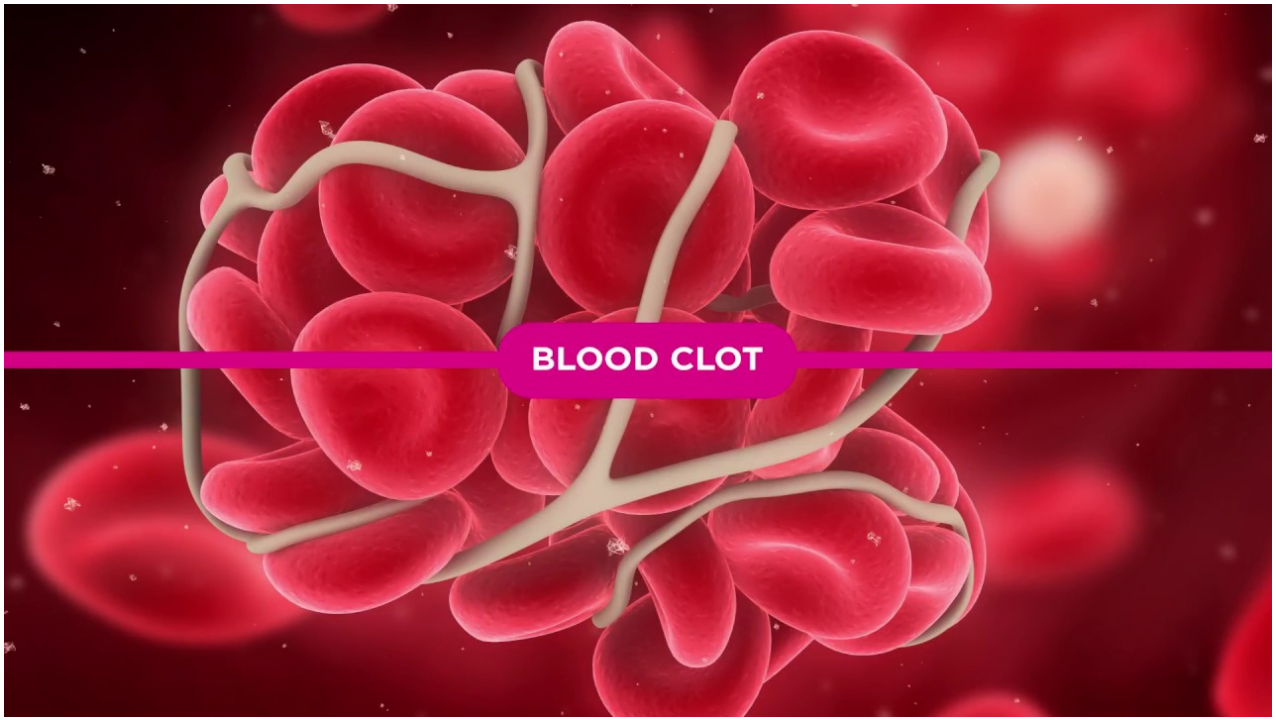
Pediatric Cancer & Hematologic Disorder
PedHemOnc-PMK

Bleeding Disorders in Children



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Objectives

สามารถซักประวัติและตรวจร่างกายผู้ป่วยที่มีความผิดปกติของการแข็งตัวของเลือดได้อย่างครอบคลุมและเหมาะสม

สามารถวินิจฉัยแยกโรคและให้การรักษาเบื้องต้นในผู้ป่วยที่มีความผิดปกติของการแข็งตัวของเลือดได้อย่างถูกต้อง

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Conclusions

The Best Laboratory Test
is
“The History Taking”

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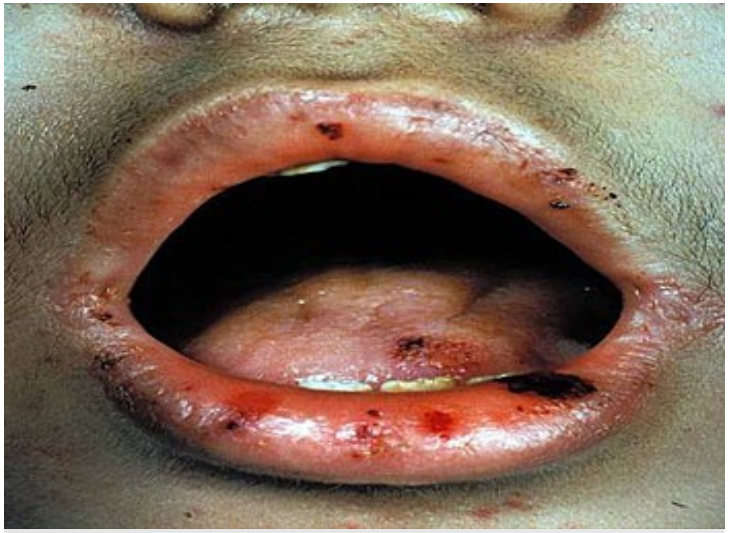
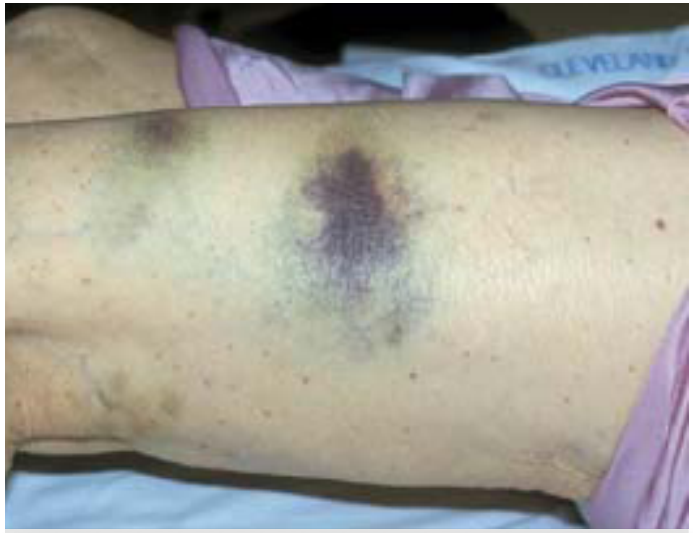
Clinical evaluation

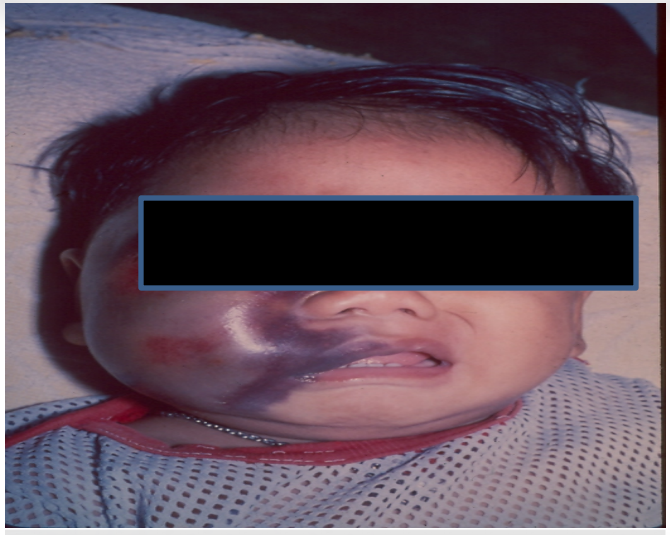
	Primary Hemostatic disorder	Secondary Hemostatic disorder
Prototypic disorders	thrombocytopenia platelet function defect von Willebrand disease	hemophilia
Bleeding	immediate	delayed
Petechiae	yes	no
Hemarthrosis	no	yes
Intramuscular Hematoma	uncommon	common
Epistaxis	common	uncommon
Menorrhagia	common	uncommon



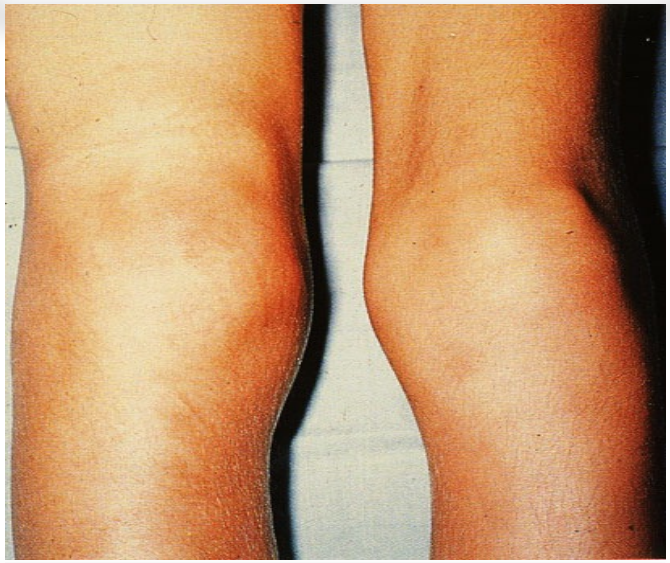
ก. Wet purpura



ข. Ecchymosis



ค. Hematoma



ง. Hemathrosis

Case Scenario #1

A 3-year-old boy was noted to have bruises over his extremities off and on.

He presented with several episodes of epistaxis.

Other history was unremarkable

Physical examination

Multiple scattered bruises over the extremities and trunk. Petechiae were seen on these areas and face.

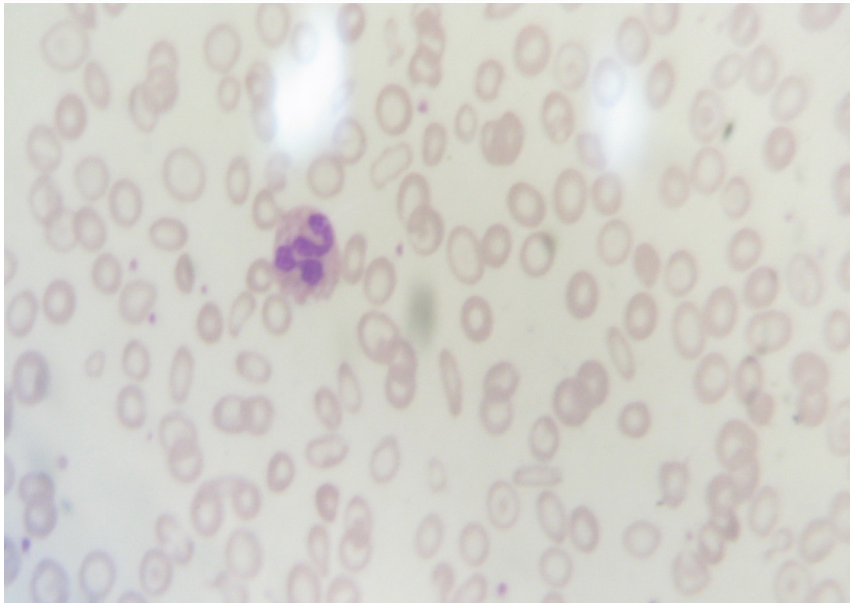
No splenomegaly. Lymph node was negative.

Neurologic examination was normal

Case Scenario #1

Complete blood count

Hb	10 g/dL
Hct	29 %
MCV	65 fL
MCH	29.6 pg
MCHC	35.9 g/dL
RDW	17 %
WBC	5.3 x 10^9/L
	(P 44, L 39, M 14, E 1, B 2)
PLT	348 x 10^9/L



Coagulogram

PT	12 sec (12-15 sec)
aPTT	29 sec (25-35 sec)
TT	12 sec (10-20 sec)

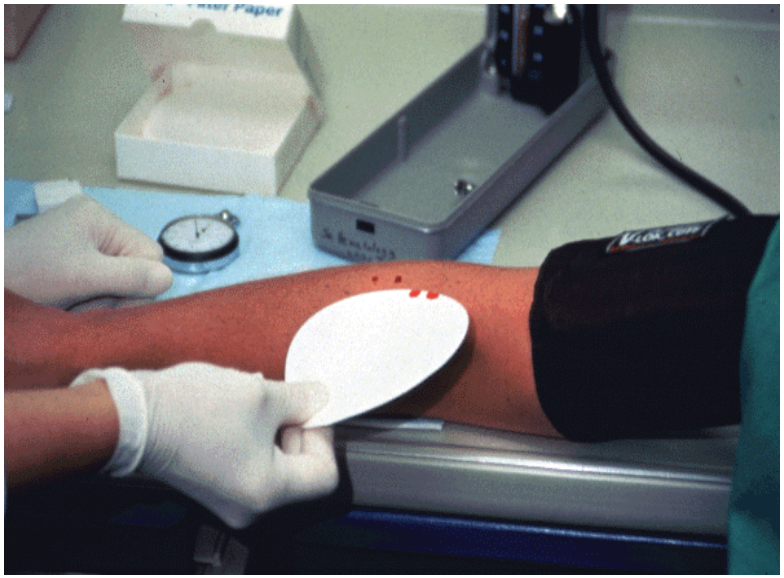
Bleeding time = 15 mins

Bleeding Time

Normal range up to 10 mins

Prolongation in

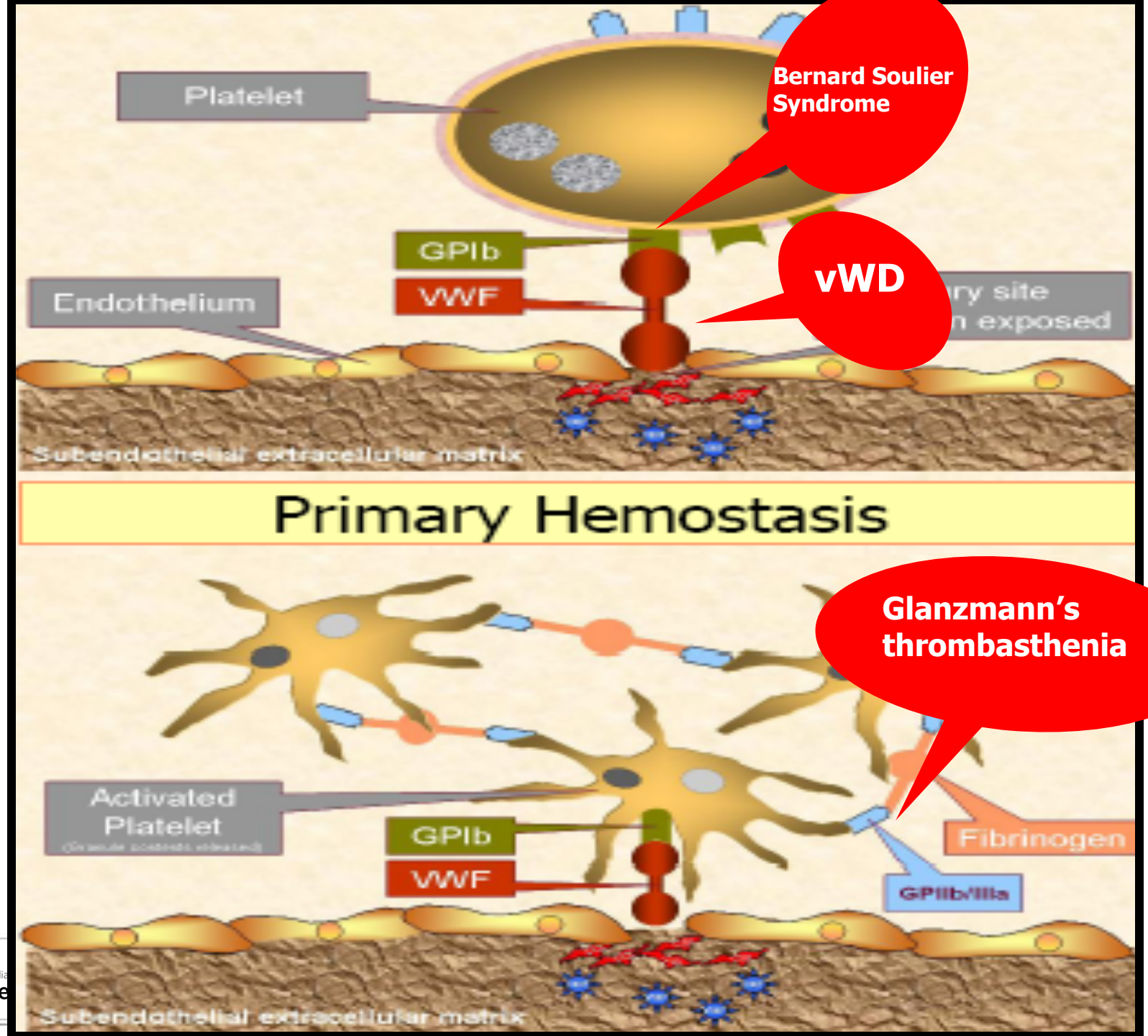
- Plt. dysfunction
- VWD (aPTT prolonged)
- Thrombocytopenia (<60 x 109/L)
- Hypofibrinogenemia (TT prolonged)
- Vascular defect



NOT recommend for Pre-operative evaluation

Poor sensitivity and reproducibility

Most preferred method: Modified Ivy method


Platelet
Bernard Soulier Syndrome
GPIb
VWF
vWD
Endothelium
ry site
n exposed
Subendothelial extracellular matrix
Primary Hemostasis
Glanzmann's thrombasthenia
Activated Platelet
GPIb
VWF
Fibrinogen
GPIIb/IIIa
Subendothelial extracellular matrix

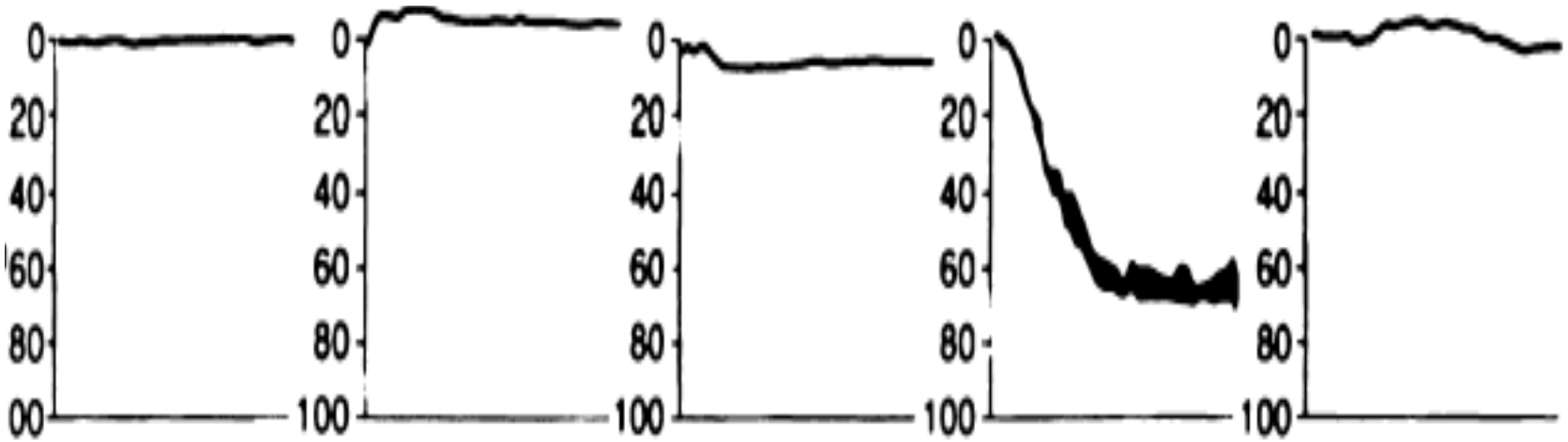
Lab investigations

vWD investigation

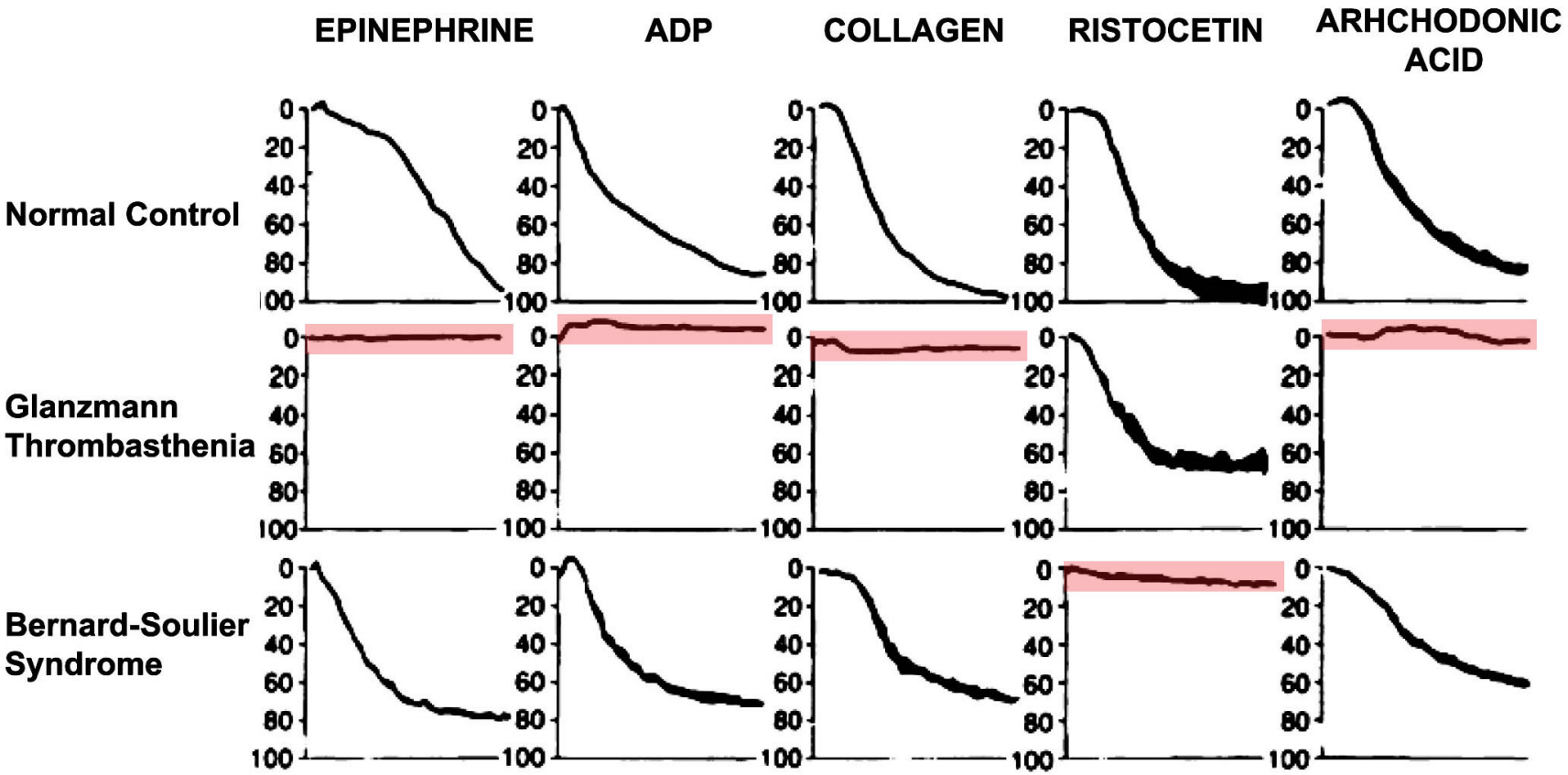
Blood group **“A”**

vWF: Ag	= 0.95U/ml (95%)
Factor VIII : C activity	= 1.2 U/ml (120%)
vWF:RCO	= 0.78 U/ml (78%)

Platelet Aggregation test



Platelet Aggregation Profiles

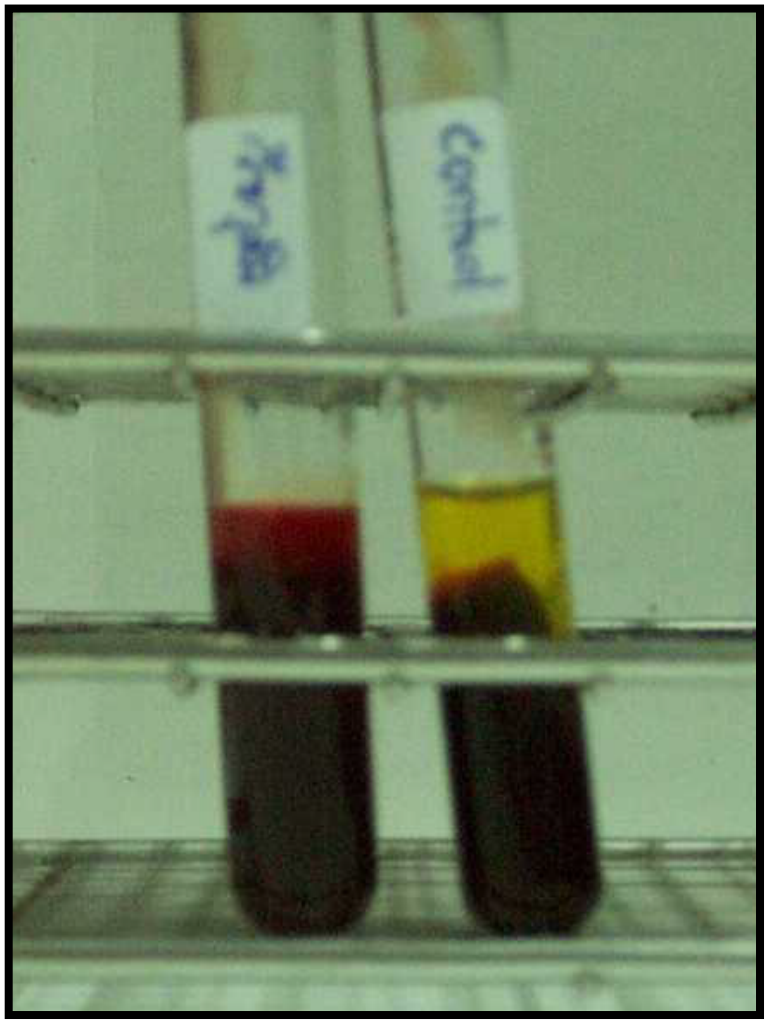


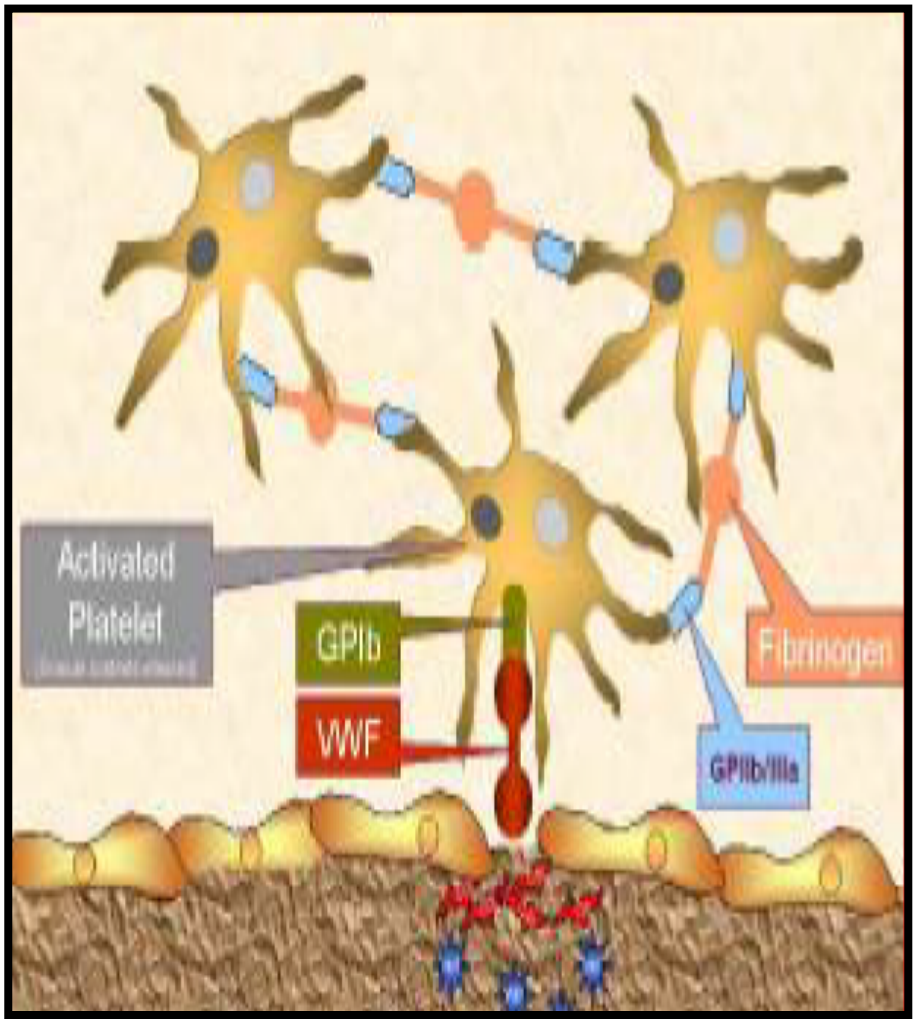
Glanzmann Thrombasthenia

- Autosomal recessive inheritance (high rate of consanguinity)
- Severe mucocutaneous bleeding starting in infancy
- **Deficiency or abnormality of GPIIb/IIIa** (platelet αIIbβ3 integrin)
- Normal platelet count and morphology
- Absent platelet aggregation in response to ADP, epinephrine, collagen
- ***Normal ristocetin-induced platelet agglutination***
- Treatment: local pressures, DDAVP, fibrinolytic inhibitors, platelet transfusion, FVIIa

Ref : Poon MC J Thromb Haemost 2004 ; 2 : 1096-1103

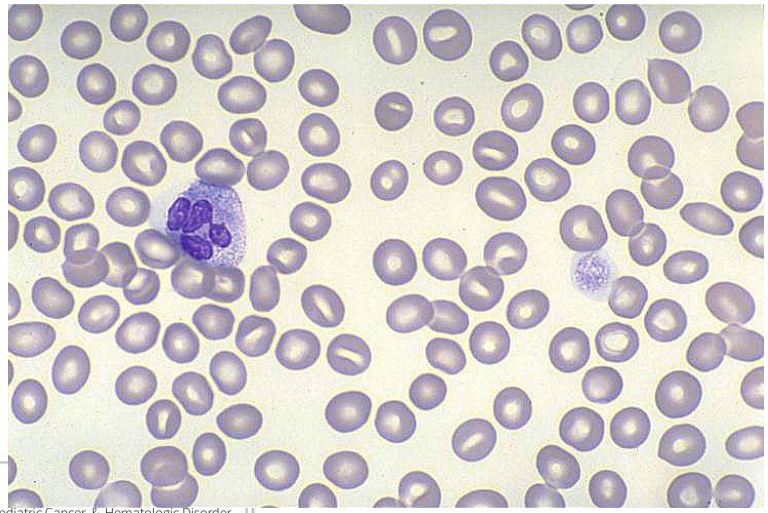
Glanzmann Thrombasthenia

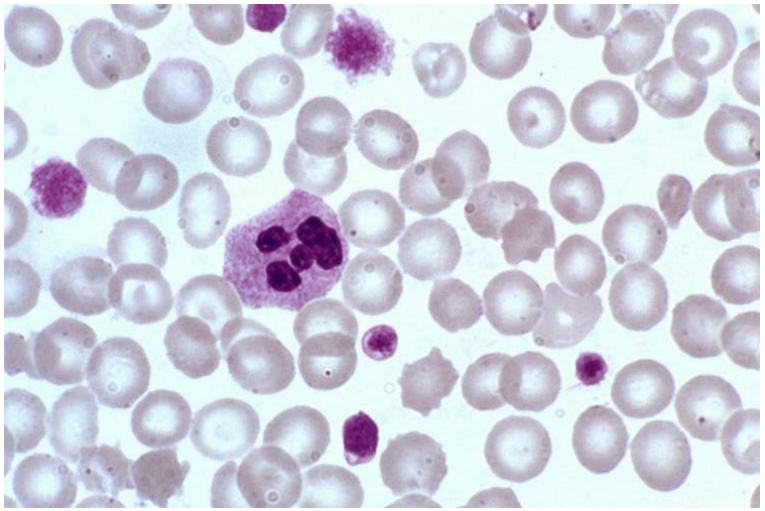




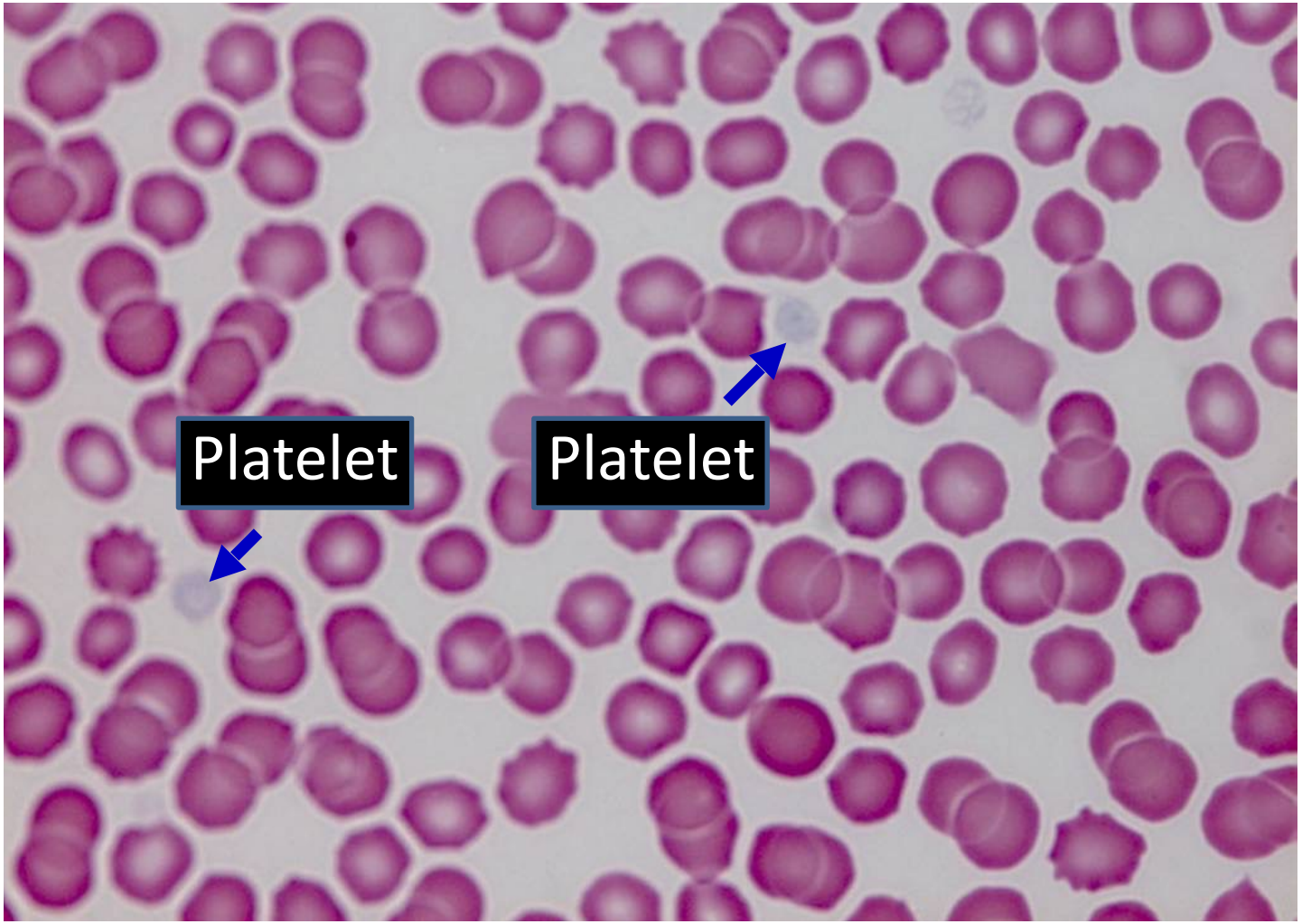
Bernard-Soulier Syndrome

- Autosomal recessive inheritance (consanguinity frequent)
- Deficiency or abnormality of GPIbα, GPIbβ, GPIX
- Prolonged bleeding time
- Normal platelet aggregation in response to ADP, epinephrine, and collagen
- ***Abnormal or absent agglutination in response to ristocetin***



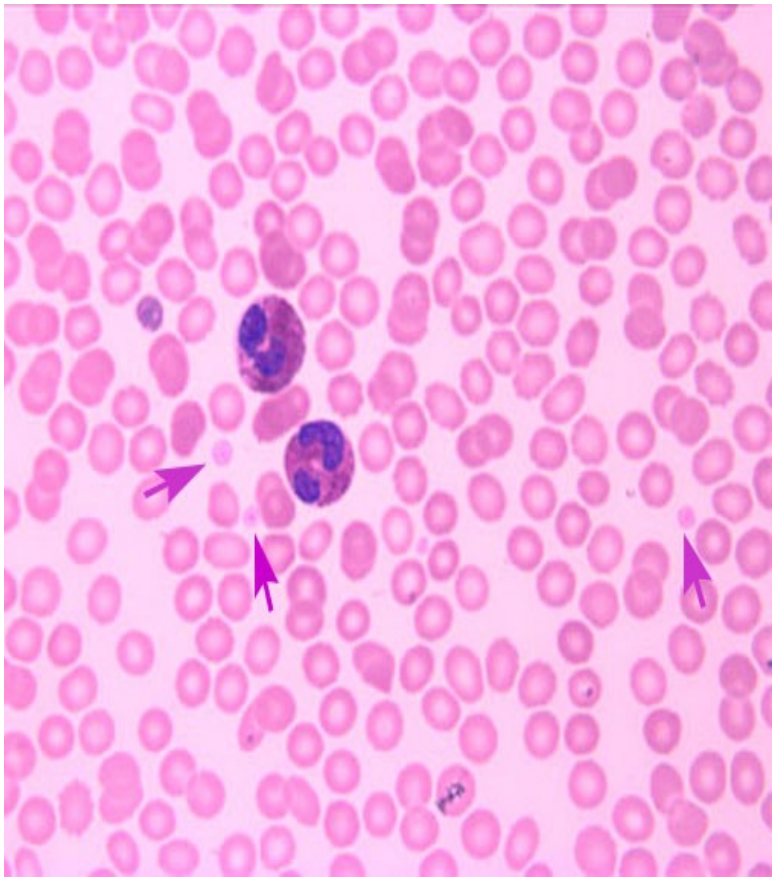


Storage Pool deficiency



Acquired Platelet Dysfunction with Eosinophilia (APDE)

- Acquired
- Normal Platelet count
- Eosinophilia
- Absent platelet aggregation in response to ADP, epinephrine, collagen
- ***Normal ristocetin-induced platelet agglutination***
- Treatment: local pressures, platelet transfusion
- ***Resolve in 6-12 mo.***



Case Scenario #2

A 12-year-old girl was planed to do elective tonsillectomy next week.

She also had a history of a heavy periods for the last 2 months and easy bruising in childhood (not often).

Family History :

His father also had a Hx of easy bruising

Physical examination

Tanner stage IV

No hepatosplenomegaly

No bruises over the extremities

Lab investigations

Complete blood count

Hb	10 g/dL
Hct	30 %
MCV	60 fL
MCH	29.6 pg
MCHC	35.9 g/dL
RDW	18 %
WBC	5.3 x 109/L
	(P 44, L 39, M 14, E 1, B 2)
PLT	350 x 109/L

Coagulogram

PT = 12 sec (12-15 sec)

aPTT = 38 sec (25-35 sec)

TT= 12 sec (10-20 sec)

Bleeding time = 12 mins

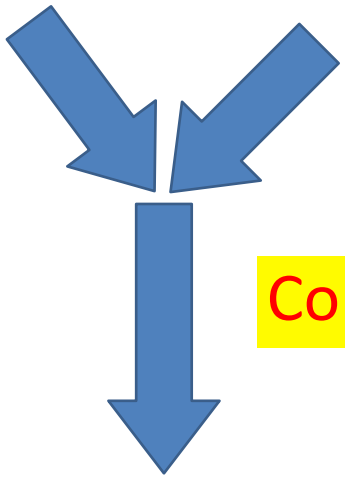
Coagulation Pathways

Partial thromboplastin time (PTT)

Prothrombin time (PT)

Intrinsic Pathway

Extrinsic Pathway



Common pathway

Thrombin time (TT)

Fibrin clot

Lab investigations

vWD investigation

Blood group **"O"**

vWF: Ag = 0.25 U/ml (25%)

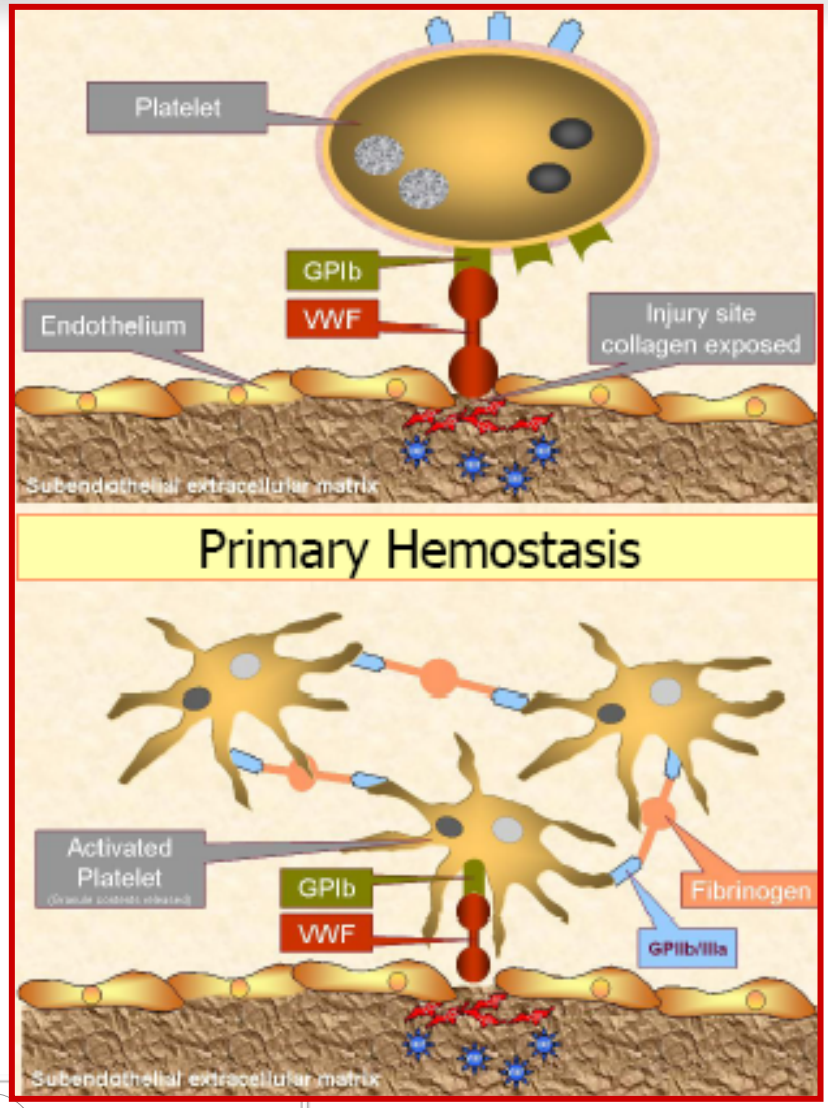
Factor VIII : C activity = 0.40 U/ml (40%)

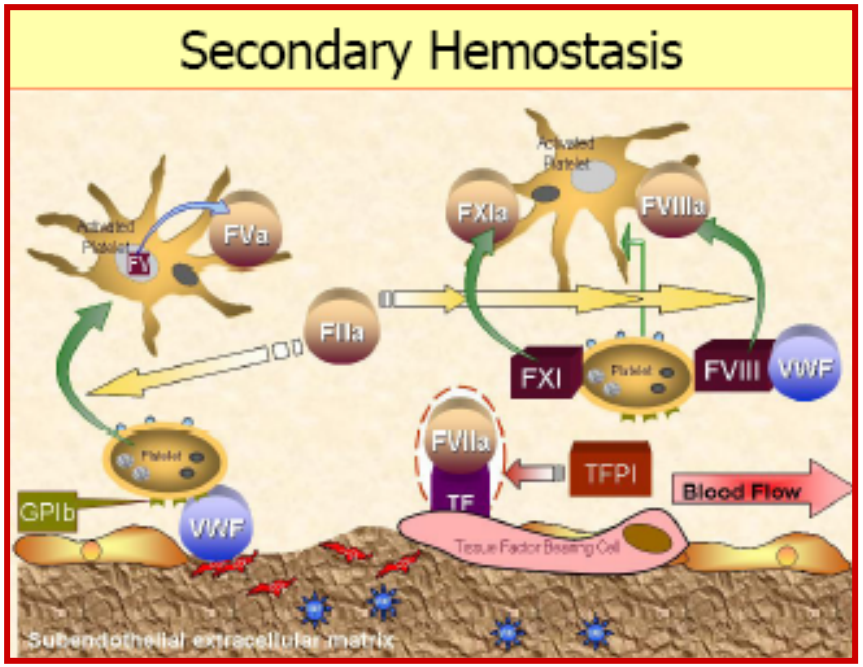
vWF:RCO = 0.48 U/ml (48%)

Liver function test : Normal

BUN / Cr : Normal

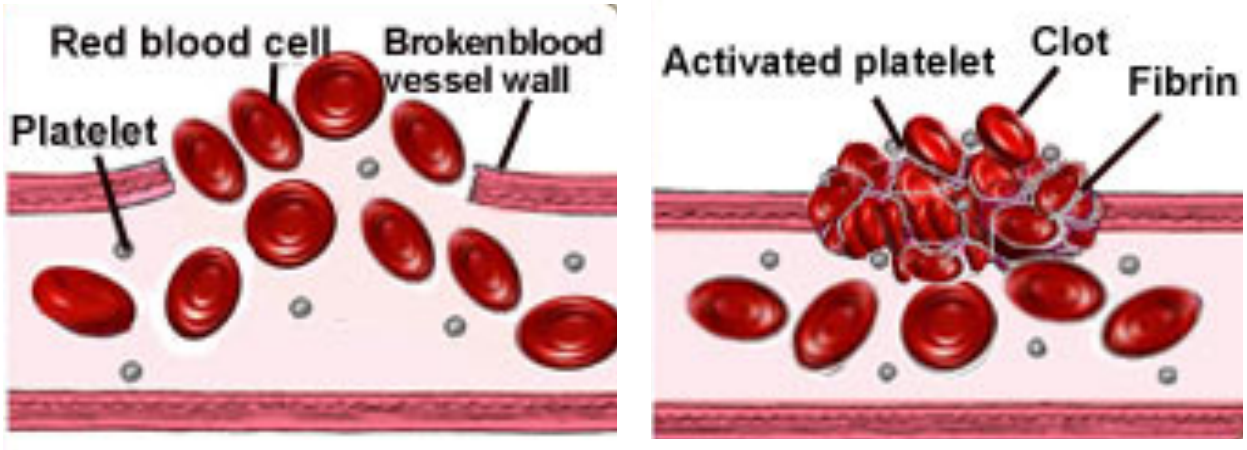
Role of VWF in Hemostasis





von Willebrand Disease (vWD)

- Most common inherited bleeding disorder
- Characterized by deficiency of von Willebrand factor (vWF)
- Variable clinical manifestations
- Autosomal dominant (Both boy and girl)



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Ref : Ewenstein B. *Annu Rev Med*. 1997;48:525-542; Hambleton J. *Curr Opin Hematol*. 2001;8:306-311; Murray E, Lillicrap D. *Transfus Med Rev*. 1996;10:93-110.

von Willebrand Disease (vWD)

- ***Mucosal-type bleeding***
  - Menorrhagia
  - Epistaxis
  - Easy bruising
- ***Excessive bleeding with trauma***
  - Postoperative bleeding
  - Bleeding following tooth extraction
- ***Gastrointestinal bleeding in patients with severe deficiency***

Ref : Hambleton J. *Curr Opin Hematol*. 2001;8:306-311.

Case Scenario #3

A 2-year-old boy who had fallen from upstairs. Then he developed drowsiness, and soft tissue swelling at right frontal area.

PH : There was only circumcision without complications.

FH : Negative for bleeding disorder

Physical examination

V/S : WNL

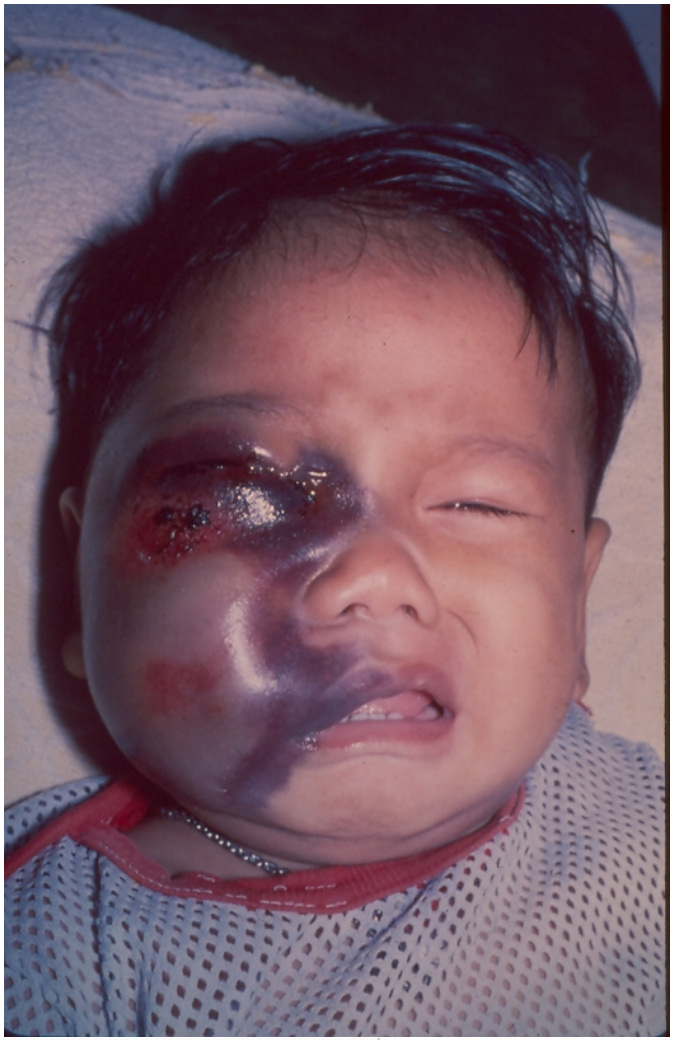
HEENT :swollen at right frontal and face area

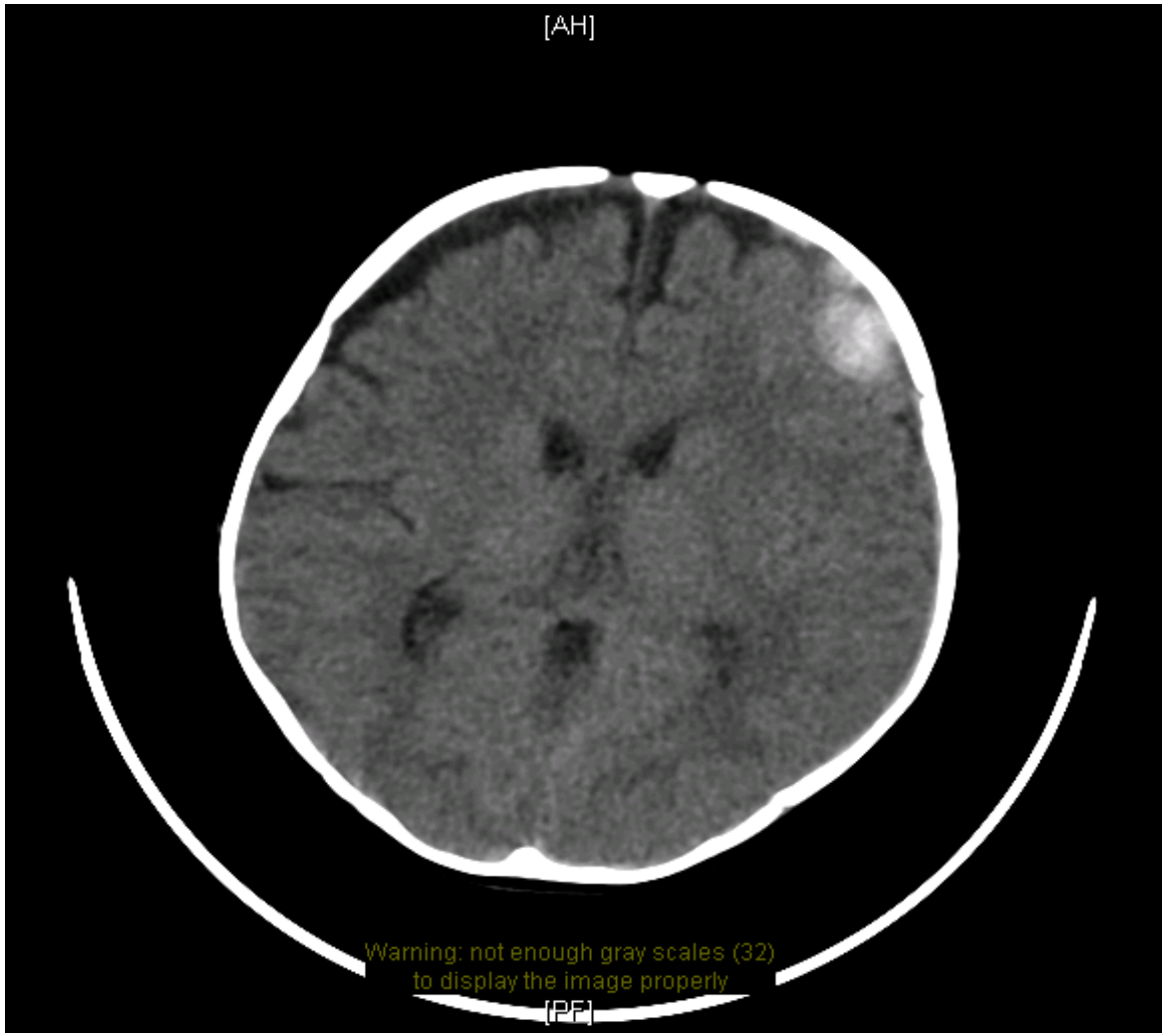
Ext. : No bruises over extremities

NS : Drowsiness

Sensory & motor : WNL

Case Scenario #3





Lab investigations

Complete blood count

Hb	12.4 g/dL
Hct	37.2 %
MCV	82.3 fL
MCH	29.6 pg
MCHC	35.9 g/dL
RDW	12.1 %
WBC	5.3 x 109/L
	(P 44, L 39, M 14, E 1, B 2)
PLT	360 x 109/L

Coagulogram

PT = 12 sec (12-15 sec)

aPTT = 40 sec (25-35 sec)

TT= 12 sec (10-20 sec)

Lab investigations

vWD investigation

Blood group **"A"**

vWF: Ag = 0.95U/ml (95%)

Factor VIII : C activity = 0.12 U/ml (12%)

vWF:RCO = 0.68 U/ml

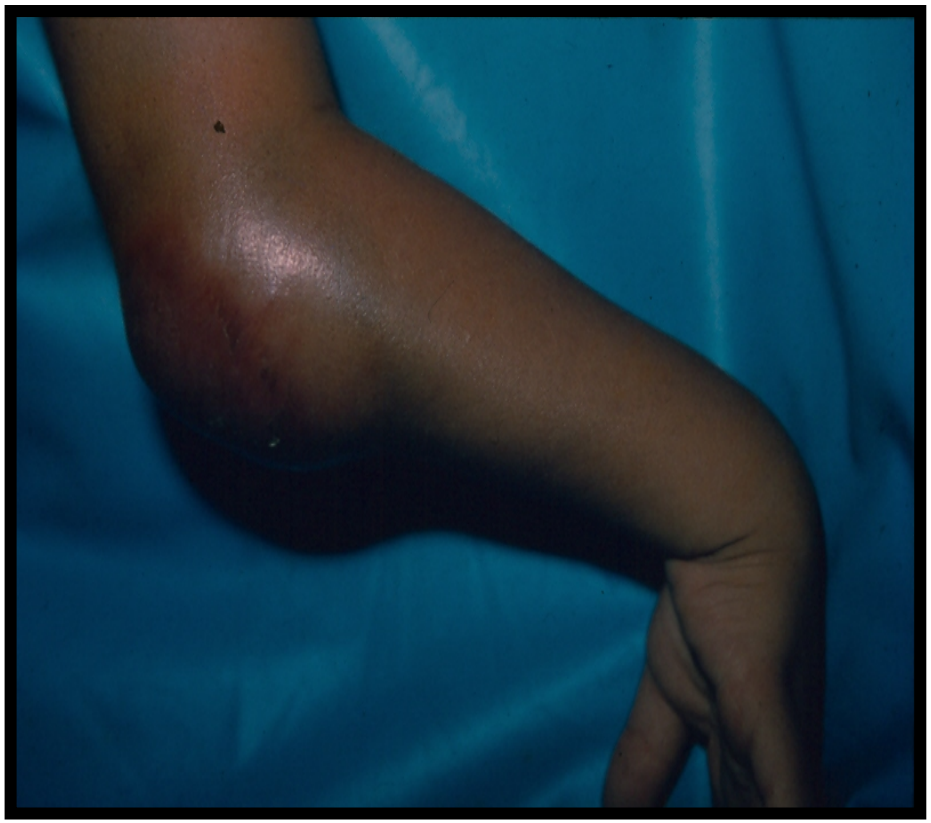
Liver function test : Normal

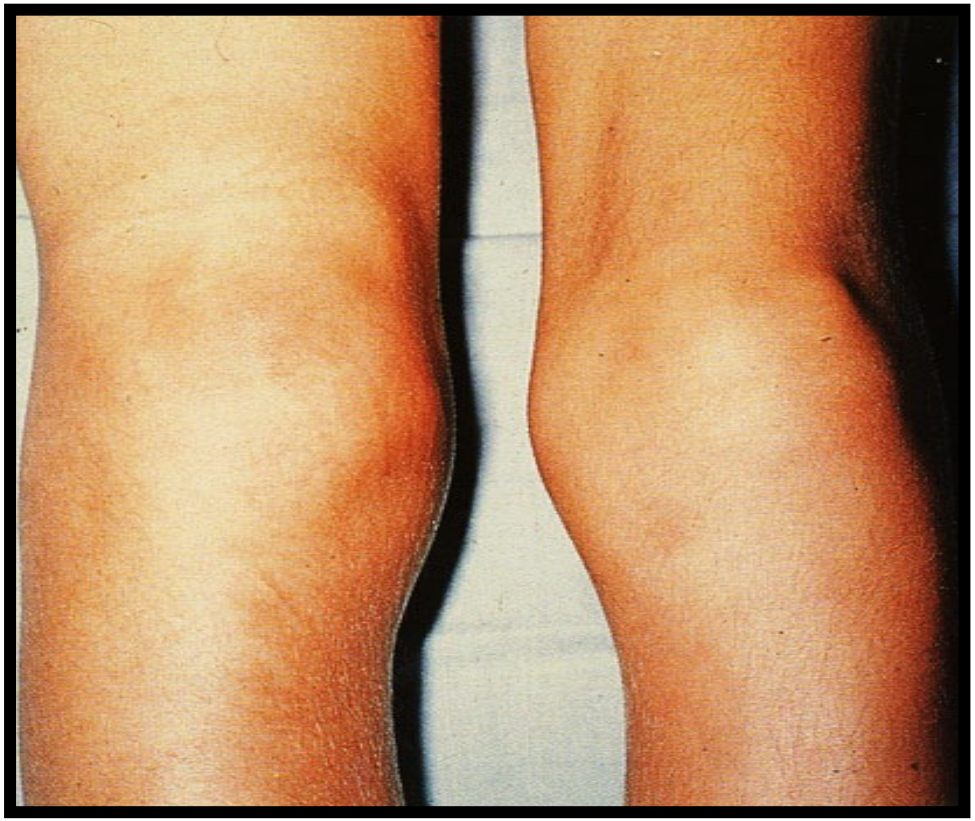
BUN / Cr : Normal

Hemophilia

Severe Haemophilia	Moderate Haemophilia	Mild Haemophilia
< 1% factor level	1% to 5% factor level	> 5% -30% factor level
Spontaneous bleeding May bleed 1-2 times per week	Can bleed with light injury May bleed 1 time per month	Can bleed with severe injury, surgery, invasive procedure
Characterized by joint involvement (haemarthrosis)	May have joint involvement	May never have a bleeding -Rarely has joint involvement

Hemarthosis





Severe to moderate hemophilia A,B

Treatment

Cryoprecipitate

Plasma-derived Factor concentrate

Recombinant Factor concentrate

Case Scenario #4

An 8-year-old boy who presented with drowsiness and fever since last 4 days.

PH: No underlying disease

Physical examination

Vital signs : T 39 C ,Tachycardia

Lung &CVS: WNL

Abdomen : hepatomegaly

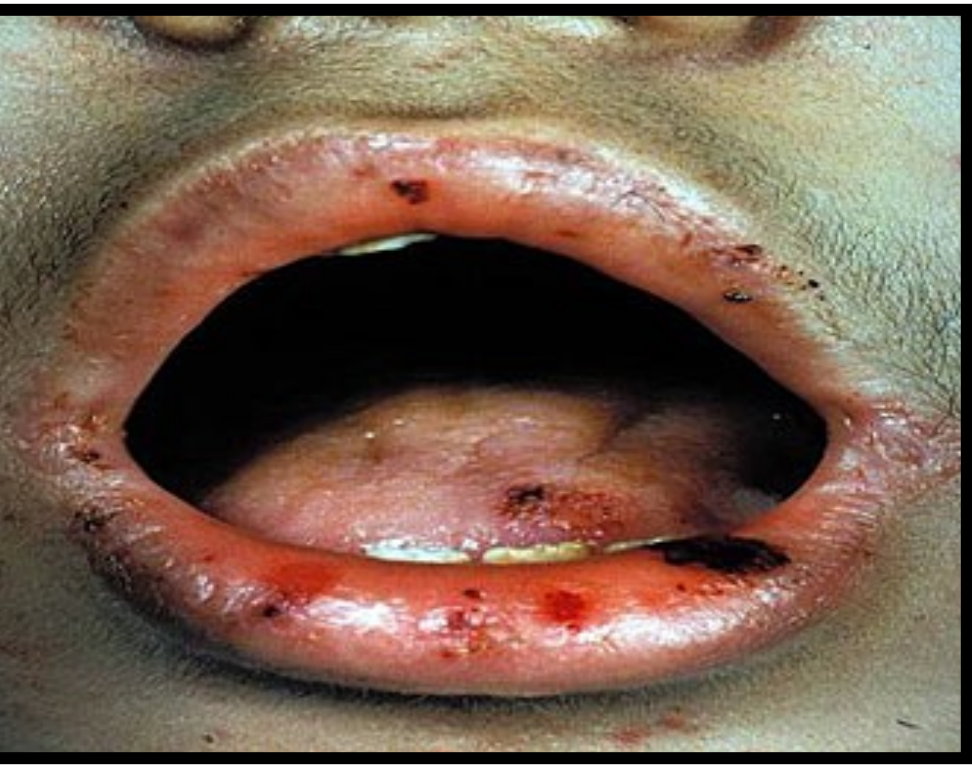
Ext. : generalized petichiae

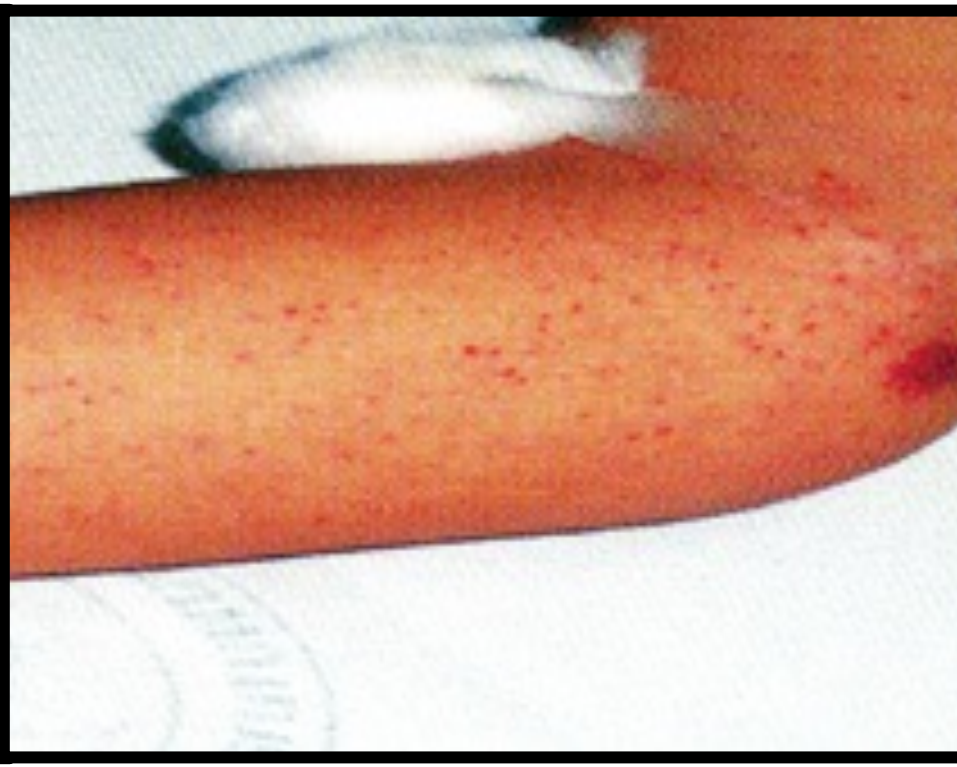
NS : Drowsiness

Sensory & motor : WNL

Sensory & motor : WNL

Case Scenario #4





Lab investigations

Complete blood count

Hb 9.8 g/dL

Hct 30 %

MCV 86 fL

MCH 28.9 pg

MCHC 35.9 g/dL

RDW 14.5 %

WBC 2.5 x 109/L

P 66 L 30 M 4

PLT 20 x 109/L

Coagulogram

PT = 20 sec (12-15 sec),

INR 1.5 (0.9-1)

aPTT = 40 sec (25-35 sec)

TT= 12 sec (10-20 sec)

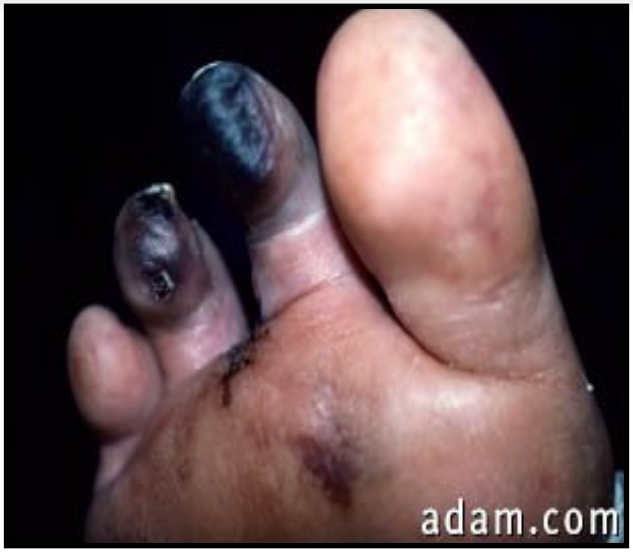
Liver Function Test : WNL

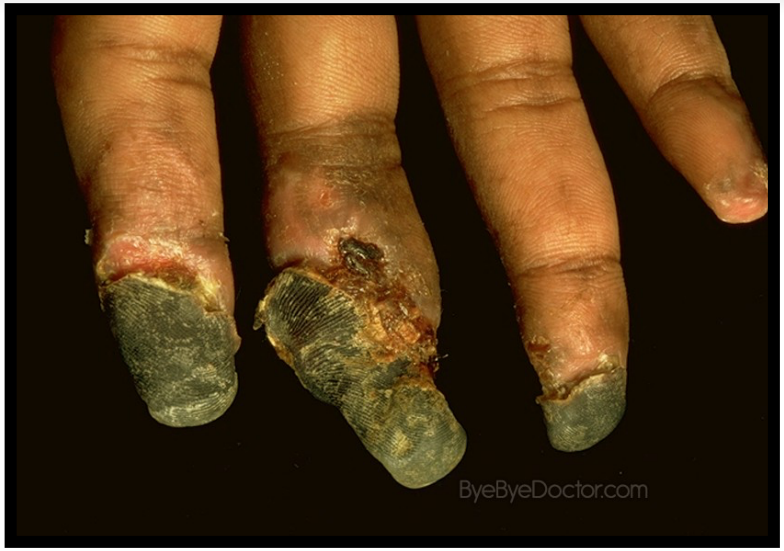
BUN / Cr : WNL

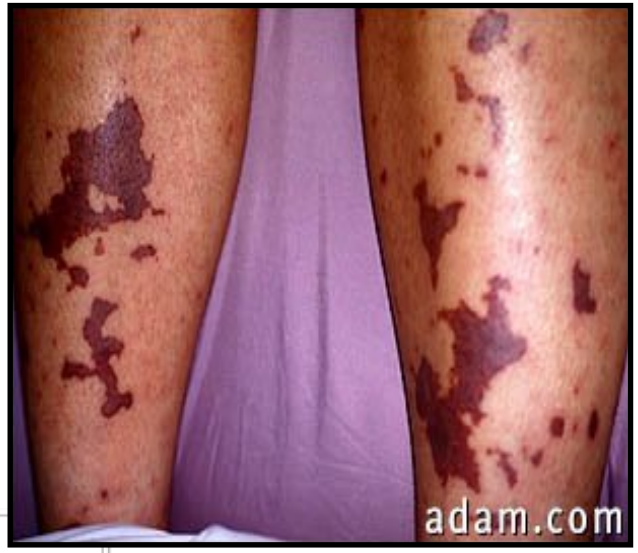
Differential Diagnosis

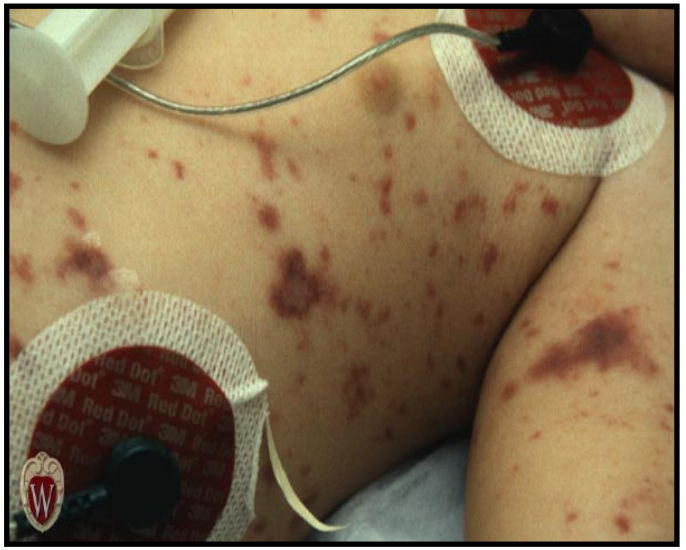
Component	Vit.K def.	Liver disease	DIC
RBC Morphology	Normal	Target cell	Fragmented cells, burr cells, schistocyte
PTT	Prolonged	Prolonged	Prolonged
PT	Prolonged	Prolonged	Prolonged
D-dimer	Normal	Normal	Markedly increased
Platelets	Normal	Normal	Reduced
Factors decreased	II, VII, IX, X	I, II, V, VII, IX, X	VIII

Clinical manifestation of DIC

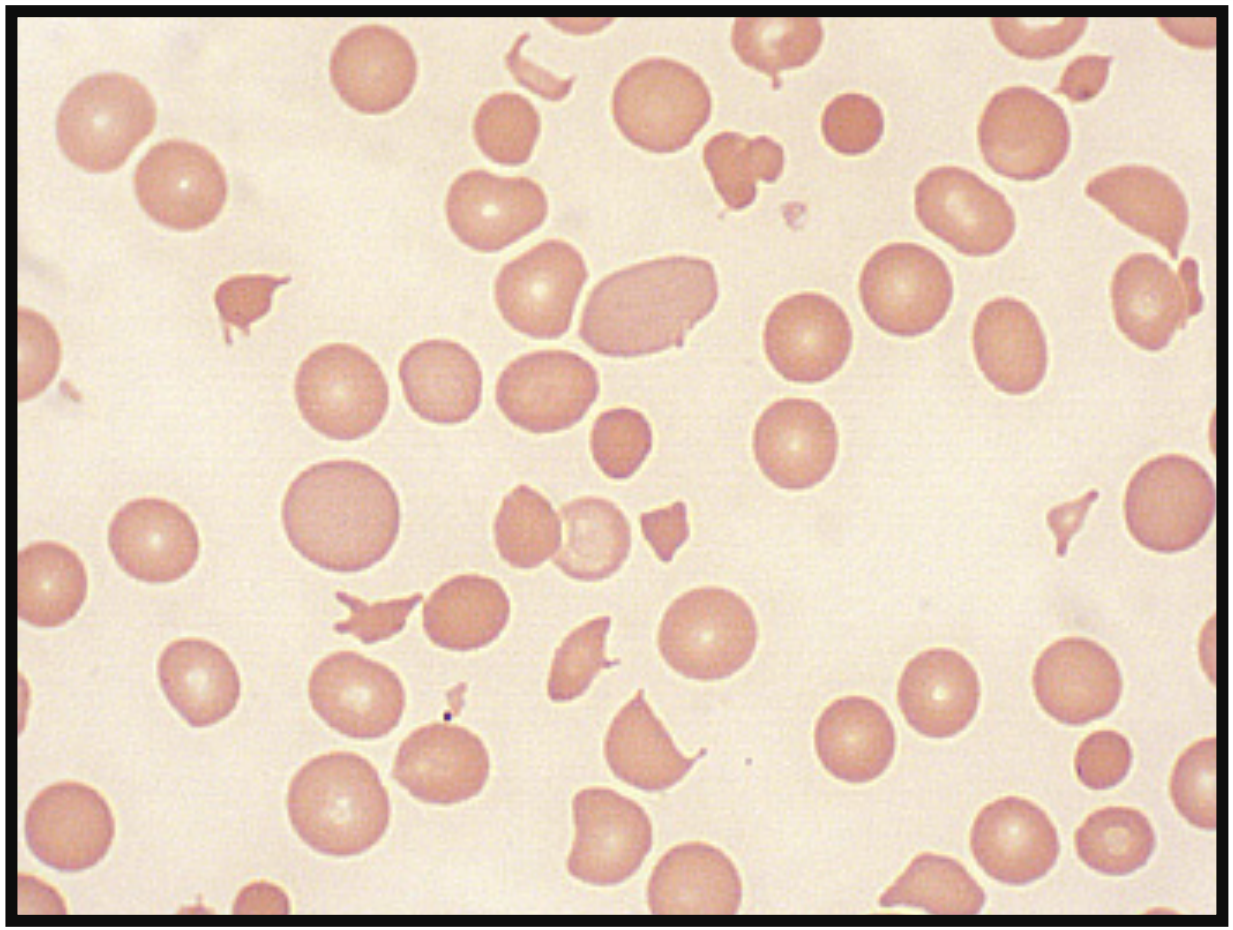








Clinical manifestation of DIC



MAHA blood picture/ Schistocytes

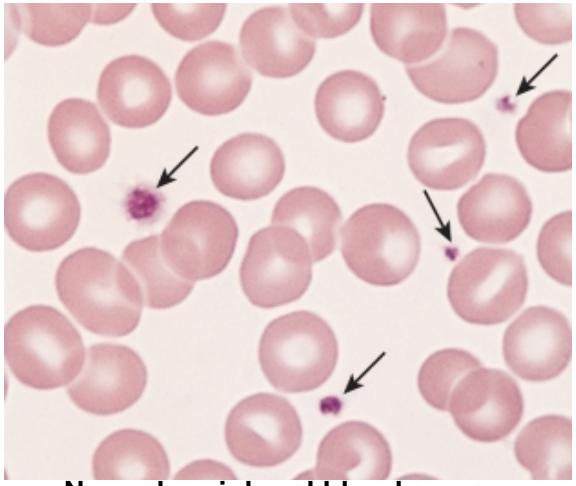
Immune Thrombocytopenia

Immune-mediated acquired disease ITP is characterised by:

A low platelet count

(<100 x 10^9/L, transient or persistent)[1]

An increased risk of bleeding due to impaired clotting mechanism[2]

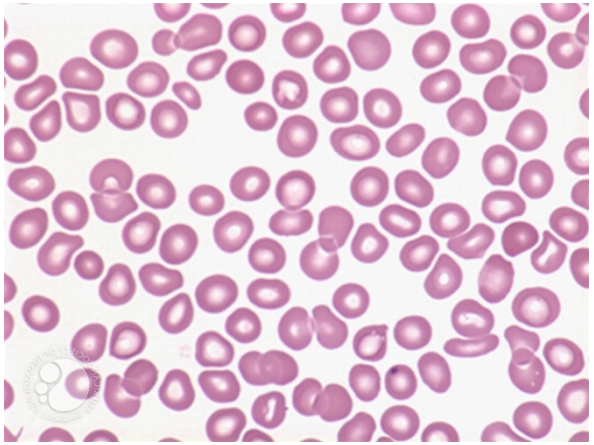


Normal peripheral blood smear

No definitive diagnostic criteria for primary ITP

Considered a diagnosis of exclusion

Thrombocytopenia may occur secondary to other conditions such as lupus, leukaemia, HIV, HCV[3]



ITP peripheral blood smear

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References

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

2.Chang M, *et al. Blood* 2003; 102: 887–95;

3.Cines D, Blanchette V. *N Engl J Med* 2002; 346: 995–1008

Immune Thrombocytopenia

Presenting Features in 471 Children with newly diagnosed ITP

Male : Female ratio = 223 : 248

Preceding infection about 64%

Hemorrhagic manifestrations

- Purpura / Petechiae 97%
- Epistaxis 30%
- Hematuria 7%
- Intracranial Hemorrhage ~ 0.2%

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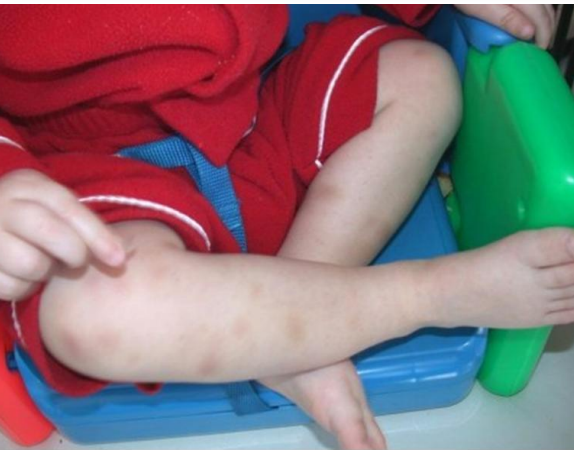
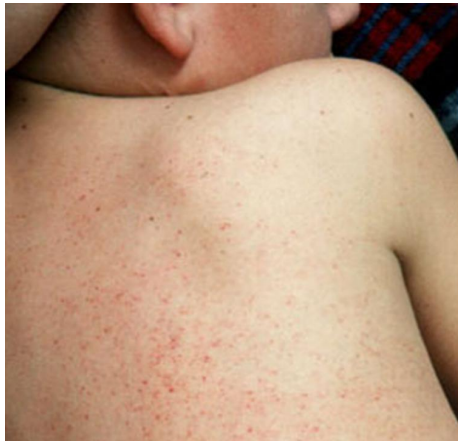
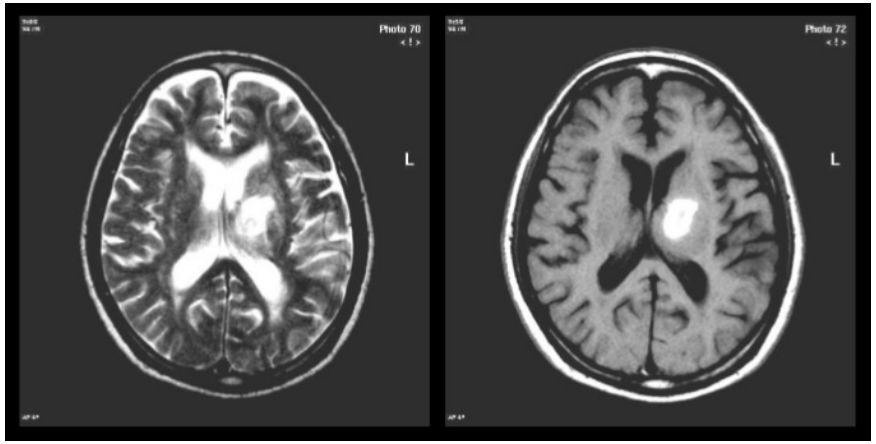
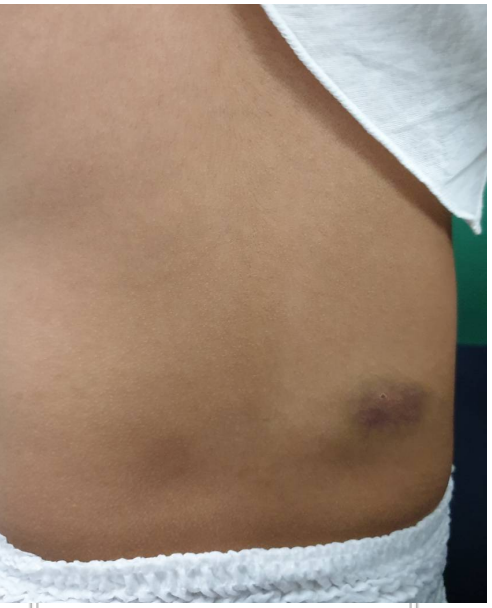
References : Blanchette V Thrombosis and Hemostasis 2003 ; 29(6) : 605-617
Lilleyman J Arch Dis Child 1994 ; 71 : 251-253

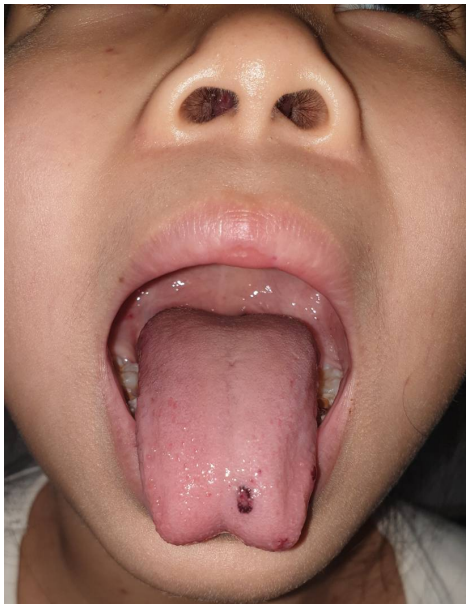
Immune Thrombocytopenia

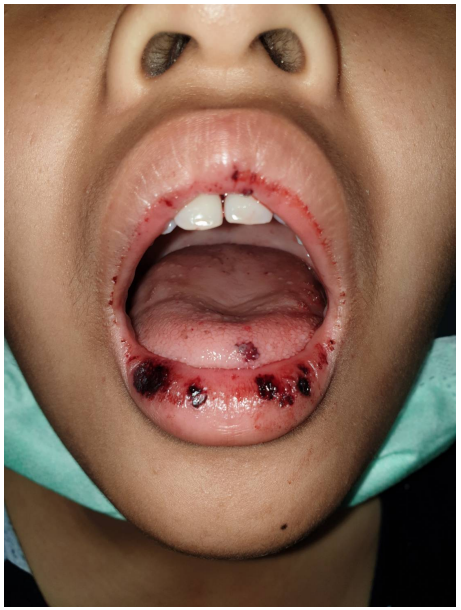


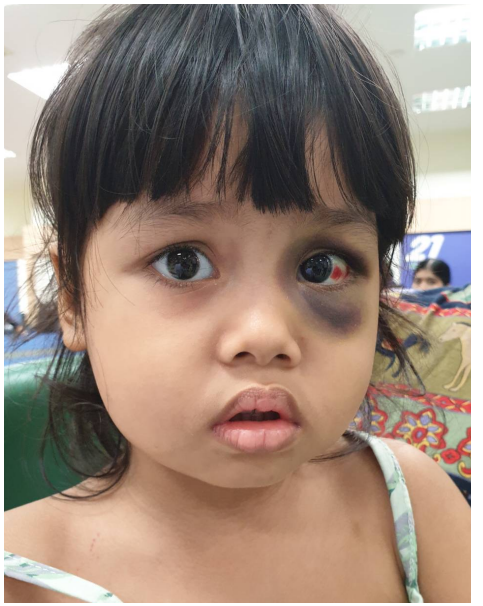






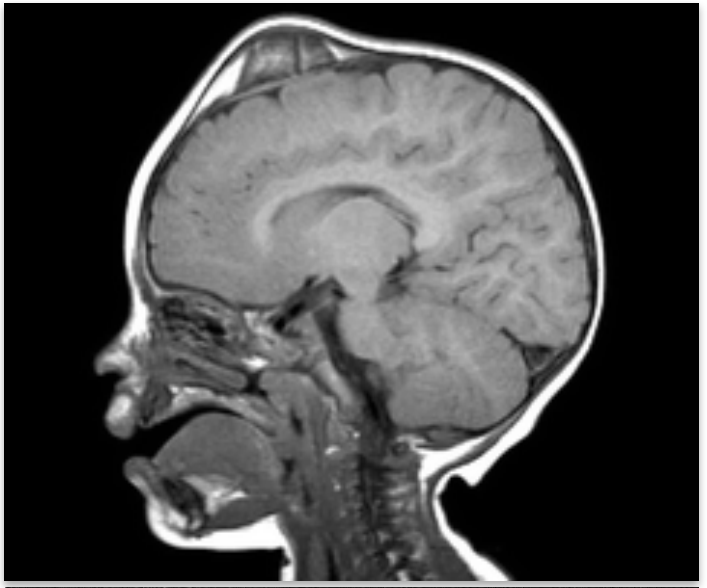


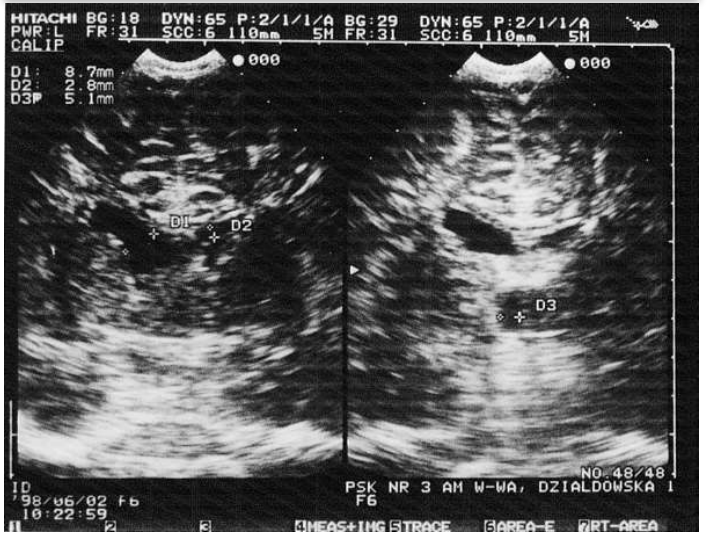




Acquired Prothrombin Complex Deficiency (APCD)

- Acquired
- CNS, GI bleeding in neonate
- ***Normal Platelet count***
- Vitamin K deficiency
- Factor II,VII, IX, X
- Prolonged PT,APPT
- Treatment: Vit K, FFP





Take Home Messages

Primary and secondary hemostasis : ***what's the different***

Platelet dysfunction

Bleeding time

Platelet aggregation study

Diseases : vWD, BS, GT, APDE

Hemophilia - Isolated APTT prolong

Take Home Messages

DIC : "consumptive coagulopathy"

Platelets counts low

FDP, D-dimer

Fibrinogen

PT, PTT prolong

APCD (Vit K deficiency)

PT,PTT prolong but normal in Platelet counts

Pretest #1

A 10-year-old boy presents with easy bruising for 10 days. Physical examination reveals afebrile, ecchymosis on both legs without hepatosplenomegaly. CBC: Hb 11.5 g/dL, Hct 35%, WBC 10,000/cu.mm. (PMN 72%, L 13%, E 15%), Platelet 360,000/cu.mm., normochromic, normocytic red cell, large platelets with pale-stain.

Which of the following is the most likely diagnosis?

(A) Hemophilia

(B) von Willebrand disease

(C) Glanzmann's thrombasthenia

(D) Acquire prothrombin complex deficiency

(E) Acquire platelet dysfunction with eosinophilia

Pretest #1

A 10-year-old boy presents with easy bruising for 10 days. Physical examination reveals afebrile, ecchymosis on both legs without hepatosplenomegaly. CBC: Hb 11.5 g/dL, Hct 35%, WBC 10,000/cu.mm. (PMN 72%, L 13%, E 15%), Platelet 360,000/cu.mm., normochromic, normocytic red cell, large platelets with pale-stain.

Which of the following is the most likely diagnosis?

(A) Hemophilia	**3.4%**
(B) von Willebrand disease	**0%**
(C) Glanzmann's thrombasthenia	**0%**
(D) Acquire prothrombin complex deficiency	**6.9%**
(E) Acquire platelet dysfunction with eosinophilia	**89.7%**

Pretest #2

A 12-month-old is brought to the hospital due to swollen and bruised knee. Physical examination reveals swelling of right knee with pain on movement and decreased range of motion. CBC shows: Hb 12 g/dL, Hct 36%, WBC 10,200/cu.mm. (PMN 35%, L 65%), Platelet 175,000/cu.mm. Coagulogram shows: aPTT 60 sec (control 36 sec), PT 10 sec (control 12 sec), TT 8 sec (control 10 sec).

Which of the following is the most likely diagnosis?

(A) Hemophilia A

(B) Dysfibrinogenimia

(C) Vitamin K deficiency

(D) von Willebrand disease

(E) Disseminated intravascular coagulation (DIC)

Pretest #2

A 12-month-old is brought to the hospital due to swollen and bruised knee. Physical examination reveals swelling of right knee with pain on movement and decreased range of motion. CBC shows: Hb 12 g/dL, Hct 36%, WBC 10,200/cu.mm. (PMN 35%, L 65%), Platelet 175,000/cu.mm. Coagulogram shows: aPTT 60 sec (control 36 sec), PT 10 sec (control 12 sec), TT 8 sec (control 10 sec).

Which of the following is the most likely diagnosis?

(A) Hemophilia A **79.3%**

(B) Dysfibrinogenimia **6.9%**

(C) Vitamin K deficiency **3.4%**

(D) von Willebrand disease **10.3%**

(E) Disseminated intravascular coagulation (DIC) **0%**

Pretest #3

A 5-year-old boy presents with easy bruising for a while. Physical examination reveals afebrile, ecchymosis on both legs without hepatosplenomegaly. CBC: Hb 10 g/dL, Hct 30%, WBC 10,000/cu.mm. (PMN 72%, L 13%, E 3%), Platelet 360,000/cu.mm., Coagulogram is within normal limit.

Which of the following is the most likely diagnosis?

(A) Hemophilia

(B) von Willebrand disease

(C) Glanzmann's thrombasthenia

(D) Acquire prothrombin complex deficiency

(E) Acquire platelet dysfunction with eosinophilia

Pretest #3

A 5-year-old boy presents with easy bruising for a while. Physical examination reveals afebrile, ecchymosis on both legs without hepatosplenomegaly. CBC: Hb 10 g/dL, Hct 30%, WBC 10,000/cu.mm. (PMN 72%, L 13%, E 3%), Platelet 360,000/cu.mm., Coagulogram is within normal limit.

Which of the following is the most likely diagnosis?

(A) Hemophilia **0%**

(B) von Willebrand disease **31%**

(C) Glanzmann's thrombasthenia **48.3%**

(D) Acquire prothrombin complex deficiency **13.8%**

(E) Acquire platelet dysfunction with eosinophilia **6.9%**

Pretest #4

A 2 month-old is admitted to the hospital because of drowsiness. Pertinent laboratory findings include a platelet count of 250,000/cu.mm., prothrombin time (PT) of 18 sec (control 11.5 sec), activated partial thromboplastin time (aPTT) of 51 sec (control 36 sec), thrombin time (TT) of 8 sec (control 10.5 sec).

Which of the following is the most likely cause of bleeding?

(A) Hemophila A

(B) Hemophilia B

(C) Vitamin K deficiency

(D) Immune thrombocytopenic purpura (ITP)

(E) Disseminated intravascular coagulation (DIC)

Pretest #4

A 2 month-old is admitted to the hospital because of drowsiness. Pertinent laboratory findings include a platelet count of 250,000/cu.mm., prothrombin time (PT) of 18 sec (control 11.5 sec), activated partial thromboplastin time (aPTT) of 51 sec (control 36 sec), thrombin time (TT) of 8 sec (control 10.5 sec).

Which of the following is the most likely cause of bleeding?

(A) Hemophila A **13.8%**

(B) Hemophilia B **10.3%**

(C) Vitamin K deficiency **44.8%**

(D) Immune thrombocytopenic purpura (ITP) **6.9%**

(E) Disseminated intravascular coagulation (DIC) **24.1%**

Pretest #5

A 7-year-old boy presents with epistaxis and ecchymosis for 3 days. Physical examination reveals no hepatosplenomegaly and no lymphadenopathy. He had a history of viral illness 10 days ago. CBC shows: Hb 12.5 g/dL, Hct 38%, WBC 7,000/cu.mm. (PMN 30%, L 70%), Platelet 10,000/cu.mm.

Which of the following is the most likely diagnosis?

(A) Aplastic anemia

(B) Immune thrombocytopenia

(C) Dengue hemorrhagic fever

(D) Hemolytic uremic syndrome

(E) Acute lymphoblastic leukemia

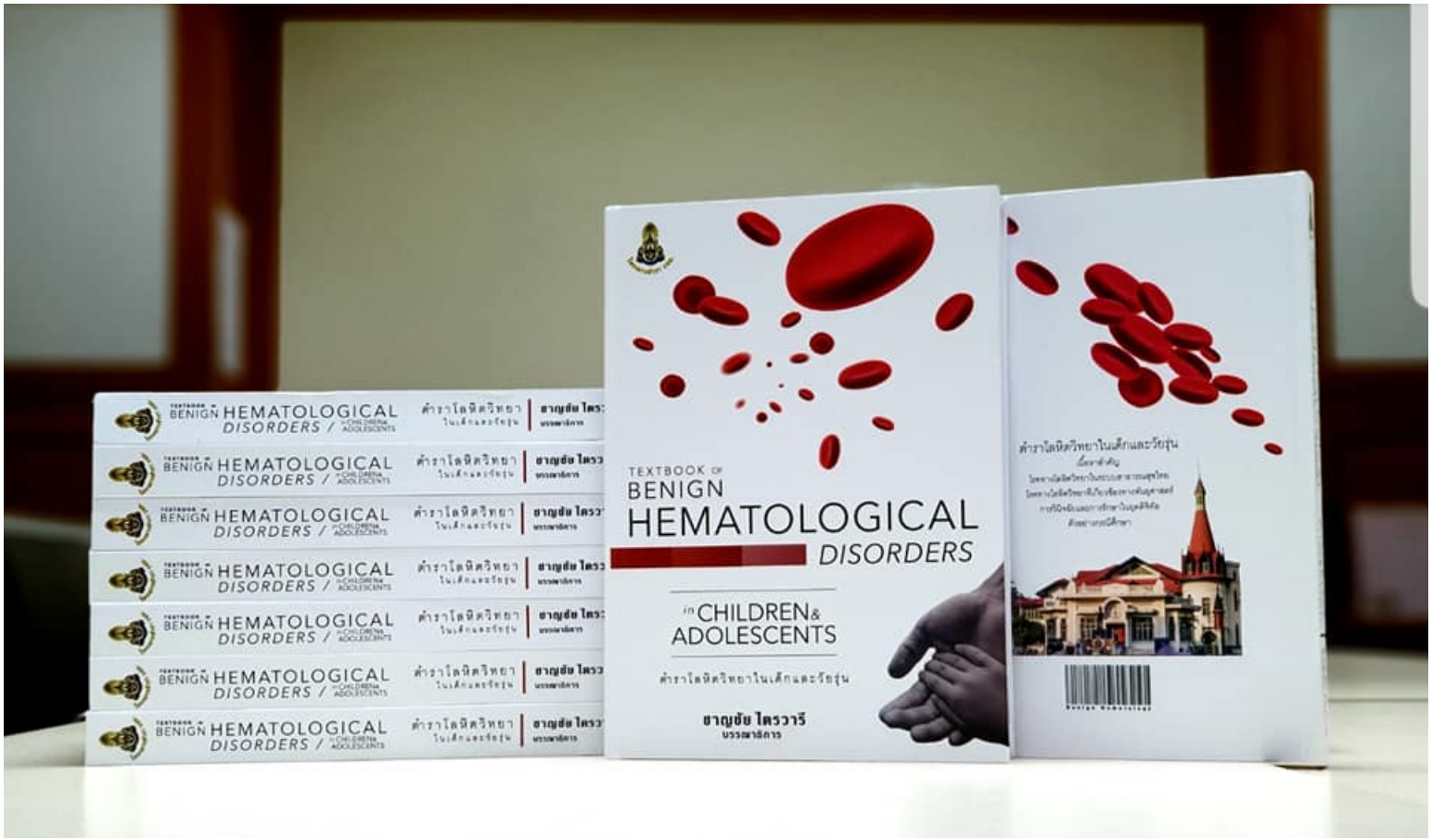
Pretest #5

A 7-year-old boy presents with epistaxis and ecchymosis for 3 days. Physical examination reveals no hepatosplenomegaly and no lymphadenopathy. He had a history of viral illness 10 days ago. CBC shows: Hb 12.5 g/dL, Hct 38%, WBC 7,000/cu.mm. (PMN 30%, L 70%), Platelet 10,000/cu.mm.

Which of the following is the most likely diagnosis?

(A) Aplastic anemia	**3.4%**
(B) Immune thrombocytopenia	**69%**
(C) Dengue hemorrhagic fever	**20.7%**
(D) Hemolytic uremic syndrome	**3.4%**
(E) Acute lymphoblastic leukemia	**3.4%**

Take Home Messages ตำราอ่านเพิ่มเติม



Textbook of Benign Hematological Disorders in children & adolescent

ชาญชัย ไตรวารี

Pediatric Cancer & Hematologic Disorder
PedHemOnc-PMK

Thank you

Take Home Messages