normal. The rare autosomal recessive Type 3 disease is a severe disorder.

Management of von Willebrand disease

At present, two main options are available for the management of patients with von Willebrand disease: DDAVP and blood products containing VWF. In addition, tranexamic acid, an anti-fibrinolytic agent, can be used alone in the management of epistaxis and menorrhagia and it is used in combination with DDAVP- or VWF-containing concentrates to cover dental extractions and surgery.

DDAVP causes VWF to be released from endothelial stores. The mechanism for the rise in factor VIII was thought to be due to its consequent stabilisation in plasma. However, the use of DDAVP in type 2N disease indicates that it must also release factor VIII from a storage pool. It is often effective in type 1 disease where increasing levels 2-5 fold is sufficient for haemostasis. It is of no use in type 3 disease. In types 2A and 2M, increasing the levels of the abnormal VWF has a variable effect. DDAVP therapy is controversial in type 2B disease as the release of the abnormal VWF may induce platelet agglutination and thrombocytopenia. If DDAVP cannot be used or is ineffective, a plasma-derived concentrate must be used.

Further reading

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Evidence-based management of deep vein thrombosis and pulmonary embolus

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Clin Med JRCPL 2001;**1**:438–41

Diagnosis of deep vein thrombosis[1,2]

Deep vein thrombosis (DVT) most commonly arises in the leg. The diagnosis is designated distal when thrombus is confined to the calf, and proximal when the thrombus extends into the popliteal, femoral or iliac veins. Recent studies indicate that DVT is present in fewer than one in four ambulant outpatients presenting with symptoms or signs suggestive of this diagnosis. Pulmonary embolus (PE) is present in at least 50% of patients presenting with DVT, indicating that PE and DVT are clinical manifestations of a single pathological process, venous thromboembolism (VTE). However, at presentation only one in five patients with VTE has symptoms due to PE.

The clinical assessment of symptoms and signs can do no more than raise a suspicion of the diagnosis. Objective diagnostic methods must be used to confirm or exclude DVT and/or PE. There is increasing interest in the negative predictive value of D-dimer tests, which can be used to limit the use of radiology. D-dimer is a fibrin degradation product indicative of *in vivo* thrombin activity. Rapid enzyme-linked immunosorbent assays (ELISA) and automated latex agglutination methods are both quick and sensitive. D-dimer tests should be used in conjunction with pre-test clinical probability scoring because the negative predictive value depends not only on the sensitivity and specificity of the test but also on the prevalence of VTE. Thus, a patient with a negative D-dimer result but a moderate pre-test clinical probability score (see Table 1) still has about a one in 50 risk of VTE, whereas a patient with a high pre-test clinical probability score has a one in five risk of VTE even with a negative D-dimer result[3].

Initial therapy: anticoagulation

Anticoagulation is standard therapy for patients with VTE who are clinically stable (other treatment options are shown in Table 2), except patients in whom anticoagulation is contraindicated. Insertion of a vena caval filter may be more appropriate. Some patients are haemodynamically unstable and may benefit from initial thrombolytic therapy before starting anticoagulation.

Unfractionated heparin

Unfractionated heparin (UFH) should be given either as a continuous intravenous infusion or by twice daily subcutaneous injection at a dose sufficient to prolong the activated partial thromboplastin time ratio to 1.5–2.5 times normal (level Ia). (The levels of evidence are according to the US Agency for Health Care Policy and Research, summarised in the British Committee for Standards in Haematology (BCSH) guidelines on oral anticoagulation[4]). Weight-based dosing schedules have been developed for both intravenous and subcutaneous therapy. Treatment with heparin should continue for at least five days (level Ib) and until the international normalised ratio (INR) is therapeutic. For patients with large thromboses heparin may be administered for a longer period (up to 10 days).

UFH should be reserved for the small number of patients who require emergency invasive procedures when it is useful to be able to 'turn on and off' the anticoagulant effect at will. This is not possible with once daily administration of low molecular weight heparins (LMWHs). Furthermore, the anticoagulant effect of UFH can be

Table 1. Pre-test clinical probability scoring system (from Wells *et al.*, *Lancet* 1997;**350**:1795).

Criteria	Score
Active cancer	1
Paralysis, plaster cast	1
Bed rest >3 days, surgery within 4 weeks	1
Tenderness along veins	1
Entire leg swollen	1
Calf swollen >3 cm	1
Pitting oedema	1
Collateral veins	1
Alternative diagnosis likely	–2
Pre-test probability score:	
low	0
moderate	1 or 2
high	3

completely reversed with protamine sulphate whereas this is not possible with LMWH.

Low molecular weight heparin

Treatment with LMWH results in a lower risk of thrombotic and haemorrhagic complications and a lower mortality than treatment with UFH[5] (level Ia). Most LMWH studies to date have selected patients with DVT. More recently, randomised studies of patients with PE have extended the treatment indications to include patients with submassive PE, thus making this class of heparin the treatment of choice for most patients with VTE.

Two multicentre clinical trials have confirmed the feasibility, efficacy and safety of outpatient treatment of DVT[6,7] (level Ib). The possibility of extending home therapy to patients with symptomatic PE is supported by a recent study[8] and also the ability to identify low risk patients suitable for home treatment[9]. Factors associated with death, recurrence or haemorrhage are cancer, heart failure, previous DVT, hypoxia, hypotension and the presence of DVT on ultrasound[9]. As outpatient therapy is now appropriate for most patients with DVT, it is likely to be extended to low risk patients with PE.

Warfarin

Warfarin can be commenced on day 1 in conjunction with heparin in most patients with VTE. A standard protocol for the commencement of oral anticoagulant treatment is recommended and treatment should be monitored with the INR[4]. A target INR of 2.5 gives the lowest VTE recurrence and bleeding rates (level Ib)[4].

Duration of anticoagulation

Opinion varies as to the optimal duration of therapy. After a first episode of VTE the recommendations range from three months when there is a reversible transient risk factor, to two years in young patients with idiopathic VTE. The BCSH considers the distinction between proximal and calf vein thrombus (CVT) as an important factor in decision analysis. It makes the following recommendations for duration of treatment (level Ib)[4]:

- patients with a first episode of proximal DVT or PE: six months
- idiopathic CVT: three months
- postoperative calf vein clots: six weeks.

Calf vein thrombi: to treat or not to treat?

When confined to the calf, DVT is associated with a low risk of clinically important PE. Untreated, or inadequately treated, CVT may extend proximally in 5–30% of patients[10]. Symptomatic CVT that extend usually do so in the first five days after symptoms develop, with extension or recurrence rare after the first week[11]. Treatment with heparin alone for five days does not eliminate the risk of extension but simply delays this complication until after anticoagulation is stopped. Treatment of CVT with anticoagulation for six weeks to three months virtually eliminates the risk of proximal extension and PE. As an alternative to anticoagulant treatment, small CVT can be monitored with serial non-invasive tests (eg compression ultrasound examination) and treated as for a proximal thrombus if extension occurs.

Influence of thrombophilia testing on management decisions

The ability to 'explain' thrombosis has led to the increasing use of thrombophilia testing in the assessment of

Table 2. Treatment options for venous thromboembolism (VTE).

Treatment		Advantages	Disadvantages
Thrombolysis	DVT	Venographic evidence of preservation of valve function	Four-fold higher risk of bleeding Incidence of venous hypertension not shown to be reduced
	PE	Early improvement of haemodynamic measurements May be life-saving in selected patients	No evidence of improved long-term benefit
Caval filters	VTE	Reduced symptomatic PE	Increased incidence of recurrent DVT Anticoagulation required to reduce risk of recurrence
Thrombectomy	DVT		No evidence of benefit
	PE	May be life-saving in selected patients	Postoperative risk of PE: 70% Anticoagulation or filter required postoperatively Prior thrombolysis is major risk factor for bleeding

DVT = deep vein thrombosis; PE = pulmonary embolus.

patients with VTE[12]. However, studies confirming a beneficial outcome from testing are lacking. Thrombophilia testing does not predict likelihood of heparin resistance, heparin failure or warfarin-induced skin necrosis[13]. At present, there is no evidence that recurrence on treatment with warfarin with a target INR of 2.5 is greater in patients with thrombophilia than in those without[13]. There is no conclusive evidence that, in general, patients with heritable thrombophilia are more likely to suffer an earlier recurrence once treatment is stopped[14]. Possible exceptions are patients homozygous for the factor V Leiden mutation and patients with very high factor VIII levels. Further management studies are required to determine whether the benefit:risk ratio of extended anticoagulant therapy is favourable in these small subgroups of patients.

In contrast to heritable thrombophilia, prospective data indicate that detection of acquired lupus anticoagulant or anti-cardiolipin in a patient with thrombosis indicates a high risk of future thrombosis[15]. However, even in this situation a conventional six-month period of anticoagulation after a first event has recently been recommended by the BCSH as only level IV evidence is available[16].

Prevention of chronic venous hypertension

The incidence of postthrombotic syndrome (PTS) due to chronic venous insufficiency has been decreasing in recent years, suggesting that more efficient treatment of VTE and the prevention of recurrent DVT can have a positive impact on this complication. A randomised study of calf length, made-to-measure, elastic compression stockings worn for two years compared with no stockings in patients with a first episode of proximal DVT demonstrated a significant reduction in PTS[17].

Key Points

- **Deep venous thrombosis is present in less than one in four ambulant outpatients presenting with symptoms or signs suggestive of this diagnosis**
- **The majority of patients can be managed with non-invasive diagnostic tests**
- **The negative predictive value of a test depends not only on the sensitivity and specificity of the test but also on the prevalence of the disease: for example, a patient with a high pre-test clinical probability score has a one in five risk of venous thromboembolism (VTE) even with a negative D-dimer result**
- **Oral anticoagulation alone is insufficient for the initial treatment of VTE**
- **Treatment with heparin should continue for at least five days**
- **Low molecular weight heparin is the treatment of choice for most patients with VTE**
- **Outpatient therapy is now appropriate for most patients with DVT**
- **A standard protocol for the commencement of oral anticoagulant treatment is recommended and a target international normalised ratio of 2.5 is recommended for most patients with VTE**
- **The relative risks and benefits of thrombolysis are uncertain and should be reserved for life-threatening VTE**
- **The value of thrombophilia testing has not been evaluated in management studies. Where data are available there is little, if any, indication of a worse prognosis in patients with laboratory evidence of thrombophilia**
- **Systematic audit and review of adverse outcomes is critical in order to determine whether new methods and practices have been implemented correctly and to ensure that acceptable standards of care have been achieved or maintained**

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Sickle cell disease

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Clin Med JRCPL 2001;**1**:441–6

Sickle cell disease (SCD) affects 12,000 individuals in the UK[1] and imposes a severe health burden on many. Frequent crises mean interrupted education and cause employment difficulties. In the third and fourth decades, chronic end-organ damage may predominate. Median life expectancy is reduced to the mid-40s even with optimal care[2].

Although some complications require hospital admission, a wider care model is appropriate involving health and social care agencies across acute and community boundaries. Full involvement of patients and carers in developing services is critical.

The term 'SCD' includes:

- homozygosity for the β^S gene, resulting in sickle cell anaemia (HbSS), usually the most severe form of SCD, and
- compound heterozygosity with other abnormal β genes, resulting in HbSC, Sβ thalassaemia, SD^{Punjab}, SE and SO^{Arab}, and some rarer phenotypes such as SLepore.

Abnormal β globin chains cause deranged conformation of haemoglobin molecules producing distorted erythrocytes, some sickle-shaped. Erythrocyte survival is shortened, rheology deranged with disturbed interaction between erythrocytes and vascular endothelium, and dysregulation of vascular reactivity. Small and large vessel occlusions result. Lack of significant morbidity for HbAS heterozygotes (sickle cell trait) and their relative protection against death from malaria in childhood are well documented. Current theories of pathogenesis are reviewed by Steinberg[3] (also at www.asheducationbook.org/current.shtml).

Screening

Up to 40% of African, Afro-Caribbean, Asian, South-East Asian and Mediterranean populations are carriers. Only in people of strictly Northern European origin are carriers rare.

Key Points

Sickle cell disease affects people from a wide range of ethnic origins. There are about 12,000 affected individuals in the UK, many of whom have major chronic health problems

Antenatal screening and counselling give carrier parents informed choice regarding their options in pregnancy. Neonatal screening identifies affected babies and reduces their risks

Pneumococcal infection has a high mortality, especially in infants. This can be reduced by regular penicillin prophylaxis and immunisation

Vaso-occlusive painful crises, often severe, dominate the clinical course but there are many additional acute and long-term complications, some life-threatening

Most pain episodes are managed at home. Although hospital analgesia has usually been with parenteral opiates, there is evidence in children that oral morphine is as effective

Management requires a comprehensive long-term multidisciplinary approach with full involvement of the patient and carers

Treatment with oral hydroxyurea and allogeneic bone marrow transplantation can change the course of the disease. These options should be discussed fully with potentially suitable, severely affected patients and families