MEDICINE

432 Team

32 Hyper-coagulation (Thrombophilia)

Team work is based on group F slides and important notes from group A & B slides were added

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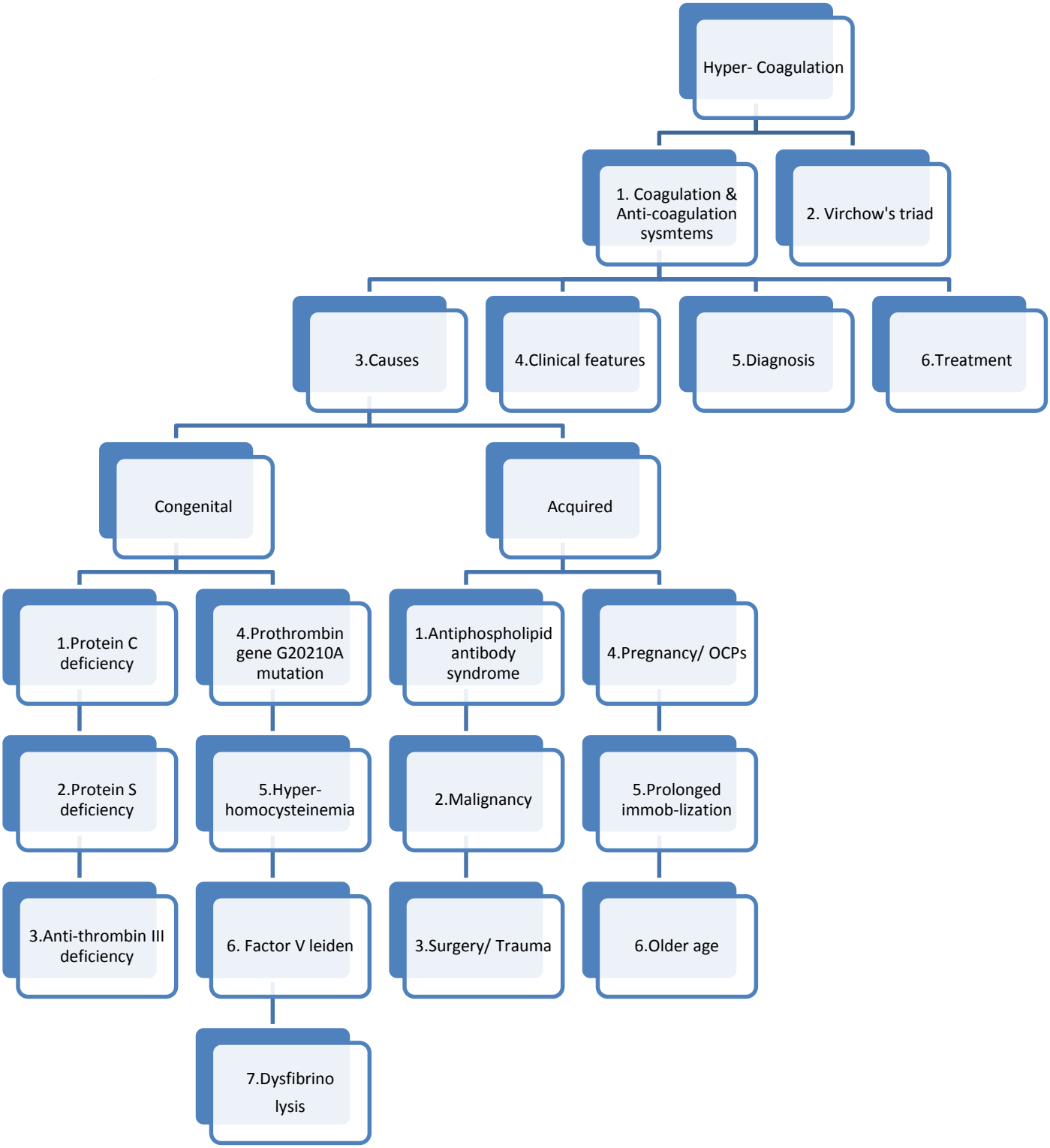
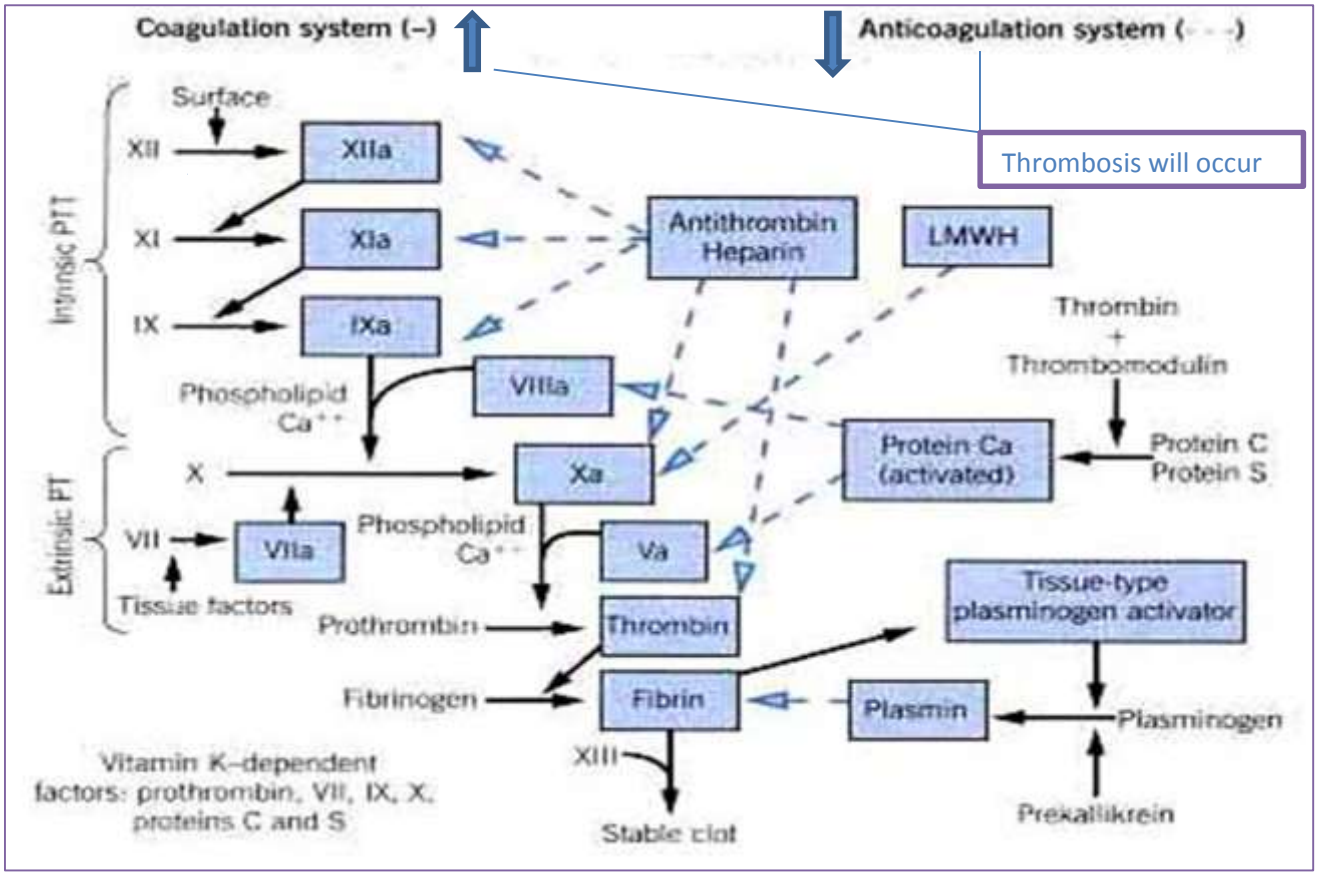
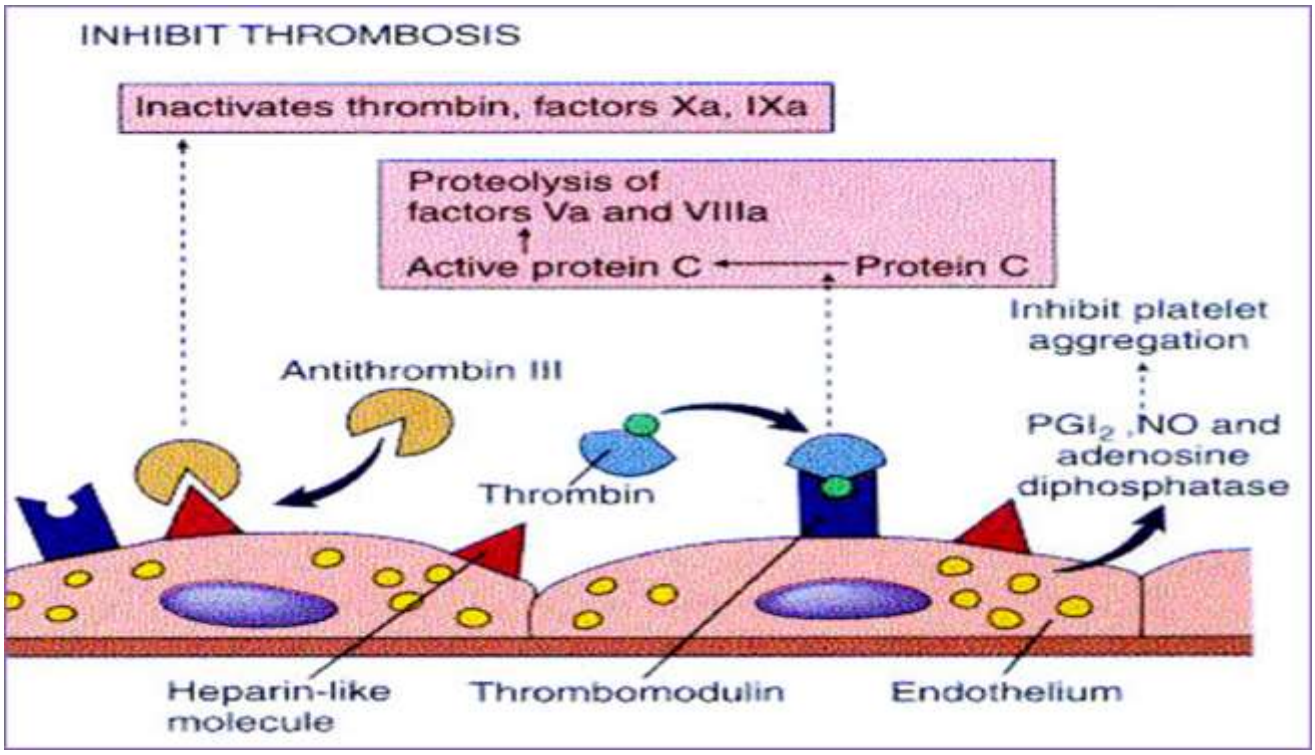
COLOR GUIDE: • Females' Notes • Males' Notes • Important • Additional

-Objectives were not given



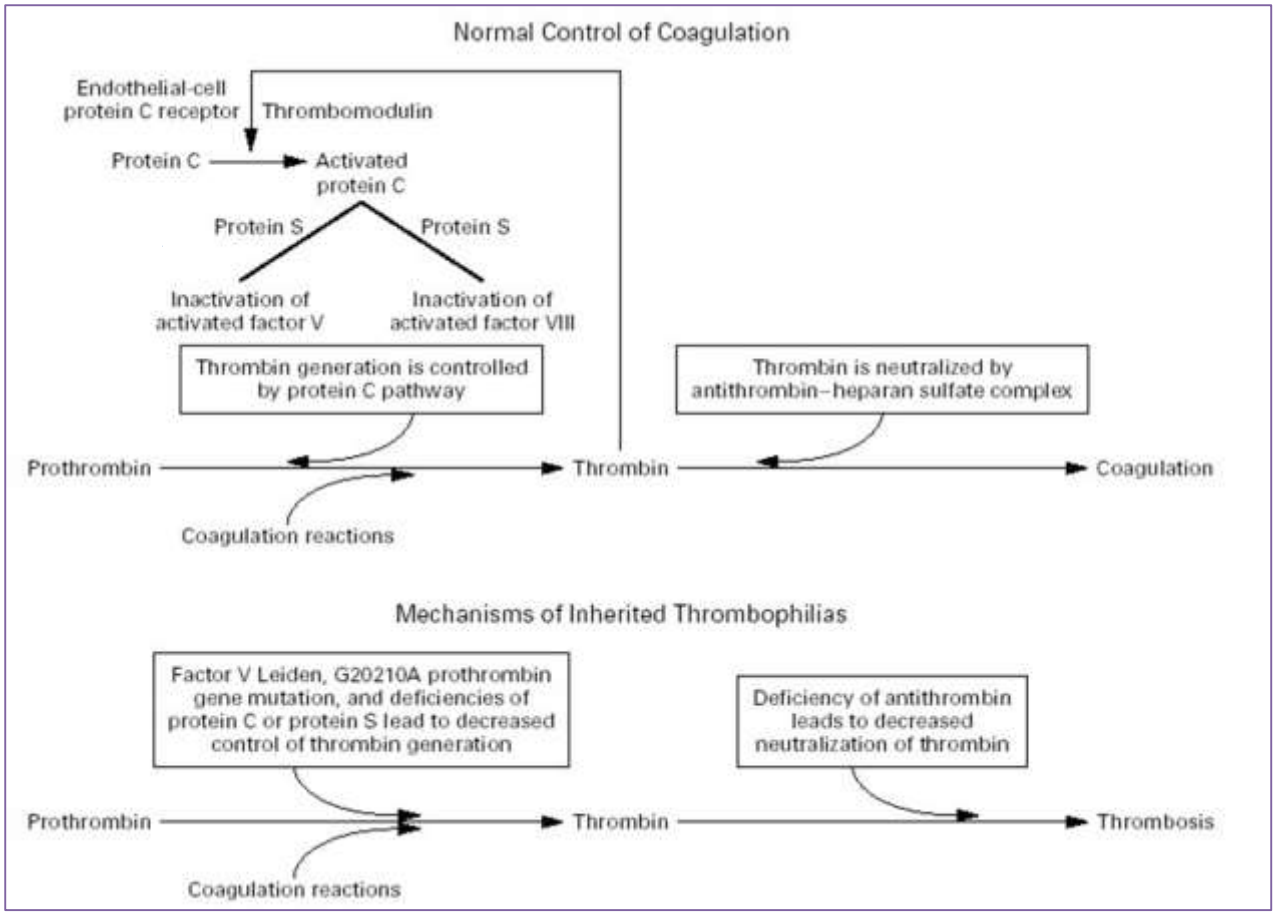
1. Coagulation and Anti-coagulation Systems: FYK





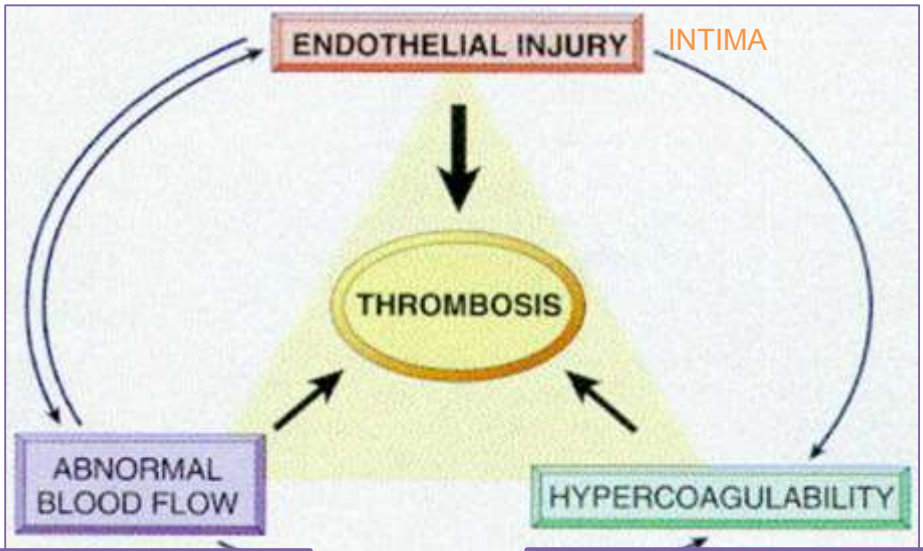
Anti-thrombotic function of endothelium:

Prostacyclin (PGI2) - Nitrous oxide (NO2)- Thrombomodulin-Heparans (proteoglycans) – Tissue factor pathway inhbitors (TFPI)- Plasminogen activator inhbitors (PAI-1).



2. Virchow's triad:

E.g. Surgeries (especially orthopedics) – I.V. lines- Trauma (Motor Vehicle Accident).



E.g. Stasis.

E.g. Loss of protein C or S.

We look here for the cause in both arterial and venous thrombi. In many cases the cause can be multi-factorial.

3. Congenital Causes:

A. Protein C Deficiency:

- Synthesis in the liver- Vit-K dependent-Autosomal dominant.
- Inactivate factor V and factor VIII and thrombin generation. It needs a co-factor (protein S).
- Deep vein thrombosis (DVT), pulmonary embolism (PE) and superficial thrombophlebitis are the most common manifestations.
- Arterial thromboses are rare.
- Protein C is consumed and levels are low in Vit-K deficiency, DIC and liver disease.
- warfarin-induced skin necrosis (WISN) is easy to occur:
  - ✓ 1/3 warfarin-induced skin necrosis are caused by protein C deficiency.
  - ✓ Rare.
  - ✓ Routinely when we give warfarin we don't test for low protein C or S so skin necrosis may happen.
  - ✓ Also known as Coumadian- induced skin necrosis (CISN).
  - ✓ More common in women.
  - ✓ Starts with painful purpura then they progress to form black necrotic tissue.
  - ✓ Mostly seen under breast tissue or along thighs or sites of I.V. lines.
  - ✓ Why the skin necrosis happens in the areas of fat abundance is unclear; possibly these areas are more susceptible because of reduced blood supply.

*http://www.dermnetnz.org/reactions/warfarin-necrosis.html

B. Protein S Deficiency:

- Synthesis in hepatocytes & megakaryocytes- Vit-K dependent- Autosomal dominant.
- Cofactor of activated protein C (APC).
- 74%: DVT; 72%: superficial thrombophlebitis.
- Warfarin-induced skin necrosis may occur.
- Protein C and S deficiency can be both inherited (autosomal dominant) or acquired (nephrotic syndrome, pregnancy and OCPs may cause acquired low Protein S).

C. Anti-thrombin III Deficiency:

- Synthesis in liver & endothelial cells.
- Activated by binding to heparin-like molecule.
- Inhibits thrombin (IIa) and factors IXa,Xa, XIa, XIIa.
- DVT, PE and mesenteric vessels thrombosis may occur.
- Resistant to unfractionated heparin.
- Must treat patients with low-molecular-weight heparin (LMWH).
- Anti-thrombin III deficiency can be either inherited (autosomal dominant) or acquired (Disseminated intravascular coagulation).
- Homozygosity for mutant alleles is not compatible with life.
- Pregnant females are at higher risk of thrombosis in case of anti-thrombin III deficiency.

D. Prothrombin G20210A Gene Mutation:

- Normal half-life of factor II is 3-5 days in the circulation.
- Prothrombin gene mutation: nucleotide position 20210: G → A.
- Elevated prothrombin levels and activity.
- Increased risk of venous thrombosis (2nd most common cause of thrombosis)
- Rare in Asians & Africans.

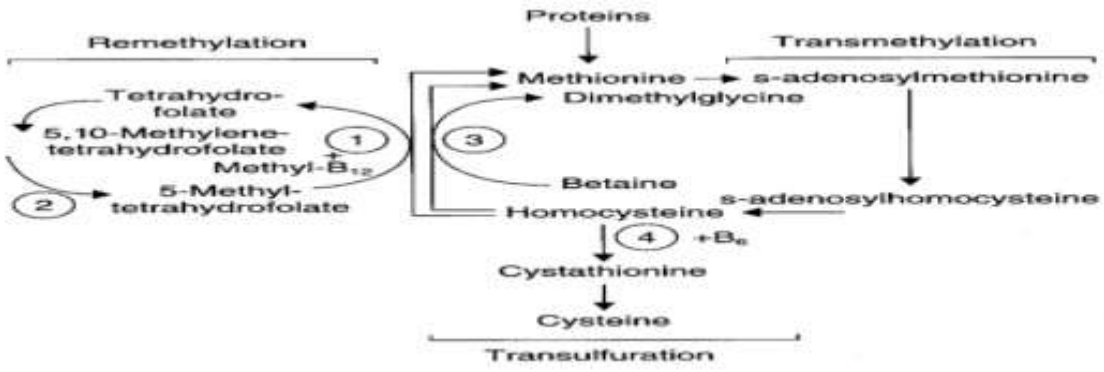
E. Factor V Leiden (Activated Protein C Resistance):

- Point mutation of factor V gene.
- Most common form of inherited thrombophilia (~50% of cases)
- Results in impaired inactivation of factor V by activated protein C.
- Present in 5% of whites; virtually absent in Asians & Africans.
- Estrogen + FV Leiden → ↑↑↑ thrombosis
- Venous thrombosis & fetal wastage
- We usually test for both factor 5 leiden and activated protein C levels.
- Heterozygosity: 2x ~ 3x risk most of the time they do not require treatment only observe them.
  Homozygosis: 80x risk
- Heterozygosity factor V Leiden is a relative mild risk factor of thrombosis, and appears not to affect life expectancy.

Racial difference:

- Asians &Africans: protein C deficiency, protein S deficiency predominant.
- Whites: Factor V Leiden, prothrombin gene G20210A mutation predominant.

F.Hyperhomocysteinemia:



- 1: methionine synthase
- 2: methylenetetrahydrolate reductase(MTFHR)
- 3: betaine-homocysteine methyltransferase
- 4: cystathionine β –synthase(CBS)

- Rare autosomal recessive disorder.
- Elevated homocysteine →

(1) Vascular endothelial injury (via free oxygen radicals).

(2) Decreased protein C activation.

(3) Increased factor V activity.

(4) Induction of endothelial cell tissue factor activity.

Causes: (1) cystathionine β–synthase def. (most common)
(2) Vit-B6, Vit-B12, folic acid deficiency

- Cause premature arterial atherosclerosis and venous thromboembolism.
- Tx: standard fashion (Oral anticoagulants) + vitamin supplementation.
- Patients with celiac disease often have vitamin deficiencies like VB6 and VB12.

G.Dysfibrinolysis:

5 major forms:

(1) Congenital plasminogen deficiency.

(2) Tissue plasminogen activator deficiency.

(3) Increased plasminogen activator inhibitor.

(4) Congenital dysfibrinogenemia.

(5) Factor XII deficiency (factor XII involved in plasmin generation - kinin cascade-).

3. Acquired Causes:

A. Anti-phospholipid Antibody Syndrome:


Livedo Reticularis

- Most common of hypercoagulable disorder.
- Heterogeneous autoantibody binds to phospholipid-protein complex.
- Include lupus anticoagulant syndrome & anti-cardiolipin antibody syndrome.
- Exact mechanism is unknown.
- Venous and arterial thrombosis, recurrent spontaneous abortion, stroke, and TIA (transient ischemic attack).
- Idiopathic (primary) or associated with SLE, infection, drug reactions (secondary).
- Livedo reticularis, thrombocytopenia and PT, PTT will be prolonged.
- Diagnosis (Both clinical and laboratory):
  1. specific assay to detect anti phospholipid antibody (lupus anticoagulants, anti-cardiolipin antibodies) in the serum; false-positive VDRL.(Laboratory)
  2. In Anti-phospholipid antibody syndrome the patient may present with multiple abortions of normal fetuses or recurrent thrombosis. (Clinical)
- The diagnosis can be hard sometimes because the clinical presentation can be typical but the laboratory results are negative.
- Usually they present with ugly thrombosis (E.g. stroke or retinal vein thrombosis or mesenteric vein thrombosis).

B .Prolonged Immobilization:

- Prolonged immobilization can sometimes be defined as decrease in the daily activity or being bedridden for 3 days or more or hx of travel for more than 4 hours.
- In medicine we don't give routinely DVT prophylaxis although many patients can stay bedridden for weeks. Therefore, the incidence of new DVT cases is increasing in medical wards.

C. Malignancy:

- 15% patients with cancer have clinical thrombosis.
- 40% of idiopathic DVTs will turn to be caused by malignancy mostly at the age of 45, so those patients need to be tested every 6 months.
- Esp. mucin-secreting adenocarcinoma (GI or lung), pancreatic cancer, acute pro-myelocytic leukemia.
- Mechanisms: hypercoagulability, endothelial injury, venous stasis.
- DVT, PE, Trousseau's syndrome (migratory superficial thrombophlebitis), non-bacterial thrombotic endocarditis (NBTE) : fibrin-platelet vegetations on heart valves→systemic embolization.
- Occurrence of Trousseau's syndrome or without known cancer → vigorous search for occult malignancy.
- Increased production of tissue factor by tumors found in many patients, which can activate FX directly.

D. Surgery / Trauma:

- Mechanisms:

  (1) Release of tissue factor from injured tissue

  (2) Decreased plasma level of anticoagulants
- Particularly common in orthopedic surgery.
- Hip and knee surgery without anticoagulant prophylaxis → 45~70% DVT.
- The incidence of new post-surgical DVT cases is decreasing, because usually surgeons give DVT prophylaxis post surgeries.

E. Pregnancy/ Oral Contraceptives:

- Pregnancy :
  1. Placenta: placental plasminogen activator inhibitors type two.
  2. Enlarged uterus→ venous stasis in the leg.
  3. Pelvic vein injury.
  4. Trauma of C- section.
- Mostly DVT will develop during the third trimester when the uterus is large enough to compress the vein especially on the left side. If a pregnant woman in her first trimester came with DVT think about other underlying causes, because it's less likely to be caused by enlarged uterus.
- Emergent C- section can cause thrombosis more than elective one.
- Post C-section we divide patients into high risk and low risk patients and we give DVT prophylaxis accordingly.
- Oral contraceptives:
  1. Oral contraceptives→ promote liver synthesis of coagulation factors.
  2. May cause Stroke and mesenteric thrombosis.
  3. Hormone replacement therapies (HRT) are thrombogenic as well.
  4. Yasmin , Desogestrel and Gestodene are third generation OCPs that are more expensive and highly thrombogenic compared to second generation pills.

4. Clinical Presentation:

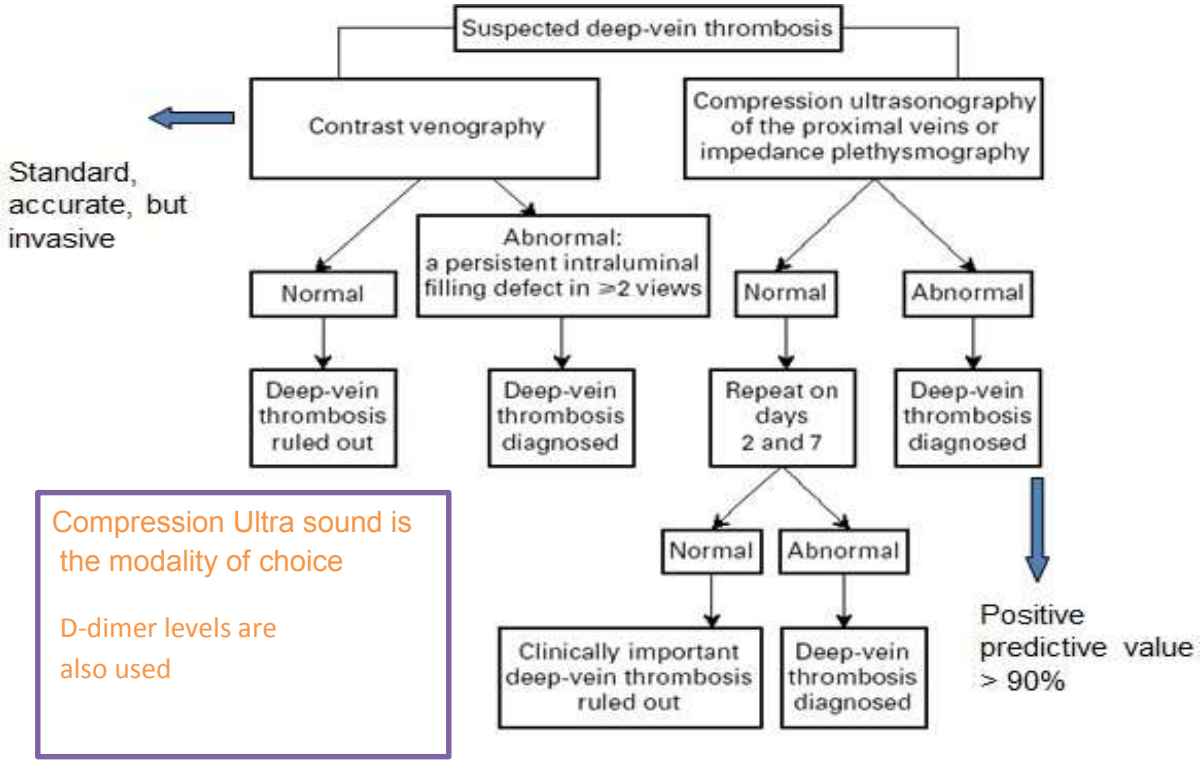
When to suspect Hypercoagulability?

- Thrombosis < 50 years.
- Family history.
- Thrombosis in an unusual site (e.g. mesenteric v. or cerebral v.).
- Idiopathic or recurrent thrombosis.
- Unexplained spontaneous abortions.
- Massive thrombosis.

Clinical Presentation for DVT and PE:

- DVT:
  1. Unilateral leg pain, swelling and dilation of superficial veins.
  2. Tenderness on compression calf muscle and increase in temperature.
  3. Homan's sign (pain during dorsiflexion of the foot).
  4. Increased circumference at least 1 cm.
- PE:
  1. Dyspnea .
  2. Tachypnea.
  3. Tachycardia.
  4. Chest pain.
  5. Decreased breathing sounds.
  6. Hemoptysis.

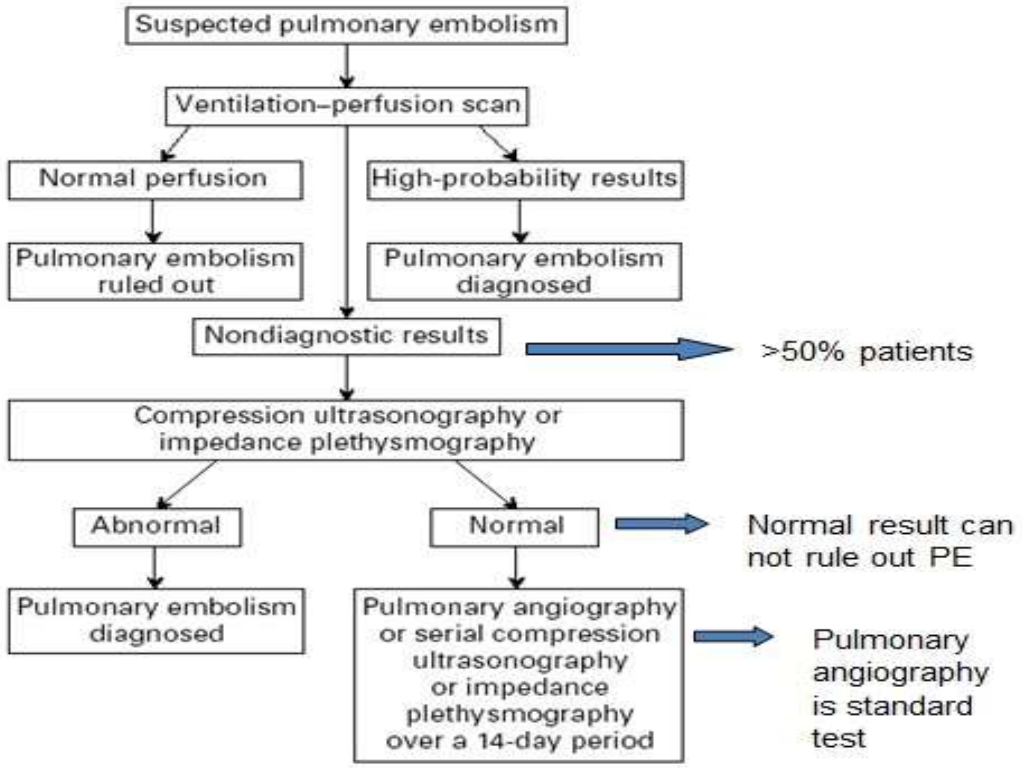
5. Diagnosis: DVT



Compression Ultra sound is the modality of choice

D-dimer levels are also used

5. Diagnosis: PE



Note that the gold standard nowadays to diagnose PE is spiral CT and not VQ scan.

5.Diagnosis: Hyper-coaguable State

- Functional, antigenic, DNA-based assays
- Avoid test when:

  (1) Active thrombosis.

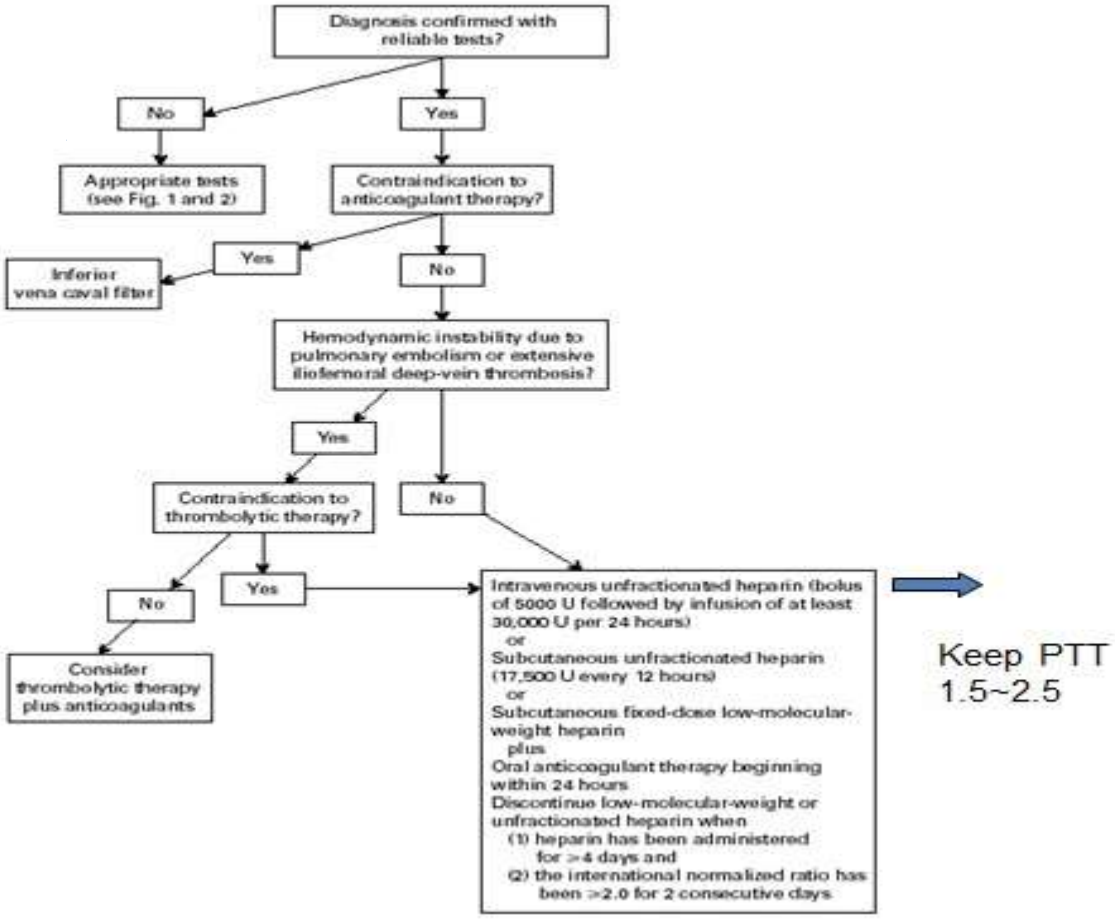
  (2) Anticoagulants treatment.

  (3) Pregnancy, estrogen use.

  (4) Liver disease.

  (5) DIC.

6. Treatment:



- Initial management: Figure above
- Long term management:
  1. Vit-K antagonist.
  2. Should be adjusted according to PT (INR).
  3. Inhibition of protein C first (6~8 hr), then inhibits other clotting factors (24~48 hr).

→ Transient hypercoagulable state → Warfarin-induced skin necrosis.

Warfarin started within 24 hr after initiation of heparin. Heparin should be given for at least 4 days and not discontinued until the INR in the therapeutic range (2.0 to 3.0) for 2 consecutive days.

- Complications:
  1. Bleeding.
  2. Heparin-induced thrombocytopenia.
  3. Heparin-induced osteoporosis.
  4. Warfarin-induced skin necrosis.
  5. Post-thrombotic syndrome (venous hypertension caused by valvular incompetence): pain, swelling, ulceration around medial malleolus is the most severe form of this syndrome.

6. Treatment:

Overdose and antidotes:

1. For heparin: protamine sulphate.

2. For warfarin: vitamin K but may take time (many hours) to act so an actively bleeding patient may also need fresh frozen plasma (FFP) or pro-thrombin complex.

New Oral anti-coagulants:

1.Direct thrombin inhibitors: Dabigatran

2.Factor X inhibitors:

- Rivaroxaban
- Apixaban
- Oral- Less bleeding -No monitoring- Good choice if we use it in the right way.

Fluctuations in INR may occur because of any one or more of the following conditions:

(1) Patient noncompliance.
(2) Changes in vitamin K intake.
(3) Other effects of concomitant drug use.
(4) Changes in warfarin metabolism.
(5) Changes in vitamin K dependent coagulation factor synthesis or metabolism.
(6) Inaccuracy in INR testing.

Summary

- None of the inherited abnormalities of coagulation is strongly associated with arterial thrombosis.
- Apart from anti-thrombin deficiency and homozygous factor V Leiden, most carriers of these genes will never have an episode of VTE; if they do, it will be associated with the presence of an additional temporary risk factor.
- None of the inherited abnormalities of coagulation per se requires treatment with anticoagulant.
- Paroxysmal nocturnal haemoglobinuria is a rare acquired cause of thrombosis.
- Malignancy and anti-phospholipid antibody syndrome are considered the most important acquired causes of hyper-coagulation.
- Sometimes it's hard to know whether thrombosis is due to malignancy or due to treatment of malignancy (chemotherapy).
- Remember that oral contraceptives are highly thrombogenic and patients may present with ugly thrombosis like stroke.
- We don't discharge patients who underwent hip replacement (orthopedic surgery) until they're fully mobilized. Therefore, mobilization is very important to reduce the risk of thrombosis especially DVTs.
- Most common surgeries to cause DVT are orthopedic surgeries and cesarean sections.
- Hepatic or portal vein or mesenteric thrombosis most commonly happen post abdominal surgeries and post- acute infections like appendicitis. (Endothelial injury)
- Hyper-coagulable state = Prothrombotic state = Thrombogenic state.
- Other acquired causes of hypercoagulation are (Obesity- Heart failure – Heparin induced thrombocytopenia (HIT)- Paroxysmal nocturnal hemoglobinuria- Myeloproliferative disorders (Polycythemia and thrombocythemia) and Hyperviscosity syndromes (Multiple myeloma or Waldenstrom's macroglobulinemia).
- Anti-phospholipid antibody syndrome is an autoimmune disorder.

Antibody is to cardiolipin in APA (ELISA assay); antibody is to *beta* 2 glycoprotein 1 and platelet phospholipids in patients with lupus anti-coagulants (aPTT and/or PT).

Note that Lupus anticoagulants are more associated with thrombosis that anticardiolipin antibody.

IMPORTANT NOTES FROM EXTERNAL RESOURCES

	Notes
Name of 1st book	Davidson 22nd Edition
Name of 2nd book	PreTest Medicine

Questions

1) A 60-year-old woman develops deep venous thrombosis aftera14-hour plane flight from New Zealand. The diagnosis is confirmed by a venous Doppler. There is no evidence of pulmonary embolism, and she is started on subcu- taneous low-molecular-weight heparin. She has no family history of venous thrombosis, and she is on no medications that would increase her risk of clotting. In addition to routine monitoring of coagulation parameters and a CBC, what diagnostic tests should be ordered next?

A. Functional test for factor V Leiden (Activated protein C resistance)
B. Protein C, protein S, and antithrombin III levels
C. Antiphospholipid antibody test
D. Genetic testing for prothrombin G20210A gene mutation
E. No further testing

2) A 65-year-old male with mild congestive heart failure is going to receive total hip replacement. He has no other underlying diseases and no history of hypertension, recent surgery, or bleeding disorder. Which of the following is the best approach to prevention of pulmonary embolus in this patient?

A. Aspirin 75 mg/d
B. Aspirin 325 mg/d
C. Warfarin with INR of 2 to 3 or low-molecular-weight heparin
D. Early ambulation
E. Heparin 5000 units subcutaneously every 12 hours

432 Medicine Team Leaders

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Answers:

1st Questions: E

2nd Questions: C