



FFP GUIDELINES

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on behalf of

BSH Transfusion Task Force



British Blood
Transfusion Society

| #BBTS2018

Journey

- December 2014
 - FFP guideline – highest number of hits
 - Getting old.....10 years (2004)
 - 2 amendments/updates (2005, 2007)
 - Needing updating
 - Should be easy.....(?!?)

Journey

- Writing group

- Laura Green (Writing chair; Haematologist)
- Paula Bolton-Maggs (Haematologist/SHOT)
- Craig Beattie (Anaesthetist)
- Rebecca Cardigan (National Head Components Development)
- Yiannis Kallis (Hepatologist)
- Simon Stanworth (Haematologist)
- Jecko Thachil (Haematologist)
- Sharon Zahra (TTF rep; Transfusion consultant)

Journey

- Scope agreed and approved
- No duplication of content of other guidelines: Major haemorrhage; paediatrics
- Work assigned
- Literature search: mammoth number of hits
- Writing.....

Journey

- Major Haemorrhage Guidelines:
 - Pre-thawed plasma for immediate management of major haemorrhage in trauma
 - 24 hour shelf life – FFP wastage
- Request for guidance re pre-thawed plasma
 - Relatively urgent - couldn't wait for guideline update

Pre-Thawed Plasma

- JPAC:
 - Pre-thawed FFP: up to 120 hours
 - Pre-thawed MB-FFP: up to 24 hours
 - Octaplas: medicinal product - follow manufacturer's instructions

Pre-Thawed Plasma

- June 2016 – Addendum: extended pre-thawed plasma
 - Only for unexpected major haemorrhage
 - Otherwise use FFP that has been thawed for a maximum of 24 hours
- Clotting factor activity (esp FV, VII, VIII) drops over time during storage at 4+/-2°C

Pre-Thawed Plasma

- Once out of controlled temp environment can accept back once if <30 minutes

(need more research: based on expert opinion and practice in other countries - ?bacterial growth)

- Minimise risk of bacterial contamination:
 - Thawing equipment cleaned daily
 - Inspect prior to release to ensure no precipitate
 - Thawing methods that do not directly expose units to water

Journey

- Main Guideline writing continuing
- Numerous versions
- Teleconferences, emails and face-to-face meetings
- Many many discussions
 - Sticking points:
 - Dose of FFP/cryo (where's the evidence!)
 - Length of guideline

Guideline

- Use of plasma in patients without major haemorrhage
- Historical/current use of plasma
 - Since 2012 FFP issue dropping, SDFFP increasing
 - Since 2004 cryo issue increasing
 - 2009 audit: 43% FFP 25% cryo - prophylaxis in the absence of bleeding ?unnecessary

Specification, Preparation, Storage and Handling

	Standard FFP	Solvent-Detergent (Octaplas LG)	Methylene Blue (Theraplex)	Amotosalen Intercept	Vitamin B2 Mirasol
Available in UK? PLASMA	YES	YES	YES	NO	NO
Volume	200-300ml	200ml	200-260ml (50ml neonatal size available)	200-300ml (input plasma 385-650ml)	170-360ml
Source of plasma (donations)	UK	Germany, USA	Austria	N/A	N/A
Virological testing (genomic unless stated)	HIV, HBV, HCV, HEV all donations. HTLV new donors.	All donations HIV, HBsAg and HCV by ELISA as well as HIV, HCV, HEV, HAV, HBV and parvovirus B19 by PCR	HIV, HBV, HCV, HEV all donations.	N/A	N/A
Residual viral risk	*HIV 1 in 15.5 million *HBV 1 in 2.1 million *HCV 1 in 95.8 million	No proven transmission of HIV, HBV, HCV, HEV	No proven transmission of HBV, HEV (one possible HCV in Europe)	No proven transmission of HIV, HBV, HCV, HEV reported.	No reported transmission of HIV, HBV, HCV, HEV
Treatment step	None	1% TNBP 1% Triton X-100	1µM MB+ visible light 30 mins	150 µM amotosalen +UVA light 4 mins YES	50 µM riboflavin+ UV 4-10 mins NO
Removal step for residual chemicals?	N/A	YES <2µg/mL TNBP <5µg/mL Triton-X	YES <0.3µmol/L MB	YES	NO
Shelf-life – frozen/at 4°C once thawed	3 years/ 24 hours (12024 hours for unexpected major haemorrhage)	4 years/ 24 hours at 2-8°C, 8 hours at 20-25°C	3 years/ 24 hours	2 years/ 24 hours	2 years/ 6 hours
Coagulation factor losses (compared to standard FFP)		Batches tested for V, VIII, XI (all >0.50 iu/mL), protein C (>0.70 iu/mL), protein S (>0.30 iu/mL), antipain (>0.20 iu/mL)	20-30% loss of FVIII, FXI & fibrinogen, others less affected	20-30% loss of FVIII & fibrinogen, others less affected	20-30% loss of FVIII, FXI & fibrinogen, others less affected
Clinical studies of plasma efficacy performed	Systematic review of studies identified only small RCT's. No consistent	Observational studies: Congenital coagulation deficiency, liver disease/transplantation and cardiac surgery,	Observational studies: Congenital coagulation deficiency, and cardiac	Observational studies: Congenital coagulation deficiency, plasma	Observational study plasma exchange for TTP

	evidence of significant benefit for prophylactic and therapeutic use across a range of indications evaluated. See text of article.	TTP	surgery No large RCTs	exchange for TTP and liver transplantation	
Indications	See text of this article	As for FFP	As for FFP Not TTP	As for FFP	As for FFP
TRALI risk	Very low, selected from male donors. No cases in UK since 2009.	Very low. No cases reported in UK according to SHOT definition.	Very low. Selected from male or females tested for HLA/HNA antibodies. No reported cases in UK.	Low if selected from male or nulliparous females	Low if selected from male or nulliparous females
Allergic reactions	7.49 per 100,000 units issued	4.33 per 100,000 units issued	None reported in 2016	N/A	N/A
Total usage in Europe		>9 million	>6 million	>1.5 million	<500,000

Specification, Preparation, Storage and Handling

	FFP	MB FFP	Octaplas LG***	Single Cryoprecip itate	Pooled cryoprecip itate	Single MB cryoprecip itate	Pooled MB cryoprecip itate
Volume (ml)	267±1 7	229±12	200	49±3	237±26	46±3	291±29
FVIII	0.96±0.27 iu/ml (average ± 256 iu/unit)	0.68±0.23 iu/ml (average ± 156 iu/unit)	Group O: 0.53 (0.52- 0.53 iu/ml) Non-O: 0.71 (63- 84) 106 (iu/unit)	108±33 (iu/unit)	324±130 (iu/unit)	65±21 (iu/unit)	385±112 (iu/unit)
Fibrinogen (Clausa)	*2.37 ± 0.48 g/l (on average ± 0.69 g/unit)	**1.70± 0.15 g/l (on average 0.39g/u nit)	2.31 (2.21- 2.41) g/l (on average 0.46 g/unit)	0.43±0.14 (g/unit)	1.67±0.27 (g/unit)	0.25± 0.09 (g/unit)	1.18 ± 0.31 (g/unit)
UK Specification for FVIII/Fibrin ogen	>75% units ≥0.70 iu/ml FVIII	>75% of units ≥0.50 iu/ml FVIII	European Pharmacop oeia requires FV/FVIII and FXI ≥0.50 iu/ml	>75% of units ≥140mg/unit Fibrinogen ≥70 iu/unit FVIII	>75% of units ≥700mg/unit Fibrinogen ≥350 iu/unit FVIII	>75% of units ≥140mg/unit Fibrinogen ≥50 iu/unit FVIII	75% of units ≥700mg/unit Fibrinogen ≥250 iu/unit FVIII

Data taken from routine quality monitoring data from NHSBT for April-June 2016.

Data given as mean with SD.

*not monitored routinely, data taken from (Lawrie, et al 2008).

**data taken from (Backholer, et al 2016)

***data taken from Lawrie et al 2010 average with range (Lawrie, et al 2010).

Specification, Preparation, Storage and Handling

- Thawing equipment cleaned and maintained according to standard operating procedures (2A).
- Component should be inspected to ensure that no precipitate is visible and that the component packaging is intact (2A).
- Thawing methods that do not directly expose the primary plasma pack to water to minimise bacterial contamination (2A).

Specification, Preparation, Storage and Handling

- Once thawed, standard FFP or MBFFP may be stored at $4 \pm 2^{\circ}\text{C}$ in an approved temperature-controlled blood storage refrigerator, as long as the infusion is completed within 24 hours of thawing (2A).
- Transfusion of FFP should be completed within 4 hours of issue out of a controlled temperature environment (2A).

Specification, Preparation, Storage and Handling

- The shelf life of pre-thawed standard FFP can be extended to 120 hours, to enable its rapid provision in unexpected major haemorrhage only (2A).
- Pre-thawed FFP that is out of a controlled temperature environment ($4 \pm 2^{\circ}\text{C}$) can be accepted back into temperature-controlled storage if this occurs on one occasion only of less than 30 minutes (2A).

Blood Group Selection

Recipients	O	A	B	AB
a) High titre (HT) positive, or HT untested units†				
1st choice	O	A	B	AB
2nd choice	A	AB	AB	A*
3rd choice	B	B*	A*	B*
4th choice	AB	---	---	---
b) HT negative†				
1st choice	O	A	B	AB
2nd choice	A	B	A	A
3rd choice	B	AB	AB	B
4th choice	AB	---	---	---

†Group O must only be given to group O recipients

*Only suitable for emergency use in adults

Blood Group Selection

- Plasma of identical ABO blood group should be used as the first choice. If not possible, ABO non-identical plasma is acceptable if it has 'low-titre' anti-A or anti-B activity (1B).
- Group O plasma should only be given to group O patients (1B).
- FFP and cryoprecipitate of any RhD group may be transfused. If RhD positive plasma is given to an RhD negative individual, no anti-D prophylaxis is required (1B).

HSC Transplantation

Recipient ABO blood group	Donor ABO blood group	Category of ABO mismatch	Phase II (when HSC are infused)		Phase III*
			First choice	Second choice	
O	A	Major	A	AB	Donor
	B	Major	B	AB	Donor
	AB	Major	AB		Donor
A	O	Minor	A	AB	Donor
	B	Major and minor	AB		Donor
	AB	Major	AB		Donor
B	O	Minor	B	AB	Donor
	A	Major and minor	AB		Donor
	AB	Major	AB		Donor
AB	O	Minor	AB		Donor
	A	Minor	AB		Donor
	B	Minor	AB		Donor

Table reproduced from (O'Donghaile, *et al* 2012), and published with permission.

*Phase III starts when both forward and reverse grouping in the recipient are consistent with the donor ABO type.

Solid Organ Transplantation

- Following ABO minor mismatch solid organ transplant, plasma components should be of recipient's ABO group (1C).
- Following ABO major mismatch solid organ transplant, plasma should be of donor's ABO group until organ accommodation (usually 4 weeks after transplant) (1C).
- Following ABO bidirectional mismatch solid organ transplant, group AB plasma should be given until organ accommodation (usually 4 weeks after transplant) (1C).

Abnormal Clotting Results

- Abnormal standard coagulation tests (PT/APTT): poor predictors of bleeding risks in non-bleeding patients (2C).
- A detailed personal and family bleeding history, drug history, and the bleeding risk associated with the planned procedure must be assessed as a matter of routine for all patients undergoing a planned procedure (1B).
- Standard coagulation tests should be considered in patients undergoing procedures with a moderate or high bleeding risk, any patients on anticoagulants, or those who have a personal/family bleeding history (1B).
- Patients with a positive personal/family bleeding history should be discussed with haematology as standard clotting test results may be normal in the presence of a significant bleeding tendency (1B).
- The impact of commonly used doses of fresh frozen plasma to correct clotting results, or to reduce the bleeding risk, is very limited particularly when the PT ratio or INR are between 1.5-1.9 (2C).

Dose - FFP

- There is insufficient evidence on which to base a recommendation about the optimal dose of FFP in patients with abnormal clotting tests undergoing procedures.
- ...

Dose - cryoprecipitate

- There is insufficient evidence on which to base a recommendation about the threshold of fibrinogen level to transfuse cryoprecipitate, or the optimal dose, in patients with hypofibrinogaenimia undergoing procedures.
- ...

Miscellaneous

- Hypovolaemia
 - Plasma should not be used for volume replacement (2C).
- ITU/acquired Vitamin K deficiency
 - There is no evidence to support prophylactic use of FFP in non-bleeding patients with abnormal standard coagulation tests pre-procedures (2C).
 - The impact of commonly used doses of fresh frozen plasma to correct clotting results, or to reduce the bleeding risk, is very limited particularly when PT ratio or INR are between 1.5-1.9 (2C).
 - Vitamin K should be administered in patients with prolonged PT likely to be due to acquired vitamin K deficiency (1B).

Miscellaneous

- Liver disease
 - PT and APTT do not reflect true haemostatic status of patients with advanced liver disease. Interpret with caution (1C).
 - No good evidence to endorse use of prophylactic FFP for correction of abnormal clotting tests in non-bleeding patients prior to interventions such as elective variceal banding (1C).
 - Endorse the liver society recommendations that prophylactic transfusion of FFP and cryoprecipitate is not given in low bleeding risk procedures such as paracentesis (1C).
 - No good evidence to support a role for prophylactic FFP to reduce the risk of bleeding from percutaneous liver biopsy. An alternative procedure with a lower bleeding risk, (e.g. transjugular liver biopsy), should be considered instead (2C).

Miscellaneous

- Inherited single clotting factor deficiency
 - If virally-inactivated specific clotting factors are not available, pathogen-reduced plasma may be used for factor replacement in congenital coagulation factor deficiency (1C).

Safety and Adverse Effects

- Allergy (not infrequent)
- Pulmonary complications: (TRALI, TACO)
- Infection (rare)
- TA-GvHD (none)

Feedback

- Transfusion Task Force June 2017
 - Minor amendments made
- Sounding Board & BSH executive August 2017
 - Some minor amendments
 - Length of document
 - Change Title
 - Dose recommendations?!?

Appendix

- vCJD risk
- Plasma exchange
 - Apart from thrombotic thrombocytopenic purpura, plasma exchange using plasma as a replacement fluid is only indicated in haemostatically compromised patients or when an invasive procedure cannot be delayed (2B).
- Liquid plasma
- Lyophilised/spray dried plasma
- Fibrinogen Concentrate
- Prothrombin Complex Concentrate

Title

- Original:

- *Guidelines for when to use, and when not to use, fresh frozen plasma and cryoprecipitate*

- To:

- *Guidelines on the use of fresh frozen plasma and cryoprecipitate in patients without major bleeding: the BSH guideline writing group*

Guidance

- Further discussions
- Not everyone agrees there should be a dose mentioned as not evidence-based

Dose - FFP

- There is insufficient evidence on which to base a recommendation about the optimal dose of FFP in patients with abnormal clotting tests undergoing procedures.
- *For patients who have abnormal clotting tests and other factors (i.e. personal/family bleeding history, drug history, bleeding risk associated with planned procedure or thrombocytopenia) that indicate a significant bleeding risk during a procedure, then a starting dose of 15ml/kg of FFP can be considered, **although this is not evidence-based.***

Dose - cryoprecipitate

- There is insufficient evidence on which to base a recommendation about the threshold of fibrinogen level to transfuse cryoprecipitate, or the optimal dose, in patients with hypofibrinogaemia undergoing procedures.
- *If Fibrinogen is $<1.0\text{g/l}$, and other factors (i.e. personal/family bleeding history, drug history, bleeding risk associated with planned procedure) indicate a significant bleeding risk prior to a procedure, then a starting dose of two five-donor pools of cryoprecipitate can be considered, **although this is not evidence-based**.*

Guidance

- All members of the writing group agreed with all recommendations, with the exception of plasma dose where there was no unanimous consensus.

Publication

- Submitted for publication 03/11/17
- Feedback 12/12/17
 - Minor comments – changes made
 - Change Title again!

Publication

- **BSH Guidelines on the spectrum of fresh frozen plasma and cryoprecipitate products: their handling and use in various patient groups in the absence of major bleeding**
 - Accepted for publication 03/01/18
 - On line March 2018...

- Next guideline.....

- Thank You for Listening!