bjh guideline

British Society of Haematology 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

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Methodology

This guideline was compiled according to the BSH process at (http://www.bcshguidances.com/BCSH_PROCESS/42_EVIDENCE_LEVELS_AND_GRADES_OF_RECOMMENDATION.html). The Grading of Recommendations Assessment, Development and Evaluation (GRADE) nomenclature was used to evaluate levels of evidence and to assess the strength of recommendations. The GRADE criteria can be found at http://www.gradeworkinggroup.org.

Literature review details

Recommendations are based on the systematic review of English language literature published since the previous guideline publication, from January 2004 to July 2016 (see Appendix S1 for further details). A literature search was undertaken in Medline and Embase from 2004 to 2016, using the following key search terms: blood component transfusion, FFP, fresh frozen plasma, plasma, transfusion, prophylaxis, thaw, prethaw, SDFFP, MBFFP, uniplas, octaplas, FP24, pathogen inactivated or pathogen reduced, cryoprecipitate, supernatant or cryosupernatant.

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Review of the manuscript. Review of the manuscript was performed by the British Society for Haematology (BSH) Guidelines Committee Transfusion Task Force, the BSH Guidelines Committee and the Transfusion sounding board of the BSH. It was also placed on the members section of the BSH website for comment.

Introduction

Fresh frozen plasma (FFP) is given primarily for three indications: to prevent bleeding (prophylaxis), stop bleeding (therapeutic) or for plasma exchange. Prophylactic transfusions are mainly used prior to surgery or invasive procedures. Many possible indications in patients without major bleeding are not substantiated by robust trial data.

Historical and current use of plasma

Fresh frozen plasma

Between 2008 and 2012 there was a steady increase in the use of FFP in the UK, possibly influenced by the publications of observational studies in trauma demonstrating that early transfusion of FFP in bleeding patients improves outcomes (Holcomb *et al*, 2007). From 2012 onward there has been a reduction in the total number of units of FFP issued in the UK, while during the same period the number of units of solvent detergent-treated FFP (SDFFP) issued has increased (Fig 1B).

In 2009 a UK-wide audit demonstrated that in adult patients 43% of FFP transfusions were administered to patients with no documented bleeding, as prophylaxis before interventions because of abnormal coagulation tests

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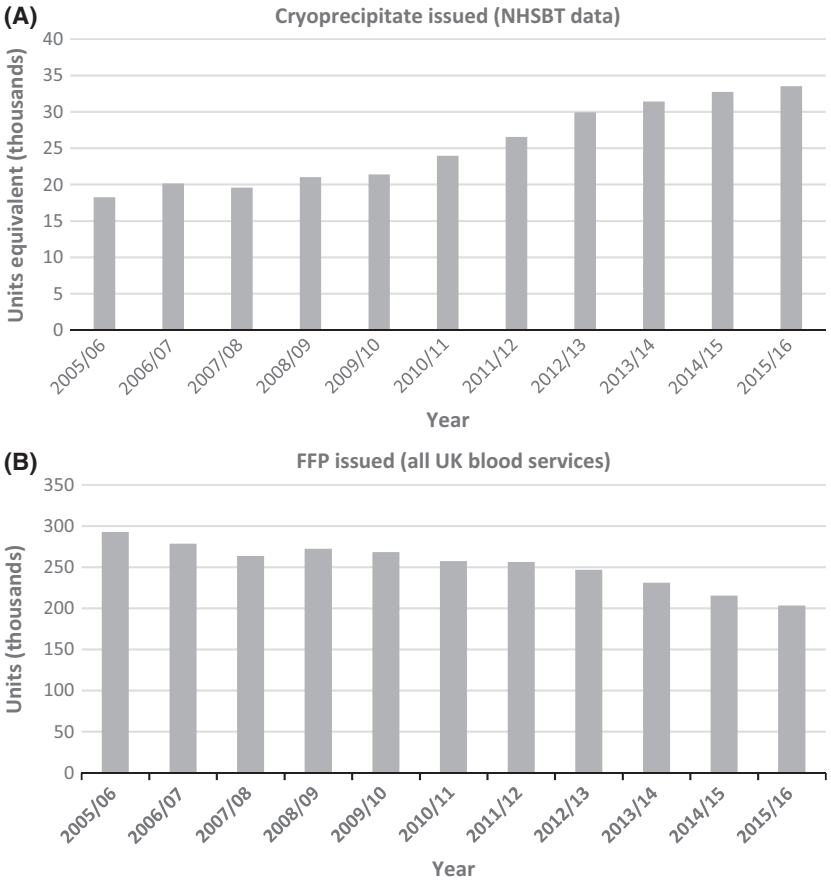

Fig 1. Total number of frozen components issued from 2003 onward. (A) Cryoprecipitate [NHS Blood and Transplant (NHSBT) data]. (B) Fresh Frozen Plasma (FFP) (all UK blood services). Data (unpublished) provided from NHSBT and Serious Hazard of Transfusion.

(Stanworth *et al*, 2011a). There is no evidence validating FFP use in these settings; this practice potentially exposes patients to unnecessary transfusion.

Cryoprecipitate

Since 2004 use of cryoprecipitate has steadily increased; in 2015/16 the number of cryoprecipitate units issued by NHS Blood and Transplant (NHSBT) had more than doubled compared with 2003 (Fig 1A). The reasons for this increase remain unclear; an audit in 39 hospitals (2009/2010) in England showed that, of 423 cryoprecipitate transfusions, 25% were transfused prophylactically and 75% were administered for bleeding, the commonest cause for all age groups being cardiac surgery, followed by trauma (Tinegate *et al*, 2012).

Specification, preparation, storage and handling of fresh frozen plasma and cryoprecipitate

Plasma specifications

Fresh frozen plasma. In the UK, FFP is produced from whole blood donations which undergo centrifugation, or by apheresis. FFP is leucocyte depleted by filtration during whole blood processing or integral to the apheresis process. Plasma is rapidly frozen to ≤−25°C to maintain the activity of labile coagulation factors. Factor VIII (FVIII) is used for quality monitoring because it is one of the most labile coagulation factors and is therefore a sensitive marker of changes to FFP induced by inappropriate processing/handling. Immediately after being thawed, standard FFP must have at least 70 iu/ml of FVIII in at least 75% of units. Other details of the quality monitoring required, such as residual levels of red cells, platelets and leucocytes are available elsewhere (http://www.transfusionguidelines.org.uk/red-book). Once frozen, FFP may be stored for up to 36 months at ≤2–5°C. Typical values for plasma are given in Table I.

Cryoprecipitate

Cryoprecipitate is manufactured by slowly thawing FFP overnight at 4°C. This precipitates out cryoproteins: FVIII, von Willebrand factor (VWF), FXIII, fibronectin and fibrinogen. After centrifugation, the cryoproteins are resuspended in a reduced volume of plasma (20–60 ml). The cryoprecipitate specification requires that 75% of packs contain at least 140 mg of fibrinogen and 70 iu of FVIII. UK Blood Transfusion Services (UKBTS) also produce pooled cryoprecipitate prepared from five single donations; the specification is five times that of a single cryoprecipitate unit (i.e. 700 mg fibrinogen and 350 iu FVIII) in a typical volume of 200–

Table I. Typical values for fresh frozen plasma and cryoprecipitate in the UK.

	FFP	MB FFP	Octaplas LG‡	Single cryoprecipitate	Pooled cryoprecipitate	Single MB cryoprecipitate	Pooled MB cryoprecipitate
Volume (ml)	267 ± 17	229 ± 12	200	49 ± 5	237 ± 28	46 ± 5	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)	524 ± 130 (iu/unit)	65 ± 21 (iu/unit)	385 ± 112 (iu/unit)
Fibrinogen (Clauss)	2·57 ± 0·48 g/l (on average 0·69 g/unit)*	1·70 ± 0·15 g/l (on average 0·39 g/unit)†	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 / fibrinogen	>75% units >0·70 iu/ml FVIII	>75% of units >0·50 iu/ml FVIII	European Pharmacopoeia requires FV, FVIII and FXI >0·50 iu/ml	>75% of units >140 mg/unit fibrinogen >70 iu/unit FVIII	>75% of units >700 mg/unit fibrinogen >350 iu/unit FVIII	>75% of units >140 mg/unit fibrinogen >50 iu/unit FVIII	75% of units >700 mg/unit fibrinogen >250 iu/unit FVIII

FFP, fresh frozen plasma; FV, factor V; FVIII, factor VIII; FXI, factor XI; MB, methylene blue.
Data taken from routine quality monitoring data from NHSBT for April-June 2016.
Data given as mean with standard deviation.
*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.

280 ml. Cryoprecipitate should be stored at a core temperature of ≤−25°C for a maximum of 36 months. Typical values for cryoprecipitate are given in Table I. Due to natural variation in coagulation factors levels between donors, there is wide variation in FVIII and fibrinogen levels between units.

There is no current clinical indication for cryoprecipitate-depleted plasma (the supernatant left after cryoprecipitate has been removed from plasma) in the UK; this product is no longer produced by the UKBTS.

Pathogen-inactivated plasma and cryoprecipitate

Pathogen inactivated (PI) plasma is indicated for all individuals born after 1 January 1996. The residual risk of a unit of plasma being infectious for known viruses that are tested for is very low (Table II). There are now three systems that are licenced in Europe for the pathogen inactivation of units of plasma within Blood centres: methylene blue (Theraflex), amotosalen (Intercept) and riboflavin (Mirasol). Of these, currently methylene blue is available in the UK. These systems are based on the addition of a photosensitiser to plasma followed by exposure to visible or ultraviolet (UV) light, and then removal of the photosensitiser (except for Mirasol). A pooled solvent-detergent treated plasma (SDFFP), Octaplas LG, which also includes a prion reduction step, is available in the UK from Octapharma AG (Lachen, Switzerland). Key features of these components are given in Table II.

All pathogen inactivation systems reduce the level of coagulation factors and inhibitors in plasma, the extent of which varies by factor and by system (Rock, 2011). In general, the worst affected factors are FVIII, fibrinogen and FXI, where losses are approximately 30–40%, although the SD process also significantly reduces protein S and antiplasmin. The FVIII specification is lower for pathogen-reduced plasma and cryoprecipitate due to the effect of pathogen-reduction on clotting factor levels (Table II). For pooled methylene blue-treated cryoprecipitate, in order to meet the specification in Table I, 6 rather than 5 units are pooled together.

All systems have good (generally >4 log) reduction of enveloped viruses, but activity against non-enveloped viruses (hepatitis A virus, parvovirus B19 and hepatitis E virus) are more variable. For this reason, plasma used as a source of SDFFP supplied in the UK is tested for the latter viruses.

Thawing of FFP

When frozen, FFP packs become relatively brittle and must be handled with care. Vulnerable parts of the pack include the stumps of the entry lines, which can break off if knocked. All UKBTS provide frozen plasma in a vacuum-packed outer container so that the plasma pack itself does not come into direct contact with thawing devices. Because of the potential for pinholes and cracks in the plastic that may not be visible, it is imperative that procedures for thawing FFP are designed

Table II. Specifications of different fresh frozen plasma.

	Standard FFP	Solvent-Detergent (Octaplas LG)	Methylene Blue (Theraplex)	Amotosalen Intercept	Vitamin B2 Mirasol
Available in UK? PLASMA	YES	YES	YES	NO	NO
Volume	200–300 ml	200 ml	200–260 ml (50 ml neonatal size available)	200–300 ml (input plasma 385–650 ml)	170–360 ml
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 and HIV in Europe)	No proven transmission of HIV, HBV, HCV. One transmission of HEV reported.	No reported transmission of HIV, HBV, HCV, HEV
Treatment step	None	1% TNBP 1% Triton X-100	1 μmol/l MB+ visible light 30 min	150 μmol/l amotosalen + UVA light 4 min	50 μmol/l riboflavin+ UV 4–10 min
Removal step for residual chemicals?	N/A	YES <2 μg/ml TNBP <5 μg/ml Triton-X	YES <0·3 μmol/l MB	YES	NO
Shelf-life –frozen/at 4°C once thawed	3 years/24 h (120 h for unexpected major haemorrhage)	4 years/24 h at 2–8°C, 8 h at −20 to 25°C	3 years/24 h	2 years/24 h	2 years/6 h
Coagulation factor losses (compared to standard FFP)		Batches tested for FV, FVIII, FXI (all >0·50 iu/ml), protein C (>0·70 iu/ml), protein S (>0·30 iu/ml), antiplasmin (>0·20 iu/ml)	20–30% loss of FVIII, FXI and fibrinogen, others less affected	20–30% loss of FVIII and fibrinogen, others less affected	20–30% loss of FVIII, FXI and fibrinogen, others less affected
Clinical studies of plasma efficacy performed	Systematic review of studies identified only small RCT's. No consistent evidence of significant benefit for prophylactic and therapeutic use across a range of indications evaluated. See text.	Observational studies: Congenital coagulation deficiency. RCTs: liver disease/transplantation and cardiac surgery, TTP	Observational studies: Congenital coagulation deficiency and cardiac surgery No large RCTs	Observational studies: Congenital coagulation deficiency, plasma exchange for TTP and liver transplantation. RCTs: liver disease, coagulopathy, warfarin reversal, plasma exchange for TTP	Observational study plasma exchange for TTP
Indications	See text	As for FFP	As for FFP Not TTP	As for FFP	As for FFP

Table II. (*Continued*)

	Standard FFP	Solvent-Detergent (Octaplas LG)	Methylene Blue (Theraplex)	Amotosalen Intercept	Vitamin B2 Mirasol
TRALI risk	Very low, selected from male donors. No cases in UK from FFP 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	7·49/100 000 units issued	4·33/100 000 units issued	None reported in 2016	N/A	N/A
Total usage in Europe		>9 million	>6 million	>1·5 million	<500 000

ELISA, enzyme-linked immunosorbent assay; FFP, fresh frozen plasma; FV, factor V; FVIII, factor VIII; FXI, factor XI;HAV, hepatitis A virus; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HCV, hepatitis C virus; HEV, hepatitis E virus; HIV, human immunodeficiency virus; HLA, human leucocyte antigen; HNA, human neutrophil antigen; HTLV, Human T-cell lymphotropic virus; MB, methylene blue; N/A, not applicable; PCR, polymerase chain reaction; RCT, randomized control trial; SHOT, Serious Hazard Of Transfusion; TRALI, transfusion-related acute lung injury; TTP thrombotic thrombocytopenic purpura; UV(A) , ultra-violet (A).
*NHSBT data calculated from 2013 – 2016 (available at: https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/645328/Safe_supplies_2016_supplementary_data.pdf)

to minimise the risk of bacterial contamination. Once thawed, the primary pack should be removed from the over-wrap bag and examined for leaks or damage. Damaged packs should not be used. If there is any unexpected appearance such as flocculation or discolouration, or apparent leaks, packs should be discarded, or referred for further opinion. There are several methods available to thaw plasma. Those that do not directly expose units to water are recommended to reduce the risk of bacterial contamination. Whatever method is used to thaw plasma, the procedure to follow, cleaning and maintenance schedules should be described by a specific standard operating procedure relevant to the method employed.

Dry heat methods. Methods that thaw plasma using dry heat with agitation are available and in use in the UK. Dry ovens (temperature-controlled fan-assisted incubators) may have a lower potential for contaminating FFP packs with microbes, although they are usually of limited capacity.

Microwave ovens. Although these can defrost FFP in 2–3 min, they have the disadvantage of limited capacity. There are also concerns over the creation of 'hot spots' in the packs and the potential for parts of the pack to act as an aerial causing arcing. Previous studies have suggested that the quality of plasma once thawed is similar to that when using water bath methods (von Heymann *et al*, 2006; Kuta *et al*, 2016).

Water bath-based methods. The majority of water baths now used in the UK do not expose plasma to water directly, but rather the unit is placed in a pocket around which a water-based solution circulates. When using a water bath, it is essential to place the FFP pack in a vacuum-sealed over-wrap to protect it from bacterial contamination. Water baths used for thawing FFP must only be used for this purpose. All maintenance should be documented and logged. The average time for thawing FFP or cryoprecipitate in water baths is 20 min.

Temperature of thawing. Scant data exist in relation to the ideal temperature for thawing of plasma. Data that do exist suggest that temperatures close to 37°C may be optimal, because cryoprecipitate will form when thawed closer to 4°C, and thawing at higher temperatures might affect the viability of plasma proteins. The current recommendation is that plasma be thawed at 33–37°C (http://www.transfusionguidelines.org.uk/document-library/supporting-papers). However, methods of thawing plasma at higher temperatures, e.g. 45°C, are available, which might improve the speed of thawing. Data on the effect of thawing plasma at 45°C or higher are lacking. It is important that alternative thawing temperatures be validated for all components, and for their maximal post-thaw shelf-life. For SDFFP, the manufacturer's instruction on thawing should be followed.

Recommendations

- **Protocols must be in place to ensure that thawing equipment is cleaned and maintained according to standard operating procedures (2A).**
- **After thawing, and at the time of administration, the 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 must be used to minimise bacterial contamination (2A).**

Storage after thawing

Fresh Frozen Plasma. Once thawed, standard FFP may be stored at +4 ± 2°C in an approved temperature-controlled blood storage refrigerator before administration to a patient as long as the infusion is completed within 24 h of thawing. Pre-thawed plasma can also be stored at +4 ± 2°C for up to 120 h for use only in patients who develop unexpected major bleeding (e.g. following trauma). This extended storage of pre-thawed FFP for patients with unexpected major haemorrhage was recommended to enable rapid provision of FFP for these patients where delay would be detrimental while also limiting FFP wastage. Data from NHSBT show that with the exception of protein C, all clotting factors decrease between 24 and 120 h after thawing. Most FVIII loss occurs within the first 24 h following thawing, after which the rate of loss decreases. For other clotting factors, the loss of activity is more linear once thawed. However, with the exception of FVIII, mean levels remain above 70% at 120 h (http://www.transfusionguidelines.org.uk/document-library/supporting-papers).

To minimise the risk of bacterial growth during extended storage of thawed plasma (>24 h), thawing methods that do not directly expose primary plasma packs to water must be used, and time out of controlled storage must be kept to a minimum. Pre-thawed FFP that is out of a controlled temperature environment (+4 ± 2°C), can be accepted back into temperature-controlled storage if this occurs on one occasion only of less than 30 min. Transfusion of FFP should be completed within 4 h of issue out of a controlled temperature environment. *At present, there is a lack of evidence relating to how long thawed plasma can safely remain out of controlled temperature storage. This recommendation is based on current practice in other countries and expert opinion, extrapolated from evidence on red cell storage with the aim of minimising FFP wastage, while also ensuring safety of the component for recipients. The recommendation may change in the future as a result of research carried out on FFP storage and bacterial growth.*

Table III. Principles of blood group selection for plasma.

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

Methylene Blue-treated FFP (MBFFP). Once thawed, MBFFP may be stored at +4 ± 2°C in an approved temperature-controlled blood refrigerator before administration to the patient, as long as the infusion is completed within 24 h of thawing. The post-thaw shelf-life of this component was reviewed in 2016 and was not extended further (http://www.transfusionguidelines.org.uk/document-library/supporting-papers), as the coagulation factor content of PI plasma is reduced compared to standard FFP, and some studies have shown an increase in coagulation activation with extended storage of thawed MBFFP (Thiele *et al*, 2016). There are no trials that have assessed the efficacy of MBFFP *versus* standard FFP.

Solvent detergent-treated FFP (SDFFP). SDFFP is a licensed medicinal product and therefore its shelf-life following thawing should be governed by the manufacturer (Octapharma).

Cryoprecipitate. Once thawed, cryoprecipitate must not be refrozen and should be used immediately. If delay is unavoidable, the component should be stored at ambient temperature and used within 4 h. NHSBT have assessed the haemostatic properties of thawed cryoprecipitate beyond 4 h (up to 72 h), and have demonstrated that these are stable [i.e. fibrinogen, FXIII, rotational thromboelastometry (ROTEM®) and thrombin generation] (Green *et al*, 2016). However, the potential risk of bacterial contamination arising from storing cryoprecipitate at ambient temperature will need to be assessed before the shelf life of thawed cryoprecipitate can be extended beyond 4 h.

Recommendations

- **Once thawed, standard fresh frozen plasma (FFP) or methylene blue treated FFP (MBFFP) may be stored at +4 ± 2°C in an approved temperature-controlled blood storage refrigerator before administration to the patient, as long as the infusion is completed within 24 h of thawing (2A).**

Table IV. Plasma selection for patients who have undergone ABO-mismatched haematopoietic stem cell (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

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.

- **Transfusion of FFP should be completed within 4 h of issue out of a controlled temperature environment (2A).**
- **The shelf life of pre-thawed standard FFP can be extended to 120 h, to enable its rapid provision in unexpected major haemorrhage only (2A).**
- **Pre-thawed FFP that is out of a controlled temperature environment (+4 ± 2°C) can be accepted back into temperature-controlled storage if this occurs on one occasion only of less than 30 min (2A).**

Selection of plasma components

Patients who are likely to receive multiple units of FFP should be considered for vaccination against hepatitis A and B (HAV, HBV), and patients who are likely to receive large or repeated doses of FFP should receive pathogen-reduced plasma. Such patients include those with congenital factor deficiencies for whom no pathogen-reduced concentrate is available, and patients undergoing intensive plasma exchange, e.g. for thrombotic thrombocytopenic purpura (TTP).

ABO blood group compatibility

In order to avoid the risk of ABO-associated haemolysis in recipients, plasma of donors with identical ABO blood group to the recipient should be used as the first choice. In an emergency, if the patient's blood group is unknown, ABO non-identical plasma is acceptable if it has 'low-titre' anti-A or anti-B activity. Group O FFP should only be given to group O patients (Table III). For more details on plasma group selection for MBFFP, please refer to the paediatric guideline (New *et al*, 2016).

RhD blood group compatibility

The risk of alloimmunisation following RhD mismatch FFP transfusion was reviewed in 2004 by UKBTS (https://www.transfusionguidelines.org/document-library/documents/rhd-grouping-of-ffp/download-file/JPAC%2005-51%20-%20RhD%20grouping%20of%20FFP.pdf); FFP and cryoprecipitate contain only a small amount of red cell stroma (red cells after FFP thawing would be expected to be <0·001 ml in 300 ml FFP). This means that sensitisation following administration of RhD-positive plasma to an RhD-negative individual is very unlikely to occur (http://www.transfusionguidelines.org.uk/document-library/supporting-papers).

Recommendations

- **Plasma of donors with identical ABO blood group to the recipient should be used as the first choice. If this is 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).**
- **Fresh frozen plasma 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).**

Haematopoietic stem cell transplantation

There are three types of ABO-incompatible haematopoietic stem cell transplants (HSCT): (i) major; (ii) minor; and (iii) bi-directional (Table IV). Currently, there is no evidence-based guidance on plasma blood group selection following ABO-mismatched HSCT, and most clinical practice relies on current

understanding of basic principles of ABO incompatibility. The knowledge of both donor and recipient blood groups are important when selecting the right plasma group for patients, as well as performing both ABO forward and reverse typing. Selection of plasma for patients undergoing ABO-mismatch HSCT is given in Table IV. For patients who relapse, selection of plasma should be guided by the ABO-blood group detected at the time.

Solid organ transplantation

As for HSCT, there is no evidence-based guidance on plasma blood group selection following ABO-mismatched solid organ transplants, and most of the clinical guidance relies on the understanding of the basic principles of ABO incompatibility, and the timing of when successful engraftment (or accommodation) of the organ is expected (Koch *et al*, 2004).

Recommendations

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

Abnormal clotting tests prior to intervention in a non-bleeding patient, and role of FFP transfusion

This section will only cover the use of FFP prior to interventions in non-bleeding patients who have abnormal clotting tests. For the use of FFP in bleeding patients, or for the role of coagulation testing in unselected patients prior to surgery or invasive procedures please refer to the relevant British Society for Haematology (BSH) guidelines (Chee *et al*, 2008; Hunt *et al*, 2015).

The UK national FFP audit in 2009 showed that ~50% of patients received FFP in the absence of clinical bleeding (Stanworth *et al*, 2011a); many of these patients received it prior to invasive procedures for mild or moderate abnormalities of prothrombin time (i.e. PT <16 s) or international normalised ratio (i.e. INR < 1·5 × mean normal). More importantly, transfusion of FFP only resulted in minimal, or no correction of PT or INR (Stanworth *et al*, 2011a).

The use of prophylactic FFP prior to procedure in non-bleeding patients with abnormal clotting tests is not supported by good quality evidence, and several systematic reviews (mainly observational studies) have concluded that an abnormal PT or INR does not predict peri-procedural bleeding (Segal & Dzik, 2005; Chee *et al*, 2008). A detailed personal and family history of bleeding, drug history and knowledge of the bleeding risks associated with each surgical or other invasive procedure (Patel *et al*, 2012), are more important than clotting tests results when assessing whether a procedure is likely to be associated with clinically significant bleeding. For patients with a personal/family history of bleeding, referral to a haematologist for further work-up is needed, as standard coagulation tests may be normal. Further, there is very little evidence to support the effectiveness of prophylactic use of FFP (in any clinical settings) in correcting abnormal clotting tests or reducing bleeding events (Stanworth *et al*, 2004). All these indicate that there is a need for clinical studies to evaluate the efficacy and safety of prophylactic FFP in non-bleeding patients with abnormal clotting tests, who are undergoing a procedure, to better understand whether benefits of FFP outweigh risks.

Other global clotting tests, such as thromboelastography (TEG) or ROTEM®, have been shown to be cost-effective in reducing blood transfusion and mortality during cardiac surgery for bleeding patients (Whiting *et al*, 2015; Wikkelso, *et al* 2017). However, their role in predicting bleeding risks in non-bleeding patients with abnormal PT or activated thromboplastin time (APTT), or monitoring the effectiveness of prophylactic FFP prior to invasive procedure or surgery, remains unknown.

Key practice point

- **Abnormal standard coagulation tests (prothrombin time [PT]/activated partial thromboplastin time [APTT]) are poor predictors of bleeding risks in non-bleeding patients prior to an invasive procedure (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 FFP to correct clotting results, or to reduce the bleeding risk, is very limited particularly when the PT ratio or International Normalised Ratio (INR) are between 1·5–1·9 (2C).**

Dosage of FFP and cryoprecipitate in non-bleeding patients

Fresh frozen plasma

The Intensive Care Study of Coagulopathy reported wide variation in the dose of FFP administered (median 10·8 ml/

kg, first to third quartile 7·2 to 14·4 ml/kg) (Stanworth *et al*, 2011b). A recent non-inferiority randomised control trial (stopped early for futility) recruited non-bleeding critically ill patients with an INR of 1·5–3·0 who were about to undergo an invasive procedure, and randomised patients to receive either FFP 12 ml/kg or no FFP (Muller & Juffermans, 2015). The authors reported a *post hoc* analysis where coagulation factors, anticoagulant levels, thrombin generation and thromboelastometry assays (ROTEM®) were measured before and after FFP transfusion at the protocol-defined doses. FFP transfusion had only a marginally beneficial effect on improving coagulation profiles, as although levels of FII, FV and FVII were elevated, thrombin generation was unaffected and anticoagulant factors levels were elevated (Muller *et al*, 2015). Earlier work by Chowdary *et al* (2004) compared standard doses of FFP (12·2 ml/kg) versus higher doses (33·5 ml/kg) in 22 critically ill patients and reported a dose-dependent relationship, such that samples from patients in the higher dose group had significantly higher increments in FI, FV, FVII, FIX, FX and FXII levels compared to the standard dose group. Although larger doses of FFP might improve standard tests of coagulation (Yang *et al*, 2012), higher doses of blood components will be associated with further adverse risks, including fluid overload. Many published studies evaluating the use of plasma are small and unable to link improvements in laboratory tests with clinical outcomes (Yang *et al*, 2012). In summary, much of the practice of plasma transfusion as prophylaxis in non-bleeding patients before invasive procedures seems unlikely to have clinical benefit; there is currently insufficient evidence to allow an evidence based recommendation on the optimal dose for prophylactic use of FFP prior to invasive procedures in patients with abnormal clotting tests. For management of major bleeding the recommended dose for FFP is 15 to 20 ml/kg (Hunt *et al*, 2015).

Key Practice Points

- **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 15 ml/kg of FFP can be considered, although this is not evidence-based.**

Cryoprecipitate

There are few data on use of cryoprecipitate in non-bleeding patients. Audits in the UK and Canada have reported that cryoprecipitate is being administered for prophylactic use (Alport *et al*, 2008; Tinegate *et al*, 2012). Cryoprecipitate can be considered in non-bleeding patients because of low fibrinogen (for example < 1 g/l) for interventions at risk of significant bleeding, or in critical sites. If cryoprecipitate is administered in such a situation, a dose of two five-donor pools will increase fibrinogen in an average-sized adult by approximately 1 g/l (Hunt *et al*, 2015). However, there is insufficient evidence to recommend the threshold of fibrinogen at which cryoprecipitate transfusion is indicated, or the optimal dose of cryoprecipitate needed for prophylaxis in non-bleeding patients before invasive procedures.

Key Practice Points

- **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 hypofibrinogenaemia undergoing procedures.**
- **If fibrinogen is <1·0 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.**

When to consider, and not consider the use of plasma

Hypovolaemia

While administration of FFP during the resuscitation of patients with major blood loss may contribute to supporting circulating volume, FFP and cryoprecipitate should not be used for volume replacement in patients who are not bleeding.

Recommendation

- **Plasma should not be used for volume replacement (2C).**

Abnormal clotting tests in the absence of bleeding

Intensive care units (ICU). Abnormal coagulation tests in critically ill patients are most frequently a result of the disease process, such as severe sepsis, organ failure, hypothermia, hypocalcaemia or acidosis. Coagulopathy in critical care may therefore range from profound derangement of haemostasis associated with major blood loss, to prolongation of PT and/or APTT in the absence of bleeding (Stanworth *et al*, 2011b; Hunt, 2014). Prolongation of PT and/or APTT do not always reflect bleeding risk in a critically ill patient and abnormalities are frequently due to vitamin K deficiency, or the presence of coagulation factor inhibitors, acquired through a critical illness.

In a small randomised controlled trial (RCT) (n = 81 patients) comparing FFP with no FFP in critically ill patients with an INR of 1·5 -, there was no significant difference in the incidence of bleeding between the two groups (Muller *et al*, 2015). A prospective study of 119 intensive care patients undergoing tracheostomy demonstrated no difference in bleeding between patients with INR of ≤ 1·2, > 1·2 or 1·3–1·84. These patients also had thromboelastometry profiles carried out with results being within the normal range in all cases except one (Durila *et al*, 2015).

Patients with traumatic brain injuries often have abnormal coagulation studies and may require insertion of an intracranial pressure monitor. Published studies where coagulation results are described quote haemorrhagic complications in 2–15% (Martinez-Manas *et al*, 2000). No high-quality data exist to guide practice in patients with a modest derangement in INR or APTT. A retrospective study examined 157 patients with traumatic brain injury, stratified according to INR [0·8–1·2 (n = 103), 1·3–1·6 (n = 42), ≥ 1·7 (n = 12)]. Twenty-two patients had component therapy prior to bolt insertion, of which 10 were in the INR 1·3–1·6 group and 12 were in the INR>1·7 group. The study described infrequent bleeding complications with one case of petechial haemorrhage in each group and found that FFP transfusion was not consistently effective in correcting the INR (Davis *et al*, 2004).

Acquired vitamin K deficiency. Many patients in ICU who are seriously ill have inadequate vitamin K intake, resulting in prolongation of the PT. This should be corrected with oral or intravenous vitamin K administration. FFP is not recommended for correction of vitamin K deficiency in such patients in the absence of significant bleeding.

Recommendations:

- **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 FFP 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).**
- **Vitamin K should be administered in patients with prolonged PT that is likely to be due to acquired vitamin K deficiency (1B).**

Liver disease. Synthesis of coagulation factors (except FVIII) decreases as liver dysfunction worsens in both decompensated cirrhosis and acute liver failure. Prolongation of coagulation tests (PT and APTT) is common, together with a perception among clinicians that this signifies increased bleeding risk. Observational studies have demonstrated that the prolongation in clotting times is not necessarily indicative of bleeding risk in these individuals, particularly in the setting of common liver-related complications, such as variceal haemorrhage (Tripodi & Mannucci, 2007; Hshieh *et al*, 2015). Indeed, while some liver patients have some bleeding tendency, others have a prothrombotic tendency with the same PT prolongation. This is primarily because of rebalanced haemostasis, wherein the levels of endogenous anticoagulants are decreased in the same manner as the clotting factor levels. PT bore no relevance to bleeding risk in a study of acutely ill cirrhotic patients on intensive care. A fibrinogen level <0·6 g/l and a platelet count of $<30 \times 10^9$/l were the most important predictors of bleeding (Drolz *et al*, 2016).

The rates of spontaneous bleeding and bleeding secondary to minimally invasive procedures in patients with liver disease are both low (DeAngelis *et al*, 2016). However, there is variable clinical practice in the use of FFP and cryoprecipitate for prophylaxis in patients with liver disease (Desborough *et al*, 2016). Transfusion of FFP in advanced liver disease may not correct abnormalities in coagulation results, and evidence that transfusion can mitigate the risk of bleeding is lacking (Abdel-Wahab *et al*, 2006). Transfusion of blood components has a potential for harm due to associated increases in portal pressure in patients with decompensated cirrhosis (Giannini *et al*, 2014). The risk factors for variceal haemorrhage in chronic liver disease are increased portal pressure, renal impairment and sepsis, rather than imbalances in haemostasis. Despite non-haemostatic factors contributing to the bleeding risk, FFP is often transfused in patients bleeding from varices leading to volume expansion, which may increase the re-bleeding rate through further increase in portal hypertension. There is no good evidence that transfusion of FFP or cryoprecipitate reduces re-bleeding rates or is of any clinical benefit in patients with acute variceal haemorrhage, and there is variable opinion in published guidance on its utility (National Institute for Health and Care Excellence, 2012;Tripathi *et al*, 2015). The most recent guidance on variceal haemorrhage from the American Association for the study of liver diseases recommends against the use of FFP and the measurement of INR in this context (Garcia-Tsao *et al*, 2017).

FFP is also often administered prior to liver biopsy. However, liver patients at true increased risk of bleeding are likely to be better served by modification of the procedure itself – e.g. liver biopsy via the transjugular, not percutaneous, route – rather than by prior administration of blood products (Segal & Dzik, 2005; Rockey *et al*, 2009). International liver society guidelines and European Association for the Study of Liver do not endorse the routine use of FFP or cryoprecipitate for low risk procedures, such as abdominal paracentesis (Runyon, 2013, European Association for the Study of the Liver 2017).

Recommendations

- **PT and APTT do not reflect the true haemostatic status of patients with advanced liver disease. Abnormalities of**

PT and APTT need to be interpreted with caution in these patients (1C).
- **There is no good evidence to endorse the use of prophylactic FFP for correction of abnormal clotting tests in non-bleeding patients prior to interventions such as elective variceal banding (1C).**
- **We endorse the liver society recommendations that prophylactic transfusion of FFP and cryoprecipitate is not given in low bleeding risk procedures, such as paracentesis (1C).**
- **There is 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).**

Inherited single clotting factor deficiency

FFP is the only currently available replacement therapy for FV deficiency and combined deficiency of FV and FVIII. It may also be effective in other rare coagulation disorders in the case of emergencies where a more specific replacement therapy is unavailable, or if the diagnosis is uncertain (Mumford *et al*, 2014).

Recommendation

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

Other indications

For further details on diagnosis and management of disseminated intravascular coagulation, reversal of anticoagulant effects, management of major bleeding, TTP, and the use of plasma in children and neonates, please refer to the relevant BSH guidelines (Levi *et al*, 2009; Keeling *et al*, 2011, 2016; Scully *et al*, 2012; Makris *et al*, 2013; Wada *et al*, 2013; Hunt *et al*, 2015; New *et al*, 2016).

Safety and adverse effects of plasmas

Pathogen-reduced plasmas

Methylene blue-treated FFP (MBFFP). In France, MBFFP was withdrawn in 2012 due to concern about an increased frequency of allergic reactions compared to other plasma components (Agence Française de Sécurité Sanitaire des Produits de Santé [AFSSAPS] 2011). Analysis of reactions to MBFFP from Serious Hazard Of Transfusion (SHOT) data (2007-2013) has not demonstrated a statistically significant increase in overall acute transfusion reactions, and non-severe or severe allergic reactions when compared to standard FFP (Joint United Kingdom Blood Transfusion Services and Health Protection Agency Professional Advisory Committee, 2012). Therefore, MBFFP continues to be used in the UK and other countries, with no concerns about safety (Politis *et al*, 2014).

SDFFP. Analysis of SHOT plasma reaction rates showed a significant reduction in all acute reactions and in non-severe reactions when comparing SDFFP with standard FFP but there was no significant difference in the rates of severe allergic or severe hypotensive reactions (Bolton-Maggs, 2016).

Cryoprecipitate

Cryoprecipitate has similar risks to FFP for allergic and febrile reactions. It has also been implicated in cases of transfusion-related acute lung injury (TRALI) (Bolton-Maggs, 2016) from the devolved countries in the UK at a time when they had yet to institute a policy of excluding female plasma (all the UK countries have now moved to male-only plasma for cryoprecipitate).

Allergy

Acute transfusion reactions (allergic, hypotensive or severe febrile). Allergic, febrile and anaphylactic reactions are defined as those occurring within 24 h of transfusion and are the most common reactions following FFP transfusion. Reports of anaphylaxis in the UK remain stable at about 30–40 per year. It occurs early, usually within the first 15 min and the treatment of choice is adrenaline. The widespread use of antihistamines and steroids in this setting is not based on evidence.

Other reactions may occur later during transfusion or after completion. Review by component type demonstrates that febrile reactions are very uncommon with FFP but moderate and severe allergic and anaphylactic reactions are more likely with FFP than any other blood component.

Causes of acute transfusion reactions to plasma. Immunoglobulin A (IgA) deficiency, although comparatively common in the population, is rarely diagnosed in this setting (Sandler *et al*, 2015). From 2010 to 2014 only two patients who developed anaphylaxis after FFP were shown to have IgA deficiency with anti-IgA antibodies. An atopic tendency in the recipient is thought to be a major contributory factor to reactions (Savage *et al*, 2011).

Pulmonary Complications

Reports of suspected TRALI have decreased, while there has been increasing recognition of transfusion associated circulatory overload (TACO): 30–40 cases reported in 2009–2010 to over 80 each year in 2012–2016 (Bolton-Maggs & Poles,

2017). Cases of acute respiratory distress occurring within 24 h of transfusion that do not fit the definition for either TRALI or TACO are grouped as transfusion-associated dyspnoea. There is some evidence that patients with underlying inflammatory conditions are more susceptible to transfusion-associated dyspnoea (Garraud, 2016).

Transfusion-related acute lung injury. Risk reduction for TRALI began in 2003 with a gradual transition to male plasma donors. Now, 100% of FFP in the UK comes from male donors. Reported suspected TRALI cases have reduced from a peak of 36 in 2003 (Chapman & Williamson, 2008) to none in 2016. Deaths related to TRALI have also reduced to between none and four each year, with 12 deaths in the 12-year period 2004-2015 (Bolton-Maggs *et al*, 2016). However, many suspected TRALI cases are complex and the diagnosis is often not clear cut. The implicated components in TRALI are now red cells or platelets with no cases associated with FFP since 2009. In 2014 and 2015 patients developed TRALI after receiving cryoprecipitate pools containing plasma from female donors, all with concordant antibodies. SHOT recommended that cryoprecipitate should also be sourced from male donors only, as is the case for FFP (Bolton-Maggs *et al*, 2016), and this has now been put into practice in the UK.

Transfusion-associated circulatory overload. TACO is now the most frequent cause of death and major morbidity reported to SHOT since 2008, but other pulmonary conditions may present with similar symptoms and signs. SHOT analyses demonstrate that although elderly patients are particularly vulnerable, TACO may occur at any age and with small volumes of components (Bolton-Maggs & Poles, 2017). Patients should be fully assessed for risk factors prior to transfusion; these include concomitant intravenous fluids, pre-existing cardiac dysfunction, evidence of pre-existing circulatory overload, pre-existing pulmonary oedema and low body weight. SHOT recommends use of a checklist prior to blood transfusion of non-bleeding patients to assess the risk of TACO (Bolton-Maggs & Poles, 2017).

Infection

Transmission of infection by blood components is rare. In the 20 years of SHOT reporting there have been few reports associated with plasma components: six with FFP (four hepatitis E virus [HEV], one HBV, and one HIV in 1996) and one from cryoprecipitate (HEV in 2015) (Bolton-Maggs *et al*, 2016). Bacterial transmissions from plasma components have not been reported.

Graft-versus-host disease

There have been no case reports of FFP-associated graft-versus-host disease.

Disclaimer

While the advice and information in this guidance is believed to be true and accurate at the time of going to press, neither the authors, the BSH nor the publishers accept any legal responsibility for the content of this guidance.

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

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The BSH paid the expenses incurred during the writing of this guidance. All authors have made a declaration of interests to the BSH and Task Force Chairs which may be viewed on request. The following authors have undertaken: JT has received speaker fees from Octapharma; RC has received corporate sponsorship from Terumo, and Macopharma for research and development projects in relation to pathogen inactivation, and has collaborative research projects with Cerus. The following members of the writing group have no conflicts of interest to declare LG, SZ, CB, PBM, YK and SS.

Review Process

Members of the writing group will inform the writing group Chair if any new pertinent evidence becomes available that would alter the strength of the recommendations made in this document or render it obsolete. The document will be archived and removed from the BSH current guidelines website if it becomes obsolete. If new recommendations are made an addendum will be published on the BSH guidelines website (http://www.b-s-h.org.uk/guidelines/).

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Appendix S1. Variant Creutzfeldt-Jacob risk

References

Abdel-Wahab, O.I., Healy, B. & Dzik, W.H. (2006) Effect of fresh-frozen plasma transfusion on prothrombin time and bleeding in patients with mild coagulation abnormalities. *Transfusion*, **46**, 1279–1285.

AFSSAPS (2011) Rapport annuel hemovigilance 2010. Available at: http://www. hemovigilance-cncrh. fr/www2/ansm/rh_2010. Pdf (10 May 2017).

Alport, E.C., Callum, J.L., Nahirniak, S., Eurich, B. & Hume, H.A. (2008) Cryoprecipitate use in 25 Canadian hospitals: commonly used outside of the published guidelines. *Transfusion*, **48**, 2122–2127.

Backholer, L., Wiltshire, M., Proffitt, S., Cookson, P. & Cardigan, R. (2016) Paired comparison of methylene blue- and amotosalen-treated plasma and cryoprecipitate. *Vox Sanguinis*, **110**, 352–361.

Bolton-Maggs, P.H.B. (2016) The 2015 Annual SHOT Report. Available at: https://www.shotuk.org/wp-content/uploads/SHOT-2015-Annual-Report-Web-Edition-Final-bookmarked-1.pdf (22 February 2017)

Bolton-Maggs, P.H.B. & Poles, D. on behalf of the SHOT steering group. (2017) The 2016 Annual SHOT Report. Available at: https://www.shotuk.org/wp-content/uploads/SHOT-Report-2016_web_11th-July.pdf (25 August 2017)

Bolton-Maggs, P.H.B., New, V.H. & Tinegate, H. (2016) Use of and reactions to fresh frozen plasma in the UK. *ISBT Science Series*, **11**, 133–139.

Chapman, C.E. & Williamson, L.M. (2008) National Blood Service TRALI Reduction Policies: Implementation and Effect. *Transfusion medicine and hemotherapy*, **35**, 93–96.

Chee, Y.L., Crawford, J.C., Watson, H.G. & Greaves, M. (2008) Guidelines on the assessment of bleeding risk prior to surgery or invasive procedures. British Committee for Standards in Haematology. *British Journal of Haematology*, **140**, 496–504.

Chowdary, P., Saayman, A.G., Paulus, U., Findlay, G.P. & Collins, P.W. (2004) Efficacy of standard dose and 30 ml/kg fresh frozen plasma in correcting laboratory parameters of haemostasis in critically ill patients. *British Journal of Haematology*, **125**, 69–73.

Davis, J.W., Davis, I.C., Bennink, L.D., Hysell, S.E., Curtis, B.V., Kaups, K.L. & Bilello, J.F. (2004) Placement of intracranial pressure monitors: are "normal" coagulation parameters necessary? *Journal of Trauma*, **57**, 1173–1177.

DeAngelis, G.A., Khot, R., Haskal, Z.J., Maitland, H.S., Northup, P.G., Shah, N.L. & Caldwell, S.H. (2016) Bleeding risk and management in interventional procedures in chronic liver disease. *Journal of Vascular and Interventional Radiology*, **27**, 1665–1674.

Desborough, M.J., Hockley, B., Sekhar, M., Burroughs, A.K., Stanworth, S.J., Jairath, V. & National Audit, C. (2016) Patterns of blood component use in cirrhosis: a nationwide study. *Liver International: Official Journal of the International Association for the Study of the Liver*, **36**, 522–529.

Drolz, A., Horvatits, T., Roedl, K., Rutter, K., Staufer, K., Kneidinger, N., Holzinger, U., Zauner, C., Schellongowski, P., Heinz, G., Perkmann, T., Kluge, S., Trauner, M. & Fuhrmann, V. (2016) Coagulation parameters and major bleeding in critically ill patients with cirrhosis. *Hepatology*, **64**, 556–568.

Durila, M., Lukas, P., Astraverkhava, M., Berousek, J., Zabrodsky, M. & Vymazal, T. (2015) Tracheostomy in intensive care unit patients can be performed without bleeding complications in case of normal thromboelastometry results (EXTEM CT) despite increased PT-INR: a prospective pilot study. *BMC anesthesiology*, **15**, 89.

European Association for the Study of the Liver (2017) EASL Clinical Practical Guidelines on the management of acute (fulminant) liver failure. *Journal of Hepatology*, **66**, 1047–1081.

Garcia-Tsao, G., Abraldes, J.G., Berzigotti, A. & Bosch, J. (2017) Portal hypertensive bleeding in cirrhosis: Risk stratification, diagnosis, and management: 2016 practice guidance by the American Association for the study of liver diseases. *Hepatology*, **65**, 310–335.

Garraud, O. (2016) Introduction to post-transfusion inflammation and the potential role of biological response modifiers. *Blood Transfusion*, **14**, s14–s15.

Giannini, E.G., Stravitz, R.T. & Caldwell, S.H. (2014) Correction of hemostatic abnormalities and portal pressure variations in patients with cirrhosis. *Hepatology*, **60**, 1442.

Green, L., Backholer, L., Wiltshire, M., Platton, S., Stanworth, S.J. & Cardigan, R. (2016) The hemostatic properties of thawed pooled cryoprecipitate up to 72 hours. *Transfusion*, **56**, 1356–1361.

von Heymann, C., Pruss, A., Sander, M., Finkeldey, A., Ziemer, S., Kalus, U., Kiesewetter, H., Salama, A. & Spies, C. (2006) Thawing procedures and the time course of clotting factor activity in fresh-frozen plasma: a controlled laboratory investigation. *Anesthesia and Analgesia*, **103**, 969–974.

Holcomb, J.B., Jenkins, D., Rhee, P., Johannigman, J., Mahoney, P., Mehta, S., Cox, E.D., Gehrke, M.J., Beilman, G.J., Schreiber, M., Flaherty, S.F., Grathwohl, K.W., Spinella, P.C., Perkins, J.G., Beekley, A.C., McMullin, N.R., Park, M.S., Gonzalez, E.A., Wade, C.E., Dubick, M.A., Schwab, C.W., Moore, F.A., Champion, H.R., Hoyt, D.B. & Hess, J.R. (2007) Damage control resuscitation: directly addressing the early coagulopathy of trauma. *Journal of Trauma*, **62**, 307–310.

Hshieh, T.T., Kaung, A., Hussain, S., Curry, M.P. & Sundaram, V. (2015) The international normalized ratio does not reflect bleeding risk in esophageal variceal hemorrhage. *Saudi journal of gastroenterology*, **21**, 254–258.

Hunt, B.J. (2014) Bleeding and coagulopathies in critical care. *New England Journal of Medicine*, **370**, 2153.

Hunt, B.J., Allard, S., Keeling, D., Norfolk, D., Stanworth, S.J. & Pendry, K. (2015) A practical guideline for the haematological management of major haemorrhage. *British Journal of Haematology*, **170**, 788–803.

Joint United Kingdom Blood Transfusion Services and Health Protection Agency Professional Advisory Committee (2012) Position Statement. Methylene Blue-treated Plasma. Available at: www.transfusionguidelines.org/document-library/documents/position-statement-methylene-blue-treated-plasma/download-file/dl_ (15 December 2016).

Keeling, D., Baglin, T., Tait, C., Watson, H., Perry, D., Baglin, C., Kitchen, S. & Makris, M. (2011) Guidelines on oral anticoagulation with warfarin - fourth edition. *British Journal of Haematology*, **154**, 311–324.

Keeling, D., Tait, R.C. & Watson, H. & British Committee of Standards for Haematology. (2016) Peri-operative management of anticoagulation and antiplatelet therapy. *British Journal of Haematology*, **175**, 602–613.

Koch, C.A., Khalpey, Z.I. & Platt, J.L. (2004) Accommodation: preventing injury in transplantation and disease. *Journal of immunology*, **172**, 5143–5148.

Kuta, P., Hauck-Dlimi, B., Strobel, J., Zimmermann, R. & Eckstein, R. (2016) Quality of clotting factor activity in fresh frozen plasma at thaw with a microwave system and after storage at 4 degrees C for 48 hours. *Clin Lab*, **62**, 987–991.

Lawrie, A.S., Cardigan, R.A., Williamson, L.M., Machin, S.J. & Mackie, I.J. (2008) The dynamics of clot formation in fresh-frozen plasma. *Vox Sanguinis*, **94**, 306–314.

Lawrie, A.S., Green, L., Canciani, M.T., Mackie, I.J., Peyvandi, F., Scully, M.A. & Machin, S.J. (2010) The effect of prion reduction in solvent/detergent-treated plasma on haemostatic variables. *Vox Sanguinis*, **99**, 232–238.

Levi, M., Toh, C.H., Thachil, J. & Watson, H.G. (2009) Guidelines for the diagnosis and

management of disseminated intravascular coagulation. British Committee for Standards in Haematology. *British Journal of Haematology*, **145**, 24–33.

Makris, M., Van Veen, J.J., Tait, C.R., Mumford, A.D. & Laffan, M. (2013) Guideline on the management of bleeding in patients on antithrombotic agents. *British Journal of Haematology*, **160**, 35–46.

Martinez-Manas, R.M., Santamarta, D., de Campos, J.M. & Ferrer, E. (2000) Camino intracranial pressure monitor: prospective study of accuracy and complications. *Journal of Neurology, Neurosurgery and Psychiatry*, **69**, 82–86.

Muller, M.C. & Juffermans, N.P. (2015) Fresh frozen plasma transfusion fails to influence the hemostatic balance in critically ill patients with a coagulopathy: reply. *Journal of Thrombosis and Haemostasis*, **13**, 1943–1944.

Muller, M.C., Arbous, M.S., Spoelstra-de Man, A.M., Vink, R., Karakus, A., Straat, M., Binnekade, J.M., De Jonge, J.E., Vroom, M.B. & Juffermans, N.P. (2015) Transfusion of fresh-frozen plasma in critically ill patients with a coagulopathy before invasive procedures: a randomized clinical trial (CME). *Transfusion*, **55**, 26–35.

Mumford, A.D., Ackroyd, S., Alikhan, R., Bowles, L., Chowdary, P., Grainger, J., Mainwaring, J., Mathias, M. & O'Connell, N. (2014) Guideline for the diagnosis and management of the rare coagulation disorders: a United Kingdom Haemophilia Centre Doctors' Organization guideline on behalf of the British Committee for Standards in Haematology. *British Journal of Haematology*, **167**, 304–326.

National Institute for Health and Care Excellence (2012) Acute upper gastrointestinal bleeding in over 16s: management. Clinical guideline [CG141]. National Institute for Health and Care Excellence, London, UK. Available at: https://www.nice.org.uk/guidance/cg141

New, H.V., Berryman, J., Bolton-Maggs, P.H., Cantwell, C., Chalmers, E.A., Davies, T., Gottstein, R., Kelleher, A., Kumar, S., Morley, S.L. & Stanworth, S.J. & British Committee for Standards in Haematology. (2016) Guidelines on transfusion for fetuses, neonates and older children. *British Journal of Haematology*, **175**, 784–828.

O'Donghaile, D., Kelley, W., Klein, H.G. & Flegel, W.A. (2012) Recommendations for transfusion in ABO-incompatible hematopoietic stem cell transplantation. *Transfusion*, **52**, 456–458.

Patel, I.J., Davidson, J.C., Nikolic, B., Salazar, G.M., Schwartzberg, M.S., Walker, T.G. & Saad, W.A., & Standards of Practice Committee, with Cardiovascular and Interventional Radiological Society of Europe (CIRSE) Endorsement. (2012) Consensus guidelines for periprocedural management of coagulation status and hemostasis risk in percutaneous image-guided interventions. *Journal of Vascular and Interventional Radiology*, **23**, 727–736.

Politis, C., Kavallierou, L., Hantziara, S., Parara, M., Zervou, E., Katsarou, O., Hatzitaki, M., Fountouli, P., Gioka, A., Tzioura, K., Koumarianos, S., Asariotou, M. & Richardson, C. (2014) Haemovigilance data on the use of methylene blue virally inactivated fresh frozen plasma with the Theraflex MB-Plasma System in comparison to quarantine plasma: 11 years' experience. *Transfusion Medicine (Oxford, England)*, **24**, 316–320.

Rock, G. (2011) A comparison of methods of pathogen inactivation of FFP. *Vox Sanguinis*, **100**, 169–178.

Rockey, D.C., Caldwell, S.H., Goodman, Z.D., Nelson, R.C. & Smith, A.D. (2009) Liver biopsy. *Hepatology*, **49**, 1017–1044.

Runyon, B.A. & AASLD (2013) Introduction to the revised American Association for the Study of Liver Diseases Practice Guideline management of adult patients with ascites due to cirrhosis 2012. *Hepatology*, **57**, 1651–1653.

Sandler, S.G., Eder, A.F., Goldman, M. & Winters, J.L. (2015) The entity of immunoglobulin A-related anaphylactic transfusion reactions is not evidence based. *Transfusion*, **55**, 199–204.

Savage, W.J., Tobian, A.A., Savage, J.H., Hamilton, R.G. & Ness, P.M. (2011) Atopic predisposition of recipients in allergic transfusion reactions to apheresis platelets. *Transfusion*, **51**, 2337–2342.

Scully, M., Hunt, B.J., Benjamin, S., Liesner, R., Rose, P., Peyvandi, F., Cheung, B. & Machin, S.J. (2012) Guidelines on the diagnosis and management of thrombotic thrombocytopenic purpura and other thrombotic microangiopathies. *British Journal of Haematology*, **158**, 323–335.

Segal, J.B. & Dzik, W.H. (2005) Paucity of studies to support that abnormal coagulation test results predict bleeding in the setting of invasive procedures: an evidence-based review. *Transfusion*, **45**, 1413–1425.

Stanworth, S.J., Brunskill, S.J., Hyde, C.J., McClelland, D.B. & Murphy, M.F. (2004) Is fresh frozen plasma clinically effective? A systematic review of randomized controlled trials. *British Journal of Haematology*, **126**, 139–152.

Stanworth, S.J., Grant-Casey, J., Lowe, D., Laffan, M., New, H., Murphy, M.F. & Allard, S. (2011a) The use of fresh-frozen plasma in England: high levels of inappropriate use in adults and children. *Transfusion*, **51**, 62–70.

Stanworth, S.J., Walsh, T.S., Prescott, R.J., Lee, R.J., Watson, D.M. & Wyncoll, D. (2011b) A national study of plasma use in critical care: clinical indications, dose and effect on prothrombin time. *Critical Care*, **15**, R108.

Thiele, T., Hron, G., Kellner, S., Wasner, C., Westphal, A., Warkentin, T.E., Greinacher, A. & Selleng, K. (2016) Thrombin generation, ProC((R)) Global, prothrombin time and activated partial thromboplastin time in thawed plasma stored for seven days and after methylene blue/light pathogen inactivation. *Blood Transfusion*, **14**, 66–72.

Tinegate, H., Allard, S., Grant-Casey, J., Hennem, S., Kilner, M., Rowley, M., Seeney, F. & Stanworth, S. (2012) Cryoprecipitate for transfusion: which patients receive it and why? A study of patterns of use across three regions in England. *Transfusion Medicine (Oxford, England)*, **22**, 356–361.

Tripathi, D., Stanley, A.J., Hayes, P.C., Patch, D., Millson, C., Mehrzad, H., Austin, A., Ferguson, J.W., Olliff, S.P., Hudson, M. & Christie, J.M. (2015) U.K. guidelines on the management of variceal haemorrhage in cirrhotic patients. *Gut*, **64**, 1680–1704.

Tripodi, A. & Mannucci, P.M. (2007) Abnormalities of hemostasis in chronic liver disease: reappraisal of their clinical significance and need for clinical and laboratory research. *Journal of Hepatology*, **46**, 727–733.

Wada, H., Thachil, J., Di Nisio, M., Mathew, P., Kurosawa, S., Gando, S., Kim, H.K., Nielsen, J.D., Dempfle, C.E., Levi, M. & Toh, C.H. (2013) Guidance for diagnosis and treatment of DIC from harmonization of the recommendations from three guidelines. *Journal of Thrombosis and Haemostasis*, **11**, 761–767.

Whiting, P., Al, M., Westwood, M., Ramos, I.C., Ryder, S., Armstrong, N., Misso, K., Ross, J., Severens, J. & Kleijnen, J. (2015) Viscoelastic point-of-care testing to assist with the diagnosis, management and monitoring of haemostasis: a systematic review and cost-effectiveness analysis. *Health Technology Assessment*, **19**, 1–228.

Wikkelsø, A., Lunde, J., Johansen, M., Stensballe, J., Wetterslev, J., Moller, A.M. & Afshari, A. (2013) Fibrinogen concentrate in bleeding patients. *Cochrane Database Systematic Review*, **8**, CD008864.

Wikkelsø, A., Wetterslev, J., Møller, A.M. & Afshari, A. (2017 Apr) Thromboelastography (TEG) or rotational thromboelastometry (ROTEM) to monitor haemostatic treatment in bleeding patients: a systematic review with meta-analysis and trial sequential analysis. *Anaesthesia.*, **72**, 519–531.

Yang, L., Stanworth, S., Hopewell, S., Doree, C. & Murphy, M. (2012) Is fresh-frozen plasma clinically effective? An update of a systematic review of randomized controlled trials. *Transfusion*, **52**, 1673–1686.