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## **Venous Thrombosis and Pulmonary Embolism in Children and Young Adults**



**An Overview for Patients and  
Health Care Providers**

**Awareness • Prevention • Treatment • Support**

**GLOSSARY:**

venous thrombosis = a condition of developing a blood clot in a vein; this can occur in the superficial or deep veins of the arms or legs, the venous circulation of the brain (cerebral sinovenous thrombosis), kidneys (renal vein thrombosis), liver (hepatic vein thrombosis, portal vein thrombosis), a central vein of the body, or other locations

deep venous thrombosis (DVT) = thrombosis of the deep veins; when this occurs in an arm or leg, it is categorized as extremity (meaning arm or leg) DVT; other examples of types of DVT are described above (under *venous thrombosis*)

pulmonary embolism (PE) = a condition in which a blood clot has traveled from a vein into the lung circulation, often suspected when there is chest pain or difficulty breathing in a patient with DVT; sometimes PE occurs in patients in whom no DVT can be found

thrombophilia = a condition of increased risk for developing blood clots in the veins or arteries due to increased blood clotting

post-thrombotic syndrome (PTS) = a chronic condition of poor venous blood circulation following DVT, often identified due to swelling of the arm/leg and pain in the arm/leg with activities; in severe cases of PTS, there may be skin breakdown as well as pain in the arm/leg at rest

antiphospholipid antibody syndrome = a type of thrombophilia (see definition above) due to proteins, called "antiphospholipid antibodies," that are consistently present in the blood over time following a stroke or blood clot in the vein, or in some women who have a history of miscarriage(s)

rheumatologic condition = a broad category of medical disorders (including lupus, juvenile rheumatoid arthritis, and others) in which the body's immune system is overactive, and sometimes found to be the cause of antiphospholipid antibody syndrome or inflammation of blood vessels in young patients with thrombosis

anticoagulation = standard blood thinner therapy, such as unfractionated heparin, low molecular weight heparin, and warfarin (Coumadin®)

thrombolysis = clot-buster therapies, including medicines such as tissue-type plasminogen activator (tPA) and the use of specialized catheter procedures to break up clots.

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### WHAT ARE VENOUS THROMBOSIS AND PULMONARY EMBOLISM?

*Venous thrombosis* is a condition of developing a blood clot in a vein, a blood vessel that returns blood from the body back to the heart. Venous thrombosis can occur in the superficial or deep veins of the arms or legs, the venous circulation of the brain (cerebral sinovenous thrombosis), kidneys (renal vein thrombosis), liver (hepatic vein or portal vein thrombosis), a central vein of the body (inferior or superior vena cava thrombosis), or other locations. Throughout most of this overview, venous thrombosis will refer to thrombosis of the deep veins (DVT).

*Pulmonary embolism (PE)* is a condition in which a blood clot has traveled from a vein into the lung circulation, often suspected when there is chest pain or difficulty breathing in a patient with DVT; sometimes PE occurs in patients in whom no DVT can be found

### WHAT ARE THE CAUSES OF VENOUS THROMBOSIS AND PULMONARY EMBOLISM?

DVT and PE in children and young adults can be caused by poor blood circulation (for example, during times of decreased mobility or vein constriction for a prolonged period), damage to the inner lining of veins (such as when a catheter is placed in a vein, or when certain drugs or toxins are circulating in the blood), and thrombophilia (excess clotting) states. In children and young adults, a combination of these risk factors is often present at the time of DVT or PE. Also, in young people, genetic causes of thrombophilia may be important contributing factors to DVT or PE. Sometimes, however, the cause of DVT or pulmonary embolism in children and young adults remains unclear. Research at some specialty centers in the U.S. is focusing on the discovery of new thrombophilia traits and other risk factors in these patients.

### **WHY ARE VENOUS THROMBOSIS AND PULMONARY EMBOLISM IMPORTANT IN CHILDREN AND YOUNG ADULTS?**

DVT and PE in young people can occur at any age, but the first month of life (especially in premature and other hospitalized infants) and the teenage years appear to be times of increased risk for blood clots. Although DVT and PE in children and young adults occur less commonly than in elderly adults, their consequences can be equally devastating. In particular, issues of evaluation for causes and risk factors, short-term treatments, and long-term prevention of future DVT and PE all play a very prominent role in the care of children and young adults with these disorders. Young people with DVT or PE appear to have single or multiple genetic thrombophilia traits more frequently than older adults, and this can affect the risk of a future blood clot in both the young patients and their family members. In addition, children and young adults appear to be at least as likely as older adults to develop a chronic condition of poor venous blood circulation called the post-thrombotic syndrome (PTS) following DVT. PTS is often diagnosed when swelling of the arm/leg and pain in the arm/leg with activities develops or persists over a period of months to years following the diagnosis of DVT. In severe cases of PTS, there may be skin breakdown as well as pain in the arm/leg at rest.

Although medical guidelines exist for the evaluation and treatment of DVT and PE in children and young adults, the medical evidence for the optimal treatment of these disorders in young people comes mostly from studies in older adults. In addition, the particular circumstances of each patient are important to consider when making long-treatment decisions. This highlights the importance of expertise in thrombosis care for young people, and is also important to keep in mind when reading this general overview.

### **KEY SUMMARY POINTS**

- Venous thrombosis and pulmonary embolism in children and young adults occur less commonly than in elderly adults, but their consequences can be equally devastating.
- Evaluation for causes and risk factors, short-term treatments, and long-term prevention of future blood clots and their complications all play a very prominent role in DVT and PE care for young people.
- Optimal DVT and PE treatment and prevention in children and young adults requires specialized care, particularly involving Hematologists with expertise in blood clotting disorders in young people.
- Thrombophilia testing is an important part of the evaluation of causes and risk factors for DVT and PE in children and young adults, and is best guided by experts in blood clotting. Thrombophilia affects decision-making for both short-term treatment and long-term prevention of future DVT and PE.
- Patients taking blood thinners should exercise appropriate bleeding precautions and seek prompt medical attention for bleeding concerns.
- Long-term management of DVT and PE is focused primarily upon safely preventing further blood clotting, as well as optimizing the child's/young adult's level of function in school, work, family, and/or society. This includes efforts to prevent and treat the post-thrombotic syndrome, a chronic condition of poor venous blood circulation following DVT.

Coumadin® dose may be required. Coumadin® educational brochures and dietary instructions are available through most anticoagulation clinics and treatment centers that specialize in thrombosis and thrombophilia.

In order to help assure the proper medical treatment during medical emergencies, patients who are on anticoagulation should wear a medical bracelet showing the blood thinner they take aspirin and carry a list of their medications in their wallet or purse at all times. Patients taking anticoagulation should also be sure to advise their physician/surgeon of their blood thinner use prior to undergoing surgery or other invasive medical procedures; typically, Coumadin® is discontinued one week prior to these procedures, while low molecular weight heparin medications like Lovenox® and Fragmin® are stopped 24 hours before surgery. In addition, other medications that increase the risk for bleeding (e.g., aspirin, ibuprofen, naproxen, certain herbal products) should be avoided while on anticoagulation therapy, unless prescribed and monitored by a physician.

Because Coumadin® can cause birth defects when used early in pregnancy, all female patients who have reached puberty should be counseled on taking adequate measures to prevent pregnancy while on Coumadin.

For non-urgent concerns relating to bleeding or blood thinners, patients should contact their Hematologist or primary care physician. A description of on of these trials can be found at [www.kids-dott.com](http://www.kids-dott.com).

#### OTHER PRACTICAL CONSIDERATIONS

***It is important to work with a knowledgeable team of health care providers***, including blood clotting specialists from Hematology, in the care of the child or young adult with DVT or PE. Thorough evaluation of DVT and PE is often challenging, and both short-term and long-term treatment decisions can be difficult. The identification of thrombophilia is an important component of this care, and is best guided by experts in blood clotting. ***Family testing should be considered for young DVT or PE patients in whom genetically-determined thrombophilia traits are identified, so that appropriate measures to prevent DVT and PE in family members can be taken.*** A list of centers specialized in clotting disorders can be found at [www.nattinfo.org/provider.htm](http://www.nattinfo.org/provider.htm).

#### HOW ARE VENOUS THROMBOSIS AND PULMONARY EMBOLISM DIAGNOSED IN CHILDREN AND YOUNG ADULTS?

##### Signs and symptoms

DVT in young people may occur with a variety of signs and symptoms, depending mainly on the area of the body that is affected and the degree of blockage of the vein(s) involved. The typical signs and symptoms of DVT in arm or leg are unexplained pain and swelling, sometimes also with redness of the skin. When a clot completely blocks blood flow in a central vein of the lower body, swelling of both legs can occur, and when a clot blocks a central vein the upper body, there can be swelling of both arms as well as swelling of the head and neck. For clots in the venous circulation of the brain, signs and symptoms can include unusually severe or persistent headache or unexplained change in vision. Clots affecting venous drainage of the kidney can cause signs and symptoms that include high blood pressure and blood in the urine.

The signs and symptoms of PE in young people include unexplained shortness of breath or difficulty breathing, and chest pain that usually is worse when taking a deep breath. When PE affects a large part of the circulation to the lung, it is often a medical emergency due to the body's inability to provide enough oxygen to vital organs.

Unfortunately, in some cases of DVT and PE, signs and symptoms can be absent. When DVT or PE are found on scans in a patient who does not have (or does not recall) any signs or symptoms, it is often difficult to know whether the clot is new or old, and this can affect treatment decisions.

##### Radiologic imaging tests (scans)

Suspected DVT or PE in children and young adults is confirmed by scans. For DVT in an arm or leg, ultrasound or computed tomography (CT) is typically used. For DVT in a central vein of the body, or in a vein draining organs like the kidneys or liver, CT is usually necessary. In some cases, a dye scan of the veins (venogram) may be required in order to be sure about the diagnosis of DVT. To diagnose clots in the venous circulation of the brain, CT or magnetic

resonance imaging (MRI) of the brain is typically used. Suspected PE is confirmed by specialized CT scans or by a nuclear medicine scan called a "V/Q" scan.

#### Laboratory tests

Another critical step in the evaluation includes laboratory testing for thrombophilia. In addition, because young people who develop DVT or PE often have an underlying illness, other laboratory testing relating to the underlying illness may be performed in order to monitor its course. For example, blood markers of inflammation and cultures of blood and other body fluids may be closely monitored closely in children and young adults who are being evaluated or treated for infections as well as blood clots. In addition, patients who have other signs and symptoms that could suggest an underlying rheumatologic condition (broad category of medical disorders -- including lupus, juvenile rheumatoid arthritis, and others -- in which the body's immune system is overactive) may have specialized testing to evaluate for these disorders.

#### **WHAT THROMBOPHILIA TESTING SHOULD BE PERFORMED IN CHILDREN AND YOUNG ADULTS WITH VENOUS THROMBOSIS OR PULMONARY EMBOLISM?**

Thrombophilia testing is an important part of the evaluation of causes and risk factors for DVT and PE in children and young adults, and is best guided by experts in blood clotting. ***Thrombophilia affects decision-making for both short-term treatment and long-term prevention of future DVT and PE.***

Thrombophilia testing for blood clotting risk factors can vary across treatment centers. However, in young people with newly-diagnosed DVT or PE, comprehensive thrombophilia testing is recommended by a group of blood clotting experts, the Scientific Subcommittee on Perinatal and Pediatric Thrombosis of the International Society on Thrombosis and Haemostasis, and is routinely performed at many specialty centers. This includes testing for: anticoagulant deficiencies (protein C activity, free protein S antigen, antithrombin activity); antiphospholipid antibodies (lupus anticoagulant, anti-beta-2-glycoprotein-I antibody, anticardiolipin antibody); elevated homocysteine concentration; factor V Leiden

#### **HOW DO COUMADIN® AND HEPARINS WORK, WHAT ARE THEIR SIDE EFFECTS, AND WHAT PRECAUTIONS SHOULD BE TAKEN WHILE ON BLOOD THINNERS?**

By blocking the effects of vitamin K, Coumadin® interferes with the function of several blood clotting proteins ("factors") that require vitamin K in order to allow proper blood clotting. In this way, Coumadin® makes the blood less clottable ("thins" the blood).

Heparins (including unfractionated and low molecular weight heparins) work somewhat differently than coumadin. These medicines make the blood less clottable by increasing the function of a natural blood thinner in the blood, called antithrombin.

Whether the anticoagulation medication being used is Coumadin®, a type of heparin, or other medications, due to the blood thinning effects, anticoagulation increases the risk for bleeding, especially after injury. For this reason, patients taking anticoagulation who develop significant bleeding or become significantly injured should seek medical evaluation. Patients on blood thinners should always use proper safety restraints (e.g., seatbelt) in a motor vehicle and wear a helmet when on a bicycle, skateboard, rollerskates, etc. High-impact physical activities and contact sports should generally be avoided while on treatment doses of anticoagulation, given the risk of bleeding from injury. The risk for life-threatening bleeding in the brain in association with head injury is of particular concern while on blood thinners.

The blood thinning effects of Coumadin®, as measured by INR levels in the blood, can be affected by other medications, including many antibiotics. The INR is also affected by the amount of vitamin K consumed in the diet. Patients should inform the physician or pharmacy doctor managing their Coumadin® treatment about any new medications or herbal supplements being taken, as well as any major changes in diet (particularly, the amount of green leafy vegetables being consumed that may contain vitamin K); in many instances, more frequent INR checks will initially be necessary following these changes, and adjustments in

DVT or PE during times of increased risk for thrombosis, such as during hospitalization for severe infection, periods of decreased mobility (for example, after a major surgical procedure or casting of a fractured upper arm or leg).

To prevent a first or subsequent DVT or PE, all patients and at-risk family members should also take care to avoid dehydration and smoking, and should adopt a regular aerobic exercise program. Some research suggests that aerobic exercise stimulates our veins to release small amounts of the stored natural clot buster tPA, and in this way helps to keep our veins “healthy” and prevent blood clots.

Prevention and treatment of post-thrombotic syndrome (PTS)

Enabling the child/young adult to function as best as possible in school, work, family, and/or society involves prevention and treatment of PTS. PTS is a chronic condition of poor venous blood circulation called the post-thrombotic syndrome (PTS) following DVT. PTS is often diagnosed when swelling of the arm/leg and pain in the arm/leg with activities develops or persists over a period of months to years following the diagnosis of DVT. In severe cases of PTS, there may be skin breakdown as well as pain in the arm/leg at rest. Clinical research studies in older adults have shown that daily continuous use of compression stockings on an affected leg or arm for a period of at least 1 year following the diagnosis of DVT can reduce the risk of developing PTS. Based on this knowledge, routine use of compression stockings should also be strongly encouraged for all young patients with DVT.

In children and young adults with DVT, if PTS is severe and does not adequately improve with the use of compression stockings, or if chronic SVC syndrome is present (a syndrome of swelling of the head and neck due to blockage of a central vein in the upper body, called the superior vena cava), other options may be available. For example, in some patients, procedures to restore or improve venous drainage may be possible. These procedures (including stenting, venous bypass grafting, and other techniques) are typically evaluated and performed by specialists in interventional radiology or vascular surgery.

mutation; prothrombin 20210 mutation; elevated factor VIII activity; and elevated lipoprotein(a) concentration. Testing for methylene tetrahydrofolate reductase (MTHFR) mutations may also be considered. For nearly all of the above-mentioned factors, clinical studies have suggested an increased association with blood clots or vascular disease in young people.

**HOW ARE VENOUS THROMBOSIS AND PULMONARY EMBOLISM INITIALLY TREATED IN CHILDREN AND YOUNG ADULTS?**

The initial treatments thrombosis of the deep veins and PE in young people are complex, and can differ somewhat for patients with different circumstances. The initial treatment involves attention to blood pressure, fluid levels, and blood levels of oxygen, sugar, salts, acid, etc. Additional important treatment decisions involve consideration of the identified causes and risk factors for DVT or PE, the amount of blood clot and degree of blockage of blood flow, the area(s) of the body affected, and the medical status of the patient. When risk factors for DVT or PE are identified, they should be treated or removed if possible. For example, adolescent girls who develop DVT or PE while taking the birth control pill should stop the pill, especially if their thrombophilia testing shows that they have the factor V Leiden mutation.

In a child or young adult with newly-diagnosed DVT, the standard treatment is anticoagulation (blood thinner therapy). Blood thinners typically used include unfractionated heparin given intravenously (I.V.) as a continuous infusion, low molecular weight heparin given under the skin as twice-daily injections, and warfarin (Coumadin®) taken as a daily pill. The dose of Coumadin® initially chosen for treatment of DVT or PE in young people is approximately 0.1 mg per kg of body weight. For unfractionated heparin, depending on the age of the young patient, the dose used may be between 15 and 25 Units per hour per kg of body weight, often after an initial loading dose of 20-50 Units per kg of body weight. For the low molecular weight heparin enoxaparin (Lovenox®), depending on the age of the young patient, between 1.0 and 1.5 Units per kg of body weight is often used for each treatment dose (for the low molecular weight heparin dalteparin (Fragmin®), a

treatment dose of 100-150 Units per kg of body weight has been suggested in young patients). The blood-thinning effect of these anticoagulation treatments is measured by blood tests in order to keep the level of blood thinning in a safe and effective range. For Coumadin®, a standardized test called the international normalized ratio (INR) is used for monitoring. For unfractionated and low molecular weight heparins, a test called the anti-factor Xa activity test is preferred, although the partial thromboplastin time (PTT) test is sometimes used when anti-factor Xa testing is not available.

In cases of acute DVT where a clot has occurred at the site of a central venous catheter, and where the clot is confined to the tip of a central venous catheter and is completely removed along with the catheter, sometimes no anticoagulation is felt necessary, and in other instances a short course of anticoagulation treatment is given. The best approach in this circumstance is not clear.

In cases of acute DVT that is large and completely blocks venous drainage from an arm or leg, special medicines or techniques to remove or break up the clot (thrombolysis) may be considered early in the initial treatment instead of routine anticoagulation (although later followed by anticoagulation). Thrombolysis can include medicines such as tissue-type plasminogen activator (tPA) and/or the use of specialized catheter procedures to break up clots. Based on clinical trials in older adults, many experts also consider thrombolysis to be the best option for treatment in young patients with acute PE in whom a large part of the circulation to the lung is affected and/or there is evidence of strain on the heart by heart ultrasound (echocardiogram). Because tPA has a higher risk of bleeding complications than standard anticoagulants, patients are monitored especially closely for signs and symptoms of bleeding during tPA treatment. In addition, monitoring of tPA involves blood markers of clot breakdown as well as blood levels of proteins involved in the clot breakdown process. While monitoring for bleeding and blood markers are essential, follow-up scans currently remain the best measures of effectiveness of thrombolysis, showing the response of the clot to this therapy by changes in clot size and degree of blockage of blood flow.

Clinical trials designed to determine the optimal treatment for DVT specifically in children have recently been proposed or are currently underway.

**HOW ARE VENOUS THROMBOSIS AND PULMONARY EMBOLISM TREATED OVER THE LONG-TERM IN CHILDREN AND YOUNG ADULTS?**

Long-term management of DVT and PE is focused primarily upon: (1) safely preventing further blood clots; and (2) enabling the child/young adult to function as best as possible in school, work, family, and/or society.

Prevention of further DVT or PE

In an effort to prevent further blood clotting (including the worsening of an existing blood clot and the development of a new DVT or PE), most children and young adults with acute DVT or PE are treated with anticoagulation for at least 3-6 months. Some patients, such as those with antiphospholipid antibody syndrome (i.e., whose thrombophilia testing showed lasting antiphospholipid antibodies in the blood since the time of stroke) or other very strong thrombophilia traits, patients with other risk factors for the development further blood clots (for example, abnormalities of blood vessel anatomy that can cause decrease blood flow, and certain strong thrombophilia traits), and individuals who have had further blood clots while on adequate anticoagulation treatment, may also be prescribed long-term blood thinners, such as Coumadin®.

In patients with certain underlying medical conditions, other treatments aimed at improving the underlying disorder may also decrease the risk of further blood clotting. For example, in patients with severe infections, antibiotic treatment is also given, and in patients with rheumatologic conditions, drugs to control the overactive immune system may also be used.

In families where several members have had DVT or PE (especially before the age of 55 years), patients and family members who test positive for milder genetic thrombophilia traits, such as single factor V Leiden or prothrombin 20210 mutations, should strongly consider using a short course of low-dose blood thinners to prevent a first or subsequent