NATIONAL BLOOD SERVICE

SAFER PLASMA IN COMPONENTS (SPIC)

Paper for MSBT on options for future provision of clinical fresh frozen plasma

1. Background

Following the development of techniques for pathogen inactivation of FFP in the early/mid 1990's, UK Transfusion Services and MSBT have at various points considered options for the most appropriate provision of FFP.

In 1998 MSBT instructed UKTS to provide a virus inactivated FFP as an option for clinicians alongside the standard product (policy confirmed in 1999). Pooled solvent detergent FFP from European sources was considered, but rejected because of concerns regarding vCJD and unknown viruses from a pooled product. NBS and SNBTS then focussed on provision of single unit methylene blue treated FFP (MBFFP) as dictated by user demand. SNBTS has implemented this for neonates. It was agreed that for NBS, implementation would follow universal leucocyte depletion, HCV genome testing and the millennium.

In February 2000, at a special meeting of MSBT, the potential for FFP (and other blood components) to transmit vCJD was reviewed. Following this, NBS initiated the Safer Plasma in Components (SPIC) project. This was initially established to oversee the implementation of MBFFP, but broadened its remit to conduct an option appraisal of the medical/scientific and operational risks and benefits of a number of FFP options. This would take into account different possible combinations of plasma source, testing strategy, and pathogen inactivation process.

Following recent discussions with DoH, it was agreed that the NBS option appraisal would not specifically assess vCJD risk, but that this would be modelled by the DoH Economic and Operational Research group.

This paper will be combined with the EOR findings for presentation to MSBT.

2. FFP Options in context

Before discussing the overall benefit of any alternatives to standard UK FFP, the following critical points should be recognised:-

- Virtually all FFP recipients receive other blood components. Any new developments regarding FFP should therefore be considered as only a small part of an overall strategy for minimising exposure to donor blood components.
- Implementation of such a strategy falls mostly outside the areas of responsibility of the UK Transfusion Services, and an NHS-wide approach is needed. This must be underpinned by resources at hospital level, to facilitate availability of a wider range of alternatives to donor blood.
- Most audits of FFP usage indicate that many patients receive FFP for doubtful reasons, or in frank contravention of national guidelines. In allocating resources, continuing education/monitoring of FFP usage may yield greater returns than liberal prescription of a 'safer' alternative. A national audit of FFP usage is planned.

- Much FFP usage is for conditions that are not associated with long survival e.g. chronic liver disease, although no precise survival data are available. NBS is beginning a study of the epidemiology and survival of recipients of blood components, including FFP.
- Neonates are a particularly important exception to the above generalisation, being both heavily transfused and with a long post-transfusion life span (SNBTS data). In addition, this group (also older babies and children born after 1996) should have had minimal exposure to BSE through foodstuffs. A more protective strategy for babies and children would be a logical alternative for all components.
- It is recognised that recommendations in this regard should ideally be taken forward in conjunction with other UK Transfusion Services, and should as far as possible have the approval of relevant Standing Advisory Committees and the Joint Executive Liaison Committee of the UKTS Guidelines for Transfusion Services.

3. Option appraisal for FFP

This was designed to identify any options which might pose unacceptable medical or operational risks. Cryoprecipitate and cryo-supernatant plasma were not considered.

Options were identified as follows:-

1. UK FFP to current specification i.e. new donors excluded, HCV genome tested
2. UK FFP, quarantined for 90 days, with donor retest
3. UK FFP, MB treated. Variations on this include an MB removal step, and whether the MB treatment is performed in-house or by an outside contractor
4. US plasma, MB treated –either in-house or by an outside contractor
5. Imported plasma –either from Europe or US, with either HCV genome testing only, or full genome testing including HBV and HIV, but without a virus inactivation step
6. UK plasma, photochemical inactivated by psoralen S59 and ultraviolet light
7. US plasma, S59 treated
8. Pooled solvent detergent (SD) FFP from European sources
9. Pooled SDFFP from US sources

Medical and operational variables relevant to FFP provision were identified e.g. loss of coagulation factors, toxicity, lead-time, security of supply. As some variables were clearly more important than others, a weighting factor was assigned to each variable. Each of the above FFP options was then scored against each variable taking the impact factor into account. A full report on the scoring of options is available.

4. Results of 'Long List' Option Appraisal

The following were eliminated from further consideration as follows:-

- Quarantining for 90 days until donor is retested

This option avoids the use of chemicals and loss of coagulation factors. However, this strategy captures only window period seroconverting donors for viruses for which we currently test. HCV genome testing has already closed the window from 80 to 10-15 days. Although quarantining would detect HBV seroconvertors, there would be no impact on viral mutants or low level carriers. This is particularly relevant for hepatitis B, in the absence of anti-hepatitis B core testing. For the future, there would

be no prevention of transmission of new viruses for which we may initially have no test.

Operational concerns are logistics, IT, a great increase in plasma wastage and a possible need to expand apheresis plasma collections. This would seem particularly inappropriate for UK, given that >80% of plasma is currently discarded. The overall 'added value' of quarantining over standard FFP in the UK is therefore minimal.

- UK plasma, Methylene Blue treated. No removal of MB

This was eliminated, having shown that Methylene Blue could be successfully removed without detriment to the product. In addition, hospitals have indicated that for neonatal use Methylene Blue removal would be an absolute requirement.

- All single donor and pooled SD plasma options involving European plasma

Recent discussions with DoH have indicated that any options involving European plasma are likely to score unfavourably with regard to possible vCJD risk. This would particularly apply to any pooled options if sourced from populations with a defined vCJD risk. These considerations have led to elimination of all options involving non-UK European plasma.

- N American plasma, HCV NAT only, without a virus inactivation step

Data on virus positivity in N American plasma indicate prevalence of viral markers 4-9 times greater than in UK donors. The additional risk of HIV and HBV transmission without genome testing or virus inactivation was considered unacceptable. HCV risk is largely though not totally prevented by genome testing.

- S59 FFP

This option involves psoralen (S59) photoinactivation of single plasma units and could be installed in Blood Centres. NBS has been involved in a trial of this methodology for platelet concentrates. However, an operational system for plasma will not be available until end 2002, at the earliest.

5. The 'short list' therefore consists of the following broad options:-

Options for UK plasma – MB treatment of a proportion of FFP

To meet MSBT's earlier recommendation that a virus inactivated FFP be available as an option for clinicians, we have investigated the feasibility of a 'mixed economy' consisting of standard FFP combined with MBFFP production only to the level of user demand.

Results of MBFFP demand questionnaire sent to 44 largest users of FFP, who collectively use >50% of national FFP production (26 replies).

For adult recipients

- Require no MBFFP –12 hospitals
- Require 100% MBFFP – 1 hospital
- Require 5-10% MBFFP, for individual patients – 10 hospitals.

For neonates

- 17 hospitals wish to be supplied with MBFFP for neonates, provided the MB is removed.

It is considered that an in-house system to meet this level of demand could be established in NBS Blood Centres using UK plasma within a period of 3-6 months, subject to availability of plasma suitable for neonates at or near production sites. The additional cost per FFP unit is c£46 (base price c£18), totalling c£1.5m / year extra needed to meet this level of demand.

For larger requirements, the use of an external contractor (e.g. Grifols) is a realistic option, and avoids capital expenditure on building works, and disruption to staff and processes. MB removal is not currently performed by Grifols, but this could be done if required. Costs are equivalent to in-house processing, but the lead-time is longer (9-12 months).

If after consideration of vCJD and viral risks, the UK remains the preferred source of plasma for FFP production, it is recommended that NBS provide MB FFP to meet a predicted demand of 5-10% of adult FFP, combined with a switch to 100% neonatal FFP. For both the adult and neonatal FFP, MB removal is recommended. Central guidance on patient selection for MBFFP would be welcomed.

Options for US plasma

- **Single unit plasma, fully genome tested +/- MB treatment**

Either 'ABRA' apheresis or American Red Cross plasma may be available. American Red Cross plasma is single unit recovered plasma from their volunteer blood donors. This plasma does not currently meet NBS specification in that new donors are included, there is no leucocyte depletion step and no separate neonatal specification. However, viral testing includes markers not tested for in UK, i.e. HIV p24 antigen and genome, anti-Hepatitis B core, to which HBV genome will be added.

Were a move to US plasma deemed desirable, the strategy for preventing viral transmission becomes critical, given the 4-9 fold increased prevalence of viral markers in the North American donor population (either ABRA apheresis or American Red Cross whole blood). The plasma is subjected to extended genome testing by the supplier, but it may be considered undesirable to rely totally on fairly new technology outside NBS control. An additional level of protection would be provided by systematic treatment of this plasma using a virus inactivation step suitable for single units. MB treatment by an outside contractor would be a logical and feasible approach.

The additional cost for either apheresed or recovered plasma, without MB treatment, would be c£28/unit, totalling c£9m / year.

The additional cost for either apheresed or recovered plasma, including MB treatment, would be c£63/unit, totalling c£20m / year.

The estimated lead time (with or without MB treatment) is estimated to be 12-15 months.

- **US Pooled Plasma, Solvent Detergent treated**

This option has recently become a possibility, as the manufacturer Vitex has applied for a UK product licence (the European equivalent, Octaplas, is already licensed). Plasma is sourced from volunteer American Red Cross whole blood collections tested as described above and treated in 500L pools. Because the process does not remove non-lipid coated viruses, parvovirus B19 and HAV genome testing is performed on final pools. A neonatal version will be produced in 2001. New developments not yet available are:- removal of anti- A, B to create a 'universal' FFP (in clinical trial), and a second VI step to eliminate non-lipid coated viruses.

This option has many attractions, given the extensive donor testing, but concerns about transmission of unknown non-lipid coated viruses remain in such a pooled product. Future enhancements to this product may deal with the residual viral concerns, if the vCJD risk is considered acceptable.

Vitex have indicated that they could replace NBS requirements by SDFFP in a few months, but it would be prudent to assume a minimum lead time of 9 months.

The additional unit cost for this product is c£63, but because the unit size is 200mL (300 mL for all single unit options), the annual cost to the NHS could be c£30m.

- **Should a move to US plasma be deemed desirable on precautionary grounds, a single unit option is preferable to a pooled option on grounds of virus risk.**
- **Further exploration of availability of fully genome tested, single unit plasma from ARC and other US sources is ongoing. Should enough plasma be available for all FFP requirements, a decision will have to be taken as to whether this plasma should systematically be MB treated.**
- **Should plasma supply be limited, an intermediate position would be to provide a US sourced product for neonates and children born after 1996. In this case, single unit MB treated FFP is recommended.**
- **Should there be greater availability of SDFFP than single unit plasma, it will have to be decided whether this licensed product is an acceptable alternative for some or all recipients. As before, the single unit product could be targeted towards neonates and children.**

Additional Recommendations

- Any strategy for FFP avoidance should be considered in the context of blood avoidance generally. This is an NHS-wide issue involving user education, audit and other medical strategies to reduce the need for FFP prescription.
- Importation and/or virus inactivation of FFP does not address the question of provision of cryoprecipitate. Most cryoprecipitate is prescribed for replacement of fibrinogen. A virus inactivated fibrinogen concentrate is in development by SNBTS and BPL. It would be helpful to expedite licensing of this option, as this would probably allow cessation of cryoprecipitate production altogether.
- Should minimisation of exposure to UK plasma be deemed important, consideration will have to be given to strategies to reduce the plasma content of platelet and red cell concentrates where possible. This would be the subject of Stage 2 of the SPIC project.

- The field of pathogen inactivation is moving rapidly. Any contracts with suppliers should be kept realistically short, such that better and newer techniques can be considered as they become available.