From the Acting Chief Medical Officer
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Health, Social Services and Public Safety
An Roinn
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www.dhsspsni.gov.uk

HSS(MD) 25/2006

To:
Chief Executives, Health & Social Services Boards/Trusts
Medical Directors, Health & Social Services Trusts
Directors of Public Health, Health & Social Services Boards
Chief Executive, NI Blood Transfusion Service

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Your Ref:
Our Ref: HSS(MD) 25/2006
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Dear Colleague

USE OF IMPORTED FRESH FROZEN PLASMA (FFP)

1. This circular is to inform all relevant clinical staff of new advice from the Advisory Committee on Microbiological Safety of Blood and Tissues and Organs (MSBTO) on the use of imported FFP.

2. FFP has been available since 1941 and is used primarily in cases of excessive bleeding or to prevent bleeding in those patients with abnormal coagulation tests undergoing an invasive procedure.

A IMPORTED FFP TREATED WITH METHYLENE BLUE FOR THE TREATMENT OF CHILDREN

3. Imported FFP is treated with Methylene Blue (MB) as a pathogen reduction step and is currently recommended for use in all patients who have not been exposed to BSE in the food chain ie patients born after 31st December 1995.

4. **This will now be extended to all children up to (but not including) 16 years of age by the end of 2005.** The MBFFP for older children will be provided by the NI Blood Transfusion Service and will be identical in specification to that currently provided for younger children.

5. This development is a precaution against the theoretical possibility of vCJD transmission in humans through blood and blood components – in line with recommendations made by the Advisory Committee on Microbiological Safety of Blood and Tissues and Organs (MSBTO).

6. The use of this particular component should be restricted to the age group defined above to ensure sufficiency of supply.

B SOLVENT DETERGENT TREATED FFP FOR ADULT PATIENTS WITH THROMBOTIC THROMBOCYTOPENIC PURPURA (TTP)

7. Patients with TTP have high donor exposure and should be treated with non-UK, virus-treated plasma. Because there is limited experience of treating TTP with MBFFP, it is recommended that Solvent Detergent treated FFP (SDFFP) is used.

8. SDFFP will also be available through the Northern Ireland Blood Transfusion Service. However, SDFFP is a commercial product and Trusts should budget for the costs associated with its use.

9 Other non-UK, virus-treated FFP products may be licensed in the future, and may also be suitable for use in the treatment of TTP.

Additional Information

10. Further information on the research and clinical background to this circular can be found in the Appendices:

Appendix 1 Background information on vCJD and use of FFP

Appendix 2 Recommendations for the paediatric use of FFP.

Action for Chief Executives of Trusts

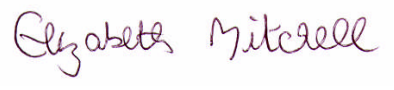
11. This circular should be brought to the attention of appropriate clinical staff and transfusion committees.

12. Trusts should comply with the recommendations for the use of MBFFP up to (but not including) age 16.

13. Trusts should comply with the recommendations for the use of SDFFP for adult TTP patients.

14. Prescribing of FFP should be clinically appropriate. Please see British Committee for Standards in Haematology guidelines for the use of fresh frozen plasma, cryoprecipitate and cryosupernatant at www.bcshguidelines.co.uk.and the recommendations for paediatric use of FFP in Appendix 2 of this letter.

Yours sincerely



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Chief Medical Officer (Acting)

This letter is available at www.dhsspsni.gov.uk and also on the DHSSPS Extranet which can be accessed directly at http://extranet.dhsspsni.gov.uk or by going through the HPSS Web at http://www.n-i.nhs.uk and clicking on DHSSPS.

Appendix 1

Background Information on vCJD and use of Fresh Frozen Plasma.

In 1996 the first cases of vCJD, a new and rapidly progressive spongiform encephalopathy, were described. At that time it was noted to be unique to the UK and followed the epidemic of bovine spongiform encephalopathy (BSE) which affected 200,000 cattle. Unlike the classical CJD prion, that for vCJD shows affinity for lymphoid tissue and this evidence, along with other studies, resulted in the universal leucocyte depletion of blood components in the UK, completed in November 1999. Analysis on the distribution of normal cellular prion (PrP^{C}) has shown that plasma is a major source (68%).

The risk of vCJD transmission by blood or blood products is currently unquantifiable, although there have been two cases of possible transmission by non-leucodepleted red cells.

The UK Departments of Health issued a recommendation that FFP for neonates and children born after 31 December 1995 be sourced from areas where BSE and vCJD are not endemic. (The rationale for this is that children living in the UK born since this date have benefited from specific actions designed to eliminate BSE from the food chain (Specified Bovine Materials Ban and the Over Thirty Months rule). The effect of these bans has reduced the risk of such children contracting vCJD from their diet to levels which may well be lower than the risk of them contracting vCJD from transfused blood donated by UK donors who, though showing no signs of vCJD, may be incubating it. This position will remain until there are more accurate data indicating the scale of the vCJD epidemic in UK adults.)

Safety of Imported FFP Treated with Methylene Blue or Solvent Detergent

Sourcing materials for FFP production from donors residing in areas where BSE and vCJD have never been endemic may introduce other risks. Although the non-UK donors of the imported FFP are unremunerated volunteers from community blood banks and extensively tested to FDA standards, an additional virus inactivation step has been introduced. The risk of transfusion-transmissible diseases caused by known organisms can be effectively eliminated from plasma by virus inactivation procedures eg treatment with methylene blue. Although these virus inactivation procedures do not inactivate prions, by applying them to imported plasma the overall risks of transmitting infection, including vCJD, from treated products will be mitigated. Therefore the imported FFP for children will have undergone a viral inactivation step involving methylene blue.

TTP is a rare condition characterised by thromobcytopenia, microangiopathic haemolytic anaemia, fluctuating neurological signs, renal impairment and fever. TTP is a clinical diagnosis. The underlying pathogenesis of TTP is the formation of platelet microvascular thrombi. This is mediated by ultra-large von Willebrand factor multimers (ULVWF). These are normally degraded by an enzyme called metalloproteinase. Deficiency of this protease is associated with TTP. The main stay of treatment of acute TTP is daily plasma exchange.

All forms of FFP contain the missing enzyme but FFP lacking ULVWF eg SDFFP or cryosupernatant may be preferred for the management of TTP. MBFFP is also efficacious but may require more plasma exchange procedures.

SDFFP from different manufacturers may differ in detail and have different efficacy and safety. The reduced activity of protein S has been associated with the development of venous thromboembolism (VTE). Eight episodes in seven of 68 patients with TTP receiving plasma exchange were reported by Yarranton et al (2003). Jain et al (2003) have reported an association of SDFFP with thromboembolic complications in patients undergoing liver transplantation. Concern has been expressed regarding possible transmission of non-lipid-coated viruses by PRFFP. In the USA, batches have been withdrawn because of possible parvovirus B19 transmission. Suppliers now specify levels of HAV and B19 antibodies in the preparation, and may also define a cut off for B19 genomes. Studies of patients treated with SDFFP compared with FFP have not revealed excessive transmissions of non-lipid-coated viruses, but the number of patients studied is still small.

Appendix 2

Recommendations for the Paediatric Use of FFP:

The British Committee for Standards in Haematology Blood Transfusion Taskforce (2004) Guidelines for the use of FFP, cryoprecipitate and cryosupernatant *British Journal of Haematology* ***2004; 126, 11-28*** list the following indications for the use of FFP:

1. In HDN (haemorrhagic disease of the newborn) with bleeding; FFP 10-20ml/kg, ***and*** iv vitamin K (Grade C recommendation, level IV evidence).

2. Neonates with coagulopathy and risk of bleeding who are about to have an invasive procedure; FFP 15ml/kg, ***and*** vitamin K (Grade C recommendation, level IV evidence). Shortening of clotting times is unpredictable; check <u>after</u> FFP.

3. Routine FFP to prevent PVH (peri-ventricular haemorrhage) in pre-term infants is ***not*** indicated (Grade A recommendation, level IIb evidence).

4. FFP is ***not*** indicated in polycythaemia in infancy.

5. There are no data to support FFP with low titre anti-T for neonates with T-activation.