Joint UKBTS / HPA Professional Advisory Committee ([1]) /Serious Hazards of Transfusion (SHOT)

Position Statement

Methylene Blue-Treated Plasma

18 November 2012

Prepared by: Helen New[1, 2, 3], Hazel Tinegate[1], Linda Hunt[1], Paula Bolton-Maggs[4], Rebecca Cardigan[1,3].

[1]NHS Blood & Transplant, [2]Imperial College Healthcare NHS Trust, [3]UK Standing Advisory Committee on Blood Components, [4]Serious Hazards of Transfusion

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BACKGROUND

In October 2011 the French regulatory authority Agence Française de Sécuité Sanitaire de Produits de Santé (AFSSAPS[1]) requested the Etablissement Français du Sang (French National Blood Service) to phase out the use of methylene blue plasma (MB FFP), due to concerns about allergic reactions to MB FFP occurring more frequently than with other plasma components. This was completed by the end of February 2012. Their decision was also influenced by 'continuous quality control of blood components identifying a greater variability of fibrinogen concentration in MB treated plasma' among regional blood centres preparing it in France.

Therefore the question has arisen as to whether MB FFP should remain as a specified component in the Guidelines for UK Blood Transfusion Services.

This paper reviews data in relation to MB FFP in the UK.

Use of MB FFP in the UK

NHS Blood & Transplant (NHSBT) started producing MB FFP in 2002 from plasma from UK donors for issue to recipients born on or after 1st January 1996. This was introduced as a prelude to producing MB FFP from plasma imported from the USA as a risk reduction measure for vCJD, which was implemented in 2004. In 2005 the use of MB FFP was extended to patients under 16 years of age, and in 2009 MB-treated cryoprecipitate was implemented for this patient group. In 2012 it was decided to continue provision for all recipients born on or after 1st Jan 1996 even once they had reached 16 yrs of age.

At the time, MB treatment of plasma was chosen because 1) pathogen inactivation of plasma from the USA was deemed necessary since there was an increased rate of viral carriage amongst the USA donor population compared with the UK and 2) MB was the only CE marked system available at that time to treat single units of plasma, and paediatricians when asked had expressed a preference for single unit FFP rather than a pooled product.

All UK Blood Services (with the exception of the Welsh Blood Service, which changed to provision of SD FFP for children during 2012 following a national policy decision) purchase MB FFP from NHSBT. Issues of MB FFP and cryoprecipitate from NHSBT are shown in the graph below. In total 135,883 units were issued until the end of 2010/11 (57,975 full-size units, 63,987 neonatal and

[1] Since 1st May 2012 known as the ANSM (National Security Agency of Medicines and Health products)

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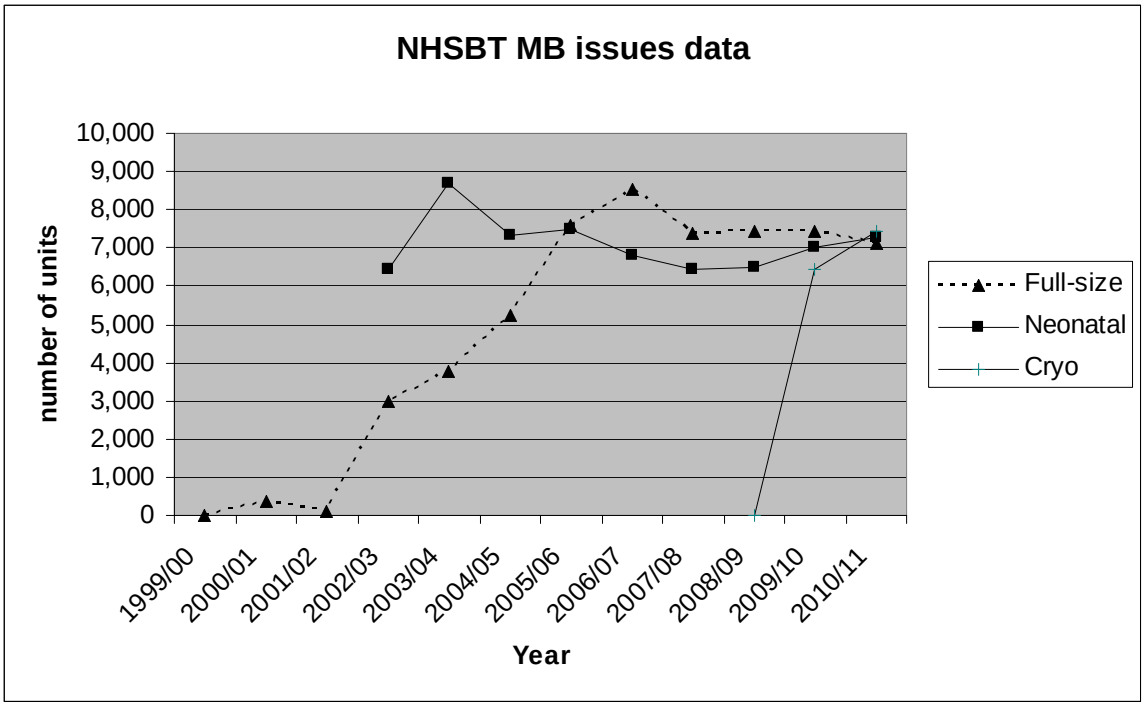
13,921 cryoprecipitate). Issues of MB FFP (but not cryoprecipitate) appear to be decreasing during the course of 2012/13.

From April 2003 to May 2010 SNBTS also produced MB FFP and cryoprecipitate for Scotland and Northern Ireland. The total number of units issued by SNBTS during this period was 24,303 (5,586 full-size units, 11,878 paediatric, 6,839 cryoprecipitate).

Therefore the total number of units transfused in the UK will now be in excess of 160,000.



Data source: Michael Bowden, NHSBT. Units prior to 2002 were part of validation studies.

MB process employed in the UK

Methylene blue treatment of plasma was developed in Europe in the 1990s. The system in use in the UK is treatment of single units of plasma using the Macopharma Theraflex MB Plasma system. Plasma that is imported is thawed, undergoes a filtration step to remove cellular debris and then 85 μg of MB is added under gravity in a closed system. The final concentration of MB can vary slightly due to differing plasma volumes between units but is in the order of 1 micromol/l. The plasma is then exposed to visible light in a MacoTronic v4 illuminator (590 nm for 180J/cm^2) for approximately 30 minutes. This results in the formation of free radicals and oxidative species that damage nucleic acids, preventing pathogen replication. However, the process can also alter plasma proteins including coagulation factors, possibly resulting in reduced activity in the final component. Following treatment the plasma is filtered to remove >90% of MB before being re-frozen. The UK specification for residual MB is that the process should be validated to produce

>75% of units with <0.3 μmol/l. Data from NHSBT between 2004-2010 shows that on average residual MB was 0.06μmol/l with 98.5% of units <0.3 μmol/l (n=744).

Use of MB FFP in other EU countries

MB-treated plasma has been used widely throughout Europe for over 10 years with more than 5.5 million units transfused from 1992 to date. The largest users of MB FFP (with approximate annual issues figures using 2011 as a guide) are: France (until 2011: 200,000), Spain (150,000), Russia (100,000), Belgium (80,000), Italy (40,000), UK (10-20,000), Austria (5,000) and Greece (4,000). Some European countries, including Spain, produce MB FFP without removing methylene blue prior to storage.

Allergic reactions to MB FFP

Allergic or other adverse reactions can occur following local instillation to patients of MB and other blue dyes such as patent blue violet and its derivative isosulfan. These dyes are commonly used for sentinal lymph node localisation and demonstration of tubal patency or fistulas. Allergic reactions are more frequently reported to patent blue violet and isosulfan than to MB (Dewachter et al, 2011, Bézu et al, 2011), but there are case reports in the literature of anaphylactic reactions to MB (Dewachter et al, 2005; Ramin et al, 2011).

HAEMOVIGILANCE DATA FOR MB FFP

As a result of the French decision to withdraw MB FFP we have undertaken a detailed analysis of the data from the UK national haemovigilance scheme, Serious Hazards of Transfusion (SHOT) in order to see if we can detect evidence of similar concern from the current UK data. We have also reviewed the available data from France to understand the basis of their decision.

Data from France

MB FFP was introduced in routine use in France in July 2008, and until the recent decision approximately 60% of all FFP was MB (approximately 200,000 units/year) - for all ages of recipient.

A severe allergic reaction leading to death was noted in 2008 in a 38 year-old man undergoing plasma exchange for multiple sclerosis with both MB-FFP and SD-FFP (solvent-detergent) and there was a higher number of allergic reactions to MB FFP than expected, with allergy to MB confirmed in two recipients (Rapport Annuel Hemovigilance 2008). The Allergy Working Group (WG) was asked to set up a protocol to investigate serious adverse allergic reactions to transfusion including to MB-FFP.

In 2009 a statistical analysis of all cases of serious allergy to plasma (quarantine, solvent detergent-treated and MB) from 2005-2009 was undertaken, and in addition a case by case analysis of the serious allergies to MB-FFP reported in 2008 and 2009 was performed (Rapport Annuel Hemovigilance 2009). The observed number of reactions to MB plasma was statistically higher than expected for severe allergic reactions to MB-FFP with imputabilities 2-4 (possible to certain, 30 reactions) and 3-4 (likely to certain, 19 reactions), based on previous plasma reaction

rates to quarantined and SD-FFP. A summary of the results of investigations of the MB-FFP reactions including skin testing and *in vitro* tests was included. Skin testing for MB was positive in 2/11 of the 30 cases with MB-FFP reactions and *in vitro* tests for MB were positive in 2/4 of the cases. In 7 cases MB was excluded as being the cause of the reaction based on clinical data. The report concluded that there was an increase in reactions to MB-FFP compared with other plasma components, with genuine allergic reactions to MB.

On the 22/12/2008 AFSSAPS sent a letter to healthcare facility managers and transfusion safety and haemovigilance managers, informing them of the potential risk of serious allergic reaction with MB FFP and inviting them to conduct the necessary investigations if faced with any new cases. This letter was posted on AFSSAPS website on 08/01/2009.

In 2010 there was further analysis of reactions to MB FFP in comparison to other forms of plasma (including all cases of plasma reactions 2005-2010; Rapport Annuel Hemovigilance 2010 report). For allergic reactions with imputability that was probable or certain, the rate of allergic reactions was higher with MB FFP (1/15,937) than 'quarantine' (standard) FFP (1/42,393) or SD FFP (1/35,349). There was also an increased rate for MB FFP for reactions with imputability possible to certain (MB FFP, 1/10,408; quarantine FFP, 1/19,269; SD FFP, 1/25,597). However, the report also stated that severe reactions to plasma are rare, and recommended that the results be interpreted with caution due to possible missed reporting of some adverse reactions, incomplete reports in some of the records and because of the weakness of the analysis related to infrequent events.

Investigation into cases of allergy in France

A recently published letter has the fullest summary, with details of a total of 34 cases of severe allergic reactions to MB FFP (imputability possible to certain) reported between 2005-2009 and giving further data on the detailed investigations (Mertes et al 2012). The rate of severe allergic reactions with imputability that was possible to certain (imputability 2-4) for 2005-2009 in France was higher with MB FFP (1/7,751) than quarantine FFP (1/19,269) or SD FFP (1/25,351) (P<0,001).

Of the 34 cases, 17 had been investigated by skin prick or intradermal tests, 3 of which were positive. Of these, 2/3 were also tested by flow cytometry for basophil activation which was also positive in both cases. In 9/34 cases MB causality was excluded based on recent previous or subsequent uneventful exposure and in 3/34 cases an allergen unrelated to transfusion was implicated. Therefore only a small proportion (3/17, 18%) of cases of hypersensitivity to MB FFP had demonstrated evidence of allergy to MB itself. The authors conclude that there may be other elements of the MB pathogen inactivation process that contribute to their observed higher rate of allergic reactions.

There have also been three recent case reports from France describing further details of anaphylactic reactions and allergy testing to MB-FFP (Dewachter et al, 2011; Nubret et al, 2011). It was concluded that the MB was the cause of the anaphylactic reactions in these cases, however it is not yet clear from the investigations by what mechanism MB elicits this response and whether it is IgE mediated.

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Data from UK

Acute transfusion reactions to MB FFP have only been reported to SHOT from patients < 16 years of age, the age group for whom this component has been recommended since 2005 (from 2012 now recommended for all patients born on or after 1st Jan 1996). Adults are not usually given MB FFP in the UK although there has been a single report of transfusion associated circulatory overload (TACO) in an adult transfused MB FFP for thrombotic thrombocytopenic purpura. Paediatric SHOT reports have only been published regularly as a separate group since 2007, with detailed reporting of paediatric subgroups since 2008. For cases prior to 2007, Stainsby et al (2008) summarised the first 9 years of paediatric SHOT reports (1996-2005) including a total of 30 acute transfusion reactions (of 321 paediatric reports) of which only 4 were to FFP, but it is not known whether these 4 cases were standard or MB FFP. Overall reporting rates have increased steadily since 2008, so although there is an apparent increase in paediatric reactions to FFP subsequent to the 1996-2005 period, it is difficult to make reliable comparisons.

Reports to SHOT of acute transfusion reactions to MB and standard FFP for the years 2007-11 have been summarised for comparison (Table 1; see Appendix 1 for list of all MB cases). This summary includes all cases where the reporters and analysts attributed the reaction primarily to FFP, although in some cases other components such as red cells may have also been transfused, for example in the same operation. For 2012 to date (10 months' data) there has been a single further report to SHOT of a possible acute transfusion reaction to MB FFP.

Reactions where any of multiple components were implicated have not been included in the main summary and analysis due to the difficulty in attributing causality. However the single example of a reaction to MB FFP in conjunction with multiple components has been included in an additional analysis to give a worst-case estimate.

In addition to reports of severe allergy or anaphylaxis, we have included hypotensive reactions to calculate an overall rate of severe acute transfusion reactions because anaphylactic/severe allergic reactions do not always present with urticaria and hypotensive reactions could be attributable to an allergic reaction. However, the hypotensive reactions to both standard and MB FFP were all in patients undergoing cardiac surgery and were difficult to assess for imputability.

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Table 1 Summary of MB and standard FFP acute transfusion reactions reported to SHOT 2007-2011

SHOT report year	MB-FFP reactions				Standard FFP reactions			
	Total reports	Severe reports			Total reports	Severe reports		
		Anaphylactic/ severe allergic	Hypo-tensive	Total		Anaphylactic/ severe allergic	Hypo-tensive	Total
2007	**0**	*0*	*0*	**0**	**20**	*8*	*0*	**8**
2008	**1**	*0*	*1*	**1**	**31**	*13*	*0*	**13**
2009	**1**	*0*	*0*	**0**	**40**	*11*	*0*	**11**
2010	**4**	*2*	*1*	**3**	**40**	*9*	*2*	**11**
2011	**1**	*0*	*0*	**0**	**42**	*9*	*2*	**11**
Total	**7**	***2***	***2***	**4**	**173**	***50***	***4***	**54**

Notes:
- *There were a total of 8 acute transfusion reactions to MB FFP from 2007-2011, but 1 recipient received other blood components and IV contrast media and has thus been excluded from the main analysis*
- *Total acute transfusion reaction numbers to standard FFP are derived from the numbers stated at the start of the Acute Transfusion Reaction (ATR) chapter in the relevant SHOT report, minus any MB FFP, SD FFP or cryoprecipitate cases that had also been included.*
- *Numbers of anaphylactic, severe allergic and hypotensive reactions to standard FFP have been derived from further analysis of the SHOT data from 2007-2011 in order to capture all severe acute transfusion reactions to standard FFP*
- *2009 standard FFP numbers include two children with standard FFP aged 10, 14 yrs (mild reactions)*
- *TACO, TRALI or TAD reports are not included in the analysis (for MB FFP there were no TRALI or TAD reports although there was 1 TACO to MB FFP in an adult in 2009)*

Comparison of UK FFP reaction rates

In order to give an estimate of reaction rates per unit of FFP transfused (Table 2), we have compared rates of acute transfusion reactions following transfusion of MB FFP or standard FFP per unit of FFP issued. Although the number of units issued is likely to overestimate the number of units actually transfused, issue data are the most robust available to estimate reaction rates per FFP unit transfused across the UK blood services (see Appendix 2 for FFP issues data from the UK blood services). The issues data includes both full-sized FFP units (from 1 donation) for MB and standard FFP, and paediatric splits (each a quarter of a full-sized donation). Since any additional reactions to MB FFP compared to standard FFP are likely to be the result of the MB treatment rather than due to donor-related parameters, the number of paediatric split units has not been adjusted for the number of FFP donors (i.e data are actual number of units issued not single full unit equivalents). This results in a larger denominator for MB FFP (and potentially lower calculated reaction rate) than if the number of paediatric splits were adjusted for the number of FFP donors, but is felt to be appropriate.

It is also important to be aware that the reaction rates per unit issued are not necessarily equivalent to rates per recipient transfusion episode as there is likely to be a difference in numbers

of units of FFP received during each episode by patients of different ages. The FFP National Comparative Audit (2009) reported that for adults the median (and interquartile range, IQR) volume of FFP transfused was 11 (8-15) ml/kg, for children aged 1-16 yrs 12 (10-18) ml/kg, and for infants less than 1 yr was 14 (10-18) ml/kg. Using these data:

- for an adult of 70 kg, an FFP transfusion of 11 ml/kg would result in transfusion of approximately 3 units of standard FFP (mean volume per unit 273 ml).
- for a child of 20 kg transfusion of 12 ml/kg would result in approximately one unit of full-sized MB FFP, but a larger child of 30 kg would require 2 units (mean volume per unit 233 ml).
- for a neonate of 2.5 kg, transfusion of 14 ml/kg would require part of a single unit of split MB FFP (mean volume per unit 56 ml)

Therefore, reaction rates based on FFP issues data are likely to underestimate the reaction rate per recipient for recipients of standard FFP compared to recipients of MB FFP splits.

For statistical analysis of reaction rates, 95% CIs were calculated for the rates assuming a Poisson distribution and comparisons between the groups were made using Poisson regression models.

Severe reactions to plasma are rare for both MB and standard FFP. Overall, the rates for all severe acute transfusion reactions were not higher for MB FFP than for standard FFP. However, the 95% confidence intervals for the MB FFP reaction rates are very wide as so few MB FFP reactions have been reported to date. The statistical analysis demonstrated no significant increase in the number of anaphylactic/severe allergic reactions with MB FFP compared to standard FFP, and this was still the case if all severe reactions to MB FFP were included in the comparison.

If in addition the single case of an acute transfusion reaction to MB FFP in a recipient who also received other blood components and IV contrast media is included in the comparison in order to calculate the 'worst-case' rates of severe reactions to MB FFP, the rate of all acute reactions increases to 1 in 10,490 [95% CI: 1 in 24,928, 1 in 5,324], anaphylactic/severe allergic to 1 in 27,973 [1 in 13,5645, 1 in 9,572] and all severe acute transfusion reactions to 1 in 16,784 [1 in 5,1691, 1 in 7,192]. None of these are significantly different to those with standard FFP (p=0.58, 0.92 and 0.29 respectively).

MB Cryoprecipitate

This was widely introduced in England for children < 16 yrs of age in 2009 and in Scotland in 2003. From 2009-11 there has been only a single SHOT report of a mild allergic reaction to MB cryoprecipitate, following issue of 21,958 units in the UK.

SD-FFP

SD FFP is not produced by UK Blood Services. Hospitals can purchase SD FFP (Octaplas) from Octapharma and some use SD FFP for paediatric patients in preference to MB FFP.

Since 2007 there have been 8 reports to SHOT of acute transfusion reactions to SD FFP, with 2 severe reactions including an anaphylactic reaction in an infant[2].[3] SHOT only asked reporters to

[2] The total of 8 SD FFP reactions were assigned following further analysis of the SHOT data. In the SHOT annual reports, 2 of the reactions were not described specifically as SD FFP reactions.

identify the type of FFP after 2007, and there were no reports of reactions to SD FFP prior to 2008. Using the information on numbers of units of Octaplas sold to hospitals over a 3 year period as quoted in the SHOT reports 2009-2011 (a combination of financial year and calendar year data), the estimated acute transfusion reaction rate is 7 in 173,664, ie 1 in 24,809 [95% CI: 1 in 61,706, 1 in 12,041] from 2009-11 with a rate of 1 in 86,832 [95% CI: 1 in 717,000, 1 in 24,038] for severe reactions. The rate of all acute transfusion reactions to SD FFP is statistically significantly lower than to standard FFP (p=0.006) but although the rate of severe acute transfusion reactions is also lower, it does not reach statistical significance (p=0.11).

[3] The MHRA have received 15 reports of adverse reactions to Octaplas since 2002. These have not been included in the analysis of SHOT data due to the possibility of replication.

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Table 2 Comparison of UK reaction rates to MB FFP (< 16yr recipients), and standard FFP from 2007-2011 (all recipients)

	Denominator (FFP issues)	All acute transfusion reactions		Anaphylactic/severe allergic reactions		All severe acute transfusion reactions (including hypotension alone)	
		n	Rate per 10^5 *[95% CI]* Ratio *[95% CI]*	n	Rate per 10^5 *[95% CI]* Ratio *[95% CI]*	n	Rate per 10^5 *[95% CI]* Ratio *[95% CI]*
FFP	1,488,995	173	11.6 *[9.9, 13.3]* *per 100,000* **1 in 8,607** *[1 in 10,114, 1 in 7,491]*	50	3.4 *[2.5, 4.4]* *per 100,000* **1 in 29,780** *[1 in 40,123, 1 in 22,588]*	54	3.6 *[2.7, 4.7]* *per 100,000* **1 in 27,574** *[1 in 36,705, 1 in 21,133]*
MB	83,920	7	8.3 *[3.4, 17.2]* *per 100,000* **1 in 11,989** *[1 in 29,818, 1 in 5,819]*	2	2.4 *[0.3, 8.6]* *per 100,000* **1 in 41,960** *[1 in 346,477, 1 in 11,616]*	4	4.8 *[1.3, 12.2]* *per 100,000* **1 in 20,980** *[1 in 77,000, 1 in 8,194]*
Comparison between FFP and MB FFP			***P=0.39***		***P=0.63***		***P=0.60***

Notes:
Denominators used are UK issues data, the closest estimate available to the number of units transfused. The issues data is expressed as total units issued, with full-size and paediatric units considered as individual units rather than full-size unit equivalents (see Appendix 2 for details).
**Standard FFP denominators: total UK issues for 5 year period 2006/7-2011, as published in relevant SHOT reports (financial year and calendar year data, Appendix 2)*
*** MB-FFP reactions denominators: total UK issues for 5 year period calendar years 2007-2011 inclusive*
All severe acute transfusion reactions includes anaphylactic, severe allergic, and hypotensive reactions.

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Conclusions from UK haemovigilance data

The analysis of UK reactions to MB-FFP from SHOT data shows no significant increase in overall reactions or severe allergic reactions when compared to standard FFP, even if the MB FFP report where the reaction was to mixed components is included. However, the overall numbers of reports of reactions to MB-FFP are very small and this has to be taken into account, together with the limitations of haemovigilance data reporting which is likely to underestimate at least the more minor reactions.

It is difficult to make a direct comparison of the UK and French data due to the different way the allergic reaction data is presented in the two haemovigilance systems and the different groups of patients and unit sizes included for MB FFP between the countries. More standardised definitions will be a help in the future for comparing haemovigilance data between countries and this is important for the most effective monitoring of reactions to new components.

It is important to note that this UK comparison of MB and standard FFP differs from comparisons in other countries such as France as the two types of FFP are received by different patient age-groups in the UK. This could affect both types of reactions, particularly in the neonatal age-group, and reporting rates.

Haemovigilance data from other EU countries

Other EU countries with experience of using MB-FFP have not published concerns of increased allergic reactions to MB-FFP. A publication from Greece compares reactions reported to the Hellenic Haemovigilance Centre from 2000-2005 for transfusion of 8,500 MB-FFP vs 54,435 standard FFP in Athens (Politis et al, 2007). For mild allergies, the MB allergy reaction rate was 1/8,500 vs standard FFP at allergy rate 1/5,444, whereas for severe allergic reactions the rates were 0/8,500 and 1/10,877. However, the numbers of MB units transfused were small. The same group have recently presented data covering the period 2007-2011 and transfusion of 127,483 units of MB FFP and 248,870 units of quaratine FFP. Allergic reactions to FFP were higher in quarantine FFP compared with MB FFP (Politis et al, 2012).

UK QUALITY MONITORING DATA ON FFP

Pathogen inactivation of plasma by any of the currently licensed methods results in a reduction in clotting factor activity. The worst affected factors following MB-treatment of plasma are Factor VIII (FVIII), fibrinogen and Factor XI (reviewed in Williamson et al 2003). The specification for MB FFP in the UK requires FVIII to be measured on a routine basis and that >75% units should contain >0.50 IU/ml. There is no requirement to routinely measure fibrinogen in MB FFP, only for MB cryoprecipitate.

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The table below summarises recent data (June 2012) for FFP from Manchester and Colindale Blood Centres, the two sites in NHSBT that produce MB FFP.

	FVIII:C (IU/ml)	Fibrinogen - Clauss (g/L)
Standard FFP (n=99)	0.92 (0.24) 83%>0.70	2.45 (0.37)
MB-treated FFP (n=127)	0.65 (0.20) 80%>0.50	1.72 (0.34)

Data are mean (SD).

These data show that there is wide variability in the levels of FVIII and fibrinogen in FFP. This is well known and reflects the wide normal range for both of these factors in healthy individuals (0.5-2.0 IU/ml for FVIII and 1.5-4.0 g/L for fibrinogen). Levels of FVIII and fibrinogen are lower in MB-treated FFP by 29% and 30% respectively, compared with untreated plasma. However, the results do not appear to be any more variable as evidenced by the standard deviation. The loss of FVIII and fibrinogen due to MB treatment of plasma when the system was originally validated by NHSBT were both 29% (Garwood et al, 2003). Therefore the current data on MB FFP are consistent with our original data, and other published studies (reviewed in Williamson et al, 2003). We have since undertaken a study to assess thrombin generation and clot formation in MB FFP and cryoprecipitate. The endogenous thrombin potential and peak thrombin are reduced by 10% and 30% respectively following MB treatment, but this was not associated with a reduction in the rate of clot formation or clot firmness by thrombelastometry (Cardigan et al, 2009).

The variability in fibrinogen levels between batches of SD FFP is lower than units of standard or MB-treated FFP since this plasma is produced from a pool of donations. A recent study on 16 batches of Octaplas LG showed that mean fibrinogen levels were 2.31 g/L with a range of 2.21-2.41 g/L (Lawrie et al, 2010).

The levels of clotting factors required in FFP for it to be clinically effective are not known, in part because in many clinical scenarios FFP has not been proven to be beneficial (Yang et al, 2012). Therefore it is not clear whether the reductions in clotting factor activity in MB FFP alter its clinical efficacy. Because the MB system was CE marked as a device rather than a drug, the clinical trial data on this product are rather limited. Despite usage of >4 million units in Europe, there have been no full reports of large, randomised trials of MB FFP using relevant endpoints such as blood loss or exposure to other blood components. However, a 7 year prospective study in Spain has shown that the ratio of red cell:plasma usage did not alter after introduction of MB FFP (Cid et al 2008), suggesting that the use of MB FFP is not associated with increased usage.

JPAC RECOMMENDATIONS

1) The UK haemovigilance data have not demonstrated a statistically significant increase in the rate of reactions to MB FFP compared to standard FFP. Although the low numbers of UK MB FFP reactions mean that it is difficult to draw robust conclusions, the data do not support the immediate withdrawal of the use of MB FFP in the UK.

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2) In view of the data from France, SHOT will undertake proactive monitoring of future FFP reaction rates and JPAC will review these data and alter the recommendations if necessary.
3) An investigation pathway should be developed in the UK so that recipients of MB plasma with severe allergic reactions are investigated in collaboration with allergy experts.

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Appendix 1

Details of individual MB FFP acute transfusion reactions reported to SHOT 2007-2011 (all < 16 yrs)

Year of report	Age of recipient	Diagnosis	Transfusion reaction	Comments
2008	11 mths	Fallot's tetralogy	Severe hypotension; circulatory collapse, cardiopulmonary resuscitation	Normal IgA, mast cell tryptase. Cultures negative
	13 yrs	Post stabbing	Anaphylaxis after *multiple components* including IV contrast medium	Subsequent re-exposure to IV contrast without problem
2009	4 yrs	Meningitis	Mild febrile reaction	
2010	3 mths	Cardiac surgery	Severe hypotension coming off bypass; required further bypass	
	11 yrs	β-thalassaemia major pre liver biopsy	Mild allergic reaction	Subsequent anaphylactic reaction to platelets
	14 yrs	Scoliosis repair	Anaphylaxis	Previous anaphylaxis to peanuts; allergy to strawberries
	15 yrs	B cell NHL, coagulopathy, pre lumbar puncture	Anaphylaxis after 50 mls third FFP unit	
2011	2 days	Suspected sepsis	Mild febrile reaction	

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Appendix 2 - FFP issues data

MB FFP

	2007	2008	2009	2010	2011	Total 2007-2011
NHSBT						
Split units	6,385	6,475	6,750	7,249	7,175	34,034
Full-sized units	7,831	7,445	7,492	7,065	5,478	35,311
Total units	**14,216**	**13,920**	**14,242**	**14,314**	**12,653**	**69,345**
Welsh Blood Service						
Split units	275	199	221	254	234	1,183
Full-sized units	256	237	176	150	155	974
Total units	**531**	**436**	**397**	**404**	**389**	**2,157**
SNBTS						
Split units	1,769	1,850	1,168	1,684	1,050	7,521
Full-sized units	870	1,040	1,358	711	918	4,897
Total units	**2,639**	**2,890**	**2,526**	**2,395**	**1,968**	**12,418**
UK totals						
Split units	8,429	8,524	8,139	9,187	8,459	42,738
Full-sized units	8,957	8,722	9,026	7,926	6,551	41,182
Total units	**17,386**	**17,246**	**17,165**	**17,113**	**15,010**	**83,920**

Note: Figures from UK blood services. The NHSBT issues data were issues to hospitals in England in North Wales, excluding any to Scotland and the Welsh Blood Service.
The SNBTS issues data include issues to N. Ireland in addition

Standard FFP

	2006/7	2007/08	2008/9	2010	2011	Total 2007-2011
NHSBT	260,159	250,644	260,265	249,509	248,163	
WBS	13,141	12,121	12,777	10,264	12,217	
SNBTS	24,166	25,554	27,077	26,275	21,596	
NIBTS	8,978	6,766	6,621	6,836	6,266	
Total UK	**306,444**	**295,085**	**306,340**	**292,884**	**288,242**	**1,488,995**

Note: Figures are from SHOT reports 2007-2011. 2006/7, 2007/8, 2008/9 were financial year data. 2010 and 2011 were calendar year data.

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SD-FFP

	2008/9	2009-10	2011	Total 2009-2011
England		48,186	53,362	
Wales		3,014	2,330	
Scotland		4,200	4,680	
N. Ireland		2,087	2,842	
Total UK	**52,963**	**57,487**	**63,214**	**173,664**

Note: Figures from SHOT reports 2009-2011. 2008/9 and 1009/10 were financial year data and 2011 were calendar year data. SD-FFP is Octaplas, manufactured by Octapharma Ltd.

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