PROSPECTIVE STUDIES ON DIAGNOSIS AND MANAGEMENT OF DEEP VEIN THROMBOSIS (DVT) AND THE POST-THROMBOTIC SYNDROME (PTS): FILLING UP THE GAP

PART 1: DEEP-VEIN THROMBOSIS (DVT): THE ROTTERDAM APPROACH

SUMMARY:
Deep venous thrombosis (DVT) is a disease with an annual incidence of 0.2% (in urban population), with a slightly higher incidence in men than in women and a maximum of frequency in persons aged between 85 and 89 years. When DVT is suspected the first step in diagnosis is the clinical score, the second step is Compression Ultrasound (CUS) combined with D-dimer test. The main complications of DVT are the pulmonary embolism (PE -especially when untreated), then post thrombotic syndrome (PTS) and recurrent thrombosis. The main prophylaxis of DVT is represented by low molecular weight heparins (LMWH) or low dose unfractioned heparins (LDUH) with or without medical elastic compression stockings (MECS). The treatment consists initially in given LMWH subcutaneously and once the diagnosis is confirmed, vitamin K antagonists will be added and ambulatory MECS will be added.

Key Words: DVT, CUS, D-dimer test, LMWH, MECS.

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EPIDEMILOGY

DVT has an annual incidence of 0.2% in the urban population (1). The disease is rare in children under 15 year of age, but its frequency increases with age, with an incidence of 1.8 per 1000 persons-years at age 65 to 69 years and 3.1 per 1000 persons–years at age 85 to 89 years (2). First-time episodes of DVT are in two-thirds of cases caused by risk factors, including cancer, immobility, or surgery. The prevalence of DVT is comparable in black and white adults and is low in Asian populations. Risk for DVT seems to be slightly higher in men than in women, and the risk of recurrence of venous thromboembolism is about 60% higher in men compared to women (3).

PATHOGENESIS

In 1856, Virchow postulated that the main causes of thrombus formation consist of damage to the vessel wall, alterations in flow, and hypercoagulability (2). This model is called 'Virchow’s triad' and and is still valid today. The maintenance of the fluidity and circulation of the blood and its ability to thrombose are essential for the maintenance of life and are governed by extremely complex homeostatic mechanisms. The mechanisms of thrombosis, a protective device to prevent loss of blood and to seal off a damaged blood vessel, and of fibrinolysis, which counteracts or stabilizes the effects of thrombosis, depend upon systems of consecutive enzyme activity with activators and inhibitors finely balanced at every stage.

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Alterations in blood coagulability, platelet population and agglutinating power, with changes in blood flow and endothelial damage, are the precursors of intravenous thrombosis. Of these, the loss of normal function of the vascular endothelium is probably of primary importance (4). Anticardiolipin antibody is also now recognized as an important cause of thrombosis (5,6). A number of other hereditary and acquired conditions that predispose to thrombosis (thrombophilia) have been recognized. (7). These include protein C and S deficiency, antithrombin III deficiency and activated protein C resistance (which is usually associated with a factor V genetic abnormality).

Screening for these thrombophilias, and for anticardiolipin antibody, should only be performed in patients having familial, sporadic or recurrent thrombosis (8). Surgical operations and pregnancy remain important triggers, and prolonged immobility as in long-haul flights, or hormonal influences, such as the contraceptive pill, are also well-documented clinical risk factors (Table 1).

### CLINICAL FEATURES

The onset of a thrombosis is often ‘silent’ and may remain so. It commonly occurs at or about day 7 to 10 after a surgical operation, parturition or the onset of an acute infection. Between one-third and two-thirds of patients complain of some swelling and pain in the leg, usually in the calf (4). An iliac thrombosis should be suspected if the whole leg is swollen and dusky. Direct pressure on the calf muscles or over the course of the deep veins usually elicits direct tenderness. There may be a cyanotic hue to the leg and superficial venous dilatation. The temperature of the leg may be raised, and oedema of one ankle is an important physical sign. However, chest pain or cardiac arrest from pulmonary embolism may be the first indications of a DVT. Pulmonary hypertension may follow repeated small emboli, and is associated with the development of progressive dyspnoea.

### DIFFERENTIAL DIAGNOSIS

Pain and tenderness in the calf and popliteal fossa may occur resulting from other conditions such as a ruptured Baker’s cyst, a torn plantaris tendon, a hematoma, or muscle tears or pulls. Cutaneous infection (e.g. cellulitis), lymphoedema, venous reflux, peripheral arterial disease, neurological and rheumatological causes should also be differentiated from DVT (alternative diagnosis, figure 1).

### DIAGNOSIS

Accurate diagnosis is mandatory in patients with suspected DVT, as an untreated thrombus may lead to pulmonary embolism, and anticoagulation in the absence of thrombosis is irresponsible. Because only a quarter of patients with suspected DVT actually have the disorder, it is important to safely rule out thrombosis by non-invasive, rapid, and cost-effective methods.

As compared with phlebography (the reference gold standard to exclude and diagnose proximal DVT in prospective management studies), the sensitivity of CUS is 97% for proximal and 73% for distal vein thrombosis (10). CUS has many advantages over phlebography. It is
noninvasive, simple, easy to repeat, relatively inexpensive, and free of complications. However, there are two main disadvantages of CUS. First, calf vein thrombosis will be overlooked by CUS because it is safe to limit CUS estimation to the subpopliteal, popliteal, and femoral veins for the diagnosis of symptomatic proximal DVT. Second, isolated thrombi in the iliac and superficial femoral veins within the adductor canal are rare but difficult to detect and therefore easily overlooked in symptomatic patients with suspected DVT (10).

Estimates of clinical score as low, moderate, and high for the probability of proximal DVT, based on medical history and physical examination is the first step when DVT is suspected (Table 2). A score of 0 (asymptomatic) means a low probability, a score of 1 or 2 a moderate probability, and a score of 3 or more a high probability for DVT.

**Table 2:** Clinical score list for predicting pretest probability for proximal DVT. The Rotterdam version of the Wells’ score (10).

<table>
<thead>
<tr>
<th>CLINICAL FEATURE</th>
<th>SCORE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Active cancer treatment ongoing or within previous 6 months or palliative</td>
<td>1</td>
</tr>
<tr>
<td>Paralysis, paresis, or recent plaster immobilization of the lower leg(s)</td>
<td>1</td>
</tr>
<tr>
<td>Recent immobilization for more than 3 days or major surgery within last 4 weeks</td>
<td>1</td>
</tr>
<tr>
<td>Localized tenderness/pain 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 by more than 2 cm when compared with the asymptomatic leg (measured 10 cm below tibial tuberosity)</td>
<td>1</td>
</tr>
<tr>
<td>Pitting oedema greater in the symptomatic leg</td>
<td>1</td>
</tr>
<tr>
<td>Collateral superficial veins (nonvaricose)</td>
<td>1</td>
</tr>
<tr>
<td><strong>Total Rotterdam DVT score</strong></td>
<td>8</td>
</tr>
</tbody>
</table>

**Figure 1:** Safe exclusion and diagnosis of deep vein thrombosis by the sequential use of CUS and SimpliRed test (10,11)
D-dimer is a degradation product of a cross-linked fibrin clot. It has gained a prominent role for ruling out DVT. The prevalence of DVT after a negative first CUS is uniformly low, 2 to 3%, during a 3 months follow-up with a NPV of 97 to 98% in large prospective management studies (figure 1) (11). The combination of a negative first CUS and a negative SimpliRed safely excludes DVT to zero or less than 1% (NPV > 99.3 to 100%) irrespective of clinical score (figure 1) (11). This simple, safe and most effective strategy obviates the need of repeated CUS on the basis of which anticoagulant therapy can safely be withheld and reduces the number of repeated CUS testing from about 75% to 30% (11).

The sequential use of a sensitive quantitative ELISA D-dimer test, clinical score, and compression ultrasound (CUS) appears to be safe and the most cost-effective diagnostic work-up of DVT (Figure 2) (10,11). However, the specificity of D-dimer is low because its concentrations can be raised in various other conditions, such as inflammation, pregnancy, or cancer. Consequently, D-dimer should not be used as a stand-alone test (2). A moderate or high probability or a low probability in combination with a high D-dimer should be followed by CUS of the legs. When the ELISA D-dimer test is increased, CUS is negative, and there is a moderate or high clinical probability, CUS should be repeated after one week (figure 2) (10,11). At that time, a thrombus can be detected in about 2 to 5% of patients with suspected DVT who had a negative first CUS (12).

**COMPLICATIONS**

Pulmonary embolism, post-thrombotic syndrome (PTS) and recurrent thrombosis are the main complications of DVT. If proximal DVT is left untreated, clinical pulmonary embolism will occur in 26 to 67% of the cases, and is associated with a mortality rate of 11 to 23%. The incidence of pulmonary embolism decreases to 5% and the mortality to less than 1% under treatment (13). About 30 to 50% of patients with DVT develop PTS. DVT has a recurrence rate of about 30% after 5 years, but the rate varies depending on the presence of risk factors (14). DVT recurrence contributes to the development of severe PTS.

**PREVENTION**

The incidence of recurrent thrombosis is reduced from approximately 30% to 10% by medical elastic compression stockings (MECS) (15). Below-knee stockings appear to be as effective as thigh-length hosiery. MECS may also be used combined with low-dose unfractionated heparins (LDUH) or low-molecular weight heparins (LMWH), and other pharmacologic or mechanical means of thrombosis prophylaxis. Pneumatic compression therapy has been proved to be effective, but is probably only realistic in post-operative circumstances, and it has shown to be effective in for example elective knee or hip replacement (16). Antiplatelet drugs such as aspirin very likely do not provide protection.
Dermatologists should be aware of risk factors for DVT, particularly in elderly bedridden inpatients with widespread skin disease, infection, or other co-morbidities (Table 1). The incidence of DVT among general medical patients with reduced mobility ranges from 10 to 26% (16). Prolonged sitting is as harmful as lying. Active exercise and early mobilization is desirable when possible. All hospitalized general medical patients should be assessed for venous thromboembolism risk factors. Those patients classified to be at moderate or high risk should be given thromboprophylaxis with LDUH (preferably 5000 U three times a day) or LMWH (4000 U or more once daily).

Surgical patients may be classified as having a low, moderate, or high thromboembolic risk. Low risk patients are patients under 60 years of age without any other risk factors for venous thromboembolism undergoing minor surgery (e.g. laparoscopic surgery, transurethral surgery, or out-patient surgery). These patients should be mobilized early and no additional thromboprophylactic regimen is required. Moderate risk patients consist of patients older than 60 years undergoing minor surgery, and patients younger than 60 years who undergo major surgery, but have no additional risks. These patients should be anticoagulated with LDUH (every 12 hours) or LMWH ($\leq$3400 U daily). Patients with high bleeding risk may be treated by MECS or intermittent pneumatic compression alone. High risk patients for venous thromboembolism are patients undergoing major surgery and being over 60 years of age, or having additional risk factors. These patients should be treated with LDUH (every 8 hours) or LMWH (>3400 U daily). MECS may be used as additional treatment (16).

Patients undergoing major orthopedic surgery face an overall DVT rate ranging from 40 to 60% and a proximal DVT rate between 10 to 30% without thromboprophylaxis. The general consensus is that these patients receive adequate thromboprophylaxis with LMWH, because these have proven to be more effective than LDUH. Moreover, patients receiving prolonged treatment duration (4 to 5 weeks) in hip surgery showed a significant reduction of DVT rate (16).

**TREATMENT**

The diagnosis DVT should be confirmed as soon as possible by compression ultrasound (CUS) if a DVT is suspected. Initial treatment with a LMWH given subcutaneously once a day (150 to 200 IU/kg). LMWH is modestly superior to LDUH for initial treatment of DVT. LMWH is also effective in an outpatient setting, and compared to LDUH it has a more predictable dose-response relationship, a longer half-life, and assigns a lower risk for osteoporosis and immune-mediated thrombocytopenia (2). As soon as the diagnosis of DVT is confirmed, vitamin K antagonists (e.g. warfarin) should be added to the heparin. Monitoring of anticoagulation is done by the prothrombin time, expressed in terms of the international normalized ratio (INR). A ratio between 2.0 and 3.0 should be achieved for the most adequate anticoagulation, and the lowest risk of bleeding. Heparin can be discontinued after 5 to 7 days, as long as the INR is stable and 2.0 or greater (2). Idiopathic venous thromboembolism is generally treated for 6 months, but anticoagulation may be for life for those with continuing risk (17).

LMWH and oral anticoagulants should be combined with ambulatory compression. Once oedema has been reduced completely, class II MECS (23 to 32 mm Hg at B measurement) are prescribed to be worn for a period of 2 years. If, during the use of MECS, oedema is still present, class III MECS (34 to 46 mm Hg at B measurement) are prescribed (18). MECS significantly reduce the development of postthrombotic syndrome.

Vena cava filters are effective in preventing the short-term incidence of pulmonary embolism in patients with proximal DVT, but they do not affect mortality. Vena cava filters are not generally recommended because of thrombogenicity and doubling the recurrence risk of DVT (2).

**REFERENCES**

REFERENCES (continued)