CLOTTING DISORDERS

VIRCHOW'S TRIAD OF HYPERCOAGULABILITY, VENOUS STASIS AND ENDOTHELIAL INJURY CONTINUES TO BE A USEFUL MODEL FOR THE INTERPLAY OF GENETIC FACTORS AND ENVIRONMENTAL TRIGGERS LEADING TO INAPPROPRIATE THROMBOSIS

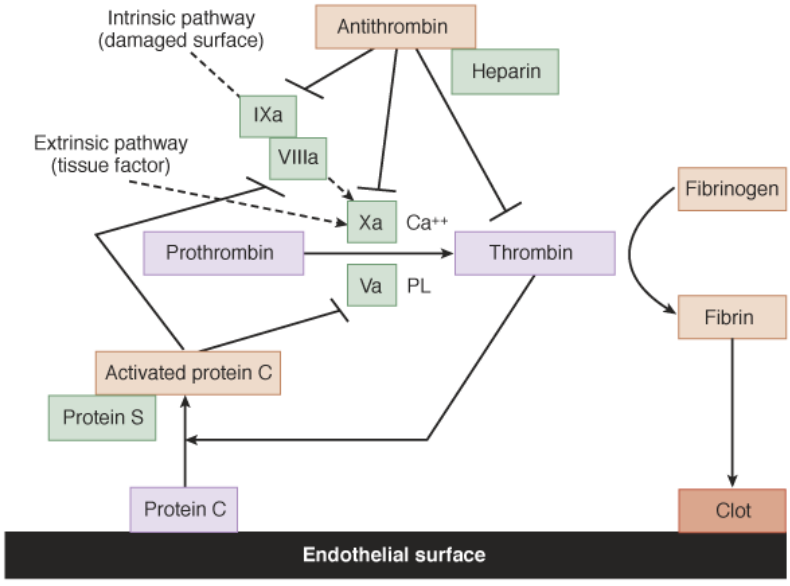
THE ED APPROACH IS SIMILAR FOR MOST COMMON INHERITED AND ACQUIRED CONDITIONS CAUSING HYEPRCOAGULABLE STATES

Table 229-1 Hypercoagulable States

Inherited	Acquired
Activated protein C resistance due to Factor V Leiden mutation	Antiphospholipid syndrome
	Pregnancy
Prothrombin gene mutation 20210A	Oral contraceptives/hormone replacement therapy
Protein C deficiency	
Protein S deficiency	Malignancy
Antithrombin deficiency	Heparin-induced thrombocytopenia
Hyperhomocysteinemia	Warfarin-induced skin necrosis
	Hyperviscosity syndromes

CLINICALLY RELEVANT PATHOPHYSIOLOGY:

- Several physiologic systems are in place to ensure that blood clots do not extend beyond where they are needs
- The two most clinically important pathways involve protein C and antithrombin



- Antithrombiin is a plasma-based protein that INHIBITS THE FUNCITON OF SEVERAL ACTIVATED COAGULATION FACTORS, PRIMARILY THROMBIN (as well as factor Xa and factor IXa)
    - Both UFH and LWMH posses anticoagulant activity by increasing the rate by which antithrombin inhibits these factors (2000-4000 for thrombin, 1000x for factor a)
- Protein C is a vitamin-K dependent plasma protein that binds to the endothelial surface and is activated by thrombin → when activated it cleaves both Factor Va and VIIIa, inhibiting both the common and intrinsic pathways
- Protein S is an other vitamin-K dependent plasma protein that is a cofactor that increases the inhibitory activity of protein C by 20-fold

Table 229-2 Functions of Coagulation Proteins in Protein C and Antithrombin Systems

Factor	Function	Pertinent Disorders
Prothrombin (Factor II)	Precursor to thrombin, which converts fibrinogen to fibrin.	Prothrombin 20210A mutation
Factor V, activated	Complexes with Factor Xa, calcium, and phospholipid to convert prothrombin to thrombin.	Activated protein C resistance due to Factor V Leiden mutation
Protein C, activated	Cleaves activated Factors Va and VIIIa.	Congenital protein C deficiency
		Activated protein C resistance due to Factor V Leiden mutation
		Neonatal purpura fulminans
		Warfarin-induced skin necrosis
Protein S	Cofactor for activated protein C.	Congenital protein S deficiency
	Cofactor for tissue factor pathway inhibitor (which inhibits extrinsic pathway of coagulation).	Neonatal purpura fulminans
	Counteracts Factor Xa's protection of Factor Va from degradation.	Warfarin-induced skin necrosis
Antithrombin	Inhibits thrombin, Factor Xa, and Factor IXa.	Antithrombin deficiency
	Binds heparins—leading to increased antithrombin activity.	
Phospholipids	Present on cell membranes of endothelial cells that line blood vessels.	Antiphospholipid syndrome
	The activity of several proteins in the coagulation cascade are enhanced when bound to phospholipids.	

PRINCIPLES OF EVALUATION:

- Thrombophilic disorders are RARELY DIAGNOSED IN ED → main goals are:
    - Recognise the inherently higher risk of thrombosis in a patient with known disorders
    - Obtain pertinent information to suspect an undiagnosed hypercoagulable state

Table 229-3 Features Suggestive of Thrombophilia
Early thrombosis (age 45 y old and younger)
Recurrent thrombotic events
Family history of thrombosis
Recurrent fetal loss
Thrombosis in unusual location (mesenteric, cerebral, axillary or portal veins)

- The vast majority of venous thromboembolic disease in the absence of hypercoagulable state involves DVT of the lower limb with or without PE ➔ the incidence of a clotting disorder rises if the patient develops clot in atypical locations without obvious precipitating factors (upper limbs, mesenteric, portal or cerebral veins)

DIAGNOSIS AND TREATMENT:

- Tests for hypercoagulable states cannot be reliably done in the setting of acute thrombosis or while the patient is taking a vitamin K antagonist (warfarin) ➔ usually testing for these factor deficiencies take place several weeks after warfarin has stopped
    - Our job is to suspect the thrombophilia, refer for evaluation and appropriately manage any acute thrombosis
    - The initial management is NO DIFFERENT regardless of the presence of a thrombophilia, WHAT DIFFERS IS THE DURATION OF TREATMENT

Clinical situation	Duration
VTE provoked by a transient major risk factor	3 months [NB1]
unprovoked distal DVT	3 months [NB1]
first unprovoked proximal DVT or PE	6 months [NB1]
first unprovoked VTE plus: ▪ active cancer ▪ multiple thrombophilias ▪ antiphospholipid antibody syndrome	indefinite
recurrent unprovoked VTE	indefinite

SPECIFIC CONDITIONS ASSOCIATED WITH THROMBOPHILIA:

INHERITED CLOTTING DISORDERS:

- ACTIVATED PROTEIN C RESISTANCE (FACTOR V LEIDEN):
    - The most prevalent inherited hypercoagulable disorder ➔ approx 5% of the population are heterozygous.
    - A single point mutation of the gene makes factor Va resistant to inhibition by activated protein C ➔ leads to overabundant conversion of prothrombin to thrombin, so more fibrin is produced leading to excessive thrombus formation

    - Heterozygotes have sevenfold increased risk of DVT, homozygotes have 20-fold increase
- PROTHROMBIN GENE MUTATION 20210A ➔ results in 30% increase in circulating prothrombin levels
- ANTITHROMBIN DEFICIENCY:
    - Can be deficient due to large number of mutations to the antithrombin gene
    - Inherited in autosomal dominant pattern
    - Heterozygous patients have 5x increased risk of thrombotic events. HOMOZYGOUS DEFICIENCY IS NOT COMPATIBLE WITH LIFE
- PROTEIN C AND S DEFICIENCIES:
    - Transmitted in autosomal dominant fashion, but with more varied clinical presentations than antithrombin deficiency
    - Homozygous deficiency is rare ➔ neonatal purpura fulminans
    - Heterozygous patients are at higher risk of VTE and warfarin-induced skin necrosis (easily avoided with small loading doses and concomitant use of LMWH)
- HYPERHOMOCYSTEINAEMIA:
    - Inherited functional deficiency in the enzymes involved in metabolism lead to increased risk of both arterial and venous thromboembolism as well as atherosclerosis
    - Patients with profound hyperhomocysteinaemia, generally because of a homozygous inheritance of a dysfunctional enzyme (CONGENITAL HOMOCYSTINURIA) → have significant skeletal and ocular problems as well as mental retardation, developmental delay and thrombotic events
        - Heterozygotes do not have other manifestations, but are at 2-3 fold higher risk of VTE
    - TREATED WITH FOLATE, PYRIDOXINE AND VITAMIN B12

ACQUIRED CLOTTING DISORDERS:

- ANTIPHOSPHOLIPID SYNDROME:
    - Common cause of acquired thrombophilia
    - Most common associated antibodies are LUPUS ANTICOAGULANT AND β-2 GLYCOPROTEIN 1
    - Lupus anticoagulant acts as a PROCOAGULANT and is associated with THROMBOSIS, but prolongs APTT
    - Antiphospholipid syndrome is more common in women
    - Generally accepted "1 in 5" rule for APS:
        - 1 in 5 young patients with stroke have APS (<45)
        - 1 in 5 patients with DVT
        - 1 in 5 patients with recurrent pregnancy loss will test positive
    - A patient with SLE and positive lupus anticoagulant has a 50% CHANCE OF DEVELOPING AN ARTERIAL OR VENOUS THROMBOTIC EVENT DURING A 20 YEAR PERIOD
    - CLINICAL FEATURES:

- Generally recognised by a combination of lab findings and clinical findings

Table 229-5 Clinical Manifestations of Antiphospholipid Syndrome

System	Examples
Venous	Deep venous thrombosis: extremities, cerebral, portal, hepatic, renal, retinal
Arterial	Premature atherosclerosis
	Acute coronary syndrome
	Ischemic stroke
	Vascular stenosis or occlusion: extremities, aorta, renal, retinal
Obstetric	Fetal loss: often after 10-wk gestation
	Preterm labor
	Low birth weight
	Preeclampsia
Neurologic	Stroke
	Migraine
	Seddon syndrome—clinical triad of stroke, hypertension, and livedo reticularis
	Cognitive dysfunction
	Subcortical dementia
	Chorea
	Dysphagia
	Guillain-Barré syndrome
	Seizures
	Optic neuritis
Skin	Livedo reticularis
Cardiac	Valvular abnormalities (Libman-Sacks endocarditis)
	Syndrome X (angina-like chest pain, cardiac stress test positive for ischemia, normal coronary angiography)
Skeletal	Osteonecrosis
Renal	Thrombotic microangiopathy
	Renal artery or vein thrombosis
	Renal artery stenosis with hypertension
Pulmonary	Pulmonary embolus
	Pulmonary hypertension (from recurrent emboli)
GI	Budd-Chiari syndrome (hepatic vein thrombosis)
	Mesenteric ischemia
	Hepatic infarction
	Acalculous cholecystitis with gallbladder necrosis
Hematologic (other than thrombosis)	Bleeding diathesis (rare)
	Acquired hypoprothrombinemia
	Thrombocytopenia
	Hemolytic anemia
Catastrophic antiphospholipid syndrome	Fulminant multisystem organ failure

- LIVEDO RETICULARIS ➔ lacy, netlike bluish mottling of the skin found in 10-20% cases of APS

- Most patients have no other predisposing conditions, but some do (SLE, infections, drug exposure [phenytoin, hydralazine, cocaine])
- Most patients with APS will present with isolated, recurrent thrombotic events ➔ HOWEVER, A SMALL PERCENTAGE OF PATIENTS WILL HAVE A **RAPIDLY PROGRESSIVE FORM OF THE SYNDROME KNOWN AS CATASTROPHIC ANTIPHOSPHOLIPID SYNDROME**
    - Occurs in ~1% patients with APS
    - Widespread small-vessel occlusion in multiple organs
    - Common triggers ➔ infection, trauma, anticoagulation problems, cancer
    - Mortality 50% despite treatment
- DIAGNOSIS OF APS:
    - Notoriously difficult
        - One or more thrombotic events or pregnancy losses
        - Repeated positive results for one or more of the antiphospholipid antibodies at least 6 weeks apart
- TREATMENT OF APS:
    - If a patients is being treated with heparin, APTT is not effective in monitoring
    - Pregnant women with APS need anticoagulation (LMWH or UFH) or low dose aspirin
    - In rare event of CATASTROPHIC APS → multipronged approach involving anticoagulation, steroids, plasmapheresis and/or IVIG is typically used

PREGNANCY AND OESTROGEN USE:

- Well-documented cause for hypercoagulability

Table 229-6 Factors Contributing to Hypercoagulable State in Pregnancy

Anatomic	Hematologic
Venous occlusion from gravid uterus.	Increased thrombin generation from placental secretion of tissue factor
Trauma to pelvic veins during delivery.	
Tissue injury during surgical delivery.	Increased production of procoagulant proteins
Left iliac vein crosses over left iliac artery, leading to relative compression (left leg deep venous thrombosis is three times more likely than right in pregnant patients).	Decreased free and total protein C
	Increased platelet activation and platelet turnover

- The current low doses for oestrogens in OCP are associated with a smaller but still clinically significant increased risk of thrombosis

MALIGNANCY:

- Long associated with increased risk for thrombus formation

- In patients with a first-time episode of VTE, approximately 10-20% will have a new diagnosis of cancer within the previous six months or subsequent year
- Some types of cancer are more likely to promote thrombosis than other:
    - Pancreatic
    - Brain
    - AML
    - Gastric
    - Gynaecologic, kidney
    - Lung
- Tissue factor is secreted by many tumours

HEPARIN-INDUCED THROMBOCYTOPAENIA:

- HIT is a CONSUMPTIVE COAGULOPATHY, similar to TTP and DIC in that components of the clotting process are inappropriately activated, forming arterial and venous thrombus
- HIT involves PATHOLOGIC ACTIVATION AND CONSUMPTION OF PLATELETS
    - PLATELET FACTOR F (PF4) is central in this syndrome
    - PF4 neutralises heparin and HIT develops when patients develop IgG antibodies against the heparin-PF4 complex
    - A complex of heparin, PF4 and antibody binds to platelets, resulting in their activation
        - Measured platelet count falls, but blood clot formation results
- HIT is much more common in use of UFH than LMWH
- Has significant morbidity and mortality
    - In HIT, incidence of thrombosis is 35-75%
    - Approximately 10% will need a limb amputation and 20-30% die within a month
- PRESENTATION

Table 229-7 Presentations of Heparin-Induced Thrombocytopenia		
Presentation	**Timing**	**Features**
Typical	5–15 d after initiation of heparin	>50% decrease in platelet count
		Thrombosis in 35%–75%
		Deep venous thrombosis or pulmonary embolism
		Cerebral vein or adrenal vein thrombosis
		Limb arterial occlusion
		Stroke
		Myocardial infarction
		Skin lesions at injection sites
Rapid onset	Within hours of initiation of heparin	Preexisting circulating IgG antibody from sensitization several weeks earlier
		Sudden drop in platelet count
		Thrombosis
		Flushing
		Tachycardia
		Hypotension
		Dyspnea
Delayed onset	Several days after heparin stopped	Strongly reactive IgG antibodies
		Severe thromboses

- DIAGNOSIS AND TREATMENT:
    - Diagnosis hinges on lab findings and cannot be diagnosed on clinical ground
    - Thrombocytopaenia is almost universally present, but expect when platelets have dropped ~50% from recent value in a patient currently or recently taking a heparin product
    - If suspected ➔ strongly consider the possibility of thrombosis or embolism.
        - Event if not found initially, 19-52% will develop a clot in the moth following heparin cessation
    - Definitive diagnosis is difficult ➔ low availability of high-specificity tests
    - Platelet count will typically normalise in the week following cessation of heparin, BUT THESE PATIENTS NEED ANTICOAGULATION, AS THE RISK OF THROMBOSIS IS HIGHEST IN THIS PERIOD
        - Recommended alternatives include LEPIRUDIN, ARGATROBAN, DANAPAROID

danaparoid (patients less than 55 kg: 1250 units; patients 55 to 90 kg: 2500 units; patients more than 90 kg: 3750 units) IV bolus, followed by 400 units/hour IV infusion for 4 hours, then 300 units/hour for 4 hours, then 150 to 200 units/hour.

        - Avoid warfarin, as it can increase the risk of microvascular thrombosis
        - IN THOSE WITH HIT (OR PRIOR HISTORY), **DO NOT HEPARIN-LOCK CVC/VASCATHS**

WARFARIN-INDUCED SKIN NECROSIS:

- Results from decrease in protein C which can lead to clinically-significant hypercoagulability

- Skin-necrosis presents with painful, red lesions usually located over extremities, breasts, trunk or penis
- PREVENTION IS KEY ➔ avoid high loading doses and continuation of LMWH or UFH until INR therapeutic
- When skin-necrosis does occur, 1/3 will be found to have inherited protein C deficiency

HYPERCOAGULABILITY ASSOCIATED WITH OTHER DISORDERS:

- NEPHROTIC SYNDROME:
    - Increased urinary excretion of anticoagulant proteins
- HYPERVISCOSITY SYNDROMES:
    - Essential polycythaemia, polycytheamia vera, Waldenstrom macroglobulinaemia, multiple myeloma, sickle cell disease all at increased risk for thrombosis