Coagulation factor concentrates

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Introduction
Coagulation factor concentrates are essential for the treatment of patients with haemophilia. Haemophilia A (factor VIII deficiency) and haemophilia B (factor IX deficiency), in their severe forms, are life-threatening and crippling disorders. Effective replacement therapy improves both the quality of life and life expectancy. Major developments in the purification of products have taken place over the last few years, stimulated chiefly by the need to prevent viral transmission. But haemophilia care is expensive; the cost of clotting factor concentrates is a very significant item on the drugs bill of many hospitals with Haemophilia Centres, and must feature largely in the current debate about the best and most appropriate treatment.

Factor VIII
Factor VIII concentrates in general use are listed in Table 1.

Cryoprecipitate
The discovery, in 1959, that the cold insoluble precipitate (cryoprecipitate) formed when frozen plasma is thawed at 4°C contained most of the plasma factor VIII was a major advance in haemophilia care. For a number of years cryoprecipitate provided a safe and effective treatment for haemophilia A and von Willebrand's disease. The development of safer factor VIII concentrates in recent years has meant that cryoprecipitate is no

Table 1: *Factor VIII concentrates*

Type	Product (Manufacturer)
Low purity	Cryoprecipitate
Intermediate purity	NHS 8Y (BPL) Profilate SD (Alpha) Haemate P (Hoechst)
High purity	
Monoclonally purified	Monoclate P (Armour) NHS 8SM (BPL)
Chromatography purified	None currently licensed

longer recommended for these conditions, although it is still sometimes used as a source of fibrinogen, and to shorten the bleeding time in uraemia and platelet storage pool disease

Intermediate purity products
In the 1970s the availability of lyophilized factor VIII concentrates that could be stored in a domestic refrigerator revolutionised the treatment of haemophilia and made home treatment possible. The use of factor VIII in the United Kingdom (UK) rose, from fewer than 10 million units in 1970 to more than 100 million units in 1990. But producing batches of concentrate on this scale required the use of pooled plasma from thousands of donations, so that viral contamination was inevitable. By the late 1970s the dangers of hepatitis and chronic liver disease were becoming apparent. Most previously untreated patients who received the concentrates showed evidence of non-A non-B hepatitis. Attempts to reduce the viral transmission became more urgent after the realisation that HIV could also be transmitted by blood products. By 1985 all factor VIII concentrates used in the UK were heat treated for safety. Most of the factor VIII concentrate now used is in the form of intermediate purity products.

High purity concentrates

High purity concentrates of coagulation factors are produced either by binding to immobilised monoclonal antibodies or by chromatography. Monoclonally purified products are significantly more expensive than intermediate purity concentrates.

Recombinant factor VIII

In 1984 the large and complex factor VIII gene was successfully cloned. Over the next few years, this development led to the production of recombinant factor VIII using cultured mammalian cells. The clinical response to recombinant factor VIII is comparable to that produced by plasma-derived factor VIII. The recombinant product is formulated in pasteurised human albumin (for stability) and is free from viral contamination. There is concern that it may provoke factor VIII antibody (inhibitor) responses. In one study', 5 of 20 previously untreated children, and one child who had previously received only fresh frozen plasma, developed inhibitors. With one exception the concentration of inhibitors was low and treatment could be continued, but further studies are needed to assess the significance of these early findings.

Factor IX

Until recently factor IX concentrates have also contained other vitamin K-dependent clotting factors, and have been known as prothrombin complex concentrates (PCCs). NHS factor IX concentrate contains factors II and X but not factor VII. Thrombotic complications can occur when high doses of prothrombin complex concentrates are used to cover major operations, so that concentrates containing only factor IX have now been produced and are likely to become standard in the treatment of haemophilia B.

Factor IX concentrate has been used to treat life-threatening bleeding in patients overdosed with coumarin anticoagulants, but this practice carries the risk of viral transmission, and the absence of factor VII is a significant shortcoming; large doses may also be thrombogenic. The use of fresh frozen plasma is to be preferred.

von Willebrand's disease

von Willebrand's disease varies in severity according to the levels of factor VIII activity and von Willebrand factor; in some patients it produces few clinical problems. If treatment is required, the use of blood products can often be avoided by giving desmopressin or the anti fibrinolytic agent tranexamic acid. Not all factor VIII concentrates contain sufficient von Willebrand's factor to be effective; Haemate P (Hoechst) and NHS 8Y (BPL) are recommended. Cryoprecipitate is occasionally required in those who fail to respond, and remains very effective.

Haemophilia A patients with inhibitors

Approximately 10% of haemophilia A patients develop antibodies to factor VIII which produce resistance to treatment. A low concentration of inhibitor may permit continued treatment with factor VIII concentrates, but at a higher dose than usual. If the patient's plasma has less antibody activity against porcine factor VIII than against human factor VIII, then the purified porcine factor VIII concentrate Hyate C (Porton) can be used, with the advantage that the rise in plasma factor VIII concentration directly monitors response. Use of porcine factor VIII sometimes leads to a fall in platelet count, but significant thrombocytopenia is rare.

Several products can be used to 'by-pass' factor VIII in this situation. These include prothrombin complex concentrates, such as the NHS factor IX concentrate 9A (BPL), activated prothrombin complex concentrates, such as FEIBA (Factor Eight Inhibitor By-passing Activity) (Immuno), and, more recently, human recombinant activated factor VII (rFVIIa) (Novo), which is now the subject of a multicentre international trial.

Which concentrate?

If blood products can be avoided by the use of alternatives, such as desmopressin in patients with mild haemophilia A and some with von Willebrand's disease, so much the better. All potential recipients of multi-donor clotting factor concentrates should be immunised against hepatitis B.

Table 2: *Cost of clotting factor concentrates*

Product	Cost per unit (see footnote)	Example cost of single treatment (1,000 units)	Example cost of one year's treatment (42,000 units)
	pence	£	£
NHS SY(NPL)	19	190	79S0
Profilate SD (Alpha)	22	220	9240
NHS SSM (BPL)	37	370	15540
Monoelate P (Armour)	3S.7	387	16254
NHS Factor IX (BPL)	25	250	10500

Note: Costs given are indicative only. They may vary with local contracts and special arrangements.

The safety of a product with regard to viral transmission can be assessed only by long-term follow-up of previously untreated patients. Because of the difficulties inherent in such studies the evidence is often inconclusive. However, it is widely felt that the risk of HIV and non-A non-B hepatitis is minimal with the current generation of products. The present debate centres on the indications for the use of high purity products in haemophilia A and the inherent economic implications.

Intermediate purity products may adversely affect immune function in recipients, independent of any alterations due to infection with HIV. The clinical significance of this finding is unclear, but it has led to suggestions that high purity products, such as Monoelate P (Armour) or 8SM (BPL), should be preferred in those at risk. This category would include: patients who are HIV-positive; patients who need a high dose to cover, for example, major surgery; and previously untreated patients, especially children. Evidence is emerging that the use of high purity products in HIV -positive patients is accompanied by stabilisation of T4 lymphocyte counts, suggesting slower disease progressiorr'. If it were not for their higher cost (see Table 2),

such products would undoubtedly be far more widely used. Like recombinant factor VIII, high purity products may promote the development of inhibitors in some patients+'.

Treatment of individual baemorrhagic events

Treatment may need to be given daily or twice daily over a period of days. However, a single *early* treatment may arrest bleeding into a joint or muscle, which is by far the commonest problem. Table 3 gives a guide to factor VIII dosage.

Table 3: *Factor VIII doses according to clinical circumstances*

Event	Required plasma level	Dose
	units/dl	units/kg
Haematoma requiring treatment, haemarthrosis	15-20	10
Severe haemarthrosis, muscle bleeding, minor surgery	30-40	15-20
Major surgery, intracranial haemorrhage	SO-IOO	50

Prophylactic use of coagulation factor concentrates

Only a low level of either factor VIII or factor IX is required to prevent bleeding - patients with moderate haemophilia (factor levels of 2-5 units/dl) have few bleeds. There is increased interest in the use of factor VIII and IX concentrates to prevent bleeding, particularly in children and teenagers. Factor VIII has a half life of 12 hours in the circulation (factor IX, 18 hours), but alternate day treatment with doses as small as 500-1,000 units greatly decreases the incidence of bleeding. Long-term prophylaxis not only increases the quality of life, but can prevent the progressive joint destruction caused by repeated bleeds, and the crippling disability seen in older generations of haemophiliac patients. In the short term, prophylaxis is often used to prevent recurrent

bleeding in a particular 'target' joint or to cover post-operative mobilisation and rehabilitation.

Conclusion

The history of blood product use in haemophilia should convince us that only the safest possible treatment is permissible and that economic factors cannot be the only, or even the most important, consideration. Haemophilia patients require replacement only of the deficient coagulation factor, not an infusion of foreign protein containing the deficient factor in trace amounts. The relative impurity of most preparations is highlighted by the fact that 2.5 kg of recombinant factor VIII would meet the world's annual need for factor VIII - and it is estimated that 65% of the world's haemophiliacs receive no treatment. The demand for high purity concentrates and recombinant products will continue to grow, not least from the patients themselves. Recent evidence suggesting a beneficial effect in HIV-positive patients will undoubtedly accelerate the change to high purity products for all haemophiliacs.

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Practical problems in immunosuppression: Heart and heart-l u ng transplants

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Introduction

The need for more effective immunosuppression has rarely been so apparent in transplantation as following the early arresting clinical experiments in human heart and heart-lung transplantation of the late 1960s. The clinical effectiveness of heart - and subsequently heart-lung - transplantation owes a great deal to the introduction of cyclosporin. Triple immunosuppression, using azathioprine, oral corticosteroids and cyc1osporin, is widely used, at least during the first 6 to 12 months after transplantation. Beyond that time efforts should be made to reduce and, if possible, to withdraw steroids in order to avoid their long-term side-effects. A few centres still prefer, where possible, to avoid steroids altogether. The regimens described below are used in our own unit.

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