# Thrombophilia: Deficiencies in Protein C, Protein S and Antithrombin

Thrombosis Canada
Thrombose Canada

## 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 AT are endogenous anticoagulants that help maintain hemostatic equilibrium. Deficiency in protein C, protein S or AT is associated with a prothrombotic state that leads to an increased risk for venous thromboembolism (VTE), mainly deep vein thrombosis (DVT) or pulmonary embolism (PE). Increased risk of arterial thrombosis has not been clearly established. Limited and weak data suggest that protein C or S deficiency might be associated with a slightly increased risk of arterial stroke, particularly in young adults; however, the clinical significance of this finding is not clear. A deficiency in protein C, protein S or AT can be inherited (as autosomal dominant traits), although such conditions are uncommon, occurring in 1 in 300 to 1 in 3000 people in the general population and in <5% of patients presenting with unprovoked (or idiopathic) DVT or PE. Acquired deficiencies of protein C, protein S, and AT are more common. For example, protein S levels are decreased during pregnancy and the post-partum period and in oral contraceptive users. Because protein C and protein S are dependent on vitamin K for their synthesis, their levels are reduced in patients who are receiving a vitamin K antagonist such as warfarin. A deficiency in AT can occur in patients with nephrotic syndrome and in those receiving L-asparaginase chemotherapy. Finally, deficiencies in all these proteins occur in patients with advanced liver disease and may occur in the presence of extensive, acute thrombosis.

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

Specialist advice should be sought before considering testing patients with DVT or PE for any thrombophilia. The reason for this conservative approach is that a confirmed positive test rarely affects patient management and may lead to inappropriate duration of therapy or inappropriate testing of relatives; a negative result may provide false reassurance as to the future risk of recurrence or the risk of a first DVT or PE in relatives. In addition, diagnosed deficiencies in clinically unaffected relatives may adversely affect the way they think about 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?

- Most patients with VTE, even in unusual sites unless discussed with experts.
- Patients with thrombosis and a clinically identifiable provoking risk factor (e.g. surgery).
- Patients with arterial thrombosis, ischemic stroke or myocardial infarction.
- Patients with an acute DVT or PE (or with another acute illness), since they may have decreased protein C, protein S and AT levels in the acute setting, leading to the incorrect assumption that the patient has a deficiency.
- Patients already on anticoagulant therapy:
    - In those receiving a vitamin K antagonist such as warfarin, protein C and protein S levels will be substantially decreased, leading to the incorrect assumption that the patient has a deficiency.
    - In patients who are taking direct oral anticoagulants (DOACs), functional assays for protein C, protein S and AT may be impacted, thus rendering these tests inaccurate.
    - In patients who are taking unfractionated heparin (UFH), low molecular weight heparin (LMWH) or fondaparinux, antithrombin levels may be falsely low.
- Women who are pregnant, postpartum, or taking an oral contraceptive, since they will have mildly to moderately decreased protein S levels.

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

- A provisional diagnosis of a deficiency in protein C, protein S and AT should be made in consultation with a specialist because of the potential for misdiagnosis due to false positive test results and the need for evidence-based patient and family counseling.
- 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**: Since the anticoagulant action of UFH, LMWH and fondaparinux depends on inhibiting AT, patients with AT deficiency may be resistant to usual doses of these anticoagulants and, therefore, may require higher doses. This would be evident, for example, when the activated partial thromboplastin time (aPTT) is not prolonged despite usually adequate doses of UFH. The anti-Xa activity of UFH and LMWH can be reduced in patients with antithrombin deficiency. Alternative anticoagulants that are independent of AT (e.g. argatroban or direct oral anticoagulants [DOACs]) can be considered, noting limited evidence in this population.

- **Protein C deficiency:** Acute DVT or PE can be managed with DOACs or parental anticoagulation/warfarin, as in patients without protein C deficiency. However, warfarin routinely reduces protein C levels. In patients who have protein C deficiency, warfarin will further reduce protein C levels quickly and this may produce a prothrombotic state that can lead to warfarin-induced skin necrosis. Therefore, initial treatment with LMWH/UFH/fondaparinux must overlap with warfarin for at least 5 days and until the international normalized ratio (INR) is ≥2.0 for at least two consecutive days before stopping the LMWH/UFH/fondaparinux. In patients with protein C deficiency, warfarin should not be started without coverage with a rapidly acting anticoagulant such as LMWH or UFH or fondaparinux. Loading doses of warfarin should not be used.
- **Protein S deficiency:** Treatment of acute thrombosis is like that of protein C deficiency.

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:

Patients with these deficiencies may be at higher risk for perioperative VTE. In all such patients, consultation with a specialist is advised to provide appropriate thrombosis prophylaxis. In selected patients with AT deficiency, AT concentrate can be used to raise AT levels around the time of surgery. AT concentrate may also be used in selected patients with AT deficiency during pregnancy to prevent DVT or PE. Protein C concentrate is also available but there is no protein S concentrate.

## Pediatrics:

Pediatricians with expertise in thromboembolism should manage, where possible, pediatric patients with thromboembolism and those with deficiencies of protein C, protein S or AT. When this is not possible, a combination of a neonatologist/pediatrician and an adult hematologist, supported by consultation with an experienced pediatric hematologist, is recommended.

## 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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