Venous thromboembolism

Pocket card

Issue number 6 2012
D-dimer

- Non-covalent bonds
- Covalent bonds
- Plasmin

Fibrin moments

Factor XIIIa

Polymerisation

Plasmin

Initial degradation

Final degradation

E Fragment

D-dimers

Fig. 1: Adapted from Figure 1. The stepwise process of Fibrin polymerization.

D-dimer antigen formation

- When a clot forms, fibrin monomers first join to form protofibrils which are held together by non-covalent bonds, and, in the presence of Factor XIIIa, by covalent bonds between the D domains. A fibrin clot is formed when these protofibrils become aligned side by side and undergo branching

- During fibrinolysis, plasmin cleaves Factor XIIIa-cross-linked fibrin into fibrin degradation products

- Initially these consist of high molecular weight fragments. Further degradation results in D-dimer/D-dimer–E complexes which contain the D-dimer antigen and E fragments
D-dimer testing\(^2\)

- Venous thromboembolism (VTE; pulmonary embolism (PE) or deep vein thrombosis (DVT)) is unlikely in the presence of a normal D-dimer level: **high negative predictive value (NPV)**
- However, although D-dimer is very specific for fibrin, the specificity of fibrin for VTE is poor because fibrin is produced in a wide variety of conditions (e.g., surgery, infection, inflammation, pregnancy): **low positive predictive value (PPV)**
- Therefore, while a negative D-dimer test can be used to exclude VTE, a positive D-dimer test alone will not confirm VTE

D-dimer assays

- D-dimer is not currently standardised, therefore results, normal ranges and cut-off values depend on the assay used
- Assay sensitivity\(^2\)
  - ELISA: sensitivity >95%; specificity ~40%; **highly sensitive assays**
  - Latex-derived assays, whole-blood agglutination assays: sensitivity ~85–90%; **moderately sensitive assays**
- Negative D-dimer result
  - Highly sensitive assay: safely excludes VTE in patients with a low or moderate clinical probability
  - Moderately sensitive assay: excludes VTE only in patients with a low clinical probability
Clinical pre-test probability (modified Wells DVT score)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Active cancer (on treatment for last 6 months or palliative)</td>
<td>1</td>
</tr>
<tr>
<td>Paralysis, paresis or plaster immobilisation of lower extremity</td>
<td>1</td>
</tr>
<tr>
<td>Immobilisation previous 4 days or major surgery within 4 weeks</td>
<td>1</td>
</tr>
<tr>
<td>Localized 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 swollen by more than 3 cm</td>
<td>1</td>
</tr>
<tr>
<td>Pitting oedema</td>
<td>1</td>
</tr>
<tr>
<td>Collateral superficial veins (non-varicose)</td>
<td>1</td>
</tr>
<tr>
<td>Probable alternative diagnosis</td>
<td>-2</td>
</tr>
</tbody>
</table>

Clinical probability (2 level)

<table>
<thead>
<tr>
<th>Probability</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>High DVT risk</td>
<td>&gt;3</td>
</tr>
<tr>
<td>Moderate DVT risk</td>
<td>1-2</td>
</tr>
<tr>
<td>Low DVT risk</td>
<td>&lt;1</td>
</tr>
</tbody>
</table>

Fig. 2: Deep vein thrombosis (DVT) diagnosis algorithm
D-dimer testing in pulmonary embolism (PE) diagnosis

Clinical pre-test probability (modified Wells PE score)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical signs / symptoms of pulmonary embolism (PE)</td>
<td></td>
</tr>
<tr>
<td>Alternative diagnosis unlikely</td>
<td>3</td>
</tr>
<tr>
<td>Heart rate &gt;100 beats/min</td>
<td>1.5</td>
</tr>
<tr>
<td>Immobilisation previous 4 days</td>
<td>1.5</td>
</tr>
<tr>
<td>Previous DVT/PE</td>
<td>1</td>
</tr>
<tr>
<td>Haemoptysis</td>
<td>1</td>
</tr>
<tr>
<td>Cancer (on treatment for last 6 months)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Clinical probability (2 level)</th>
<th>Total score</th>
</tr>
</thead>
<tbody>
<tr>
<td>PE less likely</td>
<td>0–4</td>
</tr>
<tr>
<td>PE likely</td>
<td>&gt;4</td>
</tr>
</tbody>
</table>

Fig. 3: Pulmonary embolism (PE) diagnosis algorithm
Venous thromboembolism (VTE)
• Blood clot which develops within a vein
• Annual incidence of VTE ~1–2 cases per 1000 person-years in industrialised countries
• The likelihood of developing VTE is linked to a range of risk factors

Deep vein thrombosis (DVT)
• Most common form of VTE
• Blood clot in one of the deep veins of the body, usually the leg, but also more rarely in the pelvis or arms
• May be asymptomatic or may cause pain, redness, warmth and swelling in affected limb
• Prognosis of acute DVT depends largely on the extent of the initial clot and the presence or absence of an underlying co-morbidity; in the absence of cancer, the 30-day case fatality rate is <2%
• Long-term risk of recurrent VTE
  • Potential complications of DVT include
    • Pulmonary embolism (PE)
    • Post-thrombotic syndrome (PTS)
  • Early recognition and appropriate treatment of DVT improves outcome
**Pulmonary embolism (PE)**
- The most serious complication of DVT
- Occurs when part of the DVT breaks away (embolus) and travels to the lungs
- Obstruction of the blood flow through the lungs and the resultant pressure on the right ventricle of the heart leads to the symptoms and signs of PE:
  - Difficulty breathing (dyspnoea)
  - Chest pain on inspiration
  - Palpitations
  - Low blood oxygen saturation
  - Blue discolouration of lips and/or fingers (cyanosis)
  - Rapid heart rate
- If untreated, approximately 10% of patients who develop PE die within the first hour, and 30% die subsequently from recurrent embolism
- Treatment with anticoagulant agents reduces mortality, therefore accurate diagnosis and suitable management is critical

**Post-thrombotic syndrome (PTS)**
- Potential long-term complication of DVT
- PTS affects around one third to half of patients following DVT of the leg, with around 10% going on to develop severe PTS
- Signs and symptoms of PTS include pain, swelling, varicose veins, skin discolouration and venous ulcers (severe disease)
Venous thromboembolism (VTE) risk factors

Hereditary
- Factor V Leiden mutation
- Prothrombin gene mutation (20210A)
- Protein C or S deficiency
- Antithrombin deficiency
- Hyperhomocysteinaemia
- Elevated levels of factor VIII
- Dysfibrinogenaemia

Acquired
- Surgery
- Trauma
- Immobility
- Active cancer/cancer therapy
- Age >40 years
- Obesity
- Significant medical co-morbidities (e.g., heart or respiratory disease, acute infectious diseases, inflammatory conditions)
- Previous VTE
- Close family history of VTE
- Use of oestrogen-containing oral contraceptives or hormone replacement therapy
- Varicose veins with phlebitis
- Pregnancy and post-partum period
References

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