THROMBOPHILIA

Patients with acquired hypercoagulable states or hereditary thrombophilia are more likely to develop venous thrombosis, and arterial thrombosis, than healthy individuals. Venous thrombosis and pulmonary embolism are associated with significant morbidity and mortality.

Acquired risk factors for hypercoagulability and thrombosis:

Advanced age, Immobilization, Obesity, Pregnancy.
Diabetes mellitus
Inflammation
Oral contraceptive use. Hormone replacement therapy
Cancer (especially adenocarcinoma)
Antiphospholipid syndrome.

Hypercoagulability and Thrombosis In COVID-19:

COVID-19 infection is associated with hypercoagulability. The incidence of clotting events in patients with COVID-19 varies from 11% to 70%, depending on severity of disease, and predisposing factors. COVID-19 can damage vascular endothelium, affecting many organs, promoting hypercoagulability and causing arterial and venous micro- and macrothrombosis. stroke, myocardial infarction, and limb ischemia.

Antiphospholipid syndrome :

Antiphospholipid antibodies (lupus anticoagulants) occur in about 20% of patients with systemic lupus erythematosus (SLE), but they are also associated with other autoimmune diseases. In addition, These antibodies may develop in individuals who are taking following medications : phenothiazines, phenytoin, hydralazine, quinine, amoxicillin, and oral contraceptives.
The term antiphospholipid antibody refers to both a lupus anticoagulant and an anticardiolipin antibody; individuals may be positive for one or both of these activities.

Clinical Criteria For Determining the presence of lupus anticoagulants include:

In clinical practice, two types of test are used, which detect:
Anticardiolipin antibody test: antibodies which bind to phospholipid on by ELISA test.
Lupus anticoagulant test: dilute Russell viper venom time (DRVVT) frequently causes prolonged the aPTT .

Clinical manifestations:

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

Risk of venous thromboembolism is increased in individuals with chronic hemolytic anemias. These may be inherited (eg, sickle cell anemia, beta thalassemia)or acquired as paroxysmal nocturnal hemoglobinuria.

Idiopathic (unprovoked) venous thrombotic events - Hereditary thrombophilias-are defined as: thrombosis that occurs in the absence of any of the risk factors listed above.

Hereditary thrombophilias : should be suspected in individuals with a history of:

Recurrent thromboembolism

Thrombosis at a young age (< 40 years)

Family history of thrombosis.

Thrombosis in unusual sites (eg, mesenteric vein, renal vein, hepatic, or cerebral thrombosis …)

About 50% of patients presenting with a first idiopathic venous thrombosis have an underlying thrombophilia.

Hereditary thrombophilias include the following:

- Factor V Leiden
- Protein C deficiency
- Protein S deficiency
- Antithrombin deficiency
- Prothrombin 20210A
- Others (Elevated factor VIII level, Dysfibrinogenemia ,Hyperhomocysteinemia)

Activated protein C resistance (Factor V Leiden)

Factor V Leiden is the most common inherited thrombophilia It is due to a mutation in the Factor V Leiden gene. Heterozygotes have a 5-fold risk of venous thrombosis whilst homozygotes have a 50-fold ↑ risk. Any white pt aged <45 with thrombotic event should make you think of factor V Leiden mutation.

Protein C and S deficiencies

Protein C and S are vitamin K-dependent natural anticoagulants involved in switching off coagulation factor activation and thrombin generation . Inherited deficiency of either protein C or S results in a prothrombotic state with a five-fold relative risk of VTE . Patients with protein C and S deficiencies can develop warfarin-induced skin necrosis when placed on warfarin.

Antithrombin deficiency:

An autosomal dominant inherited cause of thrombophilia occurring in approximately 1:2,000 of the population. Antithrombin III inhibits several clotting factors, primarily thrombin, factor X and factor IX. It mediates the effects of heparin .

Antithrombin III deficiency comprises a heterogeneous group of disorders, with some patients having a deficiency of normal antithrombin III whilst others produce abnormal antithrombin III.

Features

Recurrent venous and arterial thromboses

Management

Thromboembolic events are treated with lifelong warfarinization

Heparinisation during pregnancy

Antithrombin III concentrates (often using during surgery or childbirth)

as patients with antithrombin III deficiency have a degree of resistance to heparin anti-Xa levels should be monitored carefully to ensure adequate anticoagulation

Prothrombin G20210A

This gain-of-function mutation in the prothrombin gene, associated with increases in prothrombin levels . The prevalence varies from one region to another. It is prevalent in 2% of Northern Europeans, Mediterranean region but is uncommon in others.

Deficiencies of anticoagulant factors may also be acquired.

History and Physical Examination

There are no specific clinical symptoms or signs directly to a thrombophilic disorders. Rather than DVT and pulmonary embolism with underling precipitating causes.

An association between hypercoagulability and severe obstructive sleep apnea has been reported.

Purpura fulminant : is a rare, life-threatening condition, caused by congenital or acquired deficiencies of protein C or S. The condition is often fatal unless there is early recognition ,diagnosis, and judicious treatment. in infancy could suggest protein C. protein S or antithrombin III deficiency may also cause this disorder.

Laboratory Studies

It is a difficult decision to start a thrombophilia laboratory workup. However, common practical workups such as aPTT, PT, INR, LFT, CBC,CRP,ESR, D. dimer, Doppler study for venous system, Echo study, ECG, CXRAY, CT angiography for chest, and other workups related to the primary disease are performed.

Treatment :

Stasis should be eliminated whenever possible. This includes the wearing of elastic stockings and also intermittent pneumatic compression. Early ambulation is encouraged after surgery or illness.

Heparin, LMWH and Warfarin have been used to manage venous thrombosis and pulmonary embolism.

Heparins:

Unfractionated heparin (UFH)&low molecular weight heparins (LMWH)

Unfractionated heparin (UFH) and low molecular weight heparins (LMWH) both act by binding to antithrombin III which potentiates its natural anticoagulant activity. Binding of a heparins to antithrombinIII causes inhibition of thrombin(II) and the other serine proteinases (i.e., factors Xa, IXa, XIa, and XIIa and VII).

The main indications for heparin are the treatment of DVT, PE, acute myocardial infarction, and unstable angina pectoris. It is also used in cardiopulmonary bypass surgery and for anticoagulation during pregnancy as it does not cross the placenta.

UFH can be administered by intravenous or subcutaneous route.

The biological half-life is 1–1.5 h.

Heparin(UFH): dose is 80 units/kg intravenous bolus, then continuous intravenous infusion of 18 units/kg/h. In adult patients with an average weight of 70 kg, doses of 30,000–40,000 U over 24 h (1200–2000 U/ h with a loading dose of 5000 U) are usually required. Subcutaneous heparin (e.g., 15,000 U every 12 h) can be used as an alternative to the intravenous route. The therapy must be monitored by maintaining the aPTT target between 1.8 and 2.5 times the normal time.

When switching from Heparin to warfarin. Continue full heparin therapy for several days until the INR (prothrombin time) has reached a stable therapeutic range to ensure continuous anticoagulation Heparin therapy can then be stopped without being tapered.

Antidote for Heparin is protamine sulfate by slow infusion will neutralize heparin sodium.

1-1.5 mg per 100 units of heparin; not to exceed 50 mg. Monitor APTT 5-15 min after dose then in 2-8 hr.

After subcutaneous injection of heparin , the bioavailability is only 30%. This is due to binding to a variety of plasma proteins, endothelial cells, von Willebrand factor, and platelet factor neutralization (PF). As a result, the LMWH were developed.

LMWH: (Enoxaparin ,Daltaparin, tinzaparin) is made from UFH, which is generally of porcine origin . It typically works as an anti-Xa activity.The smaller size of LMWH causes less binding to plasma proteins and endothelial cells, resulting in a much better bioavailability. LMWHs are nearly 100% bioavailable and so produce reliable dose-dependent anticoagulation. and more anticoagulant response than UFH.

The longer half-life (around 4 hours) when given subcutaneously, compared with 1 hour for UFH. allows a single daily subcutaneous dosage as thrombosis prophylaxis

In contrast to UFH, LMWH have minor anti-IIa activity. Thus, even when used in higher therapeutic doses, the aPTT will not be prolonged and cannot be used for monitoring. LMWHs have less serious complications than UFH, such as bleeding, heparin-induced immune thrombocytopenia (HIT), and osteoporosis.

UFH has been replaced by LMWH in thrombosis prophylaxis in many institutions .

LMWHs are also safe and effective in the treatment of uncomplicated DVT and even PE at home as compared to intravenous UFH in the hospital in acute situation (as in Emergency ,CCU).

The dose is weight-adjusted, Enoxaparin is given at a dose of 1 mg/kg (100 IU/kg)subcutaneously (SC) every 12 hours. and laboratory monitoring is not required.

Heparin-Induced Thrombocytopenia (HIT):

a serious rare reaction resulting from irreversible aggregation of platelets after heparin therapy due to the development of antibodies to a platelet Factor 4-heparin complex. HIT may progress to the development of venous and arterial thromboses. These serious thromboembolic events include deep vein thrombosis, pulmonary embolism, cerebral vein thrombosis, limb ischemia, stroke, myocardial infarction, thrombus formation on a prosthetic cardiac valve, mesenteric thrombosis, renal arterial thrombosis, skin necrosis, gangrene of the extremities that may lead to amputation, and possibly death. Monitor thrombocytopenia of any degree closely. If the platelet count falls below 100,000 or if recurrent thrombosis develops, promptly discontinue heparin and administer an alternative anticoagulant. such as Fondaparinux, argatroban and bivalirudin.

Fondaparinux: a synthetic, short molecule shaped like heparin. Fondaparinux is a direct factor Xa inhibitor and does not inhibit thrombin (IIa) .

WARFARIN

Old Oral Anticoagulants, blocks the liver from using vitamin K to make clotting factors
Warfarin inhibits the epoxide reductase enzyme, preventing vitamin K activation.
Warfarin, as a result, inhibits the gamma carboxylation (gamma-glutamyl carboxylase) of the coagulation factors II, VII, IX, IX (2,7,9,10), as well as Protein C, Protein S, and Protein Z.
Metabolism by the cytochrome P450 system. polymorphisms in the CYP2C9 and the Vitamin K epOxide Reductase Complex (VKORC1 genes) ,which predict the metabolism and function of warfarin, respectively.

Once absorbed from the intestinal tract, they are bound to plasma proteins (97–99%), primarily to albumin. Therefore, interactions with other drugs capable of displacing these agents from binding sites must be taken into consideration.
Start warfarin on the same day as therapeutic heparin or LMWH and overlap for at least five days, or until the goal INR is reached for at least two consecutive days. Thus on days 5–7, one can expect that warfarin is in the therapeutic range (international normalized ratio [INR] > 2) , heparin can be discontinued .

Clinical indications of warfarin

Deep vein thrombosis (DVT) as long term or preparation for cardioversion of atrial fibrillation . Warfarin is used to avoid cardioembolic stroke in atrial fibrillation as well as from valvular heart disease.

Oral anticoagulant therapy should be continued for at least 3 months and longer than 3 months when the thrombophilic state persists.

The major problems with warfarin are:

- A narrow therapeutic window
- Metabolism that is affected by many factors
- Numerous drug interactions.

Warfarin interactions :

Decreased metabolism of warfarin leads to higher plasma concentrations and an increased risk of bleeding complications. Many drugs potentiating warfarin's effect are known inhibitors of CYP 2C9, including amiodarone,azithromycin . Sulfamethoxazole-Trimethoprim ,metronidazole , fluconazole, fluvastatin, fluvoxamine, isoniazid, lovastatin, phenylbutazone and Asprin ,paracetamol , others NSAID.

In contrast drugs that can decrease warfarin effect & lower INR include antacids, antihistamines, barbiturates, rifampin, sucralfate, carbamazepine, cholestyramine, griseofulvin, haloperidol, oral contraceptives, penicillin, dicloxacillin, and nafcillin.

Bleeding. Patients with life-threatening hemorrhage or overdosage (error, suicidal) require immediate correction of the PT. The administration of prothrombin complex preparations - Fresh Frozen Plasma (FFP) simultaneously with vitamin K is necessary.

Teratogenic effects have been described with coumarin derivatives. Fetal exposure during the first trimester may result in embryopathies (nasal hypoplasia, epiphyseal abnormalities) .Oral anticoagulants are contraindicated in the first trimester of pregnancy .

LMWH is recommended throughout the pregnancy, if anticoagulation is mandatory.

Novel Oral Anticoagulants (NOACs)

A new class of anticoagulant drug.

Direct Oral Anticoagulants (DOAC s) have quickly become attractive alternatives to warfarin and may be replace warfarin recently

Direct factor Xa inhibitors :rivaroxaban most popular(Xalerto), apixaban, and edoxaban)

Direct thrombin inhibitors : oral agents such as dabigatran has been approved for use in VTE prophylaxis, VTE treatment, and stroke prevention in non-valvular atrial fibrillation.

Direct oral anticoagulants (DOACs) have several possible advantages over warfarin, including the following:

- No or limited interaction with other drugs and diet
- Metabolic half-lives that allow for once- or twice-daily dosing
- No need to monitor due to predictable pharmacokinetics
- Possibly less bleeding complications

In patients with severe kidney insufficiency (creatinine clearance < 30 mL/minute), warfarin should be considered rather than LMWH or DOACs.

Andexanet alfa a reversal agent for apixaban, edoxaban, and rivaroxaban; and idarucizumab is approved by the FDA and EMA as a reversal agent for dabigatran.

Fibrinolytic Drugs

- Fibrinolytic drugs also called thrombolytic drugs can be used to dissolve thrombi by activating plasminogen and are administered systemically or can be delivered via catheters directly into the substance of the thrombus. Systemic delivery is used for treatment of acute MI, acute ischemic stroke, and most cases of massive PE, an example of fibrinolytic drugs
- **Tissue Plasminogen Activators**

  Alteplase: a recombinant form of tPA .It has a short half-life (~5 min) and therefore is usually administered as an intravenous bolus followed by an infusion, commonly used in myocardial infarction.

Retaplase :is a genetically engineered, smaller derivative of recombinant tPA that has increased potency and is faster acting than rtPA.
Tenecteplase : has a longer half-life and greater binding affinity for fibrin than rtPA.

- **Other nonspecific thrombolytic drugs (streptokinase, and urokinase)**

Absolute Contraindications for Thrombolytic Treatment:

Recent intracranial hemorrhage (ICH)
Structural cerebral vascular lesion.
Intracranial neoplasm.
Ischemic stroke within three months.
Possible aortic dissection.
Active bleeding or bleeding diathesis (excluding menses)

Antiplatelet, anticoagulant, and site of action

Antiplatelet drugs	
Aspirin	Cyclo-oxygenase (COX) inhibition
Clopidogrel	Adenosine diphosphate (ADP) receptor inhibition
Abciximab	Glycoprotein IIb/IIIa inhibition
Tirofiban	Glycoprotein IIb/IIIa inhibition
Eptifibatide	Glycoprotein IIb/IIIa inhibition
Dipyridamole	Phosphodiesterase inhibition
Oral anticoagulants	
Warfarin/coumarins	Vitamin K antagonism
Dabigatran	Direct thrombin inhibition
Rivaroxaban	Direct Xa inhibition
Apixaban	Direct Xa inhibition
Intravenous anticoagulants	
Heparin	Antithrombin-dependent inhibition of thrombin and Xa
Fondaparinux/idraparinux	Antithrombin-dependent inhibition of Xa
Lepirudin	Direct thrombin inhibition
Argatroban	Direct thrombin inhibition
Bivalirudin	Direct thrombin inhibition