
Deep Vein Thrombosis

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Background:

A venous thrombosis is a blood clot (thrombus) that forms within a vein. Most often, the blood clot develops in the deep veins of the leg or pelvis. This is known as deep vein thrombosis (DVT).¹ Although most DVT is occult and resolves spontaneously without complication, death from associated massive pulmonary embolism (PE) causes as many as 300,000 deaths annually in the United States.²

³ DVT has an annual incidence of about 1 in 1,000 people.⁴ About 50-70% of patients had readily identifiable risk factors (Table 1).⁴⁻⁷

Annual costs are estimated to be more than €3.07 billion in Europe for total direct costs associated with VTE, 8 and up to \$15.5 billion in the US for VTE diagnosis and treatment.^{4, 8}

The pathophysiology of DVT was described by Virchow in 1846 as a triad of possible changes in the venous system. The triad includes changes in the vessel wall (injury), changes in the pattern of blood flow (venous stasis), and changes in the constituency of blood (hypercoagulability).¹

Table 1: Risk Factors for DVT

Acquired • Older age • Major surgery • Cancers • Immobilization • Pregnancy and postpartum • Antiphospholipid syndrome • Trauma • Previous VTE • Combined oral contraceptives • Hormonal replacement therapy • Central venous catheters • Inflammatory & autoimmune diseases • Nephrotic syndrome • Obesity • Infection • HIV • Polycythemia vera • Chemotherapy • Intravenous drug use	Inherited • Antithrombin deficiency • Protein C deficiency • Protein S deficiency (type I) • Factor V Leiden[e] • Prothrombin G20210A • Dysfibrinogenemia • Non-O blood type Mixed • Low free protein S • Activated protein C resistance • High factor VIII levels • Hyperhomocysteinemia • High fibrinogen levels • High factor IX & factor XI levels
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Clinical Presentation:

Symptoms of DVT may include the following:^[8-10]

- Edema - Most specific symptom
- Leg pain - Occurs in 50% of patients but is nonspecific
- Tenderness - Occurs in 75% of patients
- Warmth or erythema of the skin over the area of thrombosis
- Clinical symptoms of pulmonary embolism (PE) as the primary manifestation

Physical findings in DVT may include the following:

- Calf pain on dorsiflexion of the foot
- A palpable, indurated, cordlike, tender subcutaneous venous segment
- Variable discoloration of the lower extremity
- Blanced appearance of the leg because of edema

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Diagnosis:

DVT diagnosis requires the use of imaging devices such as ultrasound. Clinical assessment, which predicts DVT likelihood, can help determine if a D-dimer test is useful. In those not highly likely to have DVT, a normal D-dimer result can rule out a diagnosis.

Probability:

In those with suspected DVT, a clinical assessment of probability can be useful to determine which tests to perform. The most studied clinical prediction rule is the Wells score (Table 2).¹¹

Table 2: Wells rule to estimate the probability of DVT

Clinical feature	Score
Recent treatment for cancer (last 6 months) or current palliation	1
Paralysis, paresis, or cast of lower extremity	1
Bedridden at least 3 days in last 4 weeks or major surgery in last 12 weeks	1
Tenderness along deep venous system	1
Swelling of entire leg	1
Unilateral calf swelling > 3 cm compared to other side	1
Unilateral pitting oedema	1
Superficial collateral veins	1
Prior DVT	1
Alternative diagnosis as or more likely than DVT	-2
Clinical probability of DVT with score	
Score > 3 High	
Score 1-2 Moderate	
Score < 1 Low	

Those with Wells scores of two or more have a 28% chance of having DVT, those with a lower score have 6% odds.¹¹

D-dimer:

D-dimers are a fibrin degradation product, and an elevated level can result from plasmin dissolving a clot. A negative D-dimer in conjunction with a low clinical probability score has good negative predictive value (96% probability of no DVT). If the clinical probability is high, then the D-dimer should be repeated. An elevated D-dimer alone is not specific for the diagnosis of a DVT, as hospitalized patients often have elevated levels for multiple reasons. Thus an elevated D-dimer level requires further investigations with diagnostic imaging to confirm or exclude DVT.¹²⁻¹⁶

Imaging:

Imaging tests of the veins are used in the diagnosis of DVT, most commonly either proximal compression ultrasound or whole-leg ultrasound. Each technique has drawbacks: a single proximal scan may miss a distal DVT, while whole-leg scanning can lead to distal DVT overtreatment. Doppler ultrasound, CT

scan venography, MRI venography, or MRI of the thrombus are also possibilities.¹⁷⁻²⁰

The gold standard for judging imaging methods is contrast venography, which involves injecting a peripheral vein of the affected limb with a contrast agent and taking X-rays, to reveal whether the venous supply has been obstructed. Because of its cost, invasiveness, availability, and other limitations this test is rarely performed.^{8,18-21}

Investigation for inherited and acquired thrombophilia should be performed in certain conditions such as recurrent venous thrombosis or thrombosis in usual sites, family history of thrombosis or recurrent miscarriage.^{22, 23}

Differential diagnosis:

The differential diagnosis includes calf hematoma, ruptured Baker's cyst, cellulitis, muscle injury, lower limb oedema or lymphatic obstruction.⁸

Management:

The primary objectives for the treatment of deep venous thrombosis are to prevent pulmonary embolism (Table 3),²⁴⁻²⁶ reduce morbidity, and prevent or minimize the risk of developing the postthrombotic syndrome (PTS).

Table 3: Methods for Preventing DVT and PE

Lifestyle modification
A. Avoid obesity and inactivity i. Nutrition without excess calories ii. Exercise 1. Daily aerobic such as walking 2. Anaerobic activity useful for muscle toning a. Heavy weightlifting may traumatize muscles b. Anaerobic does not substitute for aerobic B. Avoid dehydration i. Drink water ii. Minimize alcohol consumption C. Avoid cigarette smoking i. Quit smoking 1. Willpower is best 2. Nicotine patch, gum, nasal spray 3. Bupropion (Wellbutrin GlaxoSmithKline) D. Maintain normal blood pressure i. Note some guidelines define normal as 120/80 mm Hg rather than 140/90 mm Hg ii. If lifestyle changes do not reduce blood pressure, use medication
Mechanical measures
A. Vascular compression stockings i. 10 to 18 mm Hg if immobilized or in bed; otherwise, use higher compression levels ii. 20 to 30 mm Hg below-knee stockings if no varicose veins, swelling, or skin pigmentation changes iii. 30 to 40 mm Hg below-knee stockings if leg exam has evidence of prior venous disease B. Intermittent pneumatic compression boots i. Ideal for immobilized patients, either in hospital, skilled nursing facility, or at home ii. Device is better tolerated when combined with 10- to 18-mm Hg vascular compression stockings iii. Some devices have “cooling buttons” to enhance comfort
Pharmacological measures
A. Injectable medications i. Low-molecular-weight heparin 1. Enoxaparin 40 mg daily 2. Dalteparin 5000 Units daily ii. Unfractionated heparin 5000 Units every 8 hours iii. Fondaparinux 2.5 mg daily B. Oral medication i. Warfarin C. Baby aspirin 81 mg daily i. Provides more protection against heart attack and stroke than against DVT ii. DVT prevention effect is weak

Anticoagulation:

The mainstay of medical therapy has been anticoagulation since the introduction of heparin in the 1930s. Other anticoagulation drugs have subsequently been added to the

treatment armamentarium over the years, such as vitamin K antagonists and low-molecular-weight heparin (LMWH). Absolute contraindications to anticoagulation treatment

include intracranial bleeding, severe active bleeding, recent brain, eye, or spinal cord surgery, pregnancy, and malignant hypertension. Relative contraindications include recent major surgery, recent cerebrovascular accident, and severe thrombocytopenia.^{27, 28}

Admitted patients may be treated with a LMWH, fondaparinux, or unfractionated heparin (UFH). Warfarin 5 mg PO daily is initiated and overlapped for about 5 days until the international normalized ratio (INR) is therapeutic >2 for at least 24 hours.

For admitted patients treated with UFH, the activated partial thromboplastin time (aPTT) or heparin activity level must be monitored every 6 hours while the patient is taking intravenous (IV) heparin until the dose is stabilized in the therapeutic range. Patients treated with LMWH or fondaparinux do not require monitoring of the aPTT.²⁹

Platelets should be monitored. Heparin or LMWH should be discontinued if the platelet count falls below 75,000. Fondaparinux is not associated with heparin-induced thrombocytopenia (HIT).³⁰

Fondaparinux:

Fondaparinux, a direct selective inhibitor of factor Xa, overcomes many of the aforementioned disadvantages of LMWHs. Furthermore, a single dose of 7.5 mg is effective over a wide range of patient weights between 50 and 100 kg. Daily doses of 5 mg or 10 mg are appropriate for patients who weigh less or more than that weight range. Therapeutic monitoring of laboratory parameters such as the prothrombin time or aPTT is also not required.^{29, 30}

Rivaroxaban:

Rivaroxaban (Xarelto) is an oral factor Xa inhibitor that has been recently licensed and approved by NICE for treatment of DVT or PE and for reduction of the risk of recurrent DVT and PE after initial treatment.^{31, 32}

Complications of Anticoagulant Therapy:

Hemorrhagic complications are the most common adverse effects of anticoagulant therapy. Anticoagulation therapy for 3-6 months results in major bleeding complications in 3-10% of patients.

Additional complications include the following:^{27, 28}

- Systemic embolism

- Chronic venous insufficiency
- PTS (i.e. pain and edema in the affected limb without new clot formation)
- Soft tissue ischemia associated with massive clot and very high venous pressures - phlegmasia cerulea dolens

Thrombolytic therapy:

In selected patients with extensive acute proximal DVT (eg, those with iliofemoral DVT, upper-extremity DVT, symptoms of less than 14 days' duration, good functional status, or a life expectancy exceeding 1 y) whose bleeding risk is low, catheter-directed thrombolysis (CDT) may be used to reduce symptoms and postthrombotic morbidity if appropriate resources are available.³³

Systemic thrombolytic therapy is reserved for selected patients with extensive proximal DVT (e.g. symptoms of less than 14 days' duration, good functional status, and life expectancy exceeding 1 year) whose risk of bleeding is low to reduce post thrombotic morbidity if CDT is not available.³⁴

Endovascular and Surgical Interventions:

Endovascular therapy is performed to reduce the severity and duration of lower-extremity symptoms, prevent PE, diminish the risk of recurrent VTE, and prevent PTS. Percutaneous transcatheter treatment of DVT includes the following:^{28, 34}

- Thrombus removal with catheter-directed thrombolysis – American College of Chest Physicians (ACCP) recommends thrombolytic therapy only for patients with massive iliofemoral vein thrombosis associated with limb ischemia or vascular compromise
- Mechanical thrombectomy
- Angioplasty
- Stenting of venous obstructions

Inferior Vena Cava Filters:

American Heart Association (AHA) recommendations for inferior vena cava filters include the following:²⁸

- Confirmed acute proximal DVT or acute PE in patients contraindicated for anticoagulation
- Recurrent thromboembolism while on anticoagulation
- Active bleeding complications requiring termination of anticoagulation therapy

Use of Elastic Compression Stockings:

Below-the-knee elastic compression stockings (ECS) assist the calf muscle pump and reduce venous hypertension and venous valvular reflux. This reduces leg oedema, aids the microcirculation, and prevents venous ischemia.³⁵

Ambulation:

Controversy exists regarding the role of ambulation in the therapy of DVT. The ACCP Consensus Conference on Antithrombotic and Thrombolytic Therapy for VTE recommends ambulation as tolerated for patients with DVT. Therefore, early ambulation on day 2 after initiation of outpatient anticoagulant therapy in addition to effective compression is strongly recommended. The fear of dislodging clots and precipitating a fatal PE is unfounded.^{36, 37}

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Prognosis:

The most frequent complication of proximal DVT is post-thrombotic syndrome. An estimated 20–50% of those with DVT will develop it.³⁸⁻⁴⁰ PE is the most serious complication of proximal DVT, and the risk of PE is higher when clots are present in the thigh and pelvis. Distal DVT itself is hardly if ever associated with post-thrombotic syndrome or PE.^{2,3} Untreated lower extremity DVT has a 3% PE-related mortality rate. The presence of a remaining thrombus after a DVT frequently occurs in a minority of people, and it increases the risk of recurrence, though to a lesser extent than an elevated D-dimer. In the 10 years following a VTE, about one-third of individuals will have a recurrent episode.³⁸⁻⁴⁰

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Further Reading

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