Inherited Thrombophilia and Travel Related Thrombosis

Introduction: The most common clinical criteria for recognising Thrombophilia are, recurrent Venous Thromboembolism (VTE), a family history of venous thrombosis, unusual localisation of venous thrombosis and venous thrombosis at a young age. Thrombophilia can be divided into two broad categories, inherited and acquired. (see Table 1).

Table 1

<table>
<thead>
<tr>
<th>Inherited deficiencies</th>
<th>Acquired causes</th>
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<tr>
<td>Factor V Leiden (FVL)</td>
<td>Advanced age</td>
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<tr>
<td>Prothrombin 20210A</td>
<td>Previous thrombosis</td>
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<td>Deficiency of the anticoagulant Proteins C, S</td>
<td>Immobilisation</td>
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<tr>
<td>Antithrombin III (ATIII) deficiency</td>
<td>Major surgery</td>
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<td>High levels of homocysteine as seen in methylene tetrahydrofolate reductase deficiency.</td>
<td>Orthopaedic surgery</td>
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Factor V Leiden and Prothrombin 20210A are less frequent in African and Asian populations.

Factors V Leiden deficiency, (activated Protein C resistance), is due to a point mutation in the factor V molecule which renders it resistant to inactivation by Protein C. It is present in about 5% of Caucasians. The Prothrombin 20210A mutation is found in 1-3% of Caucasians and leads to increased levels of prothrombin.

Deficiency of the anticoagulant Proteins C, S and Antithrombin III, are less common but lead to a physiologic imbalance in coagulation homeostasis and an increase in thrombosis risk. Prevalence of Protein C deficiency in the normal population is 1:200-500, Protein S is seen in about 1:700 and Antithrombin III deficiency in 1:2000-5000.

FVL and Prothrombin 20210A are associated with a lower risk of thrombosis than Protein C, S and ATIII deficiency, with about 0.5% of FVL and Prothrombin 20210A carriers suffering thrombosis annually, compared with 1.3 - 4% annually for carriers of Protein C, S and ATIII deficiency. Rates of thrombosis are considerably higher for patients who are homozygous or compound heterozygous. For example, the homozygous FVL state is associated with an 80 fold increase in relative risk. About half of patients develop thrombosis after an initiating event e.g. recent surgery, and although thrombosis at a younger age may be a clue to the presence of thrombophilia, most patients have their first VTE in adult life. The contraceptive pill and hormone replacement therapy are associated with a risk of thrombosis, which is further increased in the presence of inherited thrombophilia, again being higher for Protein C and S deficiency compared with FVL (4% vs. 0.7% VTE/yr).

Recurrent thrombosis is more frequent in patients with Protein C and S deficiency, with a relative risk of 2.5.

While carriers of FVL and Prothrombin 20210A mutations are at lower risk: relative risk 1.3 and 1.4 respectively. As for primary thrombosis, recurrence is much more frequent in homozygotes and compound heterozygotes.

Screening

The current Medicare Australia re-imbursement arrangements do not allow mass screening for inherited thrombophilia. A rebate is available for patients with a history of VTE. If there is a known defect in a relative, a rebate is available for testing for that specific abnormality. A family history of thrombosis is not sufficient, the patient must have had a clot to be eligible or have a family member with a documented abnormality.

Therapy options

General guidelines for treatment can be given, but risk/benefit analysis should be undertaken for each patient.
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**Prophylaxis**

Primary prophylaxis for individuals with thrombophilia is generally only recommended at times of increased risk, e.g. prior to surgery. Peri-operative patients with FVL and Prothrombin 20210A mutations, are at relatively low risk and routine (short duration) Low Molecular Weight Heparin (LMWH) prophylaxis can be used. The risk period can be longer in patients with Protein C,S and ATIII deficiency and prophylaxis with LMWH may be justified for 2 – 4 weeks post-operatively. OCP and HRT are relatively contraindicated in women with Protein C, S and ATIII deficiency.

FVL is of less importance although levonorgestrel pills may be preferable.

**Treatment**

A risk adapted assessment is appropriate when making recommendations for treatment duration (see Table 2 below). For the most prevalent types of inherited thrombophilia the risk of recurrent thrombosis is only slightly greater than “normal”. Patients with thrombosis at high risk sites e.g. cerebral venous or portal vein thrombosis may require more prolonged anticoagulation.

**Travel related VTE**

(Economy Class Syndrome)

In recent years, the risk of VTE associated with airline travel, has been recognised and the term Economy Class Syndrome coined. The phenomenon is neither specific to airline travel nor to those seated in economy class. Rosendaal et al showed a 3.2 fold increase in VTE after long haul flights, with about 1 event/4656 long haul flights. The risk was increased with increasing flight duration and more flights within a short time frame. Most events occur within the first four days of travel, with risk returning to normal by eight

**Table 2**

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<th>Risk Category</th>
<th>Clinical Features</th>
<th>Treatment</th>
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<tr>
<td>Lowest</td>
<td>Provoked thrombosis</td>
<td>Initial intravenous heparin or sub cutaneous LMWH Vitamin K antagonists for 3-6 months</td>
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<tr>
<td>Intermediate</td>
<td>Spontaneous thrombosis</td>
<td>Initial intravenous heparin or sub cutaneous LMWH Vitamin K antagonists for up to 12 months</td>
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<tr>
<td>Highest</td>
<td>Recurrent spontaneous VTE, persistent risk factors eg malignancy, Homozygous or compound heterozygous</td>
<td>Initial intravenous heparin or sub cutaneous LMWH Vitamin K antagonists for 12 months to indefinitely</td>
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weeks. Many victims have well-recognised risk factors such as cancer, heart failure, recent surgery, prior stroke, previous VTE. The pathogenesis remains uncertain, but is probably multifactorial. There has been considerable speculation that the physical constraints of the economy cabin and seating may contribute. The crowded configuration leads to prolonged periods of immobility and the compression of the veins of the lower limbs; it is not surprising that higher rates of thrombosis have been suggested in obese, tall and short passengers. A systematic review of the literature by Philbrick et al. showed no evidence of efficacy for aspirin, a trend for activity of LMWH in one study and a significant advantage for graduated compression stockings. They concluded that travellers with one or more risk factors should consider compression stockings and/or LMWH for flights longer than 6 hrs. General recommendations to avoid immobilisation, dehydration and excessive alcohol intake are prudent. An approach to risk profiling and prophylaxis for airline travel is presented in Table 3.

Acknowledgements
1 Young N, Gerson S and High K. Clinical Haematology. 2006
Anticoagulation Europe – http://www.anticoagulationeurope.org

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