Thrombophilia: Deficiencies in Protein C, Protein S and Antithrombin

Thrombosis Canada
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Objective:

To assist practitioners in managing patients with a suspected or confirmed deficiency in protein C, protein S or antithrombin (AT), in consultation with a thrombosis specialist.

Background:

Protein C, protein S, and antithrombin (AT) are essential endogenous anticoagulants that maintain hemostatic balance. Deficiencies in any of these proteins are linked to a prothrombotic state, increasing the risk of venous thromboembolism (VTE), which primarily manifests as deep vein thrombosis (DVT) or pulmonary embolism (PE). While the link to arterial thrombosis is not definitively established, some limited data suggest that protein C or S deficiency might be associated with a slightly higher risk of arterial stroke, particularly in young adults, though the clinical relevance is unclear.

These deficiencies can be inherited as autosomal dominant traits, affecting approximately 1 in 300 to 1 in 3000 individuals. They are found in less than 5% of patients with unprovoked DVT or PE. Acquired deficiencies are more common. For example, protein S levels often decrease during pregnancy, the postpartum period, and with oral contraceptive use. Because protein C and S synthesis is vitamin K-dependent, their levels are reduced by vitamin K antagonists like warfarin. AT deficiency can occur in patients with nephrotic syndrome and those receiving L-asparaginase chemotherapy. Deficiencies in all three proteins can also be seen with advanced liver disease and extensive acute thrombosis.

Diagnosing these conditions is challenging because protein C, protein S, and AT levels can be transiently low. An acute thrombotic event, for instance, consumes these proteins, lowering their circulating levels. Similarly, anticoagulants (heparin, warfarin) and physiological states (pregnancy, neonatal period) can influence test results. Therefore, a single low measurement, especially during an acute phase or while on anticoagulants, does not confirm an inherited deficiency. The timing of diagnostic tests is crucial: they should ideally be performed several weeks after an acute event and 3-6 weeks after discontinuing warfarin or heparin. Repeat testing is often necessary to confirm consistently low levels and to accurately distinguish between inherited and transiently acquired deficiencies.

When should patients be investigated for a deficiency in Protein C, Protein S and AT?

Specialist advice should be sought before considering thrombophilia testing in patients with DVT or PE. The rationale for this conservative approach is that a confirmed positive test rarely affects patient management and may lead to an inappropriate duration of therapy or unnecessary testing of relatives. Conversely, a negative result may provide false reassurance regarding the future risk of recurrence or the risk of a first

DVT or PE in relatives. Furthermore, the diagnosis of these deficiencies in clinically unaffected relatives can negatively impact their perception of their health and may affect their life and disability insurance status.

Which patients should ***not*** be investigated for a deficiency in Protein C, Protein S or AT?

Clinical Scenarios Where Testing Is Not Recommended

- **Provoked VTE:** Testing is generally not advised after VTE provoked by a strong trigger (e.g., major surgery), as a detected deficiency in these cases rarely changes the duration of anticoagulation therapy.
- **Arterial Thrombosis:** Since these deficiencies are primarily associated with venous events, testing for inherited thrombophilias is not recommended for patients with arterial thrombosis, such as ischemic stroke or myocardial infarction.
- **Genereal Screening:** Thrombophilia testing is not indicated as a broad screening tool for the general population or for asymptomatic patients without a personal or significant family history of VTE.
- **Hormone Therapy and Prenatal Setting**s: Routine testing is not advised before starting oral contraceptives, hormone replacement therapy, or as a prenatal/newborn screen for asymptomatic children.

Factors That Interfere with Accurate Test Results

Several factors can cause transiently low levels of these natural anticoagulants, leading to inaccurate results and a potential false-positive diagnosis.

- **Acute Thrombotic Events:** An acute VTE or other severe illness (e.g., sepsis) can consume Protein C, S, and AT, making a definitive diagnosis of a hereditary deficiency difficult. Repeat testing during a stable period is always recommended.
- **Anticoagulant Therapy**: Testing while a patient is on anticoagulants can significantly skew results:
    - Warfarin: This vitamin K antagonist substantially decreases levels of Protein C and S, creating a false impression of deficiency.
    - Direct Oral Anticoagulants (DOACs): These drugs can interfere with the functional assays for these proteins, making test results unreliable.
    - Heparin/LMWH: Both unfractionated heparin (UFH) and low-molecular-weight heparin (LMWH) can cause falsely low antithrombin levels.
- **Physiological States:** Pregnancy, the postpartum period, and the neonatal period are associated with naturally lower levels of some anticoagulants, which can be misleading
- **Underlying Medical Conditions:** Various conditions—including liver disease, severe vitamin K deficiency, DIC, nephrotic syndrome, and certain malignancies or chemotherapeutics—can cause acquired deficiencies or interfere with test accuracy.

What if a patient has a deficiency of Protein C, Protein S or AT (without thrombosis)?

- In a patient who is confirmed to have a deficiency of protein C, protein S or AT and has not had thrombosis, appropriate patient counseling should be given about the symptoms of VTE and risk of

VTE associated with pregnancy, oral contraceptive use, surgery and other situations with a high risk of VTE.
- In patients with protein C, protein S or AT deficiency, specialist advice should be sought related to thromboprophylaxis if there are situations of increased risk such as trauma, surgery or pregnancy.

How to Manage Patients with Thrombosis and a Deficiency in Protein C, Protein S or Antithrombin:

In patients who develop acute DVT or PE and have a known deficiency in protein C, protein S or AT, consultation with a specialist is advised. The initial anticoagulant treatment is generally like that of patients who do not have a deficiency of protein C, protein S or AT, with important caveats indicated below. As in other patients, the duration of anticoagulation depends on the presence or absence of a provoking factor. Treatment duration is at least 3 months and, in many patients with these conditions, long-term.

- **AT deficiency**: is associated with one of the highest lifetime risks of VTE among inherited thrombophilias, with recurrent events common if anticoagulation is discontinued. Since UFH, LMWH, and fondaparinux exert their effect via AT-dependent inhibition of thrombin and factor Xa, patients may require higher doses to achieve therapeutic targets. Heparin resistance should be suspected when the activated partial thromboplastin time (aPTT) or anti-Xa levels are subtherapeutic despite standard dosing. AT concentrate can normalize activity and restore responsiveness; its use is particularly recommended in high-risk settings such as major surgery, pregnancy, or severe trauma. DOACs, which act independently of AT, represent a viable alternative, although published data are limited to case reports, small series, and post-hoc analyses. Expert oversight is advised before initiating DOACs in this setting, and dose reduction for secondary prevention is not recommended.
- **Protein C deficiency:** In acute VTE, management can follow standard protocols with DOACs or parenteral anticoagulation/warfarin. However, initiating warfarin in protein C deficiency carries a risk of warfarin-induced skin necrosis due to the rapid fall in protein C levels, leading to a transient hypercoagulable state. Bridging with therapeutic UFH, LMWH, or fondaparinux for a minimum of five days and until the INR is ≥2.0 for at least 48 hours is mandatory. Severe congenital protein C deficiency may require protein C concentrate in acute thrombotic events, during surgery, or in pregnancy.
- **Protein S deficiency:** Acute management is similar to that of protein C deficiency. There is no protein S concentrate; therefore, prevention and treatment rely entirely on anticoagulant therapy. Although the thrombotic risk associated with heterozygous protein S deficiency varies, high-risk families demonstrate a significant recurrence rate without anticoagulation.

Given the low frequency of protein C, protein S and AT deficiency in the population, experience with DOACs in affected individuals is limited and the literature limited mostly to case reports and post-hoc analyses of clinical trials or cohort studies. In general, expert opinion is that DOACs or parental anticoagulation/warfarin can both be used safely with Protein C or S deficiency. Evidence supporting the use of DOAC in AT deficiency is limited but their use could be considered after expert consultation.

If DOACs are used for Protein C, protein S or AT deficiency, it is advised to avoid dose reduction in the chronic prevention phase of treatment.

How to Manage Patients with a Deficiency of Protein C, Protein S or AT Who Need Surgery:

These deficiencies confer an increased perioperative VTE risk. All patients should undergo individualized thromboprophylaxis planning with specialist input.

AT deficiency

Perioperative AT concentrate may be indicated to correct activity levels, thereby improving the efficacy of heparin-based prophylaxis or treatment. Similar supplementation is recommended during pregnancy, particularly in the peripartum period, to prevent maternal DVT/PE and to improve fetal outcomes.

Protein C deficiency

Warfarin should be interrupted with appropriate bridging using LMWH or UFH. In severe cases or in patients with a history of warfarin-induced skin necrosis, protein C concentrate can be administered perioperatively to reduce thrombotic risk.

Protein S deficiency

Perioperative management mirrors that of protein C deficiency but without a specific concentrate available. Bridging strategies and mechanical prophylaxis are important adjuncts.

Pediatrics:

The diagnosis and management of protein C, S, and antithrombin deficiencies in children are challenging due to their unique physiology.

- **Diagnosis**: Neonates have naturally low levels of these proteins, which can lead to misdiagnosis. Careful interpretation of lab results is crucial, and genetic testing may be necessary.

Pregnancy:

See the **Clinical Guide** **Pregnancy: Thromboprophylaxis** for information about the prevention of pregnancy associated VTE in women with a deficiency of Protein C, Protein S or AT.

Other Relevant Thrombosis Canada Clinical Guides:

- Pregnancy: Thromboprophylaxis
- Thrombophilia: Factor V Leiden and Prothrombin Gene Mutation

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