VENOUS THROMBOEMBOLISM

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RELEVANT DISCLOSURE

Under the Oklahoma State Medical Association CME guidelines disclosure must be made regarding relevant financial relationships with commercial interests within the last 12 months.

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I have no relevant financial relationships or affiliations with commercial interests to disclose.
TOPIC OUTLINE

- Introduction
- Virchow’s Triad
- Superficial vein thrombosis
- Pulmonary embolism
- Inherited thrombophilias
- Acquired risk factors
- Elevated clotting factors and chemokines
- Anatomic risk factors
- Treatments
- Summary
- Information for patients
- References

MAIN OBJECTIVES

- Understand the economic burden of venous thromboembolism
- Review the major and minor risk factors
- Discuss diagnosis and treatments
- How to approach a patient with venous thromboembolism
INTRODUCTION

- Venous thromboembolism (VTE) includes:
  - Deep venous thrombosis
  - Pulmonary embolism
  - An important cause of preventable mortality and morbidity

- Causes of VTE are divided into 2 groups:
  - Inherited
  - Acquired
  - Or combination of both

- We are going to discuss lower extremity thrombosis
- Upper extremity thrombosis will be briefly discussed

ECONOMIC BURDEN OF VTE

Review Article

The economic burden of incident venous thromboembolism in the United States: A review of estimated attributable healthcare costs


Abstract

Venous thromboembolism (VTE), which includes deep vein thrombosis and pulmonary embolism, is an important cause of preventable mortality and morbidity. In this study, we summarize estimates of per-patient and aggregate medical costs or expenditures attributable to incident VTE in the United States. The aggregate estimate of incremental costs can be calculated as the difference in costs between patients with and without an event, after controlling for differences in underlying health status. We identified estimates of the incremental per-patient costs of acute VTE and adjusted estimates, including control for VTE risk thrombosis measure, chronic
ECONOMIC BURDEN OF VTE

- Grosse et al., summarized estimates of per-patient and aggregate medical costs or expenditures attributable to incident VTE in the US, including:
  - Acute VTE and related complications, which include:
    - Recurrent VTE, Post-Thrombotic syndrome, Chronic Thromboembolic Pulmonary Hypertension (CTEPH), anticoagulation-related adverse drug events
  - Direct cost of acute VTE on average: $12,000 to $15,000 among 1st year survivors
  - Subsequent complications increased cumulative cost to $18,000 to $23,000 per case
  - Annual incident VTE events cost US healthcare system $7-10 billion each year for 375,000 to 425,000 newly diagnosed cases
  - Costs associated with treating VTE can be used to assess potential economic benefits and cost-savings from preventive efforts

VIRCHOW’S TRIAD – THEORY EXPLAINED VTE
VIRCHOW’S TRIAD – THEORY EXPLAINED VTE

• Alterations in blood flow
• Vascular endothelial injury
• Alterations in the constituents of the blood (hypercoagulable states)

• Worcester Study – 56% of patients had 3 or more of these risk factors:
  - Prolonged immobility > 48 hours
  - Malignancy
  - Hospital admission in past 3 months
  - Infection in past 3 months
  - Surgery
  - Current hospitalization

• Many patients with VTE fulfilled most or all of Virchow’s Triad.

➤ A risk factor for thrombosis can now be identified in over 80 percent of VTE.
SUPERFICIAL VEIN THROMBOSIS

- Less severe disorder than DVT
- May progress to DVT and/or PE
- Martinelli et al. demonstrated in a study of 63 patients with SVT:
  - 32% (#20) developed DVT within 4 years
  - 24% (#15) developed recurrent episodes of SVT
  - Odd ratios with factor V Leiden, prothrombin G20210A, and combined of Antithrombin III, protein C and S deficiency were 6.1, 4.3, and 12.9
- Prevalence of DVT was 18% and PE was 7%, in a meta-analysis by Di Minno et al.
- Not to be dismissed as a “minor condition”
- Treatment depends on severity and proximity to the deep venous system

PULMONARY EMBOLISM

Pulmonary embolism can be classified by the following:

- Acute, subacute, and chronic
- Presence or absence of hemodynamic instability:
  - "Massive" or High risk – SBP < 90 mmHg for > 15 min, shock, pulselessness, bradycardia, right ventricular strain, + troponins, elevated BNP
    - Can occur with small PE and with underlying cardiopulmonary disease
  - Sub-massive or Intermediate risk – SBP > 90 mmHg, RV dysfunction, + troponins
  - Low risk - > 90 mmHg, no RV dysfunction, - troponins
- Anatomic location (saddle, lobar, segmental, sub-segmental)
- Presence or absence of symptoms
**PULMONARY EMBOLISM**

- Overall incidence is higher in men compared to women (56 vs. 48 per 100,000), increases with age to > 500 per 100,000 after the age of 75 years
- PE accounts for about 100,000 annual deaths in the US and about 300,000 in Europe
- Deaths from PE have been declining but remain high, 4% at 30 days and 13% at 1 year
- Risk factors of pulmonary embolism – same as causes for deep vein thrombosis
- Source – most arise from lower extremity proximal veins. Calf vein DVT rarely embolizes
- **BE WARE** of “PE without an apparent source” or “Idiopathic PE”

**Symptoms**

- Dyspnea (most common), chest pain, cough, hemoptysis, shock and syncope

**Diagnosis**

- D-Dimer, CTA, V/Q scan, echo and venous duplex

**Treatment**

- Oxygen, ventilation and stabilization, thrombolysis with massive and sub-massive
- Anticoagulation – usually long-term, unless contraindicated or causes reversible
  - Malignancy – LMWH over warfarin or newer agents (2016 Chest Guidelines)
  - No malignancy – Newer agents over warfarin and over LMWH
  - Pregnancy- LMWH and Heparin. Warfarin contraindicated. Newer agents ???
  - HIT – Argatroban, danaparoid, fondaparinux, bivalirudin, warfarin (slow transition)
  - Thrombolysis or embolectomy - Hemodynamically unstable or failed anticoagulation
- **IVC filters** – very few if ever. **New guidelines against IVC filter with anticoagulation**
Common inherited clotting disorders

- Factor V Leiden mutation (5%)
- Prothrombin G20210A mutation (2.7%)
- Protein C deficiency (0.4%)
- Protein S deficiency (0.003%)
- Antithrombin III deficiency (0.04%)

Rare (alleged) clotting disorders

- Heparin cofactor II deficiency
- Plasminogen deficiency
- Impaired tPA release
- Increased tPA inhibitor levels
- Dysfibrinogenemia
- Factor XII (Hageman) deficiency

**INHERITED THROMBOPHILIAS**

Antiphospholipid syndrome or Lupus Anticoagulant is not an inheritable disease.

**APPROACH TO PATIENTS WITH CLOTTING DISORDERS**

- Most clotting disorders are found after diagnosis of VTE
- These patients usually need life-long anticoagulation
- **Screen family members for inheritable clotting disorders. Why?**
  - Save these members from future events
  - It does take time, cost, and efforts in managing clotting disorders
- **What do we do with patient’s family members screened positive for clotting disorders?**
  - Assess risks for VTE
  - **Education, Education, Education** – especially young members of family
  - Avoid triggering events
  - Prophylactic anticoagulation?
ACQUIRED RISK FACTORS

- Prior thrombotic event
- Recent major surgery
- Presence of central venous catheter
- Trauma
- Immobilization
- Malignancy
- Pregnancy
- Use of oral contraceptives or heparin
- Major medical illnesses

Multiple acquired RF – Worcester study.
Six most prevalent characteristics
11% no RF vs. 36-53% 1-2 and > 3 RF

- > 48 hours of immobility – 45%
- Hosp. admission in past 3 mo. – 39%
- Surgery in the past 3 mo. – 34%
- Malignancy in the past 3 mo. – 34%
- Infection in the past 3 mo. – 34%
- Current hospitalization – 26%

ACQUIRED RISK FACTORS

- **Previous VTE** – high risk of recurrence, 18%, 25%, and 30% at 2, 5, and 8 years
  - Highest risk of recurrence – idiopathic and permanent risk factors
- **Malignancy** – 10-50% incidence, risk of VTE dependent on type of cancer and highest during initial hospitalization, onset of chemotherapy, and at time of cancer progression
  - On the reverse, patients with VTE have an average of 10% (2-25%) risk of cancer at presentation or at follow-up
- **Surgery** – low recurrence rate, can be divided into 3 groups:
  - **Low** – < 40, no risk factors, elective surgery (< 1% DVT and < 0.01% PE)
  - **Moderate** – > 40, > 1 risk factors, over 30 min anesthesia (< 10% DVT, <0.7% PE)
  - **High** – > 40, presence of clotting disorders, prolonged malignancy or orthopedic surgery (up to 20% and 5%, DVT and PE, respectively)
ACQUIRED RISK FACTORS

- **Major trauma** – 54% in head injury, 61% in pelvic fracture, 77% in tibial fracture, 80% in femoral fracture
- **Minor injuries** – 3-5 fold increase in DVT risk. Factor V Ledein increased to 50 fold
- **Pregnancy** – increased risk of DVT due to venous obstruction and hypercoagulable state, estimates of age-adjusted incidence of VTE range from 5 to 50%, further increases with other risk factors
- **Drugs**
  - Contraceptives – increase risk of VTE within first 6-12 months of initiation and returns to baseline within 1-3 months after discontinuation
  - HRT – 2 fold increase in VTE risk, greatest in first year of treatment
  - Testosterone – increases risk for VTE due to erythrocytosis, monitor hematocrit
  - Tamoxifen, bevacizumab, glucocorticoids, etc...

ACQUIRED RISK FACTORS

- **Immobilization** – prolonged bed rest, travel or “economy class syndrome,” sitting or “seated immobility thromboembolism” or “e-embolism,” all are major risk for VTE
- **Renal disease** – ESRD, CKD, Nephrotic syndrome, microalbuminuria, transplant
- **Liver disease** – Elevated INR in this group is not preventive of VTE development
- **Cardiovascular disease**
  - Heart failure – Right heart failure (edema) = greatest risk for DVT
  - Obesity (BMI > 40), male sex, black ethnicity, and diabetes - increased risk for VTE
  - Smoking – debatable. One study: OR for > 20 pack years of 4.3 in young smokers
  - Age – increasing incidence with age, HR 1.7 for every decade after 55 (ARIC, CHS)
  - **HTN, dyslipidemia, physical inactivity, and alcohol consumption** – *Not increased risks*
- **Seasonal variation** – highest rates of VTE found during winter months
ACQUIRED RISK FACTORS

• Hematologic risk factors
  • Polycystic ovary syndrome
  • Central and peripheral venous catheters
  • Rheumatoid arthritis
  • Ovarian hyperstimulation syndrome
  • Active tuberculosis
  • Asthma
  • Sepsis
  • Chronic psoriasis
  • Obstructive sleep apnea
  • Klinefelter syndrome
  • Inflammatory bowel disease

ELEVATED CLOTTING FACTORS AND CHEMOKINES

• Factor VIII:C, IX, XI, thrombin-activatable fibrinolysis inhibitor (FAFI), and interleukin 8
• Generally measured following a thrombotic event, so that a post-thrombotic phenomenon cannot be entirely excluded
• The basis for elevated levels of these factors has not yet been proven to be genetic
• Although one gain-of-function mutation in factor IX (factor IX Padua) has been described

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<thead>
<tr>
<th>Other elevated levels</th>
<th>Reduced levels</th>
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<tbody>
<tr>
<td>Factor VII</td>
<td>Tissue factor pathway inhibitor</td>
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<tr>
<td>Plasma fibronectin</td>
<td>Plasma fibrinolytic activity</td>
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<tr>
<td>Von Willebrand</td>
<td>Thrombomodulin</td>
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<td>Fibrinogen</td>
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<td>Altered fibrin clot structure and function</td>
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COMBINED ACQUIRED PLUS INHERITED

**MEGA case-control study** in 4311 consecutive patients vs. 5768 controls

- Patients with major medical illnesses (liver/kidney disease, rheumatoid arthritis, multiple sclerosis, heart failure, hemorrhagic stroke, arterial thrombosis) have OR 1.5 – 4.9
- The combination of MMI and immobilization - OR 10.9 (95% CI 4.2-28)
- MMI, immobilization, plus a thrombophilic disorder - OR 80, 35, 88, 84, and 53 for (increased Factor VIII, Factor IX, von Willebrand, Factor V Leiden, or non-O blood groups)
- The presence of a positive family history of blood clots found to be a strong additional risk factor for VTE

ANATOMIC RISK FACTORS

- Inferior vena cava abnormalities
- Paget-Schroetter syndrome
- May-Thurner syndrome
- IVC filters
INFERIOR VENA CAVA ABNORMALITIES

- IVC agenesis, hypoplasia, or malformation – very rare in my practice
- More common – IVC filter thrombosis
- Young patients with extensive bilateral DVT with negative hypercoagulable workup
- Diagnosis – testing for hypercoagulopathies and imaging
  - Ultrasound – not adequate for IVC visualization
  - CT venography
  - MR venography
  - Venography with intravascular ultrasound (IVUS)
- Treatments requires venous expertise

PAGET-SCHROETTER SYNDROME

- Compression of subclavian vein between the first rib and scalene or subclavius tendon, or the clavicle
- Young adults, athletic, weight lifting, with no genetic inheritance pattern
- Treatment – anticoagulation, avoidance of triggering activities, first rib resection
Differential Edema of The Legs

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MAY THURNER SYNDROME
Figure 5. Left common iliac vein compression by the right common iliac artery. Chronic changes in the left common iliac vein secondary to endothelial damage with (a) intraluminal spurs, (b) webs, and (c) channels are depicted.
MAY-THURNER SYNDROME

- Many patients with MTS are asymptomatic
- Kibbe et al.\(^1\) reported series of 50 consecutive patients with abdominal CT for reasons unrelated to thrombosis
  - 24% had greater than 50% compression of LCIV
  - 66% had greater than 25% compression of LCIV
  - No patients in series had symptoms of venous obstruction
- The true prevalence remains debatable
  - Up to 62% prevalence of May-Thurner anatomy found in patients with deep venous thrombosis\(^2\)
  - Up to 80% of patients with deep vein thrombosis had iliac vein compression (NIVL – Nonthrombotic Iliac Vein Lesions)\(^3\)

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1 Kibbe MR, J Vasc Surg 2004
2 Juhan C, Ann Vasc Surg 1987
3 Chung JW, J Vasc Interv Radiol 2004

INTRAVASCULAR ULTRASOUND (IVUS)
MAY-THURNER SYNDROME

- Compression of the left common iliac vein between iliac arteries and vertebral body
- Main cause of “Unprovoked” left leg DVT or pulmonary embolus without obvious DVT
- Most common in women between ages of 20-50
- Preceding symptoms – “Venous Claudication”
  - Heaviness
  - Restlessness
  - Itching
  - Achiness
  - Vague pain
  - Swelling
- Diagnosis requires disease awareness
- Treatments require venous expertise, venography and iliac vein stenting
- Treatment response – Improved quality of life

Differential Edema of The Legs

Awareness

This is a disease of the public deep venous system mainly involving iliac veins. The patients often experience pain, swelling, heaviness, restlessness at night, venous claudication, and deep venous thrombosis of the affected leg. This is one of the main causes of pulmonary embolism without apparent deep venous thrombosis in the extremities. The left leg is more commonly involved as the left common iliac vein traverses the space between the right common iliac artery and the L4 vertebral body to drain into the inferior vena cava and is often compressed. Compression can occur in the right leg as well. This disease is also referred to as May-Thurner Syndrome or Iliac Vein Compression Syndrome.

Diagnosis for this disease can be performed by any provider with Computed Tomography (CT) of the abdomen and pelvis without contrast (ICD-10 code of M87.1) and proper documentation of the patient’s signs and symptoms.

This condition can be completely curable if diagnosed and treated properly with expertise. The treatments include patient education, compression therapy, iliac vein stenting followed by a short period of anticoagulation.

The response to treatment is dramatic and life-changing. The patient’s quality of life can be significantly improved with resolution of pain and even cessation of long-term anticoagulation in the case of unprovoked deep venous thrombosis.

Please don’t ignore the signs and symptoms of this commonly occurring disease.
DIAGNOSIS OF VTE

• Ultrasound for deep venous thrombosis
• CT Angiography for pulmonary embolism
• V/Q Scan for PE usually for patients with renal insufficiency
• Echocardiogram to assess for right ventricular function in patients with PE

Lab tests
  • D-Dimer – high negative predictive value
  • Hypercoagulable workup

TREATMENTS OF VENOUS THROMBOEMBOLISM

• Principle treatment – anticoagulation (AC)
  • Types of anticoagulation – warfarin, LWMH, newer oral anticoagulants. NOT Plavix or aspirin
  • Anticoagulation duration – depends on etiologies and risk factors

• Massive and sub-massive pulmonary embolism – invasive strategies plus AC

• Low risk pulmonary embolism – conservative, AC and preventive

• Superficial vein thrombosis and below the knee DVT – conservative and AC

• Extensive DVT, symptomatic – invasive strategies and AC

• IVC filters – No patient should ever receive a permanent IVC filter !!!

• Compression stockings – works very well if appropriately fitted

PREVENTION PREVENTION PREVENTION !!!!
MONITOR, FOLLOW-UP AND PROGNOSIS

- **Early complications** – recurrence and progression of disease, sub-therapeutic INR
- **Late complications** – chronic thromboembolic pulmonary hypertension (CTEPH)
- **Complications of therapy** – bleeding and adverse effects of medications
- **Remove IVC filter** – once anticoagulation contraindication has resolved
- **Recurrent thromboembolism** – rate depends upon factors including adequate therapeutic anticoagulation and clinical nature of the embolic event *(provoked vs. unprovoked)*
- **CTEPH** – uncommon (1% to 4%), high risk of death if left untreated, mean pulmonary artery pressure > 30 mmHg portends a poor prognosis
- **Death** – mortality of untreated PE up to 30%, significantly reduced with anticoagulation
- **Most deaths occur during first week (early mortality), lingers as long as 30 years (long-term mortality) due to ensuing morbidity (cardiovascular, malignancy, and sepsis)*

WHEN YOU ENCOUNTER A PATIENT WITH VTE

- Ask yourself this question – “Why did the patient have blood clots?”
- If you know or don’t know the answer but are comfortable with VTE:
  - Cause(s) ➔ Testing ➔ Treatment ➔ Long-term follow-up
- If you know or don’t know the answer but are not comfortable with VTE:
  - Initiate anticoagulation
  - Refer to someone with expertise in venous disease
  - The problem is *Who are the experts in venous disease in Oklahoma?*
SUMMARY

- **Economic burden of VTE** – significant, can be reduced with treatments
- A risk factor can now be identified in many patients with VTE (*The "Why"*)
- **Inherited vs. Acquired** – frequently combined
- **Most frequent hereditary causes** – factor V Leiden and prothrombin gene mutations
- **Major acquired risk factors** – prior clots, recent major surgery, trauma, immobilization, APL, malignancy, pregnancy, OC, myeloproliferative disorders, non-O blood types
- **Don’t forget anatomic causes of VTE** – “Look Higher!!”
- **Diagnosis of VTE** – mainly ultrasound and CT
- **Treatments of VTE** – require understanding of underlying etiologies and expertise
- **Favorable treatment outcomes** – Improved quality of life.

INFORMATION FOR PATIENTS

- Thrombosis and Hemostasis Societies of North America – THSNA.
- National Blood Clot Alliance – Stop The Clot®.
- UpToDate™ – Basics and Beyond the Basics.
- Centers of Disease Control and Prevention – CDC.
- International Society on Thrombosis and Haemostasis – ISTH™.
- North American Society on Thrombosis and Hemostasis – NASTH.
- American Venous Forum – AVF.
- Anticoagulation Forum – ACF.
- Foundation for Women and Girls with Blood Disorders – FWGBD.
- Multiple Canadian organizations.
REFERENCES

- UpToDate – Topic 1361, Version 76.0, 2016.

THANK YOU !!!