Protein C Deficiency: A review for clinicians.

By

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Protein C deficiency is a genetic abnormality that causes thrombophilia, or hypercoagulability, and increased risk of venous thrombosis. Although the consequences of protein C deficiency have been well documented, many health care professionals may not understand this disorder. Through thorough family and personal histories, physical examinations, risk factor identification, medical management, specialist referral, and patient education, these patients can live long and healthy lives, free from thrombotic disease. This article reviews the process of coagulation, the role of protein C in anticoagulation, and appropriate risk factor identification and management of protein C deficient adults.
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Protein C Deficiency: A review for clinicians.

On Sept 6, 2008, Ben was in a serious motorcycle accident. He suffered a fractured radial head, a 3rd degree AC separation of his left shoulder, and a severely lacerated left knee. Two days later, his left leg began to hurt even more than when he had injured it. His sister, a registered nurse, immediately suspected a blood clot and brought him back to the emergency department. He was diagnosed by venous ultrasound with multiple deep vein thromboses (DVT). He was successfully treated with Coumadin and Lovenox and suffered no long term effects.

The DVTs were not unexpected. Ben was diagnosed with protein C deficiency as a teenager having been tested for this disorder after his brother developed a blood clot. The whole family was tested and multiple aunts, uncles, and cousins were found to be deficient of this very important anticoagulant protein. Unfortunately, although the consequences of protein C deficiency have been well documented, many health care professionals may not understand this disorder. This article will review the aspects of protein C deficiency significant to practitioners; including the role of protein C in coagulation, risk factor identification, and appropriate management of protein C deficiency in adults.

Pathophysiology

The normal process of coagulation begins when a vessel is injured and platelets adhere to exposed Von Willebrand Factor at the site of injury (1). Platelets then release procoagulant substances that attract other platelets, which bind together and form a platelet plug. The clotting cascade proceeds through the complicated intrinsic, extrinsic, and common pathways to ultimately create fibrin and stabilize the clot (Figure 1).

Several anticoagulant mechanisms, including protein C, are necessary to prevent inappropriate or excessive clotting. Protein C is a vitamin K dependent enzyme, produced in the liver, which normally circulates in the blood as a glycoprotein (1). It is activated by a complex of
thrombin and thrombomodulin (1). Activated Protein C forms a complex with its cofactor protein S and inactivates clotting factors Va and VIIIa, thus preventing the formation of thrombin (2) (see Figure 1). Other anticoagulant factors include protein S, antithrombin, thrombomodulin, tissue plasminogen activator, and tissue factor pathway inhibitor (2). Coagulation is precisely balanced through the activation of coagulation factors and anticoagulation factors.

Protein C Deficiency

Protein C deficiency is usually a genetic abnormality. The protein C gene has been reported to have 160 possible distinct mutations that can result in inheritable disease (3). The inherited heterozygous abnormality, the main focus of this article, is an autosomal dominant trait and is the most common protein C deficiency (4). There are two major types of heterozygous protein C deficiencies; Type I results from insufficient amounts of the protein, whereas type II results from proteins which are dysfunctional.

Protein C deficiency causes thrombophilia, or hypercoagulability, and increased risk of venous thrombosis. There are many other types of thrombophilia, including antiphospholipid antibody syndrome, activated protein C resistance, elevated coagulation factor VIII levels, sticky platelet syndrome, protein S deficiency, homocystinemia, antithrombin deficiency, and prothrombin G20210A mutation (5). Protein C deficiency is not the most common of the thrombophilias but poses a significant threat to families with the genetic abnormality. It is estimated that in the healthy general population, the incidence is 1 in 250 to 500 people (6,7). According to the Leiden Thrombophilia study, persons with hereditary protein C deficiency have a 6.5 relative risk of sustaining a thrombosis (8).
Protein C Deficiency

Risk Factors

Protein C deficiency is uncommon in Asians and Africans, and is most commonly seen in Caucasians (4). Although protein C deficiency can be diagnosed at any time, thrombotic symptoms usually occur between 30 and 40 years of age (9). Most patients are asymptomatic until after puberty. Women and men have the same risk of having protein C deficiency. Overall, families with heterozygous protein C deficiency have a mortality rate similar to that of the general population. However, morbidity increases with advancing age due to increased risk of clots (4).

Spontaneous thrombotic events are the cause of 70% of initial venous thromboembolisms in protein C deficiency, whereas 30% have co-occurring risk factors (10). Certain factors increase the likelihood of thrombosis in patients with protein C deficiency including cancer, previous thrombosis, thrombophilias, oral contraceptives, pregnancy, trauma, obesity, and immobility (11). The risk of symptomatic disease increases with each risk factor that is added.

Oral Contraception

Oral contraceptive pills (OCPs) are a known risk factor for thrombosis. High-dose estrogen is classified as pills containing over 50 mcg of ethinylestradiol, the estrogen component in contraceptive pills (12). Low-dose pills contain less than 50 mcg of ethinylestradiol. Most OCPs are currently of the low-dose variety and have less risk of thromboembolism than high risk varieties. Nonetheless, a meta-analysis of studies about patients without thrombophilia who use OCPs concluded that there is still a three to six-fold increased risk of developing thrombotic disease even with low-dose estrogen (12). Women with protein C deficiency were found to have the same overall lifetime risk of venous thromboembolism when on combined oral contraceptives, containing a combination of ethinylestradiol and a progestagen, but were more
likely to have thromboembolisms at a younger age (13). The first year of OCP use is the period with the highest risk (12). Patients found to have thrombotic events during this first year are often discovered to be thrombophilic (14). Women who are thrombophilic have a 19-fold increased risk in the first six months of OCP use and an 11-fold increased risk within the first year. The risk decreases after the first year. Another meta-analysis of studies found that third-generation progestins such as desogestrel and gestodene also increase the relative risk of venous thrombosis to six to nine times that of nonusers (12). Second generation progestins were shown to have less risk.

**Pregnancy and Puerperium**

A 2008 meta-analysis reported that pregnant women are known to have a four to five-fold increased risk of thrombosis compared to nonpregnant females (15). This is thought to be due to hypercoagulability, hypofibrinolysis, and compression of the venous system by the gravid uterus (16). Most commonly these thrombi are found in the left leg and occur in patients who undergo cesarean sections. During puerperium, or the 42 days after delivery, a woman’s chance of a venous thromboembolism is nine times higher than during pregnancy, regardless of thrombophilic states (16). For women with protein C deficiency, the relative risk of thrombosis associated with thrombophilia in pregnancy or the postpartum period is increased 13-fold (Table 1).

**Air Travel**

Persons who travel on airplanes for extended periods of time are at two to three-fold increased risk of venous thromboembolism (17). According to one study, patients with protein C deficiency, and other thrombophilias, have a 16-fold increased risk of venous thromboembolism compared to controls when traveling by plane for eight hours or more (17). The reasons for this
increased risk are not completely understood, but are thought to be due to immobility with venous stasis, fluid restriction, and hypoxic hypoxia (18).

**Surgery**

Venous thrombosis is a well-documented complication after surgery. Orthopedic, vascular, neurosurgery, and cancer surgeries have the highest associated thrombotic risk (19). The risk of thrombosis after surgery increases with age, length of general anesthesia, history of thromboembolism, lower extremity surgery, and thrombophilia (20).

**Trauma**

Traumatic events such as motor vehicle crashes can result in critical bodily injury that causes a hypercoagulable state due to significantly increased and persistent thrombin generation and disruption of its regulation (21). The risk of DVT after trauma is related to the severity and location of the trauma (22). This risk is increased in multi-system trauma, spinal cord trauma, and lower extremity blunt trauma. Trauma is considered a reversible, secondary risk factor for thromboembolism. Patients who experience such a secondary thrombosis will have less risk of recurrence than people who develop idiopathic venous thromboembolism (VTE) (23).

**Smoking and Obesity**

Smoking and obesity significantly increase the risk of venous thromboembolism. Smoking has been found to cause acquired protein C deficiency in non-thrombophilic patients (24). One retrospective, population-based study concluded that a 10-point increase in body mass index resulted in a 24% increase in a person’s risk of recurrent venous thromboembolism (25). It may also be that patients with protein C deficiency have increased risk of thrombosis if they are obese or smokers. However, to date, the effect of these risk factors on patients with protein C
deficiency has not been well researched. More research-based evidence is required before
guidelines can be created for protein C deficient patients.

Patient Screening

Protein C deficiency may be a difficult thrombophilia for clinicians to identify as there
are no presenting physical signs or symptoms in most affected individuals. The following section
provides an overview of strategies to identify at-risk patients and for determining the need for
further evaluation. A thorough personal history, family history, and physical examination can
identify the need for further evaluation for thrombophilia.

History of Present Illness

Patients with protein C deficiency will most likely present for miscellaneous complaints
or wellness exams which are unrelated to the deficiency. However, nurse practitioners must be
able to recognize the most common complaints associated with thrombotic syndromes. DVT’s
are the most common problem associated with protein C deficiency. Many patients who have
DVTs are asymptomatic. However, some may present with unilateral upper or lower extremity
edema, leg pain, tenderness to palpation, redness, and warmth (26). DVTs can lead to pulmonary
embolism (PE), which can cause sudden death. According to The Prospective Investigation of
Pulmonary Embolism Diagnosis (PIOPED), the most common symptoms in patients with PEs
are dyspnea, pleuritic chest pain, and cough (27). Other symptoms may include hemoptysis and
syncope (28).

Medical and Family History

In patient interviews, clinicians should specifically and routinely ask about venous and
arterial clotting history, clotting severity, need for anticoagulation, bleeding history, and
associated risk factors (4). They should also inquire about any previous coagulopathy workups
and their results. Patients who have a prior history of blood clots should be thought of as high risk for thrombophilias, including protein C deficiency. Family histories should be thoroughly evaluated for events such as DVTs, PEs, myocardial infarctions, cerebrovascular accidents, and sudden unexplained death. Patients with biological family members who have been diagnosed with protein C deficiency should be encouraged to undergo screening tests.

**Physical Examination**

Most protein C deficient patients will be asymptomatic; however, nurse practitioners must maintain a high level of suspicion for thrombus during physical examination. A thrombus most commonly occurs in the lower extremities. Patients presenting with subjective symptoms of DVT should be evaluated for superficial thrombophlebitis at the saphenofemoral junction, medial thigh or calf muscle tenderness, unilateral edema, cyanosis or reddish purple discoloration (26).

Pulmonary embolisms are not as common as DVTs but have a higher mortality. In fact, 10 % of patients with PE die within hours and 25% within the first year (28). Patients with large embolisms will often appear scared, in pain, and in respiratory distress. Symptoms that clinicians may see on physical examination are variable but may include hypotension, poor perfusion, tachycardia, tachypnea, S3 gallop, systolic murmur on inspiration at left sternal border, palpable impulse over second left intercostal space, dullness on percussion, diminished breath sounds, and rales or wheezing (29).

A thrombus can occur anywhere in the body. Less common sites include cerebral vein thrombosis, splanchnic thrombosis, and upper extremity thrombosis. Patients with cerebral vein thrombosis may present with symptoms of headache, lethargy, or neurologic abnormalities (30). On exam, focal neurologic deficits, seizures, stroke, and coma may be seen. Patients with
splanchnic thrombosis may present with symptoms of abdominal pain, vomiting, distension, melena, and fever. Patients with upper extremity thrombosis often present with symptoms of arm pain, swelling, vein dilation, and cyanosis. Upper extremity thrombosis is most commonly seen in women undergoing artificial reproductive technology due to high levels of estrogen. Although these sites are not commonly encountered in practice, it is important to include them in the differential diagnoses for thrombophilic patients.

**Diagnostic Workup**

Protein C deficiency is diagnosable through laboratory testing. However, there are multiple confounding variables and different types of testing available. The initial diagnostic test is a protein C activity level, or functional assay. If this level is low, an antigen assay should be performed to distinguish Type I from Type II deficiencies (31). Figure 2 presents a detailed algorithm for laboratory testing. Decreased protein C activity levels should be repeated to confirm the findings (4). Protein C levels should not be evaluated when a person is using warfarin due to warfarin-induced protein C deficiency. Other thrombophilias may be prudent to include in screening but unnecessary testing should be avoided to prevent undue expense.

**Thrombus Prevention and Management**

Nonpharmacologic treatment includes minimizing patient risk factors and educating patients on prevention of thrombus formation. Avoiding oral contraceptives, managing weight, smoking cessation, and minimizing immobility will reduce patients’ likelihood of developing thrombi. It is critical for nurse practitioners to advise their patients of the increased risk that these avoidable risk factors carry. A diagnosis of protein C deficiency, even when accompanied by the described risk factors, does not in and of itself indicate a need for pharmacologic prophylactic
therapy. Generally, patients who never experience thrombosis will never require anticoagulant medications (4). For these patients, nonpharmacologic management is sufficient.

Contraception

Due to the increased risk of thrombosis with estrogen-progestin contraceptives, it is inadvisable for women with a personal or family history of thrombophilia to use this method for contraception. However, due to the increased risk of thrombosis during pregnancy, contraception must be a priority. These patients should be encouraged to use nonhormonal contraception methods such as copper releasing intrauterine contraception, male or female condoms, or diaphragms (32). If women who are protein C deficient do not wish to use these options, they should be carefully counselled on the risks and benefits of using oral contraceptives. If the patient chooses to accept the risk, these patients should be placed on progestin-only options and thoroughly educated on the signs and symptoms of DVTs and PEs (33). The nurse practitioner should have the patient sign an informed consent form regarding the risks and benefits of oral contraceptive use. OCPs are absolutely contraindicated in women over the age of 35 who smoke or in women who have prior history of thrombosis (33).

Air Travel

Due to the increased risk of thromboembolism after long-flights, it is important to evaluate thrombophilic patients planning such a trip on a case by case basis. Evidence based guidelines for the prophylaxis against VTE resulting from air travel have not been created. The nurse practitioner may wish to make recommendations based on limited studies. One study showed that high risk individuals traveling by air for over ten hours had statistically significant decreases in thrombotic events when treated with low-molecular-weight heparin (LMWH) two to four hours prior to their flights (34). Aspirin was also shown to decrease thrombi but not to the
same degree as LMWH. Some nonpharmacologic teaching points for nurse practitioners to emphasize are adequate hydration, leg exercise, and elastic compression stockings during flights (17). These measures, however, may not be sufficient to prevent thrombotic events in thrombophilic patients, especially those with multiple risk factors.

**Surgery and Trauma**

Patients who experience surgery or trauma will require close monitoring and proper anticoagulant treatment and prophylaxis. High risk patients undergoing surgery or suffering trauma should receive prophylaxis with unfractionated heparin (UFH) or LMWH. Low risk patients may be managed with thorough education regarding DVTs and early ambulation (22). Most surgeons, especially in orthopedics, prefer LMWH for prevention of venous thromboembolism after surgery (35). The goal of DVT prophylaxis is to reduce the number of fatal pulmonary embolisms secondary to surgical intervention. DVTs which occur after trauma should be treated for 6 to 12 months with a vitamin K antagonist such as warfarin (34).

**Pharmacotherapy Guidelines**

Patients who develop thrombosis will require anticoagulation. The American Academy of Chest Physicians (ACCP) has compiled guidelines based on current research. The latest guidelines were published in 2008 but did not specifically make recommendations for thrombophilic patients. They recommend that patients who have a DVT secondary to a transient risk factor be treated with VKA for at least 3 months (36). The 2004 guidelines provided more detail regarding recommended treatments for thrombophilic patients. These guidelines recommended specifically that thrombophilic persons who develop a DVT secondary to a transient risk factor should receive 6 to 12 months of treatment with a vitamin K antagonist (VKA), such as warfarin (37). The 2004 guidelines by the (AACP), suggest indefinite therapy
with VKA in thrombophilic patients who experience idiopathic thrombosis or two or more episodes of thrombosis. When indefinite VKA therapy is required, risks and benefits should routinely be reassessed, as the risk of bleeding increases with duration of anticoagulants and with increasing age. Treatment effectiveness decreases over time (23). Eventually the risks will outweigh the benefits. Treatment periods should be no longer than three years for a spontaneous venous thromboembolism and two years for secondary thrombosis (22) (Table 2).

Patients who are treated with warfarin should be carefully monitored for warfarin-induced skin necrosis during the first several days of therapy (Bauer). This dangerous side effect is thought to be the result of increased thrombin generation during the early phase of warfarin therapy. Symptoms include skin lesions on the extremeties, breasts, trunk, and penis which spread over a period of hours and if not treated can become edematous and necrotic. Warfarin should be promptly discontinued when this condition is suspected and vitamin K and heparin administered (10).

Pregnancy

Anticoagulation treatment decisions during pregnancy differ greatly from non-pregnant states. VKAs have teratogenic effects; consequently pregnant women maintained on VKAs should be switched to low-dose heparin or LMWH during pregnancy because they do not cross the placenta (15). Higher doses will be necessary than in nonpregnant states due to shorter half-lives and lower peak plasma concentrations during pregnancy. Pregnant patients with protein C deficiency who have had one single thrombosis should receive prophylaxis with LMWH or unfractionated heparains (UFH) (38). According to AACP guidelines, pregnant women with no previous history of venous thromboembolism can be managed with increased surveillance or prophylactic anticoagulation with LMWH or UFH (37). All thrombophilic patients should
receive anticoagulants throughout puerperium. LMWH or UFH should overlap VKA dosing until the INR is greater than 2.0 (Table 2).

**Risk/Benefit Analysis**

The benefit of preventing thrombosis must be compared to the risk of bleeding due to anticoagulant medications. This can be done through tools which evaluate a patient’s risk for bleeding. The Outpatient Bleeding Risk Index developed by Beyth, et al, evaluates four categories of risk factors: age ≥ 65; previous history of stroke; recent gastrointestinal bleed; recent myocardial infarction, hematocrit less than 30%, creatinine greater than 1.5mg/dl, or diabetes mellitus. The risk of bleeding is calculated in percentages at 3 months and 12 months after initiation of anticoagulants (39). Tools such as this will help nurse practitioners tangibly evaluate the risks and benefits of anticoagulation therapy (Figure 3).

**Referral**

Due to the infrequency of encountering patients with an established protein C deficiency diagnosis, and the many caveats to patient management, specialist consultation is encouraged. Hematologist referral and consultation will be an important component to managing patient care and ensuring the safest and most up-to-date treatment is made available. Collaboration with perinatologists, obstetricians, and hematologists during the perinatal period is also advised.

**Conclusion**

Protein C deficiency can cause life-threatening thromboembolic events. However, anticoagulant treatment can cause life-threatening hemorrhage. Nurse practitioners who manage patients with protein C deficiency will find it necessary to correctly identify risk factors that can be altered or avoided to prevent negative outcomes in this patient population. Through a
thorough family and personal history, physical examination, risk factor identification, medical management, specialist referral, and patient education, these patients can live long and healthy lives, free from thrombotic disease.
References


Table 1
Risk of Venous Thromboembolism During Pregnancy and Puerperium in Protein C Deficiency

<table>
<thead>
<tr>
<th>Type of thrombophilia</th>
<th>Women with thrombosis during pregnancy or puerperium</th>
<th>Women with normal pregnancies</th>
<th>Relative risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antithrombin, protein C, or protein S deficiency</td>
<td>7.6%</td>
<td>0.9%</td>
<td>13.1%</td>
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Source-
### Table 2

**Treatment Options in Protein C Deficient Patients**

<table>
<thead>
<tr>
<th>Thromboembolism Status</th>
<th>Medication</th>
<th>Duration</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>No History of DVT</td>
<td>Surveillance without anticoagulation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>First DVT with Secondary Risk Factor</td>
<td>VKA</td>
<td>6-12 months</td>
<td></td>
</tr>
<tr>
<td>Two or more DVT's</td>
<td>VKA</td>
<td>Indefinite</td>
<td>Periodic Reevaluation of Risks/Benefits</td>
</tr>
<tr>
<td>Idiopathic DVT</td>
<td>VKA</td>
<td>Indefinite</td>
<td>Periodic Reevaluation of Risks/Benefits</td>
</tr>
<tr>
<td>First PE with Identified Risk Factor</td>
<td>VKA</td>
<td>6-12 months</td>
<td></td>
</tr>
<tr>
<td>First Idiopathic PE</td>
<td>SC LMWH or IV UFH Short Term then VKA</td>
<td>Indefinite</td>
<td>Periodic Reevaluation of Risks/Benefits</td>
</tr>
<tr>
<td>Pregnancy With History of Single VTE</td>
<td>Prophylactic LMWH or UFH, plus Postpartum VKA</td>
<td>To 6 weeks post partum</td>
<td></td>
</tr>
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</table>

SC=subcutaneous
IV= intravenous
LMWH= low molecular weight heparin
UFH= Unfractionated heparin
VKA=Vitamin K antagonist
DVT= Deep vein thrombosis
PE= Pulmonary embolism
VTE= venous thromboembolism

Source-
Figure 1
Anticoagulation Pathway and Activated Protein C

Extrinsic pathway

- Calcium
- Tissue Factor
- Factor VII
- Factor VIIa
- Factor X
- Factor VIII
- Factor VIIIa
- Platelets
- Calcium
- Factor Va
- Factor V
- Prothrombin (II)
- Thrombin (IIa)
- Factor XIII
- Factor XIIIa
- Fibrinogen (I)
- Fibrin
- Fibrin Polymer
- Crosslinked fibrin polymer

Intrinsic Pathway

- High-molecular-weight-kininogen
- Kallikrein
- Negatively Charge Surface
- Factor XII
- Factor XI
- Factor Xa
- Calcium
- Factor IXa
- Factor IX
- Calcium
- Tissue Factor
- Platelets
- Calcium
- Factor VIIIa
- Factor VIII
- Thrombin
- Factor VIIa
- Factor Va
- Thrombin/thrombomodulin complex
- Protein C

APC= Activated Protein C blocks Factor VIIIa and Factor Va thus preventing the formation of thrombin
Figure 2
Algorithm for Differentiating Type I and Type II Protein C Deficiency

Symptomatic or High Risk individual

Yes

No testing necessary

Low protein C activity level (Also known as functional assay)

No

Clot-based Assay used?

Yes

Lupus anticoagulant present?

Yes

Repeat using chromogenic functional assay

No Protein C Deficiency

Repeat activity level when off Coumadin for 2 weeks.

Recent or current coumadin use?

Yes

Repeat at later date unless known family history of same.

No Protein C Deficiency

PC Deficiency Type I

PC Deficiency Type II

Reasons for acquired protein C deficiency present?

Yes

Protein C Antigen Measurement

Antigen Low?

No

Repeat when no acquired factors present

Sources-
Laposata M, Van Cott EM. How to work up hypercoagulability. *College of American Pathologists*. 2000. Available at:

Quest Diagnostics. Thrombophilia; Laboratory support of diagnosis and management. n.d. Available at:
Summary of Beyth’s Outpatient Bleeding Risk Index

1. What risk factors are present?
   Check all that apply
   - Age > 65
   - History of stroke
   - Recent GI bleed
   - Recent MI, Hct < 30%, Creatinine > 1.5 mg/dl, Diabetes Mellitus

2. Sum of all risk factors
3. Classify your patient
4. Estimated risk of major bleeding

<table>
<thead>
<tr>
<th># of Risk factors</th>
<th>Low Risk</th>
<th>Intermediate Risk</th>
<th>High Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>In 3 months</td>
<td>2%</td>
<td>5%</td>
<td>23%</td>
</tr>
<tr>
<td>In 12 months</td>
<td>3%</td>
<td>12%</td>
<td>48%</td>
</tr>
</tbody>
</table>

GIB = gastrointestinal bleeding
MI = myocardial infarction
Hct = hematocrit
Cr = serum creatinine concentration.

Source: