Diagnosis and Management of Deep Vein Thrombosis

By

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Outline

• Introduction/ brief background
• Diagnostic Protocol
• Treatment
• DVT in pregnancy
• DVT and Surgery
• Follow up management
Introduction

• Venous thrombo-embolism (VTE), which include DVT and PE affect 0.1% of the population annually and is the third most common cardiovascular disorder.

• About 2-5% of the population will have a VTE during their lifetime
Inhibitors

Inhibitor

Factors

Inhibitors

AT III: Antithrombin
APC: activated Protein C
PS: Protein S
TFPI: Tissue Factor Pathway Inhibitor
TF: Tissue Factor

TFPI

PS

APC

TF-VIIa

Xa

XIa

XIIa

IXa

VIIIa

IIa

Xa

Va

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Virchow’s Triad = Risk

- STASIS
- THROMBOSIS
- COAGULATION CHANGES
- VESSEL WALL DAMAGE
Definition

- A DVT is the formation of a blood clot that does not break down in a deep vein of the body.
- Because the clot does not break down, it can become large and obstruct the normal flow of blood in the vein.
Considerations

- Deep veins of the lower extremities are the most common sites for a DVT.
- If the clot breaks into smaller pieces, it becomes an embolus which can travel to vital organs and cause life-threatening conditions such as a heart attack, stroke, or pulmonary embolism.
Signs and Symptoms of DVT’s

Signs/symptoms of a DVT include:

• Unilateral edema
• Pain in extremity
• Erythema
• Calf tenderness
• Pale leg & cool with diminished arterial pulse
• + Homan’s sign (discomfort in the calf muscles on forced foot dorsiflexion w/ knee straight; **NOTE:** Homan’s sign is neither sensitive nor specific; Present in <1/3 of patients with confirmed DVT; Found in >50% of patients without DVT) (Schreiber, 2009)
Diagnostic Protocol

• Long-term complications of VTE include post-phlebitic syndrome - in up to 40% (after DVT) and chronic thromboembolic pulmonary hypertension (after PE) in 1% to 4% of cases.

• Given the potential for poor outcomes of patients with VTE and the risks of major hemorrhage associated with anticoagulant therapy, it is key that timely, accurate diagnostic strategies are available to correctly diagnose VTE when present and to safely rule it out when absent.
Diagnostic Protocol

• Pts with clinically suspected VTE should undergo a careful clinical examination considering signs and symptoms of VTE, risk factors for this diagnosis, and presence of other potential explanations for their symptoms.

• In isolation, none of the symptoms or signs of VTE are diagnostic, it has been well established that clinical prediction rules incorporating signs, symptoms, and risk factors can be accurately applied to categorize patients as low, moderate, or high probability or “likely” or “unlikely” to have DVT or PE.

• Once the assessment is complete, if the clinician believes VTE is a diagnostic possibility, he or she should assign a pretest probability of VTE to decide on the best diagnostic strategy.
Diagnostic Protocol

• Usefulness of the Pre-test scoring arises from Bayes theorem which states that with a reasonably sensitive and specific test, the lower the pretest probability, the more likely a positive test result will be falsely positive, whereas with a high pretest probability, the more likely a negative test result will be falsely negative.

• Concordant results are likely to be true. For DVT, more than 14 studies have demonstrated the reproducibility of the Wells model and, for PE, more than 52 studies and 55 000 patients confirm that the Wells rule or the revised Geneva rule are acceptable for PE, although one study suggested superiority of the Wells rule.

# Pre-test Scoring for Suspected cases

<table>
<thead>
<tr>
<th>Variable</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Active cancer (treatment ongoing or within previous 6 mo or palliative)</td>
<td>1</td>
</tr>
<tr>
<td>Paralysis, paresis, or recent plaster immobilization of the lower extremities</td>
<td>1</td>
</tr>
<tr>
<td>Recently bedridden for more than 3 d or major surgery within 4 wk</td>
<td>1</td>
</tr>
<tr>
<td>Localized tenderness along distribution of the deep venous system</td>
<td>1</td>
</tr>
<tr>
<td>Entire leg swollen</td>
<td>1</td>
</tr>
<tr>
<td>Calf swelling by more than 3 cm compared with asymptomatic leg</td>
<td>1</td>
</tr>
<tr>
<td>(measured 10 cm below tibial tuberosity)</td>
<td></td>
</tr>
<tr>
<td>Pitting edema (greater in the symptomatic leg)</td>
<td>1</td>
</tr>
<tr>
<td>Collateral superficial veins (nonvaricose)</td>
<td>1</td>
</tr>
<tr>
<td>Past history of DVT</td>
<td>1</td>
</tr>
<tr>
<td>Alternative diagnosis as likely or greater than that of DVT</td>
<td>-2</td>
</tr>
</tbody>
</table>
# Two-level DVT Wells score

<table>
<thead>
<tr>
<th>Clinical feature</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Active cancer (treatment ongoing, within 6 months, or palliative)</td>
<td>1</td>
</tr>
<tr>
<td>Paralysis, paresis or recent plaster immobilisation of the lower extremities</td>
<td>1</td>
</tr>
<tr>
<td>Recently bedridden for 3 days or more or major surgery within 12 weeks requiring general or regional anaesthesia</td>
<td>1</td>
</tr>
<tr>
<td>Localised tenderness along the distribution of the deep venous system</td>
<td>1</td>
</tr>
<tr>
<td>Entire leg swollen</td>
<td>1</td>
</tr>
<tr>
<td>Calf swelling at least 3 cm larger than asymptomatic side</td>
<td>1</td>
</tr>
<tr>
<td>Pitting oedema confined to the symptomatic leg</td>
<td>1</td>
</tr>
<tr>
<td>Collateral superficial veins (non-varicose)</td>
<td>1</td>
</tr>
<tr>
<td>Previously documented DVT</td>
<td>1</td>
</tr>
<tr>
<td>An alternative diagnosis is at least as likely as DVT</td>
<td>−2</td>
</tr>
</tbody>
</table>

**Clinical probability simplified score**

<table>
<thead>
<tr>
<th>DVT <strong>likely</strong></th>
<th>2 points or more</th>
</tr>
</thead>
<tbody>
<tr>
<td>DVT <strong>unlikely</strong></td>
<td>1 point or less</td>
</tr>
</tbody>
</table>

Pre-test Scoring for Suspected cases

<table>
<thead>
<tr>
<th>Variable</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Signs or symptoms of DVT</td>
<td>3</td>
</tr>
<tr>
<td>Alternative diagnosis is less likely than PE</td>
<td>3</td>
</tr>
<tr>
<td>Heart rate &gt; 100 bpm</td>
<td>1.5</td>
</tr>
<tr>
<td>Immobilization/surgery in previous 4 wk</td>
<td>1.5</td>
</tr>
<tr>
<td>Prior history of DVT or PE</td>
<td>1.5</td>
</tr>
<tr>
<td>Hemoptysis</td>
<td>1</td>
</tr>
<tr>
<td>Active cancer</td>
<td>1</td>
</tr>
</tbody>
</table>

Original score
- < 0 points = low
- 0-2 points = intermediate
- > 2 points = high

Dichotomized score
- ≤ 1 = DVT unlikely
- ≥ 2 = DVT likely
Pre-test Scoring for Suspected cases

<table>
<thead>
<tr>
<th>Variable</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age 65 y or older</td>
<td>1</td>
</tr>
<tr>
<td>Previous DVT or PE</td>
<td>3</td>
</tr>
<tr>
<td>Surgery or fracture within 1 mo</td>
<td>2</td>
</tr>
<tr>
<td>Active malignant condition</td>
<td>2</td>
</tr>
<tr>
<td>Unilateral lower limb pain</td>
<td>3</td>
</tr>
<tr>
<td>Pain or deep palpitation of lower limb and unilateral edema</td>
<td>4</td>
</tr>
<tr>
<td>Hemoptysis</td>
<td>0</td>
</tr>
<tr>
<td>Heart rate 75-94 bpm</td>
<td>3</td>
</tr>
<tr>
<td>Heart rate 95 bpm or more</td>
<td>5</td>
</tr>
</tbody>
</table>

**Modified**

- <3 points = low
- 4-10 points = Intermediate
- >10 points = high

**Traditional**

- >6.0 = high
- 2.0-6.0 = moderate
- <2.0 = low

**Simplified**

- >4 = PE likely
- 4 or less = PE unlikely

bpm indicates beats per minute.
Algorithm for DVT diagnosis

- The first step is using a validated clinical prediction rule to determine pretest probability. If the prediction rule suggests a low, moderate, or unlikely probability of VTE, a negative VTE-validated D-dimer test rules out VTE and negates the need for diagnostic imaging.
- All other patients require imaging.
- Note: It is recommended that a negative D-dimer result should not be used to exclude VTE in patients who are high pretest probability because of the higher false negative rate in this subgroup.
Algorithm for DVT diagnosis
D-dimer

• D-dimer is a degradation product of a cross-linked fibrin blood clot that is typically elevated in patients with acute VTE, but also by a variety of non-thrombotic disorders including recent major surgery, hemorrhage, trauma, pregnancy, or cancer.

• D-dimer is a diagnostic (not screening) test and assays validated in VTE patients generally have sensitivities in the mid-90% range and specificities in the mid-40% range. Given these properties, the value of the D-dimer resides with a negative test.
Fibrinolysis

Plasminogen

Tissue plasminogen activator (TPA)
Urokinase plasminogen activator (UPA)

Inhibited by plasminogen activator inhibitor type 1 (PAI-1)

Plasmin

Degradation of factors V and VII

Inhibited by α2 antiplasmin

Fibrin

Fibrin degradation products (FDPs)

D-dimer
D-dimer E fragments
Oligomers of fragments X and Y
Crosslinked FDPs
XDPs

X Y D E fragments
Fibrinolysis

Adapted from Moseson MW, J Lab Clin Med, 1990

Diagnostica Stago training, 2005
Fibrin Degradation Products

From Physiologie de la Fibrinolysse, Alessi et al., Manuel d'hémostase, Option Bio, 1996, pp. 70
Fibrinogen Degradation Products (FDP)

Fibrinogen -> FDP-X
FDP-X -> FDP-Y
FDP-Y -> FDP-D
FDP-D -> FDP-E
Plasmin action
Coagulation and fibrinolysis

Fibrinogen

D - Dimer

Fibrin Degradation Products

Thrombin

Fibrin Monomer + fibrinopeptides

Soluble fibrin Polymer

XIIIa

Fibrin clot

E

Fibrin Degradation Products

D-Dimer
Imaging tests

• Compression ultrasonography is the diagnostic imaging test of choice for DVT. Lack of compressibility of a venous segment is the most sensitive and specific diagnostic criterion for a first episode of DVT.

• The addition of Doppler (including color flow) can be useful to accurately identify vessels and if there is doubt as to the compressibility of a particular segment.
Imaging tests

- For PE, although many diagnostic imaging tests such as conventional contrast pulmonary angiography, thoracic ultrasound, and magnetic resonance angiography are proposed for the diagnosis of PE, ventilation-perfusion (V/Q) lung scans and computerized tomographic pulmonary angiography (CTPA) currently are the most widely used and evaluated tests for the diagnosis. A recent randomized controlled study showed that when the two techniques are compared, CTPA diagnoses approximately 33% more PE.
Imaging tests

- Patients in whom PE is excluded with V/Q lung scans are not more likely to return with consequences of undetected VTE than patients in whom PE was ruled out by CTPA. For most clinicians, CTPA has become the preferred diagnostic test because of its higher sensitivity and simpler reporting system.
- Concerns that widespread use of CTPA has resulted in increased numbers of patients being diagnosed with PE, some of whom have minimal symptoms and minor thrombi involving only segmental and sub-segmental vessels.
Old vs New clot imaging

• Ideal strategy for diagnosing DVT in patients with a prior DVT in the symptomatic leg is still a subject of debate. Ultrasound abnormalities may persist indefinitely with DVT, the criterion of vein compressibility may not distinguish patients with acute recurrent DVT from patients with chronic findings.

• It is helpful to recognize that acute DVT is usually occlusive, not echogenic, and it tends to be continuous. If ultrasound reveals thrombosis that is echogenic, non-occlusive, or discontinuous, then chronic DVT should be considered. Comparison with previous ultrasound results - Increase in clot diameter by 4 mm or evidence of new areas of thrombosis not previously seen on ultrasonography are strongly suggestive of recurrence.
Treatment

• The goal of the therapy for VTE is to prevent the extension of thrombus, PE, and to relieve symptoms in the short term while preventing recurrent events in the long term.
Treatment

• Initial therapy must involve therapeutic doses of either unfractionated heparin or LMWH, fondaparinux or rivaroxaban. Initial therapy with vitamin K antagonists (VKAs) alone is unacceptable.

• The ease of administration and efficacy of LMWH make this the preferred anticoagulant over IV or subcutaneous unfractionated heparin irrespective of outpatient or inpatient mgt. Meta-analysis comparing effectiveness of fixed-dose LMWH Vs adjusted-dose unfractionated heparin, significantly fewer deaths, major hemorrhaging, and recurrent VTE occurred with LMWH.

• Current standard initial treatment is to administer once-daily weight adjusted LMWH until INR from VKA therapy is therapeutic (Usually 5 to 10 days). It is unknown whether twice-daily dosing of LMWH is superior to once-daily dosing of LMWH.

Treatment

The duration of long-term treatment varies depending on risk (the recent American College of Chest Physicians [ACCP] guidelines provides an excellent guide) and can be divided into 5 categories as follows.

(1) First VTE that occurs in the context of a transient risk factor (such as surgery or trauma) has a very low risk of recurrence and 3 months duration is adequate.
(2) Patients with malignancy have a higher incidence of recurrent thrombosis and bleeding complications while receiving anticoagulation therapy. Long-term anticoagulation with LMWH instead of warfarin appears to be more effective at preventing recurrent venous thrombosis without a statistically significant increase in bleeding risk. Treat all patients with active malignancy with at least 6 months of LMWH if there is adequate renal function. Generally wait 6 months after cure or complete remission before stopping therapy.
Treatment

(3) Recent data suggest that factor V Leiden, prothrombin gene mutation, protein C, protein S, anti-thrombin deficiency, and increased factor VIII levels do not sufficiently alter recurrence risk to be necessary for decisions about duration of therapy unless patients have combined or homozygous genetic defects or very strong family history of VTE associated with the thrombophilic defect. Patients with persistently elevated antiphospholipid antibodies determined by either ELISA or clotting assays have a 2-fold higher relative risk of recurrence within 4 years after stopping anticoagulation and therefore are generally treated indefinitely.

Treatment

(4) After a second VTE, the risk of further thromboembolic events after the discontinuation of anticoagulation is excessive if only 6 months of oral anticoagulation is given. Recommend continuing anticoagulation in this situation with yearly visits to assess bleeding risk, which enables a risk-benefit evaluation to determine whether anticoagulation should continue. If the bleeding risk is very high, then indefinite therapy may not be ideal.

(5) First VTE that occurs in the absence of temporary or identifiable ongoing risk factors for thrombosis - unprovoked. Decisions on the need for indefinite therapy must be made because recurrence risk may be significant.
Intensity of anticoagulation

• Standard intensity of oral anticoagulation with VKAs is determined by an INR of 2-3. Patients with antiphospholipid antibody-related thrombosis, it has long been felt that higher intensity anticoagulation is needed to prevent recurrence, but RCTs found that standard anticoagulation is as effective as high-intensity treatment even in this subgroup of patients.

• High-intensity anticoagulation is not recommended in any patient with VTE. Maintaining good INR control will decrease the risk of developing post-phlebitic syndrome.
Intensity of anticoagulation

- Debate on the usefulness of a reduced intensity regimen of anticoagulation (INR 1.5-1.9) long-term to prevent recurrent thrombosis while reducing the risk of bleeding. A large randomized trial has shown that low-intensity anticoagulation is less effective at preventing recurrent thrombosis and does not lead to a lower risk of bleeding.

- Low-intensity therapy is not recommended, but is more effective than no therapy.

Upper extremity DVT

- Upper extremity DVT (UEDVT) can be subdivided into catheter-related and non-catheter-related thrombosis. There is a risk of PE with this condition, so treatment with anticoagulation is generally recommended.

- Thrombolytic therapy as initial therapy for acute UEDVT has been used with some success, but no randomized controlled trials comparing thrombolytic therapy with anticoagulation alone have been performed.
Pregnancy

- The treatment of VTE during pregnancy deserves special mention because treatment with oral anticoagulation is generally avoided during pregnancy due to the teratogenic effects in the first trimester and the risks of fetal intracranial bleeding in the third trimester.
- LMWH is the treatment of choice for VTE during pregnancy. However, there is no consensus as to what the appropriate dose should be and whether anti-Xa levels need to be monitored.
- Stop 24 hours before delivery and recommence 48 hours post-delivery. Reverse effect with FFP or Activated Factor complexes in emergency.
Surgery

- Elective Surgery: Discontinue LMWH 12 – 24 hours pre-op. Recomence 48 hours post-op, to allow wound haematoma to clot.
- Emergency Surgery: Use Fresh frozen plasma, Protamine sulphate or Activated clotting factor complexes to abort effect of previous anticoagulant. Recomence anticoagulation 48 hours post-op.
Other interventions for VTE Treatment

- Thrombolytics and inferior vena cava filters: The addition of systemic thrombolysis to standard anticoagulation leads to earlier patency of an occluded vein, but does not affect the rate of PE.
- There is a definite increase in major hemorrhage, including intracranial hemorrhage, with thrombolytics. Catheter-directed thrombolysis have been reported to increase bleeding complications. It is unclear whether the earlier recanalization seen with thrombolytics translates into lower rates of post-thrombotic syndrome long term. **Thrombolysis for DVT is not generally recommended except in the case of massive DVT leading to phlegmasia cerulea dolens and threatened limb loss.**
Thrombolytics

- Systemic administration of thrombolysis for PE has now been the subject of 2 well performed randomized trials, but it does not appear to result in a mortality reduction and due to higher risk of significant hemorrhage should likely be reserved for those with hemodynamic compromise or deterioration on standard anticoagulant therapy.

Inferior vena cava filters

• IVC filter placement in addition to anticoagulation has not been found to prolong survival in patients with DVT. Although it prevents PE, the insertion of a filter increases the risk of recurrent DVT.

• A retrievable filter is indicated when there is a contraindication to anticoagulation therapy (recent hemorrhage, impending surgery) in patients with newly diagnosed proximal DVT.

LOVE = HEMOSTASIS

Everybody talks about it, nobody understands it.

JH Levy 2000
Thanks
for
Listening