DEFICIENCIES IN PROTEIN C, PROTEIN S AND ANTITHROMBIN

Thrombosis Canada
Thrombose Canada

TARGET AUDIENCE: All Canadian health care providers.

OBJECTIVE:

To assist practitioners in managing patients with a suspected or confirmed deficiency in protein C, protein S and antithrombin and to facilitate appropriate referrals to a coagulation specialist.

ABBREVIATIONS:

aPTT	activated partial thromboplastin time
AT	antithrombin
DVT	deep vein thrombosis
INR	international normalized ratio
LMWH	low-molecular-weight heparin
PE	pulmonary embolism
UFH	unfractionated heparin

BACKGROUND:

Protein C, protein S and antithrombin (AT) are endogenous anticoagulants that act as a balance against clotting factors to maintain a hemostatic equilibrium. A deficiency in protein C, protein S or AT may be associated with a prothrombotic state and can predispose patients to an increased risk for thrombosis, mainly deep vein thrombosis (DVT) (see DVT diagnosis guide) or pulmonary embolism (PE). A deficiency in protein C, protein S and AT can be inherited (as autosomal dominant traits) but such conditions are rare, occurring in 1 in 300 to 1 in 500 people overall and in < 5% of patients presenting with unprovoked (or idiopathic) DVT or PE. Acquired deficiencies in 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, these levels can be reduced in patients who are receiving a vitamin K antagonist such as warfarin. A deficiency in AT can occur in patients with the nephrotic syndrome. Finally, deficiencies in all these proteins may occur in patients with advanced liver disease.

When could patients be investigated for a deficiency in protein C, protein S and AT?

In general, a work-up for thrombophilia (including investigation for a deficiency in protein C, protein S and AT) should be done in consultation with a thrombosis specialist, because of challenges in interpretation of the results (see below).

When should patients *not* be investigated for a deficiency in protein C, protein S and AT?

- In patients who are receiving a vitamin K antagonist, protein C and protein S levels will be substantially decreased and this is an acquired (and expected) finding.
- In patients who are pregnant or taking an oral contraceptive, protein S levels will be mildly to moderately decreased.
- In patients with an acute DVT or PE (or with another acute illness) protein C and protein S levels can be decreased as a consequence of these conditions.

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

- As discussed above, 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.
- In a patient who is confirmed to have a deficiency of protein C, protein S or AT and ***has not had thrombosis***, counseling should be given to a woman of child-bearing age regarding the risks for thrombosis if there is use of an oral contraceptive or in the event of a pregnancy (see Thromboprophylaxis: Pregnancy guide).

MANAGEMENT:

How to manage patients with thrombosis and a deficiency in protein C, protein S or AT?

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 should be similar to that of patients with DVT or PE who do not have a deficiency of protein C, protein S or AT, with caveats as indicated below. The duration of anticoagulation is least 3 months and, in selected patients, long-term anticoagulation should be considered.

- **AT deficiency**: Acute thrombosis can usually be managed with low-molecular-weight heparin (LMWH). Some patients may be resistant and, therefore, require higher doses of LMWH or unfractionated heparin (UFH). This would be evident, for example, when the activated partial thromboplastin time (aPTT) is not prolonged despite adequate UFH administration. Alternative anticoagulants that are antithrombin-independent (e.g. argatroban, rivaroxaban) may be considered.
- **Protein C deficiency:** Acute DVT or PE can be managed with LMWH/UFH and warfarin, as in patients without protein C deficiency. Because of the risks of warfarin-induced skin necrosis, special attention should be given to ensure that patients reach a therapeutic level of anticoagulation with warfarin (international normalized ratio [INR] ≥ 2.0 for two consecutive days) before stopping the initial treatment with LMWH/UFH because of the effect of warfarin to further reduce protein C and protein S levels during the initial 1-3 days of this treatment.

- **Protein S Deficiency:** Treatment of acute thrombosis is similar to that of protein C deficiency.

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 peri-operative DVT or PE (see Thromboprophylaxis: Surgery guide). In all such patients, consultation with a specialist is advised. In 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 pregnancy to prevent DVT or PE.

PEDIATRICS:

In children < 5 years of age, definitive diagnosis of heterozygous protein C, protein S or AT deficiency is difficult, due to developmental hemostasis. Severe (homozygous) protein C deficiency in neonates with the clinical presentation of purpura fulminans is a medical emergency. Pediatricians with expertise in thromboembolism should manage, where possible, pediatric patients with thromboembolism. 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.

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