Case 7: VTE/ MS4
29/Oct/2015

49 yr old lady complains of painful swelling and hotness of her L leg following coming back from visiting her relatives in USA. She had repeated attacks of cough with hemoptysis and shortness of breath. P/E

Duplex Us: DVT common femoral vein with PE

DVT
Case 10 investigation & Diagnosis
Importance of VTE (DVT/PE)

A- PREVENTABLE
B- LIFE THREATENING
C- LONG TERM COMPLICATIONS
D- COMMON
E- COSTLY
VTE is a multifactorial and often silent disease

- Hypertension
- Diabetes
- Smoking
- Age
- Pregnancy
- Cancer
- Antiphospholipid syndrome
- Congenital Thrombophilia
- HIT
- Acute infection
- Hyperlipidaemia
- Others

THROMBOSIS

A multifactorial accident
Venous thrombo-embolism is a multifactorial disease

- Genetic factors
- Environmental factors
- Triggering factors
Risk Factors for VTE

Stasis
- Age > 40
- Immobility
- CHF
- Stroke
- Paralysis
- Spinal Cord injury
- Hyperviscosity
- Polycythemia
- Severe COPD
- Anesthesia
- Obesity
- Varicose Veins

Hypercoagulability
- Cancer
- High estrogen states
- Inflammatory Bowel
- Nephrotic Syndrome
- Sepsis
- Smoking
- Pregnancy
- Thrombophilia

Endothelial Damage
- Surgery
- Prior VTE
- Central lines
- Trauma

## Risk Factors for VTE

<table>
<thead>
<tr>
<th>Stasis</th>
<th>Hypercoagulability</th>
<th>Endothelial Damage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &gt; 40</td>
<td>Cancer</td>
<td>Surgery</td>
</tr>
<tr>
<td>Immobility</td>
<td>High estrogen states</td>
<td>Prior VTE</td>
</tr>
<tr>
<td>CHF</td>
<td>Inflammation</td>
<td>Central lines</td>
</tr>
<tr>
<td>Stroke</td>
<td>Inflammatory Bowel</td>
<td>Trauma</td>
</tr>
<tr>
<td>Paralysis</td>
<td>Nephrotic Syndrome</td>
<td></td>
</tr>
<tr>
<td>Spinal Cord Injury</td>
<td>Sepsis</td>
<td></td>
</tr>
<tr>
<td>Hypercoagulability</td>
<td>Thrombophilia</td>
<td></td>
</tr>
<tr>
<td>Obesity</td>
<td>Varicose Veins</td>
<td></td>
</tr>
<tr>
<td>Anesthesia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Smoking</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pregnancy</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Most hospitalized patients have at least one risk factor for VTE.

ICOPER: CUMULATIVE MORTALITY AFTER DIAGNOSIS

Mortality (%)

Days From Diagnosis

17.5%

Figure 1. Annual incidence of VTE among residents of Worcester MA 1986, by age and sex. (Reproduced by permission from Anderson FA, et al. Arch Intern Med. 1991;151:933–938.)
The Burden of Venous Thrombo Embolism

1. Post-thrombotic Syndrome (40%)
2. PE (30%)
3. Death (3%)
4. Pulmonary Hypertension (5%)
5. DVT

References:
Post DVT Syndrome/ V. Stasis
VTE - A Public Health matter

- Annually, **1.5 million VTE events** occur in the European Union and **900,000** in the United States\(^1\)\(^2\).

- The subsequent yearly VTE-related complications account for more than **500,000 deaths** in Europe and **300,000 fatalities** in the United States\(^1\)\(^2\).

=> It represents more than the mortality related to AIDS, breast cancer and road traffic accidents combined \(^1\)-\(^4\)

---

Effective, safe, and cost-effective VTE prophylaxis is available!

- Pharmacologic Prophylaxis reduces DVT and PE by 50-65%.
- Symptomatic and Asymptomatic VTE reduced.
- Bleeding risk due to prophylaxis is rare.
- HIT
  - 2.37% with UFH (occasionally very serious)
  - .06% with LMWH
- Cost effectiveness of VTE prophylaxis has been repeatedly demonstrated.
Thromboprophylaxis reduces the burden of VTE

Risk Assessment for VTE

1. Identifying at-risk patient
2. Counselling at-risk patient
3. Prescribing thromboprophylaxis
Risk Assessment for VTE

- Identifying at-risk patient
- Counselling at-risk patient
- Prescribing thromboprophylaxis
Jordan University Hospital
Venous Thromboembolism Risk Factor Assessment

Patient's Name:______________________ Age: __________ Sex: ___ Wgt:___Kg. Hospital No. ____________

Choose All That Apply

Each Risk Factor Represents 1 Point
- Age 41-60 years
- Minor surgery planned
- History of prior major surgery
- Varicose veins
- History of inflammatory bowel disease
- Swollen legs (current)
- Obesity (BMI >30)
- Acute myocardial infarction (< 1 month)
- Congestive heart failure (< 1 month)
- Sepsis (< 1 month)
- Serious lung disease incl. pneumonia (< 1 month)
- Abnormal pulmonary function (COPD)
- Medical patient currently at bed rest
- Leg plaster cast or brace
- Other risk factors

Each Risk Factor Represents 2 Points
- Age 60-74 years
- Major surgery (> 60 minutes)
- Arthroscopic surgery (> 60 minutes)
- Laparoscopic surgery (> 60 minutes)
- Previous malignancy
- Central venous access
- Morbid obesity (BMI >40)

Each Risk Factor Represents 3 Points
- Age over 75 years
- Major surgery lasting 2-3 hours
- BMI > 50 (venous stasis syndrome)
- History of SVT, DVT/PE
- Family history of DVT/PE
- Present cancer or chemotherapy
- Positive Factor V Leiden
- Positive Prothrombin 20210A
- Elevated serum homocysteine
- Positive Lupus anticoagulant
- Anti-cardiolipin antibodies
- Heparin-induced thrombocytopenia (HIT)
- Other thrombophilia

For Women Only (Each Represents 1 Point)
- Oral contraceptives or hormone replacement therapy
- Pregnancy or postpartum (<1 month)
- History of unexplained stillbirth infant, recurrent spontaneous abortion (≥ 3), premature birth with toxemia or growth - restricted infant

Total Risk Factor Score

VTE Risk and Suggested Prophylaxis

<table>
<thead>
<tr>
<th>Total Risk Factor Score</th>
<th>Incidence of DVT</th>
<th>Risk Level</th>
<th>Prophylaxis Regimen**</th>
<th>Legend</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-1</td>
<td>&lt;10%</td>
<td>Low Risk</td>
<td>No specific measures; early ambulation.</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>10-20%</td>
<td>Moderate Risk</td>
<td>LWMH, UFH (5000 U BID), ES, or IPC.</td>
<td>ES- Elastic Stockings</td>
</tr>
<tr>
<td>3-4</td>
<td>20-40%</td>
<td>High Risk</td>
<td>LWMH, UFH (5000 U TID), or IPC.</td>
<td>IPC- Intermittent Pneumatic Compression</td>
</tr>
<tr>
<td>5 or more</td>
<td>40-60% - 1-5% mortality</td>
<td>Highest Risk</td>
<td>Pharmacological: LWMH*, UFH, Warfarin*, or in combination with ES or IPC.</td>
<td>UFH- Unfractionated Heparin</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>LMWH- Low Molecular Weight Heparin</td>
</tr>
</tbody>
</table>

* Use for major orthopedic surgery
** For the appropriate prophylaxis is in a particular patient, check with your consultant concerning best method and dose.

Choice of VTE prophylaxis: ___________________________ Duration: ___ Days: ___

Signature: ___________________________ Date: __________

4 YR Prospective study in inpatients
Total 217 patients: 102 m, 115 f
Total of 49 (22.5%) had inherited VTE
PC DEF  17 (35%)
PS DEF  15 (31%)
ATIII DEF 10 (20%)
Others  7 (14%)
## Risks and Incidence of a First Episode of Venous Thrombosis

<table>
<thead>
<tr>
<th>Condition/risk factor(s)</th>
<th>Relative risk</th>
<th>Incidence, percent per year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>1</td>
<td>0.008</td>
</tr>
<tr>
<td>Hyperhomocysteinemia</td>
<td>2.5</td>
<td>0.02</td>
</tr>
<tr>
<td>(MTHFR 677T mutation)</td>
<td>1</td>
<td>--</td>
</tr>
<tr>
<td>Prothrombin gene mutation</td>
<td>2.8</td>
<td>0.02</td>
</tr>
<tr>
<td>Oral contraceptives</td>
<td>4</td>
<td>0.03</td>
</tr>
<tr>
<td>Factor V Leiden (heterozygous)</td>
<td>7</td>
<td>0.06</td>
</tr>
<tr>
<td>Oral contraceptives plus heterozygous factor V Leiden</td>
<td>35</td>
<td>0.29</td>
</tr>
<tr>
<td>Factor V Leiden (homozygous)</td>
<td>80</td>
<td>0.5 to 1.0</td>
</tr>
</tbody>
</table>

† Adult subjects only. Data from the Leiden Thrombophilia Study.
FACTOR V LEIDEN (APC RESISTANCE)

- **G-to-A substitution at nucleotide 1691 in the gene of F V**
- **Single AA replacement in plasma F Va** (ARG 506 Gln) at 1 of 3 cleavage sites in F Va molecule
- **F V Leiden is inactivated at a rate 10 times slower**
FACTOR V LEIDEN IN JORDAN

- 400 healthy subjects
- 52 (13%) had APC resistance
- 49 (12.25%) were F V Leiden (DNA test)
- 42 (10.5%) were heterozygs for F V Leiden
- 7 (1.75%) were homozygous for F V Leiden

Venous thromboembolism

MAIN OBJECTIVES OF TREATMENT

- Reduction of fatality
- Prevention of recurrence
- Prevention of late sequelae
PULMONARY EMBOLISM and DVT TREATMENT

INITIAL

- Thrombolytic treatment
- Heparin (UFH or LMWH)
- Oral anticoagulant therapy (OAT) and new antithrombotics

LONG-TERM

- OAT and new antithrombotics
- LMWH

HOME

- OAT and new antithrombotics
- LMWH
TREATMENT OF VTE

*HEPARIN (UFH): 80u/kg loading > 18u/kg/hr
PTT 1.5-2.5

OR

*HEPARIN (LMW): 1mg/kgx2 enoxaparin
175u/kgx1 tinzaparin

4hrs post injection blood level 0.6-1u

*WARFARIN: 5mgx1 keep INR 2-3

OVERLAP HEPARIN + WARFARIN
VTE - Duration of therapy
ACCP Guidelines 2001

3-6 months
  - 1st event with time-limited risk factor

?6 months
  - 1st idiopathic

12 months-lifetime
  - 1st event with*
    • Cancer until resolved
    • ACA
    • AT deficiency
  - Recurrent event

All recommendations to be individualised

* Unclear for homozygous fVL, homocysteinemia, protein S or C deficiency
VTE: OTHER TREATMENT MODALITIES

* THROMBOLYTIC THERAPY
  SK 250K loading > 100k/hr 24-72 hr (pe, dvt)
  TPA (pe) 100mg over 2 hrs
* V. Thrombectomy
* IVC Filters
* Pulmonary embolectomy
* Post DVT syndrome
Heparin Preparations Used Clinically

Molecular Weight

- 3000
- 6000
- 9000
- 12000
- 15000
- 18000
- 21000

Factor Xa inhibition (≥5 monosaccharide units)

Thrombin inhibition (≥18 monosaccharide units)

- Penta
- LMW Heparin
- Unfractionated Heparin

Molecular Weight
Warfarin

Identified (1924) as a toxic substance in spoiled sweet clover that caused bleeding in cattle

Pharmacokinetics
- Plasma concentration peaks 2-8 h after an oral dose
- 99% bound to plasma proteins (albumin)
- Half-life in plasma ~25-60 h

Inhibits biosynthesis of vitamin K-dependent zymogens (delayed onset of action)

Prothrombin
Factor VII
Factor IX
Factor X
Protein C
Protein S

procoagulant
anticoagulant
Vitamin K Cycle

Zymogen → γ-Carboxylated Zymogen

Oxygen (O₂) and Carbon Dioxide (CO₂) are required for the conversion of Zymogen to γ-Carboxylated Zymogen.

Warfarin inhibits vitamin K epoxide reductase (mutations cause warfarin resistance).

Warfarin inhibits vitamin K epoxide reductase.
Clearance of Vitamin K-dependent Proteins

Activity (%)

Time after administration of warfarin (hours)
International Normalized Ratio (INR)

\[ \text{INR} = \left( \frac{\text{Patient PT}}{\text{Control PT}} \right)^C \]

\( C = \text{International Sensitivity Index} \)

- ISI = 1.2 (sensitive PT reagent)
- ISI = 2.5 (insensitive PT reagent)

Therapeutic range:

\( 1 \leq \text{INR} \leq 4 \)
Clearance of Vitamin K-dependent Proteins

![Graph showing the clearance of Vitamin K-dependent Proteins over time after administration of warfarin.](image)

- **Activity (%)**
  - Prothrombin
  - Factor X
  - Factor IX
  - Factor VII
  - Protein C

- **Time after administration of warfarin (hours)**
  - 0
  - 20
  - 40
  - 60
  - 80

- **INR**
  - Antithrombotic effect
  - Prothrombotic effect
Conditions that Alter the Response to Warfarin

Compliance

Drugs
- Affect hepatic metabolism of warfarin
- Affect binding to plasma proteins

Diet
- Availability of vitamin K

Other conditions
- Nephrotic syndrome (low plasma albumin)
- Pregnancy (high levels of coagulation factors)
- Liver disease (low levels of coagulation factors)
Complications of Warfarin Therapy

Bleeding
Risk increases with INR > 4
Treated with vitamin K
or fresh-frozen plasma (immediate response)

Birth defects and abortion
Skeletal and CNS abnormalities (hypoplastic nose, flat face, altered calcification)
**Contraindicated during pregnancy**
(heparin may be used)

Skin necrosis
Microvascular thrombosis
In patients with heterozygous protein C or S deficiency if a high initial dose is used or heparin overlap is inadequate
Case 8

50 yr old man complains for several weeks of hotness in his face, itching and severe acute pain in his big toe. Hb 19, WBC 17k, Platelets 500K, Serum Uric acid 12mg/dl, Po2 Saturation 95%, serum erythropoeitin 10 mU/ml. JakII Mutation +.
Diagnosis: polycythemia rubra vera with acute gouty arthritis.
Myeloid Malignancies

1- CML
2- AML
3- CMPN or disorders:
   PRV
   ET
   MF
Myeloproliferative Neoplasms

Common features

- Specific clinicopathologic criteria for diagnosis and distinct diseases, have common features
- Increased number of one or more myeloid cells
- Splenomegaly
- Hypercatabolism: wt loss, gout
- Clonal marrow hyperplasia without dysplasia
- Predisposition to evolve

- Generalized pruritus (after bathing)
- Unusual thrombosis (e.g., Budd-Chiari syndrome)
Role of mutations in chronic phase of MPN

Gain of function
- JAK2
- MPL
- CBL

Loss of function
- LNK
- NF1

STAT3/5 activation

Immune response
- Inflammation
- Angiogenesis
- Proliferation
- Apoptosis
Janus Kinase 2 (JAK2-V617F)

- Gain-of-function mutation is present in
  - \(~95\% \) of cases of PV
  - 23-57\% of cases of ET
  - 43-57\% of cases of MF
Risk classification of PV and ET

High risk*

- Age > 60 years
- Previous thrombosis

Low risk

- Age ≤ 60 years
- No previous thrombosis

* For practical purposes, platelets > 1,500 x 10^9/L also considered high risk

Barbui et al., JCO 2011 (E-pub ahead of print)
Diagnostic Criteria (Conventional): PRV

A1  Raised red cell mass
A2  Normal O2 sats and EPO
A3  Palpable spleen
A4  No BCR-ABL fusion
B1  Thrombocytosis >400 x 10⁹/L
B2  Neutrophilia >10 x 10⁹/L
B3  Radiological splenomegaly
B4  Endogenous erythroid colonies

A1 + A2 + either another A or two B establishes PV
JAK2/ serum erythropoietin
## Polycythemia Vera Diagnostic Criteria

### Table 4. WHO diagnostic criteria for P-vera

<table>
<thead>
<tr>
<th>Major Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Elevated RBC mass &gt; 25% above mean normal predicted value or hemoglobin &gt; 18.5 gm/dL (male) or 16.5 gm/dL (female)</td>
</tr>
<tr>
<td>2. Presence of JAK2 V617F</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Minor Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. BM trilineage myeloproliferation</td>
</tr>
<tr>
<td>2. Low serum erythropoietin levels</td>
</tr>
<tr>
<td>3. Endogenous erythroid colony formation</td>
</tr>
</tbody>
</table>

Diagnosis requires both major criteria or one major and two minor criteria.
FIGURE 1. Diagnostic algorithm for polycythemia vera (PV).

*Clinical clues for PV include splenomegaly, thrombosis, aquagenic pruritus, and erythromelalgia. Laboratory clues for PV include thrombocytosis, leukocytosis, and increased leukocyte alkaline phosphatase score. Janus kinase 2 (JAK2) screening is to detect the V617F mutation that occurs in most patients with PV. BM = bone marrow; CBC = complete blood cell count; MPD = myeloproliferative disorders.

†Alternatively, one can consider mutation screening for JAK2^{V617F} to help decide necessity of BM examination.
First-line therapy of PV

**When:**
- High-risk (age >60 years, thrombosis)
- Poor tolerance to or high need of phlebotomy
- Symptomatic or progressive splenomegaly
- Platelet >1.500 x 10⁹/L
- Progressive leukocytosis
- Disease-related symptoms

**How:**
- Phlebotomy (Hct < 45%)
- Low-dose aspirin
- Hydroxyurea or IFN-α
  - Caveat on HU for young < 40 years
- Busulphan in elderly
- Manage generic cardiovascular risk factor

First-line therapy of ET

When:
- High-risk patients (age > 60 years, prior thrombosis)

How:
- Hydroxyurea at any age
- Manage generic cardiovascular risk factors
- Aspirin if microvascular disturbances

Essential Thrombocythemia: Diagnostic Criteria

- Platelet count $\geq 450,000$

- JAK2 V617F$^+$ OR no evidence of reactive thrombocytosis

- Not meeting WHO criteria for other MPNs (e.g. PV, CML)

- Megakaryocyte proliferation with large and mature morphology; no or little granulocyte or erythroid proliferation

- ALL FOUR CRITERIA ARE “REQUIRED”
Essential Thrombocythemia

- Bone marrow: Hypercellularity with marked megakaryocytic hyperplasia
Ruxolitinib in the treatment of MPN

Selective JAK I & II inhibitor
Second line after hydroxyurea
Offers improvement of systemic symptoms, trx requirements.
No survival benefit as yet