THROMBOPHILIA

Thrombophilia

- Thrombophilia

  is technical term for hypercoagulable state

- Thrombosis (arterial or venous)

  is produced by a shift in the balance between procoagulant and profibrynolytic system

Thrombophilia

- inherited
- acquired

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Epidemiology of VTE

- pulmonary embolism/deep vein thrombosis
- annual incidence: 1.5/1000

  (900000 patients each year in the USA)
- majority of cases is associated with a transient risk factor
- majority of VTE events occurs in the elderly

Hereditary thrombophilia

- is a genetically determined increased risk of thrombosis

Inherited thrombophilia

can be due to

- a deficiency of natural anticoagulant

(such as protein C, protein S or antithrombin) or

- mutation in clotting factor genes, making it resistant to inhibiton (Factor V gene 1691A>G, factor V Leiden) by activated protein C (APC-resistance) or resulted in high prothrombin level (mutation of G2010A of prothrombin gene)
- abnormalities of fibrinolytic system leading to impaired its function (i.e. PAI-1 gene polymorphisms)

Hereditary thrombophilia

- Characteristics:

- **thrombosis without any predisposing condition**

- **thrombosis at young age**

- **thrombosis in unusual sites**

(upper extremities, mesenteric vessels, hepatic or portal veins)

- **family history of thrombosis**

Neonatal purpura fulminans (homozygous PC or PS deficiency)

Inherited thrombophilia

- Factor V Leiden mutation

  (Resistance to activated protein C)

- Prothrombin gene mutation

  (Hyperprothrombinemia - prothrombin variant G20210A)

- Protein S deficiency

- Protein C deficiency

- Antithrombin (AT) deficiency

- Dysfibrinogenemia

- Hyperhomocysteinemia

Acquired predisposing risk factors for VTE

- Malignant neoplasms
- Presence of a central venous catheter
- Surgery, especially orthopedic
- Trauma
- Prolonged immobilization
- Congestive heart failure
- Pregnancy
- Oral contraceptives
- Hormone replacement therapy
- Antiphospholipid antibody syndrome
- Myeloproliferative neoplasms (Polycythemia vera, Essential thrombocythemia, Primary myelofibrosis)
- Paroxysmal nocturnal hemoglobinuria
- Tamoxifen, Thalidomide, Lenalidomide
- Inflammatory bowel disease
- Nephrotic syndrome

Factor V Leiden mutation

- Activated protein C resistance (APC resistance)
- Activated protein C promotes enzymatic degradation of factor VIIIa and Va
- The most common cause of inherited thrombophilia (40-50%)
- 3-13% of the population in Europe are heterozygous for FVL
- The mutation is not present in African Blacks, Chinese, or Japanese populations

Clinical manifestation of factor V Leiden

- is deep vein thrombosis with or without pulmonary embolism

  (ie, venous thromboembolic disease)

- the mutation is also a risk factor for cerebral, mesenteric, and portal vein thrombosis

Prothrombin G20210A

- Prothrombin (factor II) is the precursor of thrombin, the end-product of the coagulation cascade
- Heterozygous carriers have 30% higher plasma prothrombin levels than normals
- Heterozygous carriers have an increased risk of deep vein and cerebral vein thrombosis

Protein C (PC) deficiency

- Protein C is a vitamin K-dependent protein synthesized in the liver
- The primary effect of aPC is to inactivate coagulation factors Va and VIIIa
- The inhibitory effect of aPC is markedly enhanced by protein S, another vitamin K-dependent protein

Protein C (PC) deficiency

- Heterozygous protein C deficiency is inherited in an autosomal dominant fashion

Types:

I – decreased synthesis of normal protein

II – production of an abnormally functioning protein

PC deficiency –clinical manifestation

- Venous thromboembolism
- Neonatal purpura fulminans in homozygous
- Warfarin-induced skin necrosis in certain heterozygous teenagers or adults (in some cases similar symptoms may occur after heparin administration)

Protein S (PS) deficiency

- a vitamin K-dependent glycoprotein
- is a cofactor of the protein C system
- only the free form has activated protein C cofactor activity
- In the presence of PS, activated protein C inactivates factor Va and factor VIIIa

Protein S deficiency

- 3 of phenotype of PS deficiency have been defined on the basis of total PS concentrations, free PS concentrations, and activated protein C cofactor activity
- **Type I**

— reduced synthesis in active protein (ie, a quantitative defect)

- **Type II**

— normal synthesis of a defective protein (ie, a qualitative defect)

- **Type III**

— low levels of free protein S with normal level of bound protein S

CLINICAL MANIFESTATIONS OF PS DEFICIENCY

- **Autosomal dominant trait**
- **Similar to those of PC deficiency**

Antithrombin deficiency

- AT, formerly called AT III, also known as heparin cofactor I
- is a vitamin K-independent glycoprotein that is a major inhibitor of thrombin and factors Xa, Ixa and XIa
- AT slowly inactivates thrombin in the absence of heparin

In the presence of heparin, thrombin or factor Xa is rapidly inactivated by AT; this is referred to as the heparin cofactor activity of AT

Antithrombin deficiency

- Autosomal dominant inheritance
- Quantitative and qualitative defects
- Thrombotic phenomena in adolescence or even earlier
- Frequently pulmonary embolism as first clinical manifestation

Acquired deficiency of natural anticoagulant

Acquired AT deficiency
Acquired Protein C deficiency
Acquired Protein S deficiency

- neonatal period
- liver disease
- DIC
- acute thrombosis

Acquired deficiency of natural anticoagulant

Acquired AT deficiency:

pregnancy, nephrotic syndrome, major surgery, treatment with L-asparaginase, heparin or estrogens

Acquired Protein C deficiency:

chemotherapy, inflammation,
treatment with warfarin or L-asparaginase

Acquired Protein S deficiency:

pregnancy,
treatment with warfarin, L-asparaginase or estrogens

The antiphospholipid syndrome (APS)

- APS is an acquired thrombotic disorder associated with circulating autoantibodies to phospholipidprotein complexes
- Definite APS is considered present if at least one of the following clinical criteria and at least one of the following laboratory criteria are satisfied

The antiphospholipid syndrome (APS) - clinical criteria

- **1≥ episodes of venous, arterial, or small vessel thrombosis and/ or morbidity with pregnancy**

  Pregnancy morbidity –

- **Otherwise unexplained death at ≥10 weeks gestation of a morphologically normal fetus, OR**
- **1≥ premature births before 34 weeks of gestation because of eclampsia, preeclampsia, or placental insufficiency, OR**
- **3≥ embryonic (<10 week gestation) pregnancy losses unexplained by maternal or paternal chromosomal abnormalities or maternal anatomic or hormonal causes**

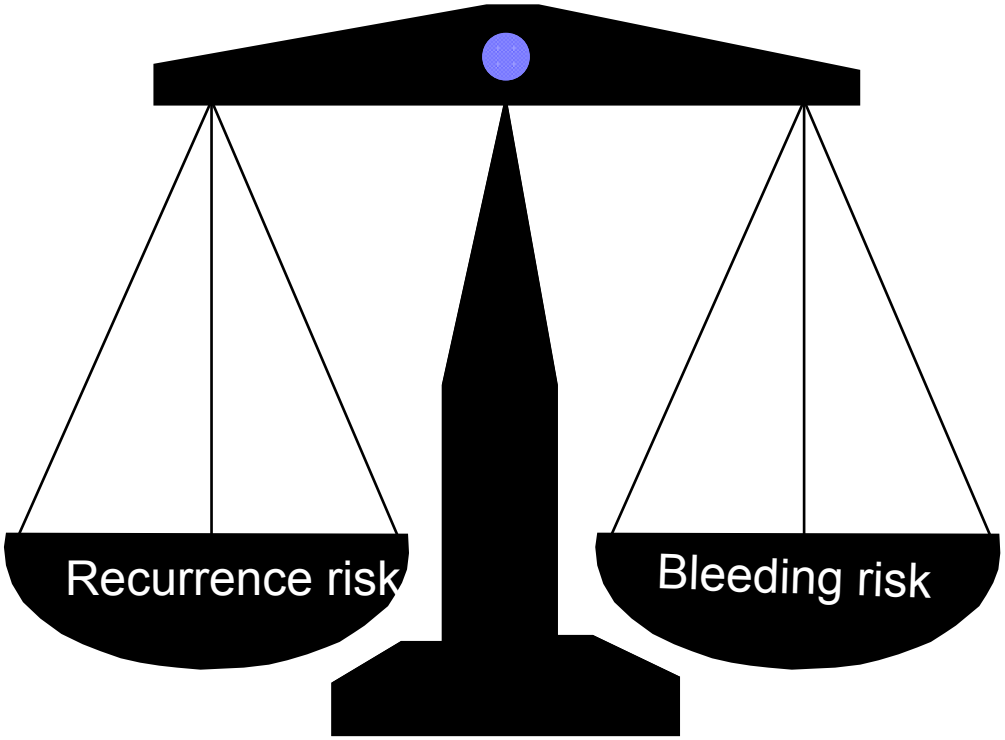
The antiphospholipid syndrome (APS) laboratory criteria

The presence of aPL on two or more occasions at least 12 weeks apart and no more than five years prior to clinical manifestations, as demonstrated by one or more of the following:

- IgG and/or IgM aCL in moderate or high titer
- Antibodies to ß2-GP-I of IgG or IgM

  (a titer >99th percentile)
- LA activity detected according to published guidelines

Optimal duration of anticoagulation



The decision on duration of antithrombotic treatment should be individualized, taking into consideration the estimated risk of recurrent VTE, risk of bleeding, patient compliance and preference

Guidelines ACCP 2012

- **Duration of Long-term Anticoagulant Therapy**

- **First/second DVT**
- **Provoked/unprovoked DVT**
- **Proximal/distal DVT**
- **Low/moderate/high bleeding risk**

9th The ***American College of Chest Physicians*** (ACCP) Consensus Conference on Antithrombotic Therapy, Chest 2012

Guidelines ACCP 2012

- **In patients with an unprovoked DVT of the leg, we recommend treatment with anticoagulation for *at least 3 months* over treatment of a shorter duration** (Grade 1B)

- **After 3 months of treatment, patients with unprovoked DVT of the leg should be evaluated for the risk-benefit ratio of extended therapy**

Guidelines ACCP 2012

- **In patients with a *first* VTE**
  that is an unprovoked
  proximal DVT of the leg and
  who have a low or moderate bleeding risk,
  we suggest extended anticoagulant therapy
  over 3 months of therapy (Grade 2B)

Guidelines ACCP 2012

- **In patients with a first VTE**

that is an unprovoked proximal DVT of the leg and who have a high bleeding risk, we recommend 3 months of anticoagulant therapy over extended therapy (Grade 1B)

Guidelines ACCP 2012

- **In patients with a second unprovoked VTE,**
we recommend extended anticoagulant therapy
over 3 months of therapy
in those who have a low bleeding risk (Grade 1B),
and we suggest extended anticoagulant therapy
in those with a moderate bleeding risk (Grade 2B)

- **In patients with a second unprovoked VTE who have a high bleeding risk, we suggest 3 months of anticoagulant therapy over extended therapy** (Grade 2B)

Guidelines ACCP 2012

- **Intensity of Anticoagulant Effect**

In patients with DVT of the leg

who are treated with VKA,

we recommend

a therapeutic INR range of 2.0 to 3.0 (target INR of 2.5)

over a lower (INR <2) or higher (INR 3.0-5.0) range for all treatment durations (Grade 1B)

Guidelines ACCP 2008

- „ The presence of

<u>hereditary thrombophilia</u>

has **not** been **used** as major factor **to**

guide duration of anticoagulation for VTE in these guidelines because evidence from prospective studies suggests that these factors are not major determinants of the risk of recurrence“

Guidelines ACCP 2016

- For VTE and no cancer, as long-term anticoagulant therapy, we suggest dabigatran (Grade 2B), rivaroxaban (Grade 2B), apixaban (Grade 2B) or edoxaban (Grade 2B) over VKA therapy, and suggest VKA therapy over LMWH (Grade 2C).
- For VTE and cancer, we suggest LMWH over VKA (Grade 2B), dabigatran (Grade 2C), rivaroxaban (Grade 2C), apixaban (Grade 2C) or edoxaban (Grade 2C).

10th The ***American College of Chest Physicians*** (ACCP) Consensus Conference on Antithrombotic Therapy, Chest 2016

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