Approach to Bleeding disorders

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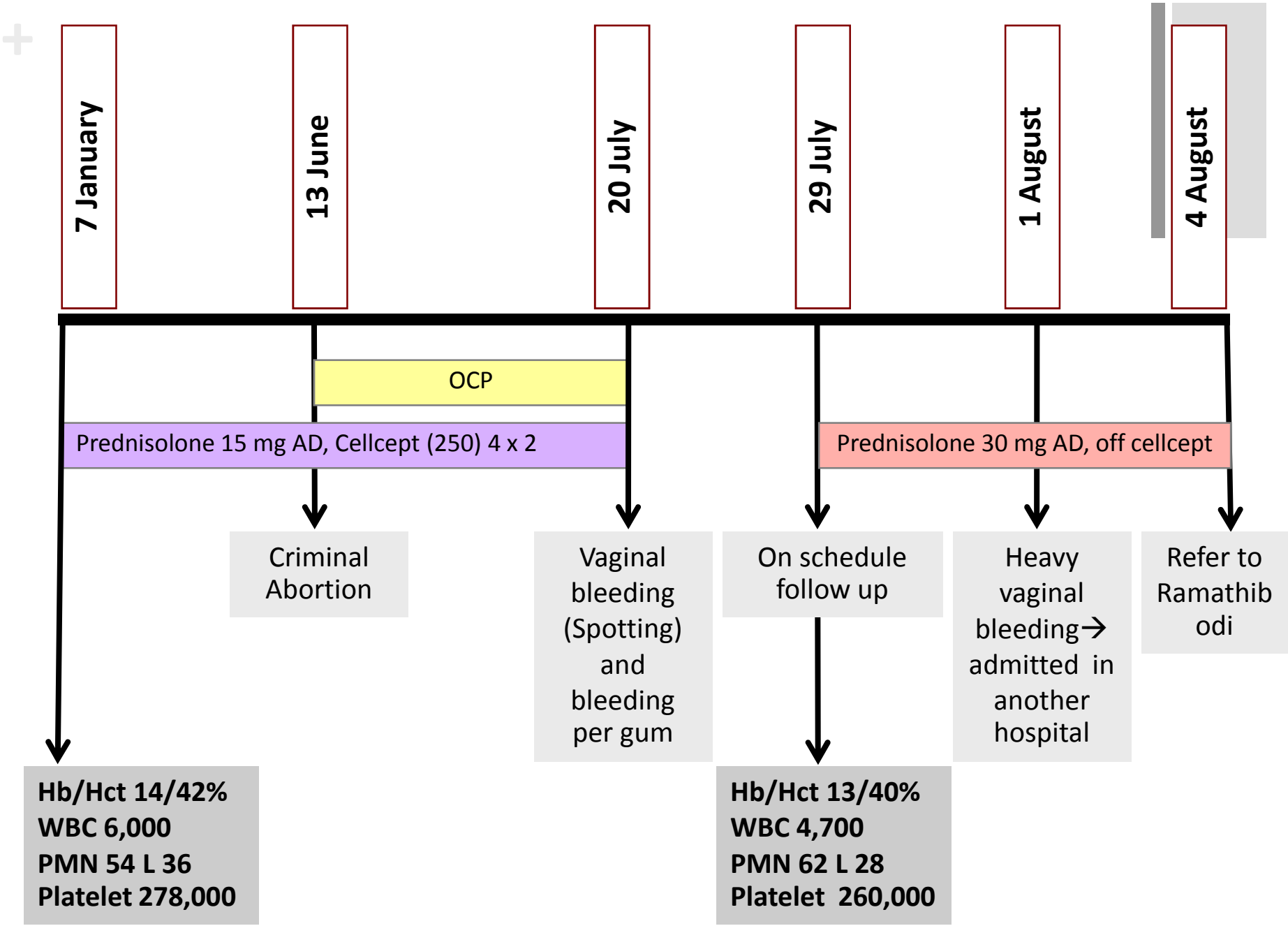
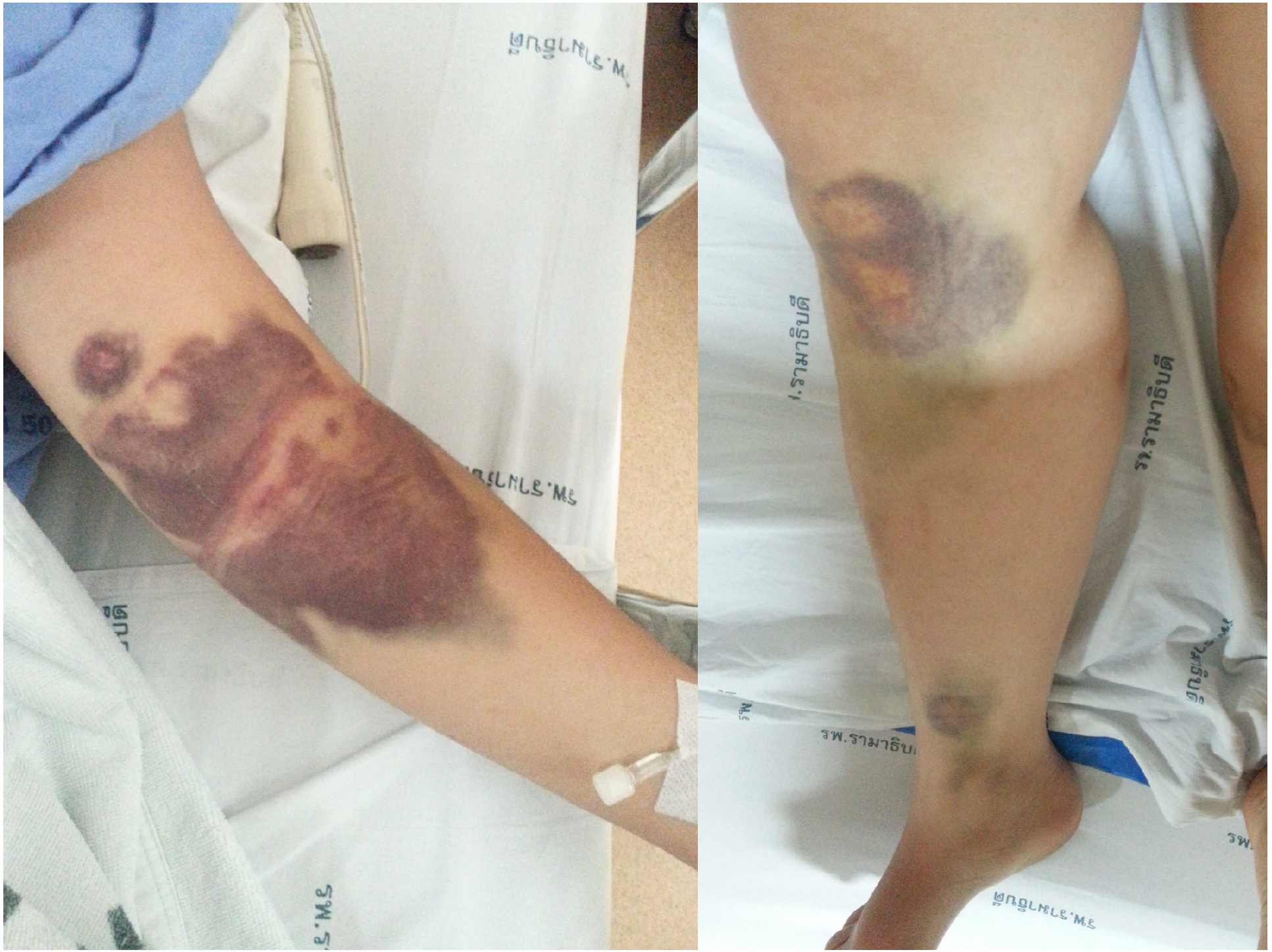
Case 1 : 29 YOF with dermatomyositis, bleeding per vagina

- 6 weeks PTA, underwent criminal abortion (GA ~ 2 months) She continued taking OCP for 1 month
- 4 days PTA she had bleeding per vagina 7-8 pads/day and cramping pain in her lower abdomen.
- She was admitted and found hypotensive which respond to fluid resuscitation. She received blood transfusion


7 January
13 June
20 July
29 July
1 August
4 August
OCP
Prednisolone 15 mg AD, Cellcept (250) 4 x 2
Prednisolone 30 mg AD, off cellcept
Criminal Abortion
Vaginal bleeding (Spotting) and bleeding per gum
On schedule follow up
Heavy vaginal bleeding→ admitted in another hospital
Refer to Ramathib odi
Hb/Hct 14/42%
WBC 6,000
PMN 54 L 36
Platelet 278,000
Hb/Hct 13/40%
WBC 4,700
PMN 62 L 28
Platelet 260,000



Approach bleeding disorder

1) Is the bleeding appropriate?

↓

2) Localized VS Systemic

↓

3) Congenital VS Acquired

↓

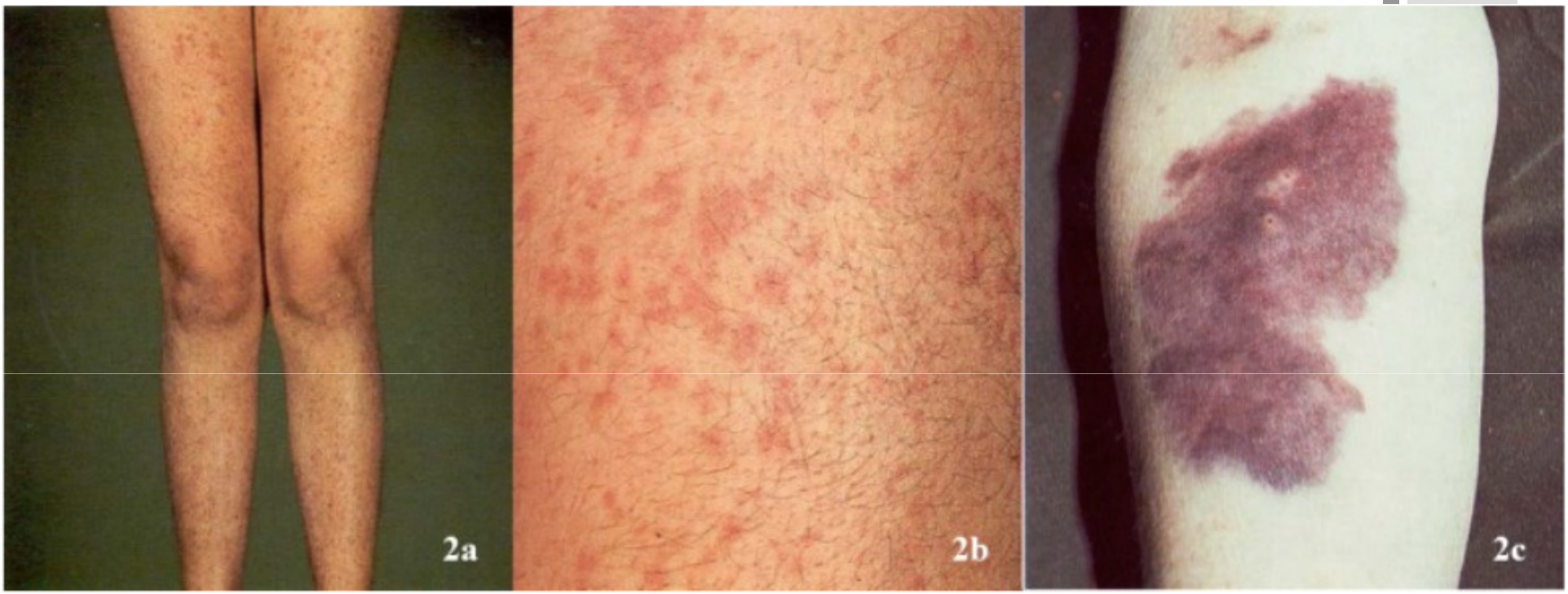
4) Primary VS Secondary hemostasis

↓

5) Medications and other disorder e.g. liver disease, renal failure, paraproteinemia, BM disease

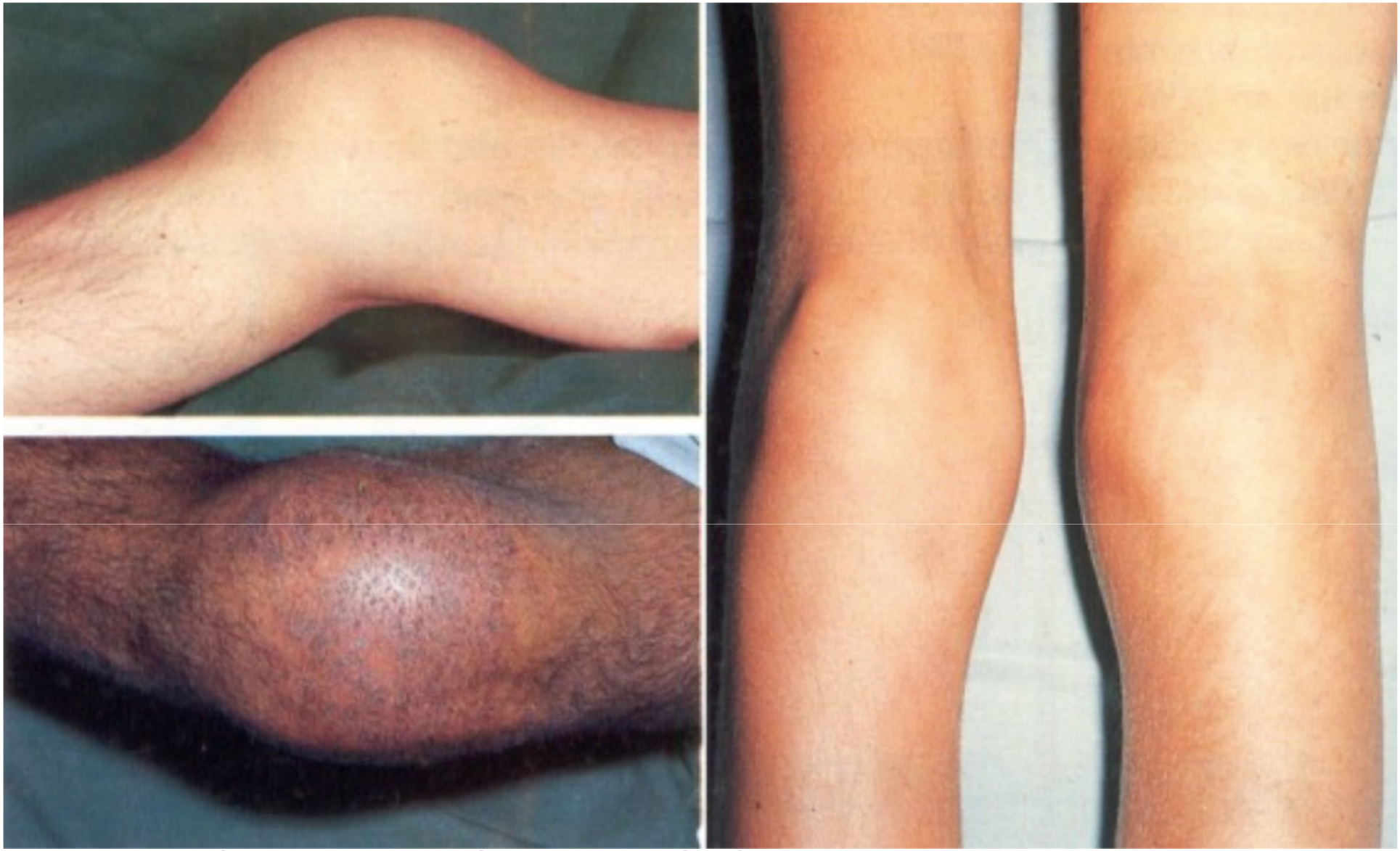
Characteristic clinical features that differentiate primary hemostatic disorders from coagulation disorders

Finding	Primary hemostatic disorder	Coagulation disorder
Petechiae	Characteristic	Rare
Deep/disecting hematoma	Rare	Characteristic
Superficial ecchymoses	Characteristic : small, multiple	Common usually large & solitary
Hemarthrosis	Rare	Characteristic
Delayed bleeding	Rare	Common
Bleeding from superfial cuts & scratches	Persistant ofter profuse	Minimal
Epistaxes	Common	Rare
Menorrhagia	Common	Rare
Sex	Relatively more common in females	80-90% of inherited forms - males
Positive family history	Rare (except vWD)	Common



Petechiae **Purpura** **Large ecchymosis**

J Family Community Med. 2007 May-Aug; 14(2): 53–58.



Hematrosis in hemophilia

J Family Community Med. 2007 May-Aug; 14(2): 53–58.

Investigations

	4 Aug	5 Aug	7 Aug	8 Aug	11 Aug	12 Aug
Hb/Hct	7/22	10/30	11.8/35.2	11.4/36	9/28.9	8.8/26
WBC	7,240	7,700	5,900	12,400	10,010	7,100
Neu	83	63	79	78	80	83
Lym	16	31	19	17	17	11
Platelet	241 K	221 K	198 K	216 K	237 K	241 K
PTT		72.3	72.6	58.4	55.9	54.1
PT		10.9	10.9	11.5	11.7	12.9
TT		9.5				
D-dimer			1021			
Fib			335			

Tests of Hemostatic Function

Basic screening tests

- Complete blood cell count (CBC, platelet count and mean platelet volume)
- Peripheral blood smear
- Bleeding time (BT) or platelet function assay (PFA)
- Prothrombin time (PT)
- Partial thromboplastin time (PTT)
- Plasma clot solubility assay
- Fibrin clot retraction assay

Tests of Hemostatic Function

>> Specific laboratory assays

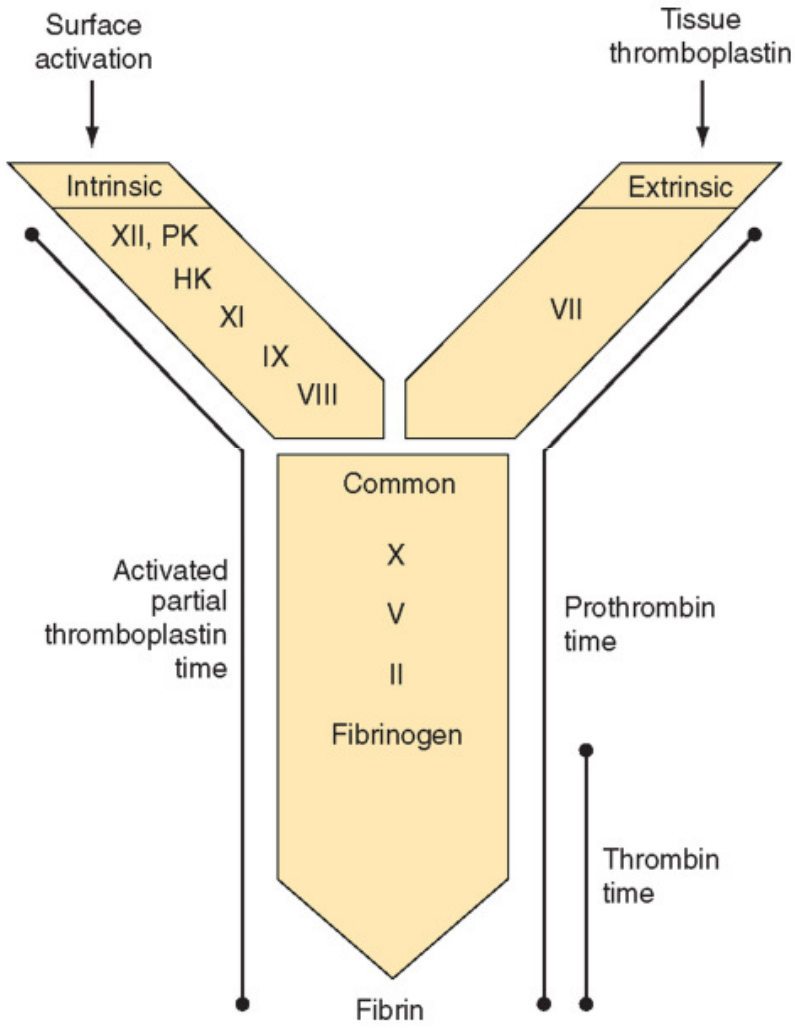
Suspected platelet disorder

- ✓ Platelet aggregation studies
- ✓ BM aspirate and biopsy
- ✓ Platelet-associated immunoglobulin levels
- ✓ EM for platelet morphology

Suspected coagulation factor abnormalities

- ✓ Mixing studies
- ✓ Fibrinogen levels, D-dimer levels
- ✓ Specific clotting factor levels
- ✓ Bethesda assay (for inhibitors)
- ✓ Thrombin time (TT)
- ✓ Reptilase time
- ✓ Euglobulin clot lysis assay
- ✓ Molecular and immunologic fibrinogen assays

Coagulation and tests



Screening tests

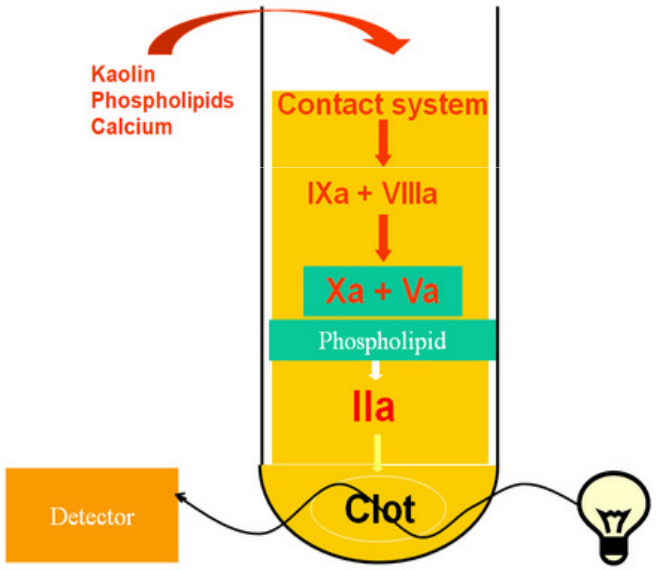
- PTT
- PT
- TT

Additional tests

- Fibrinogen
- Mixing test
- LA
- Factor activity assays
- Inhibitor

Activated partial thromboplastin time (APTT)

Measures the activity of the intrinsic and common pathways of coagulation.



Assay

1. Citrated plasma (platelet poor plasma-PPP)

2. Surface activator e.g. kaolin, silica, ellagic acid

3. Phospholipid e.g cephalin

4. Calcium

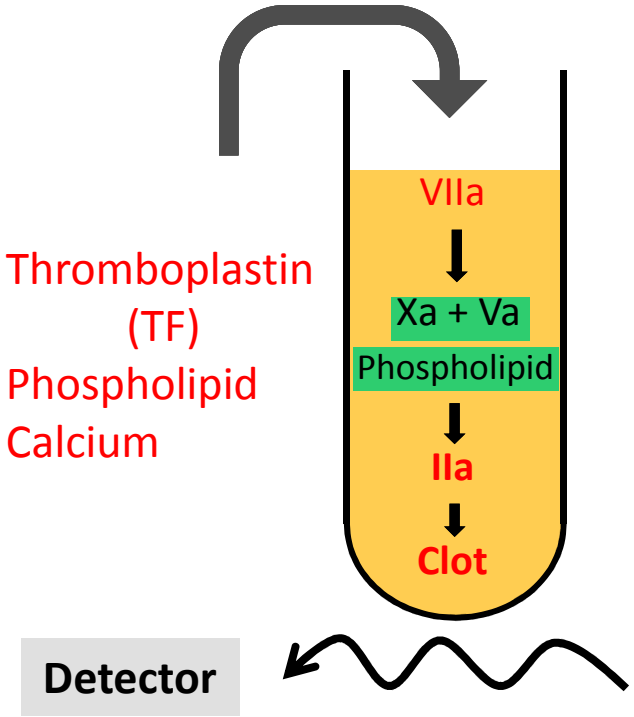
Measure

: Time to fibrin formation

: Detect by clot formation or optical density

Prothrombin time (PT)

Measures the activity of the extrinsic and common pathways of coagulation.



Assay

1. Citrated plasma (platelet poor plasma-PPP)
2. *Thromboplastin (TF)*
3. Phospholipid
4. Calcium

Measure

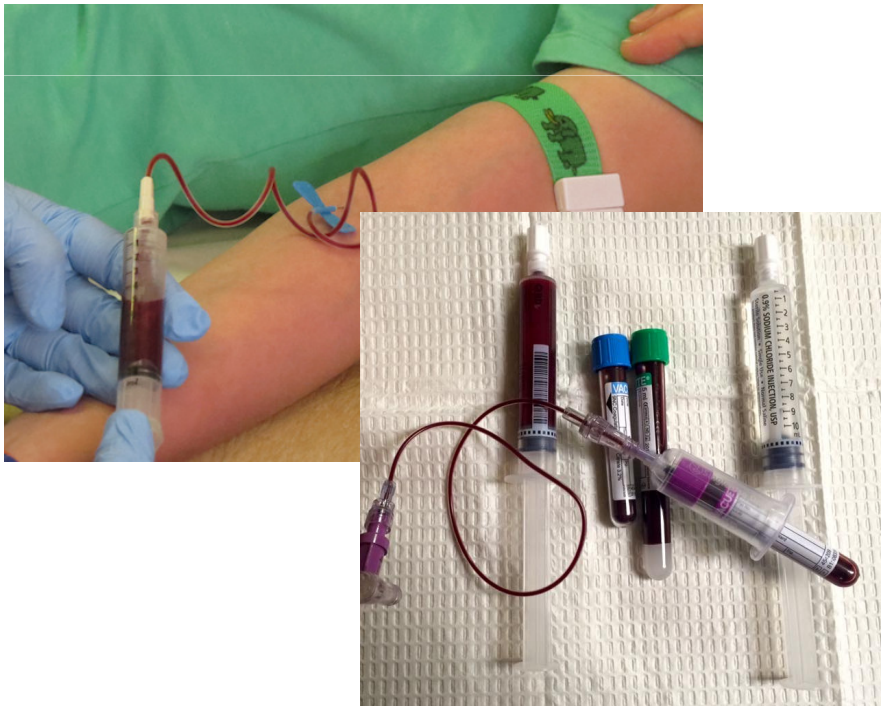
: Time to fibrin formation

: Detect by clot formation or optical density

Abnormal APTT, PT

⇩

Pre-analytical error



Double syringe technique

Abnormal APTT, PT

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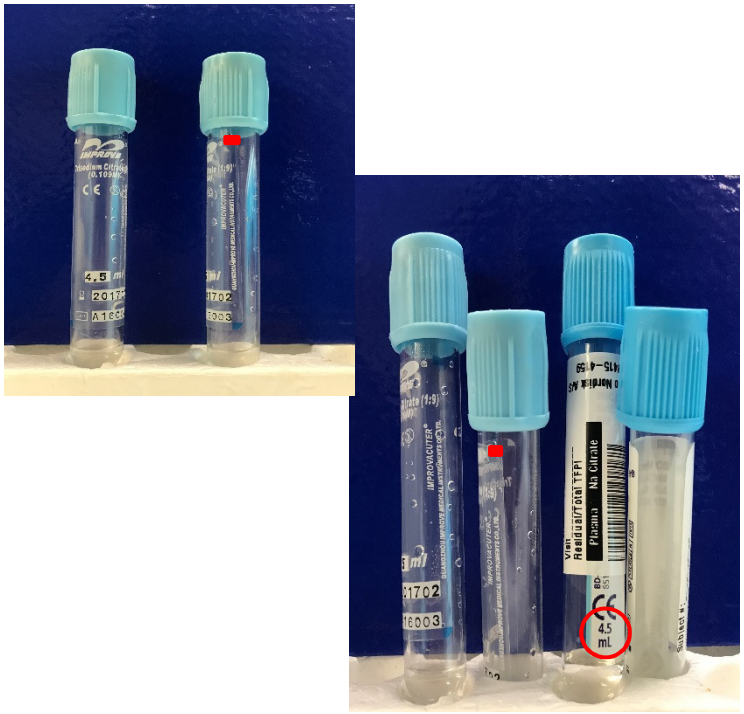
Pre-analytical error



Na Citrate : whole blood ratio
= 1: 9

1. Vacuum tube
2. Patient with high hematocrit

Hematocrit – anticoagulant adjustment

$$C = (1.85 \times 10^{-3})(100\text{-}Hct)(V_{blood})$$

C= volume of citrate remaining in the tube, V = volume of blood added

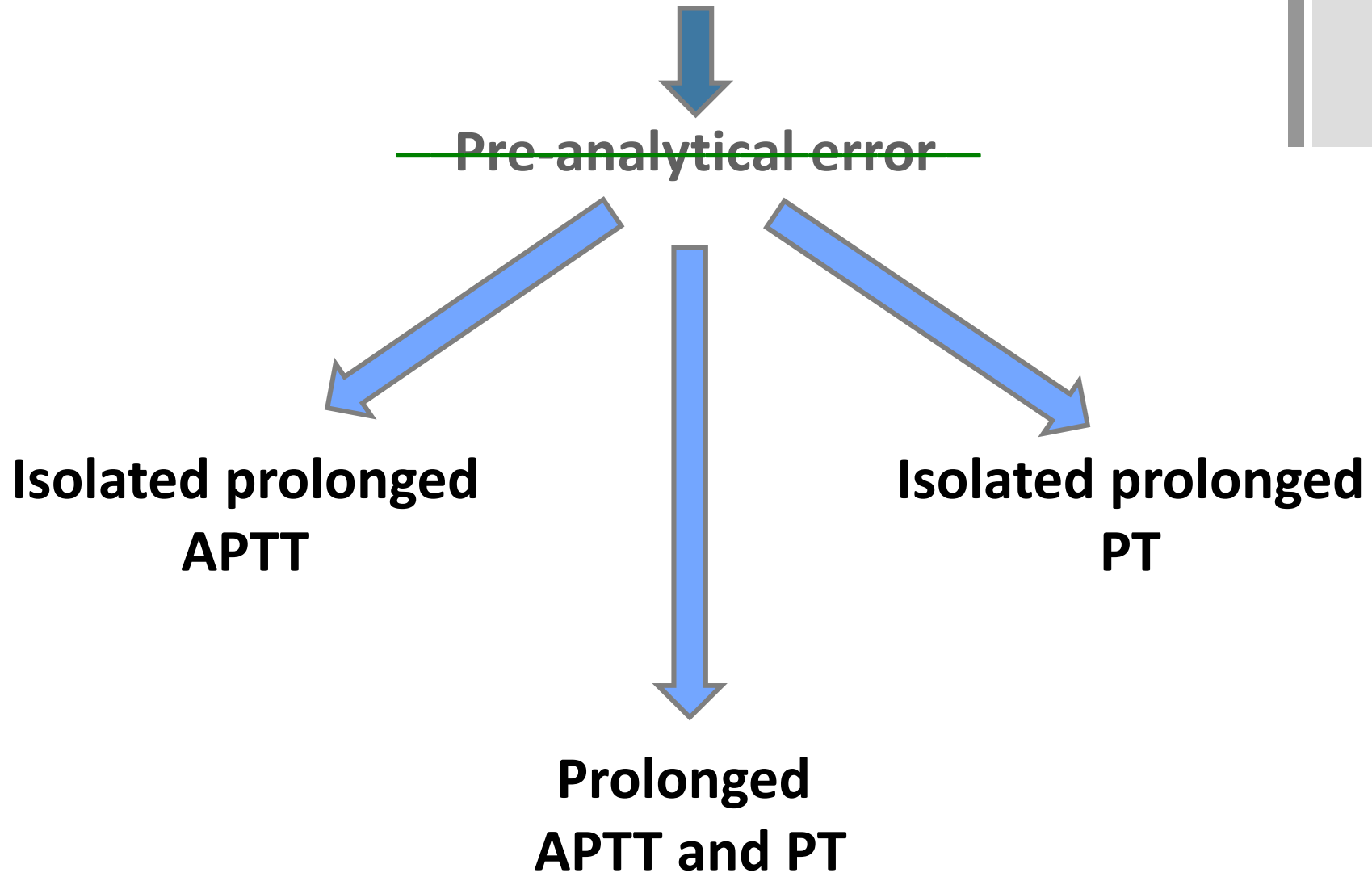
Correction Chart — 4.5 mL tube		
HCT	Citrate Volume Needed	mL To Remove
57	0.36	0.14
60	0.33	0.17
63	0.31	0.19
66	0.28	0.22
69	0.26	0.24
71	0.24	0.26
74	0.22	0.28
77	0.29	0.31

5 ml tube

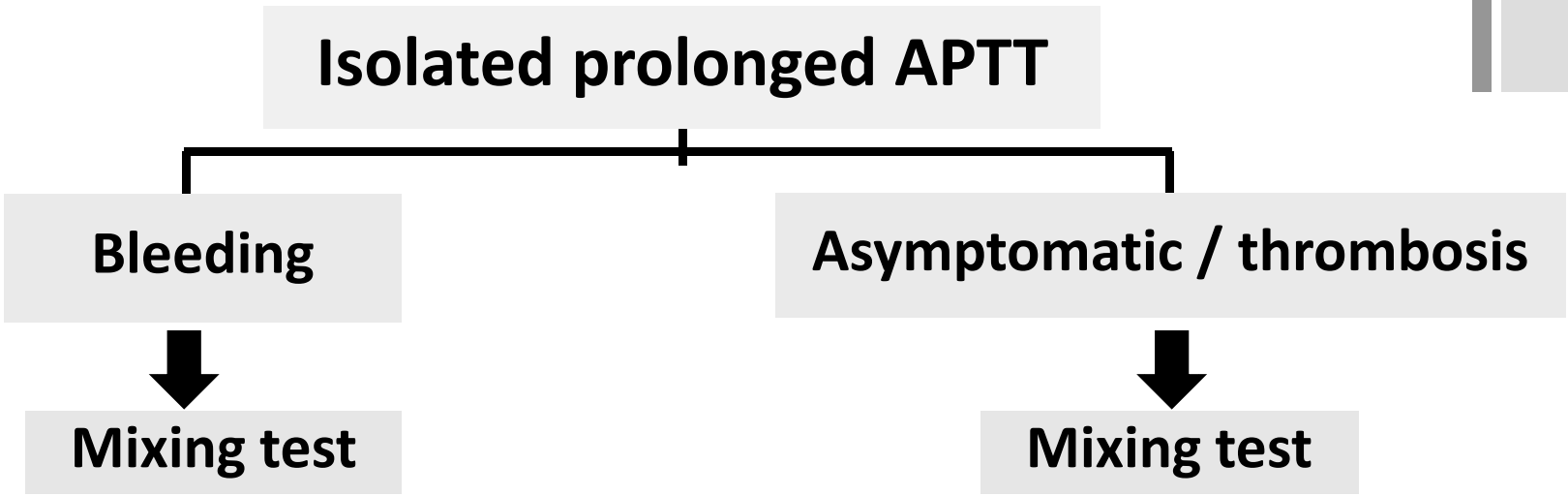
Correction Chart — 2.7 mL tube		
HCT	Citrate Volume Needed	mL To Remove
57	0.21	0.09
60	0.20	0.10
63	0.18	0.12
66	0.17	0.13
69	0.15	0.15
71	0.14	0.16
74	0.13	0.17
77	0.11	0.19

3 ml tube

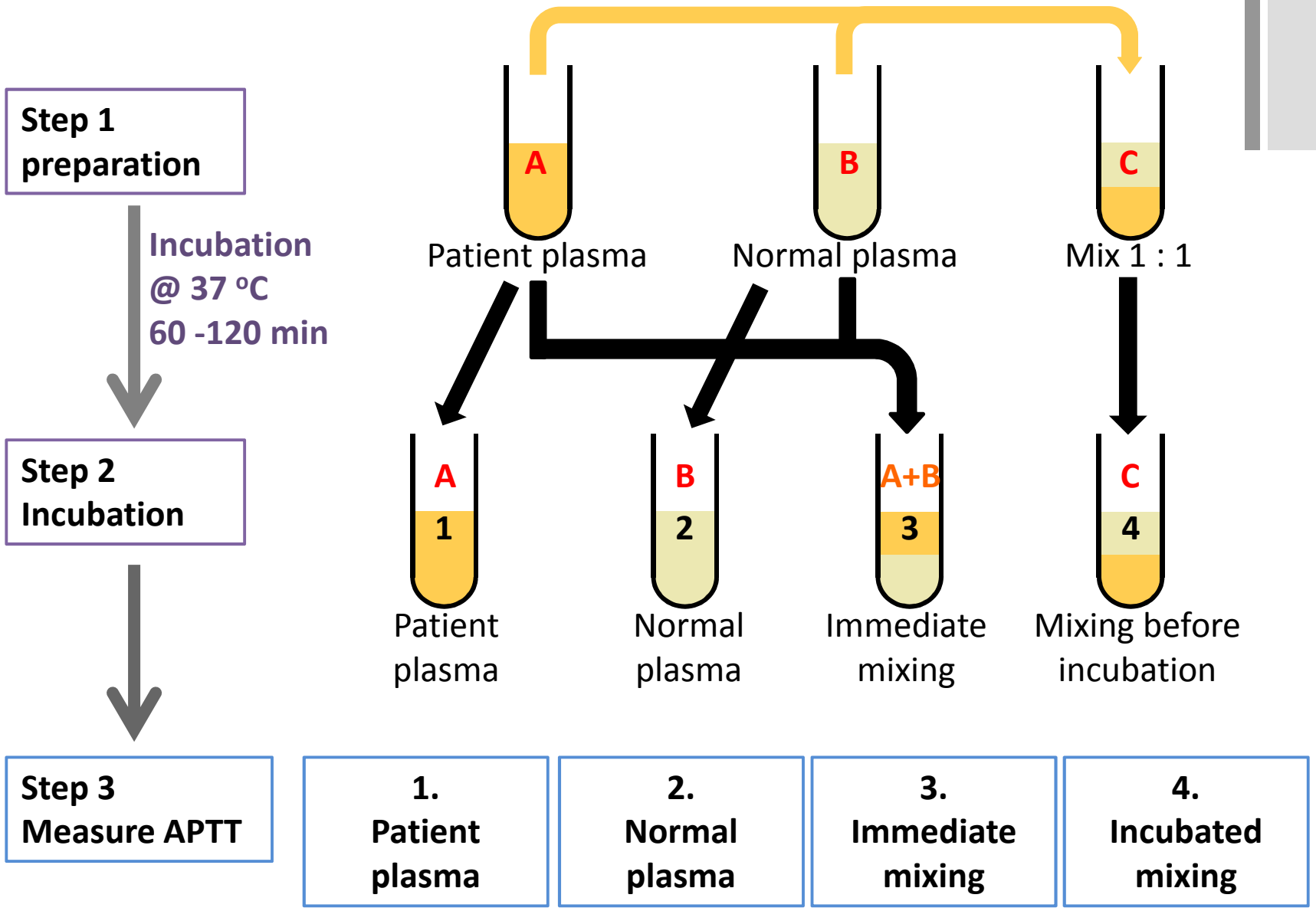
Abnormal APTT, PT



Etiology of isolated prolonged APTT



Classical 1 : 1 mixing test for APTT



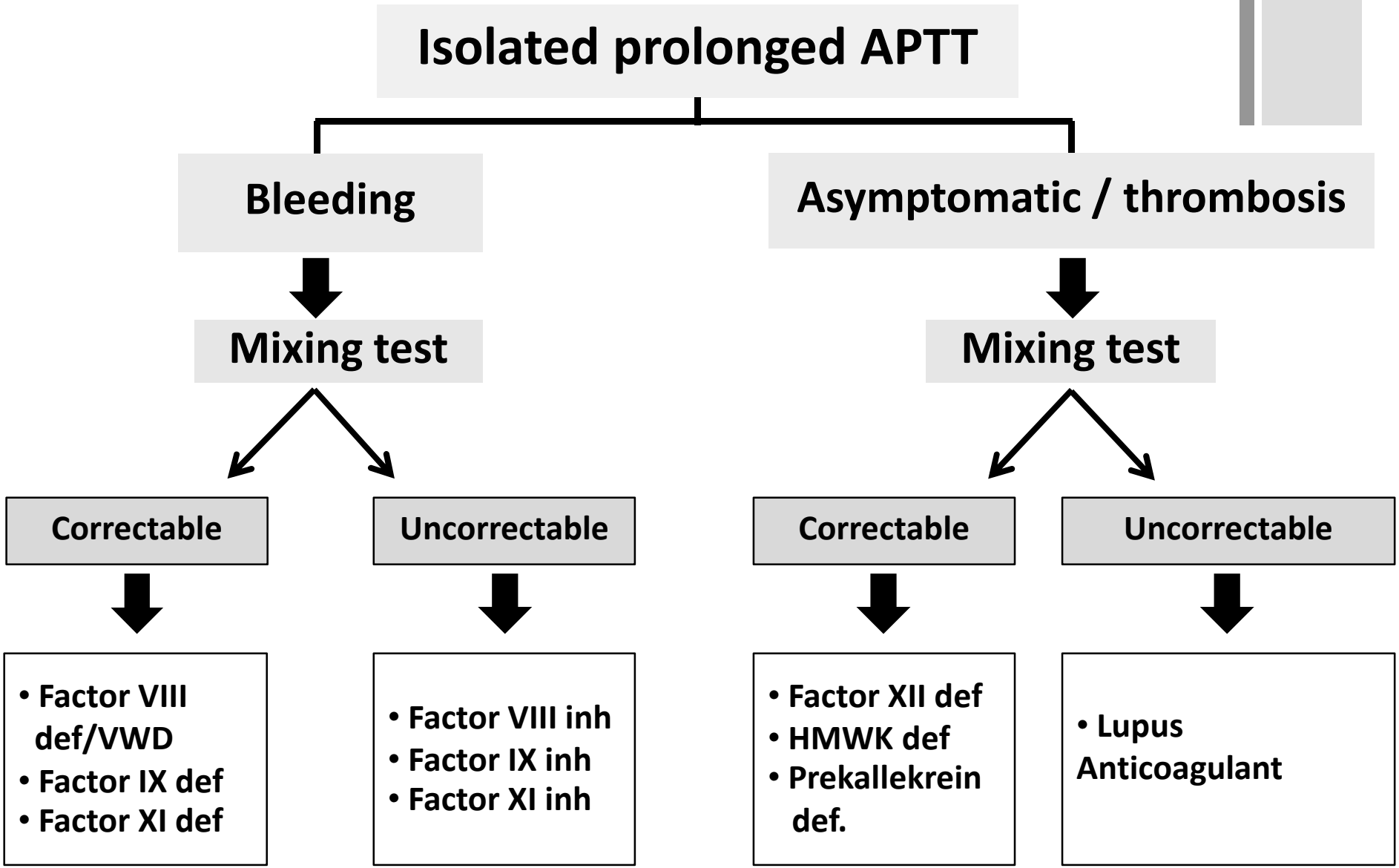
Mixing test for APTT

Distinguish between

- Clotting factor deficiency
- Inhibitor: if the mixture fails to correct the APTT within 3-4s e.g. FVIII inhibitor, lupus anticoagulant

Immediate	Incubated	Suggested
✓	✓	Factor deficiency
✓	✗	Factor inhibitor
✗	✗	Lupus anticoagulant

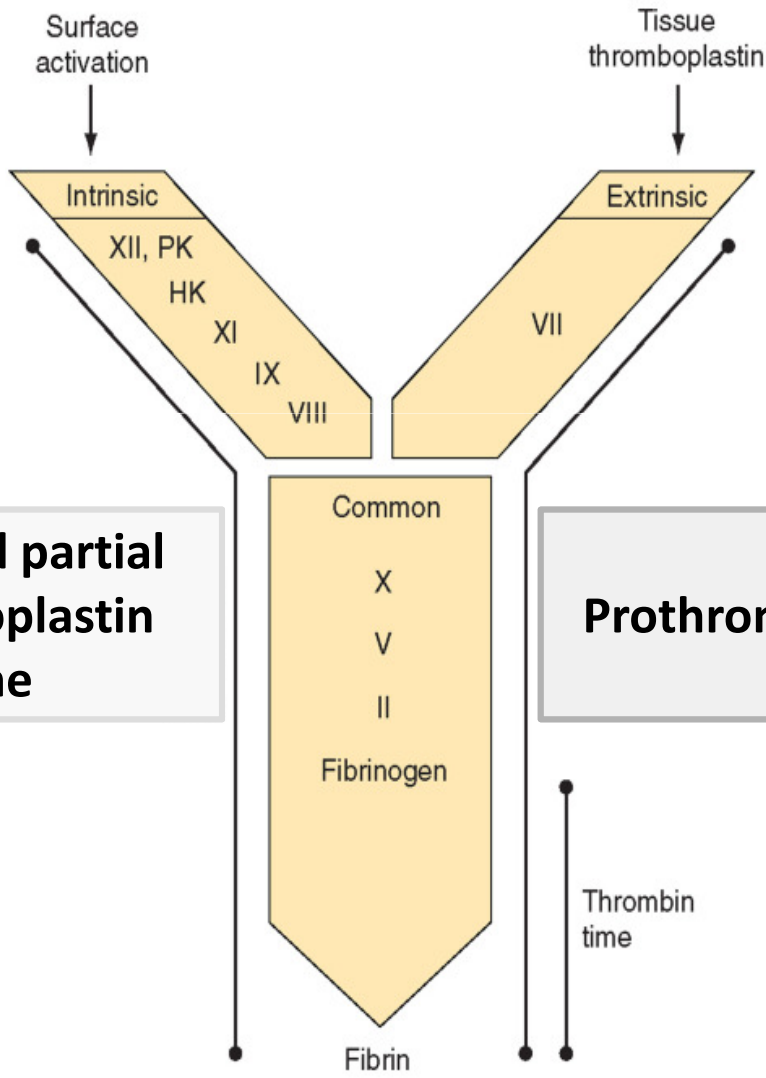
Etiology of isolated prolonged APTT



Etiology of prolonged PT

- Factor VII (rare) deficiency
- Mild vitamin K deficiency
- Mild liver insufficiency
- Low dose vitamin K antogonists

Etiology of *prolonged aPTT and PT*



Activated partial thromboplastin time

Prothrombin time

Etiology of *prolonged aPTT and PT*

Multiple factors deficiency

- Vitamin K deficiency
- Vitamin K antagonist
  : Warfarin
- Severe liver disease

Common

Factor (common pathway) deficiency

- Congenital factor II, V, X deficiency
- Acquired FX deficiency in amyloidosis
- Acquired FII deficiency (LA)

Rare

Fibrinogen abnormality

- Hypofibrinogenemia
- Dysfibrinogenemia

Inhibitors

- Heparin
- Direct thrombin inhibitor

Interfere fibrin polymerization

- Paraproteinemia : MM, WM
- Fibrin split products (high)

Mixing test aPTT : result

- APTT (Patient) 75.5 sec
- APTT (Normal control) 26 sec
- APTT (after mixing) 31 sec
- APTT (after incubate) 46 sec

>> Delayed partial correction

- Factor VIII activity : 1%
- Factor VIII inhibitor 19 BU

“Factor VIII inhibitor : acquired hemophilia A”

Management of acquired hemophilia : Principle

- Early and rapid diagnosis
- Avoid iatrogenic induced bleeds
  - No invasive procedure unless essential
- Control bleeding
  - Bypassing agents
- Eradicate inhibitor
  - Immunosuppression

Inhibitor eradication in AHA

The optimal immunosuppressive regimen in AHA is unknown

- Most common regimens
  - Steroid
  - Steroid and cyclophosphamide
  - Rituximab based regimen

- Outcome is a balance between
  - Inhibitor eradication
  - Adverse effects
  - Risk of relapse

Treatment of bleeding : principles

- Many bleeds do not need treatment
  - 20 – 30%
  - NB thrombotic risk of agents
- If a bleed needs treating start early
- Options
  - Bypassing agents : rFVIIa, FEIBA
  - Raising FVIII : FVIII, DDAVP

Haemostatic response (bleeds resolved)		
– rFVIIa	90%	
– FEIBA	95%	
– FVIII/DDAVP	71%	EACH2 trial

Case 2 : 34 YOF, preg G2P1 GA 30 weeks

Thrombocytopenia

BP 145/94 mmHg, PR 98 BPM, Temp 37 ^{o}C

CBC : Hb/Hct 9.1/26.7, MCV 83 fL

WBC 12,000 PMN 85 % L 10%

Platelet count 5 k/uL

Thrombocytopenia in pregnancy

- Gestational thrombocytopenia
- Immune thrombocytopenia
- Preeclampsia and HELLP syndrome
- TTP/HUS
- DIC

Gestational thrombocytopenia (GT 70%)

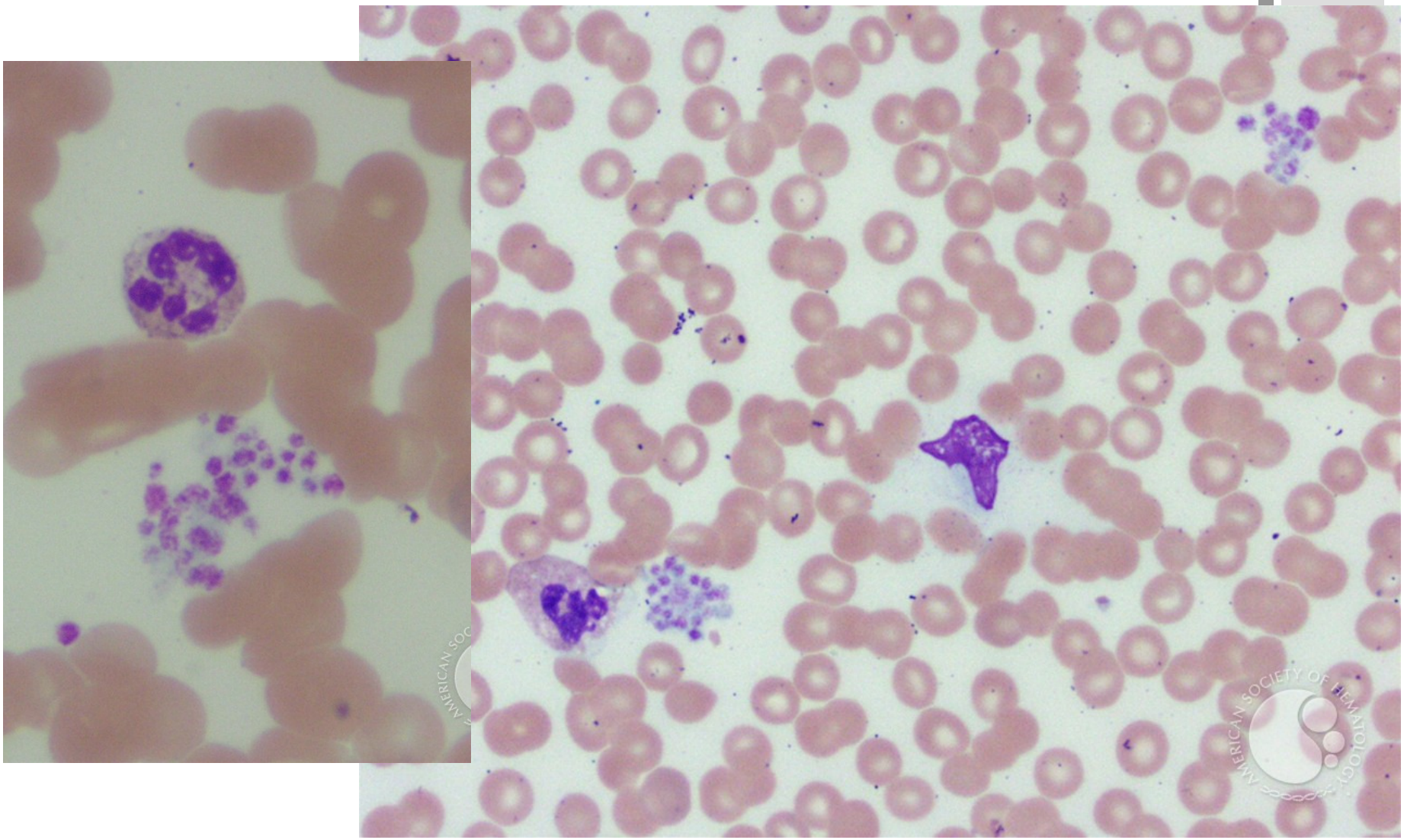
- Second to third trimesters
- Count < 70 k/uL : suspisious of alternative Dx
- Dx by exclusion
- Spontaneuos recovery within 1-2 months after delivery

ITP

- 1-2 per 1000 pregnancies
- May develop at any times during pregnancy
- 2/3 cases are in pt with preexisting ITP

ASH | Image Bank

Pseudothrombocytopenia



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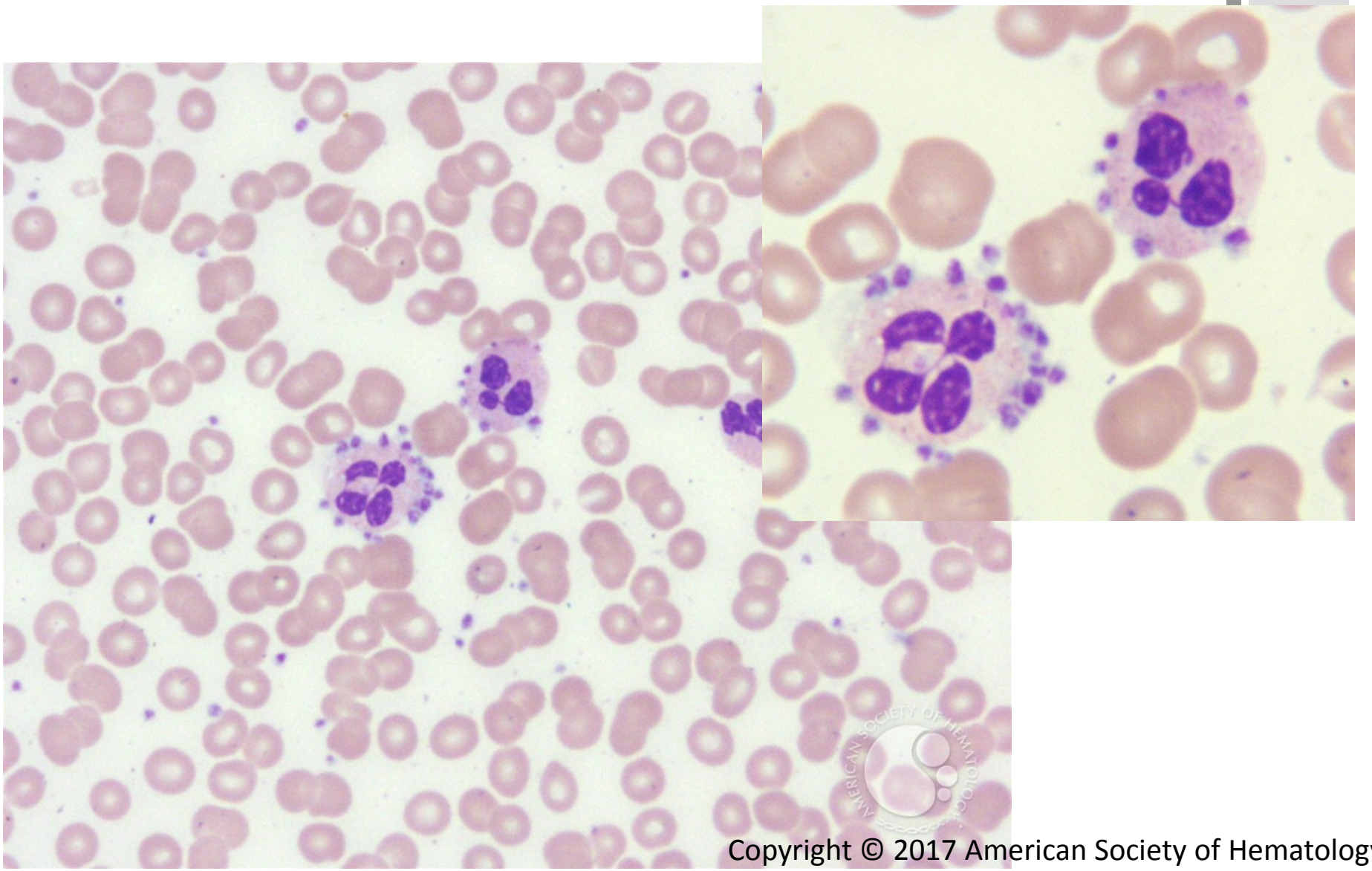
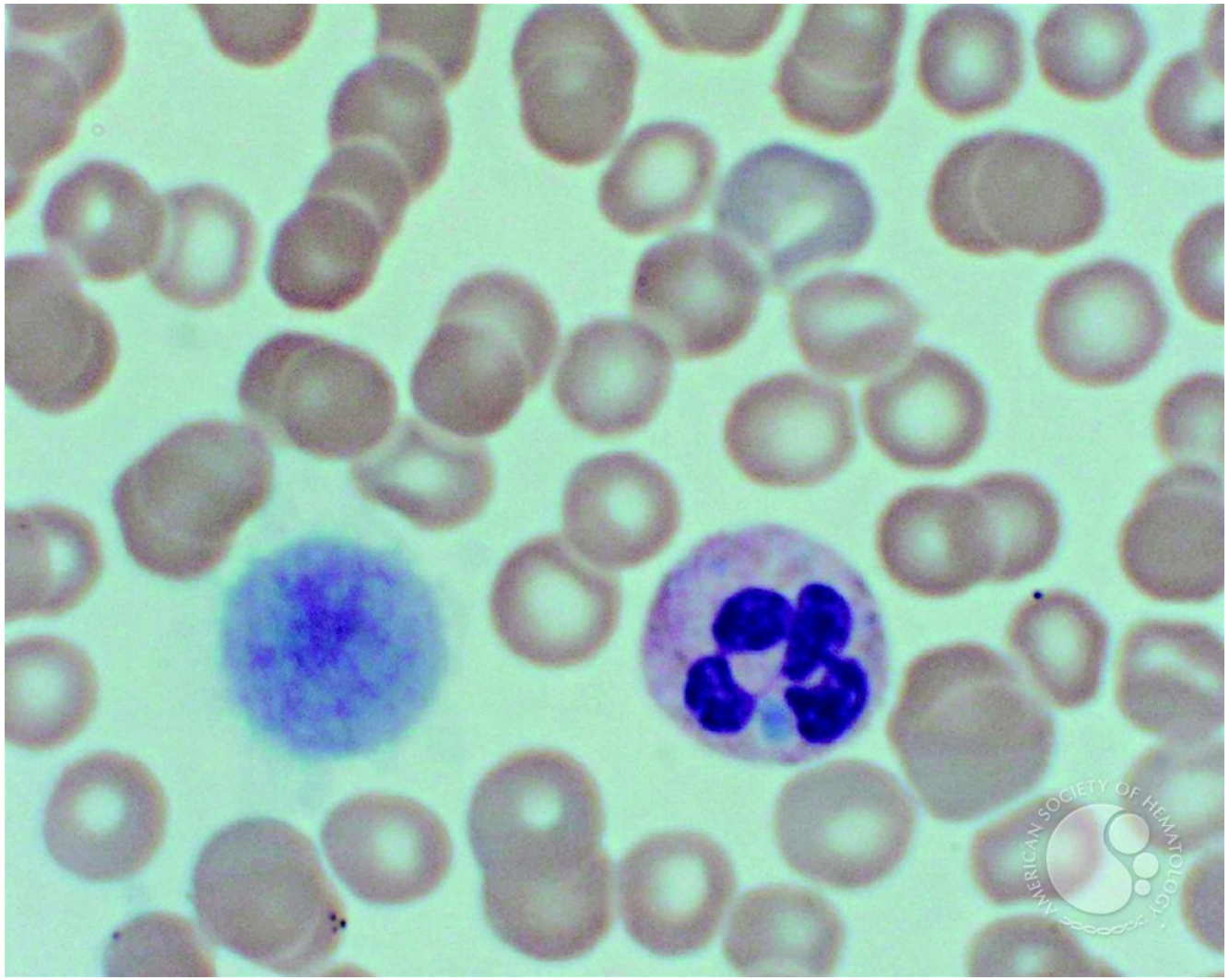
Platelet satellitism



Giant platelet in the May-Hegglin Anomaly



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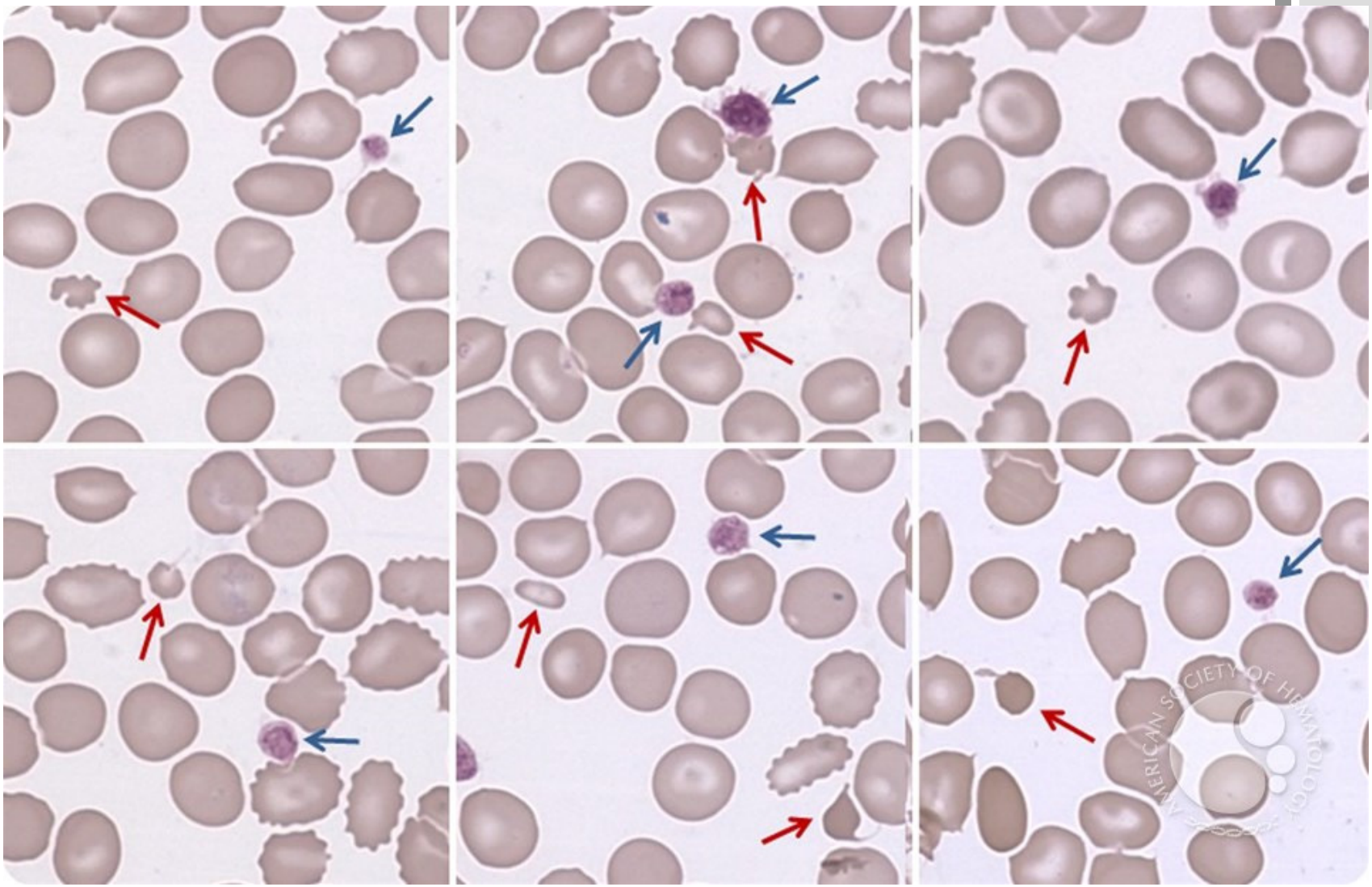
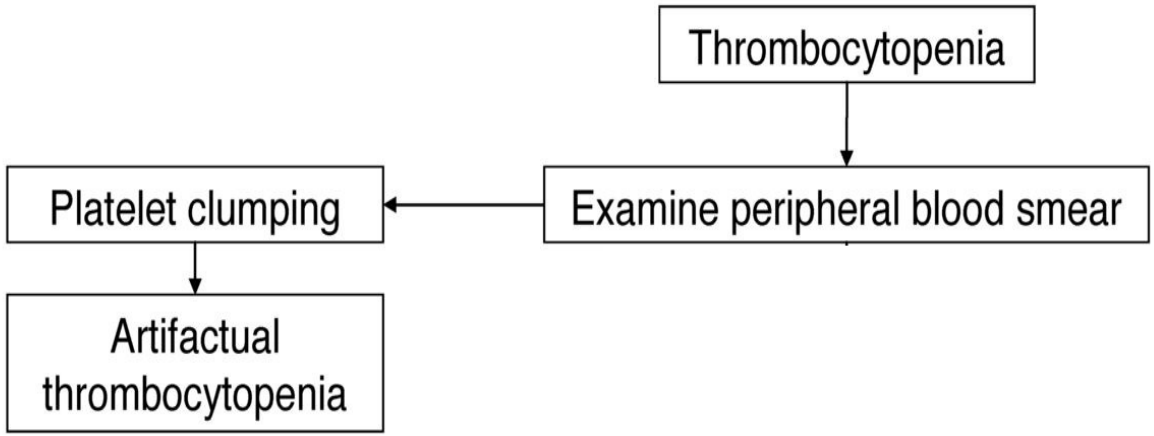
Small red blood cells mimicking platelets

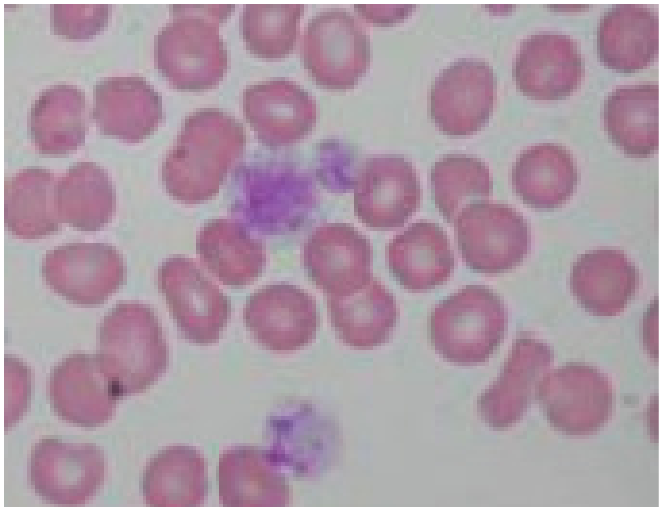


Morphologic aspects relevance to the diagnosis of thrombocytopenia

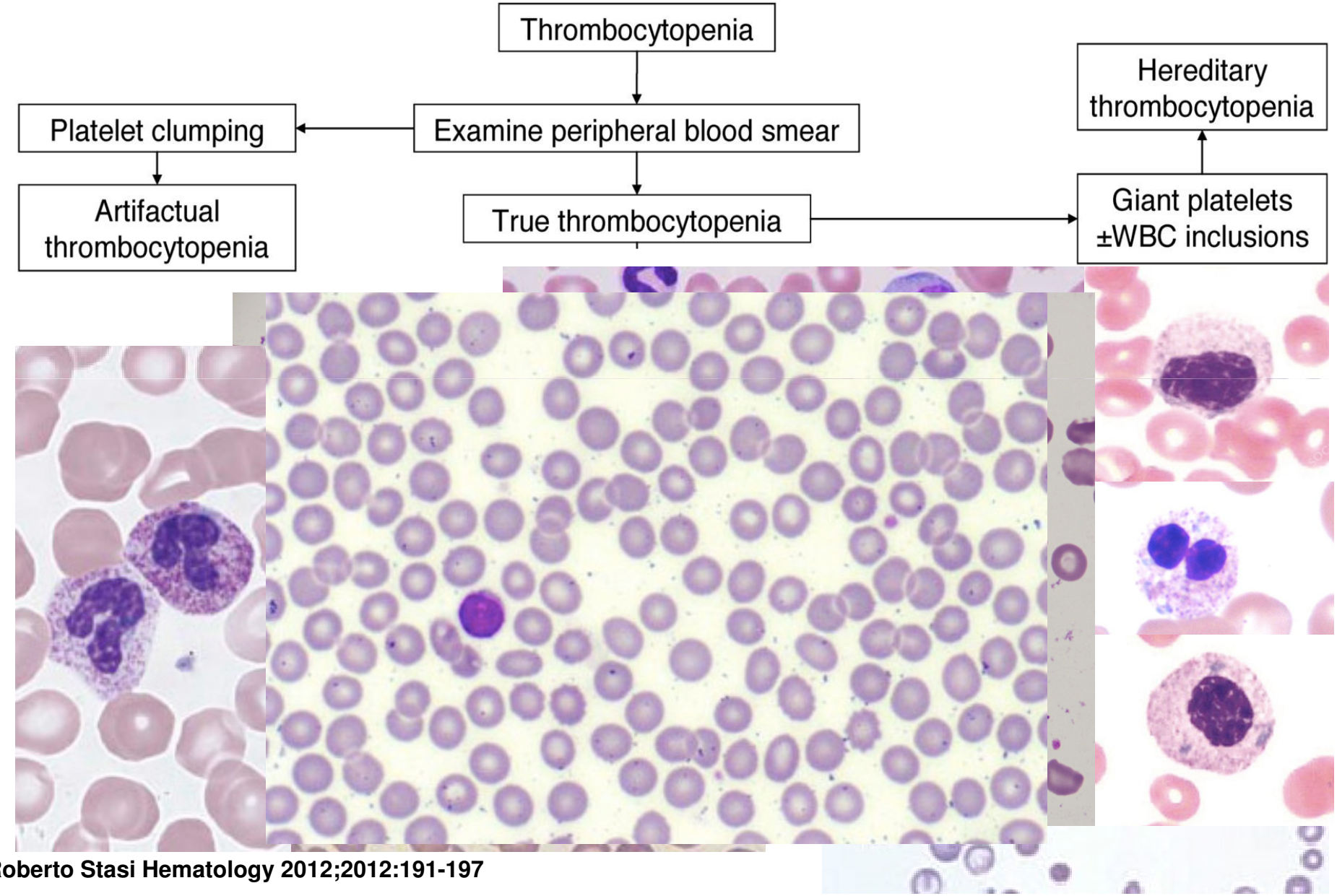


Platelet

- Platelet size and granularity
  - large platelets > hereditary macrothrombocytopenia



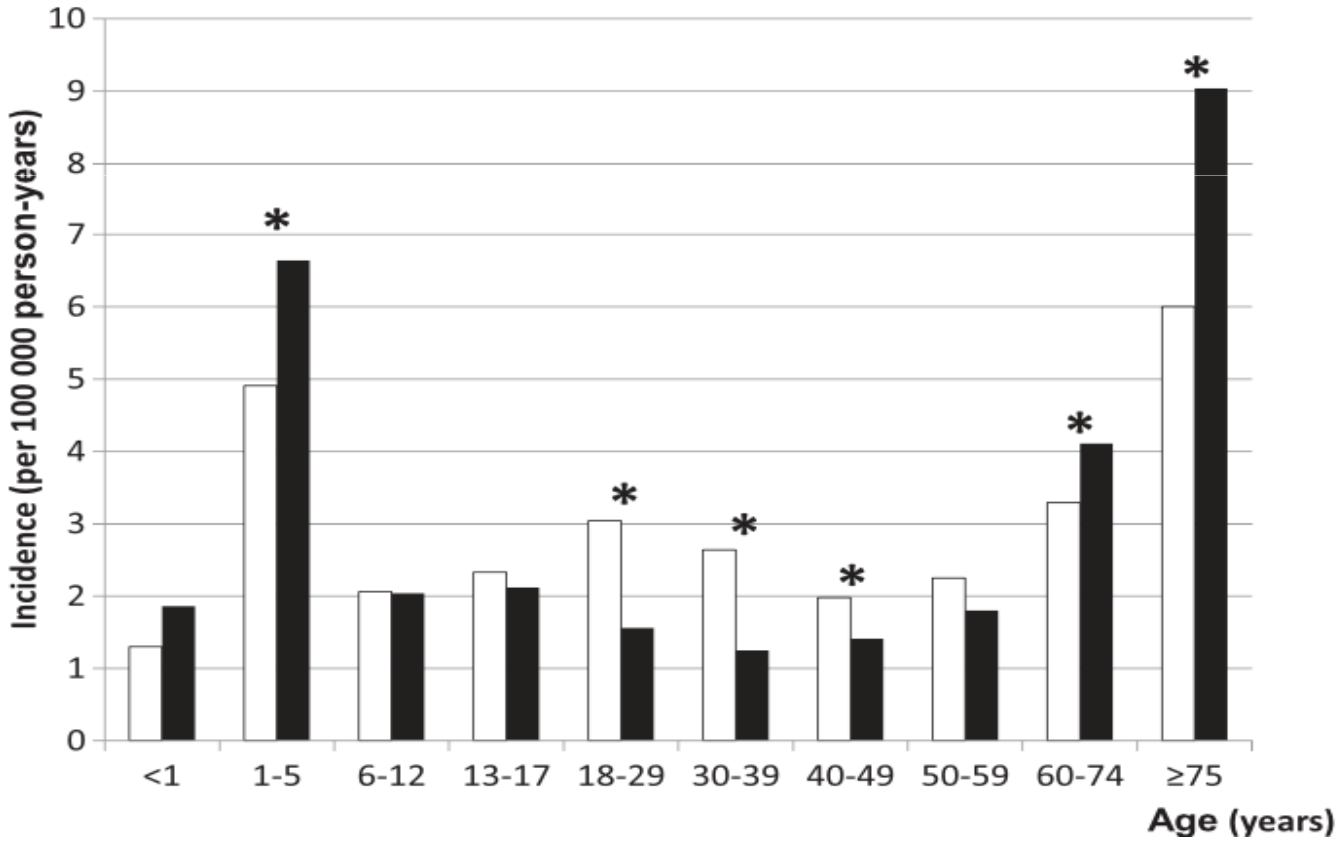
Approach to thrombocytopenia



Roberto Stasi Hematology 2012;2012:191-197

Immune thrombocytopenia

- In children, ITP presents acutely and resolves within several weeks even in the absence of intervention.
- Adult ITP



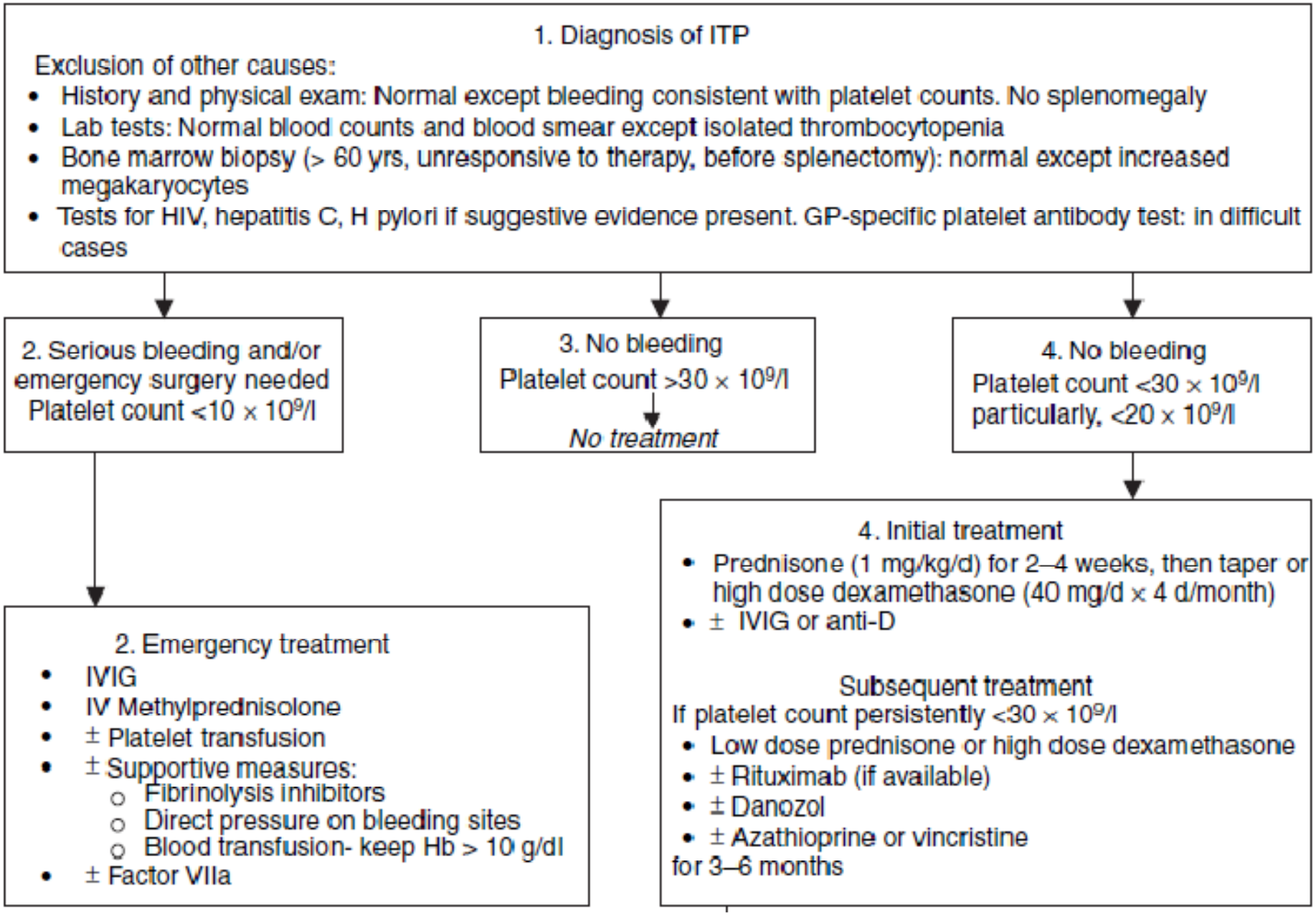
BLOOD 2014

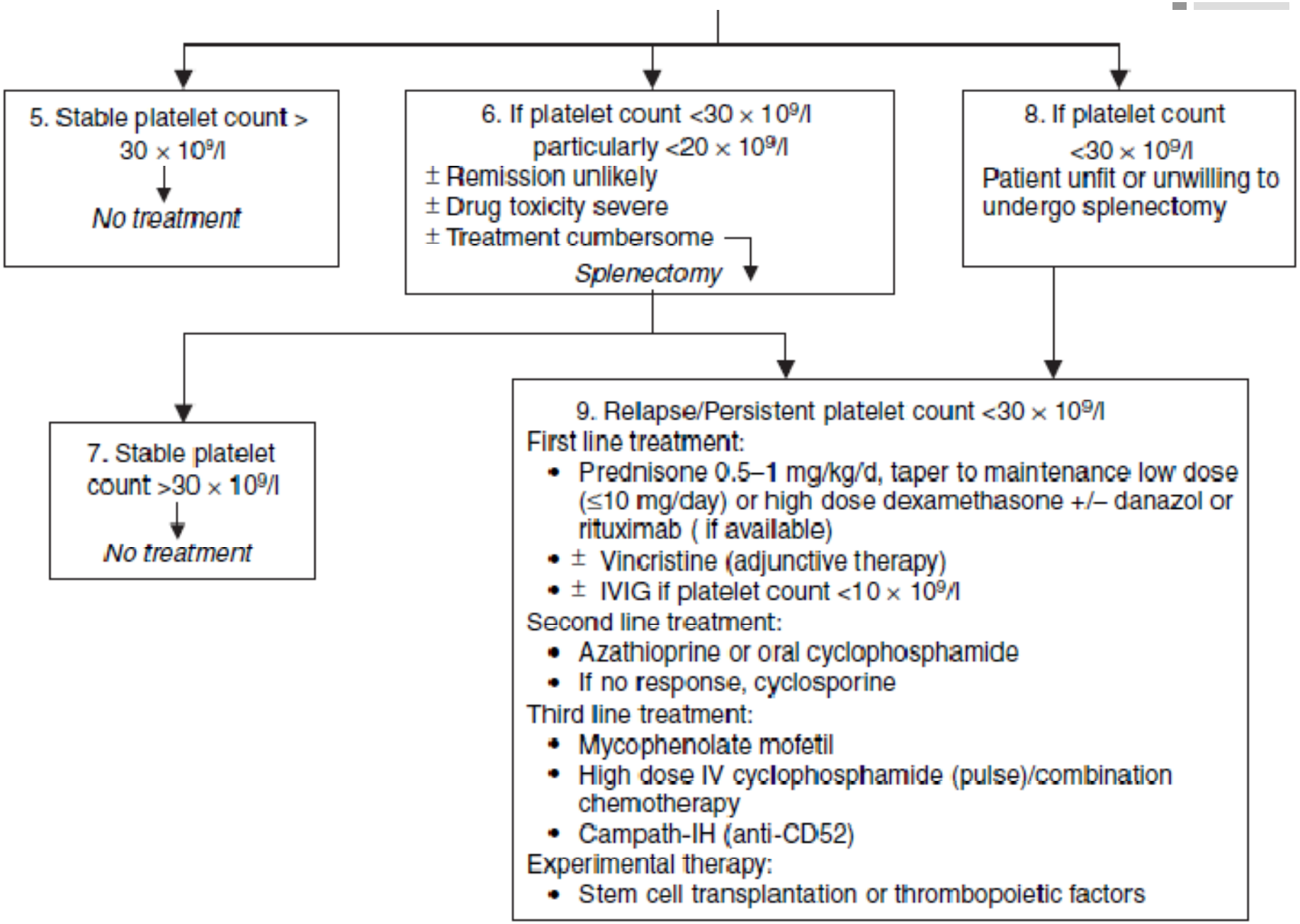
Pathogenesis of ITP

- Increased platelet destruction
  - AutoAbs bind to platelet antigen
  - Ab-coated platelets are opsonized and premature destroyed by macrophages
- Impaired platelet production
  - AutoAbs may bind to Ag on megakaryocytes and their precursors
  - Megakaryocytes in chronic ITP patients may have abnormalities that lead to apoptosis cell death

Secondary ITP

- Antiphospholipid syndrome
- Autoimmune thrombocytopenia (eg, Evans syndrome)
- Common variable immune deficiency
- Drug administration side effect
- Infection with cytomegalovirus, *Helicobacter pylori*, hepatitis C, human immunodeficiency virus, varicella zoster
- Lymphoproliferative disorders
- Bone marrow transplantation side effect
- Vaccination side effect
- Systemic lupus erythematosus


1. Diagnosis of ITP
Exclusion of other causes:
• History and physical exam: Normal except bleeding consistent with platelet counts. No splenomegaly
• Lab tests: Normal blood counts and blood smear except isolated thrombocytopenia
• Bone marrow biopsy (> 60 yrs, unresponsive to therapy, before splenectomy): normal except increased megakaryocytes
• Tests for HIV, hepatitis C, H pylori if suggestive evidence present. GP-specific platelet antibody test: in difficult cases
2. Serious bleeding and/or emergency surgery needed
Platelet count <10 × 10⁹/l
3. No bleeding
Platelet count >30 × 10⁹/l
No treatment
4. No bleeding
Platelet count <30 × 10⁹/l
particularly, <20 × 10⁹/l
2. Emergency treatment
• IVIG
• IV Methylprednisolone
• ± Platelet transfusion
• ± Supportive measures:
○ Fibrinolysis inhibitors
○ Direct pressure on bleeding sites
○ Blood transfusion- keep Hb > 10 g/dl
• ± Factor VIIa
4. Initial treatment
• Prednisone (1 mg/kg/d) for 2–4 weeks, then taper or high dose dexamethasone (40 mg/d × 4 d/month)
• ± IVIG or anti-D
Subsequent treatment
If platelet count persistently <30 × 10⁹/l
• Low dose prednisone or high dose dexamethasone
• ± Rituximab (if available)
• ± Danozol
• ± Azathioprine or vincristine
for 3–6 months


5. Stable platelet count > 30 × 10⁹/l
No treatment
6. If platelet count <30 × 10⁹/l particularly <20 × 10⁹/l
± Remission unlikely
± Drug toxicity severe
± Treatment cumbersome
Splenectomy
8. If platelet count <30 × 10⁹/l
Patient unfit or unwilling to undergo splenectomy
7. Stable platelet count >30 × 10⁹/l
No treatment
9. Relapse/Persistent platelet count <30 × 10⁹/l
First line treatment:
• Prednisone 0.5–1 mg/kg/d, taper to maintenance low dose (≤10 mg/day) or high dose dexamethasone +/– danazol or rituximab (if available)
• ± Vincristine (adjunctive therapy)
• ± IVIG if platelet count <10 × 10⁹/l
Second line treatment:
• Azathioprine or oral cyclophosphamide
• If no response, cyclosporine
Third line treatment:
• Mycophenolate mofetil
• High dose IV cyclophosphamide (pulse)/combination chemotherapy
• Campath-IH (anti-CD52)
Experimental therapy:
• Stem cell transplantation or thrombopoietic factors

First-line treatment options for immune thrombocytopenia (ITP)

Agent	Typical dosing	Time to response
Prednis(ol)one	0.5–2 mg kg^{-1} day^{-1} × 2–4 weeks followed by slow taper	Several days to several weeks
Methylprednisolone	30 mg kg^{-1} day^{-1} × 7 days	2–7 days
Dexamethasone	40 mg day^{-1} for 4 days every 2–4 weeks for 1–4 cycles	Several days to several weeks
IVIG	0.4 g kg^{-1} day^{-1} × 5 days or 1 g kg^{-1} day^{-1} × 1–2 days	1–4 days
Anti-Rh(D)	50–75 μ kg^{-1}	1–5 days

IVIG, intravenous immune globulin G.

ISTH 2012

Second-line treatment options for immune thrombocytopenia (ITP)

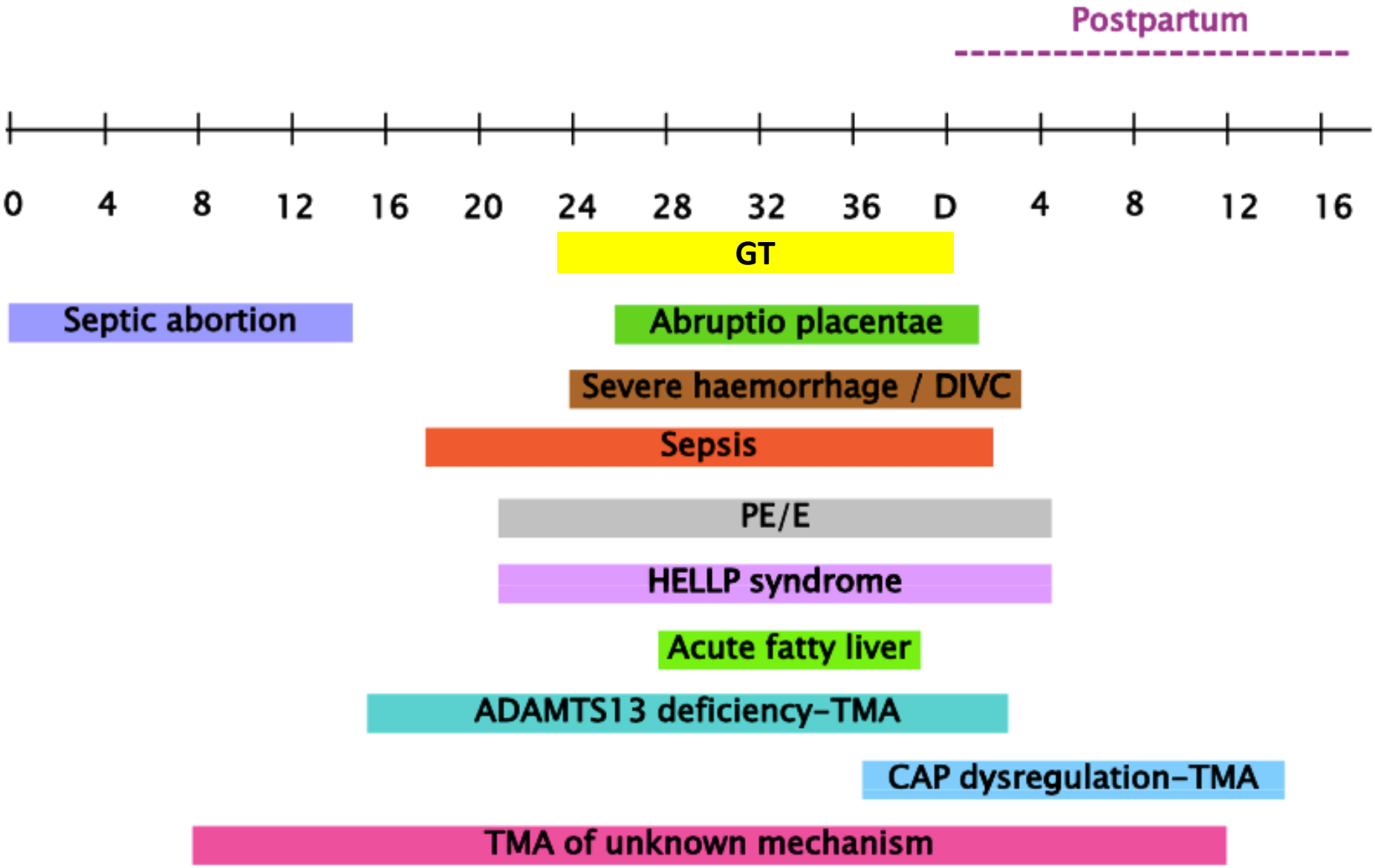
Approach	Typical dosing	Response rate	Time to response
Splenectomy	N/A	Two-thirds of patients achieve long-term remission	0–24 days
Rituximab	375 mg m^{-2} weekly × 4 weeks (lower doses may be effective)	40% at 1 year; 20–25% at 5 years	1–8 weeks
Eltrombopag Romiplostim	12.5–75 mg PO daily 1–10 μg kg^{-1} SC weekly	> 80%. Most responses are sustained for up to 3–5 years with continual administration	1–4 weeks

ISTH 2012

Difference between HELLP and its imitators

	HELLP	AFLP	TTP	HUS
Hemolysis	+ to +++	0 to +	+++	++ to +++
Schistocytosis	+ to ++	0 to +	+++	++ to +++
Elevated LDH	++ to +++	+ to ++	+++	++ to +++
Elevated liver enzymes	++ to +++	++ to +++	0 to +	0 to +
Low platelet count	++ to +++	+ to ++	+++	++ to +++
Factor V	N or ↓	↓↓	N	N
Total bilirubin	+	++ to +++	+ to ++	+ to ++
Proteinuria	+++	+	+ to ++	+ to +++
Renal failure	0 to ++	+	0 to ++	++ to +++
DIC	+ to ++	+ to +++	0	0
Hypoglycemia	0 to +	+ to +++	0	0
ADAMTS 13 activity	Detectable	NA	Undetectable	Detectable
Fever	0	+	++	0
	1/500	1/1,000	1/100,000	

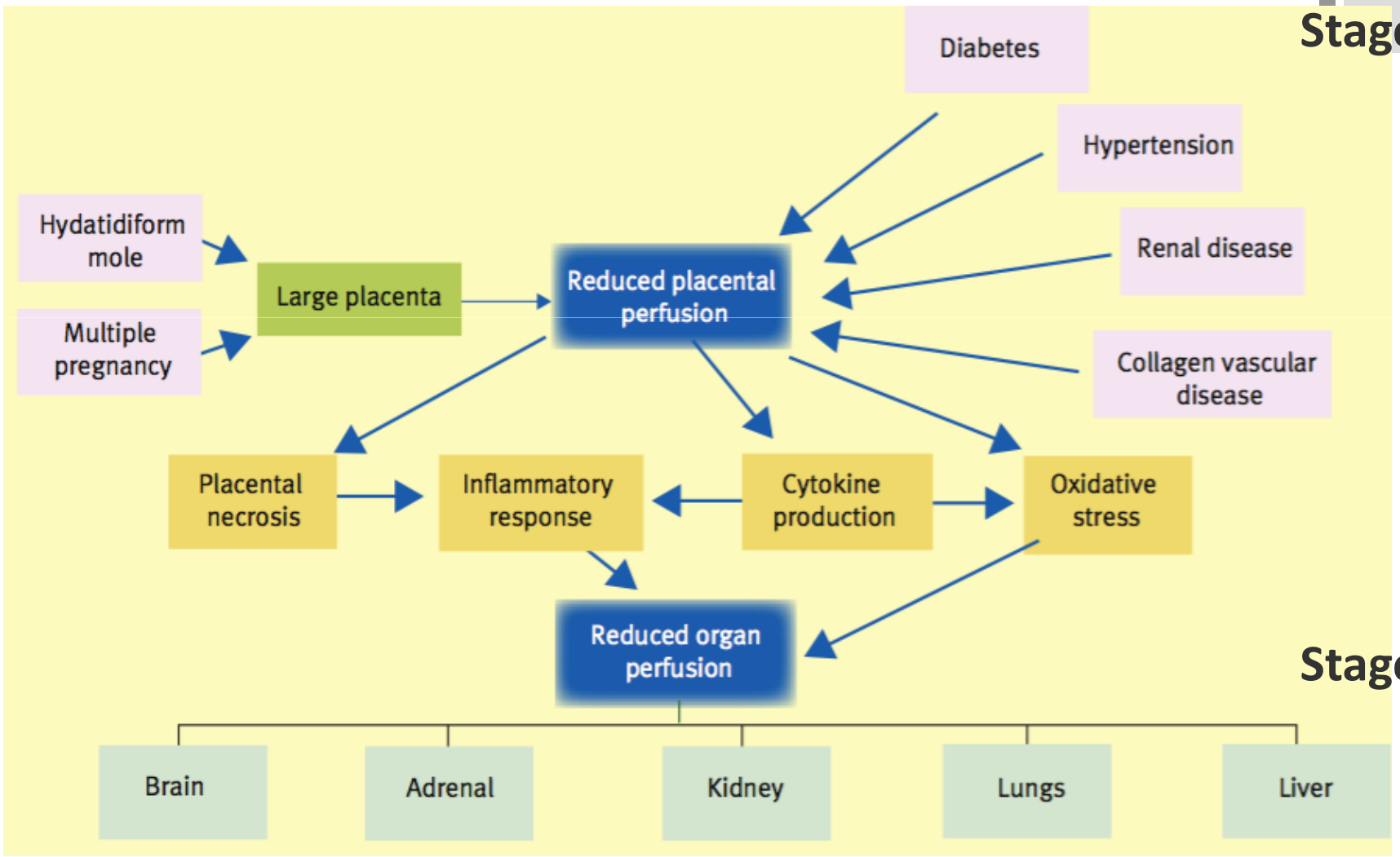
Main causes of pregnancy-related TMA depending on timing of occurrence during pregnancy



Preeclampsia and HELLP syndrome

- Hypertensive disorder
  - BP > 140/90 mmHg
- HELLP syndrome ~ 3% of women with pre-eclampsia
  - **H**aemolysis **E**levated **L**iver enzymes **L**ow **P**latelet count
- Differential diagnosis
  - Preexisting hypertension
  - Gestational hypertension
  - Eclampsia

Pathophysiology of pre-eclampsia



Acute fatty liver during pregnancy

Classical presentation

- Upper right-side abdominal pain
- Vomiting
- Hypoglycemia
- Severe retentional jaundice and a sharp increase in conjugated bilirubin without any clear increase in free bilirubin

Hepatic failure syndrome

- Hypoglycemia
- coagulopathy

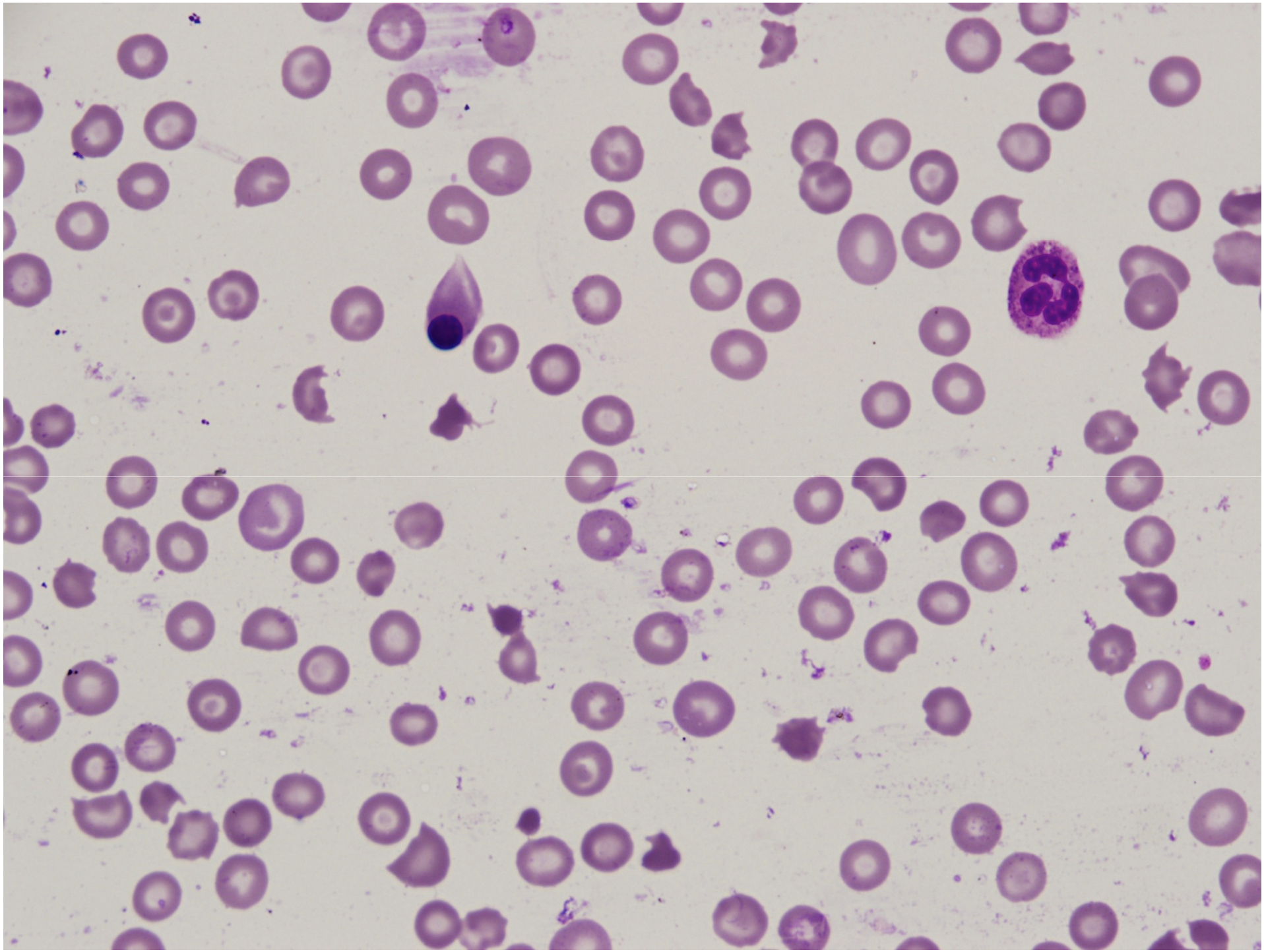
ARF

Hematologic involvement

- Thrombocytopenia : moderate (due to DIC)
- Hemolytic anemia : rare

34 YOF, preg G2P1 GA 32 weeks

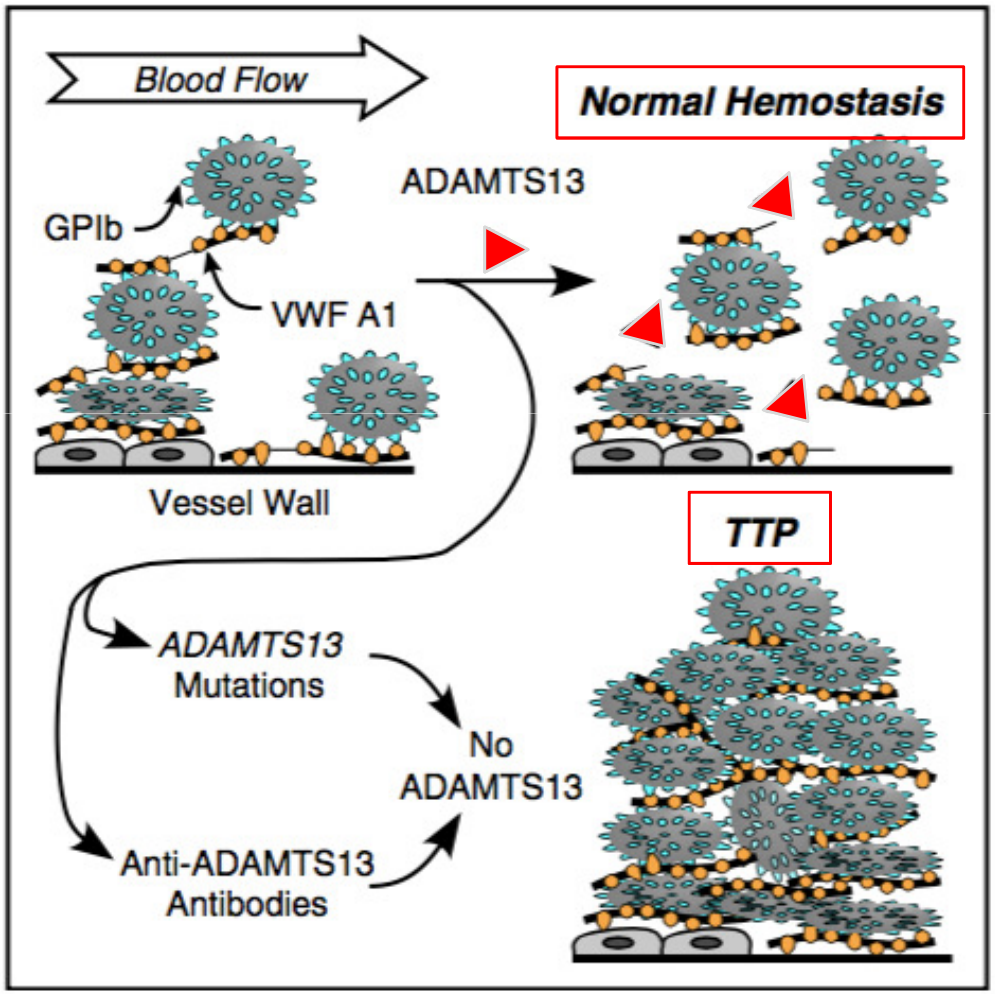
แรกรับ	BP 130/80 mmHg, PR 80 BPM, Temp 37 ^{o}C		
Hb/Hct	9.1/26.7, MCV 83 fL		
WBC	12,000 PMN 85 % L 10%		
Platelet count	5 k/uL		
Coagulogram			
PTT	21 sec (22-33 sec)	TT	11 sec (11-14 sec)
PT	10.5 sec (10-13 sec)		
LFT	ALP/GGT	86/110	
	AST/ALT	124/35	
LDH	1250		



TTP in pregnancy

- Approximately 10% of cases of idiopathic **TTP** occur in association with pregnancy
- Mean gestational age of 23.5 weeks (in second trimester)
- Mortality 90% (untreat)

Role of VWF and ADAMTS13 in platelet adhesion



- Thrombocytopenia
  - platelet sequestration in the microvasculature
- Hemolysis & production of schistocytes
  - require obstruction of blood flow in high-shear regions by microthrombi, or perhaps by VWF fibers
- Tissue injury
  - depends on the location of a thrombus and the quality of collateral circulation.

J. Evan Sadler, Blood. 2017;130(10):1181-1188

Treatments of TTP

1. **Replacing ADAMTS13**
   - Plasma infusion
   - Recombinant ADAMTS13
2. **Suppressing anti-ADAMTS13 antibodies**
   - Plasma exchange therapy : 1-1.5 plasma volume
   - Immune suppressive therapy : Rituximab, bortezomib
3. **Depolymerizing VWF multimers : N-acetylcysteine**
4. **Inhibiting VWF-platelet interactions : Caplacizumab**
5. **Splenectomy**

J. Evan Sadler, Blood. 2017;130(10):1181-1188

73 YOF, treated with UFH

“ปรับ PTT ไม่ได้, prolonged INR”

Underling : CAD, AF on warfarin

Admit acute arterial occlusion (rt. Leg)

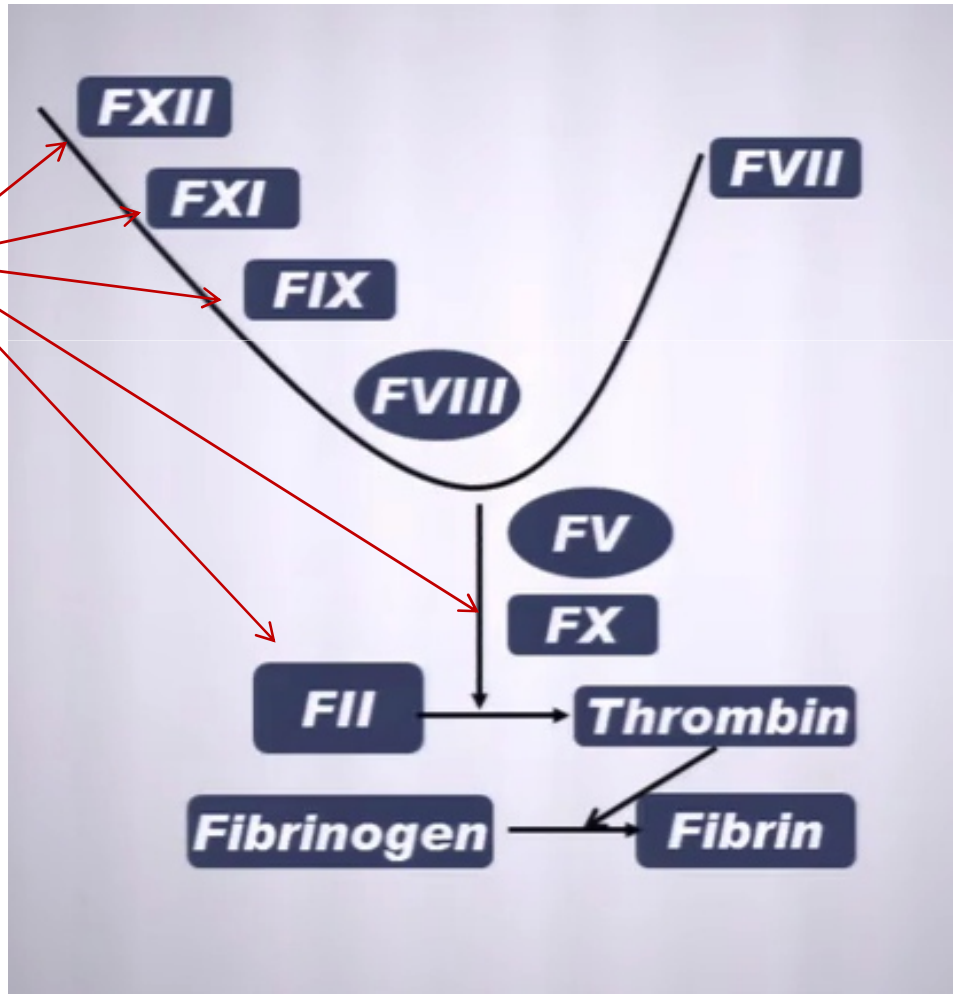
	31/7/56	11/9/56	2/10/56	3/10/56	4/10/56	4/10/56	6/10/56	7/10/56	12/10/56	14/10/56
PTT	22-33 sec		27.8	109.1	51.7	117.9	56.6	72.6	57.2	94.7
PT	11.8	30.7	13.9	23.4	28.4	49.1	59.2	83.1	72.4	85.7
INR	0.99	2.41	1.16	1.89	2.27	3.74	4.45	6.21	5.36	6.27
TT	11-14 sec		10.6							
Plt			231 K				109 K	126 K		
Fib			342				192			

Effect of anticoagulants on routine coagulation assays : UFH

UFH

AT

A non-specific indirect inhibitor

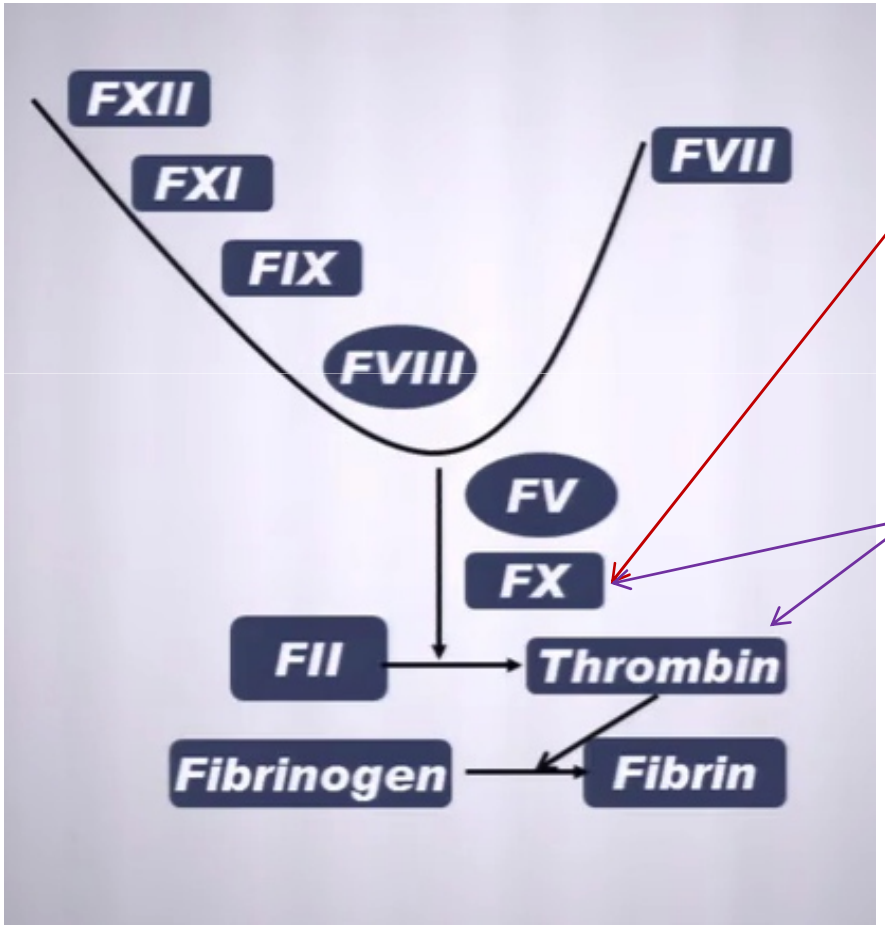


Effect on coag test :

- PTT – prolongation
- TT – prolongation
- PT – no effect **

*** PT reagent contain heparin neutralizer (heparinase)*

Effect of anticoagulants on routine coagulation assays : LMWH and Fondaparinux



AT

Fondaparinux

Effect on coag test :

- PTT ± prolongation

depend on type of reagent

LMWH **AT**

Effect on coag test :

- PTT - prolongation
- TT - prolongation

Effect of anticoagulants on coagulation assays

UFH

- Incomplete correction with 1:1 plasma mix
- Decreased APTT-based factor activities
- Correction/neutralization with addition of plt (PF4) of PL --> false positive LA

LMWH or fondaparinux

- Less effect on assays (than UFH)
- ± false positive LA results

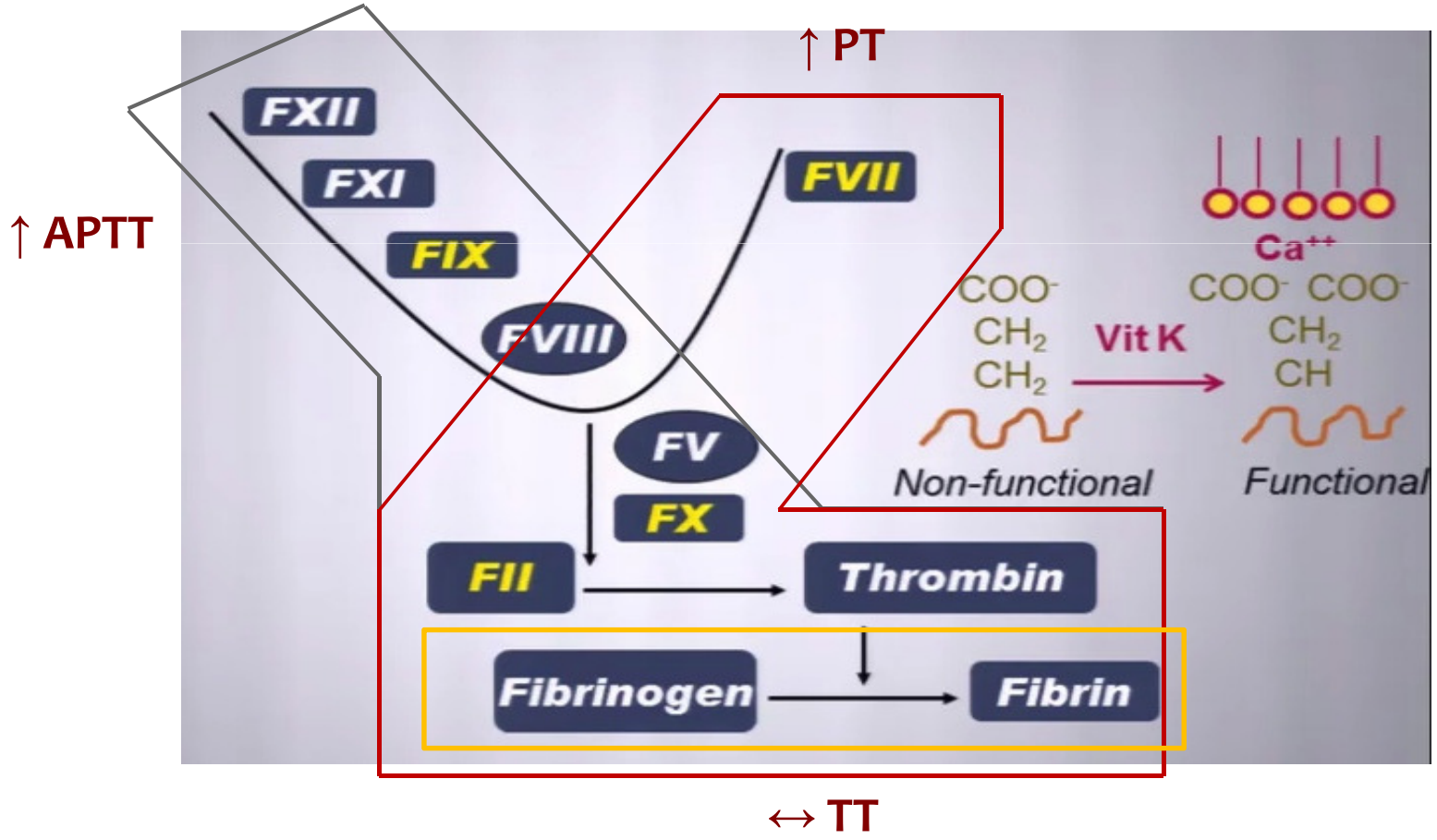
Effect of anticoagulants on coagulation assays

VKAs

- Correction with APTT 1:1 plasma mix
- No interference with factor assays
- Decrease on vitamin K dependent factors
  - Protein C, Protein S and Protein Z
- Elevated dRVVT screen and confirm
  - False positive LA

Effect of anticoagulants on coagulation assays

Vitamin K antagonist (Warfarin) : impairs synthesis of functional factor, therefore decreases factor activity



73 YOF, treated with UFH *"ปรับ PTT ไม่ได้, prolonged INR"*

DDx. - Multiple factor deficiency

- Factor deficiency : common P'w

"R/O Vit K def : II, VII, IX, X"

Plan - Factor II, VII, IX, X, V, VIII activity levels

	2/10/56	3/10/56	4/10/56	4/10/56	6/10/56	7/10/56	12/10/56	14/10/56	15/10/56
PTT	27.8	109.1	51.7	117.9	56.6	72.6	57.2	94.7	37.9
PT	13.9	23.4	28.4	49.1	59.2	83.1	72.4	85.7	21.6
INR	1.16	1.89	2.27	3.74	4.45	6.21	5.36	6.27	1.75
TT	10.6								
Plt	231 K				109 K	126 K			
Fib	342				192				

Vitamin K
~~10~~ mg PO