Thrombophilia (Hypercoagulable state)

435 medicine teamwork

[Important | Notes | Extra | Editing file]

lecture objectives:

- Not given

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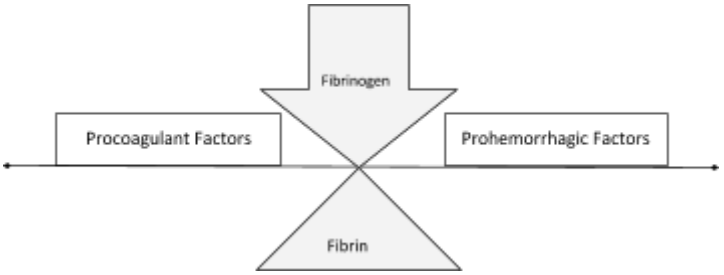
Thrombophilia

Balance of homeostasis :



- **Balance of bleeding and clotting.**
- **Imbalance in one direction can lead to:**

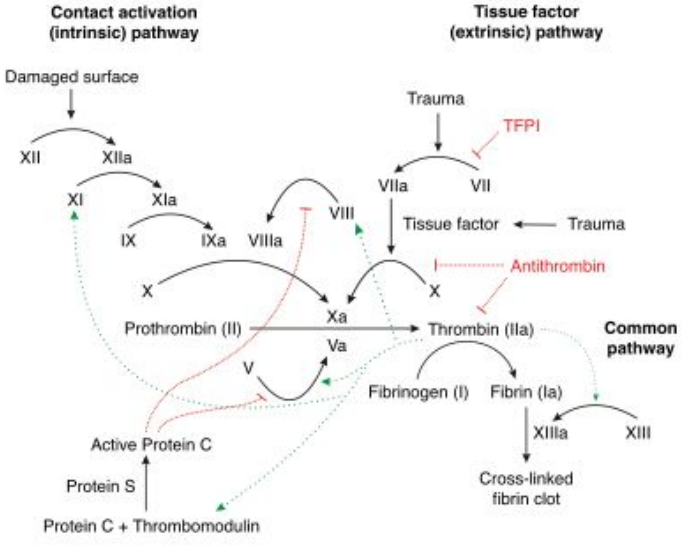
1. Hypocoagulable state ⟶ *bleeding*
2. Hypercoagulable state ⟶ *thrombosis*

The major components of the hemostatic system are :

1. The vessel wall.
2. Platelets (and other blood elements).
3. Plasma proteins (coagulation and fibrinolytic factors).

Stages of normal hemostasis			
Pre-injury	**Fibrin clot formation**	**Limiting clot formation**	**Fibrinolysis**
• The endothelium produces anti-thrombotic agents. (thus platelets & coagulation factors circulate in non-activated state)	•The endothelium is injured. •Platelets are activated. •Then Coagulation cascade is activated. •Fibrin clot forms.	•Once hemostasis has been secured, the propagation of clot is halted by **natural anticoagulants.**	•The insoluble clot needs to be broken down for vessel recanalization. •Plasminogen is activated by tissue plasminogen activator (t-PA)⟶plasmin. •Plasmin hydrolyse the fibrin clot, producing fibrin degradation factors including D-dimer.

Natural anticoagulants		
Antithrombin	**Tissue factor pathway inhibitor**	**Protein C & S**
•Serine protease inhibitor synthesized by the liver. •Destroys activated factors such as **XIa, Xa & thrombin (IIa).**	•Binds to and inactivates **VIIa & Xa.**	•Protein C is activated through binding of thrombin to thrombomodulin (structure on the endothelium), activated protein C binds to its **co-factor** protein S ⟶ then cleaves **Va & VIIIa.** •Both protein C & S are K-dependent and are depleted by warfarin.



how does the coagulation cascade start?
all our vessels are lined by tissue factor,so whenever there's endothelial injury->tissue factor will be released ->that will activate factor 7 to 7a ->and this will activate factor 10 to 10 a, and starts the process...
***so tissue factor is very imp ,and it might be increased in some conditions like cancer causing thrombosis .**
so what's the job of tissue factor phosphate inhibitor?after the initial activation and release of tissue factor,it will inhibit any further activation[check in balance"feedback" mechanism]

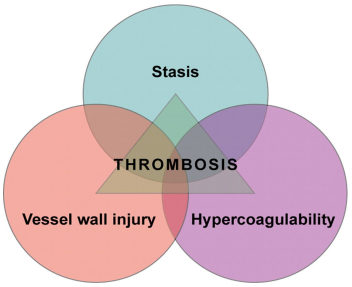
★ Take a deep breath & appreciate this graph while paying attention to the red & green dotted arrows.

Antithrombotic functions of endothelium:[1]	
Prostacyclin (PGI2)	Prevents formation of the platelet plug.
Nitrous oxide (NO2)	Vasodilation to avoid the stasis of blood and ↓ the chance of thrombus
Thrombomodulin	Thrombomodulin is protein cofactor expressed on endothelial cell surfaces that modifies the substrate specificity of thrombin.The thrombin-thrombomodulin complex activates **protein C**, initiating an essential anticoagulant pathway.
Heparans (proteoglycans)	Heparan sulfate (HS) proteoglycans are expressed on cell surfaces and in the extracellular matrix, having essential functions in development and homeostasis, as well as playing various roles in disease processes. The functions of HSPGs are mainly dependent on interactions between the HS-side chains with a variety of proteins including cytokines, growth factors, and their receptors.
Tissue factor pathway inhibitors (TFPI)	Inhibit the tissue factor to stop the coagulation
Plasminogen activator inhibitors (PAI-1)	PAI-1's main function entails the **inhibition** of urokinase plasminogen activator (uPA), an enzyme responsible for the cleavage of plasminogen to form plasmin. Plasmin mediates the degradation of the extracellular matrix either by itself or in conjunction with matrix metalloproteinases.

Coagulation factors :					
I	Fibrinogen	**II**	Prothrombin	**III**	Thromboplastin AKA tissue factor
IV	Calcium	**V**	Proaccelerin (Labile factor)	**VII**	Proconvertin (Stable factor)
VIII	Antihemophilic globulin A	**IX**	Christmas factor	**X**	Stuart-power factor
XI	Plasma thromboplastin antecedent	**XII**	Hageman factor	**XIII**	Fibrin stabilizing factor

Altered homeostatic balance :

- Alteration in the hemostatic balance between blood fluidity and clot formation due to genetic or acquired disorders which shift the balance toward **excessive platelet aggregation and thrombin generation** (clot formation) that lead to **thrombosis**. This is known as **Thrombophilia (Hypercoagulable state)**. Synonyms are : *Hypercoagulable state, prothrombotic state and thrombogenic state.*



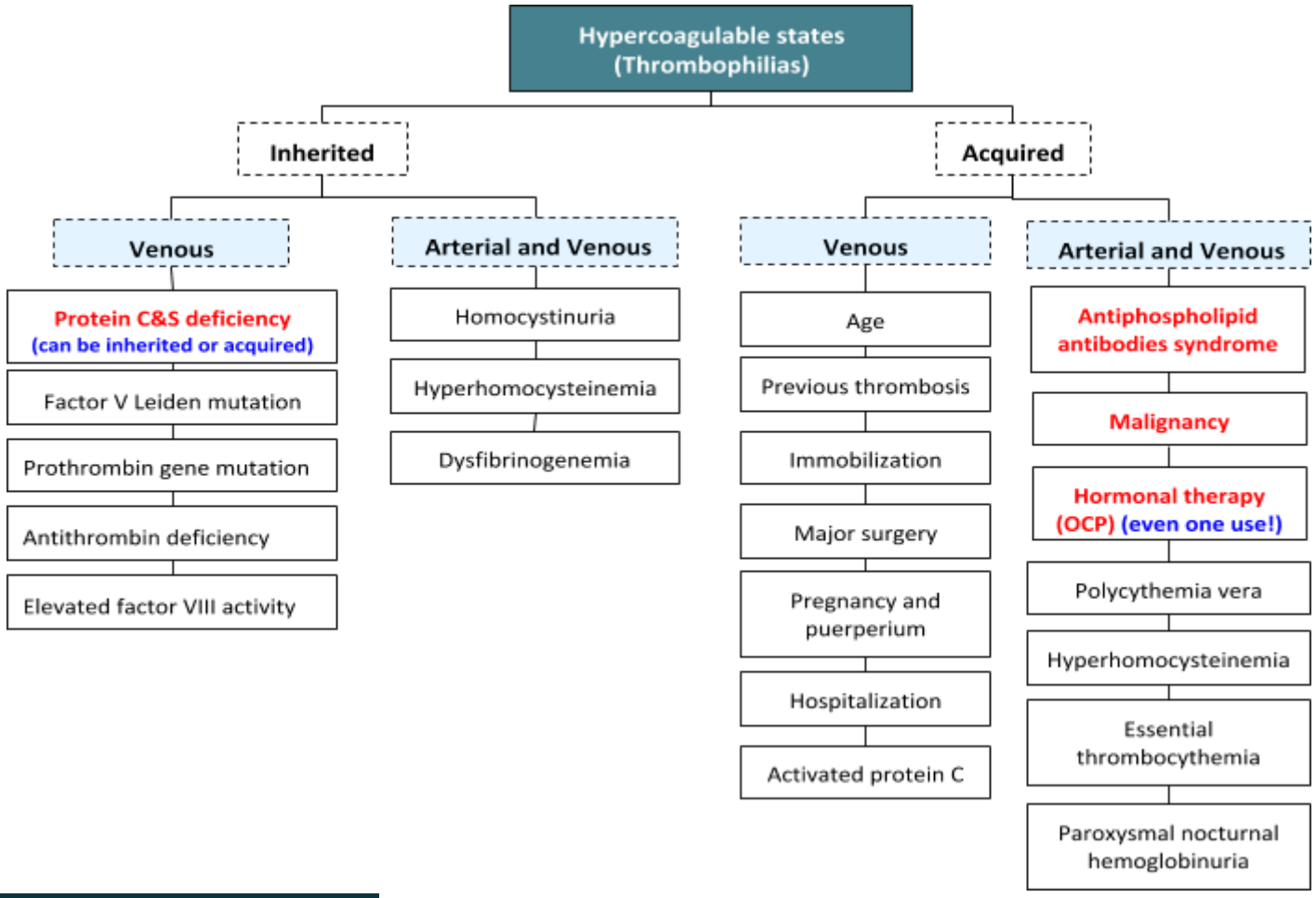
Risk factors for thrombosis :

In 1856, Rudolf Virchow postulated a triad of factors that leads to intravascular coagulation :

1. Local trauma to the vessel wall.
2. Hypercoagulability (Thrombophilia).
3. Stasis.

Stasis	Endothelial injury	Hypercoagulable states
• Immobility. • Paralysis (e.g. CVA). • Obesity. • Postoperative & casting. Heparin is given up to 2 months after orthopedic surgeries. Risk of DVT is age related thus older pts need prophylaxis more than younger pts. • Heart & Respiratory Failure.	• Trauma & major surgery. • Central venous catheters. Differentiate between thrombosis & cellulitis (especially at catheter site) & also pay attention that they can happen together!	• Conditions that predispose to an increased risk for thrombosis *either **venous (most common)**, arterial or both.* • These conditions are being identified more frequently and may be classified as inherited or acquired. Pregnancy is natural prothrombotic state,the reason behind that there some coagulation factors increase during pregnancy and there are other reasons as well. postpartum period is also prothrombotic state especially within 4-6 weeks of delivery,"participated by C section.

[1] (Substances that are released from endothelial cells and have physiological antithrombotic effects)



Venous thrombosis :

- Venous thrombosis could be ***inherited, acquired or mixed/unknown***.

Acquired	Inherited	Mixed/Unknown
• Advancing age • Prior Thrombosis or family history. • Immobilization • Major surgery[Especially orthopedic:hip replacement,knee..],the type and also the duration of surgery play a rule. • Presence of a CENTRAL venous catheter[any foreign in blood vessels can cause thrombosis] • Malignancy[↑ *tissue factor*, also pt with cancer r usually sick ,don't move ,and they r receiving chemotherapy which cause damage to endothelium] • Estrogens • Antiphospholipid antibody syndrome • Myeloproliferative Disorders(like essential thrombocythemia or Polycythemia vera):platelets are increasing in number,as a part of myeloprolifration. • Heparin-induced thrombocytopenia (HIT)[rare ,we usually use heparin as anticoagulant,but occasionally some pt will develop antibodies against heparin so they have tendency to thrombosis] • Prolonged air travel	• **Antithrombin deficiency** • **Protein C deficiency** • **Protein S deficiency** • **Factor V Leiden mutation** (Factor V-Arg506Gln) [Estrogen + FV Leiden → ↑↑↑ thrombosis]. • **Prothrombin gene mutation** (G A transition at position 20210) • Dysfibrinogenemias (rare) **None** of them is strongly associated with arterial thrombosis. All are associated with VTE (venous thromboembolism) & with adverse outcomes on pregnancy (**early fetal loss**).[DVT pt half of them will have those risk factors] Factor V Leiden & Prothrombin gene mutation: with those mutations factor V and prothrombin become Resistance to deactivation,and continue to work more than they are needed leading to clot formation.	• Hyperhomocysteinemia(rare, no need to know it,it can be congenital or acquired due to Vitamin deficiencies i.e.folate, Vit B6, and/or Vit B12) • High levels of factor VIII • Acquired Protein C resistance in the absence of Factor V Leiden • High levels of Factor IX, XI

Prevalence of Defects In Patients with Venous Thrombosis

Thrombophilic Defect	Rel. Risk
Antithrombin deficiency	8 – 10
Protein C deficiency	7 – 10
Protein S deficiency	8 – 10
Factor V Leiden/APC resistance	3 – 7
Prothrombin 20210 A mutation	3
Elevated Factor VIII	2 – 11
Lupus Anticoagulant	11
Anticardiolipin antibodies	1.6-3.2
Mild hyperhomocysteinemia	2.5

Risk vs. Incidence of First Episode of Venous Thrombosis

	Risk	Incidence/year (%)
Normal	1	.008
Oral Cont. Pills	4x	.03
Factor V Leiden (heterozygote)	7x	.06
OCP + Factor V L.	35x	.3
Factor V Leiden homozygotes	80x	.5-1

Risk of Recurrent Venous Thromboembolism (VTE) in Thrombophilia Compared to VTE Without a Thrombophilic Defect

Thrombophilic Defect	Rel. Risk
Antithrombin, protein C, or protein S deficiency	2.5
Factor V Leiden mutation	1.4
Prothrombin 20210A mutation	1.4
Elevated Factor VIII:c	6 – 11
Mild hyperhomocysteinemia	2.6 – 3.1
Antiphospholipid antibodies	2 – 9

Antithrombin deficiency :

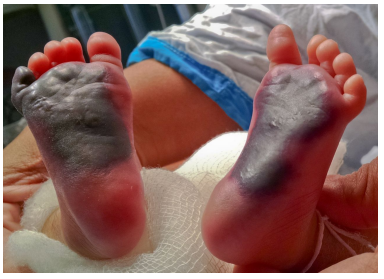
- Rare,Also known as **Antithrombin III deficiency.**
- Normally antithrombin III Inhibits coagulation by irreversibly binding the thrombogenic proteins thrombin (IIa), IXa, Xa, XIa and XIIa.
- Antithrombin's binding reaction is amplified 1000-fold by heparin, which binds to antithrombin to cause a conformational change which more avidly binds thrombin and the other serine proteases.
- Antithrombin deficiency is **autosomal dominant**(affect both sex equally).
- Females with AT deficiency are at particularly high-risk for Venous thromboembolism during pregnancy
  - DVT occurred in 18% of pts with AT deficiency, and in 33% in the postpartum period,here when multiple conditions accumulate.

Protein C deficiency :

- Protein C is a **vitamin K dependent** glycoprotein produced in the liver. (remember vit K dependent proteins, factors II, VII, IX, X,proteins C, S and Z)
- In the activation of protein C, thrombin binds to thrombomodulin, a structural protein on the endothelial cell surface.
- This complex then converts protein C to activated protein C (APC), which degrades factors **Va and VIIIa, limiting thrombin production**
- For protein C to bind, cleave and degrade factors Va and VIIIa, protein S must be available.
- Protein C deficiency, whether inherited or acquired, may cause thrombosis when levels drop to 50% or below.
- Protein C deficiency also occurs with surgery, trauma, pregnancy, OCP, liver or renal failure, DIC,or warfarin.
  OCPs are major cause of thrombosis, let it be estrogen or progesterone, hormonal therapy increases the risk of thrombosis.

Protein S, C4b Binding Protein and Protein S Deficiency :

- Protein S is an essential cofactor in the protein C pathway.
- Protein S exists in a free and bound state.
- 60-70% of protein S circulates bound to C4b binding protein.
- The remaining protein S, called free PS, is the functionally active form of protein S.
- Inherited PS deficiency is an **autosomal dominant** disorder, causing thrombosis when levels drop to 50% or lower.



Deficiency of proteins s & c are prominent causes of thrombophilia in our region. Marriages within relatives (consanguineous marriages) is thought to contribute to that. Homozygous protein C deficiency leads to retinal hemorrhage shortly after birth resulting in blindness along with generalized microthrombi (very serious). **However in other regions (globally) factor v Leiden is most common form of inherited thrombophilia (~50% of cases)**

Causes of Acquired Protein S Deficiency :

1. May be due to elevated C4bBP, decreased PS synthesis, or increased PS consumption.
2. C4bBP is an acute phase reactant and may be elevated in inflammation, pregnancy, SLE, causing a drop in free PS.
3. Functional PS activity may be decreased in vitamin K deficiency, warfarin, liver disease.
4. Increased PS consumption occurs in acute thrombosis, DIC, MPD, sickle cell disease.

Activated Protein C (APC) Resistance due to Factor V Leiden:

- Activated protein C (APC) is the functional form of the naturally occurring, vitamin K dependent anticoagulant, protein C.
- APC is an anticoagulant which inactivates factors Va and VIIIa in the presence of its cofactor, protein S.
- Alterations of the factor V molecule at APC binding sites (such as amino acid 506 in Factor V Leiden **"mutated form of FV**") impair, or resist APC's ability to degrade or inactivate factor Va.

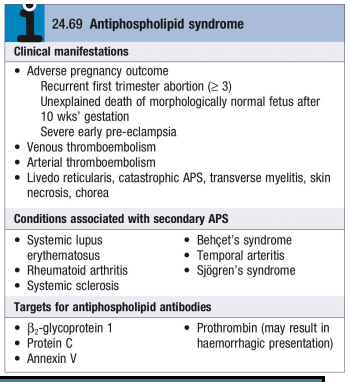
Prothrombin G20210A Mutation:

- second most common prothrombotic mutation after factor 5 leiden mutation.
- A G-to-A substitution in nucleotide position 20210 is responsible for a factor II polymorphism.
- The presence of one allele (heterozygosity) is associated with a 3-6 fold increased for all ages and both genders.
- The mutation causes a 30% increase in prothrombin levels $[\uparrow factorII \rightarrow thrombosis]$.

Antiphospholipid Syndrome[it's common;u need to know it]:

Antiphospholipid syndrome (APS) is a autoimmune condition with constellation of clinical presentations, alone or in combination, is found in association with a **persistently positive test for an antiphospholipid antibody.** The antiphospholipid antibodies are heterogeneous and typically are directed against proteins which bind to phospholipids. The term antiphospholipid antibody encompasses both a **lupus anticoagulant** and **an anticardiolipin antibody**; individuals may be positive for one or both of these activities.

[2 main clinical features of this syndrome:thrombosis+multiple abortion]



24.69 Antiphospholipid syndrome

Clinical manifestations

- Adverse pregnancy outcome
  - Recurrent first trimester abortion (≥ 3)
  - Unexplained death of morphologically normal fetus after 10 wks' gestation
  - Severe early pre-eclampsia
- Venous thromboembolism
- Arterial thromboembolism
- Livedo reticularis, catastrophic APS, transverse myelitis, skin necrosis, chorea

Conditions associated with secondary APS

- Systemic lupus erythematosus
- Rheumatoid arthritis
- Systemic sclerosis
- Behçet's syndrome
- Temporal arteritis
- Sjögren's syndrome

Targets for antiphospholipid antibodies

- β_2-glycoprotein 1
- Protein C
- Annexin V
- Prothrombin (may result in haemorrhagic presentation)

Diagnosis [you need at least: 1 of the clinical criteria to be positive + 1 positive antibody]

A.Clinical Criteria

- Thrombosis—arterial or venous
- Pregnancy loss(RECURRENT ABORTION)[why?bc APS act directly on placental vein causing thrombosis → placental ischemia → abortion]
- Thrombocytopenia
- CNS syndromes—stroke, chorea
- Cardiac valve disease
- Livedo Reticularis

B. Laboratory Criteria

- IgG or IgM anticardiolipin antibody-medium or high titer
- Lupus Anticoagulant

انتبه انتبه! مو اذا عملت antibodes وطلعت teste واحد منهن مرتفع تقول خلاص هذا عنده antiphospholipid syndrome لازم تعيد التيست مره ثانيه بعد 3 اشهر اذا مازال مرتفع هنا تمام سميها antiphospholipid syndrome طيب ليش لازم انتظر 3 there're some conditions i.e:viral infection cause transient elevation in one of these AB

The Lupus Anticoagulant (LAC)

الاسم كله على بعضه لحسة مخ:)) مسميه لوبس لأنه اول ماكتشفوه اكتشفوه على مريضة لوبس ,فإذا لقيته بمريض مومعناته انه فيه لوبس لايخدعك الاسم! والخدعة الثانية انهم مسميه انتي كواقيلنت وهو بالحقيقه كواقيولنت يسبب ثرمبوزس,طيب ليه سموه كذا؟إليه كذا بيون يلحسون مخوخنا!:)))bc they found طيب كيف كذا يطول الclotting time بس يسبب ثرمبوزس,الحد الحين مافي شي مثبت بس فيه نظريات تفسر هالظاهره العجيبه منها APTT is prolonged انه

Lupus anticoagulant is thought to prolong clotting times by binding to phospholipids and thereby limiting the phospholipid surface necessary for binding of the prothrombinase

! الوضع كله على بعضه لحسه(ايموجي يهرب)

- APTT- Usually prolonged, does not correct in 1:1 mix(vitro phenomenon, when APTT is prolonged it gives u an idea that pt might have lupus anticoagulant)
- DRVVT- venom activates F. X directly; prolonged by LAC's
- Prothrombin Time- seldom very prolonged

Anticardiolipin Antibodies

- ACAs are antibodies directed at a protein-phospholipid complex
- Detected in an ELISA assay using plates coated with *cardiolipin* & *B2-glycoprotein*

Treatment

- Patients with thrombosis- anticoagulation, INR 3
- Anticoagulation is long-term—risk of thrombosis is 50% at 2 years after discontinuation
- Women with recurrent fetal loss and APS require LMW heparin and low-dose heparin during their pregnancies. APS management sometimes require blood filtering + steroids when the presentation is "catastrophic" i.e. Clotting in more than 3 organs.

Thrombosis manifestations :

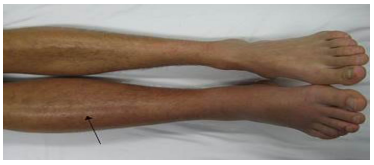
Venous – superficial vein or deep veins

While the most common presentation of venous thromboembolic disease (VTE) is with **deep vein thrombosis (DVT) of the leg and/or pulmonary embolism** , similar principles apply to rarer manifestations such as jugular vein thrombosis, upper limb DVT, cerebral sinus thrombosis and intra-abdominal venous thrombosis (e.g. Budd–Chiari syndrome).

Clinical presentation: DVT (Deep vein thrombosis)

- Lower limb DVT characteristically starts in the distal veins, causing pain, swelling, redness, an increase in temperature and dilatation of the superficial veins.
- It is typically **unilateral** but may be bilateral, and clot may extend proximally into the inferior vena cava.
- Can happen in upper limb, abdominal veins(may cause bowel ischemia), cerebral veins & sinuses.
- **Lower limb most common site**
- Symptoms & signs depend on the site.
- Often, however, symptoms and signs are minimal.

DVT prophylaxis is not 100%.



Pic : A right-sided acute deep vein thrombosis.The leg is swollen and red due to venous outflow obstruction.

Clinical presentation: Pulmonary embolism (PE)

- Shortness of breath that may occur suddenly.
- Sudden, sharp chest pain that may become worse with deep breathing or coughing (can be pleuritic type).
- Palpitation (tachycardia).
- Rapid breathing (tachypnea).
- Sweating & anxiety.
- Hemoptysis or pink, foamy sputum.
- Dizziness and fainting (low BP).
- **PE with low BP (<90 mmHg) is called massive PE**.these pt should be treated by thrombolytic therapy, anticoagulant won't resolve the clot .

Lately, simple PE (non-massive) can be treated outpatient.

Arterial – coronary, carotid and femoral (Less common)

- Acute MI, Angina
- CVA, TIA
- Claudication

Hypercoagulability Workup / diagnosis :

- **No consensus on who to test**
- **Increased likelihood if:**
  - Age <50 y/o without immediate identifiable risk factors (idiopathic or provoked)
  - Family history
  - Recurrent clots
  - If clot is in an unusual site (portal, hepatic, mesenteric, cerebral)
  - Unprovoked upper extremity clot (no catheter, no surgeries)
  - Patient's with warfarin induced skin necrosis (they may have protein C deficiency
- **DVT and pulmonary embolism** are the two most common manifestations of the same disease:VTE
  - 90% of cases of acute PE are due to emboli emanating from the proximal veins of the lower extremities; proximal DVTs are clinically most significant due to high morbidity and mortality.

- **Consider the differential diagnosis of DVT**
  - Popliteal (Baker) cyst, superficial thrombophlebitis, muscle pulls/tears, chronic venous insufficiency, cellulitis.[2]
- **Consider pre-test probability for VTE before proceeding further in diagnostic evaluation**
  - Among those with suspected of DVT of the LE, a minority (17-32%) actually have the disease.
- **Clinical criteria can be used to rank patients according to their likelihood of DVT or PE: for example, by using scoring systems such as the Wells score**[the higher the score the higher the probability]

Modified Wells Prediction Rule (criteria) for Diagnosing Pulmonary Embolism: Clinical Evaluation Table for Predicting Pretest Probability of PE

Clinical Characteristic	Score
Previous pulmonary embolism or deep vein thrombosis	+ 1.5
Heart rate >100 beats per minute	+ 1.5
Recent surgery or immobilization (within the last 30 d)	+ 1.5
Clinical signs of deep vein thrombosis	+ 3
Alternative diagnosis less likely than pulmonary embolism	+ 3
Hemoptysis	+ 1
Cancer (treated within the last 6 mo)	+ 1

→ **Clinical Probability of PE :**

- Low (score : 0-1)
- Intermediate (score 2-6)
- High (score : ≥ 6).

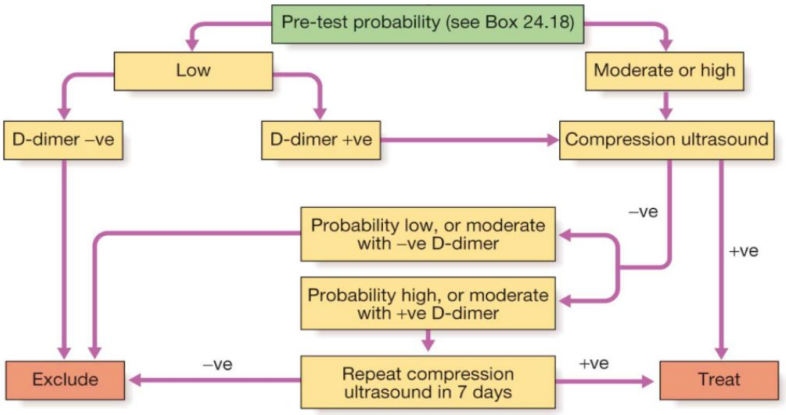


Diagram : investigation of suspected DVT based on initial Wells score. In patients with a low ('unlikely') pre-test probability of DVT, **D-dimer** levels can be measured; *if these are normal, further investigation for DVT is unnecessary.* In those with a moderate or high ('likely') probability of DVT or with elevated D-dimer levels, objective diagnosis of DVT should be obtained using appropriate imaging.

Diagnosis	
Clinical Examination (Non-Specific)	• Palpable cord over the calf • Ipsilateral edema, warmth • Superficial venous dilatation
Non-Invasive Testing	• **Impedance plethysmography** - Measure arterial and venous blood volume changes in nearly each body segment (arms, legs, head, …) non-invasively and continuously and is, therefore, suitable to be used for vascular diagnosis. • **Compression ultrasonography[the most commonly used these days]** Ultrasound probe is placed over the suspect vein → compress the vein by the probe → normally veins are highly compressible → when difficult to compress→ reliable indicator of the presence of clot → additionally the clot & blood flow can be visualized. - Recommended in moderate to high pre-test probability

[2] The differential diagnosis of unilateral leg swelling includes a spontaneous or traumatic calf muscle tear or a ruptured Baker's cyst, both characterised by sudden onset and localised tenderness. Infective cellulitis is usually distinguished by marked skin erythema and heat localised within a well-demarcated area of the leg and may be associated with an obvious source of entry of infection (e.g. insect bite, leg ulcer).

	• **D-dimer** - Useful in low pre-test probability to exclude diagnosis of VTE - Sensitivity and negative predictive value are high (~99%) - HIGH D-dimer in: trauma, pregnancy and malignancy • **Magnetic resonance venography** • **Computed tomography[with contrast]**very useful • **Echocardiography, ventilation-perfusion (V/Q) scanning (useful for pregnancy / small clots) and pulmonary**
Invasive Testing	• **Contrast venography**

Management:

- The mainstay of treatment is **anticoagulation with low molecular weight heparin (LMWH)**, **followed by a coumarin anticoagulant, such as warfarin**.
- An **alternative** is the oral Xa inhibitor, rivaroxaban, which has a rapid onset of action and can be used immediately from diagnosis without the need for LMWH.
- Treatment of acute Venous thromboembolism(VTE) with LMWH should continue for **at least 5 days.**

Treatment of Venous thromboembolism(VTE)	
Anticoagulation	**1) Unfractionated (UFH) and low-molecular weight heparin** (LMWH, ie, enoxaparin, tinzaparin, dalteparin, etc) - if the pt is stable give sc LMWH ,it will work within short period - Enable antithrombin to accelerate many-fold its inactivation of thrombin - LMWH should be avoided in CKD*; contraindicated in Stage-V CKD * Most of anticoagulants are contraindicated in CKD pt, only 2 anticoagulants are save for them which they are unfractionated heparin and warfarin. **2) Vitamin K antagonists (warfarin)** - Heparin + warfarin is more effective than warfarin alone; all cases of Venous thromboembolism should be "bridged" with heparin **3) Factor Xa inhibitors** (fonduparinux) **4) Hirudins** (lepirudin, bivalirudin)(when to use it?if CKD pt develop HIT from unfractionated heparin,the drug of choice to give them is hirudins,then if they become stable give them warfarin) **5) Direct oral Anticoagulants (DOACs).**
Thrombolysis	**Usually reserved for massive PE** - Tissue plasminogen activators (t-PA, u-PA, urokinase, alteplase)
Thrombectomy (arterial)	Surgical treatment

Anticoagulation :

- Start during resuscitation phase itself
- If suspicion high, start empiric anticoagulation
- Evaluate patient for absolute contraindication (i.e.: active bleeding)

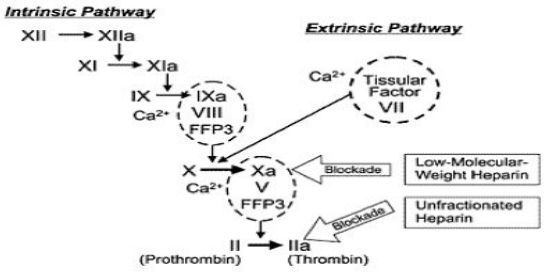
Anticoagulation

Conventional Anticoagulation

- Treatment always started with **heparin** (immediate action)
- Warfarin can be started at the same time
  - Warfarin takes time to work & may increase the tendency to further thrombosis initially (reduces level of Protein C & S).
- Around 4 days of warfarin & heparin overlap needed(to avoid thrombosis)
- Heparin can be stopped when INR reaches therapeutic levels (2-3) (normal INR 0.9 – 1.3).
- LMWH (SC) in stable cases of VTE but UNH (IV) needed in hemodynamically unstable patients or pts who need procedures.[3]

Heparin (LMWH)

- **Lovenox:** if hemodynamically stable, no renal function(1 mg/kg BID OR 1.5mg/kg QDay)
- **Heparin gtt:** if hypotension, renal failure(80 units/kg bolus then 18 units/kg infusion_Goal PTT 1.5 to 2.5 times the upper limit of normal)
- Antidote : protamine sulphate



Warfarin

- Warfarin will inhibit vit k dependents clotting factors.
- No fixed dose of warfarin, every patient needs a different dose (loading dose + maintenance)
- INR (International normalized ratio)then we do daily INR to know what is the appropriate dose for the pt
  - Therapeutic INR 2-3 in most cases
- **Initially heparin is a must as warfarin slow to act and initially prothrombotic**
- Treatment continued for 3-12 months mostly but longer or life long anticoagulation may be needed in **RECURRENT** cases of VTE.PE needs longer duration,bc PE is killer!!!
- Plz remember if someone develop PE he is in high chance to develop second episode of PE,in other hand if someone develop DVT he is in high chance to develop second episode of DVT.

How to treat warfarin overdose?

- **Antidote : vitamin K** but may take time (many hours) to act
- An actively bleeding patient may also need fresh frozen plasma (FFP) or ,prothrombin complex(better than FFP)

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

- Patient non-compliance
- Changes in vitamin K intake (diet)
- Effect(s) of concomitant drug(s) use
- Changes in warfarin metabolism
- Changes in vitamin K dependent coagulation factor synthesis or metabolism
- Inaccuracy in INR testing

★One might wonder can we use Aspirin in venous thrombotic problems? Answer is no.
Aspirin is an antiplatelet it blocks the function of the platelet (doesn't reduce the number of the platelet).
Aspirin is more effective in **arterial thrombotic problems** rather than venous thrombotic problems.

[3] UFH: is the IV anticoagulant, the rest are Oral or SC . UFH: is Suitable for unstable patient because the absorption won't be good from SC root (LMWH)

	Aspirin is used in condition where there over-activation of platelet causing clot formation within the **artery**, like (**ischemic heart disease, ischemic stroke**)
Direct oral anticoagulants (DOACs)[4]	• **Direct thrombin inhibitors (DTI) :** Dabigatran • **Factor X inhibitors :** Rivaroxa**ban**, Apixa**ban**, Adoxa**ban**

Pros	cons
• Fixed daily dose • No need for monitoring • **Quick** onset of action .in ER. • Bleeding risk similar to warfarin (GI bleed more common),(however the risk for IC bleeding is lesser) • Smaller doses can be used as prophylaxis.	• More expensive • Reversal a problem (Antidote available now) • Can not be used in end stage renal failure and in pts with metallic heart valves

IVC filter [5]

Indications: LAST RESORT, carries risk of thrombosis.

- Absolute contraindication to anticoagulation (i.e. active bleeding)
- Recurrent PE during adequate anticoagulation
- Complication of anticoagulation (severe bleeding)
- Pts with poor cardiopulmonary reserve
- Recurrent P.E. will be fatal
- Patient's who have had embolectomy
- Prophylaxis against P.E. in select patients (malignancy)

Embolectomy (Surgical or catheter)

Indications:

- Those who present severe enough to warrant thrombolysis
- In those where thrombolysis is contraindicated or fails

Notes

- In pregnancy, we use Heparin. Why? because it cannot cross the placenta = safe.
- Thrombosis in cancer patients? LMWH.
- Side effect of heparin? Thrombocytopenia (low platelet count).

[4] AKA new oral anticoagulants.

[5] Patients who have had a DVT and have a strong contraindication to anticoagulation, and those who, despite therapeutic anticoagulation, continue to have new pulmonary emboli, should have an **inferior vena cava filter** inserted to prevent life-threatening PE.

Clinical case scenario *(From Dr.farjah slides)*

★ **In the exam you should be able to recognize a case of DVT (presentation, risk factors) & also you need to know the next step (investigations, management)**

• Case 1 (John) :

John is a 75-year old man with a recent (4 weeks ago) admission to hospital for hip replacement. The procedure was performed under general anaesthetic. During admission, John received the following VTE prophylaxis (to be continued until John no longer had significantly reduced mobility): antiembolism stockings, pharmacological VTE prophylaxis. John reports that his right leg has been swollen for over 2 weeks. He thought it was healing after the operation, which is why he has not told anyone sooner. He presented to his GP and the GP has referred him to your accident and emergency (A&E) department.

1.1 Question

You believe John has symptoms of DVT. What would you do next?

Carry out an assessment of John's general medical history and a physical examination to exclude other causes.

1.2 Question

John reports that he had a DVT 20 years ago and that he has osteoarthritis. On admission, he is apyrexial with a temperature of 37°C and his right calf and ankle are red, blotchy and swollen with pitting oedema. His heart rate is 80 beats per minute, respiratory rate 15 breaths per minute, blood pressure is 136/80 mmHg and SpO2 96% in air. You suspect DVT: **what would you do next?**

Even though John received VTE prophylaxis, the diagnosis of DVT should still be highly considered. Use the two-level DVT Wells score to estimate the clinical probability of DVT.

1.3 Question

John's two-level DVT Wells score is 3 (DVT likely):

Major surgery within 12 weeks requiring general or regional anaesthesia = 1. Pitting oedema confined to symptomatic leg = 1. Previously documented DVT = 1. You do not consider that an alternative diagnosis is at least as likely as DVT. You suspect DVT: **what would you do next?**

Organise a proximal leg vein ultrasound scan. Unfortunately, in your organisation, this scan is not available within 4 hours of being requested. Therefore, you offer a D-dimer test, an interim 24-hour dose of a parenteral anticoagulant and a proximal leg vein ultrasound scan carried out within 24 hours of being requested.The D-dimer test is positive and the proximal leg vein ultrasound scan is also positive.

1.4 Question

What would you do next?

Diagnose DVT and start treatment with low molecular weight heparin (LMWH) or anticoagulant as soon as possible.

MCQs

1) All the following are vitamin K–dependent coagulation factors *except*?

a. factor X
b. factor VII
c. protein C
d. protein S
e. factor VIII

2) A 23-year-old woman is diagnosed with a lower extremity deep venous thrombosis. Which of the following medical conditions represent a contraindication to therapy with low-molecular-weight heparin (LMWH)?

a. Pregnancy
b. Obesity
c. Dialysis-dependent renal failure
d. Uncontrolled diabetes mellitus
e. Jaundice

3) The most common inherited prothrombotic disorder is?

a. activated protein C resistance
b. prothrombin gene mutation
c. protein C deficiency
d. protein S deficiency
e. antithrombin deficiency

4) SA 16-year-old male has recurrent thigh hematomas. He has been active in sports all of his life and has had 3 episodes of limb-threatening bleeding with compartment syndrome. A family history is notable for a maternal grandfather with a similar bleeding history. Paternal family history is not available. Laboratory analysis in clinic reveals a normal platelet count, a normal activated partial thromboplastin time (22 s) and a prolonged prothrombin time (25 s). He takes no medications. What is the most likely reason for his coagulation disorder?

a. Factor VIII deficiency
b. Factor VII deficiency
c. Factor IX deficiency
d. Prothrombin deficiency
e. Surreptitious warfarin ingestion

5) A 52-year-old man is admitted with recurrent hemarthrosis of his knees. He is an electrician who is still working but over the last year has had recurrent hemarthrosis requiring surgical evacuation. Before one year ago, he had no medical problems. He has no other past medical history and seldom sees a physician. He smokes tobacco regularly. His platelet count is normal, erythrocyte sedimentation rate is 55 mm/hr, hemoglobin is 9 mg/dL and albumin is 3.1 mg/dL. Coagulation studies show a prolonged activated partial thromboplastin time (aPTT) and a normal prothrombin time (PT). Adding plasma from a normal subject does not correct the aPTT. What is the cause of his recurrent hemarthrosis?

a. Acquired inhibitor
b. Factor VIII deficiency
c. Factor IX deficiency
d. Secondary syphilis
e. Vitamin C deficiency

6) During a pre-employment physical and laboratory evaluation, a 20-year-old male is noted to have a prolonged activated prothromboplastin time (aPTT). On review of systems, he denies a history of recurrent mucosal bleeding and has never had an issue with other major bleeding. He has never had any major physical trauma. A family history is limited because he doesn't know his biologic family history. Mixing studies correct the aPTT when normal serum is used. You suspect an inherited hemorrhagic disease such as hemophilia. Which other laboratory abnormality would you most likely expect to find if this patient has hemophilia?

a. Low Factor VIII activity
b. Low factor IX activity
c. Prolonged bleeding time
d. Prolonged prothrombin time
e. Prolonged thrombin time

Answer key:

1 (E) | 2 (C) | 3 (A) | 4 (B) | 5 (C) | 6 (A)|

Not convinced?check out the link