Thromboembolic Disorders

Thrombosis is the development of thrombus consisting of platelets, fibrin, RBC & WBC in the arterial or venous circulation causing occlusion & then arterial venous thrombo embolism.

Venous Thromboembolism

- Venous Thrombosis
- Pulmonary embolism.

Deep vein thrombosis :-

Blood cellular materials (RBC, WBC, platelets).

with

fibrin strands.

Formed in the venous portion of vasculature.

Pulmonary Embolism :-

A thrombus or foreign substances which is arises from the systemic circulation and lodges in the pulmonary artery or its branches → complete or partial obstruction of pulm. blood flow.

Three 1° components that play a Role in the development of thrombosis :-

1. Venous stasis (Sluggish blood flow)
   a) Altered or ↓ed blood flow in the deep
   b) veins of lower limbs resulting from
      (i) Immobility
      (ii) prolonged bed Rest
      (iii) massive obesity
      (iv) Venous Obstruction.

(v) CHF,

(vi) Hypovolemia,

(vii) Varicose vein,

(viii) late-stage pregnancy,

(ix) Shock OR Severe MI.

(2) Vascular Wall injury OR Endothelial damage.

(a) Mechanical

Eg: → Venipuncture,

→ fracture.

(b) Chemical

Eg: → K^+

→ hyperosmolar glucose

(c) Trauma

There will evoke inflammatory response (phlebitis) in addn to locally activating coagulation cascade.

→ Intramural thrombosis.

(3) Hypercoagulability

Excessive activation of coagulation cascade.

occurs in activated protein C Resistance.

→ Deficiency of protein C, protein S OR Anti-thrombin III.

→ Certain types of malignancy.

The coagulation cascade can be triggered through either → Intrinsic pathway or
→ Extrinsic pathway.

Intrinsic pathway activated through Contact of factor XII with exposed collagen from the damaged subendothelial vessels. aPTT ✓

Extrinsic pathway – Exposure of blood with tissue thromboplastin [A tissue factor released after vascular wall damage). PT ✓

Thrombus

It denotes formation of a clotted mass of blood within the non-interrupted vascular system.

A pathogenic extension of normal haemostasis.

Endothelial injury :-

Imp. in forms of thrombi within heart and arteries. Thrombi develop within the LV in myocardial infractions and on ulcerated plaques in atherosclerosis of aorta and arteries. Also develop within the cardiac chambers when there is any damage to the myocardium [Endocardium].

Eg:- Cardiac surgery and infections of myo-cardium.

Valves → Inflammatory valve diseases and

Haemodynamic changes in HTN and turbulant blood flow also affect the endothelium.

* Radiation injury,
* Chemical agent (Exogeneous)

  Eg:- Cigarette smoking. → CO will cause endo. damage.

* Chemical agents (Endogeneous)

  Eg:- Hypercholesterolemia, homocystine.

* Bacterial toxins,
* Immunological injuries

  Eg:- Transplant rejection, Immune complex formation.

Alteration in normal blood flow :-

I. Turbulant blood flow → arterial and cardiac thrombi.

II. Venous stasis → Venous thrombi.

In the normal Laminar blood flow, all the ~~axial~~ formed blood elements occupy the central "axial" streams.

The periphery of the blood stream adjacent to endothelial layer move most slowly and is free from formed elements.

In stasis and turbulance —

(1) They disrupt laminar flow and bring the platelets in contact with endothelium.

(ii) They prevent dilution by fresh blood flow and hepatic clearence of activated coagulation factors.

(iii) They retard the inflow of inhibitors of clotting factors and permit the build-up of thrombi.

(iv) Turbulance may cause dysfunc^n or damage to the endothelium favoring platelets and fibrin deposition and Reducing the release of prostacyclin and t-PA.

Thrombi forms ulcerated atherosclerotic plaques. This will cause turbulance. Thrombi forms also due to aneurysm.

In heart MI cause endothelial injury. In this the necrote muscle does not contract. Most thrombi develops within the abnormally dilated Vesicose veins arise within the pokets created by venous valves, where is used stasis or turbulence.

Hyper viscosity syndromes such as polycythemia, cryoglobulinemia, macroglobulinemia. In this used resistance to the blood flow → stasis.

In Sickle cell anemia the deformed RBCs tend to cause a logjam and stasis predisposes to thrombosis.

Hypercoagulability

Hypercoagulability can be defined as alteration in the blood coagulation mechanism that may predisposes to thrombosis.

Either primary → due to genetic defects in the one OR more coagulation factors.

OR

Secondary → occuring in a variety of clinical condⁿ associated with recurrent thrombosis.

primary → Due to defects in clotting proteins.

Due to inherited lack of Anticoagulants like

Anti thrombin III

protein C,

protein S.

Also due to defects in fibrinolytic system.

Mutation in one OR more coagulation protein genes.

Secondary → such as Nephrotic syndrome, Severe trauma OR burns, late-pregnancy, Cardiac failure and disseminated cancer.

Oral contraceptives → ↑ the conc. of plasma fibrinogen, prothrombin, and factors VII, VIII and X

→ ↓ the fibrinolytic activity.

In patients with disseminated cancer, secretion OR Release of procoagulant tumor pdts that activate factor X directly OR thromboplastic substances,

that trigger the extrinsic pathway → thrombosis. This paraneoplastic syndrome, known as Trousseau's Sign. characterised by migratory thrombosis.

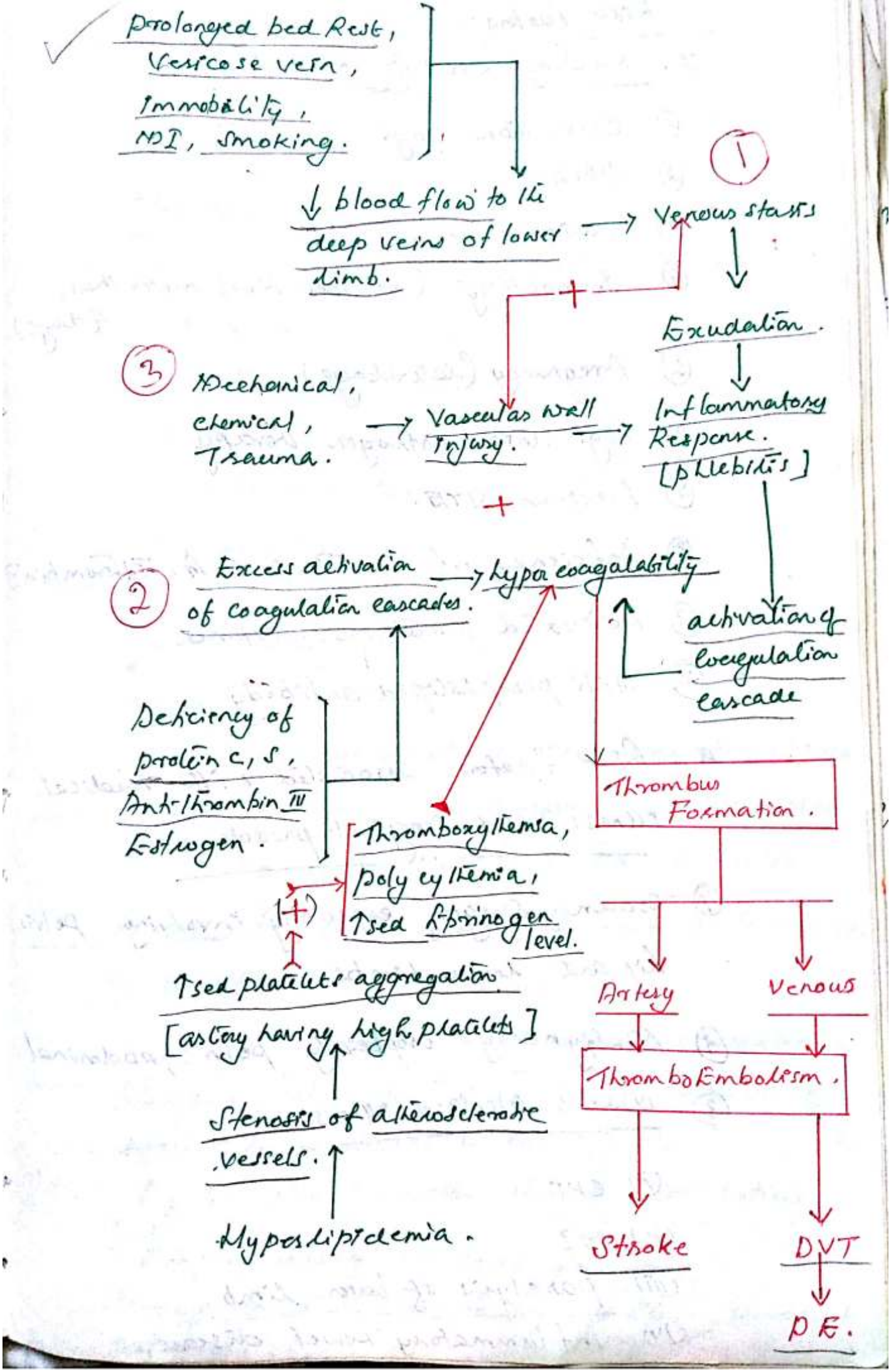
Patients having high titers of auto antibodies directed against anionic phospholipids [Cardiolipin] have a high frequency of arterial and venous thrombosis.

Eg:- SLE. (Antibody is called as lupus anticoagulant)

Mech:-

(i) Induction of platelet aggregation, (ii) Inhibition of prostacyclin OR NO path by endothelial cells OR (iii) by interference in the generation of protein C.

Other factors like smoking, Obesity, Reduced PGI_2 release and Reduced fibrinolytic Response.



Risk factors :-

I. Patient specific Risk factors :-

1. Older than 40yr.
2. Obesity
3. Varicose vein
4. Immobility (i.e; Bed Rest more than 4 days)
5. Pregnancy (late stage)
6. High dose estrogen therapy.
7. Previous VTE.
8. Deficiency of protein C, S, Anti thrombin III
9. Activated protein-C resistance.
10. Anti phospholipid antibody.

II. Risk factors associated with medical illness and surgical procedures :-

1. Trauma, surgery especially (involving pelvis, hip and lower limbs.)
2. Malignancy especially pelvic, abdominal.
3. Major Medical Illness :-
   - (i) CHF
   - (ii) MI
   - (iii) paralysis of lower limb.
   - (iv) Inflammatory bowel disease.

(v) Sepsis.
(vi) Kidney disease.
(vii) Beckett's syndrome.
(viii) polycythemia.

Treatments :-

Non-pharmacological approach :-

TED is prevented by
→ Reducing Venous stasis with external pneumatic compression OR
→ graduated compression stockings.

Pharmacological Treatments :-

Unfractioned heparin :-

Mech :-

Inhibits coagulation by catalysing the inhibition of thrombin. Act as anticoagulant by catalysing inactivation of thrombin (Factor IIa), activated factor X (factor Xa), activated factor IX (factor IXa) by anti thrombin.

Prevents further growth and propagation of thrombus, allowing the endogenous thrombolytic system to eradicate the existing clot.
Heparin also promotes thrombus Resolution.

Dosing :-
Empiric dosing → 1000 units / hr.
It may cause sub therapeutic OR supra therapeutic outcomes.

If; Activated PTT below OR above the targeted range.

* Weight based nomogram method -

15-25 units / kg / hr.

Lower doses → Thrombotic Indications.

pulmonary embolism require aggressive therapy (upto 25 units / kg / hr)

Monitoring :-

By aPTT.

. Measured 6hrs after commencing therapy.

aPTT Ratio :

$$\frac{\text{Observed aPTT}}{\text{Normal lab control aPTT.}}$$

NV → 1.5 – 2.5

Oral anticoagulants

Warfarin :-

Mech:-

Warfarin are oral Vitamin K antagonists act by interfering with cyclic interconversion of Vit. K and its 2,3 Epoxide (Vit. K epoxide).

⟶ depletion of Vit K dependent coagulation proteins OR coagulation factors [. Prothrombin OR factors II, VII, IX, X.

Dosing and admn.

Administered orally.

Indications and use:-

1. 1° and 2° prevention of VTED.
2. Prevention of systemic arterial embolism, in patients with A. Fibrillation
3. Prevention of acute MI in patients with peripheral arterial disease.
4. Prevention of stroke and recurrent infarct and death in patients with acute MI.
5. Also used in patients with valvular heart disease to prevent systemic arterial embolism.

Low molecular weight Heparin.

Approx. 1/3 size of heparin.

Mech. of Action:-

Binding with antithrombin.

LMWHs catalyses the inactivation of factor IIa (thrombin) by binding to anti-thrombin through the unique pentasaccharide sequence and to thrombin to form a 3° complex.

LMWH has an antifactor Xa : antifactor IIa binding affinity ratio of approx. 1:1. (Varying from 2:1, 4:1)

* Mainly for Venous thromboembolism.

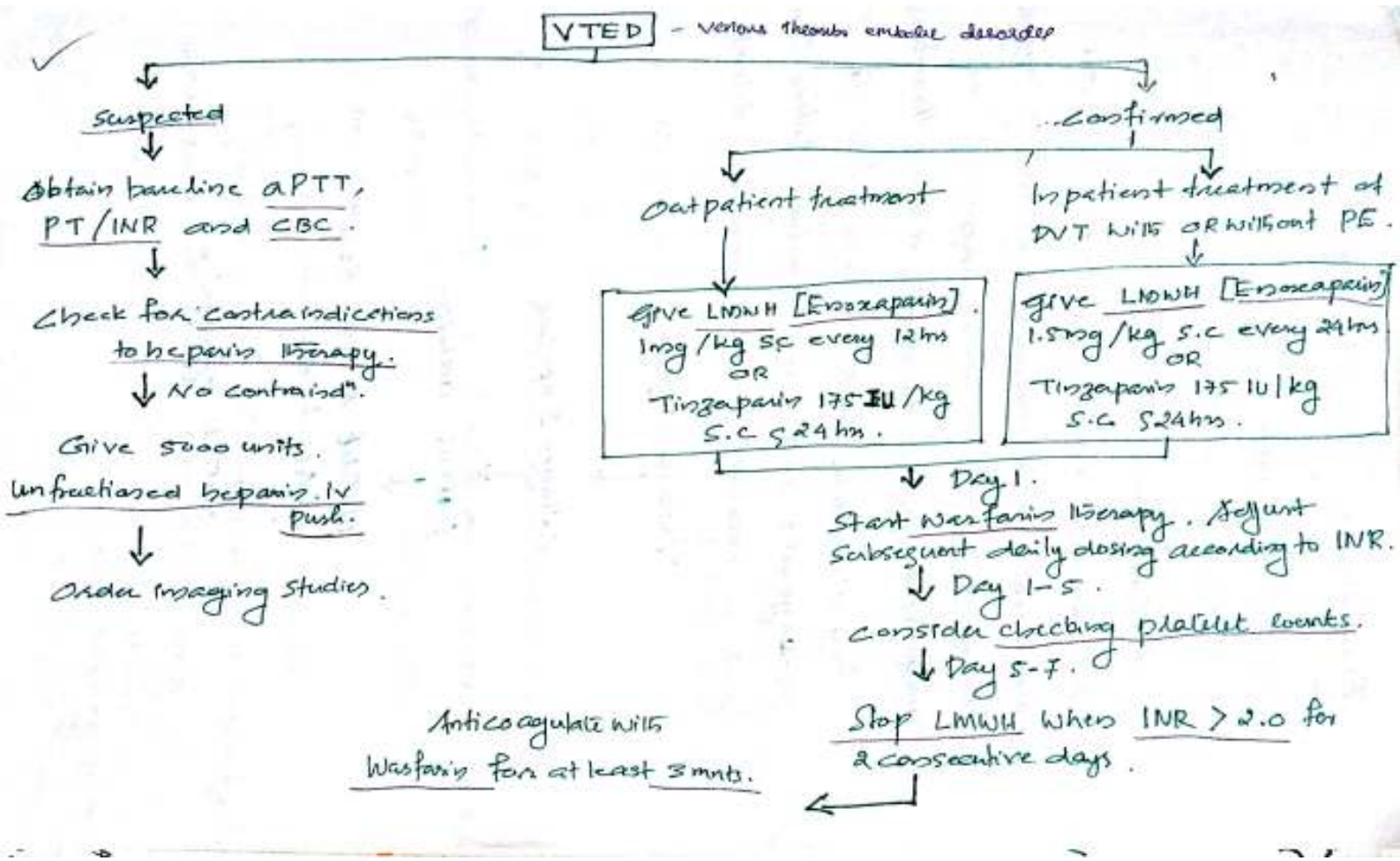
Synthetic pentasaccharides:-

Selective factor Xa inhibitor.

Mech of Action:-

Antithrombin mediated selective inhibition of factor Xa. Neutralizn of factor Xa interrupts the blood coagulation cascade and thus inhibits thrombin formn and thrombus devlpmt.

Thromboprophylaxis against DVT/PE after, hip-fracture repair surgery, hip-replacement surgery, knee-replacement surgery.



Formation of platelet plugs.

Coagulation system involves :-

1. platelet mediated haemostasis
2. Coagulation cascade.

This both will work in concert to prevent haemorrhage or to injury. Natural anticoagulant process in the body closely regulate the coagulation system to avoid diffuse thrombosis.

Any disturbances in the balance b/w the procoagulant and anticoagulant systems can leads to haemorrhage or thrombotic diseases.

Vascular injury

↓

Collagen Exposure.

↓

Platelet adhesion.

↓

platelet release Reaction.
(ADP Release)

↓

platelet aggregation.