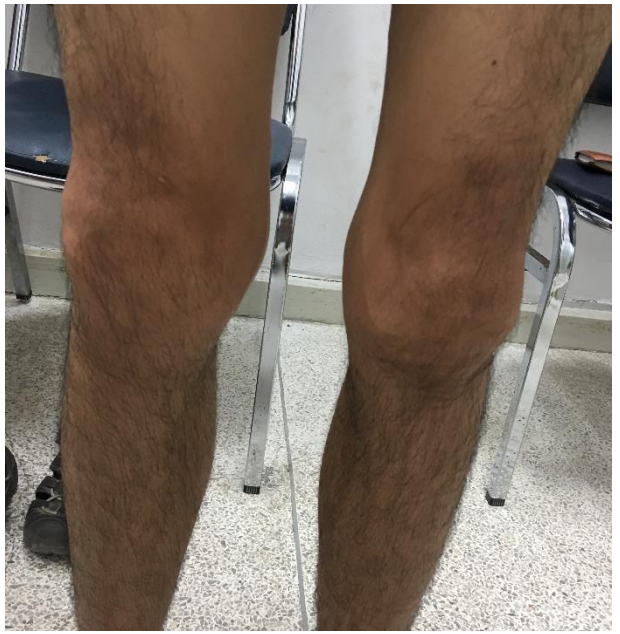
- The family history of bleeding is commonly obtained. Spontaneous mutation is occurred in 1/3 of all patients

- The severity of bleeding manifestations is generally correlated with the clotting factor level

Bleeding Manifestations

- Hemarthrosis: 70-80%
- Muscle/soft tissue: 10-20%
- Other major bleeds: 5-10%
- Central nervous system (CNS) bleeds:<5%





Diagnosis of Hemophilia

- Screening test will show a prolonged aPTT in severe cases and moderate cases
- Factor assay: FVIII and FIX
- DNA for FVIII gene

Severity of Hemophilia

Severity	Clotting factor level % activity (IU/ml)	Bleeding episodes
Severe	1% (< 0.01)	Spontaneous bleeding, predominantly in joints and muscles
Moderate	1%-5% (0.01-0.05)	Occasional spontaneous bleeding. Severe bleeding with trauma, surgery
Mild	5%-40% (0.05-0.40)	Severe bleeding with major trauma or surgery

Management

Management

Comprehensive care: keys to improvement of health and quality of life include

- Prevention of bleeding
- Long-term management of joint and muscle damage and other sequelae of bleeding
- Management of complications from treatment

Management

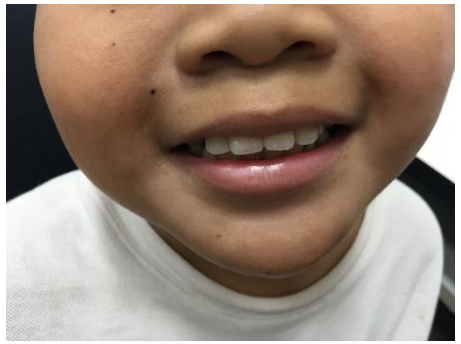
Principles of care

- Prevention of bleeding should be the goal
- Acute bleed should be treated early (within 2 hrs, if possible) resulting in less tissue damage and the use of less clotting factor concentrates
- An assessment should be performed to identify the site of bleeding

General Management

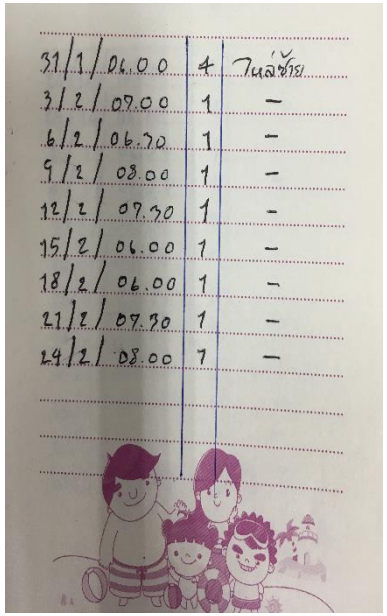
- Clotting factor concentrate replacement or DDAVP therapy should be given to achieve appropriate factor levels prior to any invasive procedure
- Patients should avoid trauma by adjusting their lifestyle
- Patients should be advised to avoid use of drugs that affect platelet function except certain COX-2 inhibitors.
- Intramuscular injections, difficult phlebotomy, and arterial punctures must be avoided
- Regular exercise should be encouraged to promote strong muscle, protect joints and improve fitness
- Contact sports should be avoided, but swimming and cycling with adequate gear should be encouraged

Comprehensive Care



Comprehensive Care

Comprehensive Care



หลักการเพิ่มระดับปัจจัยการแข็งตัวของเลือด

ชนิดของอาการเลือดออก	ระดับปัจจัยการแข็งตัวของเลือด (%)	
	จุดเริ่มต้น	ระดับต่ำสุดที่ยอมรับได้
1. เลือดออกที่กล้ามเนื้อ การเย็บแผล หัตถการทางทันตกรรม*	20-30	–
2. เลือดออกในกล้ามเนื้อขนาดใหญ่ (ยกเว้น ileopsoas) เลือดออกในข้อ ปัสสาวะเป็นเลือด แผลฉีกลึก	40-60	20-30 (นาน 3-7 วัน)
3. ผ่าตัดขนาดเล็กถึงปานกลาง เช่น ผ่าตัดไส้ติ่งอักเสบ, เลือดออกในสมอง, ทางเดินอาหาร, ลำคอ, อวัยวะสำคัญ และ ileopsoas	80-100	40-50 (นาน 1 สัปดาห์)
4. ผ่าตัดขนาดใหญ่ เช่น ผ่าตัดข้อ	80-100	40-50 (นาน 1-2 สัปดาห์หรือจนแผลหาย)

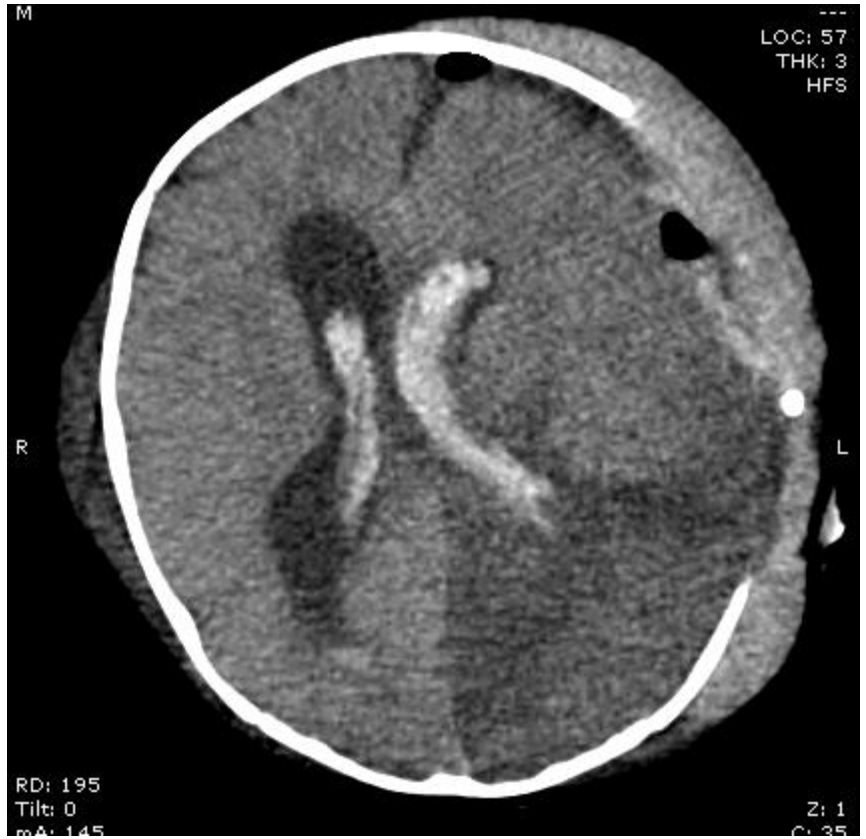
*การเย็บแผล ตัดไหม ถอนฟัน ให้แฟคเตอร์เข้มข้นหรือส่วนประกอบของเลือดเพียงครั้งเดียวในเช้าวันที่ทำหัตถการ ยกเว้นทันตแพทย์ใช้

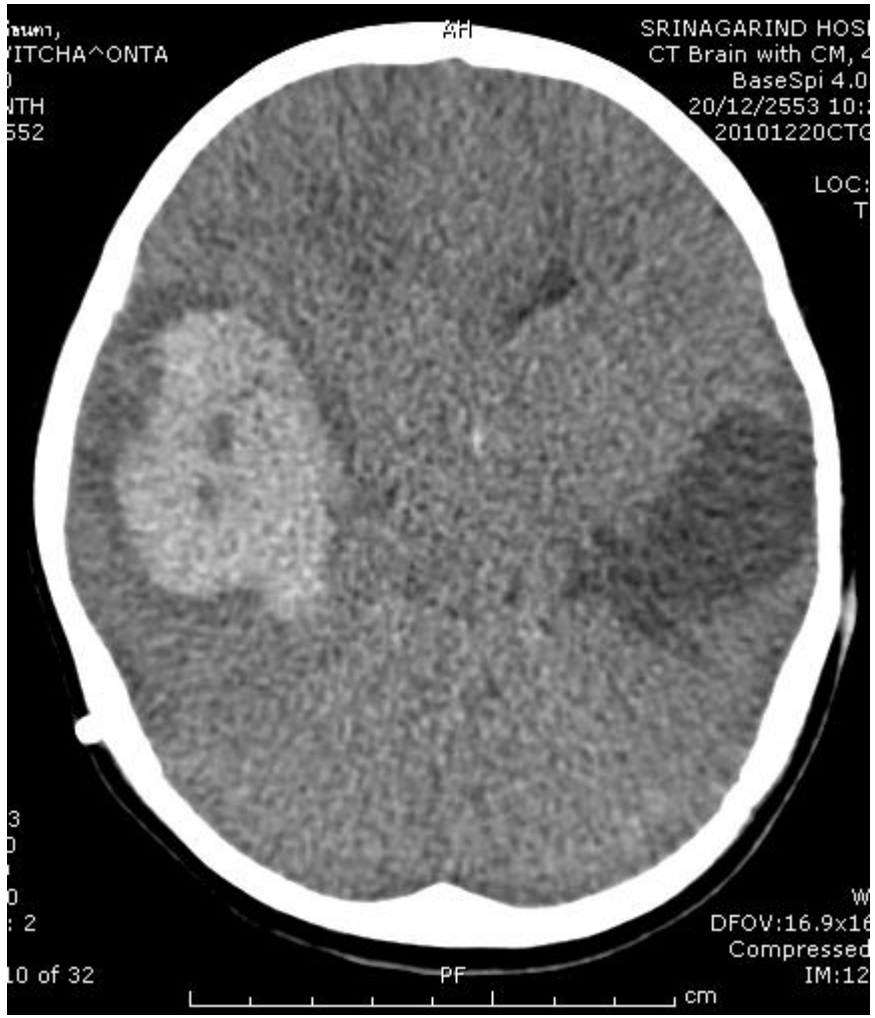
Blood Component

- FFP, FDP 10 ml/kg ↑ FVIII:C 10-15%
  ↑ FIX:C 5-7%
- Cryoprecipitate 0.1 bag/kg ↑ FVIII:C 10%
- Lyophilized cryoprecipitate (250 units) 1 unit/kg ↑ FVIII:C 2%
- Factor VIII concentrate 1 unit/kg ↑ FVIII:C 2%
- Prothrombin complex concentrate (factor IX complex) 1 unit/kg ↑ FIX:C 1%
- Factor IX concentrate 1 unit/kg ↑ FIX:C 1%

Bypassing Product

- Prothrombin complex concentrate (PCC)
- Activated prothrombin complex concentrate (APCC)
- Dose 50-75 u/kg every 12-24 h (max 200 u/kg)


M
LOC: 57
THK: 3
HFS
R
L
RD: 195
Tilt: 0
Z: 1


AH
SRINAGARIND HOS
CT Brain with CM,
BaseSpi 4.0
20/12/2553 10:
20101220CTC
LOC:
T
DFOV:16.9x16
Compressed
IM:12
10 of 32
PF
cm

กรณีเร่งด่วน

- ถ้ามีอาการเลือดออกรุนแรง เช่น หกล้มศีรษะกระแทก เลือดออกในปาก บริเวณฟันกรามล่าง เลือดออกใต้ลิ้น เลือดออกที่บริเวณศีรษะ คาง คอ ทรวงอก ช่องท้อง

- ให้รีบไปพบแพทย์ที่โรงพยาบาลใกล้บ้านในภูมิลำเนา แพทย์จะต้องรีบให้ส่วนประกอบของเลือดหรือแฟคเตอร์เข้มข้น

Prevention

- Sex-linked recessive pattern of inheritance
- Average 5 females at risk : mother, sister, aunt
- Identify type of carrier
- Laboratory testing
    - clotting factor assay
    - restriction fragment length polymorphism

Obligate Carrier

- Daughter of hemophiliac patients
- Mother with two hemophiliac sons
- Mother with one hemophiliac son and hemophiliac brother/maternal uncle

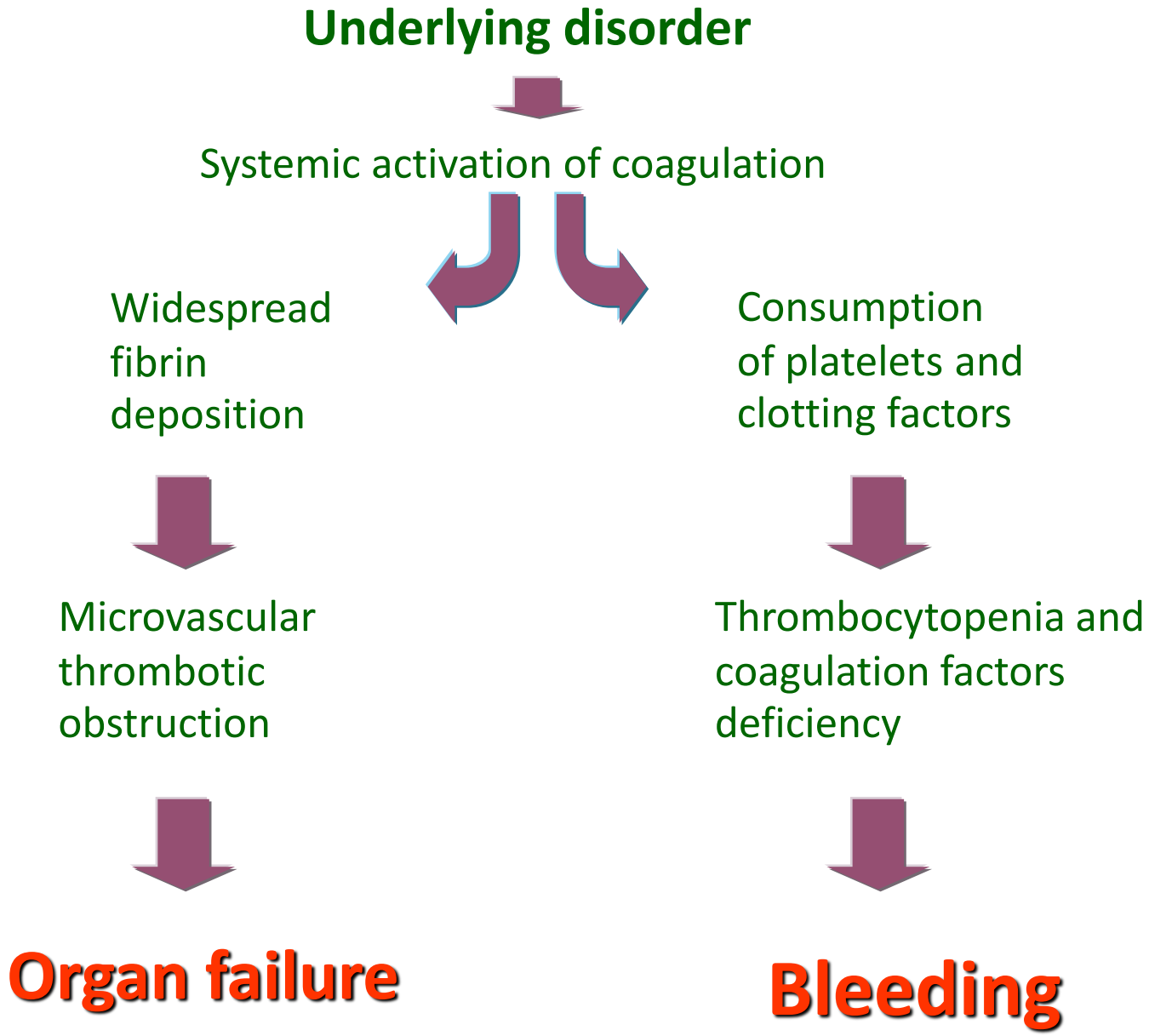
Possible Carrier

- Daughter of an obligate carrier
- Mother with one hemophiliac son
- Female with family history of hemophilia

DISSEMINATED INTRAVASCULAR COAGULOPATHY

Definition

- An acquired syndrome characterized by the intravascular activation of coagulation with loss of localization arising from different causes. It can originate from and cause damage to the microvasculature, which if sufficiently severe, can produce organ dysfunction”.


Underlying disorder
Systemic activation of coagulation
Widespread fibrin deposition
Consumption of platelets and clotting factors
Microvascular thrombotic obstruction
Thrombocytopenia and coagulation factors deficiency
Organ failure
Bleeding

Introduction

- Procoagulant activation
- Fibrinolytic activation
- Inhibitor consumption
- Biochemical evidence of end-organ damage or failure

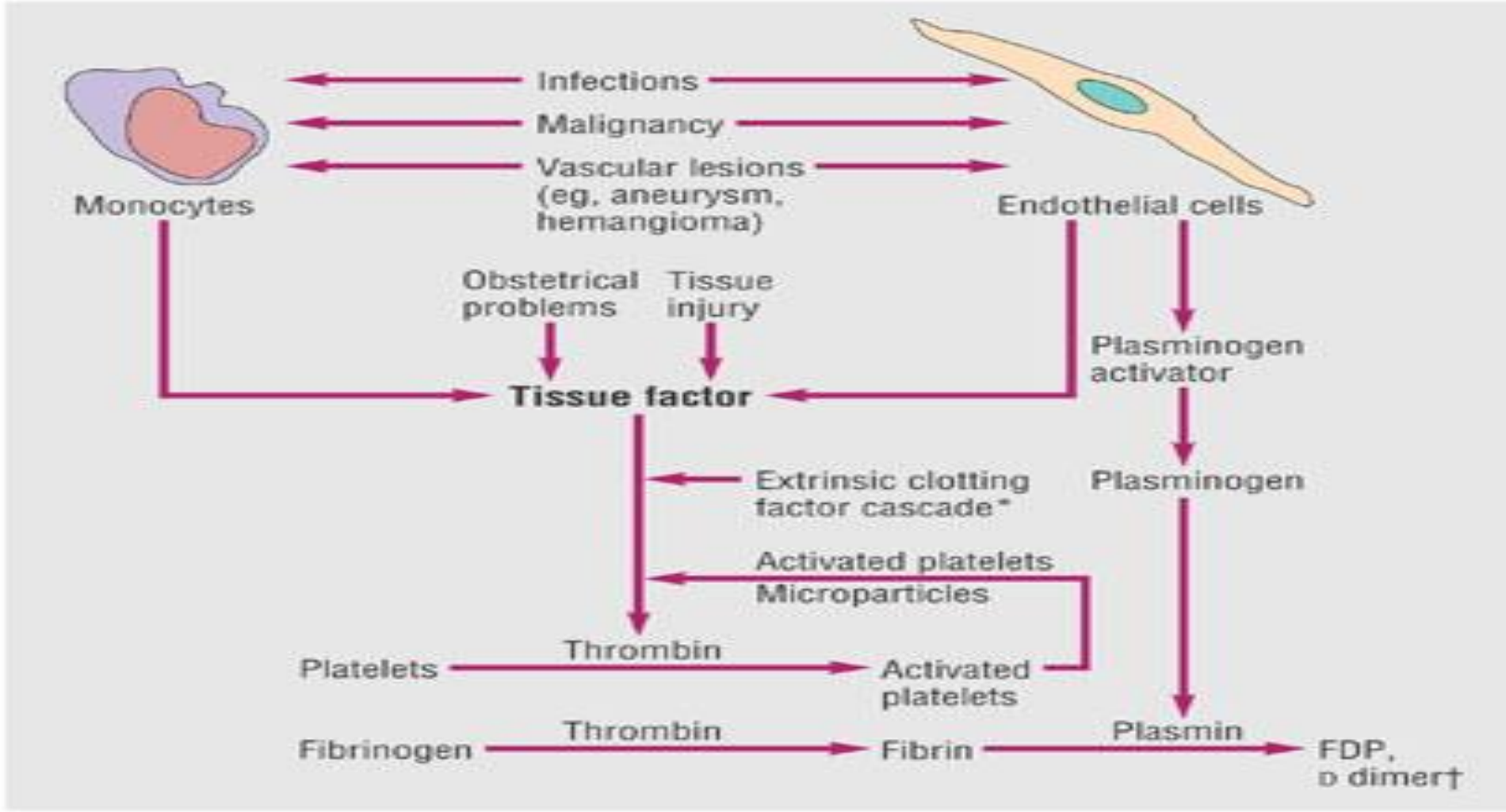


Figure 1. Cascade leading to fibrin generation and platelet activation in disseminated intravascular coagulation (DIC). FDP, fibrin-fibrinogen degradation products.

*Extrinsic factors V, VII, and X and prothrombin

†D dimer is a fragment of cross-linked fibrin and is specific for thrombosis. The FDP test detects fragments D and E, the degradation products of fibrinolysis and fibrinogenolysis. This is a screening test for DIC; it is sensitive but not specific. By comparison, the D-dimer test is positive only when fibrin is somewhere in circulation; it does not determine whether the fibrin is circulating (DIC) or is localized (venous or arterial thrombosis).

Causative factors associated with DIC

- Tissue injury

  - Trauma, head injury, burns, malignancy

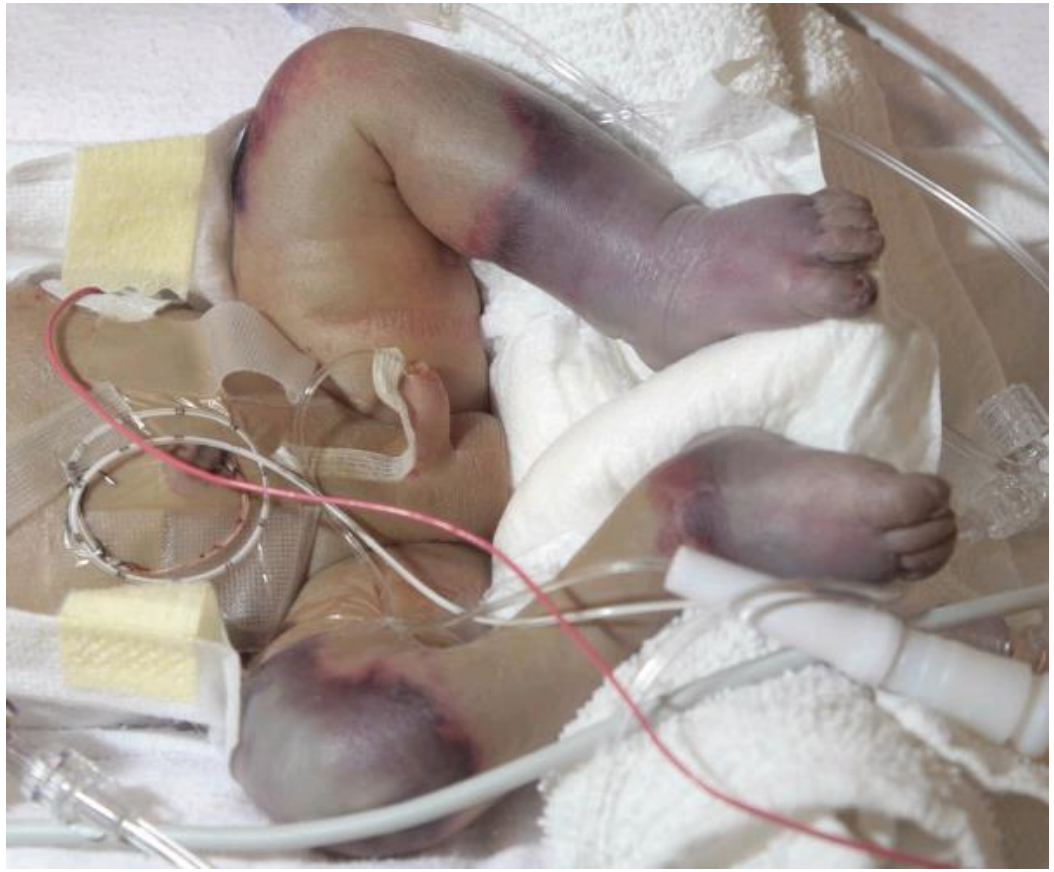
- Endothelial cell injury and/or abnormal vascular surfaces

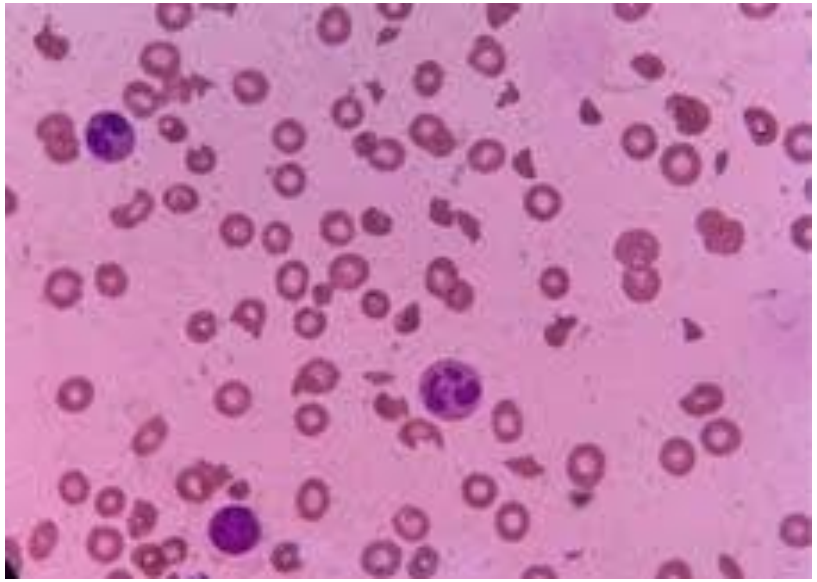
  - Infection, immune complexes, giant hemangioma, eclampsia

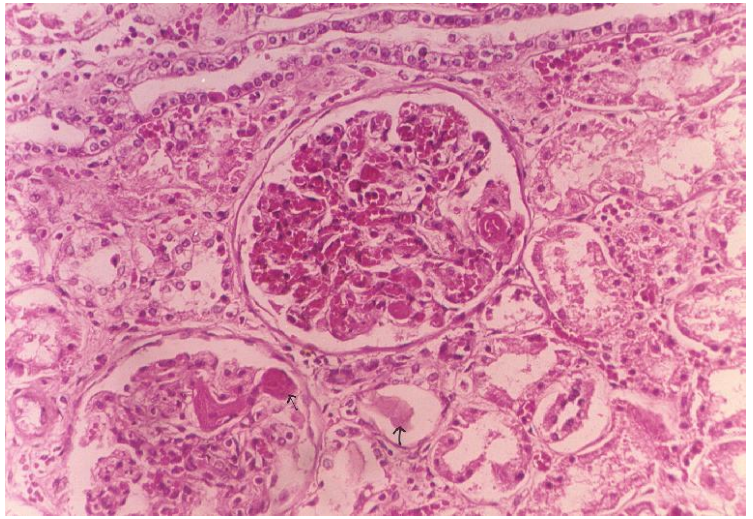
- Platelet, leukocyte, or red cell injury

  - infection, malignancy

Clinical Manifestations







Laboratory

- **No single diagnostic test** exists for DIC. DIC is initially suggested by the following combination:
  - a clinical condition consistent with DIC
  - thrombocytopenia (< 100 X 109/L)
  - prolonged PT and aPTT
  - presence of FDP/D-dimer

Laboratory

- Anemia; schizocytosis
- Decreased coagulation factors
  - Factor V
  - Factor VIII
  - Factor X
  - Factor XIII
  - Protein C, Antithrombin III level
- Thrombin time: prolonged

Laboratory

D-dimer test

- D-dimer is an antigen formed as a result of plasmin lysis of cross-linked fibrin clots
- The presence of this fragment documents the presence of thrombin (cross-linking) and plasmin (fibrinolysis)
- This monoclonal antibody test has the greatest specificity and is a highly reliable test for diagnosis of DIC

Diagnostic algorithm for the diagnosis of overt disseminated intravascular coagulation (DIC).

1. Risk assessment: Does the patient have a underlying disorder known to be associated with overt DIC?
   If yes, proceed. If no, do not use this algorithm;
2. Order global coagulation tests (platelet count, prothrombin time [PT], fibrinogen, soluble fibrin monomers, or fibrin degradation products).

3. Score global coagulation test results:
- platelet count (> 100 = 0, < 100 = 1, < 50 = 2)
- elevated fibrin-related marker (e.g. soluble fibrin monomers/fibrin degradation products)
  (no increase: 0, moderate increase: 2, strong increase: 3)*
- prolonged prothrombin time
  (< 3 sec. = 0, > 3 but < 6 sec. = 1, > 6 sec. = 2)
- fibrinogen level
  (> 1.0 g/L = 0, < 1.0 g/L = 1)

4. Calculate score.

5. If >5: compatible with overt DIC; repeat scoring daily.
   If <5: suggestive (not affirmative) for non-overt DIC; repeat next I -2 days.

*) In the prospective validation studies D-dimer assays were used and a value above the upper limit of normal was considered moderately elevated, whereas a value above 5 times the upper limit of normal was considered as a strong increase.

Treatment

- The cornerstone of DIC management is treatment of the underlying disorders
- The following supportive measures are essential:
- Monitor vital signs, assess and document extent of hemorrhage and thrombosis, correct hypovolemia, and administer basic hemostatic procedures when indicated
- Attend to life-threatening issues such as airway compromise or severe hemorrhage
- Determine the underlying cause of the patient's DIC and initiate therapy. Obtain appropriate imaging studies if necessary
- Draw specimens for appropriate coagulation studies and other diagnostic laboratory tests

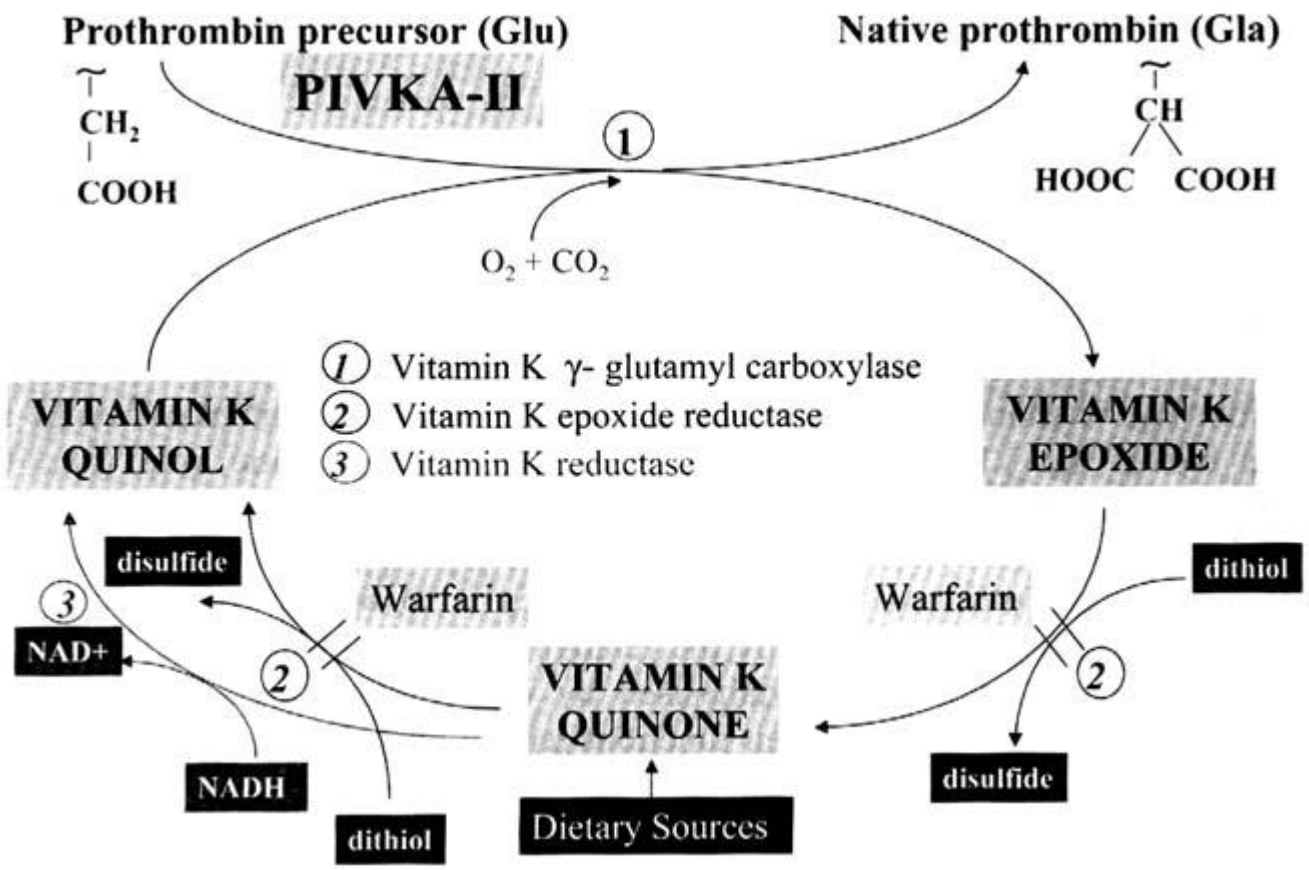
Treatment

- Replace blood products as indicated
  - RBC transfusion
  - Platelet concentrates
  - Fresh frozen plasma (FFP)
  - Cryoprecipitate

- Antithrombin III concentrate

VITAMIN K DEFICIENCY

Vitamin K cycle



Conditions Associated with Deficiency of Vitamin K-Dependent Factor

- Normal newborn
- Dietary
- Altered bacterial colonization
  - Vomiting
  - Severe diarrhea
  - malabsorption syndrome
- Hepatocellular disease
- Drugs; coumarins

Prothrombin complex deficiency

- Normal physiologic deficiency in the newborn
- Secondary prothrombin complex deficiency
- The hemorrhagic disease of the newborn
- Acquired prothrombin complex deficiency syndrome

Acquired prothrombin complex deficiency syndrome

- Occurred in infant age ½-2 months, breastfeeding and did not received vitamin K at birth
- Symptoms; mostly occurred in subdural, subarachnoid hemorrhage, anemia, sometimes hepatomegaly
- Treatment; vitamin K, FFP, subdural tap, anticonvulsant therapy

Laboratory findings in Vitamin K deficiency, liver disease, and DIC

Component	Vitamin K deficiency	liver disease	DIC
Red cell morphology	normal	Target cells	Fragmented cells, burr cells, helmet cells, schistocytes
PTT	Prolonged	Prolonged	Prolonged
PT	Prolonged	Prolonged	Prolonged
Fibrin Split products	normal	Normal or Slightly increased	Markedly increased
Platelets	normal	normal	reduced
Factors decreased	II, VII, IX, X	I,II, V, VII, IX, X, XI	Assays are of limited utility

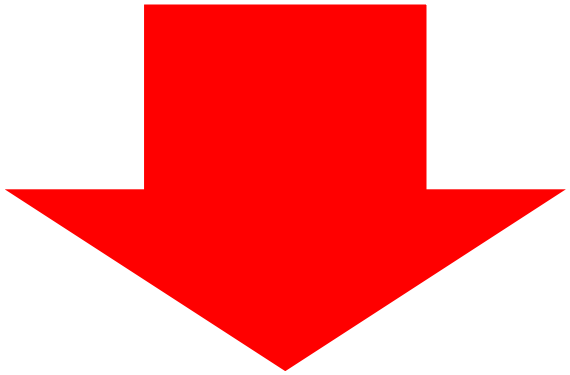
PLATELET DEFECTS

Pathophysiological Classification of Thrombocytopenic State

- Increased platelet destruction
- Disorders of platelet distribution or pooling
- Decreased platelet production- deficient thrombopoiesis
- Pseudothrombocytopenia

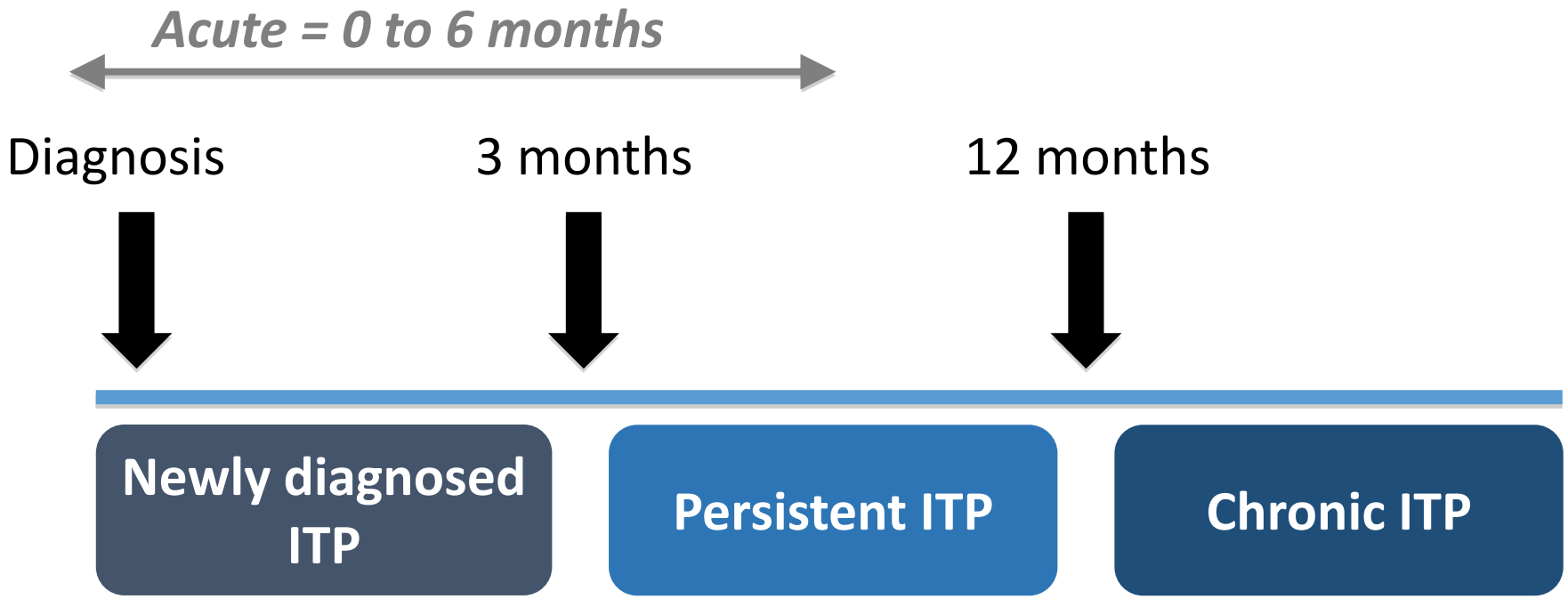
Definition

Peripheral platelet count less than 100,000 cells/cu.mm



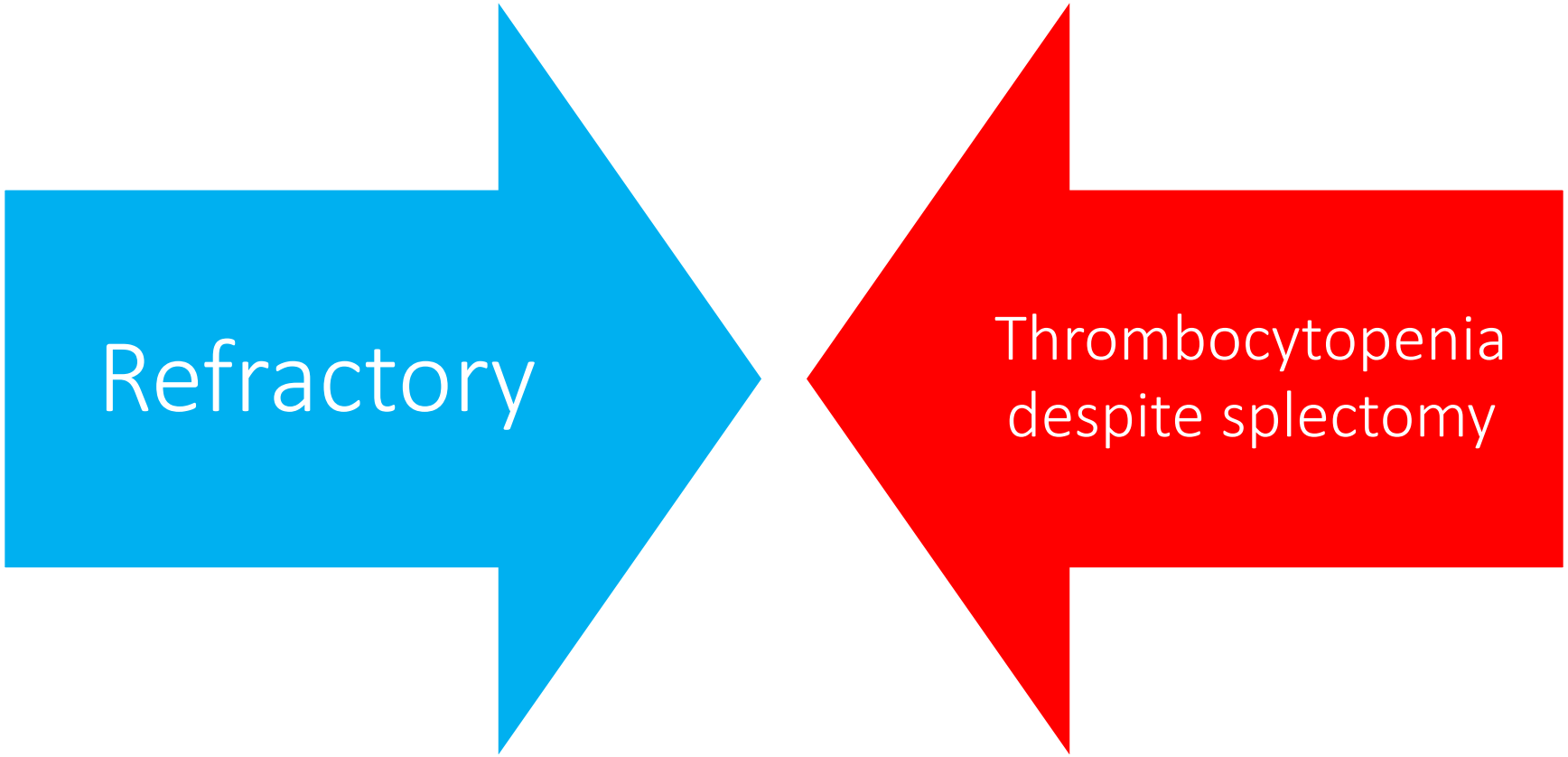
× Peripheral platelet count less than 150,000 cells/cu.mm

The prognosis for ITP varies considerably with classification



Rodeghiero F, *et al*. *Blood* 2009; **113**: 2386–93

Definition



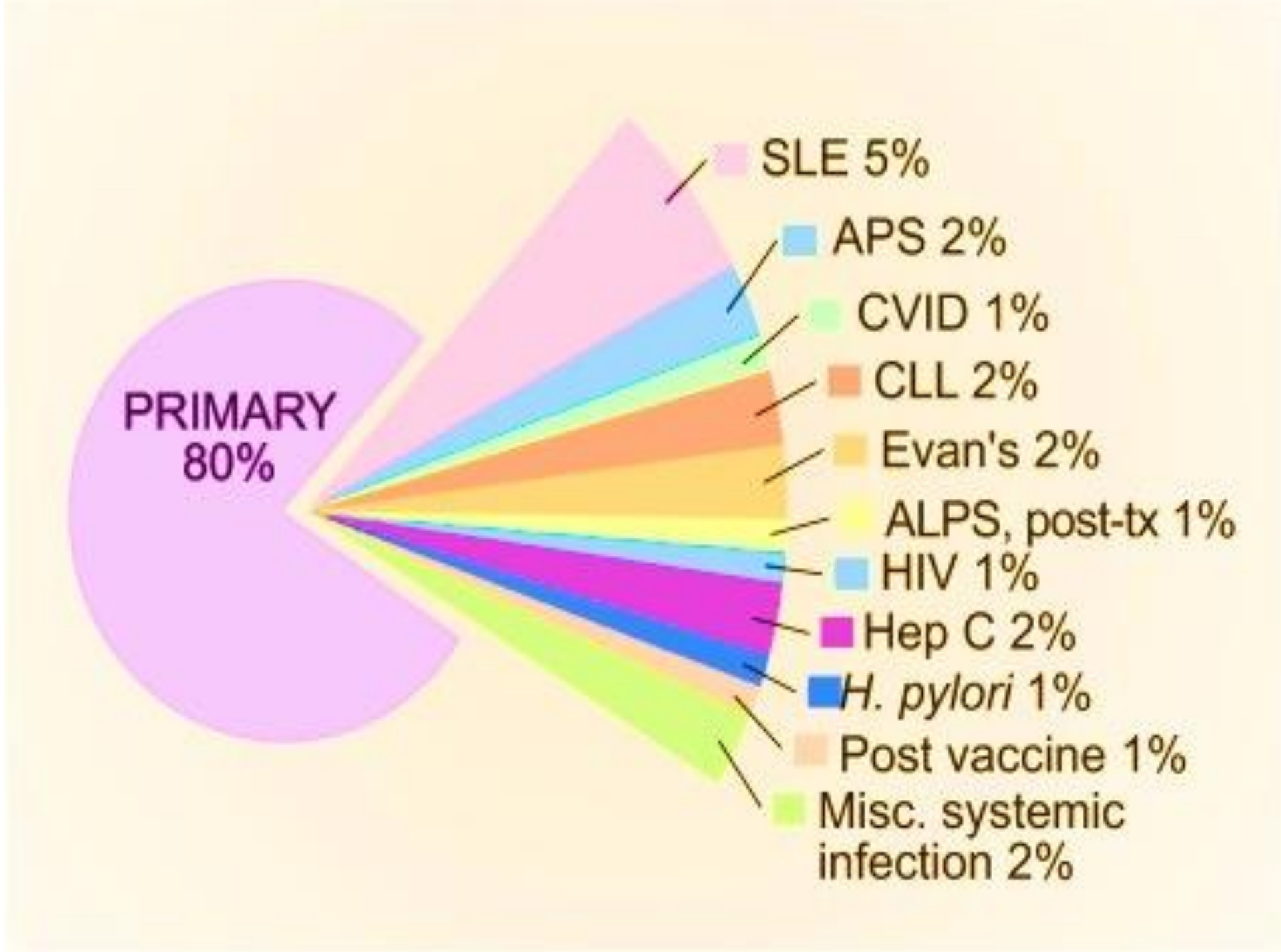
Definition

Primary

- the absence of other causes or disorders that may be associated with thrombocytopenia

Secondary

- All forms of immune-mediated thrombocytopenia


PRIMARY
80%
SLE 5%
APS 2%
CVID 1%
CLL 2%
Evan's 2%
ALPS, post-tx 1%
HIV 1%
Hep C 2%
H. pylori 1%
Post vaccine 1%
Misc. systemic
infection 2%

Introduction

- Peak age in children is approximately 5 years

- Previously healthy, presented with sudden onset of petechiae and purpura for a few days or weeks after an infectious illness

ITP involves diverse autoimmune mechanisms

- Although the exact pathology behind ITP remains unclear, recent advances have indicated two broad routes

- Immune dysfunction may play a key role in these processes, including **B-cell abnormalities**, a **T-cell disorder**, **abnormality of thrombopoiesis** or **increased mononuclear phagocyte activation**[1]

1. Cooper N, *et al*. *Br J Haematol* 2006; **133**: 364–74; 2. Gernsheimer T. *Eur J Haematol Suppl* 2008; **80**: 3–8;
3. Provan D, *et al*. *Blood* 2010; **115**: 168–86

Laboratory Findings

- Blood smear
  - normal. apart from thrombocytopenia
  - anemia present only in proportion to amount of blood loss
- Bone marrow
  - Increased megakaryocytes
  - Normal erythroid and myeloid cells
- Coagulation profile
  - Bleeding time- usually abnormal
  - PT and aPTT : normal

Diagnosis of ITP is primarily by exclusion

- Other possible causes of thrombocytopenia to consider include:
  - Lupus erythematosus, infection, thrombotic thrombocytopenic purpura
  - Hereditary thrombocytopenia: absent radius syndrome, radioulnar synostosis, congenital amegakaryocytic thrombocytopenia, Wiskott-Aldrich Syndrome, MYH9-associated thrombocytopenia, Bernard-Soulier Syndrome
  - Vaccinations and transfusions
  - Medication/drugs/diet (e.g. platelet-lowering treatments, alcohol, vitamin deficiency, quinine from tonic water)
  - Liver disease
  - Other bone marrow disease/leukaemia

Provan D, *et al*. *Blood* 2010; **115**: 168–86

Treatment

- is aimed at rapidly obtaining a safe platelet count to prevent or stop hemorrhages

- to ensure an acceptable quality of life with minimal treatment-related toxicity

Factors that contribute to ITP management decisions

- Newly diagnosed (acute) ITP may require no treatment and thus a “watch and wait” approach may be taken[1,2]
- Treatment should be considered in children at risk of bleeding[1]
- Management decision factors:[1,2]
  - The presence and extent of active bleeding
  - Impact on daily life
  - Psychological impact
  - Presence of additional risk factors for bleeding
  - Tolerance of side-effects

The goal of treatment in children with chronic/persistent ITP is to achieve a haemostatic platelet count[1,2]

1. Provan D, *et al. Blood* 2010; **115**: 168–86; 2. Neunert C, *et al. Blood* 2011; **117**: 4190–207

Treatment

No treatment is required when

- the platelet count is greater than 20,000 /mm3
- The patient is asymptomatic or has mild bruising but no evidence of mucous membrane bleeding

Treatment

Treatment is indicated

- Children with platelet count less than 20,000 /mm3 and significant mucous membrane bleeding

- The patients with platelet counts less than 10,000 /mm3 and minor purpura

Steroid Therapy

Rationale

1. Inhibits phagocytosis of antibody-coated platelets in the spleen and prolonged survival
2. Improves capillary resistance and thereby improves platelet economy
3. Inhibits platelet antibody production

High-Dose Intravenous Gammaglobulin

Mechanisms of action

- Reticuloendothelial Fc-receptor blockade
- Activation of inhibitory pathways
- Decrease in autoantibody synthesis

Platelet Transfusions

Indication

- there are neurologic signs suggestive of intracranial bleeding
- signs of internal bleeding
- an emergency surgery

Splenectomy

Indications

- Severe acute ITP with acute life-threatening bleeding which is nonresponsive to medical treatment
- Chronic ITP with bleeding symptoms or platelet count persistently below 30,000 /mm3 which is nonresponsive to medical treatment for several years

Emergency Treatment

- In organ- or life-threatening situations

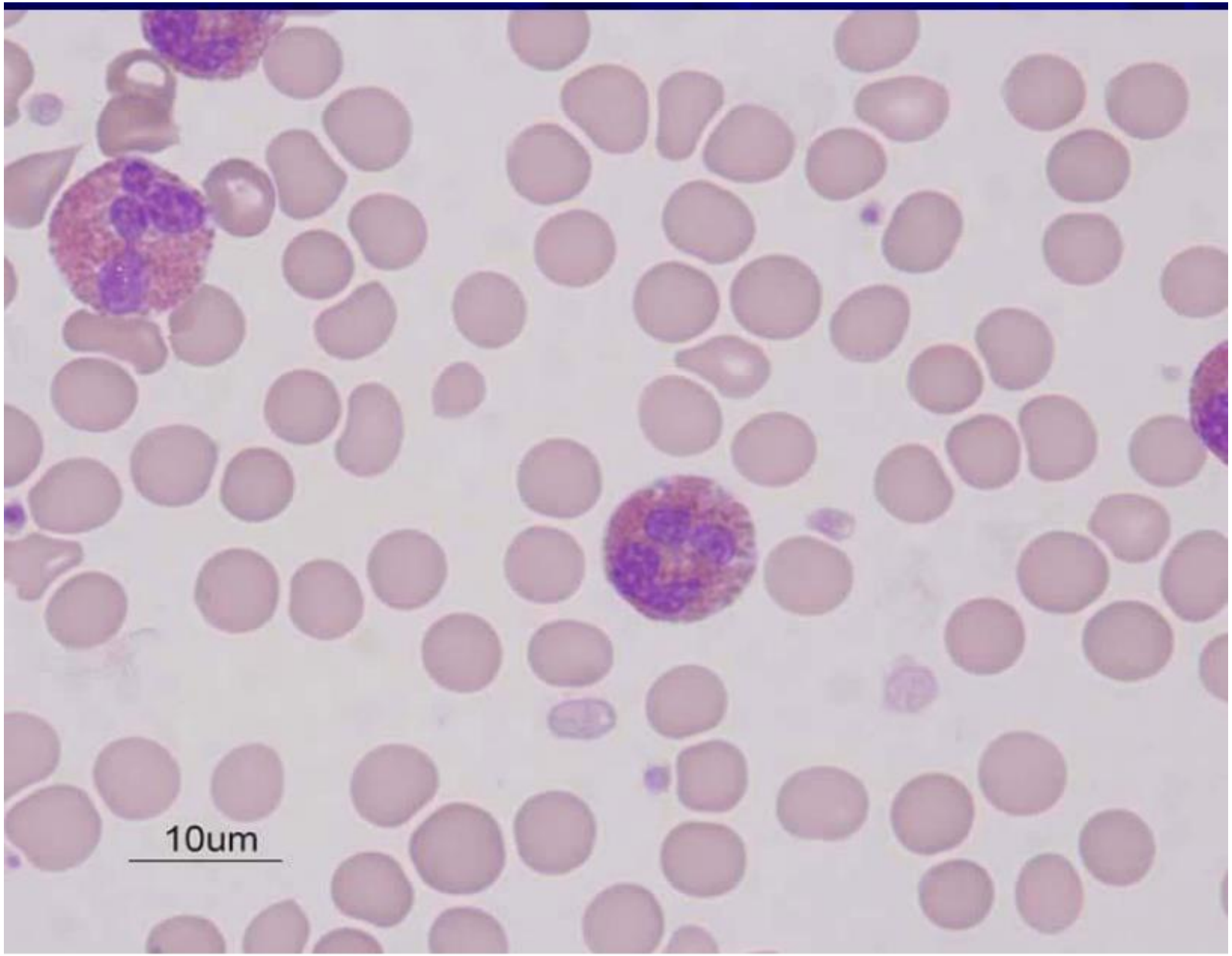
- The goal of treatment is to elevate the platelet count to a level where the risk of severe bleeding is minimized as soon as possible

Treatment of Children with Life-Threatening Hemorrhage

- Platelet transfusion
- Methylprednisolone 500 mg/m2 IV per day for 3 days
- IVGG 2 g/kg
- Emergency splenectomy

Acquired Platelet dysfunction with eosinophilia (APDE)

- Commonly found in age 2-10 years
- Incidence in male is more common than female
- Symptoms; purpura, ecchymosis with no a previous history of bleeding disorders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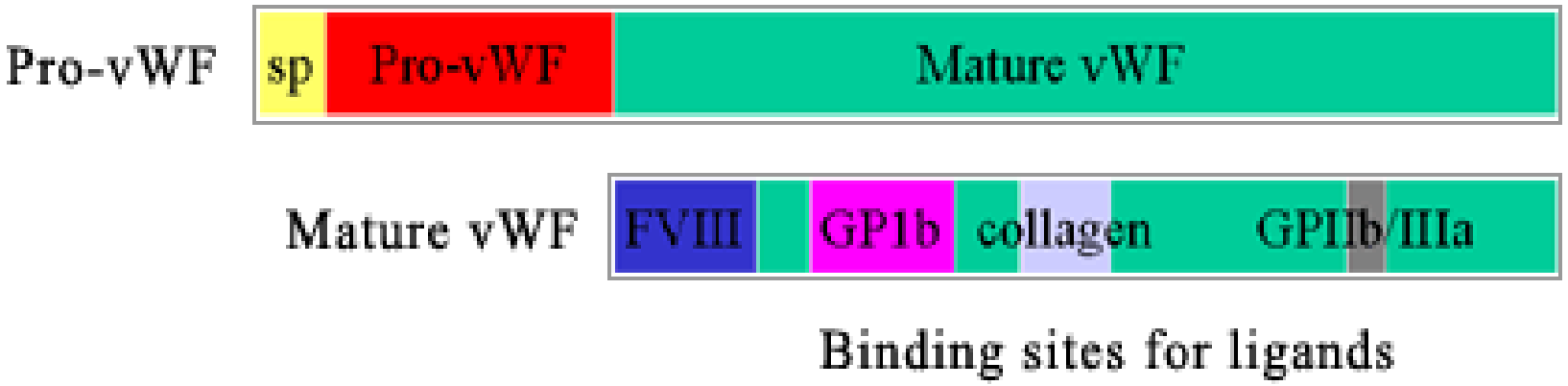
Treatment

- The majority of patients did not receive any treatment
- Patients with severe bleeding, excessive bleeding after tooth extraction or large hematoma were treated by platelet transfusion to stop bleeding and packed red cell transfusion to correct anemia from blood loss
- All of the patients had good responses

von Willebrand disease (vWD)

- *VWF* gene : short arm of chromosome 12
  - *VWF* gene is expressed in endothelial cells and megakaryocytes
- vWF is produced as a propeptide which is extensively modified to produce mature vWF
  - Two vWF monomers bind through disulfide bonds to form dimers
  - Multiple dimers combine to form vWF multimers



vWF Function

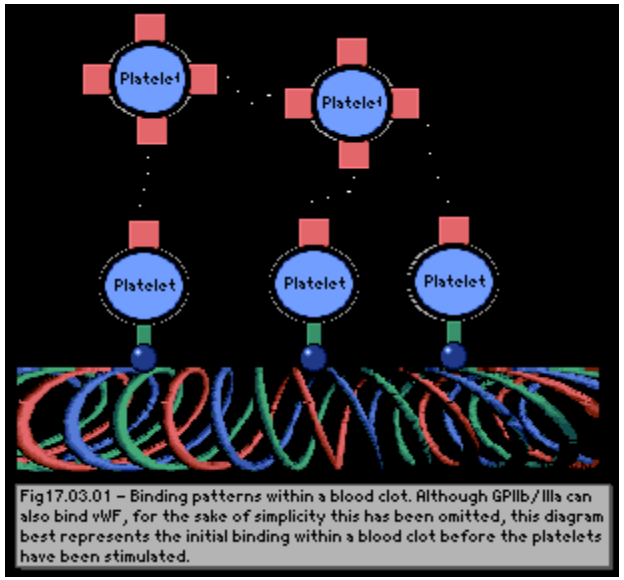


Fig17.03.01 – Binding patterns within a blood clot. Although GPIIb/IIIa can also bind vWF, for the sake of simplicity this has been omitted, this diagram best represents the initial binding within a blood clot before the platelets have been stimulated.

Adhesion

- Mediates the adhesion of platelets to sites of vascular injury (subendothelium)
  - Links exposed collagen to platelets
- Mediates platelet to platelet interaction
  - Binds GPIb and GPIIb-IIIa on activated platelets
  - Stabilizes the hemostatic plug against shear forces

Carrier protein for Factor VIII

Classification

A- Quantitative deficiency of VWF

Type 1: Partial quantitative deficiency of vWF
Type 3: Virtually complete deficiency of vWF

B- Qualitative deficiency of VWF

Type 2A: Qualitative variants with decreased platelet dependent function associated with the absence of high and intermediate molecular weight vWF multimers

Type 2B: Qualitative variants with increased affinity for platelet GPIb

Type 2M: Qualitative variants with decreased platelet dependent function not caused by the absence of high-molecular weight vWF multimers

Type 2N: Qualitative variants with markedly decreased affinity for factor VIII

Diagnosis of vWD

- Personal and family history of bleeding symptoms
- Blood work to check von Willebrand levels and type
- Type 1 disease often diagnosed later in life after extensive dental work or heavy menses.
- Often adult parent diagnosed after child found to have the disease

Treatment for von Willebrand disease

- DDAVP
- Cryoprecipitate
- Factor VIII/ristocetin cofactor