bjh guideline

Guidelines for the use of fresh-frozen plasma, cryoprecipitate and cryosupernatant

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The indications for transfusing fresh-frozen plasma (FFP), cryoprecipitate and cryosupernatant plasma arc very limited. When transfused they can have unpredictable adverse effects. The risks of transmitting infection are similar to those of other blood components unless a pathogen-reduced plasma (PRP) is used. Of particular concern are allergic reactions and anaphylaxis, transfusion-related acute lung injury, and haemolysis from transfused antibodies to blood group antigens, especially A and B. FFP is not indicated in disseminated intravascular coagulation without bleeding, is only recommended as a plasma exchange medium for thrombotic thrombocytopenic purpura (for which cryosupernatant is a possible alternative), should never be used to reverse warfarin anticoagulation in the absence of severe bleeding, and has only a very limited place in prophylaxis prior to liver biopsy. When used for surgical or traumatic bleeding, FFP and cryoprecipitate doses should be guided by coagulation studies, which may include near-patient testing. FFP is not indicated to reverse vitamin K deficiency for neonates or patients in intensive care units. PRP may be used as an fiternative to FFP. In the UK, PRP from countries with a low ~ovine spongiform encephalopathy incidence is recommenled by the Departments of Health for children born after January 1996. Arrangements for limited supplies of single lonor PRP of non-UK origin are expected to be completed in. 2004. Batched pooled commercially prepared PRP from donors in the USA (Octaplas) is licensed and available in the JK. FFP must be thawed using a technique that avoids risk of bacterial contamination. Plastic packs containing any of these plasma products are brittle in the frozen state and must be handled with care.

Keywords: fresh-frozen plasma, clinical use, guideline.

Clinical indications for the use of fresh-frozen plasma (FFP), cryoprecipitate and cryosupernatant (see Section 10)

Single coagulation factor deficiencis (Section 10.1)

Fresh-frozen plasma should only be used to replace single inherited clotting factor deficiencies for which no virus-safe fractionated product is available. Currently applies mainly to factor (F) V.

Multiple coagulation factor deficiencies (Section 10.2); disseminated intravascular coagulation (DIC) (Sections 10.3 and 10.4)

Fresh-frozen plasma and platelets are indicated when there are demonstrable multi-factor deficiencies associated with severe bleeding and/or DIC.

Cryoprecipitate may be indicated if the plasma fibrinogen is less than 1 g/l, although there is no clear threshold for clinically significant hypofibrinogenaemia.

Fresh-frozen plasma is not indicated in DIC with no evidence of bleeding. There is no evidence that prophylactic replacement regimens prevent DIG or reduce transfusion requirements.

Thrombotic thrombocytopenic purpura (TTP) (Section 10.5)

Single volume daily plasma exchange should be commenced at presentation (grade A recommendation, level lb evidence) and ideally within 24 h (grade C recommendation, level IV evidence). Daily plasma exchange should continue for a mini

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mum of 2 d after remission is obtained (grade C recommendation, level IV evidence).

Reversal of warfarin effect (Section 10.6)

Over-anticoagulation fromexcessive effects of warfarin should he managed according to the British Committee for Standards in Haematologv Guidlines (BCSH, 1998). FFP has only a partial effect, is not the optimal treatment, and should never he used for the reversal of warfarin anticoagulation in the absence of severe bleeding (grade B recommendation, level Ila evidence).

Vitamin K deficiency in the intensive care unit (ICU) (Section 10.7)
Fresh-frozen plasma should not he used to correct prolonged clotting times in ICU patients; this should be managed with vitamin K (grade B recommendation, level Ila evidence).

Liver disease (Section 10.8)
Fresh-frozen plasma is advocated by some for the prevention of bleeding in patients with liver disease and a prolonged prothromhin time (PT), although the response may he unpredictable and complete normalization of the haemostatic defect does not always occur.

If FFP is given, coagulation tests should be repeated postinfusion to guide decision-making.

There is no evidence to substantiate the practice in many liver units of undertaking liver biopsy only if the PT is within 4 s of the control (grade C recommendation, level IV evidence).

Surgical bleeding and massive transfusion (Section 10.9)
Whether and how much FFP should be used for treating a patient with massive blood loss should he guided by timely tests ot coagulation, including near-patient tests. FFP should never he used as a simple volume replacement in adults or children (grade B recommendation, level IIb evidence).

Paedicitric use of FFP (Section 11.0) (see BCSH, 2004)

Children born after 1 January 1996 should only receive pathogen-reduced FFP (PRFFP) (see Section 3).

When bleeding due to haemorrhagic disease of the newborn (HDN) occurs, FFP 10—20 mI/kg is indicated, as well as intravenous vitamin K. Prothrombin complex concentrate (PCC) would reverse the defect, hut there are no data to guide dosage in this situation (grade C recommendation, level IV evidence).

Neonates with coagulopathy who are bleeding, or who are about to undergo an invasive procedure, should receive FFP and vitamin K (grade C recommendation, level IV evidence). Shortening of prolonged clotting times is unpredictable and should be checked following administration.

Routine administration of FFP to prevent periventricular haemorrhage (PVH) in preterm infants is not indicated (grade A recommendation, level IIb evidence).

Fresh-frozen plasma is not indicated in polycythaemia in infancy.

There are no definitive data to support clinical decisions regarding the use of FFP with low anti-T activity in neonates with T activation.

Choice of FFP
Fresh-frozen plasma prepared from units of whole blood (recovered FFP) and from plasmaphaeresis are therapeutically equivalent in terms of haemostasis and side-effect profile (grade A recommendation, level I evidence).

The risks of pathogen transmission are very small (see Section 9.5); the clinical benefits anticipated from using FFP should he weighed against the sequelae of possible pathogen transmission (grade B recommendation, level Il/Ill evidence).

Patients likely to receive multiple units of FFP should be considered for vaccination against hepatitis A and B (grade C recommendation, level IV evidence).

In addition, patients likely to receive large or repeated doses of FFP may benefit from products with a reduced risk of transmitting infection, such as pathogen-reduced plasma (PRP). 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 TTP (grade C recommendation, level IV evidence).

The two types of PRP available are methylene blue and light-treated FFP (MBFFP) and solvent detergent-treated FFP (SDFFP). Each type has certain potential drawbacks that may influence the clinical decision on which to use (see Section 3). Furthermore, even PRP may transmit hepatitis A virus (HAV) or parvovirus Bl9.

Blood group status (see Table I). Group 0 FFP should only hc given to group 0 patients. For patients of group A, B, or

Table I. Principles of selection of fresh-frozen plasma according to donor and recipient blood group (ABO).

Recipient group	0	A	B	AB
(a) High titre (HT) positive or HT untested units*				
1st choice	0	A	B	AB
2nd choice	A	AB	AB	A+
3rd choice	B	B+	A+	B+
4th choice	AB	—	-	-
(b) HT negative units ±				
1st choice	0	A	B	AB
2nd choice	A	B	A	A
3rd choice	B	AB	AB	B
4th choice	AB	—	-	-

Group 0 must only be given to group 0 recipients. Group AB plasma is haemolysin free, but often in short supply.
+Only suitable for emergency use in adults.
+Group 0 must only be given to group 0 recipients.

AB, FFP of the patient's ABO group should be the first choice. If this is not possible, FFP of a different group may be acceptable if it does not possess 'high-titre' anti-A or anti-B activity (grade B recommendation, level III evidence).

Infants or neonates who are not group 0 may be particularly susceptible to haemolysis from group 0 FFP because of the relatively high volumes required (grade B recommendation, level III evidence).

Handling of FFP, cryoprecipitate and cryosupernatant

Procedures for thawing any of these products must be designed to avoid bacterial contamination.

After thawing, and when FVIII replacement is not required, FFP and cryosupernatant may be stored at 4°C in an approved blood storage refrigerator before administration to the patient, so long as the infusion is completed within 24 h of thawing (grade B recommendation, level III evidence).

Purpose of this guideline

The purpose of this guideline is to assist clinical decisions about the transfusion of FFP. Many of the conventional and widely taught indications for the transfusion of FFP are not supported by reliable evidence of clinical benefit. Ihe largest avoidable risk to patients from transfusion is probably due to the transfusion of FFP for inappropriate or unproven clinical indications (Cohen, 1993). These guidelines are targeted to all clinical staff involved in acute care including clinical haematologists, paediatricians, surgeons, anaesthetists, blood transfusion practitioners, biomedical scientists, and nurses including ward and theatre staff.

Methods

These guidelines are based on MedLine literature searches using appropriate keywords (including: plasma, plasma + randomized, plasma + trial, plasma + therapy, plasma + liver, plasma + cardiac surgery, plasma + surgical bleeding, plasma + thawing and plasma .-+ storage). All these searches were repeated substituting either cryoprecipitate or cryosupernatant for plasma. A draft of the systematic review (Stanworth *et al,* 2004) was also consulted. Existing guidelines were also reviewed, including that by the College of American Pathologists (1994) and several published by the BCSH (1988, 1990a,b, 1992, 1994, 1998, 1999, 2003, 2O04). Grading of evidence and strength of recommendations used originated from the US Agency for Health Care Policy and Research (see Appendix A).

1. Introduction

1.1. Historical and current use of FFP

Fresh-frozen plasma has been available since 1941 and was initially often used as volume replacement. With the availability of albumin and hydroxyethvl starch, and a better understanding that FFP is contraindicated for volume expansion, it is now usually used in cases of excessive bleeding or to prevent bleeding in those patients with abnormal coagulation tests that are undergoing an invasive procedure. Its use has been extended to patients with a coagulopathv hut who are not bleeding (for instance, in the ICU).

The use of FFP in hospital practice has risen by over 20% in the past few years, 59% in the past year, and concern has been raised about the appropriateness of its clinical use. The UK Transfusion Services issued 365 547 units of FFP and 94 114 units of cryoprecipitate in 1999—2000; 374 760 units of FFP and 95 456 units of crvoprecipitate in 2000—2001; and 385 236 units of FFP and 88 253 units of crvoprecipitate in 2001—2002 [Serious Hazards of Transfusion (SHOT), 2001, 2002, 2003). The UK Census of 2001 revealed a total population of 58 789 194.

Indications for appropriate use of FFP, as then perceived. were last published by the BCSH in 1992. Three audits in London and Oxford between 1993 and 2000 identified that 34% of transfusions were for reasons outside those guidelines (Eagleton *et* a!, 2000). A similar unpublished audit, with comparable results, was conducted in the Wessex Region in 1998, and Stainshy and Burrowes-King (2001) have described the first phase of a national audit in England as showing , disappointing level of implementation of policies and strategies for the use of plasma components. Despite strict policies for release of FFP from blood banks, inappropriate use (19%in Oxford, and 1 5% in Southampton in 2000) remains a concern (O'Shaughnessy, 2000).

1.2. The problems of variant Creutzfeldt—Jakob disease (vCJD) and the use of non-UK plasma (see thev CJD position statement in the document library of the UK Blood Services; h ttp://www. transf usionguidelines. org. uk)

In 1996, the first cases of vCJD, a new and rapidly progressive spongiform encephalopathy, were described (Will *et al,* 1996). At that time, it was noted to be unique to the UK and followed the epidemic of bovine spongiform encephalopathv (BSE) that affected 200 000 cattle and resulted in the slaughter of 750 000 animals. By 1 December 2003, there were 143 cases of definite or probable vCJD. It is untreatable and universally fatal within months of the first appearance of symptoms, although there is considerable interest in the first two cases that have been treated with pentosan polysulphate (Dyer, 2003). The vCJD prion shows affinity for lymphoid tissue and has been demonstrated in the tonsillar tissue of affected individuals and in the appendix of an asymptomatic patient, months before obvious onset of disease (Hilton *et a!,* 2002). Animal experiments have demonstrated infectivity of both plasma and buffy coat as well as whole blood in transferring the infective prion agent (Houston *et al,* 2000; Hunter *et a!,* 2002). This evidence, along with studies showing that B lymphocytes appeared to be necessary for the transfer of prions from the periphery to the brain, resulted in the

universal leucocyte depletion of blood components in the UK, completed in November 1999 (Det Norske Veritas, 1999; Murphy, 1999).

Subsequent analysis on the distribution of normal cellular prion (PrP) has shown that plasma is a major source (68%) with only 26% present on platelets and the remainder on red cells and leucocvtes (MacGregor *et* a!, 1999). As the mechanism of infection appears to involve the alteration of the normal cellular PrP~ to PrP~, and as exclusion of UK donors for all products is neither feasible nor acceptable, it seemed prudent to exclude UK plasma for fractionation whilst still accepting UK donors for cellular products and individual units of FFP (Turner & Ironside, 1998). It is for these reasons that plasma for the production of 'batch products' in the UK has been sourced from the USA and Germany since 1998.

The risk of vCJD transmission by blood or blood products could be considerable. Fifteen people who later developed vCJD max' have donated blood in the UK. In December 2003, the UK Department of Health reported the)irst case of possible transmission of vCJD by transfusion (Pincock, 2004). In 2002, the UK Departments of Health issued a reconimendation that FFP for neonates and children born after I January 1996 be sourced from areas where BSE and vC}D are of low endemicity. Children born since this date and living in the UK have benefited from regulations enacted by the Food Standards Agency affecting meat quality, which keep infected material out of the human food supply. These are the Specified Bovine Materials Ban and the Over Thirty Months rule. Both rules have been enhanced progressively since 1996 (Food Standards Agency, 2003). The effect of these bans has reduced the risk of such children contracting vCJD from their diet to levels which may well be lower than the risk of them contracting vCJD from transfused blood donated by UK donors who- although showing no signs of vCJD -may be incubating it. This position will remain until there is more accurate data indicating the scale of the vCJD epidemic in UK adults.

Although sourcing materials for FFP production from donors residing in areas where BSE and vCJD are of low endemicity may introduce other risks (e.g. if prevalence of transfusion-transmissable diseases caused by known organisms is relatively high) most of these diseases can be effectively eliminated from plasma by pathogen reduction procedures. Although these procedures do not inactivate prions, by applying them to imported plasma the overall risks of transmitting infection (including vCJD) from treated products will be mitigated. At present two procedures are currently licensed to reduce pathogens in FFP; MBFFP (as currently applied by the UKBTS), and SDFFP (available commercially -Octaplas'). Because a methylene-blue/light process has been developed within the UKBTS, limited supplies of FFP of UK origin and treated this way are already available. Plans are nearing completion for the UKBTS to provide MBFFP sourced trom male donors in the United States. From 1998 Octaplas for use in the UK has been sourced by the manufacturer, Octapharma, from. donors in the United States.

Arguably, PRFFP sourced from non-UK untransfused male donors should be used wherever possible (see Sections 1.3 and 9.2 on the choice of untransfused men as donors). There are obvious difficulties in establishing a year of patient birth after which only the nllcrobiologically safest available FFP must be used, especially if many patients (such as adults) are excluded. Although extending the use of PRP sourced from noli-UK donors to all recipients deserves careful consideration, the main constraint at present is cost. The following guidelines preclude neither the use of non-PRFFP from UK donors, nor the use of PRP for older patients, although no specific conditions are identified for the latter option. As many elderly UK patients will have been exposed to BSE in their diet, the only justification for the use of PRP in adults would be a reduction in the risk of pathogen transmission. This is already low for FFP from UK donors (see Sect ion 9.4).

lhese issues emphasize the need to ensure that all blood products are prescribed only when appropriate.

1.3. The problems of transfusion-related acute lung injury (TRALI) and the use of plasma from male donors (see Section 9.2)

Transfusion-related acute lung injury is significantly but not solely associated with the presence of leucocyte alloantibodies in donor plasma. Such antibodies are found most frequently in women after pregnancy, and are not present in plasma from men unless they have been transfused. Even then, such antibodies seem less active than those found in women who have been pregnant. Restricting the source of plasma for FFP production to men seems likely to reduce the incidence of TRALI.

2. Specifications, preparation, storage and handling of FFP and cryoprecipitate

2.1. FFP

In the UK, FFP is produced from donations by previously tested donors, either of whole blood, which undergoes hard centrifugation, or by aphaeresis. The current guidelines (United Kingdom Blood Transfusion Services/National Institute for Biological Standards and Control, 2002) give the quality monitoring requirements, including the degree of platelet and leucocyte depletion, and specify that FFP should be rapidly frozen to a temperature that will maintain the activity of labile coagulation factors. Donations from first-time donors are not used to produce FFP.

- FFP prepared from units of whole blood and from plasmaphaeresis may differ only in the quantity of plasma in the pack. The volume may vary between 180 and 400 ml. Procedures for thawing FFP must be designed to avoid bacterial contamination (see Section 6.1).

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Table II. Fresh-frozen plasma (FFP) content of electrolytes, etc. (mmol/l; an average 'unit' of FFP contains 300 ml)

Na	165 (48 mmol/unit)
K	33 (10 mmol/unit)
Glucose	20
Calcium	18 (low)
Citrate	20
Lactate	3
PH	7.2-7.4
Phosphate	363 (high)

These values were determined in the Pathology Laboratories of Southampton University Hospitals Trust. The high sodium, glucose, citrate and phosphate levels derive from the anticoagulant preservative mixture, which also lowers the ionized calcium level.

- Collected plasma is frozen rapidly to —30°C, the recommended temperature for storage. The interval between collection and storage is no longer defined in the guidelines (United Kingdom Blood Transfusion Services/National Institute for Biological Standards and Control, 2002), provided the specification is achieved.
- When frozen, the plastic packs containing the FFP 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.
- Immediately after being thawed, the standard FFP must have at least 70 lU/ml of FVIII in at least 75% of the packs. This requirement has been reduced for PRP (see Section 3, and Table III).
- Packs should be inspected immediately before infusion and rejected, or referred for further opinion, if there is any unexpected appearance such as flocculation or discolouration, or apparent leaks when the pack is put under pressure. Other details of the quality monitoring required are available elsewhere (United Kingdom Blood Transfusion Services/National Institute for Biological Standards and Control, 2002).

Recommendation

Fresh-frozen plasma prepared from units of whole blood and from plasmaphaeresis are therapeutically equivalent in terms of haemostasis and side-effect profile (grade A recommendation, level I evidence).

2.2. Cryoprecipitate and cryosupernatant ('cryo-poor plasma')

The current guidelines (United Kingdom Blood Transfusion ~Services/National Institute for Biological Standards and Con~ol, 2002) specify cryoprecipitate as 'the cryoglobulin fraction ~of plasma obtained by thawing a single donation of FFP at 4 ± 2°C; while 'pla~ma, cryoprecipitate depleted' (also known as 'cryo-poor plasma' or 'cryosupernatant') is 'the supernatant plasma removed during the preparation of cryoprecipitate'. The precipitable cryoproteins are rich in FVIII, von Willebrand factor (VWF), FXIII, fibronectin and fibrinogen. After centrifugation, the cryoproteins are separated and resuspended in a reduced volume of plasma. Although the guidelines set no limit, most UK blood centres prepare cryoprecipitate in volumes of 20—40 ml. The cryoprecipitate specification requires that 75% of packs contain at least 140 mg of fibrinogen and 70 lU/mI of FVI1I. it should therefore he noted that multiple packs of cryoprecipitate may provide less fibrinogen than two or three packs of FFP (depending on volumes of original component in each final pool).

Cryosupernatant plasma is depleted in FVIII and fibrinogen; but whereas the FVIII concentration may only be about 011 IU/mI proportionately less fibrinogen may the removed, leaving up to 70% remaining (Shehata *et al*, 2001). ,Cryosupernatant is deficient in high molecular weight (HMW) multimers of VWF, but contains VWF metalloproteins.

3. Pathogen-reduced plasmas (PRFFP and PRP)

The UK Departments of Health have recommended that the FFP given to neonates and children born after 1 January 1996 should be obtained from an area free of BSE and subjected to pathogen-reduction procedures. Older patients whose previous exposure to other blood components is limited but who are likely to be exposed to many doses of FFP (such as plasma exchange for TTP) may also benefit if PRP is used, but it may be difficult to anticipate the likely scale of need. In order to reduce the risk of the recipient developing TRALI (see Section 9.3), the donors should preferably be male.

3.1. Methods of producing PRP: quality monitoring

There are two methods of inactivating pathogens in plasma for clinical use: treatment with methylene blue and light (MBFFP); and solvent detergent (SDFFP). The key features of these products are shown in Table III (modified from Williamson, 2001).

3.1.1. MBFFP. The United Kingdom Blood Transfusion Services/National Institute for Biological Standards and Control (2002) specify MBFFP in which the pathogen-reducing methylene blue is not removed (so the product will contain about 1.0 p.mol of methylene blue) and also 'FFP, methylene blue-treated and removed' which contains no more than 0.30 p.mol of methylene blue. The latter option is usually preferred. MBFFP derived from UK donors of group AB is available for children and neonates.

At the time of writing (December 2003) supplies of the different types of MBFFP varied geographically within the UK,

Table III. A comparison of standard fresh-frozen plasma (FFP) with methylene blue-treated FFP and solvent detergent-treated FFP.

	Standard FFP	Methylene blue FFP*	Solvent detergent FFP
Source	UK donors, all previously virus tested. Single unit format.	USA volunteers donors, all male. Single unit format.	Non-UK donors; pools of up to 380 l (600–1500 ABO identical donations)
Donation tests			
Serology	HIV, HBV, HCV, HTLV	HIV, HBV, HCV, HTLV	HIV, HBV, HCV, HTLV
Genomic	HCV	HCV, HIV	HAV, HCV, B19, HIV, HBV
Virus risk			
HIV 1 + 2	1:10 million	No proven cases reported to date for HIV, HBV, HCV (one possible HCV transmission)	No reported transmissions to date of HIV, HBV, HCV in SDFFP or SD treated plasma products
Hepatitis C	1:50 million		
Hepatitis B	1:1·2 million		
Hepatitis A	Rare event		None reported
Parvovirus B19	Rare event	No greater than for standard FFP. None reported to date.	Batch withdrawals due to possible B19 content. Seroconversion in patients no greater than with untreated FFP.
Volume	180–300 ml + 50 ml paediatric size.	235–305 ml + 30 ml paediatric size.	200 ml; no paediatric size.
Coagulation factor content	Variable between units. 75% units >0·7 IU/ml FVIII	Variable between units. 75%: units FVIII >0·5 IU/ml; all other factors >0·5 IU/ml; no reduction AT III, protein C, protein S. No coagulation factor/complement activation.	Constant within batch. All factors >0·5 IU/ml.
Cryoprecipitate/ cryosupernatant	Available	May become available	Not available
Residual additives	None	<0·3 μmol/l MB. No toxicity seen or predicted at this level, even in premature neonates.	<2 μg/ml TNBP**; <5 μg/ml Triton-X 100. Residual levels not toxic.
Allergic reactions	May be reduced by leucocyte depletion	Reactions attributable to cells would be expected to be reduced.	Probably less frequent than FFP.
Mild	1%	No data	
Severe	0·1%	No data	
Adverse reactions due to antibody		As for standard FFP	Pooling reduces all of these risks.
Red cell	Tested for high titre anti-A,B	Not tested for high titre anti-A,B	High titre anti-A,B not a problem since donations pooled.
TRALI	>20 cases/year (SHOT)	None reported to date.	Only one possible TRALI case reported
Thrombocytopenia	Very rare		
Cellular content	Leucocyte depleted; No need to RhD match	Leucocyte depleted, No need to RhD match	No intact cells or fragments; no need to Rh D match
Product licence	Not required	Medical device; CE marked	Licensed, batched product
Indications		As for FFP	As for FFP
Usage to date	300 000 units/year in UK	>1 000 000 units in Europe	3 000 000 units in Europe

TRALI, transfusion-related acute lung injury; SDFFP, solvent detergent treated FFP; AT III, antithrombin III.

*See also Garwood *et al* (2003).

**TNBP, tri-(N-butyl)-phosphate.

and no non-UK plasma was yet available. Although FFP from male donors may reduce the risk of inducing TRALI, such preparations are not universally available. MBFFP from AB male donors is sometimes available in packs containing 50- 75 ml. During 2004, donor plasma from parts of the world believed to be of low BSE incidence, and pathogen reduced by the MB process, will be supplied for children born after 1996 when it becomes available.

3.1.2. SDFFP. Earlier materials, such as the 'Octaplas' used by Solheim *et a!* (2000), were prepared from pools of 400 to 1200 donations. More recent batches are made from up to 2500 pooled units of thawed FFP. SDFFP lacks HMW-VWF and has a reduced activity of protein S. 'Octaplas' is licensed and available on prescription. The product must be ABO group compatible with the patient.

3.1.3. Pathogen-reduced cryoprecipitate and cryosupernatant currently these are not generally available in the UK.

3.1.4. Quality monitoring. The current guidelines (United Kingdom Blood Transfusion Services/National Institute for Biological Standards and Control, 2002) specify that, in addition to the features described in Section 2.1, MBFFP has at least 0.50 lU/ml of FVIII. This is in contrast with standard FFP (070 lU/ml FVIII).

3.2. Efficacy and safety

Each type of FFP has a spectrum of potential adverse effects; the decision on which to use may depend on specific clinical circumstances and availability.

3.2.1. MBFFP and SDFFP. Both pathogen reduction methods cause some loss of coagulation factors. MBFFP has relatively low FVIII and fibrinogen activity (Atance *et a!*, 2001). These authors also claim reduced clinical efficacy. SDFFP has reduced activity of VWF and FVIII. It also has reduced functional activity of protein S (Jam *et a!*, 2003; Yarranton *et al*, 2003).

3.2.2. MBFFP

Viral safety. There has been one possible, but not proven, case of HCV transmission from a single donor unit of 1BFFP (Pamphion, 2000). However, single donor products avoid the risk of pooling, which may cause 1 unit infectious for HCV or other non-inactivated organisms to infect many -recipients.

Toxicological safety. Doses of MB that are much larger than amount present in MBFFP are well established as a treatment for methemoglobmnaemia (Mansouri & Lurie, 1993). There is no need for concern regarding patients with glucose.6Lphosphate dehydrogenase deficiency (grade A recommendation, level I evidence.

3.2.3. SDFFP. Materials from different manufacturers may differ in detail and have different efficacy and safety profiles (Soiheim & Hellstern, 2003). The reduced activity of protein S has been associated with the development of venous thromboembolism (\'TE). Eight episodes in seven of 68 patients with TTP receiving plasma exchange were reported by Yarranton *et al* (2003). Jam *et a!* (2003) have reported an association of SDFFP with thromboembolic complications in patients undergoing liver transplantation. Concern has been expressed regarding possible transmission of non-lipid-coated viruses by PRFFP. In the USA, batches have been withdrawn because of possible parvovirus B19 transmission. Suppliers now specify levels of HAV and Bl9 antibodies in the preparation, and max' also define a cut off for B19 genomes. Studies of patients treated with SDFFP compared with FFP have not revealed excessive transmissions of non-lipid-coated viruses, but the number of patients studied is still small.

Recommendation

In any patient for whom PRI~ is being considered, the risks of HAV and parvovirus B19 transmission and their clinical sequelae should he weighed against the likely benefits (grade B reccomendation, level Il/Ill evideih.e).

4. Selection of FFP packs by blood group

The following recommendations have been updated from previous guidelines.

4.1. ABO blood group compatibility (see Table I)

Group 0 plasma is more likely to contain high titres of ABO antibodies than plasma from group A or B donors, although activities vary widely between donors. The UK Blood Services test all donations for 'high-titre' antibodies. Unreactive donations are labelled to indicate a relatively low risk of causing ABO related haemolysis. Although there were no reports of ABO-. associated haemolysis from FFP in the first 5 years of the SHOT scheme, in the year 2000 three patients of blood group A who received recovered pooled group 0 platelets suspended in plasma had haemolytic reactions; for one of these the platelets were obtained by aphaeresis and the plasma was not found to have high-titre haemolysins according to the testing criteria.

Fresh-frozen plasma which is not of the same ABO group as the patient should only be used if it contains no high-titre anti-A and anti-B; it is preferable to use group A FFP for group B patients and vice versa where ABO-identical FFP is not available. However, as no *in vitro* test can always predict *in **vivo*** haemolysis, especially when large volumes are transfused. clinicians and hospital blood bank staff should be aware that

haemolysis could occur with ABO-incompatible FFP. This includes plasma of group A given to patients of group B and vice versa, even if the donation has been tested and labelled high-titre negative' correctly according to the protocol.

Group AB FFP can be used in an emergency if the patient's ABO blood group is unknown, but is likely to be in short supply.

Recommendation

With regard to ABO blood groups, the first choice of FFP is that of the same ABO group as the patient. If this is not available, FFP of a different ABO group is acceptable so long as it has been shown not to possess anti-A or anti B activity above a Iimit designed to detect high titres FFP of group *0* should only he given to 0 recipients (grade B recommendation, level Ill evidence).

For infants and neonates, plasma should be free of clinically significant irregular blood group antibodies. FFP from group AB donors has no anti-A or anti-B antibodies, and is frequently preferred.

Recommendation

Group 0 FFP should not be used in infants or neonates who are not group 0 because the relatively large volumes required can lead to passive immune haemolysis (grade B recommendation, level III evidence).

4.2. *Rh blood group compatibility*

Although FFP and MBFFP may contain small amounts of red cell stroma, sensitization following the administration of Rh D-positive FFP to Rh D-negative patients is most unlikely as stroma is less immunogenic than intact red cells (Mollison, 1972). The 10th edition of the Council of Europe Guidelines do not require FFP packs to be labelled according to their Rh Status (Council of Europe, 2004).

Recomemndation

Fresh-frozen plasma, MBFFP and SDFFP of any Rh type may be given regardless of the Rh status of the recipient. No anti-D prophylaxis is required if Rh D-negative patients receive Rh D-positive FFP (grade B recommendation, level I La evidence).

Dosage

The volume of each pack is stated on the label and may vary between 400 ml. The traditional dose of I0—15 ml o! plasma per kg body weight may have to be exceeded in massive bleeding (Helistern & Haubelt, 2002). Therefore, the dose depends on the clinical situation and its monitoring.

6. Thawing and storage of thawed product

Frozen plastic containers are brittle and vulnerable to damage, particularly at the seams and the attached tube remnants, which can be snapped off with ease.

6. 1. Thawing of FFP, cryoprecipirate and cryosupernatant

Frozen plasma products must be thawed at 37°C (if thawed at 4°C, cryoprecipitate will form). There are several ways this can he achieved, the most common of which uses a recirculating water bath. This carries a risk of bacterial contamination and must be maintained according to a controlled sterility protocol. Dry heating systems, which avoid denaturing the plasma proteins, are preferred.

6.1.1. Dry ovens (temperature controlled fan-assisted incubator).

These may have a lower potential *for* contaminating FFP packs with microbes, although they are usually of limited capacity. The time for thawing the FFP is usually 10 mm for 2 units.

6.1.2. Microwave ovens. Although these defrost in 2—3 mm, they have the disadvantage of being expensive and 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. 5,

6.1.3. Water baths. It is essential to place the primary FFP pack in a vacuum-sealed over-wrap to protect it from 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. Water baths used for thawing FFP must only be used for this purpose. They should be cleaned regularly (at least once a day) and filled with clean, laboratory grade water. Water bath use and maintenance schedules should be described by a specific standard operating procedure. All maintenance should be logged. The average time for 2 units to thaw is 20 mm.

6.2. Storage after thawing

Thawed plasma and cryosupernatant should be kept at 4°C if there is any delay in transfusion. Current UK guidelines United Kingdom Blood Transfusion Services/National Insti:ute for Biological Standards and Control, 2002), require transfusion within 4 h; whereas the American Association of 3lood Banks (2002) allow a delay of up to 24 h. The FVIII activity in FFP will decline after 24 h at 4°C by up to 28%, but all other factors remain stable for 5 d (see Table IV). ihehat~i *e a!* (2001) showed that storing FFP for up to 72 h after thawing caused about 40% of the FVIII activity to be

Table ***W.*** Haemostatic factor content of thawed fresh-frozen plasma
(FFP), and after storage at 4°C. A typical unit of 300 ml includes (lU/ml), except fibrinogen (gil).

	Levels when freshly thawed	Levels at 24 h	Levels at 5 d
Fibrinogen	367	225	225
FIl	80	80	80
FV	80	75	66
FV11	90	80	72
FVIII	92	51	41
FIX	100		
FX	85	85	80
FXI	100		
FXII	83		
FXIII	100		
Antithrombjn III	100		
VWF	80*		

These values were determined in the Pathology Laboratories of Southampton Unive~sity Hospitals Trust. Protein C and antithrombin levels are in the 'normal range' *With some loss of HMW multimers, particularly if SD-treated.

lost, although the F\'III activity and fibrinogen content were still substantially higher than in cryosupernatant. The activities of FlI and FV in FFP were maintained up to 72 h after thawing. These authors recommended that FFP stored for up to 72 h after thawing can, like cryosupernatant plasma, be used when FVIII replacement is not required. Another concern is safety from contamination with microorganisms that may be introduced during thawing, particularly if a water bath is used. Proper protocols and documentation, and a method of thawing which does not rely on immersion in water, will reduce this risk. Therefore, further study is needed before post-thaw storage beyond 24 h could be recommended.

Recommendation

After thawing, and when FVIII replacement is not required, FFP and cryosupernatant may be stored at 4°C in an approved blood storage refrigerator before administration to the patient so long as the infusion is completed within 24 h of thawing (grade B recommendation, level III evidence).

7. Control of issue and transfusion

The recommendations, of the BCSH guidelines for the administration of blood and blood components and management of transfused patients should be followed (BCSH, 1990b, 1994, 1999). As for all blood components, FFP should be administered to adults and children only after being passed through a 170-200 jim filter, as provided in standard giving sets.

Fresh-frozen plasma and cryoprecipitate should be issued from hospital blood banks using the same criteria as for red cells and platelets. The same standard of care should be taken to ensure that blood samples are collected from the correct patient when completing the request form or prescription, and when administering and documenting the transfusion. Hospitals should have a policy for handling FFP that is in accordance with these guidelines.

8. Response to FFP transfusion

Responses should he monitored, as they will serve as a guide to further supportive care. If FFP is given because the patient is bleeding, the clinical response may well be the best indication of effectiveness of transfusion. If FFP is given to correct abnormal coagulation parameters, the degree of correction should be recorded. Monitoring may be through measuring coagulation activities by traditional laboratory techniques, or through various 'near-patient' testing devices; the chosen methods should be timely and suit the clinical situation.

9. Adverse effects

9.1. Allergy

Allergy resulting in urticaria has been reported in 1—3% of transfusions, whilst anaphylaxis is rare (Bjerrum & Jersild, 1971; SandIer *et* a!, 1995). In the first 6 years of the SHOT scheme, 23 allergic and 25 anaphylactic reactions were reported to FFP, and one acute reaction in which IgA antibodies were implicated. For patients who have proven sensitivity to IgA, IgA deficient plasma is available on request. Patients suffering severe adverse effects of transfusion should be managed according to McClelland (2001).

9.2. TRALI

Transfusion-related acute lung injury is manifest clinically as severe respiratory distress, with hypoxia, pulmonary oedema, infiltrates or 'white-out' on chest X-ray, and sometimes fever and hypotension, which usually develops within 4 h of transfusion (Kopto & Holland, 1999). It cannot be distinguished clinically from adult respiratory distress syndrome or other forms of acute lung Injury (Popovsky *et il.* 1992; Murphy. 2001; Palfi *et a!*, 2001). Symptoms usually improve after a few days, although morbid signs can persist for at least 7 d.

Since 1996, the SHOT scheme has received reports of TRALI in 109 transfusion recipients of whom 30% died usually of compound reasons. In the 15-month period 2001-2002, FFP was the implicated component in 12 of 22 cases of TRALI. Of these cases, one (who received only FFP) died.

According to some authors, TRALI develops in two steps (Silliman et al, 2003). First, a predisposing condition, such as

surgery or active infection, releases cytokines and encourages neutrophils to attach to the vascular endothelium particularly in the pulmonary capillaries. The second step is that lipid and other cytokines, or human leucocyte antigen or granulocyte alloantibodies (found in 80% of the donors in some series, most of whom are women who have been pregnant) cause further neutrophil priming, activation and pulmonary damage.

If alloantibodies to leucocytes are important in TRALI, the incidence associated with plasma might be reduced by using FFP from male donors. Plans for expediting such availability in parts of the UK may provide further support for this as yet unproved hypothesis. No substantiated case of TRALI has been reported after SDFFP. This may he because the pooling process dilutes any unit with high titre alloantibodies.

9.3. Complications associated will leucocyte depletion

Thcre are few reports ot complications. Those relating *to* red eyes' in the USA (a form of allergic conjunctivitis) were reported after red cells were given using one type of leuco-filter from one particular batch. Hypotension has occurred after bedside filtration of cellular products in patients on angiotensin converting enzyme inhibitors, but has not been a problem with prestorage filtration because bradykinin is rapidly degraded in normal plasma. Although bedside filtration is no longer performed in the UK, this is a reminder to report any complication, including red eye syndrome, to the SHOT scheme (Williamson, 2001).

94. *Infection*

The freezing process inactivates bacteria. Bacterial contamination and growth. with endotoxin production, prior to freezing is unlikely, and has not been reported in the UK in the past *5* years (Sazama, 1994; SHOT, 2001, 2002, 2003). The removal of cellular components also removes cell-associated bacteria, most protozoa (except *Tryponasoma*i) and cell-associated viruses. Thus, transmission of malaria, cytomegalovirus and human T-lymphotropic virus have not been reported with H-P. However, freezing does not remove free viruses such as hepatitis A, B and C, human immunodeficiency virus (HIV) 1 + 2, and parvovirus B19 (Pamphilon, 2000). Taking into account the exclusion of first-time donors for FFP production and HCV genome testing (Garwood *et a!,* 2003; R. Eglin & K. Davison, personal communication), the estimated residual risk that a unit of FFP might contain the following viruses is: 10 in 1.0 million for HIV 1 + 2; 0.2 in 10 million for hepatitis C, and 0.83 in 10 million for hepatitis B.

Nevertheless, vaccination for hepatitis A and for hepatitis B should be considered for patients who are transfused frequently. Note, the vaccine for hepatitis A is not licensed for children younger than 2 years old.

Recommendation

Patients likely to receive multiple units of FFP, such as those with a congenital coagulopathy, should be considered for vaccination against hepatitis A and B (grade C recommendation, level IV evidence).

9.5. Graft versus host disease (GvHD)

There have been rio case reports of FFP-associated GvHD. FFP does not need to be irradiated.

9.6. VTE

See Section 3.2.3 (VTE associated with use of SDFFP in plasma exchange for TTP).

9.7. Reporting of adverse reactions

As both SDFFP and MBFFP are new products to the UK, it is important to report unexpected problems. For SDFFP the 'Yellow Card' system of the Medicines Control Agency for drug reactions applies. Adverse reactions to MBFFP should be discussed immediately with the supplying blood centre, and adverse reactions to either MBFFP or SDFFP, as well as to cryoprecipitate and cryosupernatant, should be reported to the SHOT office (details in Appendix B).

10. Clinical indications for the use of FFP, cryoprecipitate and cryosupernatant

10. 1. Single factor deficiencies

Fresh-frozen plasma should only be used to replace single inherited clotting factor deficiencies for which no virus-safe fractionated product is available. Currently, this only applies to FV. FFP should also be used, rather than FXI concentrate, in patients with congenital FXIdeficiency where there is concern about the potential thrombogenicity of FXI, for example, during the peripartum period (see recommendation in Section 3.2.3). More details about individual clotting factor concentrates and their application are available in the United Kingdom Haemophilia Centre Directors' Organisation (1997, 2003). PRP is recommended for children born after 1 January 1996, and there is a case for considering PRP (Section 3) for patients of all ages.

10.2. Multiple coagulation factor deficiencies

Fresh-frozen plasma is indicated when there are multi-factor deficiencies associated with severe bleeding and or DIC, as indicated in the following paragraphs.

10.3. Hypofibrinogenaemia

The most common use for cryoprecipitate is to enhance fibrinogen levels in dysfibrinogenaemia and the acquired hypofibrinogenaemia seen in massive transfusion and DIC. Treatment is usually indicated if plasma fibrinogen is less than I *g/l,* although there is no absolute threshold value for diagnosing clinically significant hypofibrinogenaemia. Results of fibrinogen assays vary according to the method used. A pathogen reduced fibrinogen concentrate of higher purity is under development but not yet available.

10.4. DIC (see Section 10.9.2)

Disseminated intravascular coagulation occurs when septicaemia, massive blood loss, severe vessel injury or toxins (such as snake venom, amniotic fluid, pancreatic enzymes) trigger the haemostatic mechanism. This may be clinically compensated and only demonstrable by laboratory tests. However, a 'trigger' may cause decompensation, resulting in overt microvascular bleeding as well as microangiopathic thrombosis. All coagulation factors are depleted, but particularly fibrinogen and FV, FVIII and FXIII.

Treating the underlying cause is the cornerstone of managing DIC. Although transfusion support may be needed, there is no consensus regarding optimal treatment. If the patient is bleeding, a combination of FFP, platelets and cryoprecipitate is indicated. However, if there is no bleeding, blood products are not indicated, whatever the results of the laboratory tests, and there is no evidence for prophylaxis with platelets or plasma (Levi & ten Cate, 1999).

10.5. TTP (Machin, 1984; BCSH, 2003)

Most patients with TTP have normal or near-normal clotting tests, although in a few patients late findings may be similar to those found in DIC — low platelet count, abnormal PT and activated partial thromboplastin time (APTT). Neurological abnormalities develop late, and indicate serious deterioration requiring prompt intervention. Furlan *et* a! (1998) demonstrated that most patients are deficient in an active metalloproteinase enzyme resulting in the accumulation of HMW-VWF, which leads to excess platelet activation and consumption.

The mainstay of treatment of acute TTP is daily plasma exchange (Evans *et a!,* 1999). Prior to its institution mortality rates were in excess of 90%. With plasma infusion alone mortality rates improved to 37% and plasma exchange improved mortality further to 22%. All forms of FFP contain the missing enzyme, but FFP lacking HMW-VWF may be preferred, namely SDFFP (Harrison *et a!,* 1996) or cryosupernatant (cryo-poor FFP). This is based on a study using historical controls (Rock *et a!,* 1996), is currently the subject of a Canadian randomized trial of cryosupernatant *versus* SD FFP, but is in contrast to a report by Zeigler *et a!* (2001).

Methylene blue and light-treated FFP is also efficacious in this setting, but may require more plasma exchange procedures (De la Rubia *eta!,* 2001). Although no randomized studies have been carried out to compare SD and MB products in this scenario, De Ia Rubia *et al* (2001) stated that MBFFP was less efficacious than standard FFP (grade C recommendation, level III evidence). SDFFP has been associated with the development of VTE when used as the plasma exchange medium in TTP. MB cryosupernatant may be more effective than standard FFP in the treatment of TTP (grade C recommendation, level III evidence), but at the time of writing is not routinely available in the UK.

Although plasma exchange with FFP is undoubtedly effective, the optimal regimen has not been determined, but the current recommendation is for at least l.0 plasma volume exchange daily until at least 2 d after remission is achieved (defined as normal neurology, platelet count over 150 x $I0^{9/1}$, normal lactate dehydrogenase levels and rising haemoglobin concentration). -

Recommendation

Single volume daily plasma exchange should ideally be begun at presentation (grade A recommendation, level lb evidence) and preferably within 24 h of presentation (grade C recommendation, level IV). Daily plasma exchange should continue for a minimum of 2 d after remission is obtained (grade C recommendation. level IV evidence).

10.6. Reversal of warfarin effect (see BCSH, 1990b; BCSH, 1998; Baglin, 1998; *Makris & Watson, 2001)*

Warfarin achieves its anticoagulant effect by inhibiting the vitamin K-facilitated carboxylation of FIl, FVII, FIX and FX. It thereby causes a functional deficiency of these procoagulants as well as of the anticoagulants proteins C and S. Warfarin's anticoagulant effects may be indicated by prolongation of the PT standardized by the international normalized ratio (INR). Target INRs for different thrombotic indications are given in

BCSH (1998).

Over-anticoagulation from excessive effects of warfarin can be reversed by a range of measures. From the most mild to the most severe circumstances these, are: withdrawing warfarin, giving vitamin K orally or parenterally (e.g. 5 mg by slow intravenous injection; grade B recommendation, level III evidence); transfusing FFP, or transfusing PCC (FII, FVII, FIX and FX, or separate infusions of FlI, FIX and FX concentrate and FVII concentrate). PCC (50 units/kg) is preferred to FFP. Details have been previously published (BCSH, 1998; Makris & Watson, 2001). Makris *et a!* (1997) showed that FFP contains insufficient concentration of the vitamin K factors (especially FIX) to reverse warfarin, supporting the finding that FFP is not

the optimal treatment. The BCSH guidelines on oral anticoagulation (BCSH, 1998) only recommend FFP (15 mI/kg) if there is major bleeding in a patient on warfarin if PCC is not available. Simultaneous administration of intravenous vitamin'K (5 mg) is also recommended, although they comment that levels of individual factors will typically remain less than 20%.

Reconi menda tion

Fresh-frozen plasma should never he used for the reversal of warfa~in anticoagulation when there is no evidence of severe bleeding (grade B recommendation, level Ila evidence).

10.7. Vitamin K policies in ICUs

Many patients in *ICU* have an inadequate vitamin K intake, particularly as parenteral iuitrition for the seriously ill usually has a restricted lipid contonent. This can lead to a prolonged PT, which is usually correctable by oral or injected vitamin K; the vitamin K intake should be sustained. FFP is not the treatment of choice for correcting inadequate vitamin K intake, even if clotting times are prolonged and an invasive procedure such as liver biopsy is being contemplated.

Recommendation

Intensive care unit patients should routinely receive vitamin K; 10 mg thrice weekly for adults and 0.3 mg per kg for children (grade B recommendation, level IIa evidence).

10.8. Liver disease

A variety of abnormalities of coagulation is seen in patients with liver disease. The magnitude of haemostatic abnormalities correlates with the degree of parenchymal damage. Reduced clotting factor synthesis, reflected in a prolonged PT, may predispose to bleeding, which may be exacerbated by dysfibrinogenaemia, thrombocytopenia and increased fibrinolysis. However, bleeding seldom occurs without a precipitating factor such as surgery, liver biopsy, or variceal rupture.

Fresh-frozen plasma is still advocated by some for the prevention of bleeding in patients with liver disease and a prolonged PT, although complete normalization of the haemostatic defect does not always occur (Williamson *et a!*, 1999). Routine use of FFP in these circumstances is therefore questionable. Platelet count and function, as well as vascular integrity, may be more important in these circumstances. Although PCCs have been shown to sufficiently correct abnormal clotting in liver disease (Green et *al,* 1975; Mannucci ***et*** *a!,* 1976), their use, even of the more recently available and less thrombogenic preparations, is not recommended in view of the high risk of DIC. For similar reasons, it may also be advisable to avoid giving SDFFP in this situation in view of the relative depletion of protein S.

Many liver units will only undertake liver biopsy if the PT is no more than 4 s longer than the upper limit of the normal range. There is no evidence to substantiate this. Other tests, such as the APTT' and thrombin time, do not normally help the decision-making. The response to FFP in liver disease is unpredictable. If FFP is given, repeat coagulation tests should be conducted as soon as the infusion is completed if it is to inform future decision-making. The merits of different infusion regimens, such as 5 rnl/kg/h *versus* intermittent boluses, have not been addressed. These are areas that need more research. More work needs to be conducted to establish the role, if any, of FFP in patients with liver disease to correct the bleeding tendency prior to biopsy.

Recommendation

Available evidence suggests that patients with liver disease and a PT more than 4 s longer than control are unlikely to benefit from FFP (grade G recommendation, level IV evidence).

10.9. Surgical bleeding

There is much debate about managing extensive bleeding arising during or after surgery. Goodnough (1999) described a wide variation in use of blood components, including FFP. Recent advances in understanding coagulation has also led to a re-appraisal of traditional clotting tests (PT, APTT, TT) and of near-patient tests such as the thromboelastogram (TEG) (Shore-Lesserson *et al,* 1999).

10.9.1. Coronary artery bypass graft (CABG) surgery. Patients undergoing GABG surgery are heavily heparinized to counteract the thrombogenicity of the bypass circuit, receiving 25 000—30 000 units of heparin. Their blood clotting is usually monitored by the activated clotting time (ACT), and at the end of surgery the heparin is reversed by protamine. Excessive postoperative bleeding may require more protamine (Bull *et al,* 1975). In the past, blood transfusion requirements have been high, but with improved facilities and techniques, the use of blood products has declined and many patients undergoing 'first-time' procedures now require no transfusion. Recently developed 'near-patient' coagulation testing devices have enabled surgeons and anaesthetists to manage non-surgical causes without transfusing blood products. These devices include the TEG, which is used in several UK Cardiac Centres; the Sonoclot (Hett *et al,* 1995); Plateletworks (Lakkis *et a!,* 2001); and the Platelet Function Analyser 100 (Wuillemin *et al,* 2002). The use of

pharmacological agents (such as tranexarnic acid and aprotonin), used either prophylactically or to curtail established bleeding when excessive fibrinolysis is suspected, have been accompanied by further reduction of blood product use (Horrow *et a!,* 1990; Hunt, 1991; Laupacis *et a!,* 1997; Peters & Noble, 1998).

10.9.2. Massive transfusion. This may be defined as the replacement of a patient's total blood volume with stored blood in less than 24 h, although alternative definitions allowing more anticipation (such as 50% blood volume loss within 3 h, or a loss of 150 mi/mm) may be a more useful clinical guide (Stainsby *et al,* 2000). Earlier guidelines and reports stated that early adequate resuscitation from shock is most important in preventing coagulopathy, although prophylactic replacement regimes neither prevent the process nor reduce transfusion requirements (Harke & Rahman, 1980; Mannucci *et a!,* 1982; Ciavarella *et a!,* 1987; Carson *et al,* 1988; Hewitt & Machin, 1990). Like most of these reports, the last BCSH guidelines on the management of extensive bleeding (BCSH, 1988)- were prepared when most transfused red cell components were either 'packed cells' or 'whole blood'. These contained 150—300 ml of donated plasma, while current UK preparation, with the exception of red cells for exchange transfusion, are resuspended in additive solutions and contain only about 30 ml residual plasma. BCSH (1988) stated that coagulation factor depletion is 'not a frequent occurrence' in massive blood loss in the absence of DIC which, when it occurs, is 'a likely consequence of delayed resuscitation'. They referred to the use of FFP in this situation guardedly, stating that, although in theory abnormal PT or APPT should indicate treatment with FFP, there is 'still a paucity of objective clinical evidence that it is of any benefit'. This situation has not substantially changed. Ciavarella *et a!* (1987) found that using replacement formulae to guide the use of blood products, including FFP, in massive bleeding was no more effective than basing replacement policies on timely clotting tests and clinical signs. They also stated that platelet counts correlate highly with microvascular bleeding and recommend platelet transfusion if this falls below 50 x *iO~Il.* More recently Hiippala *et al* (1995) found that clinically significant fibrinogen deficiency develops after a loss of about 150% of the blood volume — earlier than any other haemostatic abnormality — when plasma-poor red cell concentrates are used in replacing major blood loss; and Stainsby and Burrowes-King (2001) stated that 'use of FFP in massive transfusion (and cardiac surgery) should be guided by tests of coagulation, and if a rapid iurn-around cannot be achieved near-patients tests merit consideration'.

In their 'Commentary' on massive blood loss (which gives a 'template guideline'), Stainsby *et a!* (2000) recommended that, if bleeding continues after large volumes of (crystalloid-resuspended) red cells and platelets have been transfused, FFP and cryoprecipitate may be given so that the PT and APTT ratios are shortened to within l~5, and a fibrinogen concentration of at least 1.0 gil in plasma obtained.

Recommendation
Whether and how much FFP should be used for treating a patient with major blood loss should be guided by timely tests of coagulation (including near-patient tests). 'Formulae' to guide replacement strategies should not be used (grade B recommendation, level lib evidence).

11. Paediatnc use of FFP (see BCSH, 2004)

Children born after 1 January 1996 should only receive PRP (see Section *3).* MBFFP is available in small packs. SDFFP has been used in neonates and infants and no short-term toxicity has been reported, but clinical experience is limited. From early 2004, MBFFP, used for children, should be available from North America.

The most common causes of neonatal bleeding are vitamin K deficiency and inherited deficiencies of clotting factor activities. Prematurity may predispose to longer clotting times but on its own is not an indication for FFP. It should be noted that the clotting times of normal infant blood are longer than those of adults; those of premature infants (with reduced protein synthesis by the liver) may be even longer even in the absence of further pathology (Male *et a!,* 1999).

11.1. Inherited deficiencies of c!otting factors

See Section 10.1.

11.2. Haemorrhagic disease of the newborn (HDN)

Vitamin K prophylaxis for HDN has been routine in many countries since the 1960s. Without such prophylaxis, one in 200—400 live births will suffer from HDN (Zipursky, 1998). Those defined as at 'high risk' are babies born prematurely, born with liver disease or born to mothers on anticonvulsant drugs, or on isoniazid or warfarin (Department of Health, 1998). Early HDN (within 24 h) and classic HDN (2—5 d) are usually severe, while late HDN (2—12 weeks) is not often severe.

11.2.1. Management of acute haemorrhage. FFP

Recommendation
When haemorrhage due to HDN occurs, FFP (10-20 ml/kg) is indicated, as well as intravenous vitamin K (grade C recommendation, level IV evidence).

PCC (see Section 10.6). At present these agents are only conveniently available for use in centres with large paediatric ICUs and are not available to most paediatricians. As yet there is no data to guide dosage for their use, but they should he considered for severe HDN because of rapid reversibility of the

abnormal coagulopathy. All acute service hospitals should have access to PCCs.

Recommendation

Although the coagulation defect in HIDN may be reversed by PCC, there are no data to guide dosage in this situation (grade C recommendation, level IV evidence).

11.3. Neonates with coagulopathyy and bleeding, or at risk of bleeding from an invasive procedure

Fresh-frozen plasma is indicated for sick infants with hypoxia(respiratory distress), hypotension, sepsis or liver disorders associated with significant coagulopathy and bleeding, or who are at risk of bleeding from an invasive procedure because of significant coagulopathy.

Recoin iii enda tion

Neonates with significant coagulopathy, and risk of bleeding or who are about to undergo an invasive procedure, should receive approximately IS mi/kg of FFP as well as a dose of vitamin K (grade C recommendation, level IV evidence). Shortening of the prolonged clotting times is unpredictable and should be checked following administration.

11.4. Prevention of intra ventricular haemorrhage in preterm infants

A trial by the Northern Neonatal Nursing Initiative Trial Group (*1996)* showed that there was no evidence that the routine early use of FFP, or some other form of intravascular volume expansion. affects the risk of death or disability in babies born more than S weeks before term.

Recommendation

Routine administration of FFP to prevent PVH in preterm infants is not indicated (grade A recommendation, level IIb evidence).

11.5. *Po1cythaemia in infancy*

There is no indication for the use of FFP in this situation.

11.6. Red cell T antigen activation

T activation can occur through exposure of the crypt antigen on neonatal red cells when the patient is infected with clostridia, streptococcus or pneumococcuS in conditions such as necrotizing enterocolitis (NEC). 'Anti-T' antibody occurs naturally in virtually all donor plasma, but the clinical significance of T activation in relation to transfusion policies is not certain. Debate regarding appropriate transfusion management centres on whether transfusing plasma actually causes haemolysis (Eder & Manno, 2001). If clinically significant haemolysis occurs in this situation, a logical approach would be to restrict plasma transfusions to preparations containing only 'low-titre anti-T', which are not common. This approach has its advocates, but requires donations with low titres of anti-T to be identified.

T activation is associated with significant morbidity and mortality, and has been reported in up to 27% of selected infants with NEC requiring surgery, in contrast to 11% not requiring surgery and up to only 1% of otherwise normal infants. There are subtypes (T, Th, Tk, Tx, etc.) which may or may not be exposed by different infections; but Eder and Manno (2001) stated that discriminating types of T activation may not be practical or useful in a clinical setting, while Osborn *et al* (1999) found that the clinical course of NEC in infants with T-activated cells did not differ from those with Tk-activated cells. Furthermore, haemolysis rarely follows transfusion even in critically ill children with NEC and T activation, and when haemolysis does occur, it may not be immune mediated. Definitive data to support clinical decisions in these circumstances are lacking.

A randomized controlled trial of screening for T activation in high-risk infants, and provision of low titre anti-T plasma components, may provide definitive data on which to base recommendations (Eder & Manno, 2001), but such products may not be readily available and delay in treating with standard blood productes may be more hazardous for the patient.

Recoin inenda tions

In the absence of definitive data, each clinical unit should formulate its own policies and protocols for the investigation of any unexpected haemolysis associated with a transfusion of plasma to a baby with-NEC or a similar septic condition. A selective testing strategy and transfusion management protocol may be required (grade C recommendation, level IV evidence).

If there is a high suspicion of T-activated haemolysis, an exchange transfusion using low titre anti-T plasma and red cell products may be indicated. In this situation, administration of low anti-T titre (washed/resuspended) platelet concentrates may be indicated (grade C recommendation, level IV evidence). Note, avoiding transfusion of plasma-containing blood components in infants with T-activated red cells may risk suboptimal treatment for patients requiring haemostasis support (grade B recommendation, level Il/Ill evidence).

12. Advance directive for patients who, for reasons of conviction, refuse transfusion

These patients include 'Jehovah's Witnesses', who usually refuse plasma (FFP) but sometimes accept blood fraction (such as clotting factor concentrates even if they are no recombinant and contain donor-derived albumin as a vehicle) Every hospital should have an advance directive consent forrr which all such patients are required to sign on admission t hospital and before products are issued.

13. No justification for the use of FFP

13.1. Hypovolaemia

Fresh-frozen plasma should never be used as a simple volurn~ replacement in adults or in children. Crystalloids are safer. cheaper and more readily available.

13.2. Plasma exchange (except for TTP)

Although using plasma-free replacement fluids results in the progressive reduction of coagulation factors, immunoglohulins, complement and fibronectin; haemorrhage and/or infections are not encountered. In the rare event that haemorrhage occurs, a platelet count check before giving FFP is advisable. There may be a problem with pseudocholinesterase levels being low as a result of many plasma exchanges with saline/albumin if the patient then needs an anaesthetic. This can be corrected with FFP, although alternative drugs are available that can be used providing the anaesthetist is aware.

13.3. Reversal of prolonged INR in the absence of bleeding

There is no justification for using FFP to reverse a prolonged INR in the absence of bleeding.

Disclaimer

While the advice and information in these guidelines is believed to be true and accurate at the time of going to press, neither the authors nor the publishers can accept any legal responsibility or liability for any omissions or errors that may be made.

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