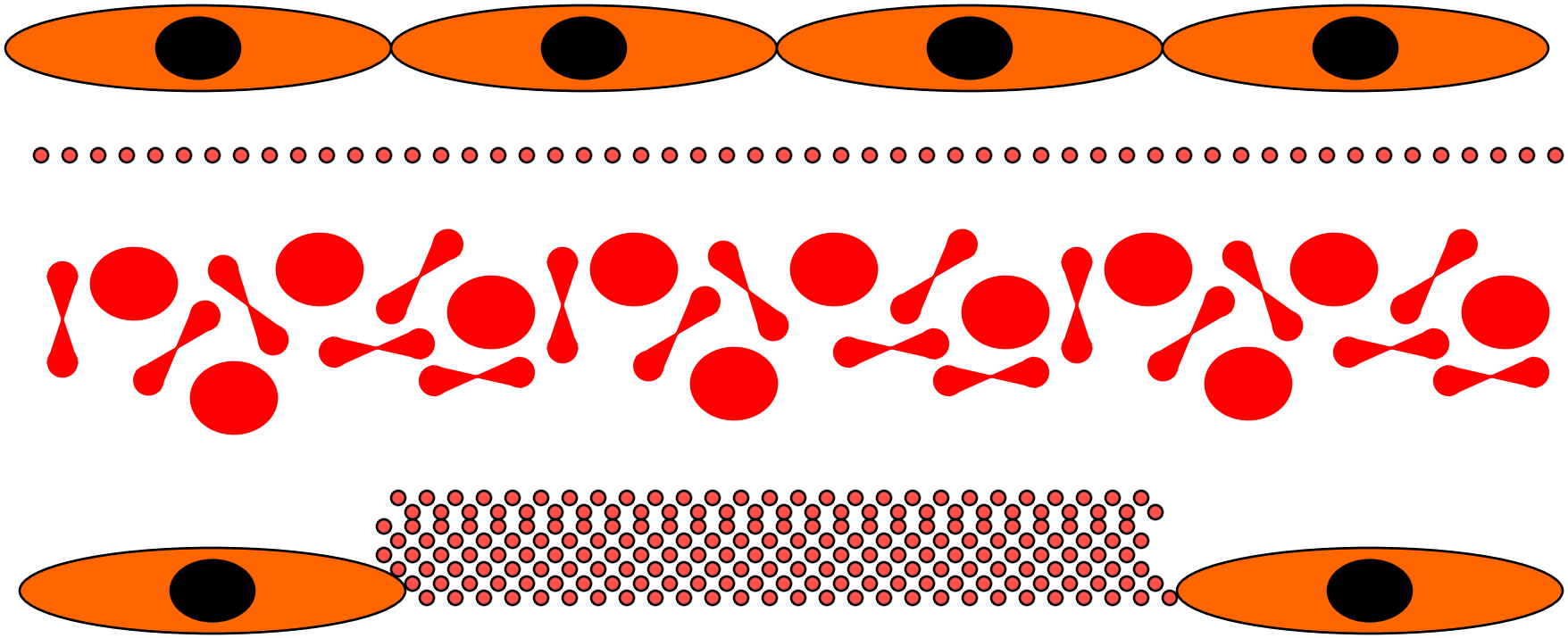
Pitfalls in Management of Bleeding Disorders

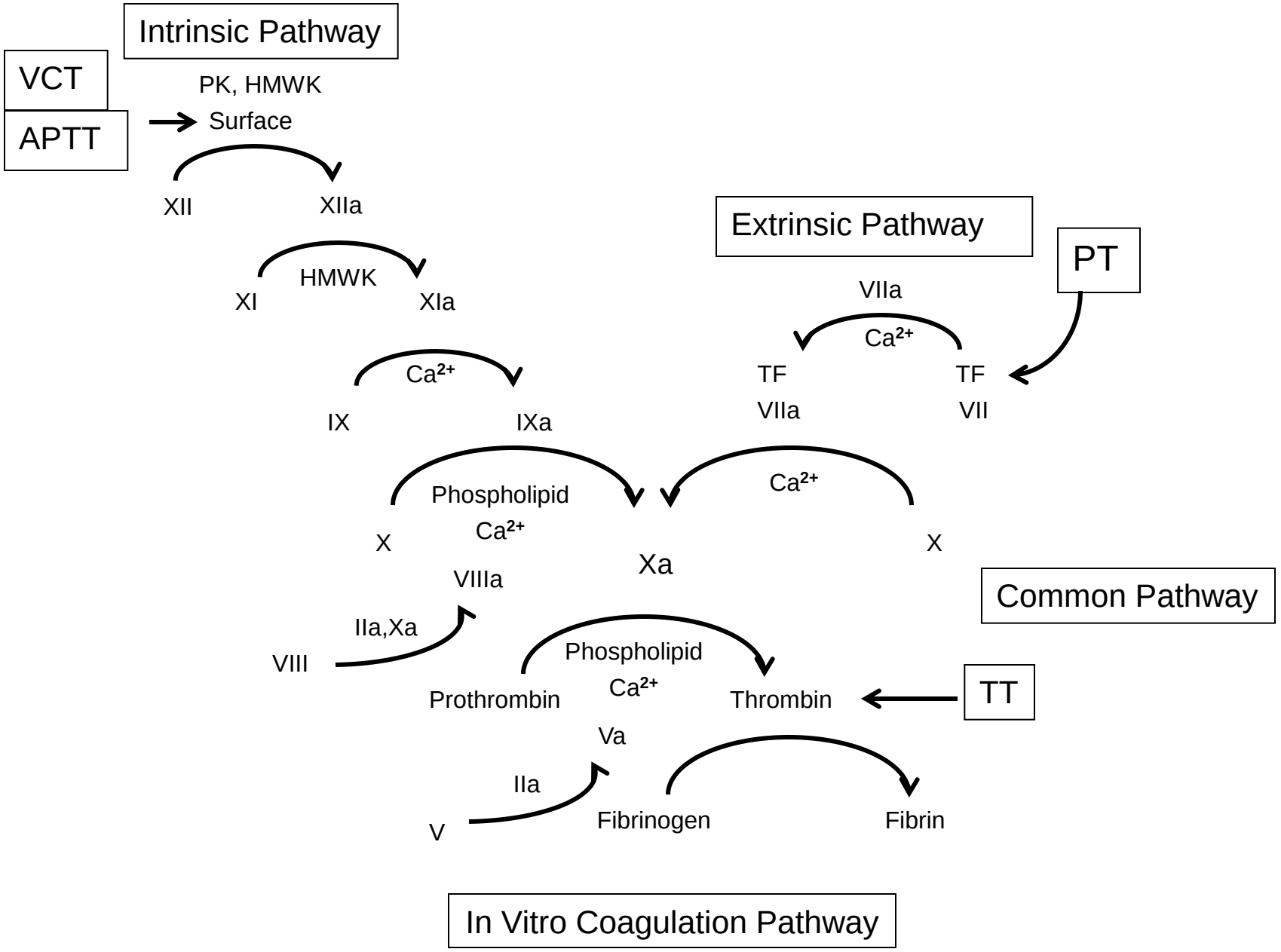
Ponlapat Rojnuckarin
Chulalongkorn University

Primary platelet plug

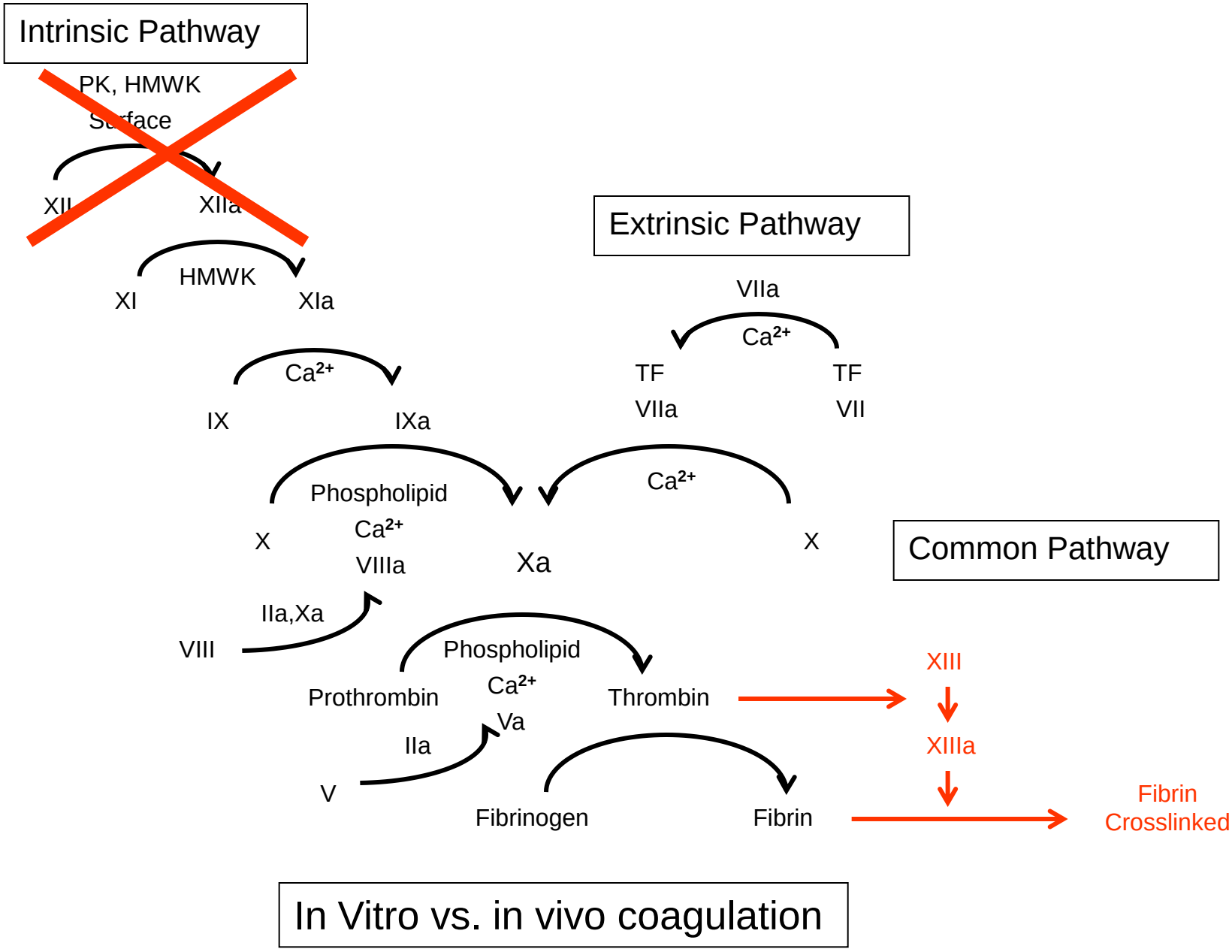
Adhesion and aggregation



Collagen and von Willebrand Factor (vWF)

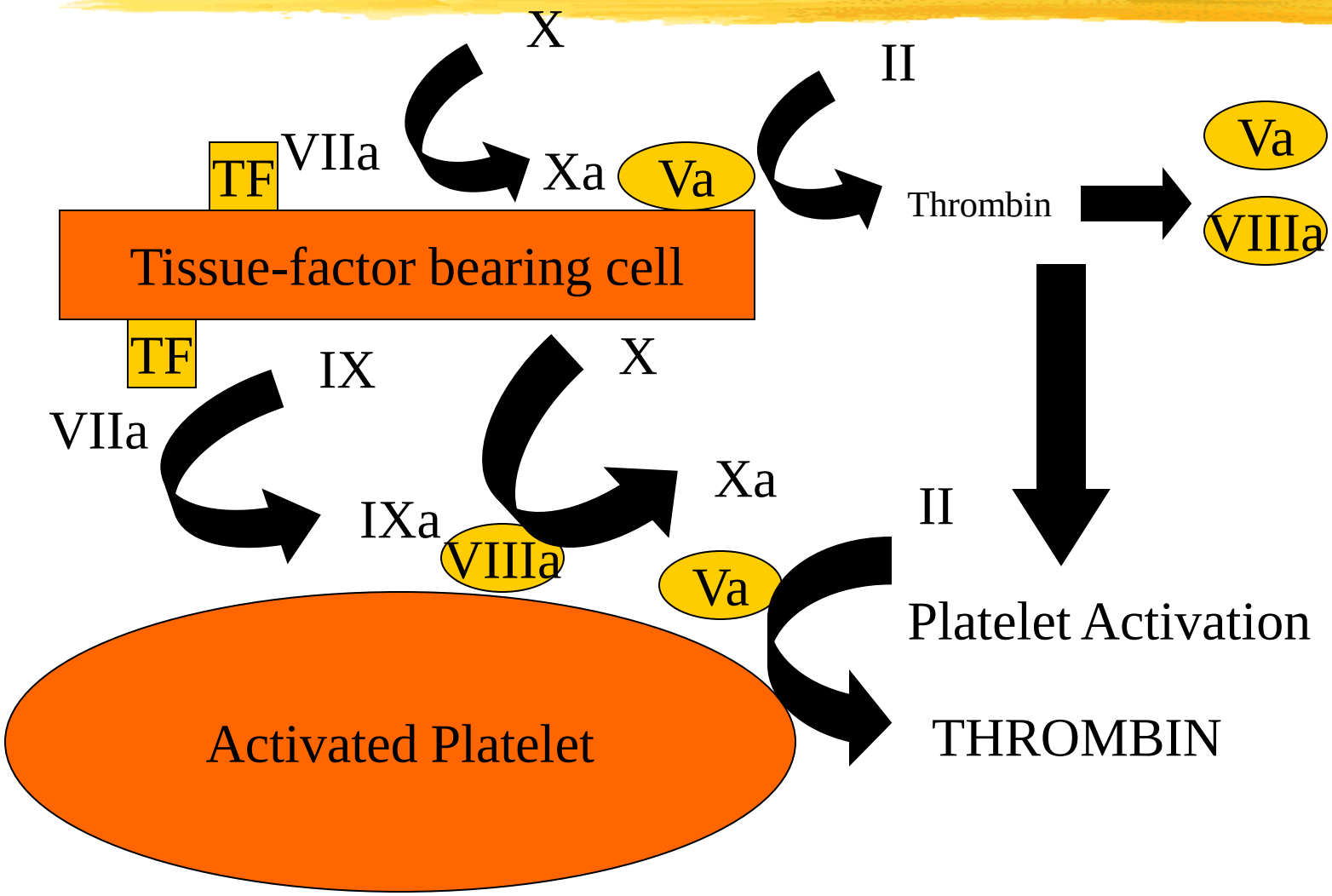


In Vitro Coagulation Pathway

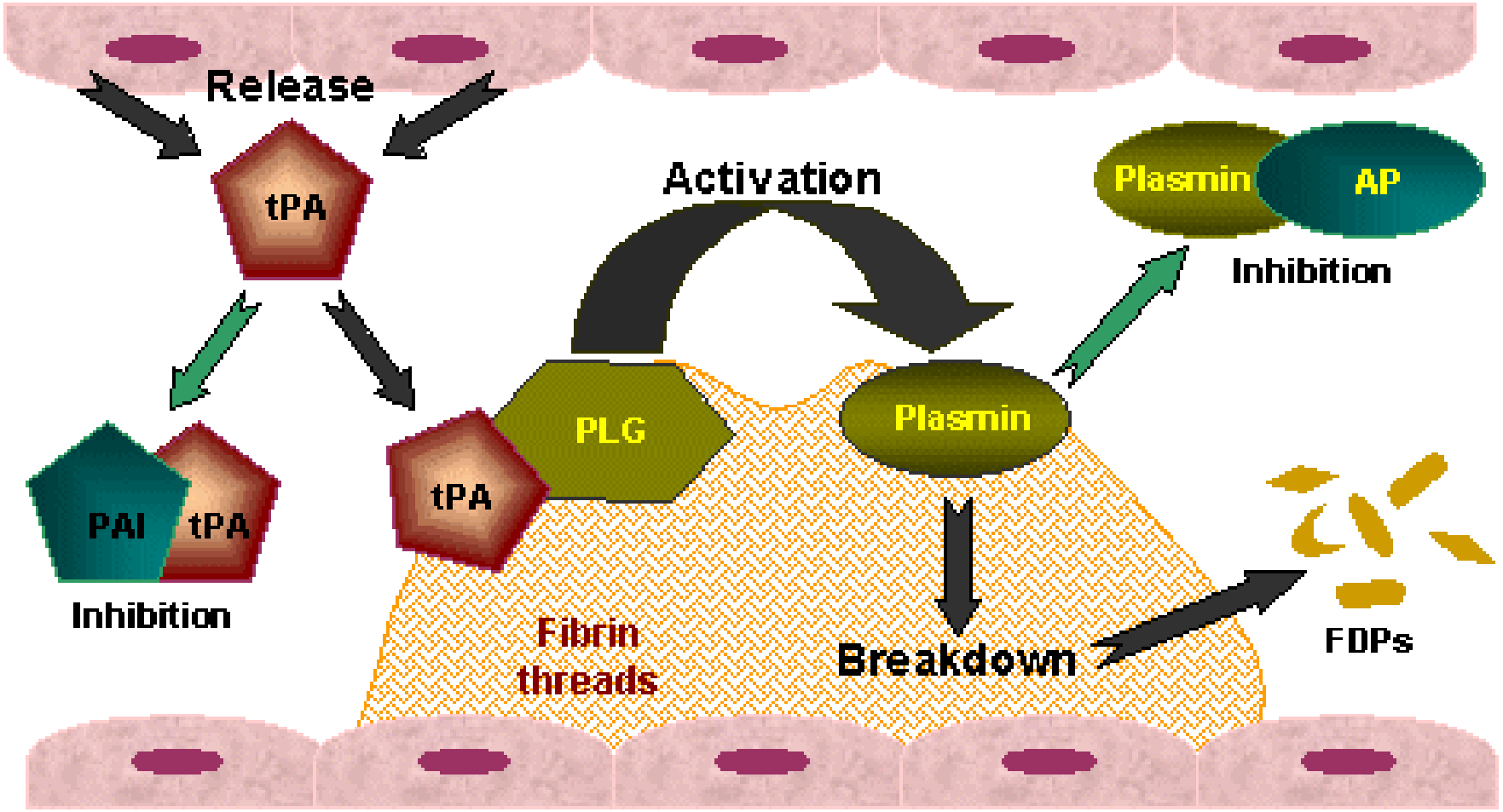


In Vitro vs. in vivo coagulation

Cell-based coagulation



Localization of fibrinolysis



Screening Coagulogram

Platelet count

Peripheral blood smear

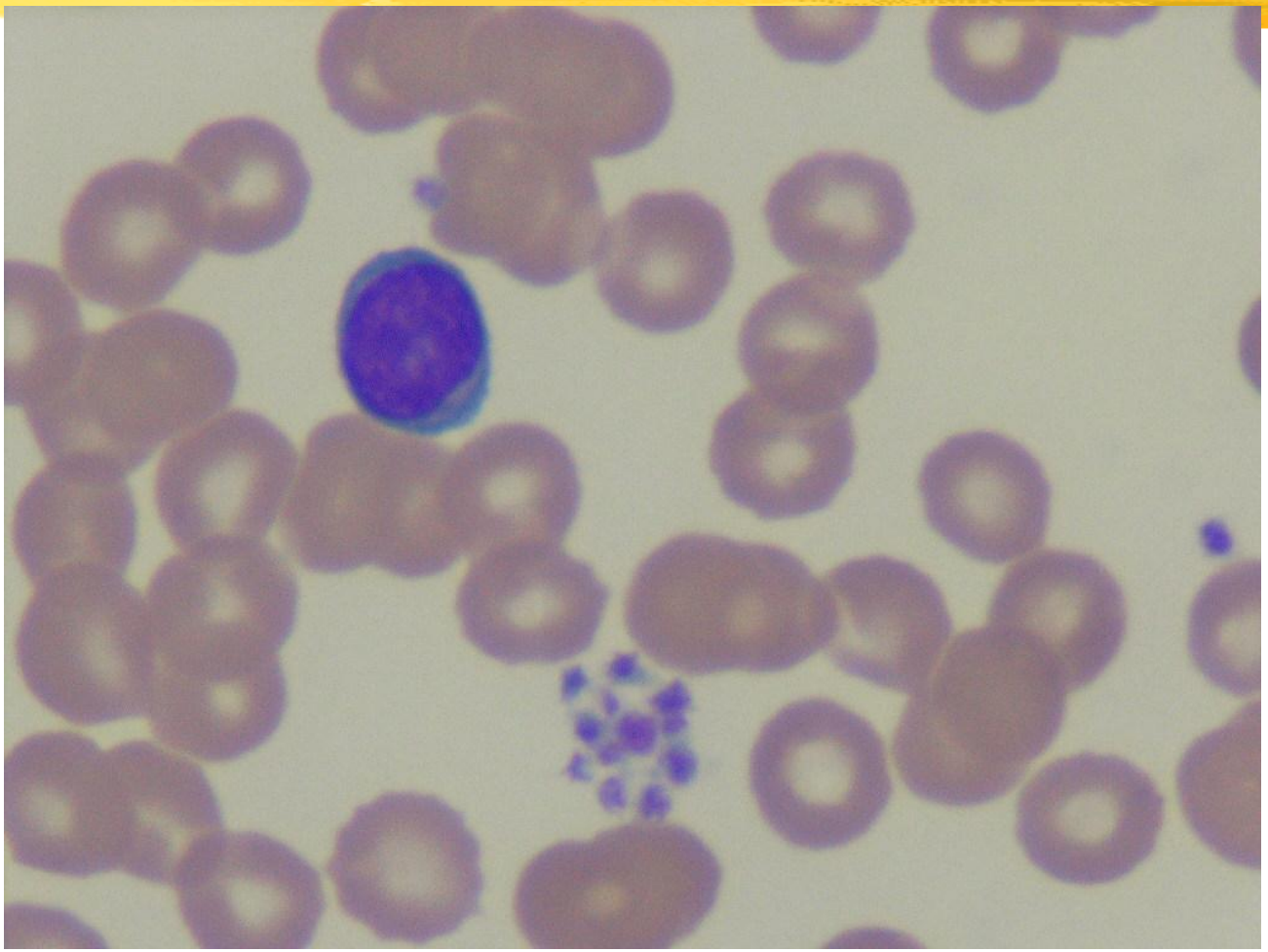
Bleeding time

APTT

PT

TT

Blood smear: Pseudothrombocytopenia



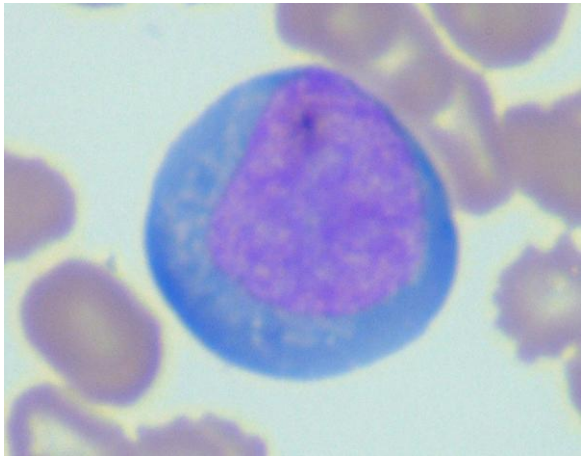
Platelet clumping

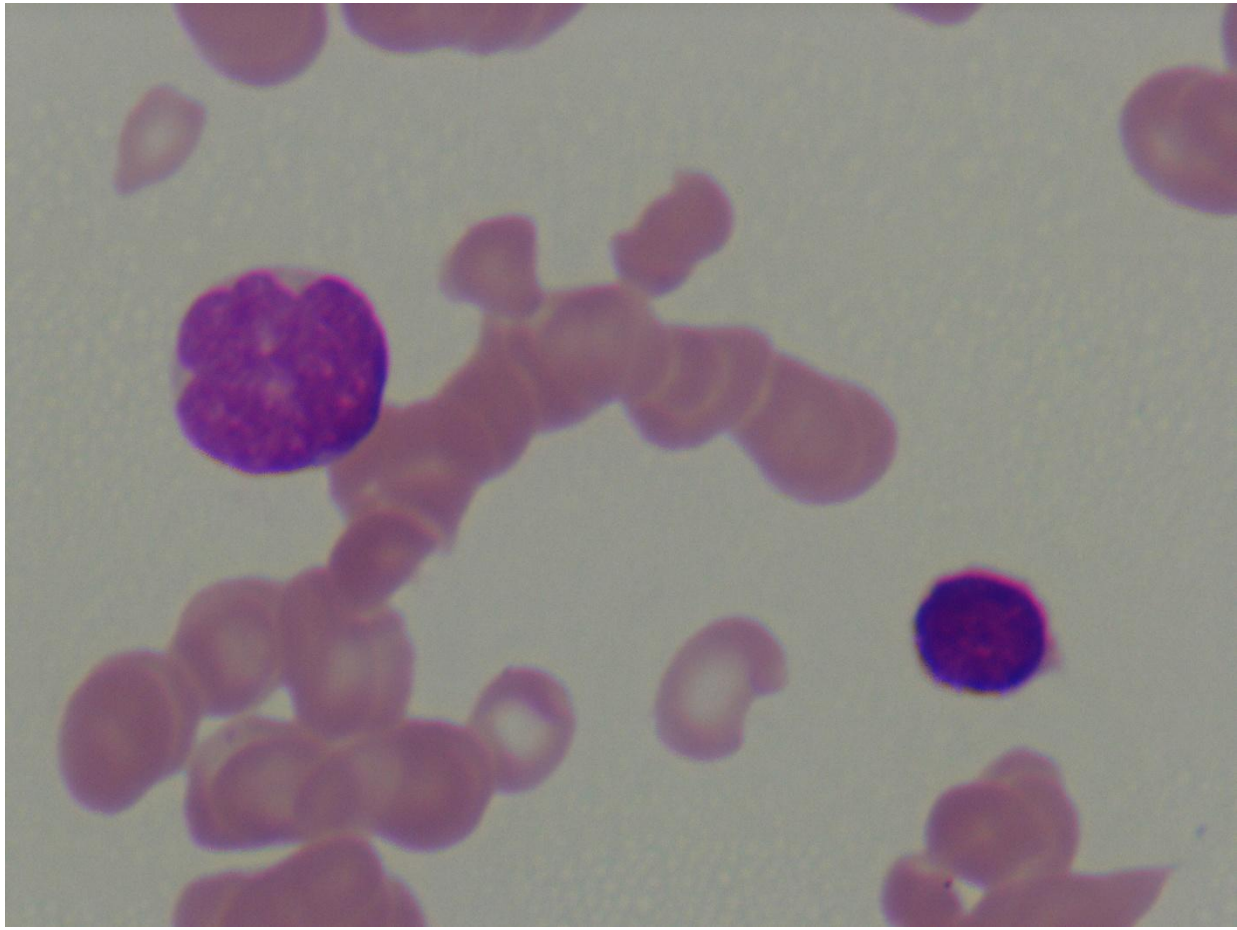
EDTA-dependent pseudothrombocytopenia

- Presence of autoantibody that agglutinates platelet in EDTA at RT
- 20% IgM that also agglutinates at 37 C and in citrate
- In vitro artifact, No clinical significance
- Avoid unnecessary investigations, transfusion or delaying procedure
- May repeat count in heparin

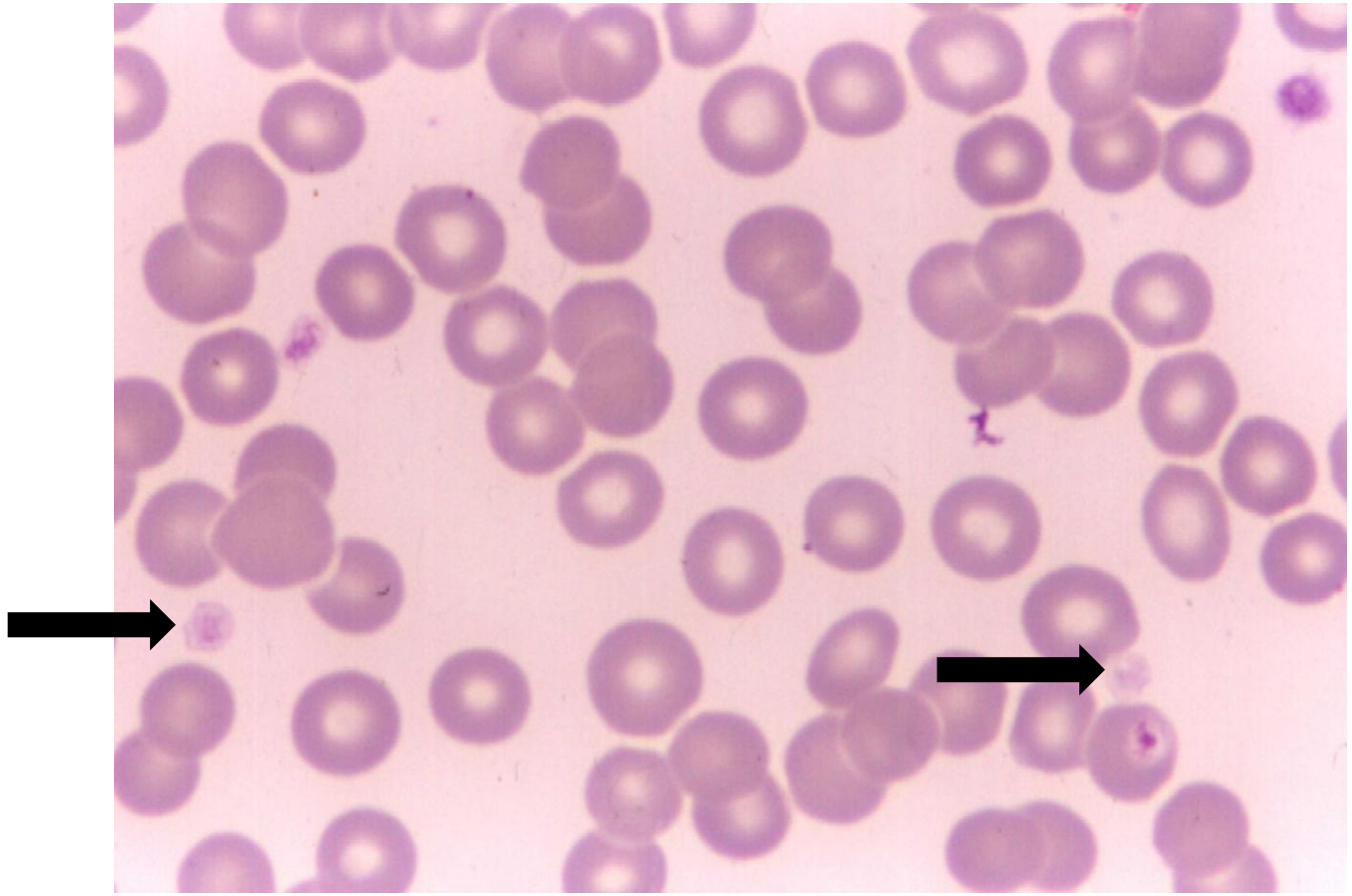
Am J Hematol. 1995; 50: 103-9

Blood smear: Causes of thrombocytopenia



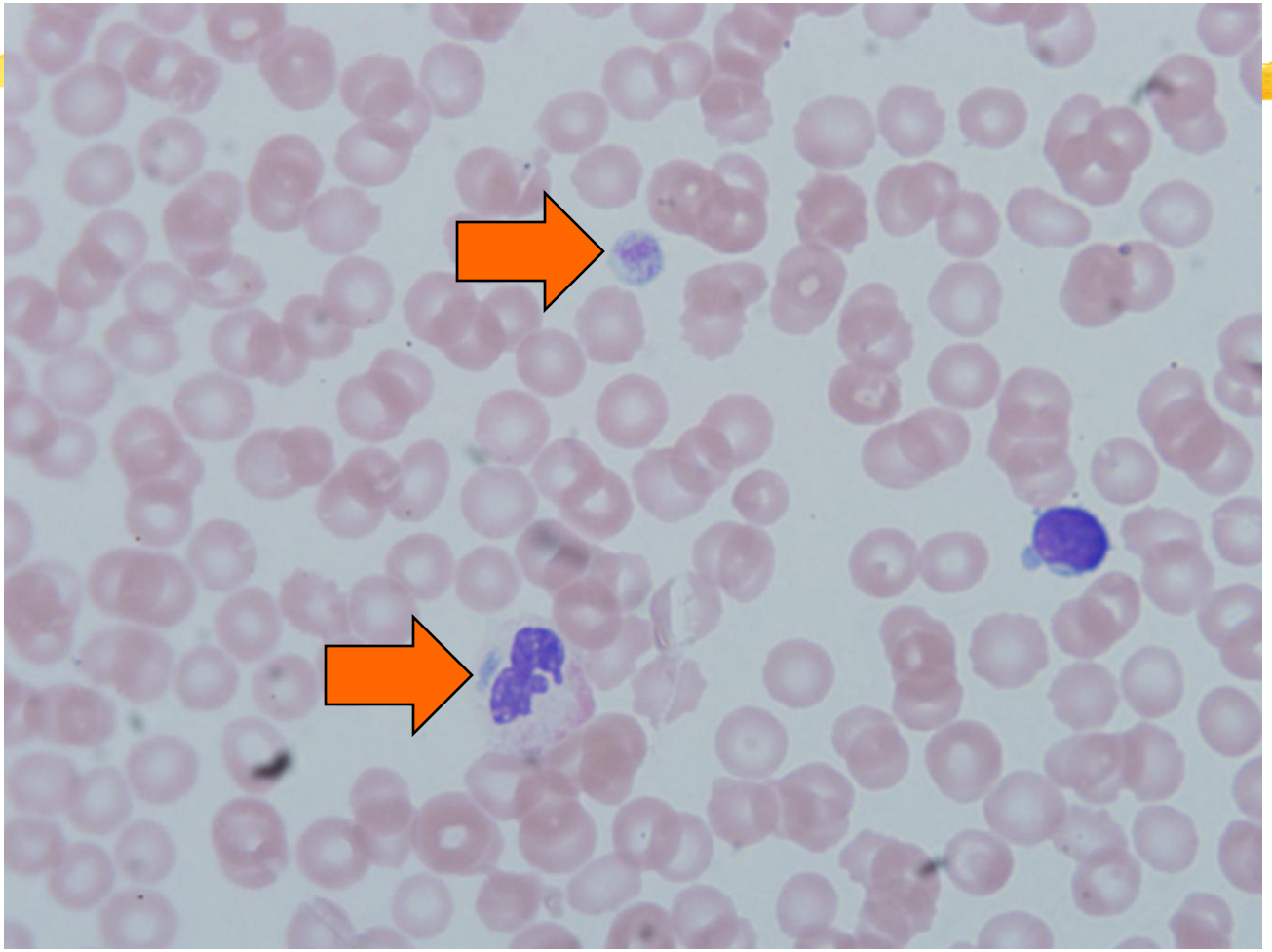


Blood smear: Platelet granularity



Storage pool disease: Hypogranular platelets

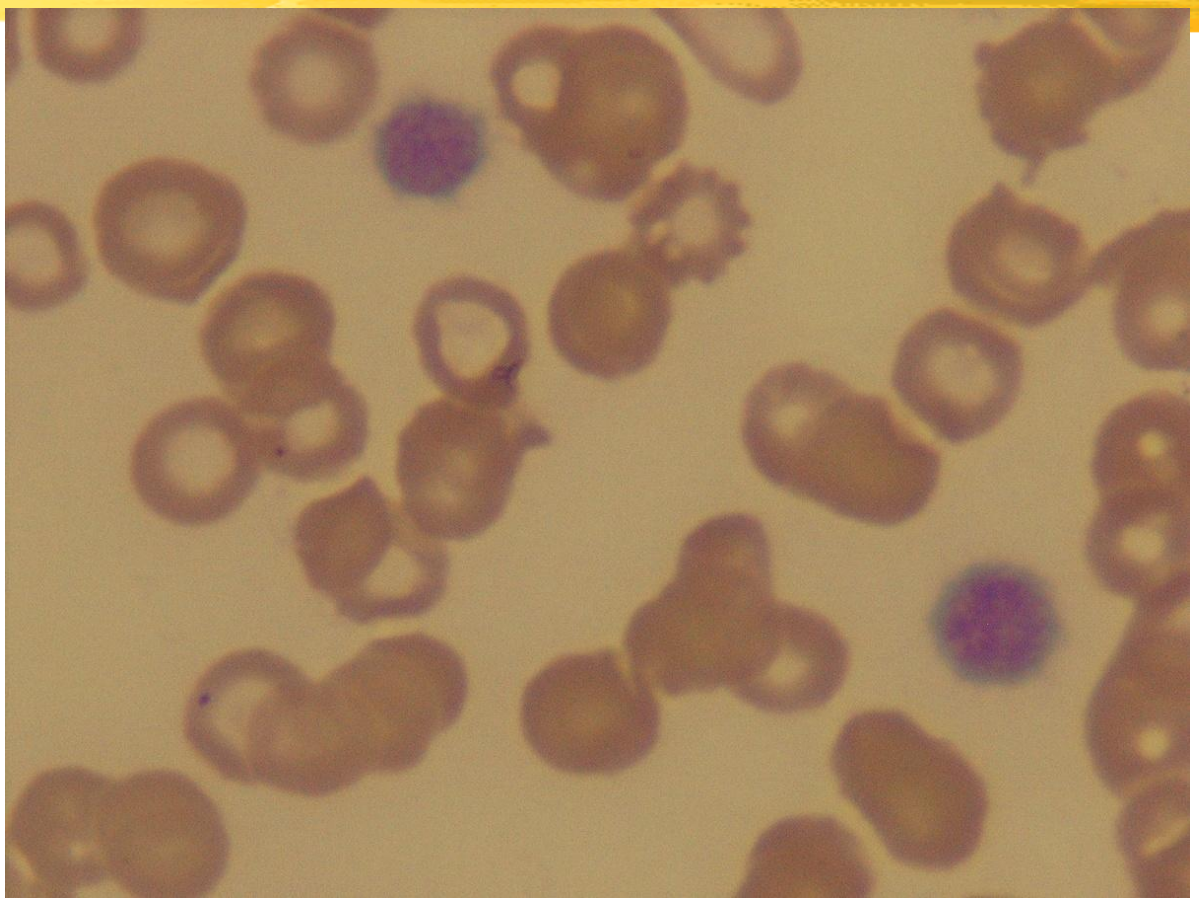
Blood smear: Platelet size



May-Hegglin Anomaly:

No bleeding, Thrombocytopenia, Giant platelets and Döhle body

Blood smear: Platelet size



Bernard-Soulier syndrome:

Severe bleeding, Thrombocytopenia, Giant platelets

Thrombocytopenia

- Hematological diseases
  - Impaired production (Pancytopenia)
  - Peripheral destruction
- Systemic diseases
  - Any critical illnesses
  - Special situations

ผู้ป่วยหญิงอายุ 24 ปี

5 วัน จุดแดงออกตามตัว มีอาเจียนเป็นเลือด

PE: Afebrile, extensive petechiae at her body and legs, others: WNL

CBC: Hb 12.0 g/dl, MCV 82 fl, WBC 4.7 x 10^9/L, N 75%, L 20%, M 4%, Eo 1%, PBS: no abnormal cells, platelet 4.0 x10^9/L. Anti HIV is negative.

ITP: Diagnosis by exclusion

- Blood smear
- Liver diseases: Asymptomatic
- Anti HIV
- Anti HCV

- Bone marrow: Abnormal RBC/WBC, old age, refractory

ITP with Major bleeding

- High dose steroid

Ex. Dexamethasone 40 mg/d

- Intravenous immunoglobulin
- Avoid invasive procedures, e.g. surgery, endoscopy, NG larvage
- Still bleeding after improving platelet counts: look for local lesion

ผู้ป่วยหญิงอายุ 40 ปี underlying ITP on prednisolone และ cyclophosphamide

มาด้วยพูดจาสับสน 1 วัน ตรวจร่างกาย T 39 C, PR 120, BP 90/60 mmHg, Petechiae both legs, No focal sign

CBC: Hb 11 g/dL, WBC 20 x 10^9/L, N 80%, L 20%, Platelet 5.0 x10^9/L

CT brain: No CNS bleeding

A. **IVIg**

B. **Antibiotic**

C. **Platelet transfusion**

D. **Pulse dexamethasone**

Thrombocytopenia in critically ill patients

- Sepsis
- DIC
- Spleen
- Drug-induced
- Dilutional: Massive Transfusion
- Indwelling Catheter
- Cardiopulmonary bypass

- TTP/HUS
- HIT
- Post transfusion purpura
- Catastrophic APA syndrome

Thrombocytopenia in critically ill patients

Combinations or Unknown*

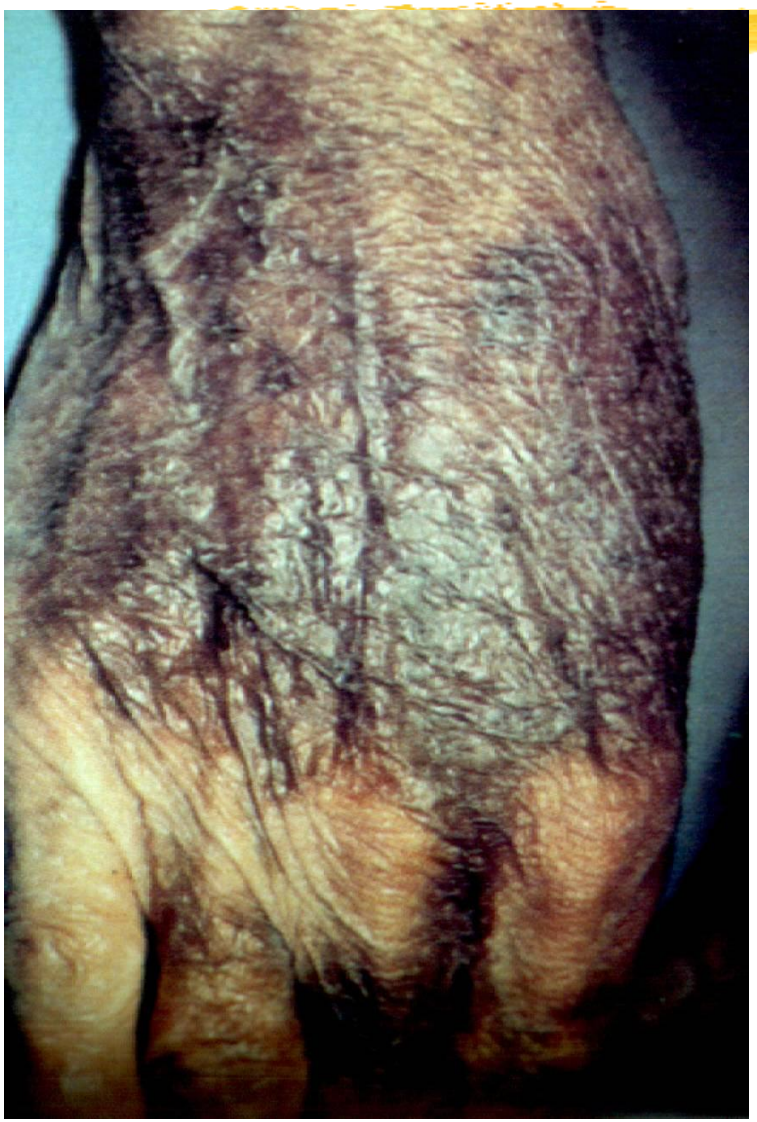
Platelet transfusion:

keep $\geq$ 10-20 x 10^9/L, if no bleeding

keep $\geq$ 50-100 x 10^9 /L, if bleeding

*Chest. 1999;115:1363

A 70-yr-old woman with easy bruising, normal CBC, PT, PTT



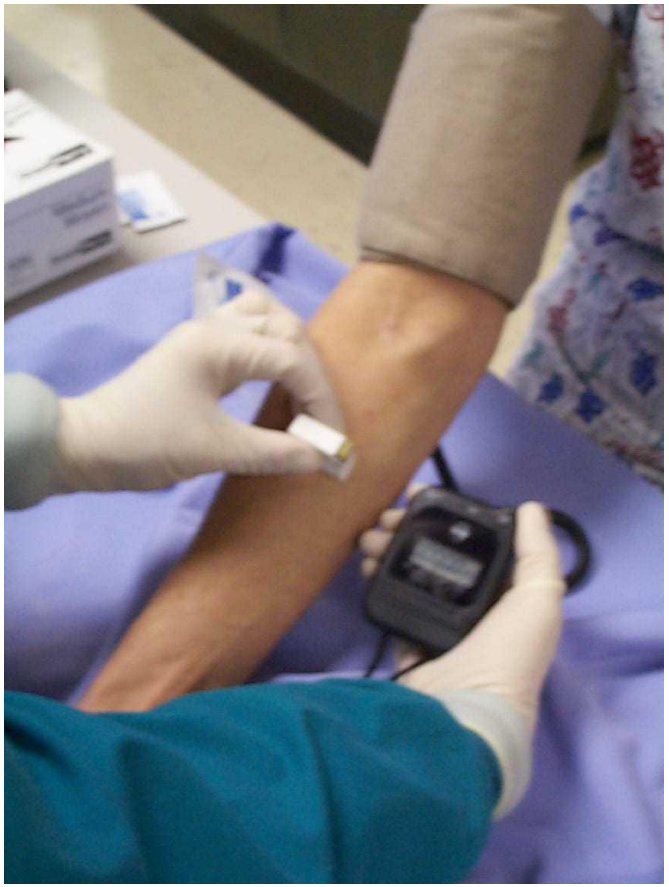
The most appropriate test

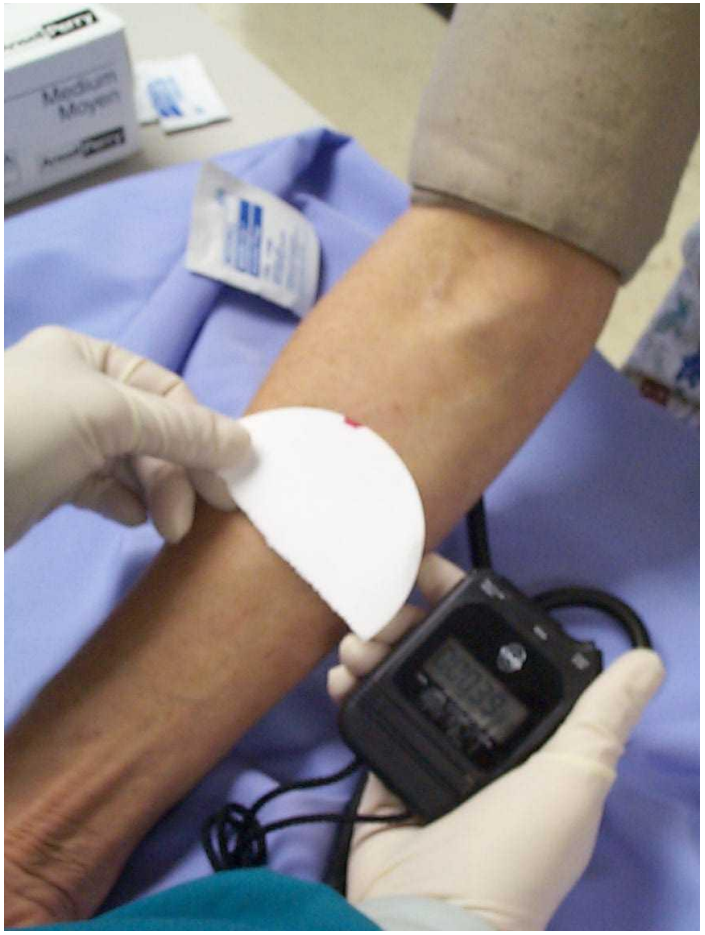
1. Bleeding time
2. Thrombin time
3. Skin biopsy
4. Fibrinolytic test
5. No further test

Bleeding Time

- Platelet Dysfunction
- Some vascular diseases

Bleeding time





Bleeding time

- Variable, affected by anemia and platelet count
- Cannot be used as a screening test for asymptomatic patients (e.g. pre-operation) due to low positive predictive value.
- May cause scar
- Can cause large hematoma in senile purpura

Blood 1991; 77: 2457-62

Low Sensitivity of bleeding time

- Prolonged bleeding time (N=148)
  - von Willebrand disease type 1: 42%
  - Platelet secretion defect: 42%
- Prolonged bleeding time (N=128)
  - von Willebrand disease type 1: 29%
  - Platelet secretion defect: 33%

JTH 2004; 2: 892, JTH 2007;5: 2393

Is there any use of bleeding time before special tests?

- Clinically suggestive: Special tests
  Clinically unlikely: No test

- Emergency setting: active bleeding from suspected platelet dysfunction or vWD
  (Anemia: prolonged bleeding time)

- If BT > 20 min: Likely to be true positive

Coagulation tests

Specimen Collection

1. Avoid stasis, probing
2. Double syringe, plastic syringe
3. Plastic tube, exact ratio of anticoagulant
4. Immediate centrifugation
5. Immediate testing and freezing
6. Correction for high hematocrit

Pooled normal plasma (Control)

- Mixture of plasma from 20-30 healthy individuals
- The factor activity should be about 100% activity (or 1U/ml).
- Report as control values. They are performed daily.
- Control values from the same lab should be within the acceptable range.

Normal range

- Normal range should be defined locally by each laboratory
- Tests are performed in at least 30 healthy individuals giving the normal distribution of the results.
- Normal range = mean $\pm$ 2 SD

Mixing study

Prolonged coagulation assay

1:1 mixing of patient v.s. normal plasma

Correctable : Factor deficiency

Uncorrectable : Factor inhibitor

Isolated prolonged APTT

Without Bleeding

- Mix Correctable: Contact factor def.
- Mix not Correctable: lupus anticoagulant
- Pre-analytical error: Heparin, too long storage

With Bleeding

- Mix Correctable: Hemophilia A, B, C, vWD
- Mix not Correctable: F VIII inhibitor

Isolated prolonged PT

Early vitamin K deficiency or antagonist

Mild liver disease

Factor VII deficiency (rare)

Prolonged APTT& PT, Normal TT

Vitamin K deficiency or antagonist*

Moderate to severe liver diseases*

Massive transfusion

Common pathway deficiency: congenital or acquired

* PT prolonged > APTT

Prolonged TT

Without bleeding

Heparin contamination

Hyperfibrinogenemia

Bleeding Hypofibrinogenemia

Dysfibrinogenemia

Impaired fibrin polymerization

Heparin, Paraprotein, FDP, anti IIa

Bleeding with normal screening coagulogram

1. Mild bleeding disorders vWD
2. Factor XIII deficiency
3. Hyperfibrinolysis: antiplasmin deficiency, tPA excess, PAI deficiency
4. Vascular diseases

Male 53 yr
Left Chest wall mass for 1 week

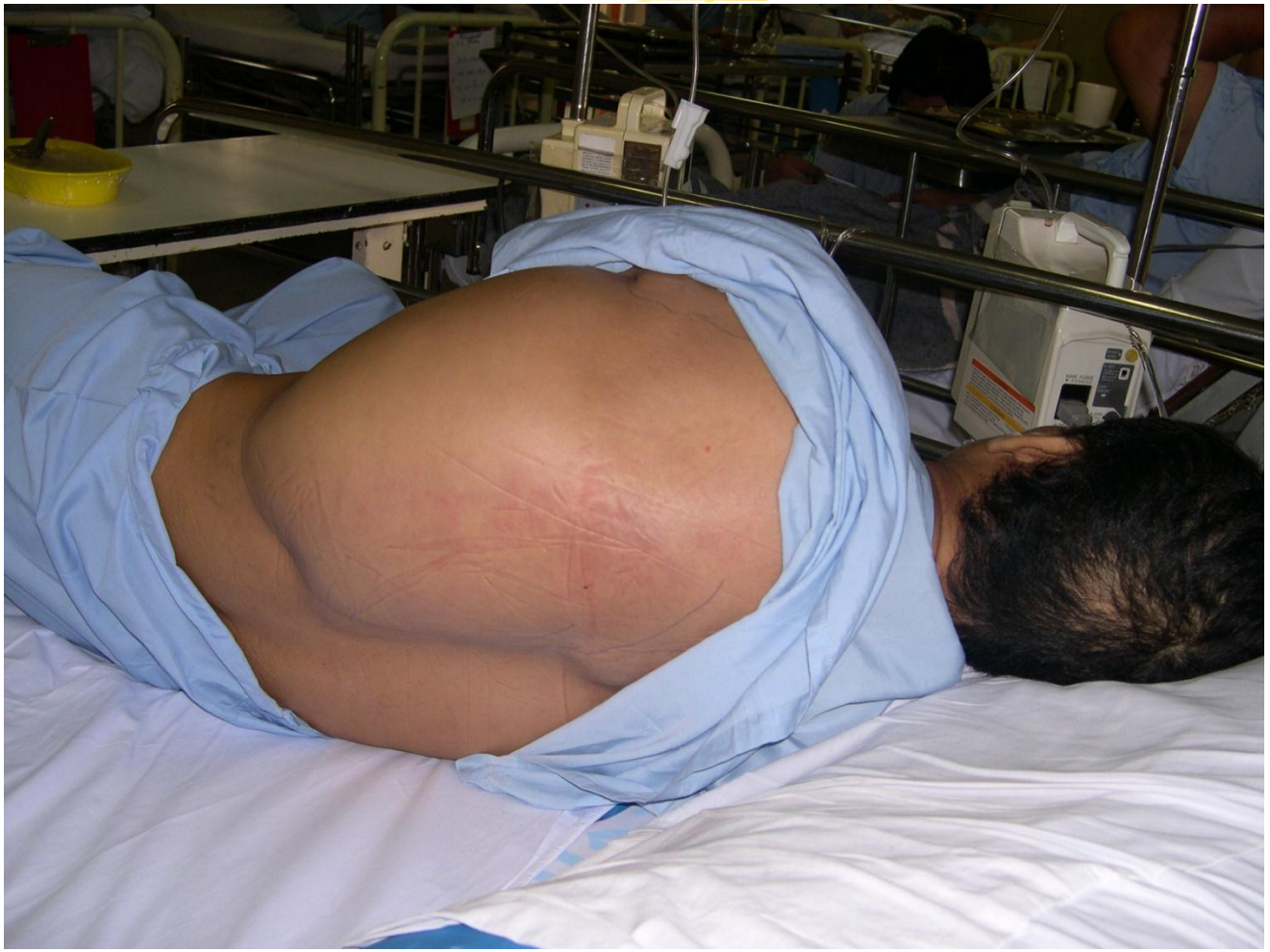
PH: No previous history of bleeding

PE: Huge mass with massive pleural effusion

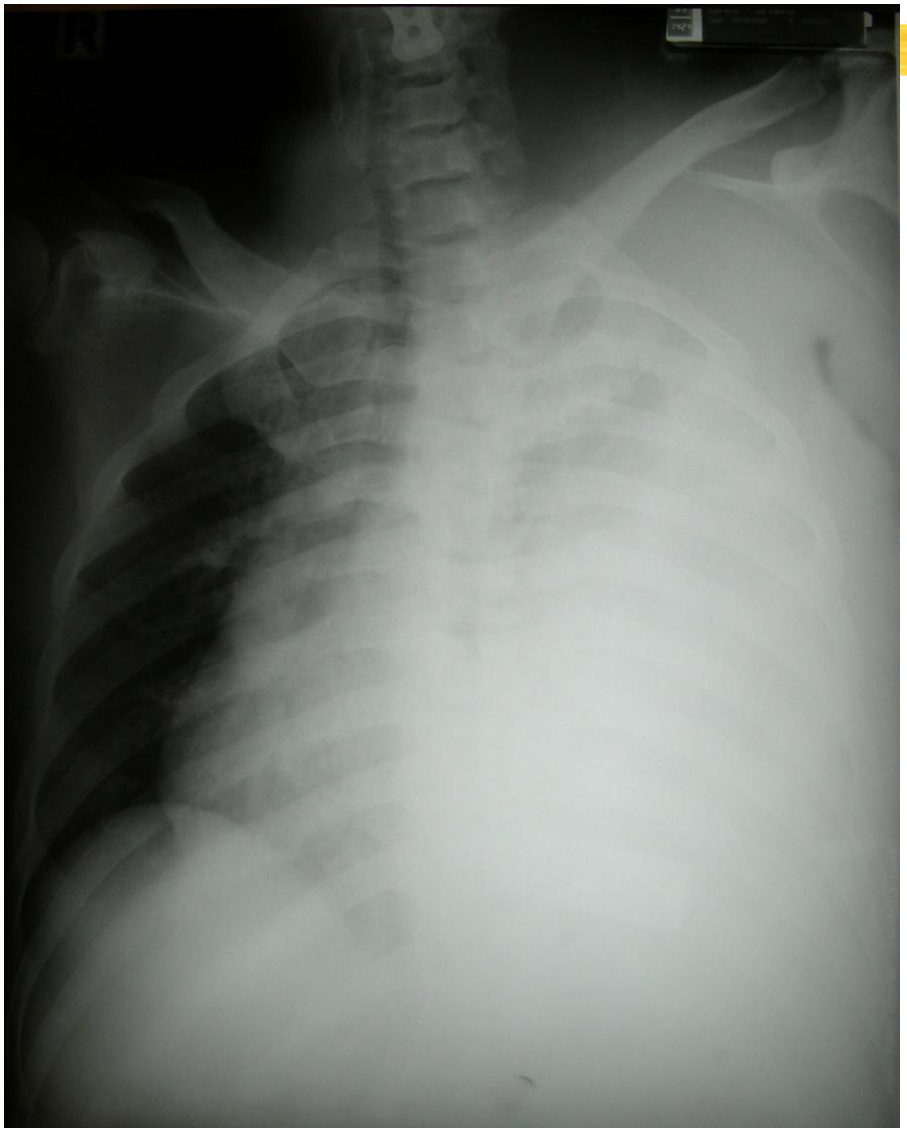
CBC: Hb 7.5 g/dL, MCV 83 fl, WBC 8.5 $x10^9$/L, N 69%, L 21%, M 10% Platelet 305 $x10^9$/L

APTT	105.2 sec	(25-42 sec)
PT	15.4 sec	(11-15 sec)
TT	11.0 sec	(10-15 sec)

Ecchymosis



Chest X ray



The most helpful investigation?

A. Liver function test
B. Lupus anticoagulant
C. Mixing study
D. Factor XII assay
E. Pleural tapping

Clinical Approach

- ? Bleeding tendency
  - Spontaneous Bleeding, multiple sites
- ?Congenital vs Acquired
  - Acquired
- ?Primary vs Secondary defect
  - Secondary
  - Ecchymosis, deep tissue bleeding

Isolated prolonged APTT

- Improper specimen collection
- Mixing study (with bleeding)
  - Correctable: Hemophilia A, B, C, vWD
  - Uncorrectable: Inhibitor

Male 53 yr
Left Chest wall mass for 1 week

Large Hematoma with pleural effusion

Lab: Anemia and Normal platelet count

APTT	105.2 sec (25-42 sec)
Mixing study:	uncorrectable
Factor VIII	1%
Factor VIII inhibitor	12 Bethesda unit

Appropriate treatment?

A. Cryoprecipitate
B. Tranexamic acid
C. Corticosteroid
D. Surgical removal of clot

Acquired Hemophilia

Secondary causes (40-50%)

- Post-partum (1-4m, recovery in 30 m)
- Autoimmune disease
- Malignancies
- Drug e.g. penicillins, sulphonamides, phenyltoin

Br J Haematol 2003; 121:21

Treatment of bleeding

- Low Titer < 5 BU
  High dose factor VIII concentrate
- High titer > 5 BU
  Bypassing agents: Recombinant factor VIIa, FEIBA

Immunosuppressive

- 36% spontaneous resolution
- Prednisone (1 mg/kg/d) abolishes the inhibitor in 30% of patients (Green & Lechner, 1981; Spero et al, 1981; Green et al, 1993)
- Addition of cyclophosphamide (1-2 mg/kg/d) response rate: 60-100%(Green et al, 1993; Shaffer & Phillips, 1997; Bayer et al, 1999)

Female 24 yr
Major bleeding after dental extraction 2 times

Lab: Platelet 325x10^9/L

APTT 39.0 sec. (26.7-38.3)

PT 12.5 sec. (10.3-13.2)

Which is a possible diagnosis?

A. Lupus anticoagulant

B. Von Willebrand disease

C. Vitamin K deficiency

D. Liver disease

Clinical Approach

- ? Bleeding tendency
  - Bleeding after surgery (repeatedly)
- ?Congenital vs Acquired
  - Congenital vs acquired?
- ?Primary vs Secondary defect
  - ?undefined

Detailed bleeding history

- Bruise (> 4 cm, >4 sites, hematoma)

Normal: Shin (1 ft over the ground), forearm

- Epistaxis (> 15 min)
- Bleeding after dental extraction or surgery requiring medical attention and/or transfusion

Menorrhagia

- นานเกิน 7 วัน
- ใช้ผ้าอนามัยมากกว่า 30 ผืนต่อ 1 cycle
- เปลี่ยนผ้าอนามัยทุกชั่วโมง (0.5-2 hr)
- ต้องใช้ผ้าอนามัยที่ซึมซับดีเป็นพิเศษ
- ประจำเดือนเปื้อนผ้าบ่อยครั้ง
- เคยมีเลือดจางเนื่องจากขาดเหล็ก
- ต้องหยุดงานหรือหยุดเรียนเพราะมีประจำเดือน

Haemophilia 2002; 8: 330–338

Isolated prolonged APTT

- With bleeding
  - Von Willebrand Disease
  - Carrier of Hemophilia (lyonization)
  - Inhibitor (usually transient)

Isolated prolonged APTT

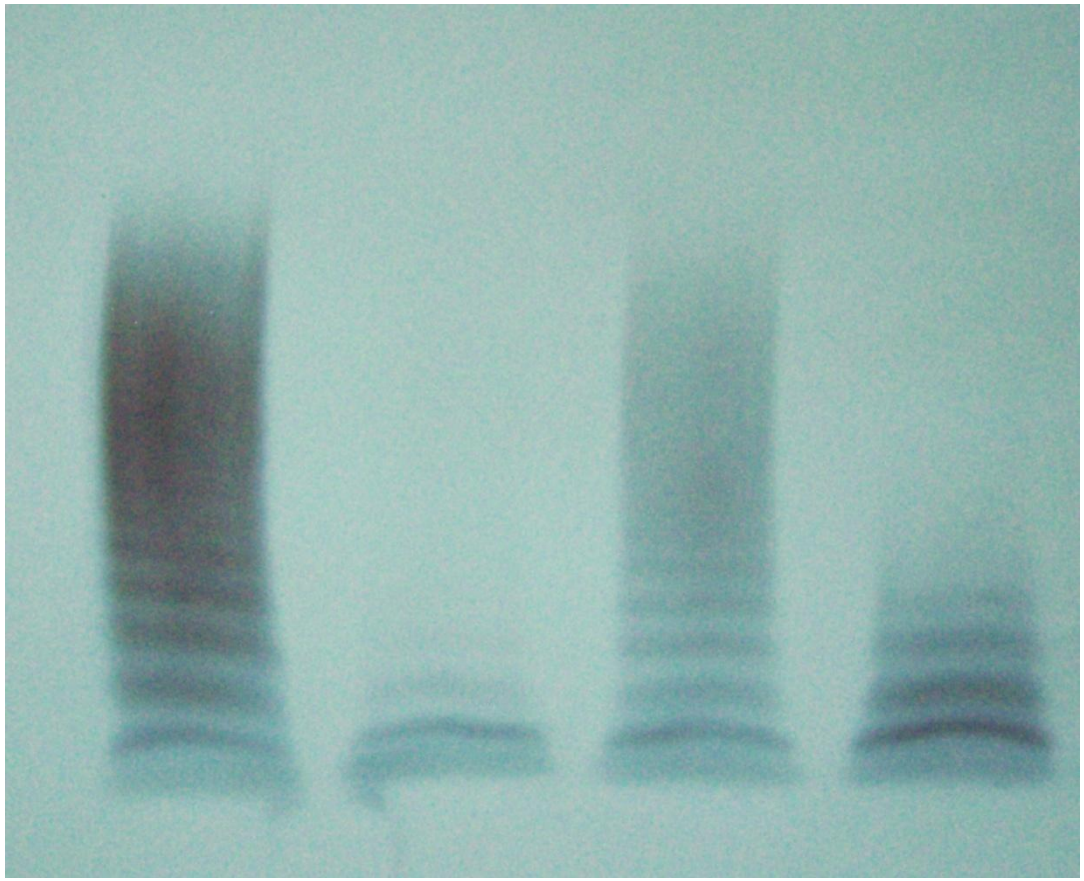
- With bleeding
  - Von Willebrand Disease
  - Carrier of Hemophilia (lyonization)
  - Inhibitor (usually transient)

- Bleeding time 16 min. (<9 min.)
- Blood group O

von Willebrand disease

- Type 1 (partial quantitative defect)
- Type 2 (qualitative defect)
  - 2A, 2B loss high MW multimer
  - 2N (Normandy): loss factor VIII binding (low F VIII, normal plt function)
  - 2M Normal multimer, normal factor VIII binding
- Type 3 (complete deficiency)

vWF multimer assay



Normal Type 3 Type 1 Type 2 A or 2B

von Willebrand factor

- Antigen: ELISA
- Activity
  - Ristocetin cofactor activity (RiCof)
  - Collagen binding assay (CBA)
- Factor VIII activity

Female 24 yr
Major bleeding after dental extraction 2 times

1. Factor VIII assay 45% (60-150)
2. vWF antigen (ELISA) 40% (50-150)
3. vWF function
   - Ristocetin cofactor activity 14% (50-150)
   - Collagen binding assay 12% (50-150)

Dx von Willebrand disease type 2

Disproportion of vWF function: Ag (activity: antigen < 0.6)

- Suggests type 2 vWD
- Run vWF multimer
- Type 2B will be hyper-aggregable to low dose ristocetin. DDAVP causes thrombocytopenia

Von Willebrand's disease

Before surgery

- DDAVP IV (Not in type 2B)
- Cryoprecipitate
- Factor VIII concentrate

- Tranexamic acid during menstruation for hypermenorrhea

Female 22 yr
Admitted to ICU for sepsis
Now, clinically improved, no bleeding

Lab: Platelet count 330 x 10^9/L

APTT	64.3 sec	(25-35 sec)
PT	15.7 sec	(10-13 sec)

Which is a possible diagnosis?

A. Lupus anticoagulant
B. Hemophilia carrier
C. Liver disease
D. Pre analytical error

Female 22 yr
Admitted to ICU for sepsis
Now, clinically improved, no bleeding

Lab: Platelet count 330 x 10^9/L

APTT 64.3 sec (25-35 sec)

PT 15.7 sec (10-13 sec)

TT > 120 sec (10-13 sec)

Fibrinogen 4.5 g/L (1.7-4.0)

Repeat venepuncture from peripheral line: normal TT

Heparin contamination

Female 75 yr
Spontaneous bruising 3 days

2 wk History of Rt leg pain went to another hospital, unknown medication

PH: no peripartum bleeding

PE: ecchymosis and hematoma

Lab: APTT 266.3 sec (25-35)

PT 300.0 sec (10-13)

TT 11.5 sec (10-13)

Prolonged APTT& PT, Normal TT

Vitamin K deficiency or antagonist*

Moderate to severe liver diseases*

Massive transfusion

Common pathway deficiency: congenital or acquired (inhibitor)

* PT prolonged > APTT

Female 75 yr
Spontaneous bruising 3 days

2 wk History of Rt leg pain went to another hospital, unknown medication

PH: no peripartum bleeding

PE: ecchymosis and hematoma

Lab: PT 300 sec

PT (mix with normal plasma 1:1) 13.4 sec

LFT normal

Female 75 yr
Spontaneous bruising 3 days

2 wk History of Rt leg pain went to another hospital, unknown medication

PH: no peripartum bleeding

PE: ecchymosis and hematoma

Rx: Vitamin K 10 mg IV PT became normal within 24 hrs

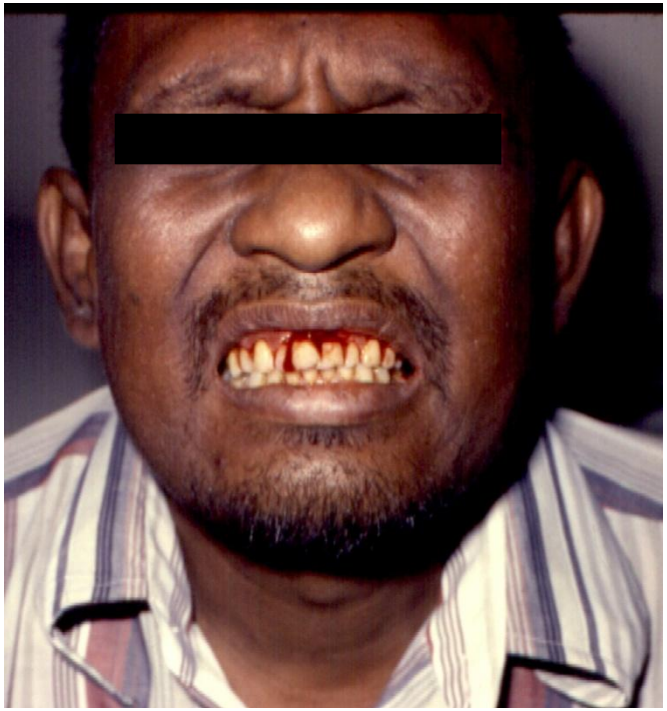
Medication is warfarin (prescribed 3/wk, but she took t.i.d.)

Male 55 yr
with diagnosis of cirrhosis, stable condition
Bleeding per gum

PE: poor oral hygiene

Platelet count 90 $x10^9/L$

APTT	38.2 sec (25-35)
PT	17.0 sec (10-13)



Bleeding tendency in liver diseases I

Thrombocytopenia

- Splenic pooling
- Alcohol & Folate def.
- Thrombopoietin def.
- DIC (with acute complication)

Bleeding tendency in liver diseases II

Coagulation defects

- Synthetic failure: VIII and I preserved
- Hyperfibrinolysis: ⇓ t-PA clearance
- DIC: ⇓ Antithrombin, protein C, S
  - ⇓ activated clotting factors clearance
- Dysfibrinogenemia: Hepatoma

Bleeding tendency in liver diseases

Most common: combination of all

Treatment according to the predominant mechanisms

DIC is often found in cirrhosis with acute complications.

Hyperfibrinolysis

Bleeding unresponsive to transfusion

Bleeding per gum (Fibrinolytic activity in saliva)

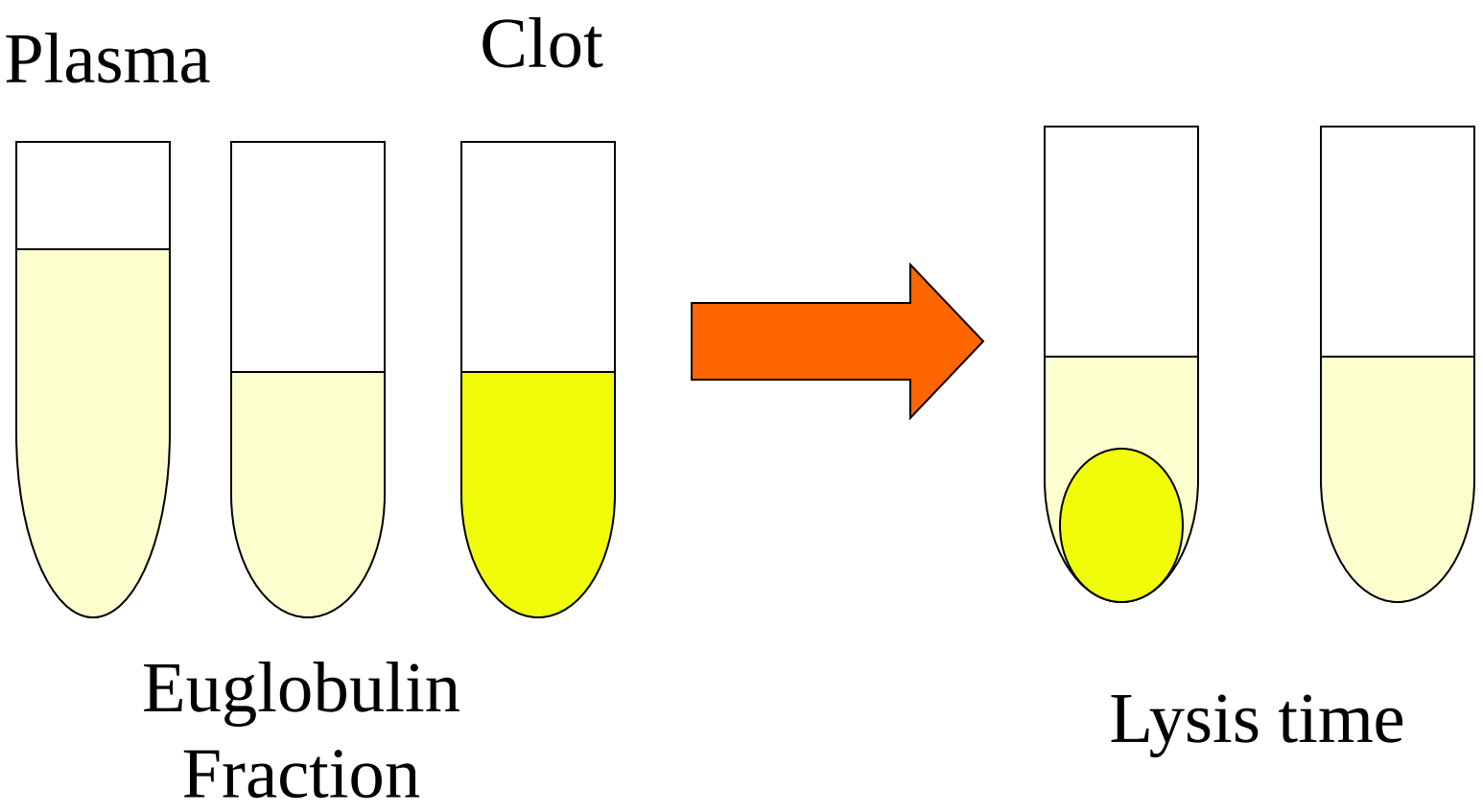
Differential Diagnosis

- Thrombocytopenia and coagulopathy
- Cirrhosis with hyperfibrinolysis
- DIC in acute complications

Euglobulin lysis time (ELT)

- Plasma clot: takes 24 hr to lyse
- Euglobulin fraction of plasma: high fibrinolytic activity
- Euglobulin clot: observe lysis time (Hyperfibrinolysis: lysis within 4 h)

Euglobulin lysis time



Coagulogram

- Fibrinogen 3.3 g/L (1.7-4.0)
- Euglobulin lysis time 85 min (> 240)
- D dimer 800 ng/ml

Tranexamic acid

- Hyperfibrinolysis: Liver, cardiac bypass surgery
- Low thrombin burst: susceptible to fibrinolysis
  - Friable fibrin
  - Low thrombin activatable fibrinolysis inhibitor

Tranexamic acid and oral surgery

- High fibrinolytic acitivity in saliva
- Systemic tranexamic acid: undetectable in saliva
- Mouthwash 5% w/v (1 cap/H_2O 1 ml) 2 minutes q.i.d. for 7 days after surgery

RCT: Tranexamic acid in trauma

Tranexamic acid 1 g q 8h

	Tranexamic acid (n=10 060)	Placebo (n=10 067)	RR (95% CI)	p value (two-sided)
Any cause of death	1463 (14·5%)	1613 (16·0%)	0·91 (0·85–0·97)	0·0035
Bleeding	489 (4·9%)	574 (5·7%)	0·85 (0·76–0·96)	0·0077
Vascular occlusion*	33 (0·3%)	48 (0·5%)	0·69 (0·44–1·07)	0·096
Multiorgan failure	209 (2·1%)	233 (2·3%)	0·90 (0·75–1·08)	0·25
Head injury	603 (6·0%)	621 (6·2%)	0·97 (0·87–1·08)	0·60
Other causes	129 (1·3%)	137 (1·4%)	0·94 (0·74–1·20)	0·63

CRASH-2 trial. Lancet 2010; 376: 23

ผู้ป่วยหญิง อายุ 35 ปี

G2P0A1, GA 38 wk

- แข็งแรงดีมาก่อน ไม่มีเลือดออกง่ายมาก่อน
- มาคลอดบุตรตามปกติ แต่หลังคลอดประมาณ 2 ชั่วโมง มีเลือดออกประมาณ 2 ลิตร จากทาง ช่องคลอด
- PE: BP 90/60 mmHg, HR 120/min
  Multiple skin ecchymoses and bleeding from IV site

ผู้ป่วยหญิง อายุ 35 ปี G2P0A1, GA 38 wk Massive post-partum hemorrhage

- Systemic bleeding disorder?
  - Local and systemic
- Congenital or Acquired?
  - Acquired
- Platelet or Coagulation?
  - Coagulation by clinical

Causes

- Retained product of conception:
  - Check the placenta
- Uterine atony:
  - Check uterine contraction
- Genital tract trauma:
  - PV exam
- Coagulation abnormalities: DIC
  - Coagulogram if available, VCT

Diagnosis of DIC

- Clinical features
  - Cause of DIC
  - Bleeding and/or thrombosis
- Laboratory features
  - Thrombocytopenia
  - Prolonged coagulation time
  - FDP or D-dimer

Treatment of DIC

1. Correction of the underlying diseases

2. Replacement therapy (If bleeding)
   Cryoprecipitate, Platelet, FFP
3. Heparin (if thrombosis)

Conclusions

Diagnosis of bleeding disorders

- History and physical examinations
- Screening coagulogram

- Special laboratory tests

ผู้ป่วยหญิง อายุ 35 ปี G2P0A1, GA 38 wk Massive post-partum hemorrhage

CBC: Hb 7.0 g/dL, WBC 20.6 x 10^9/L, Platelet 12.0 x 10^9/L

PT 70.6/12.8 sec, APTT 60.5/27.4 sec

Disseminated Intravascular Coagulation