

Ministry of Defence

Synopsis of Causation

Deep Vein Thrombosis (DVT) (incorporating Superficial Thrombophlebitis, Pulmonary Embolism and Venous Thromboembolism)

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Disclaimer

This synopsis has been completed by medical practitioners. It is based on a literature search at the standard of a textbook of medicine and generalist review articles. It is not intended to be a meta-analysis of the literature on the condition specified.

Every effort has been taken to ensure that the information contained in the synopsis is accurate and consistent with current knowledge and practice and to do this the synopsis has been subject to an external validation process by consultants in a relevant specialty nominated by the Royal Society of Medicine.

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1. Definition

- 1.1 The term “**venous thromboembolism**” (VTE) encompasses **deep vein thrombosis** (DVT) and **pulmonary embolism** (PE). VTE often arises as a complication in sick, hospitalised patients, but may also affect ambulant and apparently healthy individuals.
- 1.2 Venous thrombi are composed mainly of fibrin and red blood cells, and frequently cause obstruction at the point of formation. Although venous thrombosis may occur in any vein of the body, it most commonly affects the **lower limbs**. When the process occurs in the deep veins, especially those that are situated above the calf, there is an associated risk that all or part of the thrombus may become detached. The thrombus will then be carried through the [vena cava](#) and the heart to lodge in the arterial tree of the lungs as an embolus, with the potential to cause respiratory distress, respiratory failure and, not infrequently, death.
- 1.3 The clinical impact of pulmonary embolism depends on the size of the embolus and the cardiorespiratory reserve of the patient. Despite effective [prophylaxis](#) against VTE now available for most high-risk patients, PE remains the most common preventable cause of hospital death.¹
- 1.4 Properly treated, **superficial thrombophlebitis** can be benign. However, the condition may not remain superficial. In the leg, the thrombus may propagate through one of the hundreds of perforating veins that communicate between the superficial and deep veins, with the attendant risk of embolism.
- 1.5 Although at least 90% of pulmonary emboli originate from thrombi in the lower limbs, other less common sources are recognised. These include the deep pelvic, renal, mesenteric, hepatic, and cerebral veins, the inferior vena cava, the right ventricle of the heart, and the upper venous tree including the subclavian, axillary and brachial veins.
- 1.6 The frequency and severity of pulmonary embolism are unrelated to the presence or absence of symptoms of DVT. Two-thirds of patients with proven PE have no symptoms of DVT, whereas half the patients with proven DVT will be found on investigation to have undiagnosed pulmonary emboli of significant size. Thus, the incidence of VTE is generally underestimated. Nonetheless, early diagnosis is vital to prevent subsequent morbidity and mortality. One in nine people will develop DVT before age 80, and VTE accounts for one of every 20 deaths after age 50. Autopsy results demonstrate that up to 60% of patients who die in hospital have evidence of pulmonary embolism, and the diagnosis will have been missed in more than 70% of these patients whilst they were alive.²
- 1.7 Extensive venous thrombosis causes venous valvular damage which, along with persistent obstruction to the venous flow, may lead to the **postphlebotic syndrome** in as many as 33% of patients.³

2. Clinical Features

- 2.1 VTE occurs most commonly over the age of 40 years. However, the first episode in patients suffering from an inherited hypercoagulable state (see section 3.4) occurs typically in early adulthood. Gender does not act as a risk factor.
- 2.2 The clinical features of DVT include leg pain, tenderness, swelling, a palpable cord, [erythema](#), and distension and prominence of the superficial veins. However, 50% of patients with classical symptoms are not confirmed to have a DVT on subsequent investigation whilst, conversely, 50% of patients who have a DVT lack any of these findings. Any otherwise unexplained diffuse leg pain or swelling warrants consideration of possible DVT.
- 2.3 Specialised tests employed in the diagnosis of DVT include ultrasonography and ascending venography. The only laboratory test of value in diagnosing DVT is that used to detect D-dimer, which is a fibrin degradation fragment. Laboratory investigations for the detection of inherited hypercoagulable conditions (see section 3.4) entail an individual test for each specific disorder.
- 2.4 The two cardinal symptoms that should prompt consideration of pulmonary embolism are unexplained chest pain and shortness of breath. Other symptoms include apprehension, cough, [haemoptysis](#), sweating, and syncope. However, many patients will present with only a few subtle clinical findings and, moreover, the presentation of PE may mimic several other diseases. Most patients who die of PE succumb suddenly or within 2 hours of the acute event.
- 2.5 The symptoms of the postphlebotic syndrome may not appear until months or years have elapsed following the original DVT. The syndrome is characterised by oedema, pigmentation and [induration](#) around the ankle and lower third of the calf and, in its most severe form, venous ulceration, most commonly in the region of the [medial malleolus](#). Pain in the calf may occur, relieved by rest and elevation.

3. Aetiology

- 3.1 Venous thrombosis takes place when activation of blood coagulation exceeds the ability of the natural anticoagulant mechanisms and the [fibrinolytic](#) system to prevent [fibrin](#) formation. The “**hypercoagulable states**” (also known as “pre-thrombotic states” or “thrombophilia”) encompass a group of inherited and acquired disorders that are associated with an increased risk of VTE.
- 3.2 **Inherited hypercoagulable states** are associated with a lifelong predisposition to thrombosis.
- 3.3 **Acquired thrombophilic states** comprise a diverse group of conditions, which exert an effect through a variety of mechanisms, as follows:
- **Alterations to blood flow:** venous stasis may result from immobility, venous obstruction, increased venous pressure, venous dilation and increased blood viscosity
 - **Alterations to the blood components:** effects on coagulation factors and [platelet](#) function
 - **Damage to vessel walls:** DVT may arise in response to even a minimal injury to the venous [endothelium](#)
 - **Combinations** of the above factors, and **interactions** with the inherited hypercoagulable states
- 3.4 Acquired conditions may lead to VTE in individuals in the **absence** of inherited factors, or may **precipitate** an event where an inherited defect exists. Multiple overlapping mechanisms come into play. To illustrate this point, the increased incidence of VTE in pregnancy may be attributable to a combination of platelet activation, decreased fibrinolytic activity, venous stasis in the legs caused by the pregnant uterus, oestrogen-related venous dilation, pelvic vein injury during labour and, where applicable, the trauma of Caesarean section. These risks are magnified for women who, in addition, have an inherited hypercoagulable state. The increased incidence of VTE in many other situations e.g. following surgery and in malignancy is similarly multifactorial in origin.
- 3.5 **Inherited risk factors:** The most common disorders involve an inherited mutation in one of the specific proteins (antithrombin III, protein C, and protein S) involved in the inhibition of the blood coagulation process. These and other less common inherited conditions are described below.^{2,4,5}
- 3.5.1 **Antithrombin III deficiency** is inherited as an [autosomal dominant](#) trait. In all patients with VTE, antithrombin deficiency will be detected in around 1%, although this figure rises to 2.5% for patients with recurrent thromboses or who have developed the condition before the age of 45 years. Type I antithrombin deficiency involves reduced levels of antithrombin, whilst patients with type II antithrombin deficiency have normal levels of a functionally defective molecule.
- 3.5.2 **Protein C deficiency** is inherited in an autosomal dominant manner. Type I refers to a quantitative deficiency, type II to a qualitative defect. Protein C deficiency is found in 3-4% of patients with VTE. [Homozygotes](#) may develop a

severe thrombotic tendency in infancy, and [heterozygotes](#) identified by mass screening may have a benign form with a low risk of venous thrombosis.

- 3.5.3 **Protein S deficiency** is inherited in an autosomal dominant manner. Once again, there are quantitative and qualitative defects. Protein S deficiency is found in 2-3% of patients with VTE.
 - 3.5.4 **Activated protein C resistance** is the most common hereditary condition associated with VTE, being found in 16-30% of cases. Most patients with activated protein C resistance have an inherited abnormality in their blood clotting factor V gene known as **factor V Leiden**, present in 7% of the general population.
 - 3.5.5 **Prothrombin gene mutation** (G20210A) leads to elevated basal [prothrombin](#) levels, which predispose to VTE. The incidence of this mutation is uncertain, but it may approach or even exceed that of factor V Leiden.⁶
 - 3.5.6 **Hereditary [fibrinolytic](#) disorders** that lead to impaired degradation of [fibrin](#) have been reported in a number of families, probably occurring much less frequently than the conditions mentioned above. They include hypoplasminogenaemia, dysplasminogenaemia, [plasminogen](#) activator deficiency and dysfibrogenaemia.
 - 3.5.7 **Hyperhomocysteinaemia** results from an inherited defect in the metabolic pathways for homocysteine. Heterozygous adults with this condition are prone to arterial and venous thrombosis due to effects of the blood vessel walls.
 - 3.5.8 **Thrombomodulin dysfunction** is an uncommon abnormality in the protein C anticoagulant pathway.
 - 3.5.9 **Heparin cofactor II deficiency:** the current consensus is that there is insufficient evidence to recommend testing for heparin cofactor II deficiency in patients with thromboembolic disease.
- 3.6 **Acquired risk factors:** Previous DVT, surgery, cancer and immobilisation are the most common acquired risk factors for DVT. These factors are considered in more detail below, along with other known risk factors.^{2,4,5}
- 3.6.1 **Previous DVT:** Patients with a history of venous thrombosis are 5-30 times more likely than patients with no such history to have a new DVT in response to a triggering event. This tendency is in part linked to venous abnormalities from the previous DVT, such as [endothelial](#) irregularity, chronic venous stasis, and valvular damage.
 - 3.6.2 **Surgery:** the increased incidence of VTE is likely to be due to a combination of mechanical factors and activation of the coagulation system. Depending on the type of operation performed, the incidence of DVT following general surgery without the use of [thromboprophylaxis](#) is about 20-25%, with around 0.8-2% of such patients experiencing clinically significant PE. Major hip or knee surgery conveys a higher risk. Following hip and knee reconstruction without

[prophylaxis](#), the incidence of DVT is 45-70%, with pulmonary embolism occurring in up to 5-10% of patients undergoing hip surgery.

- 3.6.3 **Trauma:** symptomless DVT has been detected in over 50% of hospitalised trauma patients. The risk is highest in patients who require surgery or transfusion, in the presence of lower limbs fractures, and with spinal cord injury.
- 3.6.4 **Immobilisation:** after 1 week, DVT can be identified in 15% of patients on bed rest in a general medical ward, and in twice as many in an intensive care unit.
- 3.6.5 **Paraplegia and stroke:** in patients who have suffered a [hemiplegic](#) stroke, the risk is far greater in the paralysed limb compared to the non-paralysed limb.
- 3.6.6 **Severe burns.**
- 3.6.7 **Malignant disease:** VTE is associated with cancer at many sites, and is particularly prominent in patients with cancers of the colon, ovary, pancreas and stomach. In some cases, thrombosis may antedate the diagnosis of cancer by months or even years. In up to 10-17% of patients who experience a DVT in the absence of any other identifiable risk factor, cancer will be newly diagnosed within 2 years.
- 3.6.8 **Pregnancy and the postpartum period:** pulmonary embolism is the most common non-traumatic cause of maternal death during pregnancy. The incidence of pregnancy-associated VTE is 1-4 per 1000 births.
- 3.6.9 **Oestrogen-containing medication:** oral contraception and hormone replacement therapy.
- 3.6.10 **Myeloproliferative disorders:** bone marrow stem cell disorders including polycythaemia vera, essential thrombocythaemia, chronic myelogenous leukaemia, myelofibrosis, myeloid metaplasia, and the related disorder, paroxysmal nocturnal haemoglobinuria.
- 3.6.11 **Acquired deficiencies of antithrombotic factors** can result from cancer, chemotherapy, vitamin K deficiency, nephrotic syndrome, liver disease, and disseminated intravascular coagulation. An acquired form of hyperhomocysteinaemia may result from nutritional deficiencies of pyridoxine, cobalamin and folate.
- 3.6.12 **Heparin-induced thrombocytopenia**, a rare immune-mediated complication of heparin treatment, may be accompanied by arterial or venous thrombosis.
- 3.6.13 **Antiphospholipid syndrome** occurs as either a primary condition or secondary to other diseases, mainly **autoimmune disorders** including systemic lupus erythematosus. Autoantibodies are produced, of which there are two main groups, anticardiolipin antibodies and lupus anticoagulants. The syndrome is characterised by both venous and arterial thrombosis, with around two-thirds of events being venous.

- 3.6.14 **Immunodeficiency:** The incidence of DVT in patients with HIV/AIDS is approximately 10 times greater than in the general population.⁷
- 3.6.15 **Inflammatory bowel disease:** ulcerative colitis and Crohn's disease.
- 3.6.16 **Coronary artery disease:** myocardial infarction and heart failure.
- 3.6.17 **Varicose veins:** when exposed to a secondary risk factor such as surgery, the incidence of DVT is twice as high in patients with varicose veins, as compared to those who do not have this condition.
- 3.6.18 **Catheter-associated thrombosis:** 25-33% of patients develop DVT after femoral vein cannulation. DVT in the upper extremities has been linked to transvenous pacemakers and central venous catheters.
- 3.6.19 **Anaesthesia:** the incidence of DVT is lower after epidural anaesthesia than after general anaesthesia.
- 3.6.20 **Obesity:** doubts have been raised as to whether obesity acts as an independent risk factor, but in one recent large-scale prospective study, one third of patients with DVT were found to be clinically obese, and a further 31% were overweight.³
- 3.7 Despite detailed investigation, many patients who present with VTE exhibit **no clinically recognisable risk factors**.
- 3.8 There has been recent controversy surrounding the "**economy-class syndrome**", a term first coined in 1998. A more accurate title is "travellers' thrombosis" referring to a probable link between thrombosis and long-distance travel. The most likely mechanism is prolonged immobilisation. The association appears to be confined to individuals with additional risk factors, and fatal pulmonary embolus is very rare.⁸ One study found that symptomless DVT may occur in up to 10% of airline passengers following a long haul flights (defined as over 8 hours), although this finding has yet to be validated with appropriate modalities.⁹ A review of the database of the Civil Aviation Authority revealed a low incidence of VTE in airline pilots.¹⁰

4. Prognosis

- 4.1 Treatment of acute episodes should be maintained for a minimum of 3-6 months. However, the most effective treatment is **preventative**. As described earlier, a history of venous thrombosis is associated with an increased risk of repeat episodes, particularly when patients are exposed to high-risk situations.
- 4.2 The primary [prophylactic](#) measures include low-dose unfractionated heparin or low molecular weight heparin, with or without the addition of the mechanical approach of thromboembolic-deterrent compression stockings. Oral anticoagulants are used for the long-term prevention of recurrent VTE. Rarely, surgical intervention is indicated for the treatment of VTE, involving the insertion of an [inferior vena caval](#) filter.
- 4.3 When considering long-term oral anticoagulant therapy, the protective effect against VTE must be weighed against the risk of bleeding complications. Careful monitoring is required as severe haemorrhage may occur if the anticoagulant dose is not adjusted accurately. Interactions with a wide range of drugs may disrupt a hitherto stable situation of anticoagulant control. Indefinite anticoagulation is considered for those individuals who are deemed to be at high risk of VTE. Otherwise, vigorous prophylaxis should be initiated whenever a patient encounters a high-risk situation.^{1,4}
- 4.4 The high early mortality associated with VTE has already been emphasised. In addition, disability associated with the development of chronic [cor pulmonale](#) affects most patients who survive a large pulmonary embolus or who suffer multiple small recurrent pulmonary emboli. In the presence of extensive disease, exercise tolerance is severely compromised, and death ensues within a few years.
- 4.5 It has been estimated that around one-third of patients with DVT in the lower limbs will develop symptoms and signs of the postphlebotic syndrome within 5 years of follow-up. Such manifestations vary from mild to severe. The most effective approach is preventative, pursued with the avoidance of recurrent thromboses and the use of compression elastic stockings. Once the condition has developed, the treatment of postphlebotic syndrome can be frustrating and, although several surgical procedures have been tested, conservative management is usually preferable. More than 50% of patients either remain stable or improve during long-term follow-up if carefully supervised and instructed to wear proper elastic stockings.¹¹

5. Summary

- 5.1 Deep vein thrombosis most commonly affects the lower limbs. If all or part of the thrombus becomes detached, it will be carried through the circulation to lodge as a pulmonary embolus in the arterial tree of the lungs. Pulmonary embolism remains the most common preventable cause of hospital death.
- 5.2 Several inherited conditions have been identified that give rise to a lifelong increased propensity to VTE. Numerous acquired risk factors have also been identified, notably previous DVT, surgery, cancer and immobilisation. There is potential for multiple interactions to take place between these various aetiological factors.
- 5.3 The most important aspect of treatment is preventative. [Cor pulmonale](#) and the postphlebotic syndrome are important disabling sequelae of VTE.

6. Related synopses

7. Glossary

autosomal dominant	Requires that only one parent need have the trait (characteristic) to pass it to the offspring.
cor pulmonale	Congestive heart failure resulting from enlargement and weakening of the right ventricle of the heart.
endothelium	The layer of cells lining the cavity of blood vessels.
erythema	Redness of the skin.
fibrin	An insoluble protein formed from fibrinogen during the blood clotting process.
fibrinolytic	Relating to the dissolution of fibrin by enzymatic action.
haemoptysis	Coughing up blood or bloodstained sputum.
hemiplegia, hemiplegic	Paralysis of one side of the body.
heterozygote	An individual having two versions of the same gene, one version on one chromosome and the second version on the other.
homozygote	An individual having two identical versions of the same gene, one on either chromosome.
induration	An abnormal hardening.
medial malleolus	The projection at the lower end of the tibia, which is clearly evident on the medial (inner) side of the ankle.
plasminogen	The inactive precursor of plasmin, an enzyme that is responsible for digesting fibrin in blood clots.
platelets	Particles that circulate in the bloodstream and bind to fibrinogen to begin the blood clotting process.
prophylaxis	Preventative treatment. Hence: thromboprophylaxis, the prevention of thrombosis.
prothrombin	Clotting factor II.
thrombophlebitis	Inflammation of a vein associated with thrombus formation.
vena cava	The large vein that returns blood to the heart. The inferior vena cava receives blood from the lower extremities, pelvis and abdominal organs.

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