CHAPTER 3
CLOTTING DISORDERS

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Introduction

The normal balance between **clot formation** and breakdown can be changed by the presence of certain genetic or acquired defects leading to abnormal clot formation. Reasons for the **clot formation** and breakdown processes to be unbalanced toward abnormal clot formation include **blood vessel injury**, **venous stasis** (lack of movement of the blood in the veins), and **clotting disorders**. These three factors make up **Virchow's triad**. An alteration in any one of these three factors can lead to abnormal clotting. All **risk factors** for **DVT** or **PE** fall into one of these three categories. A **venous thromboembolic** event (**VTE**) is either a **DVT** or **PE** or both in the same patient.

Clotting disorders are present in the majority of patients who have a **DVT**. The typical story for a person with an inherited **clotting disorder** is a spontaneous **DVT** at an early age. Doctors now have a variety of tests that can be done to test for an inherited **clotting disorder**. There is controversy over which patients should get which tests and what positive results mean. This chapter reviews the most common **clotting disorders**.

What is a D-Dimer Level?

D-dimer is a by-product of clot breakdown. The **D-dimer** level is not really a risk factor for getting a **DVT** or **PE**, but it may be elevated when a **DVT** or **PE** is present. The **D-dimer** level is used to "rule out" (show it is not present) **DVT** when the suspicion for **DVT** is low. This is because if the level is normal, it is unlikely that a **DVT** exists. However, if the level is high, **DVT** may or may not be present. Elevated **D-dimer** levels can indicate the presence of abnormal clot, but levels can also be elevated from other causes such as recent surgery, bleeding, trauma, pregnancy, cancer or abnormal blood clot in an artery.

Clotting Disorders

There are 2 types of **clotting disorders**. The first is a **hereditary disorder** that is inherited from one or both parents. The second is an **acquired disorder**, which a person is not born with, but that develops later in life.

Hereditary Clotting Disorders

The hereditary clotting disorders come in 2 groups:
Group 1: A lack of anti-clotting factors in the blood
Group 2: An increased amount of pro-clotting factors in the blood

Group 1 disorders include **anti-thrombin deficiency**, **protein C deficiency**, and **protein S deficiency**. **Group 2 disorders** include **activated protein C resistance** (**Factor V Leiden mutation**), **prothrombin G20210A mutation**, and elevated levels of **Factors VIII, IX, and XI**. In general, the Group 1 disorders are less common but more likely to cause abnormal clotting than Group 2 disorders. Patients with Group 1 disorders usually have their first **DVT** at a young age, have a higher likelihood of recurrence, and are more likely to have a family history of **DVT** or **PE** than patients with a Group 2 disorder.

GROUP 1 DISORDERS:

A LACK OF ANTI-CLOTTING FACTORS IN THE BLOOD

Antithrombin Deficiency

Antithrombin is a natural blood thinner found in the body. It works to reduce clot formation. Over 100 gene mutations have been found that can lead to antithrombin deficiency. This disorder is inherited as an **autosomal dominant trait**, which means that if a person gets an abnormal gene from one parent and a normal gene from the other parent, they will have the disease.

How common is it?
Antithrombin deficiency is present in 0.07-0.2% of the general population and 0.5-8% of those with **DVT**.

How and when do you test for it?
The amount of antithrombin in the blood can be tested with a blood test.

Tests should be drawn 3 months after the **VTE** happens, and at least 5 days after any **blood thinner** has been stopped. This is because **blood thinners** affect the levels of **antithrombin** in the blood. Many other conditions can also affect the **antithrombin** levels, so test results should be interpreted with the patient's entire medical history taken into account.

What is the risk of VTE in a person with antithrombin deficiency?
Antithrombin deficiency is a strong risk factor for **DVT**. The risk in most people with **antithrombin deficiency** is increased by 5 to 50 times. Most patients with this disorder will have had a **DVT** by age 30. Abnormal clotting in the arteries has been reported in people with this deficiency but it is uncommon and its association with the deficiency is not clear.

How do you treat antithrombin deficiency?
Patients with **antithrombin deficiency** are resistant to **heparin** therapy because **heparin** requires the presence of **antithrombin** to work. **Heparin** is a commonly used

intravenous **blood thinner**. Patients with **antithrombin deficiency** who need **blood thinners** should get another type of **blood thinner** that does not need **antithrombin** to work. **Antithrombin** itself can be given if necessary. After a **VTE** has occurred, lifelong oral **anticoagulation** is generally recommended.

Protein C Deficiency

Protein C is a natural **anticoagulant** that is made primarily in the liver. During the clotting process, **protein C** is activated, and along with **protein S** acts as a **blood thinner** to keep the clotting process in check. **Deficiency in protein C** results in decreased ability to keep the clotting process in check, leading to abnormal clot formation.

How common is it?

Protein C deficiency is present in up to 0.4% of the population and may be present in about 4% of patients with **DVT** or **PE**.

How and when do you test for it?

The amount of **protein C** in the blood can be tested for with a blood test. The test should be done 2-4 weeks after any **warfarin** therapy is stopped. Many things can cause **protein C** to be low, such as new clot formation, low **Vitamin K**, liver disease, severe infections (sepsis), kidney failure, post-operative state, breast cancer patients after certain chemotherapies, and massive bleeding.

A normal **protein C** level after a new clot has occurred rules out the disease, but a low level in this situation would need to be re-checked after therapy for the new clot is completed before the diagnosis could be made.

What is the risk of VTE in a person with protein C deficiency?

People with **protein C deficiency** are about 3 times more likely to experience a **DVT** or **PE** than the general population. By age 40, about 50% of those with **protein C deficiency** will have had a **DVT** or **PE**. There is not a significantly increased risk of artery clot in these patients.

How do you treat protein C deficiency?

If a person has **protein C deficiency**, and they have never had a **VTE**, then no medication is required. They need to have **blood thinners** given to prevent **VTE** prior to surgery or during other situations where they would be at increased risk of **VTE**.

If a person who has **protein C deficiency** has a **VTE**, they will need to have blood thinners. It is important for patients with **protein C deficiency** to have a fast-acting **blood thinner** such as **heparin** started before starting **warfarin** (an oral **blood thinner**). **Warfarin** alone may initially make the patient more likely to clot than less, until the appropriate levels have been reached. Therefore, a **fast acting anticoagulant** is used first and then stopped once the **warfarin** level is adequate.

Protein S Deficiency

Protein S acts with **protein C** to keep the body's natural clotting process controlled. A low **protein S** level has similar effects as a low level of **protein C**.

How common is it?
About 0.2% of the general population has **protein S deficiency**. In patients with **DVT** or **PE**, up to 5% have **protein S deficiency**.

How and when do you test for it?
The level of **protein S** can be tested from a blood sample. However, diagnosis of this condition can be challenging because many things can affect the **protein S** level. Conditions associated with decreased **protein S** include use of **warfarin** (an **oral blood thinner**) and contraceptive use, pregnancy, liver disease, nephrotic syndrome, and severe clot formation.
As with **protein C** and **antithrombin**, a normal test at the time of a new clot rules out the disease, but an abnormal test must be repeated after **warfarin** has been stopped for 2-4 weeks. If it is still abnormal on re-check, then the diagnosis can be made.

What is the risk of VTE in a person with protein S deficiency?
Varying rates of **DVT** or **PE** have been reported with **protein S deficiency**. It is difficult to study given that it is so uncommon. The risk of **VTE** in **protein S deficiency** has been reported from 0 to 11.5 times over that of patients without deficiency. There is no proven increase in artery clot with **protein S deficiency**.

How do you treat a person with protein S deficiency?
As with **protein C deficiency**, patients with **protein S deficiency** who have never had a **VTE** don't need any specific treatment, but if they are to be in any situation that would put them at risk for **VTE**, they should have preventative blood thinners.

A person who has an episode of **VTE** should have a **fast-acting blood thinner** such as **heparin** started prior to starting a longer term **blood thinner** such as **warfarin**.

GROUP 2 DISORDERS:

AN INCREASED AMOUNT OF PRO-CLOTTING FACTORS IN THE BLOOD

Activated Protein C Resistance/Factor V Leiden Mutation

Activated Protein C (APC) resistance refers to the resistance of **Factor V** (one of the proteins in the blood that helps to regulate clot formation) to the activated protein C in the clotting reaction. Since **activated protein C** works on **Factor V** to slow down the clotting reaction, resistance to this causes increased risk of clotting. The majority of **APC resistance** is due to the **Factor V Leiden mutation**, which is a mutation in the gene that codes for Factor V.

How common is it?
Factor V Leiden is the most common inherited **blood clotting disorder**, with an especially high occurrence in people of Caucasian or European descent. It occurs in about 5% of Caucasians, 1.2% of African Americans, 2.2% of Hispanic Americans, 1.2%

of Native Americans, and 0.45% of Asian Americans. In patients with **VTE**, 10-20% have this gene mutation.

How and when do you test for it?
There is a test that looks at whether the **Factor V** is resistant to the **APC**, and there is a genetic test for the **Factor V Leiden mutation**. Either test can diagnose the condition.

What is the risk of VTE with APC resistance?
APC resistance is a relatively weak risk factor for abnormal clot formation. People with one abnormal gene for **Factor V** have a 3 to 7 fold increased risk of clot, and people with both genes abnormal have a 50 to 100 fold increase in risk. The lifetime probability of a symptomatic **DVT** or **PE** in patients with one abnormal gene for **Factor V** is about 10%, thus the vast majority of patients with this condition will never have a **DVT** or **PE**.

However, when a person with **APC resistance** has another **risk factor** for clot, such as oral contraceptive use, hormone replacement therapy or pregnancy, they have increased risk for abnormal clot formation. **APC resistance** may increase the risk of recurrent pregnancy loss and obstetric complications. It is also associated with poorer outcomes in kidney transplant recipients. Whether this condition is associated with abnormal clot in the arteries is unknown.

Prothrombin Defects; Prothrombin Gene 20210A Mutation

The **prothrombin G20210A mutation** is an inherited defect of the gene for **prothrombin**. **Prothrombin** is a protein in the blood that helps clot to form. A person with this condition has high levels of **prothrombin**, which increases the risk of abnormal clot formation.

How common is it?
This disorder is the second most common **inherited clotting disorder**. It is present in 2% of Caucasians, 3% in people of southern European descent, and rare in Native Americans, Asian-Americans or African-Americans. Between 5 to 10% of patients with **VTE** have this disorder.

How and when do you test for it?
There is a blood test that can find the defect in the gene. This test can be accurately performed at any time before, during or after a clot has formed.

What is the risk of VTE with this disorder?
The risk of abnormal clotting is relatively low, with a 2 to 3 times increased risk of **VTE**. Most patients with this **prothrombin gene mutation** will not have had an episode of **VTE** by age 50. Half of clotting episodes in patients with this disorder occur around surgery, trauma, prolonged immobilization, pregnancy or estrogen therapy. This disorder doesn't appear to increased the risk of abnormal clot in an artery.

Factor Elevations (Elevations in the levels of different proteins in the blood that participate in the clotting process.)

The elevation of **coagulation Factors V, VII, VIII, IX, X, and XI** can occur. The association of these with increased risk of clotting is unclear, but persistently high factor levels are more common in patients with a history of VTE.

How and when do you test for elevated factor levels?
There are blood tests available for all of the factor levels. Knowing what the results mean is more difficult. Many things can affect the factor levels. This makes diagnosis of an ongoing elevation of one of these factors challenging. Conditions that can affect factor levels include **Vitamin K** deficiency, malnutrition, liver disease, biliary disease, oral contraceptive use, pregnancy, abnormal cholesterol, obesity, aging, stress, chronic inflammation, recent aerobic exercise, and blood type. Therefore, interpreting the levels of these factors is difficult, as is making the diagnosis of persistent elevated factor levels.

What is the risk of VTE with this condition?
Elevated levels of **Factors V and VII** have not been clearly associated with abnormal vein clot formation, but may be associated with abnormal artery clot formation. In contrast, elevation of **Factors VIII, IX,** and **XI** likely increase the risk of **VTE** slightly. **Factor VIII** elevation has the strongest association with **VTE** with the risk of **VTE** increasing as the level of **Factor VIII** increases.

Hyperhomocysteinemia

Hyperhomocysteinemia refers to an acquired or inherited elevation of the level of the amino acid **homocysteine**. Amino acids are the building blocks that make up proteins in the body. **Homocysteine** is one of several types of amino acids. Acquired **hyperhomocysteinemia** can occur with certain medical conditions, such as kidney failure, hypothyroidism, folate deficiency or Vitamin B6 or B12 deficiency. Inherited hyperhomocysteinemia results from mutations in the genes coding for enzymes that break down homocysteine. These enzymes are **methylene-tetrahydrofolate reductase (MTHFR)**, **cystathione B sytnthase (CBS),** or **methionine synthase**. Defects in these enzymes may or may not lead to **hyperhomocysteinemia**, depending on their severity. **Hyperhomocysteinemia** is associated with both artery and vein clotting problems. How **hyperhomocysteinemia** affects blood clotting is not fully known.

How common is it?
Up to 50% of the general population may have one mutation affecting the metabolism of **homocysteine**. This doesn't result in high **homocysteine** levels in every case.

How and when do you test for this condition?
The diagnosis of **hyperhomocysteinemia** is based on the blood level of **homocysteine**. Levels of **homocysteine** may be elevated for several months after a new **VTE** event, so testing must be done several months after the **VTE** is discovered in order to be accurate.

What is the risk of VTE in a person with hyperhomocysteinemia?
Hyperhomocysteinemia is associated with both abnormal artery and vein clotting, although it is not clear whether **hyperhomocysteinemia** is just a sign of the clotting, or a cause of the clotting. The **homocysteine** level can be lowered with medication, but this doesn't change the risk of **VTE**, therefore the value of testing for this condition is unclear.

How do you treat Hyperhomocysteinemia?
High **homocysteine** levels can be decreased with folic acid, vitamin B6 and vitamin B12 therapy. However, the value of lowering the **homocysteine** level is in question.

Other Inherited Clotting Disorders

There are likely other **inherited clotting disorders** that are not yet fully known. As more of these disorders are figured out, many of the people who now get a **DVT** or **PE** for "unknown" reasons will likely be found to have an inherited condition that increases **VTE** risk.

AntiPhospholipid antibody Syndrome (APS)

Antiphospholipid antibodies are a family of antibodies that are directed against proteins in the blood that are important for coagulation. These antibodies include the lupus anticoagulants and the anticardiolipin antibodies. **Primary APS** includes patients who have **APS** but do not have lupus or other autoimmune diseases. **Secondary APS** includes those patients with **APS** and systemic lupus erythematosus (SLE).

How common is it?
This condition is reported in only 2% of healthy individuals, but is found in up to 20% of patients with **VTE**.

How and when do you test for this?
Diagnosis of this condition is based on both clinical and laboratory tests. In order to be diagnosed with this condition a person must have elevated antibody levels on two tests at least 6 weeks apart, and they must have had an abnormal clotting event or have had pregnancy related complications.

What is the risk of VTE in people with APS?
The risk of **VTE** in people with **APS** is relatively high. Approximately 1/3 of people with **APS** have had an abnormal clotting event. Usually this event is a **DVT**. People with **APS** who do not have lupus have an 11-fold increase in risk of **VTE** over those who do not have **APS**. They also have an increased risk of artery clot formation. Patients with lupus are at increased risk of abnormal clot formation even if they don't have the antibodies.

How do you treat APS?
People with **APS** who have a first **VTE** are usually treated with a short acting **blood thinner** such as **heparin**, and then change over to **warfarin** therapy after 5 days. The length of time to continue the **blood thinners** after the first abnormal clotting event is somewhat controversial and can range from 12 months to lifelong. In patients with **APS** who have not had a **VTE** event, daily aspirin therapy is recommended, but if other additional risk factors exist, **warfarin** or **heparin** therapy should be considered.

Heparin Induced Thrombocytopenia

Heparin induced thrombocytopenia (HIT) is a severe side effect of **heparin** therapy that can cause abnormal clotting. This condition occurs when a person's body makes an antibody against the **heparin**, and that antibody also targets their platelets. The antibody binding to the platelets causes them to clump up, which forms a clot.

How common is HIT?
Although **heparin-induced antibodies** form in 10-20% of people who get heparin, most of these patients do not develop **HIT**. Only 1-3% of people who use **heparin** for 5 days get **HIT**. This can go up to 6% after 14 days of continuous use. **Low-molecular weight heparin** (a more purified form of **heparin**) has a lower risk of **HIT**, but is harder to reverse and is more expensive.

How and when do you test for HIT?
A person who develops a new clot while on **heparin** is suspicious for **HIT**. A falling platelet count in the blood is another sign of **HIT**. In **HIT**, platelet counts fall starting 5-10 days after the start of **heparin** therapy, and reach a low by 7-14 days. This is known as "typical-onset" **HIT**. "Delayed-onset" **HIT** occurs when the platelet count falls later (up to 20 days after **heparin** starts) and can even occur after a patient has stopped the **heparin**. "Rapid-onset" **HIT** can occur within 24 hours of starting **heparin**. This can occur in patients who have had **heparin** before. A drop in the number of platelets by 50%, or a fall to below 100,000 is considered suspicious for **HIT**. To make the diagnosis of **HIT**, a lab test needs to be done. There are several available tests, some that look at platelet function, and one that looks for the antibodies themselves. If a patient is suspected of having **HIT**, the heparin should be stopped immediately while testing is done.

What is the risk of VTE in a person with HIT?
The most common complication of **HIT** is abnormal clot formation. About 50% of patients with **HIT** will develop a clot or die within 30 days if not treated. The risk of abnormal clot formation is increased 30 times in **HIT** patients. The most common clotting event is **DVT**. **PE** is also common in these people. Abnormal artery clotting is less common. Abnormal skin lesions can form in patients with **HIT** about 20% of the time.

How do you treat HIT?
The first thing to do is to stop all sources of **heparin**. Also, a different **blood thinner** should be started to help prevent the abnormal clot formation. Other **blood thinners** that could be used include **lepirudin, argatroban** and **bivalirudin**. **Low-molecular weight heparin** is still a **heparin**, and should not be used. Once the platelet count has come back up to normal, **warfarin** can be started, but should overlap with the other blood thinner by 5 days.

A person who has had **HIT** should not get heparin again in their life, unless under rare and very special circumstances.

Cancer

VTE is a major cause of complications in **cancer** patients. **PE** is the cause of death in one of seven hospitalized **cancer** patients who dies. The risk of **VTE** is much higher in **cancer** patients than in non-**cancer** patients, and most of the clots occur without another **risk factor** being present. Surgery, chemotherapy, central venous line placement, and immobility all further increase the risk of clotting in **cancer** patients. Treatment of **VTE** in cancer patients should continue until the **cancer** is in remission and no further chemotherapy is planned.

CONCLUSION

There are many different factors that can increase the risk of **VTE**. Some of these increase the risk more than others. These conditions should be looked for in any person who has a **VTE**, unless the cause is already known.