Hemostasis and Related Disorders

- Integrity of blood vessel is necessary to carry blood to tissues.
- damage to vessel wall is repaired by hemostasis
  ↓
- involves formation of a thrombus (clot) at the site of vessel injury.

- hemostasis occurs in 2 stages.

① primary haemostatic plug.

② secondary hemostasis stabilizes platelet plug.
↓
mediated by coagulation cascade.

Primary hemostasis & related bleeding Disorders.

→ step 1 of 1° hemostasis

- transient vasoconstriction
- blood vessel will constrict quickly

} immediate reflex.

Mediated by :

→ neural reflex

→ Endothelin → released from damaged endothelium.

Step 2

vWF

- damaged part will be coated with vWF
- vWF will line damage site at lvl of subendothelial collagen.
- vWF binds to collagen.
- once endothelial cells are disrupted we expose both subendothelial collagen & basement membrane but also contains collagen
→ vWF will now act as a linker molecule for platelet binding
→ platelet will bind with vWF using GP1b receptor
↓
platelet adhesion.

→ Impt: source of vWF

① Endothelial cells.

② platelets.

↓

Weibel palade bodies

↓ other stuff from WP:

p-Selectin

vWF

next

platelets get activated.

↓

shape change

↓ &

degranulate → dumping of mediators

↓ 2 imp ones

✓ ADP.

✓ thromboxane A_2.

{platelet cyclooxygenase derivative}

→ ADP causes expression of another receptor

↓

GP2b 3a.

↓

necessary for platelet aggregation

→ TXA_2 → signal for further aggregation

→ linker molecule btw platelets

↳ fibrinogen

Summary

primary hemostasis occurs by:

- step 1 → transient constriction of damaged vessel.
  - mediated by reflex neural stimulation and endothelin release from damaged endothelial cells
- step 2 → platelet adhesion to surface of disrupted vessels
  - vWF binds exposed subendothelial collagen.
  - platelets bind vWF using GP1b receptor.
  - vWF is derived from Weibel Palade bodies of endothelial cells and α-granules of platelets.
- step 3: Platelet degranulation.
  - adhesion induces shape change in platelets.
  - degranulation releases multiple mediators
  - ADP (dense granules) promotes exposure of GPIIb/IIIa receptor on platelets.
  - TXA_2 promote platelet aggregation.

Step 4: platelet aggregation.

- platelets aggregate at site of injury via GPIIb/IIIa using fibrinogen as a linking molecule. (not fibrin ✗)
- results in formation of platelet plug (temporary) (weak)
  - ↓
  - to strengthen → secondary → next chapter

Disorders of primary hemostasis

- usually due to abnormalities in platelets
  - quantitative (not enough number)
  - qualitative.
- when patients are having disorders of 1° h. they'll present with very classical symptoms;
  - ↓
  - mucosal & skin bleeding
    - ↓
    - predominant picture of such patient
  - + easy bruising.

→ what are the mucosal bleeding?

- → epistaxis (commonest)
- → hemoptysis (blood coughing)
- → GI bleeding
- → hematuria
- → menorrhagia (as endometrium is also mucosal surface)

- all these are manageable but,

Feared complication is:

Intracranial bleeding

↓

due to severe thrombocytopenia

→ what are skin bleedings?

- Petechiae (pin point bleeding)
- Purpura (larger)
- Ecchymoses (largest). >1cm.

→ easy bruising.

→ Petechiae are a sign of thrombocytopenia (only). And are not usually seen with qualitative disorders.

Useful lab studies

- platelet count.
- bleeding time
- Blood smear
- Bone marrow biopsy.

Disorders

ITP

- autoimmune production of IgG against platelet antigens (eg: GPIIb/IIIa)
- This is the most common cause of thrombocytopenia in children & adults
- Auto-antibodies are produced by plasma cells in spleen.
- antibody-bound platelets are consumed by splenic macrophages, resulting in thrombocytopenia.

Acute form of this occurs in children
↓
usually thrombocytopenia. after weeks of immunization. due to IgG against GP2a/3b.

chronic form → adults.

- usually women in child bearing age.
- may be 1° or 2° (eg: SLE, Lupus).

In chronic form:
- may cause short-lived thrombocytopenia in offspring as anti platelet IgG can cross placenta.
- But this IgG stops causing after delivery & eventually die ... so transient.

Laboratory findings

↓ platelet count, often < 50K/μL.
- Normal PT/PTT.
- ↑ megakaryocyte on bone marrow biopsy.

Initial treatment

↓
Corticosteroids.

⇒ children respond well
⇒ Adults may show early response, but often relapse.

* If a person has symptomatic bleeding and we are fearing IC/bleeding
↓
IV-Ig can raise platelet count.

* But effect is short-lived

* How does this work?

- the splenic macrophages will start eating these Ig instead of Ig bound to platelets
* once the Ig are over. these will start destroying platelets again.

Splenectomy

- Eliminates primary source of antibody and site of destruction
- performed in refractory cases.

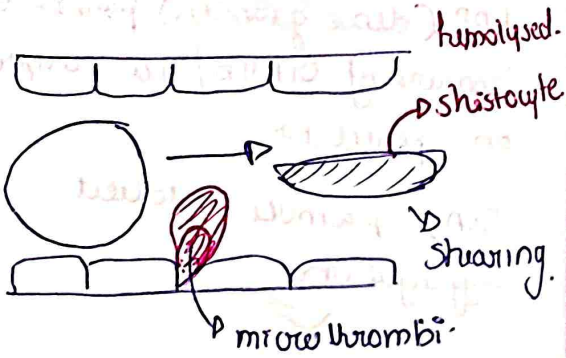
→ Ig against platelets GP2b/3a are produced by ~~platelet~~ spleen
→ and spleen is the source of splenic macrophages that eats these IgG bound platelets.

Microangiopathic Hemolytic Anemia

- Microangio ⇒ associated with small blood vessels.
- Hemolytic anemia.

Microangiopathic - due to some pathology in small blood vessels
↓
- there is Hemolytic Anemia.

* pathologic formation of platelet microthrombi in small vessels due to some condition



platelet microthrombi
⇒ only platelets are there inside

- RBC's are "sheared" as they cross microthrombi, resulting in hemolytic anemia with Schistocytes.
- ⇒ thrombocytopenic.
- platelets are consumed in the formation of microthrombi.

schistocytes.

- Helmet cell ☆

- patients with TTP have.

ADAMS TS13 Enzyme.

Enzyme decrease.

normally VWF are produced as multimers.

In order to degrade them into monomers → we chop them using this enzyme.

- So if it is deficient... we can't degrade VWF multimer.
- If there is no enzyme... they'll pile up and will lead to abnormal platelet adhesion & will lead to this microthrombi

HUS - classically in children

hemolytic uremic syndrome.

Hemolytic ⇒ shearing & hemolysis occurring due to microthrombi

Uremic syndrome ⇒ this is going to predominantly occurs kidney, leading to kidney damage & causing uremia.

where does microangiopathic hemolytic anemia occurs?

↓

seen in TTP (thrombotic thrombocytopenic purpura.)

HUS

↓

hemolytic uremic syndrome.

TTP is due to.

- ADAMS TS 13 deficiency

Why does HUS patients get microthrombi?

It occurs after infection by

E.coli - O157:H7 (O157H7)

↓

E.coli vira toxin.

↓

damage endothelial cells

↓

platelet.

Micro thrombi

into children gets this by eating undercooked beef.

TTP.

Thrombotic → platelet micro to thrombi

- Thrombocytopenic ⇒ low platelet, as they are used up
- purpura due to thrombocytopenia.
- Here also, ~~microangiopathic~~ hemolytic ↓.

platelet micro thrombi are formed.

- Why do they get this microthrombi?

- large uncleaved multimers lead to abnormal platelet adhesion, resulting in microthrombi

reasons for ADAM TS13 deficiency?

① genetic defect but, MC

② auto antibodies against them.

classic patient → adult female having

E-coli 0157:H7 dysentry.

CF. in HUS & TTP.

- skin & mucosal bleeding.
- microangiopathic hemolytic anemia
- Fever
- CNS.

In TTP & HUS.

predominently Brain & kidney tissues are affected

TTP - CNS mainly

HUS - kidney mainly.

Lab findings

- ↑ bleeding time
- PT, PTT Normal
- Anemia with schistocytes.
- ↑ megakaryocytes on bone marrow biopsy.

Treatment.

- plasmapheresis & corticosteroids. especially in TTP.

Qualitative Disorders.

Bernard - Soulier syndrome.

- genetic.
- GPIb/2a deficiency.
- platelet adhesion is impaired.
- Blood Smear:
- mild thrombocytopenia.
- enlarged platelets.

- why mild thrombocytopenia?

→ platelets with GPIb dysfunction. doesn't live that long & are destroyed early.

- enlarged platelets?

- platelets are immature in some way.

↓ way to remember.

In (B)ernard-(S)oulier syndrome.

↓

Big Suckers.

↓

enlarged platelets.

Glanzmann thrombasthenia.

- genetic GP2b/3a dysfunction.
- platelet aggregation is impaired.

Aspirin - causes qualitative disorder.

- Aspirin - irreversibly inactivates cyclooxygenase.
- lack of TXA_2 impairs platelet aggregation.
- TXA_2 is must for aggregation.

Uremia - disrupts platelet function.

- Uremia is a condition that patients have. poor kidney function.

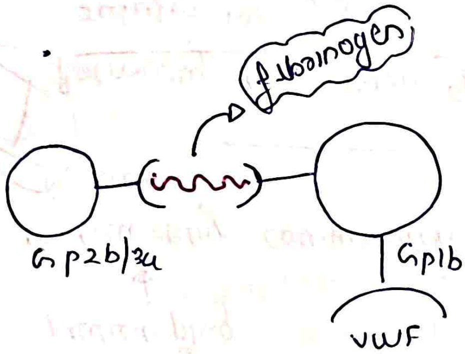
- → build up of nitrogenous waste products.
- & they disrupt both adhesion and aggregation.

2° Hemo

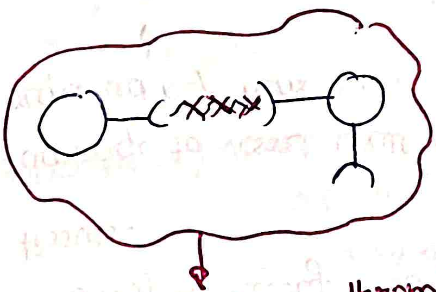
Turn pages.

Secondary Hemostasis

- The goal of secondary hemostasis is to stabilize the weak platelet plug.
- Occurs via coagulation cascade.



- fibrinogen is then converted to fibrin by thrombin at end of 2° hemostasis
- fibrin is cross linked & stabilizes this interaction.



↓
platelet - fibrin thrombus
↓
stable.

- thrombus is bond area to cover area of disruption.

* coagulation cascade generate thrombin.

- converts fibrinogen in platelet plug to fibrin.

fibrin is then cross linked, yielding a stable platelet-fibrin thrombus.

---

factors of coagulation cascade are produced by Liver. in Inactive state.

Activation requires.

- Exposure to an activating substance
- phospholipid surface. → surface of platelets. ★ → more numbers = PTT
- calcium. → dense core granules of platelet

Disorders of 2° hemostasis is usually due to factor abnormalities

Clinical features.

* deep tissue bleeding into muscle & Joints.

* Rebleeding after surgical procedures.
↓
eg wisdom tooth removal

Laboratory studies measure.

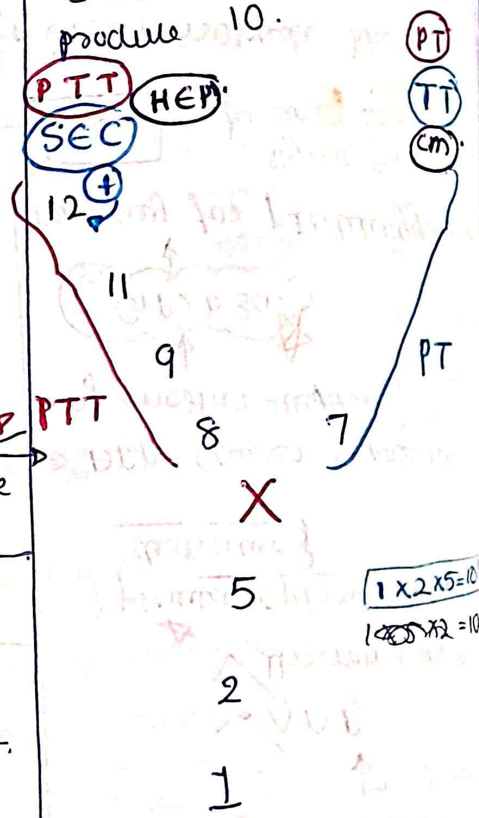
PT → Extrinsic + Cm pathway

PTT → Intrinsic + Cmn pathway

PT K പുറത്ത് പോണം.

Coagulation Cascade.

- Goal of the Entire cascade is to produce 10.



way to remember.

12, 11, 9, 8, more letters
↓
so PTT (3 letters).
activated by SEC (3 letters)

- 7 - less number ∴ PT & TT.

SEC → Subendothelial collagen
TT - tissue thromboplastin

* for measuring heparin effect is, (HEP)
(PTT) is more useful.

- for measuring Coumarin effect (PT) is more useful.

Hemophilia A (Right 8)

- Genetic F VIII deficiency.
- X linked recessive.
  i.e, predominantly affects males.
- Can arise from a new mutation without any F/H. family Hist
- F/H is always not necessary

CF

- presents with:
  deep tissue / joint / post surgical bleeding.
- Clinical Severity depends on degree of deficiency.

Lab findings.

- ↑ PTT, normal PT.
- F 8 ↓.
- Normal platelet count & bleeding time.

Treatment

- recombinant factor VIII.

Hemophilia B.

- factor IX deficiency.
- Resembles Hem A, except F IX levels are decreased & F VIII is normal.

Coagulation factor Inhibitors

- acquired antibody against coagulation factor resulting in impaired factor function.
- Anti-FVIII is most common.
- It will be very similar to Hem A. So how will you differentiate.
- Clinical & lab findings are similar to hem A.

differentiation high yield!

In CFI → PTT does not correct upon mixing normal plasma with patient's plasma [mixing study]
In hem A → PTT will get corrected.

Von Willebrand Disease

Most Common inherited coagulation disorder.

Multiple Subtypes exist.
qualitative. quantitative.

- m/c → autosomal dominant with decrease vWF levels.
- ↑° hemostasis is disrupted

CP →
mild mucosal & skin bleeding.

Lab findings
↑ bleeding time.
- ↑ PTT
vWF is necessary to stabilize FVIII
- normal PT.
- Abnormal ristocetin test.

Ristocetin test - negative
- there is no enough level of FVIII stability so as to create problem in 2° clotting.

Treatment

Desmopressin

↓

- Increases VWF release from Weibel-Palade bodies of endothelial cells.

Vitamin K deficiency

necessary for γ carboxylation of.

2, 7, 9, 10
Protein C, S.

- Vitamin K is activated by epoxide reductase.
- coumarin actually ⊖

deficiency occurs in.

- Newborns {gut not colonized by bacteria yet}

↓

we give vit K injection prophylactically to Newborns.

- long term antibiotic therapy
- malabsorption.

Liver Failure.

* production of coagulation factors ↓
* decreased activation of {precursors in liver} vitamin K by epoxide reductase.
- effect of liver failure on coagulation is followed using PT.
- effect of liver failure is followed by

↓

PT.

Large volume transfusion.

→ Dilutes coagulation factors.

→ results in relative deficiency.

Other disorders of Hemostasis.

Heparin Induced Thrombocytopenia.

- Heparin can form complex with

↓

Platelet factor (4)

↓

present on platelet surface

IgG ab are formed against this complex.

↓

platelet destruction arises. Secondary to Heparin therapy.

- fragments of destroyed platelets may activate normal platelet causing

↓

Thrombosis

↳ feared complication of (HIT).

DIC

- pathologic {abnormal} activation of coagulation cas
- widespread microthrombi result in ischemia & infarction.

- consumptions of platelets & factors result in bleeding, especially from IV sites & mucosal surface.

Clotting & Bleeding occurs.

* DIC is almost always 2° to another disease process.

- It can occur in:

① obstetric complication.

amniotic fluid contains tissue thromboplastin which is a strong activator of coagulation cascade.

if amniotic fluid enters mom's circulation → DIC occurs

② sepsis.

→ endotoxin of bacteria can (+) coagulation cascade.

or

→ IL-1 & TNF produced by macrophages can also (+).

③ adenocarcinoma.

- mucus from adenocarcinoma can (+).

④ Acute promyelocytic leukemia.

primary granules {forming auer rods} can reach circulation & (+).

⑤ Rattle snake bite.

venom → (+).

Lab findings.

↓ platelet count.

- ↑PT & ↑PTT.
- ↓ fibrinogen.
- microangiopathic hemolytic anemia.
- Elevated fibrin split products.

↓

D-dimer

Best screening test.

Rx:

- address underlying 2° cause.
- Transfuse blood products & cryoprecipitate as needed.

Disorders of fibrinolysis.

- due to plasmin overactivity resulting in excessive cleavage of fibrinogen.

plasminogen —tPA→ plasmin.

↓ Cleaves

- fibrin & fibrinogen
- destroys CF
- blocks platelet aggregation.

α-2 antiplasmin is the one that inactivates plasmin.

see, there is no ↑ clots.

- Some pathology overactivates plasmin...

{see there is not too much clot & thus plasmin is getting (+) because of that}.

- some pathology (+) plasmin.
- plasmin is gonna know out CF, prevent aggregation & also cleaves

↓

fibrinogen {normally in blood} see

eg:

- Radical prostatectomy — urokinase release during this procedure can (+) plasmin
- ~~cirrhosis of liver~~ — ↓ production of α2 - antiplasmin.

* presents with ↑ bleeding.
- presents similar to DIC.

Lab findings:

- ↑PT, ↑PTT
- ↑ bleeding time.
- Normal platelet count.
- ↑ fibrinogen split products
- No D-dimers