British Journal of Anaesthesia **113** (6): 922–34 (2014)
Advance Access publication 27 June 2014 · doi:10.1093/bja/aeu158

BJA

Cryoprecipitate therapy

B. Nascimento[1], L. T. Goodnough[2] and J. H. Levy[3]*

[1] Department of Surgery, Sunnybrook Health Sciences Centre, University of Toronto, Toronto, Canada
[2] Departments of Pathology and Medicine, Stanford University School of Medicine, Palo Alto, CA, USA
[3] Departments of Anesthesiology and Surgery, Duke University School of Medicine, 2301 Erwin Road, 5691H HAFS, Box 3094, Durham, NC 27710, USA

* Corresponding author. E-mail jerrold.levy@duke.edu

Editor's key points

- The authors review the evolving usage of cryoprecipitate, noting the uncertainty of appropriate dosing and optimal administration.
- They call for randomized controlled trials to help guide the use of cryoprecipitate and current, alternative therapeutic options.

Cryoprecipitate, originally developed as a therapy for patients with antihaemophilic factor deficiency, or haemophilia A, has been in use for almost 50 yr. However, cryoprecipitate is no longer administered according to its original purpose, and is now most commonly used to replenish fibrinogen levels in patients with acquired coagulopathy, such as in clinical settings with haemorrhage including cardiac surgery, trauma, liver transplantation (LT), or obstetric haemorrhage. Cryoprecipitate is a pooled product that does not undergo pathogen inactivation, and its administration has been associated with a number of adverse events, particularly transmission of blood-borne pathogens and transfusion-related acute lung injury. As a result of these safety concerns, along with emerging availability of alternative fibrinogen preparations, cryoprecipitate has been withdrawn from use in a number of European countries. Compared with the plasma from which it is prepared, cryoprecipitate contains a high concentration of coagulation factor VIII, coagulation factor XIII, and fibrinogen. Cryoprecipitate is usually licensed by regulatory authorities for the treatment of hypofibrinogenaemia, and recommended for supplementation when plasma fibrinogen levels decrease below 1 g litre^{-1}; however, this threshold is empiric and is not based on solid clinical evidence. Consequently, there is uncertainty over the appropriate dosing and optimal administration of cryoprecipitate, with some guidelines from professional societies to guide clinical practice. Randomized, controlled trials are needed to determine the clinical efficacy of cryoprecipitate, compared with the efficacy of alternative preparations. These trials will allow the development of evidence-based guidelines in order to inform physicians and guide clinical practice.

Keywords: blood; blood coagulation factors; coagulation protein disorders; cryoprecipitate coagulum; fibrinogen; transfusion

Concentrated antihaemophilic factor (AHF), or factor VIII (FVIII), was first produced in the 1940s by Edwin J. Cohn, via the fractionation of plasma with ethanol.[1] Modest amounts of this product were used as a treatment for haemophilia throughout the 1950s,[2] and in the early 1960s attempts were made to create an improved FVIII concentrate, which led to the discovery that cryoprecipitate, which forms when frozen plasma is allowed to thaw slowly at 1–10°C, is rich in fibrinogen, AHF, and factor XIII.[3] This product was first discovered and introduced by Pool and colleagues nearly 50 years ago, as a therapy for patients with AHF deficiency or haemophilia A;[4 5] however, its major use today is far removed from that for which it was originally intended. As a labile blood product derived from plasma, cryoprecipitate is enriched with fibrinogen and also high concentrations of FVIII, von Willebrand factor, and factor XIII. Its main use today is to replenish fibrinogen levels during coagulopathies associated with massive haemorrhage, in which fibrinogen decreases to a critical level[6 7] because of processes such as consumption through clotting, dilution, blood loss, or all.

Cryoprecipitate has been withdrawn from many European countries because of safety concerns such as the transmission of pathogens.[8 9] Instead, commercial fibrinogen preparations are available for fibrinogen replacement therapy.[10] Nevertheless, cryoprecipitate remains available for haemostatic therapy in several countries, including the USA and Canada, but Level 1 evidence in the form of prospective, randomized, controlled trials to support its efficacy is lacking. Here, we examine the clinical evidence and current guidelines for the use of cryoprecipitate to treat patients with acquired coagulopathy.

Preparation

Each unit (U) of cryoprecipitate is commonly prepared from 1 unit of fresh frozen plasma (FFP; plasma which is frozen

within 8 h of collection[11]). FFP is thawed at 1–6°C and centrifuged to remove the supernatant. The remaining insoluble precipitate, which is enriched with clotting factors, is re-suspended in plasma and refrozen at −18°C or colder. Alternatively, cryoprecipitate can be made from FP24, plasma which is frozen within 24 h of collection.[11]

Although cryoprecipitate is commonly believed to contain the majority of fibrinogen from plasma, in fact it contains only ~32%; the rest remains in the cryosupernatant.[12] However, because cryoprecipitate is re-suspended in a relatively small volume, it contains fibrinogen at a higher concentration than in plasma, although the actual concentration of fibrinogen in cryoprecipitate varies widely (~3–30 g litre^{-1}) because of variability between donors and institution-specific practices (Table 1). For example, one recent study measured the fibrinogen concentration of 11 different units of cryoprecipitate prepared in the same hospital;[25] the concentrations per unit ranged from 3.2 to 8.2 g litre^{-1}, with a mean concentration of 5.6 (1.7) g litre^{-1}. Volume per unit was high, at 35–40 ml [mean fibrinogen content 195.3 (58.3) mg U^{-1}].[25]

Table 1 Variability between centres of cryoprecipitate pool content and volume. *Values calculated from data provided

Source	Fibrinogen Per pack (mg U^{-1})	Volume (ml) Concentration (g litre^{-1})	
AABB, the American Red Cross, America's Blood Centers, and the Armed Services Blood Program[13]	≥150	≥7.5–30*	5–20
Council of Europe Recommendation, 12th Edition[14]	≥140	–	–
United Kingdom Blood Transfusion Services[15]	75% of packs should contain ≥140 mg	≥3.5–7*	20–40
Ahmed and colleagues[9] *Transfus Med*	290 (min 140 mg U^{-1})*	–	–
Alport and colleagues[16] *Transfusion*	250	16.7–25*	10–15
Bass and colleagues[17] *Vox Sang*	152 (50)	~6.6*	23.2 (6.6)
Callum and colleagues[18] *Transf Med Rev*	388 (range 120–796)	25.9–77.6*	5–15
Cardigan and colleagues[19] *Transfusion*	–	9.26 (SD 3.59)	
Caudill and colleagues[20] *Transfusion*	183 (44) (measured by Clauss fibrinogen) 319 (76) (measured by delta optical density)	8.8 (2.6) 15.2 (4.2)	
Franchini and Lippi[21] *Blood Transfus*	150–300*	~15 g litre^{-1}	10–20
Goodnight[22] *JAMA*	233–310 (range 63–417)	16–62*	5–15
Hoffman and Jenner[23] *Am J Clin Pathol*	281 (85)	16.9*	16.6
Ketchum and colleagues[24] *J Trauma*	250	25*	10
Lee and colleagues[25] *Transfusion*	195 (58)	5.6 (1.7)	35–40
Levy and colleagues[7] *Anesth Analg*	388 (range 120–796)	7.8–19.4*	20–50
Miller and colleagues[26] *American Red Cross*	≥150	≥7.5–30*	5–20
Millgan and colleagues[27] *J Clin Pathol*	–	8.4	–
Pantanowitz and colleagues [28] *Am J Clin Pathol*	150–300	10–30*	10–15
Poon[29] *Transf Med Res*	100–250	5–25*	10–20
Rahe-Meyer and Sørensen[30] *J Thromb Haemost*	200*	16.7*	60
Soloway and Bereznak[31] *Transfusion*	205 (30)	–	–
Stinger and colleagues[32] *J Trauma*	250*	16.7*	150
Theodoulou and colleagues [33] *Transfus Apher Sci*	150–300*	6–30*	10–20

Cryoprecipitate is usually prepared as a small pool from multiple donors rather than being issued in single units. In a recent UK report, 334 of 423 episodes treated with cryoprecipitate were treated with pooled cryoprecipitate.[34] However, the rate of pooling in other countries is unknown. Typically, five single units are pooled into one bag before issue. A commonly used adult dose is two pools (10 single units) of cryoprecipitate,[28 35] which should increase plasma fibrinogen levels by ~1 g litre^{-1},[36] depending on the clinical setting.

Pooling of cryoprecipitate can be performed before freezing by the central blood bank[6] or after thawing by licensed centres.[16] Centres in the EU must be licensed under the European Union Blood Directive, which in the UK includes only ~20% of laboratories.[37] Furthermore, licensed centres are subject to tight regulations, which has contributed to many facilities abandoning the practice of pooling cryoprecipitate.[38] At licensed centres pooling may be performed upon thawing, either by the blood bank or at the bedside. Each method leads to a delay, either before or after the treating physician receives the blood product from the blood bank, and the optimal method of pooling has not been investigated.[18 24] In addition, there have been concerns regarding how effectively the relatively low volume of cryoprecipitate is removed from bags during the pooling process.[39]

The freezing and thawing of plasma during the preparation process generates platelet membrane microparticles, which are concentrated by cryoprecipitation; the microparticle concentration of cryoprecipitate is 265-fold greater than that of the source plasma.[18] These microparticles have been found to contain glycoproteins which are able to interact with fibrinogen, platelets, von Willebrand factor, and other proteins, and this interaction may be enhanced by cryoprecipitation.[40] However, it is unknown whether these microparticles retain haemostatic function after freezing and thawing. Further studies are needed to determine their role in haemostasis, and to understand their potential role in adverse reactions to cryoprecipitate, such as immune reactions and thrombosis. In addition, a recent study has shown that the observable clots that are, in very rare cases, present in thawed cryoprecipitate pools are formed of both cross-linked (soluble) and non-cross-linked (insoluble) fibrin.[41] This study highlights the importance of filtration as a step in the blood collection process to protect patients from the potential harmful effects of transfusion of a blood product in which clots have already formed.

Clinical settings with acquired coagulopathy

Trauma

Despite the widespread and steadily increasing use of cryoprecipitate in many clinical settings for nearly 50 yr,[42] few studies have evaluated its efficacy. In the setting of trauma, the use of cryoprecipitate was investigated by Rourke and colleagues.[43] Coagulopathic patients administered with two pools of cryoprecipitate (the standard UK dose) maintained their average fibrinogen level throughout further transfusions of red blood cells (RBCs), although the results did not differ significantly from those observed in patients who had not received cryoprecipitate. In addition, there was no difference in mortality at either 24 h or 28 days between patients who received cryoprecipitate during infusion of the first 12 U RBCs and those who did not. However, for patients who survived the first 12 h after admission, the risk of death reduced by a factor of 0.91 for every 1 g fibrinogen administered within the first 12 h (P=0.08). Another study of trauma patients at an Army combat hospital found that a high ratio of fibrinogen to RBCs (≥0.2 g fibrinogen per unit of RBCs transfused) was independently associated with improved survival to hospital discharge.[32] The authors stated that this ratio could be achieved by transfusing one 10-unit bag of cryoprecipitate for every 10 U RBCs (assuming a cryoprecipitate fibrinogen content of 250 mg U^{-1}). This requirement could also be met by transfusing 1 U whole blood for every 4 U RBCs, or 1 U FFP for every 2 U RBCs. More recently, a retrospective observational study in a military hospital examined the use of cryoprecipitate and tranexamic acid alone and in combination to treat patients injured in combat.[44] Mortality was slightly lower for patients who received cryoprecipitate when compared with those who did not (21.4% *vs* 23.6%, respectively), and this benefit was associated with an odds ratio of 0.61 (95% confidence interval: 0.40–0.94). For patients administered with both cryoprecipitate and tranexamic acid, mortality rates were more than halved (11.6%), although mathematical modelling determined that this effect was not synergistic. Finally, in a secondary analysis of 1238 of 1245 PRospective Observational Multicenter Major Trauma Transfusion (PROMMTT) study patients who had transfusion data, cryoprecipitate use was not associated with in-hospital mortality after adjusting for baseline pH and haemoglobin; emergency department systolic arterial pressure and Glasgow Coma Scale (GCS) score; blood product use; injury severity score; and trauma centre. However, the majority of patients in this study did not receive cryoprecipitate.[45]

In 2007, the first version of the European guidelines on the management of bleeding after major trauma recommended treatment with fibrinogen concentrate or cryoprecipitate if significant bleeding is accompanied by a plasma fibrinogen level <1 g litre^{-1}.[46] Updates to these guidelines in 2010, and more recently in 2013, recommend supplementation of fibrinogen if significant bleeding is accompanied by thromboelastometric signs of a functional fibrinogen deficit or a plasma fibrinogen level of <1.5–2.0 g litre^{-1}.[47 48] Fibrinogen concentrate or cryoprecipitate are the recommended options for fibrinogen supplementation.

Obstetric patients

Acquired hypo- or afibrinogenaemia in pregnancy and consequent obstetric bleeding represents historically the first indication for fibrinogen supplementation in a non-congenital fibrinogen deficiency and was described as a case report in the literature by Moloney and colleagues in 1949.[49] Fibrinogen supplementation in this patient was done using Cohn Fraction I,[50 51] a fibrinogen enrichment technique (ethyl alcohol precipitation step under specific temperature, pH and ionic strength)

that was invented by Edwin Cohn in the 1940s.[1 52] Modern fibrinogen concentrates can be derived from either Cohn Fraction I or cryoprecipitate.

Current options to increase plasma fibrinogen level in obstetric and peripartum bleeding are mainly represented by cryoprecipitate[53–55] and fibrinogen concentrate.[56–60] In the UK guidelines for the management of postpartum haemorrhage (PPH) published in 2009 and updated in 2011, fibrinogen supplementation with cryoprecipitate is recommended if fibrinogen levels are <1.0 g litre^{-1}.[53] In contrast, the 2013 European guidelines on the management of severe perioperative bleeding[56] suggest that a higher trigger value for treating hypofibrinogenaemia may be required, given the physiologically elevated fibrinogen concentrations in pregnancy. This recommendation is also based on the initial observations of Charbit and colleagues[61] who showed that a plasma fibrinogen level of <2 g litre^{-1} had 100% positive predictive value for evolution to severe PPH, while a plasma fibrinogen level >4 g litre^{-1} had a 79% negative predictive value for this complication in women with non-severe PPH. Furthermore, the risk for severe PPH was 2.63-fold higher for each 1 g litre^{-1} decrease in the fibrinogen level.[61] The findings were confirmed in a more recent multicentric study which showed that women whose PPH did not worsen had a mean plasma fibrinogen level of 4.2 g litre^{-1} at the time of the PPH diagnosis, while women who went on to develop severe PPH had a mean of 3.4 g litre^{-1}.[62] In addition, the plasma fibrinogen level was associated with PPH severity independently of other factors [adjusted odds ratio 1.90 (1.16–3.09) for plasma fibrinogen level 2–3 g litre^{-1} and 11.99 (2.56–56.06) for fibrinogen <2 g litre^{-1}].[62] The 2013 European guidelines[56] also mention that empirical use of fibrinogen concentrate in bleeding patients (8–33% obstetric) has indicated potential reductions in blood loss and transfusion requirements, while studies investigating cryoprecipitate in obstetric patients were not identified at the time of writing of these guidelines.

Cardiac surgery

A small number of studies have examined the use of cryoprecipitate in cardiac surgery. In one study,[63] 30 patients undergoing thoracic aortic surgery were treated with FFP alone or FFP plus cryoprecipitate. Patients administered with cryoprecipitate experienced significantly less blood loss and required significantly fewer units of FFP. In another study, results of the thromboelastometry (ROTEM) fibrin-based assay (FIBTEM) during cardiopulmonary bypass were successfully used to predict cryoprecipitate transfusion requirement after reversal of protamine.[64] Another recent study found that administration of cryoprecipitate in 13 patients undergoing aortic surgery with deep hypothermic circulatory arrest raised mean plasma fibrinogen levels from 1.54 to 1.93 g litre^{-1} ($P=0.01$), and FIBTEM clot amplitude at 10 min (A10) from 3.5 to 5.8 mm ($P=0.04$).[25] *In vivo* recovery of fibrinogen, which indicates the percentage actual increase in plasma fibrinogen level compared with the expected increase after cryoprecipitate administration, was 61.6%. A retrospective analysis of patients receiving blood transfusions during cardiac surgery found that cryoprecipitate transfusion was independently associated with increased 5-yr mortality when compared with a non-transfused matched control group.[65]

Liver disease

One study investigated the use of cryoprecipitate for acquired hypofibrinogenaemia after massive haemorrhage in LT.[66] The study found that intraoperative transfusion of cryoprecipitate was associated with biliary complications, a significant source of patient morbidity and mortality in patients undergoing LT. The authors concluded that cryoprecipitate should only be used in this setting after careful consideration.

In patients with liver disease, the efficacy of cryoprecipitate was compared with that of FFP.[67] Seventeen patients received either 4 U FFP or 5 U cryoprecipitate. Although cryoprecipitate improved coagulopathy, 4 U FFP were more efficacious, produced a significantly greater improvement in international normalized ratio and activated partial thromboplastin time parameters, and resulted in less exposure to blood products than 5 U cryoprecipitate. Patients with liver disease often have multiple deficiencies of both procoagulant and anticoagulant factors. FFP contains both procoagulant and anticoagulant factors at close to normal or below normal concentrations, which may suggest that FFP is more suitable than cryoprecipitate for haemostatic therapy in these patients. At the same time, it must be kept in mind that transfusion may aggravate portal hypertension in these patients, and may paradoxically result in an increased bleeding tendency.[68] Therefore, the matter of the choice of haemostatic agent in this setting is still under debate.

Commercial fibrinogen preparations

Purified, pasteurized fibrinogen concentrate offers an alternative to cryoprecipitate for fibrinogen supplementation therapy, and two recent studies directly compared the efficacy of these two therapies.[9 33] The first report involved 100 transfusion episodes where either cryoprecipitate or fibrinogen concentrate were administered to patients with acquired hypofibrinogenaemia from a variety of clinical settings.[33] For patients administered with two pools of cryoprecipitate (10 U, corresponding to $\sim$1.8–2.2 g fibrinogen) the mean increase in plasma fibrinogen post-infusion was 0.26 g litre^{-1}, when compared with 0.44 g litre^{-1} for patients administered with 2 g fibrinogen concentrate. In addition, in 7 of 64 episodes where cryoprecipitate was administered, plasma fibrinogen levels decreased after infusion.[33] The second report was a retrospective study assessing the impact of the legislated replacement of cryoprecipitate with fibrinogen concentrate in Ireland in 2009, in the setting of major obstetric haemorrhage (MOH).[9] Blood product utilization and clinical outcome were assessed in 77 women with MOH during a 2.5-yr study period. A total of 14 women received cryoprecipitate and 20 received fibrinogen concentrate to treat hypofibrinogenaemia; haemostasis was successfully achieved in all cases. The correlation between dose and subsequent plasma fibrinogen level was stronger for fibrinogen

concentrate than for cryoprecipitate. Mean estimated blood loss, RBC transfusion, and plasma transfusion were lower in the fibrinogen group than in the cryoprecipitate group. Together, these results suggest that fibrinogen concentrate is at least as efficacious as cryoprecipitate in increasing plasma fibrinogen concentration, as a haemostatic agent in this setting, or both. A recent prospective, randomized, placebo-controlled study of patients undergoing elective cardiac surgery showed that patients administered with fibrinogen concentrate required significantly fewer allogeneic blood product transfusions when compared with patients in the placebo group (2 U *vs* 13 U, respectively).[69] Moreover, total avoidance of transfusion was achieved in nearly half of patients who received fibrinogen concentrate, *vs* none who had received placebo. Given that fibrinogen concentrate has a superior safety profile with regard to transmission of infectious diseases and a smaller transfusion volume, fibrinogen concentrate may be preferable as haemostatic therapy compared with cryoprecipitate.

In summary, despite the use of cryoprecipitate in current strategies to treat acquired coagulopathy and the current level of acceptance across a range of clinical settings, surprisingly few trials have examined its efficacy. Therefore, few conclusions can be drawn regarding its effectiveness. Large randomized controlled trials are urgently required to assess the efficacy of cryoprecipitate in correcting afibrinogenaemia and coagulopathy in patients with acquired bleeding. Such studies should take care to eliminate survivor bias (where patients who live longer have a greater probability of receiving treatment, leading to a false association between treatment and survival) and should compare the efficacy of cryoprecipitate with alternative approaches for fibrinogen replacement.

Safety

Few reports have described the rate of adverse events associated with cryoprecipitate, but results from a haemovigilance scheme in Quebec reported 6.57 events per 10 000 U (from a total of 13 692 U administered).[70]

Typical adverse events associated with the administration of cryoprecipitate include transmission of infectious diseases, transfusion-associated circulatory overload (TACO), and transfusion-related acute lung injury (TRALI). In a haemovigilance report in the UK from 1996 to 2003, the risk of TRALI was estimated at 1 in 317 000 U of cryoprecipitate issued,[71] although this may be a conservative estimate as TRALI is commonly underdiagnosed.[72] In the 2011 Serious Hazards of Transfusion report, only one incidence of an acute transfusion reaction was reported in the UK; the patient suffered from urticaria and a sudden decrease in cardiac output.[73] There have also been reports implicating cryoprecipitate in cases of acute anaphylactic shock, pulmonary oedema, intravascular haemolysis, and biliary complications.[42 66 74] FFP transfusion in non-massively transfused trauma patients has been shown to be associated with adverse events in a dose-dependent manner;[75] the same can be assumed to be true for cryoprecipitate. However, given that an adult dose of cryoprecipitate of ~10 U is sourced from multiple donors, it carries a greater risk of viral transmission per dose.[18] The risk of viral infection with cryoprecipitate is higher than that of fibrinogen concentrate, despite fibrinogen concentrate being produced from a larger donor pool, because the production of fibrinogen concentrate involves numerous stringent steps including pasteurization, adsorption, and precipitation, which remove or inactivate a wide range of enveloped and non-enveloped viruses.[76 77]

In most of the few countries in which it is still available, cryoprecipitate is no longer used as a treatment for haemophilia because of the lack of anti-viral processing. Although the lifetime exposure for patients with acquired bleeding is less than for patients with haemophilia, in our view its continued use in surgical settings and acquired bleeding nevertheless represents a double standard.[8 78 79] Cryoprecipitate has been accepted into general use as it has been used for many years, despite the absence of evidence to confirm efficacy and rigorous clinical proof of safety, as is currently required for the approval of new biological therapies. Given that cryoprecipitate is not virus-inactivated, is a pooled product, there is a lack of evidence demonstrating its efficacy and there are potentially safer alternatives currently available, it is unlikely that regulatory approval for its use would be granted today.[80]

Current licensing and regulatory status

Currently, cryoprecipitate is licensed for use in certain indications in the UK, the USA, Canada, Australia, and New Zealand; however, it has been withdrawn from use in most of Western Europe because of safety concerns. Cryoprecipitate was also recently withdrawn from use in Ireland, where fibrinogen concentrate is now used for fibrinogen supplementation in its place, despite a lack of formal licensing.[9]

Country-specific guidelines and recommendations for the content and use of cryoprecipitate are outlined in Table 2. In the UK, the British Committee for Standards in Haematology state that 75% of packs of cryoprecipitate should contain >140 mg fibrinogen and 70 IU ml^{-1} FVIII, usually prepared in a volume of 20–40 ml;[81] however, the Council of Europe recommend that all packs of cryoprecipitate must contain these concentrations of fibrinogen and FVIII as a minimum.[14] In the USA, the Food and Drug Administration (FDA) state that cryoprecipitate should contain a minimum of 150 mg fibrinogen and 80 IU FVIII;[13] these values are also recommended by Canadian guidelines[88] (Table 2).

The recommended dose of cryoprecipitate varies between institutes and countries. The FDA advises giving 0.2 U per kg bodyweight (equivalent to 14 U in a 70 kg adult) to raise plasma fibrinogen by ~0.5–1.0 g $litre^{-1}$,[13] the British Society of Haematology advises that a dose of ~10 U would raise plasma fibrinogen by ~1.0 mg dl^{-1},[36] and the European Trauma Guidelines suggest an initial dose of 3–4 g or 50 mg kg^{-1} (equivalent to 15–20 U in a 70 kg adult).[48] The American Association of Blood Banks[90] recommends dosing according to the following formulae to achieve a specific increase in plasma fibrinogen levels:

Table 2 Country-specific guidelines and recommendations for the content and use of cryoprecipitate. DDAVP, desmopressin; DIC, disseminated intravascular coagulopathy; FFP, fresh frozen plasma; tPA, tissue plasminogen activator; vWD, von Willebrand disease

Country	Licensing body/authority	Threshold for fibrinogen supplementation	Indication in acquired bleeding	Indication in congenital bleeding
UK	British Committee for Standards in Haematology (BCSH) *Guidelines for the use of fresh-frozen plasma, cryoprecipitate and cryosupernatant*[81] *Guidelines on the management of acute myeloid leukaemia in adults*[82]	<1.0 g litre^{-1}, although there is no clear threshold for diagnosing clinically significant hypofibrinogenaemia; aim for a target of 2 g litre^{-1} in acute promyelocytic leukaemia	• Most common use is to enhance fibrinogen levels in dysfibrinogenaemia and acquired hypofibrinogenaemia in massive transfusion and DIC • If there is no bleeding, blood products are not indicated regardless of laboratory test results; there is no evidence for prophylaxis	
UK	British Committee for Standards in Haematology (BCSH) *Guidelines on the management of massive blood loss*[83]	<1.0 g litre^{-1}	• FFP alone, if given in sufficient quantity, will correct fibrinogen but large volumes may be required • Cryoprecipitate therapy should be considered for afibrinogenaemia. It is rarely needed except in DIC	
UK	Association of Anaesthetists of Great Britain and Ireland (AAGBI) *Management of massive haemorrhage*[84]	<1.0 g litre^{-1} represents established haemostatic failure and is predictive of microvascular bleeding	• Fibrinogen replacement in established coagulopathy: give fibrinogen concentrate or cryoprecipitate if fibrinogen is unavailable • Fibrinogen replacement can be achieved much more rapidly and predictably with fibrinogen concentrate	
UK	British Society for Haematology (BSH) *Guidelines for the diagnosis and management of disseminated intravascular coagulation*[36]	<1.0 g litre^{-1}	• Severe hypofibrinogenaemia that persists despite FFP replacement • $\sim$10 donor units (containing $\sim$3 g fibrinogen) are expected to raise plasma fibrinogen by around 1 g litre^{-1}	
Europe	Task Force for Advanced Bleeding Care in Trauma *Management of bleeding after major trauma*[48]	$<1.5-2.0$ g litre^{-1}, in the presence of significant bleeding	• Supplementation with fibrinogen concentrate or cryoprecipitate is recommended if accompanied by thrombelastometric signs of a functional fibrinogen deficit in the presence of significant bleeding • Initial dose of 50 mg kg^{-1} cryoprecipitate ($\sim$15–20 units in a 70 kg adult) or use of fibrinogen concentrate. Repeat doses may be guided by ROTEM or laboratory assessment of fibrinogen levels	
Europe	Expert panel on behalf of the European LeukemiaNet *Management of acute promyelocytic leukemia*[85]	Target $>1-1.5$ g litre^{-1}	FFP, fibrinogen, cryoprecipitate and platelet transfusions, or all should be used as replacement therapy for low fibrinogen or platelet levels. Such replacement therapy should continue until disappearance of all clinical and laboratory signs of coagulopathy	
Australia	National Health and Medical Research Council (NHMRC) *Patient Blood Management Guidelines*[86]	<1.0 g litre^{-1} with clinical bleeding.	Patients with critical bleeding requiring massive transfusion	Second-line therapy for vWD and haemophilia A (Factor VIII deficiency). Should not be used if virus-inactivated factor concentrates are available

Continued

Table 2 *Continued*

Country	Licensing body/authority	Threshold for fibrinogen supplementation	Indication in acquired bleeding	Indication in congenital bleeding
USA	Circular of information for use of human blood and blood components[13]	–	• Control of bleeding associated with fibrinogen deficiency • Factor XIII deficiency • Second-line therapy for vWD and haemophilia A (Factor VIII deficiency). Should not be used if virus-inactivated factor concentrates are available • Control of uraemic bleeding only after other modalities have failed • Do not use unless results of laboratory studies indicate a specific haemostatic defect for which this product is indicated	Indicated as second-line therapy for vWD and haemophilia A. Coagulation factor preparations other than cryoprecipitate are preferred when blood component therapy is needed for management of vWD and haemophilia A. Every effort must be made to obtain preferred factor concentrates for haemophilia A patients before resorting to the use of cryoprecipitate
USA	The ASA *Practice Guidelines for Perioperative Blood Transfusion and Adjuvant Therapies: An Updated Report–2006*[87]	$<0.8–1.0$ g litre^{-1} with clinical bleeding	• When fibrinogen concentration is $<80–100$ mg dl^{-1} in the presence of excessive microvascular bleeding • To correct excessive microvascular bleeding in massively transfused patients when fibrinogen concentrations cannot be measured readily • Rarely indicated if fibrinogen concentration is >150 mg dl^{-1} • Bleeding patients with vWD should be treated with specific concentrates if available; cryoprecipitate is indicated if not	For patients with congenital fibrinogen deficiencies if factor concentrates are not available
Canada	Transfusion Medicine Advisory Group of British Columbia, Canada *Guidelines for cryoprecipitate transfusion*[88]	<1.0 g litre^{-1} with clinical bleeding	• FFP or cryoprecipitate indicated for hypodysfibrinogenaemia if fibrinogen levels are <1.0 g litre^{-1} and bleeding is present • If fibrinogen levels are >1.0 g litre^{-1} with active bleeding secondary to DIC, FFP should be given. Cryoprecipitate may be given when a large volume of plasma is contraindicated • Cryoprecipitate can be used to manage intracranial bleeding during or post-tPA administration in stroke patients, or other clinical scenarios • Cryoprecipitate can be used to treat FXIII deficiency if specific coagulation factor concentrate is not available	Cryoprecipitate can be used in vWD unresponsive to DDAVP and in those locations where Factor VIII: C concentrates are not available for haemophilia A patients. Every effort must be made to obtain the preferred recombinant factor concentrate for haemophiliacs before the use of cryoprecipitate
Worldwide	World Federation of Hemophilia (WFH) *Guidelines for the management of hemophilia*[89]			The WFH strongly recommends the use of viral-inactivated plasma-derived or recombinant concentrates in preference to cryoprecipitate for the treatment of haemophilia and other inherited bleeding disorders

(1) Blood volume=weight (kg)×70 ml kg^{-1}.
(2) Plasma volume=blood volume×(1−haematocrit).
(3) mg of fibrinogen required=(desired fibrinogen−current fibrinogen in mg dl^{-1})×plasma volume divided by 100 ml dl^{-1}.
(4) Bags of cryoprecipitate required=mg of fibrinogen divided by 250 mg.

Over the last 20 yr, clinical indications for the use of cryoprecipitate have changed because of several reasons; namely, a better understanding of haemostasis and coagulopathy and the critical role of fibrinogen levels in these processes, increased awareness of pathogen transfer and other side-effects associated with allogeneic blood products, and the introduction of alternative therapies such as coagulation factor concentrates. Currently, guidelines from the USA, Canada, the UK, and Australia are generally united in recommending the use of cryoprecipitate to treat acquired afibrinogenaemia where fibrinogen levels are diagnosed as falling below a set threshold, usually <1.0 g $litre^{-1}$,[35 36 68 81] although higher recommended minimum levels have been recently introduced[48] (discussed later in more detail). The majority of guidelines also state that cryoprecipitate should only be administered in the presence of clinical bleeding.[35 36 68 81] In the USA, Canada, the UK, and Australia, guidelines are in agreement that cryoprecipitate should not be used to treat von Willebrand disease or haemophilia A, or may only be considered if virus-inactivated factor concentrates or recombinant factor preparations are unavailable (Table 2).

The preference for use of factor concentrates over allogeneic blood products is also beginning to emerge in guidelines for the treatment of afibrinogenaemia. Recently, guidelines from the Association of Anaesthetists of Great Britain and Northern Ireland have stated that cryoprecipitate should only be used to treat established coagulopathy if fibrinogen concentrate is unavailable, as fibrinogen replacement can be achieved more rapidly and predictably with fibrinogen concentrate.[84]

Dosing strategies

Cryoprecipitate is indicated for use in acquired hypofibrinogenaemia and is administered in a wide range of clinical settings, the most common of which is cardiac surgery, accounting for ~32–45% of all transfusions.[16 34 91] A report from the UK estimated that 95% of cryoprecipitate given during cardiac surgery was administered in response to haemorrhage and not given prophylactically.[34] Cryoprecipitate is also commonly given to trauma (12–29%) and non-cardiac surgery (12–13%) patients,[16 34 91] and to patients in other clinical scenarios including obstetrics, liver failure, oncology, and gastrointestinal bleeding.[16 34 91] It is also commonly used in acute promyelocytic leukaemia, where fibrinogen supplementation with cryoprecipitate is recommended to target a plasma fibrinogen level of 1–2 g $litre^{-1}$ in coagulopathic patients.[82 85]

Despite similar recommended doses (as described above) and annual use [e.g. ~2.0 U per 1000 people annually in the UK (126 170 U[73]/62 million people) and ~1.8 U per 1000 people annually in Canada (46 000 U[92]/25 million people)] across institutions and countries, actual administered doses of cryoprecipitate vary widely, suggesting inconsistent practice and uncertainty over the evidence informing optimal use.[16 28 34 37 91]

The indications for cryoprecipitate have been developed in guidelines by some professional societies (Table 2). As described in the Circular of Information for Blood and Blood Components[13] and licensed by the FDA, use of cryoprecipitate is specified for patients with acquired hypofibrinogenaemia, which is almost always seen in acquired coagulopathies. In the course of transfusion, it is given almost exclusively after RBCs, FFP, and platelets. In a study of cryoprecipitate use in Canadian hospitals, a mean dose of 7.9 U was administered per patient across all clinical settings; however, cryoprecipitate was only administered after transfusion of an average of 10.5 U RBCs, 6.5 U plasma, and 9.4 U platelet concentrate.[91] A recent study of 1238 trauma patients found that the median time from admission to first administration of cryoprecipitate was 2.8 h (inter-quartile range, 1.7–4.5 h); this is essentially very late, given that the median time to death from haemorrhage in this study was 2.6 h.[45 93] In addition, a study in New Zealand found that under-dosing of cryoprecipitate was far more common than overdosing.[94] Almost a quarter of patients with a bodyweight >15 kg received less than half of the 1 U per 30 kg bodyweight dose specified by the New Zealand Blood Service guidelines.[94] During the study period, 134 episodes in 86 patients were identified where cryoprecipitate was not administered, despite fibrinogen levels of <1.0 g $litre^{-1}$ (*vs* 181 episodes where cryoprecipitate was administered).

There have also been widespread reports of inappropriate dosing of cryoprecipitate.[16 28 34 37 91 94] For example, up to 62% of cryoprecipitate transfusions were deemed as inappropriate in a survey in New South Wales, Australia,[95] and an audit of Canadian hospitals reported that the majority of cryoprecipitate use is not in accordance with published guidelines.[16] A study in the USA involving 88 transfusions of cryoprecipitate in 51 patients found that 20% of cryoprecipitate used during the study period was administered for inappropriate indications.[28] Moreover, in a survey of cryoprecipitate use in UK hospitals, cryoprecipitate was administered to 101/423 patients without prior assessment of fibrinogen levels (i.e. given 'blind').[34] Finally, an audit in Canada found that 9 of 25 hospitals did not have transfusion guidelines for cryoprecipitate in place.[16] In these hospitals, cryoprecipitate was more likely to be administered inappropriately, demonstrating the importance of clear transfusion guidelines.

Currently, many guidelines and massive transfusion protocols recommend administering cryoprecipitate for plasma fibrinogen levels of <1.0 g $litre^{-1}$; however, this threshold is not based on solid clinical evidence (discussed in more detail in a recent review by Levy and colleagues).[79] Recent recommendations suggest that higher target plasma fibrinogen levels may be more appropriate;[48 84 96] for example, the European Trauma Guidelines, which recommend supplementation for fibrinogen levels of <1.5–2.0 g $litre^{-1}$.[48] In addition,

different thresholds may be required in different clinical settings, such as paediatric surgery or PPH.[79] Finally, the standard cryoprecipitate dose recommended in most guidelines causes a modest increase in plasma fibrinogen levels in bleeding trauma patients. In a cohort of massively transfused trauma patients (who received no other blood products in the 2 h before cryoprecipitate transfusion), a dose of 8.7(1.7) U cryoprecipitate caused a mean increase in fibrinogen levels of 0.55(0.24) g litre^{-1}.[91 92]

Point-of-care monitoring

Most guidelines recommend that cryoprecipitate be administered in response to fibrinogen levels decreasing below a certain threshold; however, in an emergency setting, turnaround times for the Clauss fibrinogen assay are too long to effectively guide administration of haemostatic therapy in patients with acquired coagulopathic bleeding. In an attempt to address this issue, Chandler and colleagues proposed a revised fibrinogen assay in their emergency haemorrhage panel.[97] The revised assay resulted in emergency coagulation testing turnaround times for fibrinogen levels of $<$20 min for the majority of cases. Furthermore, viscoelastic methods such as ROTEM and thrombelastography (TEG) can be performed at the bedside and provide rapid assessment of multiple coagulation parameters. For each of these methods, a specific fibrin test is available (FIBTEM and the functional fibrinogen test, respectively). Point-of-care monitoring may prevent over- and under-dosing, potentially reducing side effects and costs while ensuring that patients are given sufficient coagulation therapy. Point-of-care tests are effective for guiding targeted haemostatic therapy; there is growing evidence that their use is associated with lower transfusion requirements for allogeneic blood products in a variety of clinical settings.[98–102] In addition, a favourable survival rate was observed in patients administered with fibrinogen concentrate with or without prothrombin complex concentrate guided by ROTEM.[103]

Although there is a growing body of literature on the use of viscoelastic tests to guide the administration of coagulation factor concentrates, few studies have been published on their use to guide administration of cryoprecipitate.[25 43 64 104] In an audit of cryoprecipitate transfusion in the UK, point-of-care testing was used in only 11% of patients.[34] Although point-of-care testing facilitates rapid diagnosis of coagulopathy, cryoprecipitate is not quickly available as it must be ordered from the blood bank, thawed and pooled, which can take 25–45 min.[16] Even if cryoprecipitate has been preordered, it takes ~30 min to infuse a standard dose of two pools. In contrast, fibrinogen concentrate is reconstituted as a smaller volume, which allows large doses to be administered in a few minutes.[103] In cases of severe bleeding, it has been reported that it is possible to infuse 1 g fibrinogen concentrate in 20 s.[105] Importantly, cryoprecipitate also contains varying concentrations of fibrinogen (Table 1) and is not as suitable as fibrinogen concentrate for targeted dosing.

Cost

Cost is highly influential in decision-making policies. Cryoprecipitate is generally perceived as being cheaper than fibrinogen concentrate; however, the true cost of blood products such as cryoprecipitate is higher than the direct acquisition cost of the drug: indirect costs must also be taken into account. Following manufacture, indirect costs include storage, preparation, thawing, processing, and compatibility testing. Moreover, blood products are wasted if they cannot be used as planned,[106] and haemovigilance schemes must be maintained.

Transfusion of cryoprecipitate is also affected by the cost of treating adverse events[107 108] and infectious disease associated with transfusion.[109] Methylene blue-treated cryoprecipitate undergoes viral inactivation and therefore may avoid some of these costs, but the acquisition cost is higher than that of fibrinogen concentrate.[77] In addition, transfusion of allogeneic blood products is associated with mortality caused by TRALI and TACO,[110] longer hospital stays and increased healthcare costs.[111] To date, the true cost of cryoprecipitate has not been calculated.

Future directions

Further developments may address one of the main concerns regarding the use of cryoprecipitate, namely the risk of pathogen transmission. Pathogen inactivation steps have previously been described for the production of FFP,[112] and recent studies have described the production of cryoprecipitate from plasma treated with riboflavin and UV light,[113] amotosalen and UV light[114] and solvent-detergent filtration.[115] However, as with pathogen-inactivated FFP, these products have reduced levels of coagulation factors, with ~35% less fibrinogen than standard plasma.[113 114] A retrospective analysis found that introduction of methylene blue-inactivated plasma led to an increase in demand for plasma and cryoprecipitate.[116] In addition, extra steps during production also add to the cost, although these may be offset by a reduction in the cost of treating adverse events.[117]

Fibrinogen concentrate may provide a favourable alternative to cryoprecipitate, such as is currently practiced in most of the EU. It can be stored at room temperature, is readily available for use, and is easy to reconstitute and administer. Fibrinogen concentrate also undergoes virus removal and inactivation steps, which have been shown to be effective against both enveloped and non-enveloped viruses.[76] These steps additionally remove antibodies and antigens, greatly reducing the risk of immunological and allergic reactions. Results from recent clinical studies show promising efficacy of fibrinogen concentrate in various clinical settings.[69 98 100 105 118] Further studies are required to confirm and support the existing data on the efficacy and safety of fibrinogen concentrate.

Current guidelines specify that coagulation factor concentrates should be used in preference to cryoprecipitate for the treatment of haemophilia A and von Willebrand disease because of safety reasons[13 86–89] (Table 2). Although fibrinogen concentrate is now used as a first-line haemostatic

treatment for acquired hypofibrinogenaemia in some European countries, it is licensed only for congenital afibrinogenaemia/hypofibrinogenaemia in other countries including the USA. Thus, local licensing and availability largely dictates in which countries cryoprecipitate and fibrinogen concentrate are used. It is anticipated that further evidence from high-quality trials will inform local licensure and treatment guidelines in the future.[80]

Conclusion

Despite the acceptance of cryoprecipitate for fibrinogen supplementation in acquired coagulopathy in many countries, there remains a lack of Level 1 evidence to support its use. In addition, there is undoubtedly inappropriate administration of cryoprecipitate. As with all allogeneic blood products, cryoprecipitate carries a risk of pathogen transmission and transfusion-associated adverse events. There is a need for prospective, randomized, controlled clinical trials to determine the haemostatic efficacy of cryoprecipitate compared with the efficacy of alternative preparations. It is anticipated that these trials will lead to the production of evidence-based guidelines to inform physicians and guide clinical practice.

Declaration of interest

J.H.L. has served on steering committees for CSL Behring, Grifols and LFB Biotechnologies.

Funding

Editing support was provided by Meridian HealthComms Ltd. with a grant from CSL Behring.

References

1 Cohn EJ, Strong LE, Hughes WL, *et al.* Preparation and properties of serum and plasma proteins; a system for the separation into fractions of the protein and lipoprotein components of biological tissues and fluids. *J Am Chem Soc* 1946; **68**: 459–75

2 McMillan CW, Diamond LK, Surgenor DM. Treatment of classic hemophilia: the use of fibrinogen rich in factor VIII for hemorrhage and for surgery. *N Engl J Med* 1961; **265**: 277–83

3 Kasper CK. Judith Graham Pool and the discovery of cryoprecipitate. *Haemophilia* 2012; **18**: 833–5

4 Pool JG, Gershgold EJ, Pappenhagen AR. High-potency antihaemophilic factor concentrate prepared from cryoglobulin precipitate. *Nature* 1964; **203**: 312

5 Hershgold EJ, Pool JG, Pappenhagen AR, Nuenke JM. A more potent human antihemophilic globulin concentrate: preparation and clinical trial. *Bibl Haematol* 1965; **23**: 1214–18

6 Fries D, Martini WZ. Role of fibrinogen in trauma-induced coagulopathy. *Br J Anaesth* 2010; **105**: 116–21

7 Levy JH, Szlam F, Tanaka KA, Sniecienski RM. Fibrinogen and hemostasis: a primary hemostatic target for the management of acquired bleeding. *Anesth Analg* 2012; **114**: 261–74

8 Sorensen B, Bevan DH. A critical evaluation of cryoprecipitate for replacement of fibrinogen. *Br J Haematol* 2010; **149**: 834–43

9 Ahmed S, Harrity C, Johnson S, *et al.* The efficacy of fibrinogen concentrate compared with cryoprecipitate in major obstetric haemorrhage—an observational study. *Transfus Med* 2012; **22**: 344–9

10 Yang L, Stanworth S, Baglin T. Cryoprecipitate: an outmoded treatment? *Transfus Med* 2012; **22**: 315–20

11 Eder AF, Sebok MA. Plasma components: FFP, FP24, and thawed plasma. *Immunohematology* 2007; **23**: 150–7

12 Napier JA, Bass H, Pengilley R. Technical method. Fresh frozen cryosupernatant in place of fresh frozen plasma for broad spectrum coagulation factor replacement. *J Clin Pathol* 1985; **38**: 475–7

13 The US Food and Drug Administration, American Association of Blood Banks, American Red Cross, America's Blood Centers, Armed Services Blood Program. Guidance for Industry: Circular of information for the use of human blood and blood components. 2013. Available from http://www.fda.gov/biologicsbloodvaccines/guidancecomplianceregulatoryinformation/guidances/blood/ucm364565.htm (accessed 16 December 2013)

14 Council of Europe. Guide to the preparation, use and quality assurance of blood components, 2006. 12th Edn. Strasbourg, Council of Europe Publishing

15 United Kingdom Blood Transfusion Services. Guidelines for the Blood Transfusion Services in the UK. 8th Edition. 2013. Available from http://www.transfusionguidelines.org.uk/index.aspx?Publication=RB (accessed 16 December 2013)

16 Alport EC, Callum JL, Nahirniak S, Eurich B, Hume HA. Cryoprecipitate use in 25 Canadian hospitals: commonly used outside of the published guidelines. *Transfusion* 2008; **48**: 2122–7

17 Bass H, Trenchard PM, Mustow MJ. Microwave-thawed plasma for cryoprecipitate production. *Vox Sang* 1985; **48**: 65–71

18 Callum JL, Karkouti K, Lin Y. Cryoprecipitate: the current state of knowledge. *Transfus Med Rev* 2009; **23**: 177–88

19 Cardigan R, Philpot K, Cookson P, Luddington R. Thrombin generation and clot formation in methylene blue-treated plasma and cryoprecipitate. *Transfusion* 2009; **49**: 696–703

20 Caudill JS, Nichols WL, Plumhoff EA, *et al.* Comparison of coagulation factor XIII content and concentration in cryoprecipitate and fresh-frozen plasma. *Transfusion* 2009; **49**: 765–70

21 Franchini M, Lippi G. Fibrinogen replacement therapy: a critical review of the literature. *Blood Transfus* 2012; **10**: 23–7

22 Goodnight SH Jr. Cryoprecipitate and fibrinogen. *JAMA* 1979; **241**: 1716–7

23 Hoffman M, Jenner P. Variability in the fibrinogen and von Willebrand factor content of cryoprecipitate. Implications for reducing donor exposure. *Am J Clin Pathol* 1990; **93**: 694–7

24 Ketchum L, Hess JR, Hiippala S. Indications for early fresh frozen plasma, cryoprecipitate, and platelet transfusion in trauma. *J Trauma* 2006; **60**: S51–8

25 Lee SH, Lee SM, Kim CS, *et al.* Fibrinogen recovery and changes in fibrin-based clot firmness after cryoprecipitate in patients undergoing aortic surgery involving deep hypothermic circulatory arrest. *Transfusion* 2013; **54**: 1379–87

26 Miller Y, Bachowski G, Benjamin R, *et al.* Practice guidelines for blood transfusion: a compilation from recent peer-reviewed literature. 2nd Edn. *American Red Cross*. 2007. Available from http://www.sld.cu/galerias/pdf/sitios/anestesiologia/practical_guidelines_blood_transfusion.pdf (accessed 16 December 2013)

27 Millgan G, Graham R, Hanratty S, Muir W, Mitchell R. Production of freeze-dried human antihaemophilic cryoprecipitate. *J Clin Pathol* 1981; **34**: 1091–3

28 Pantanowitz L, Kruskall MS, Uhl L. Cryoprecipitate. Patterns of use. *Am J Clin Pathol* 2003; **119**: 874–81

29 Poon MC. Cryoprecipitate: uses and alternatives. *Transfus Med Rev* 1993; **7**: 180–92

30 Rahe-Meyer N, Sorensen B. For: Fibrinogen concentrate for management of bleeding. *J Thromb Haemost* 2011; **9**: 1–5

31 Soloway HB, Bereznak CE. Plasma fibrinogen levels following cryoprecipitate infusion. *Transfusion* 1970; **10**: 326–8

32 Stinger HK, Spinella PC, Perkins JG, *et al.* The ratio of fibrinogen to red cells transfused affects survival in casualties receiving massive transfusions at an army combat support hospital. *J Trauma* 2008; **64**: S79–85

33 Theodoulou A, Berryman J, Nathwani A, Scully M. Comparison of cryoprecipitate with fibrinogen concentrate for acquired hypofibrinogenaemia. *Transfus Apher Sci* 2012; **46**: 159–62

34 Tinegate H, Allard S, Grant-Casey J, *et al.* Cryoprecipitate for transfusion: which patients receive it and why? A study of patterns of use across three regions in England. *Transfus Med* 2012; **22**: 356–61

35 Stanworth SJ. The evidence-based use of FFP and cryoprecipitate for abnormalities of coagulation tests and clinical coagulopathy. *Hematology Am Soc Hematol Educ Program* 2007: 179–86

36 Levi M, Toh CH, Thachil J, Watson HG. Guidelines for the diagnosis and management of disseminated intravascular coagulation. British Committee for Standards in Haematology. *Br J Haematol* 2009; **145**: 24–33

37 NHS Operational Impact Group (OIG). The impact of blood safety and quality regulations 2005 on hospital transfusion laboratories. 2005. Available from http://www.transfusionguidelines.org.uk/regulations/archive/oig-report (accessed 16 December 2013)

38 Salter D, Lloyd A. EU Blood Directive—blood safety and quality regulations. Welsh Health Circular. 2005. Available from http://www.wales.nhs.uk/documents/WHC_2005_066.pdf (accessed 16 December 2013)

39 California Blood Bank Society. Rinsing bags of cryoprecipitate with saline before pooling. 2004. Available from http://www.cbbsweb.org/enf/2004/cryo_rinse.html (accessed 16 December 2013)

40 George JN, Pickett EB, Heinz R. Platelet membrane microparticles in blood bank fresh frozen plasma and cryoprecipitate. *Blood* 1986; **68**: 307–9

41 MacPhee M, Wilmer B, Beall D, Moroff G. Protein composition of clots detected in pooled cryoprecipitate units. *Transfusion* 2013; **53**: 651–4

42 McVerry BA, Machin SJ. Incidence of allo-immunization and allergic reactions to cryoprecipitate in haemophilia. *Vox Sang* 1979; **36**: 77–80

43 Rourke C, Curry N, Khan S, *et al.* Fibrinogen levels during trauma hemorrhage, response to replacement therapy, and association with patient outcomes. *J Thromb Haemost* 2012; **10**: 1342–51

44 Morrison JJ, Dubose JJ, Rasmussen TE, Midwinter MJ. Military Application of Tranexamic Acid in Trauma Emergency Resuscitation (MATTERs) Study. *Arch Surg* 2012; **147**: 113–9

45 Holcomb JB, Fox EE, Zhang X, *et al.* Cryoprecipitate use in the PROMMTT study. *J Trauma Acute Care Surg* 2013; **75**: S31–9

46 Spahn DR, Cerny V, Coats TJ, *et al.* Management of bleeding following major trauma: a European guideline. *Crit Care* 2007; **11**: R17

47 Rossaint R, Bouillon B, Cerny V, *et al.* Management of bleeding following major trauma: an updated European guideline. *Crit Care* 2010; **14**: R52

48 Spahn DR, Bouillon B, Cerny V, *et al.* Management of bleeding and coagulopathy following major trauma: an updated European guideline. *Crit Care* 2013; **17**: R76

49 Moloney WC, Egan WJ, Gorman AJ. Acquired afibrinogenemia in pregnancy. *N Engl J Med* 1949; **240**: 596–8

50 Edsall JT, Ferry RM, Armstrong SH. Chemical, clinical, and immunological studies on the products of human plasma fractionation. XV. The proteins concerned in the blood coagulation mechanism. *J Clin Invest* 1944; **23**: 557–65

51 Blomback B, Blomback M. Purification of human and bovine fibrinogen. *Arkiv fur Kemi* 1956; **10**: 415–43

52 Cohn EJ, Oncley JL, Strong LE, Hughes WL, Armstrong SH. Chemical, Clinical, and Immunological Studies on the Products of Human Plasma Fractionation. I. The Characterization of the Protein Fractions of Human Plasma. *J Clin Invest* 1944; **23**: 417–32

53 Royal College of Obstetricians and Gynaecologists. Prevention and management of postpartum haemorrhage. Green-top Guideline No. 52. 2009. Available from http://www.rcog.org.uk/files/rcog-corp/GT52PostpartumHaemorrhage0411.pdf (accessed 16 December 2013)

54 Adukauskiene D, Veikutiene A, Adukauskaite A, Veikutis V, Rimaitis K. The usage of blood components in obstetrics. *Medicina (Kaunas)* 2010; **46**: 561–7

55 Pacheco LD, Saade GR, Costantine MM, Clark SL, Hankins GD. The role of massive transfusion protocols in obstetrics. *Am J Perinatol* 2013; **30**: 1–4

56 Kozek-Langenecker SA, Afshari A, Albaladejo P, *et al.* Management of severe perioperative bleeding: guidelines from the European Society of Anaesthesiology. *Eur J Anaesthesiol* 2013; **30**: 270–382

57 Mercier FJ, Bonnet MP. Use of clotting factors and other prohemostatic drugs for obstetric hemorrhage. *Curr Opin Anaesthesiol* 2010; **23**: 310–6

58 Bell SF, Rayment R, Collins PW, Collis RE. The use of fibrinogen concentrate to correct hypofibrinogenaemia rapidly during obstetric haemorrhage. *Int J Obstet Anesth* 2010; **19**: 218–23

59 Glover NJ, Collis RE, Collins P. Fibrinogen concentrate use during major obstetric haemorrhage. *Anaesthesia* 2010; **65**: 1229–30

60 Kikuchi M, Itakura A, Miki A, Nishibayashi M, Ikebuchi K, Ishihara O. Fibrinogen concentrate substitution therapy for obstetric hemorrhage complicated by coagulopathy. *J Obstet Gynaecol Res* 2013; **39**: 770–6

61 Charbit B, Mandelbrot L, Samain E, *et al.* The decrease of fibrinogen is an early predictor of the severity of postpartum hemorrhage. *J Thromb Haemost* 2007; **5**: 266–73

62 Cortet M, Deneux-Tharaux C, Dupont C, *et al.* Association between fibrinogen level and severity of postpartum haemorrhage: secondary analysis of a prospective trial. *Br J Anaesth* 2012; **108**: 984–9

63 Tomita Y, Shimode N, Ide T, Ueki R, Tatara T, Tashiro C. [Efficacy of cryoprecipitate transfusion for coagulopathy after cardiopulmonary bypass in thoracic aortic surgery]. *Masui* 2011; **60**: 830–4

64 Lee SH, Lee SM, Kim CS, *et al.* Use of fibrin-based thromboelastometry for cryoprecipitate transfusion in cardiac surgery involving deep hypothermic circulatory arrest during cardiopulmonary bypass. *Blood Coagul Fibrinolysis* 2010; **21**: 687–91

65 Shaw RE, Johnson CK, Ferrari G, *et al.* Blood transfusion in cardiac surgery does increase the risk of 5-year mortality: results from a contemporary series of 1714 propensity-matched patients. *Transfusion* 2013; **54**: 1106–13

66 Liu S, Fan J, Wang X, *et al.* Intraoperative cryoprecipitate transfusion and its association with the incidence of biliary complications after liver transplantation—a retrospective cohort study. *PLoS One* 2013; **8**: e60727

67 French CJ, Bellomo R, Angus P. Cryoprecipitate for the correction of coagulopathy associated with liver disease. *Anaesth Intensive Care* 2003; **31**: 357–61

68 Massicotte L, Sassine MP, Lenis S, Seal RF, Roy A. Survival rate changes with transfusion of blood products during liver transplantation. *Can J Anaesth* 2005; **52**: 148–55

69 Rahe-Meyer N, Solomon C, Hanke A, *et al.* Effects of fibrinogen concentrate as first-line therapy during major aortic replacement surgery: a randomized, placebo-controlled trial. *Anesthesiology* 2013; **118**: 40–50

70 Robillard P, Nawej KI, Jochem K. The Quebec hemovigilance system: description and results from the first two years. *Transfus Apher Sci* 2004; **31**: 111–22

71 Chapman CE, Stainsby D, Jones H, *et al.* Ten years of hemovigilance reports of transfusion-related acute lung injury in the United Kingdom and the impact of preferential use of male donor plasma. *Transfusion* 2009; **49**: 440–52

72 Wallis JP. Transfusion-related acute lung injury (TRALI)–underdiagnosed and under-reported. *Br J Anaesth* 2003; **90**: 573–6

73 Serious Hazards of Transfusion (SHOT) Annual Report. 2012. Available from http://www.shotuk.org/wp-content/uploads/2012/07/SHOT-ANNUAL-REPORT_FinalWebVersionBookmarked_2012_06_22.pdf (accessed 16 December 2013)

74 Burman D, Hodson AK, Wood CB, Brueton NF. Acute anaphylaxis, pulmonary oedema, and intravascular haemolysis due to cryoprecipitate. *Arch Dis Child* 1973; **48**: 483–5

75 Inaba K, Branco BC, Rhee P, *et al.* Impact of plasma transfusion in trauma patients who do not require massive transfusion. *J Am Coll Surg* 2010; **210**: 957–65

76 Groner A. Reply. Pereira A. Cryoprecipitate versus commercial fibrinogen concentrate in patients who occasionally require a therapeutic supply of fibrinogen: risk comparison in the case of an emerging transfusion-transmitted infection. *Haematologica* 2007;**92**:846–9. *Haematologica* 2008; **93**: e24–6

77 Elliott BM, Aledort LM. Restoring hemostasis: fibrinogen concentrate versus cryoprecipitate. *Expert Rev Hematol* 2013; **6**: 277–86

78 Bevan DH. Cardiac bypass haemostasis: putting blood through the mill. *Br J Haematol* 1999; **104**: 208–19

79 Levy JH, Welsby I, Goodnough LT. Fibrinogen as a therapeutic target for bleeding: a review of critical levels and replacement therapy. *Transfusion* 2013; **54**: 1389–405

80 Ranucci M, Solomon C. Supplementation of fibrinogen in acquired bleeding disorders: experience, evidence, guidelines, and licences. *Br J Anaesth* 2012; **109**: 135–7

81 O'Shaughnessy DF, Atterbury C, Bolton Maggs P, *et al.* Guidelines for the use of fresh-frozen plasma, cryoprecipitate and cryosupernatant. *Br J Haematol* 2004; **126**: 11–28

82 Milligan DW, Grimwade D, Cullis JO, *et al.* Guidelines on the management of acute myeloid leukaemia in adults. British Committee for Standards in Haematology. *Br J Haematol* 2006; **135**: 450–74

83 Stainsby D, MacLennan S, Thomas D, Isaac J, Hamilton PJ. Guidelines on the management of massive blood loss. *Br J Haematol* 2006; **135**: 634–41

84 Thomas D, Wee M, Clyburn P, *et al.* Blood transfusion and the anaesthetist: management of massive haemorrhage. *Anaesthesia* 2010; **65**: 1153–61

85 Sanz MA, Grimwade D, Tallman MS, *et al.* Management of acute promyelocytic leukemia: recommendations from an expert panel on behalf of the European LeukemiaNet. *Blood* 2009; **113**: 1875–91

86 National Health and Medical Research Council (NHMRC). Patient Blood Management Guidelines Critical Bleeding Massive Transfusion. 2011. Available from http://www.blood.gov.au/pbm-module-1 (accessed 16 December 2013)

87 The American Society of Anesthesiologists. Practice guidelines for perioperative blood transfusion and adjuvant therapies: an updated report by the American Society of Anesthesiologists Task Force on Perioperative Blood Transfusion and Adjuvant Therapies. *Anesthesiology* 2006; **105**: 198–208

88 Droubatchevskaia N, Wong M. Guidelines for cryoprecipitate transfusion. Transfusion Medicine Advisory Group for British Colombia, Canada. Available from http://www.pbco.ca/images/TMAG/May%2010%202006%20FINAL%20Cryo%20Guidelines.pdf (accessed 16 December 2013)

89 World Federation of Hemophilia. 2012. Guidelines for the management of hemophilia. 2nd Edition. Available from http://www1.wfh.org/publications/files/pdf-1472.pdf (accessed 16 December 2013)

90 Brecher ME. American Association of Blood Banks Technical Manual. 2005. 15th Edn. American Association of Blood Banks.

91 Nascimento B, Rizoli S, Rubenfeld G, *et al.* Cryoprecipitate transfusion: assessing appropriateness and dosing in trauma. *Transfus Med* 2011; **21**: 394–401

92 Nascimento B. Cryoprecipitate transfusion: assessing appropriateness and dosing in trauma. A thesis submitted for the degree of Master of Science, Institute of Medical Sciences, University of Toronto, Canada. 2012. Available from https://tspace.library.utoronto.ca/bitstream/1807/32611/1/NascimentoJr_Bartolomeu_201206_MSc_thesis.pdf (accessed 16 December 2013)

93 Holcomb JB, del Junco DJ, Fox EE, *et al.* The prospective, observational, multicenter, major trauma transfusion (PROMMTT) study: comparative effectiveness of a time-varying treatment with competing risks. *JAMA Surg* 2013; **148**: 127–36

94 New Zealand Blood Service. Cryoprecipitate audit within six centres in New Zealand. 2005. Available from https://www.clinicaldata.nzblood.co.nz/resourcefolder/audits/Cryoprecipitate%20audit%20final%20report.pdf (accessed 16 December 2013)

95 Schofield WN, Rubin GL, Dean MG. Appropriateness of platelet, fresh frozen plasma and cryoprecipitate transfusion in New South Wales public hospitals. *Med J Aust* 2003; **178**: 117–21

96 Fries D, Innerhofer P, Perger P, *et al.* [Coagulation management in trauma-related massive bleeding. - Recommendations of the Task Force for Coagulation (AGPG) of the Austrian Society of Anesthesiology, Resuscitation and Intensive Care Medicine (OGARI)]. *Anasthesiol Intensivmed Notfallmed Schmerzther* 2010; **45**: 552–61

97 Chandler WL, Ferrell C, Trimble S, Moody S. Development of a rapid emergency hemorrhage panel. *Transfusion* 2010; **50**: 2547–52

98 Schöchl H, Nienaber U, Maegele M, *et al.* Transfusion in trauma: thromboelastometry-guided coagulation factor concentrate-based therapy versus standard fresh frozen plasma-based therapy. *Crit Care* 2011; **15**: R83

99 Noval-Padillo JA, Leon-Justel A, Mellado-Miras P, *et al.* Introduction of fibrinogen in the treatment of hemostatic disorders during orthotopic liver transplantation: implications in the use of allogenic blood. *Transplant Proc* 2010; **42**: 2973–4

100 Rahe-Meyer N, Pichlmaier M, Haverich A, *et al.* Bleeding management with fibrinogen concentrate targeting a high-normal plasma fibrinogen level: a pilot study. *Br J Anaesth* 2009; **102**: 785–92

101 Gorlinger K, Dirkmann D, Hanke AA, *et al.* First-line therapy with coagulation factor concentrates combined with point-of-care coagulation testing is associated with decreased allogeneic blood transfusion in cardiovascular surgery: a retrospective, single-center cohort study. *Anesthesiology* 2011; **115**: 1179–91

102 Girdauskas E, Kempfert J, Kuntze T, *et al.* Thromboelastometrically guided transfusion protocol during aortic surgery with circulatory arrest: a prospective, randomized trial. *J Thorac Cardiovasc Surg* 2010; **140**: 1117–24, e2

103 Schöchl H, Nienaber U, Hofer G, *et al.* Goal-directed coagulation management of major trauma patients using thromboelastometry (ROTEM)-guided administration of fibrinogen concentrate and prothrombin complex concentrate. *Crit Care* 2010; **14**: R55

104 Coakley M, Reddy K, Mackie I, Mallett S. Transfusion triggers in orthotopic liver transplantation: a comparison of the thromboelastometry analyzer, the thromboelastogram, and conventional coagulation tests. *J Cardiothorac Vasc Anesth* 2006; **20**: 548–53

105 Solomon C, Pichlmaier U, Schoechl H, *et al.* Recovery of fibrinogen after administration of fibrinogen concentrate to patients with severe bleeding after cardiopulmonary bypass surgery. *Br J Anaesth* 2010; **104**: 555–62

106 Wehrli G, Taylor NE, Haines AL, Brady TW, Mintz PD. Instituting a thawed plasma procedure: it just makes sense and saves cents. *Transfusion* 2009; **49**: 2625–30

107 Birkmeyer JD, Goodnough LT, AuBuchon JP, Noordsij PG, Littenberg B. The cost-effectiveness of preoperative autologous blood donation for total hip and knee replacement. *Transfusion* 1993; **33**: 544–51

108 Denton TA, Diamond GA, Matloff JM, Gray RJ. Anemia therapy: individual benefit and societal cost. *Semin Oncol* 1994; **21**: 29–35

109 Shander A, Hofmann A, Gombotz H, Theusinger OM, Spahn DR. Estimating the cost of blood: past, present, and future directions. *Best Pract Res Clin Anaesthesiol* 2007; **21**: 271–89

110 Pandey S, Vyas GN. Adverse effects of plasma transfusion. *Transfusion* 2012; **52** (Suppl 1): 65S–79S

111 Popovsky MA, Audet AM, Andrzejewski C Jr. Transfusion-associated circulatory overload in orthopedic surgery patients: a multi-institutional study. *Immunohematology* 1996; **12**: 87–9

112 Rock G. A comparison of methods of pathogen inactivation of FFP. *Vox Sang* 2011; **100**: 169–78

113 Ettinger A, Miklauz MM, Bihm DJ, Maldonado-Codina G, Goodrich RP. Preparation of cryoprecipitate from riboflavin and UV light-treated plasma. *Transfus Apher Sci* 2012; **46**: 153–8

114 Cid J, Caballo C, Pino M, *et al.* Quantitative and qualitative analysis of coagulation factors in cryoprecipitate prepared from fresh-frozen plasma inactivated with amotosalen and ultraviolet A light. *Transfusion* 2012; **53**: 600–5

115 El-Ekiaby M, Sayed MA, Caron C, *et al.* Solvent-detergent filtered (S/D-F) fresh frozen plasma and cryoprecipitate minipools prepared in a newly designed integral disposable processing bag system. *Transfus Med* 2010; **20**: 48–61

116 Atance R, Pereira A, Ramirez B. Transfusing methylene blue-photoinactivated plasma instead of FFP is associated with an increased demand for plasma and cryoprecipitate. *Transfusion* 2001; **41**: 1548–52

117 Custer B, Agapova M, Martinez RH. The cost-effectiveness of pathogen reduction technology as assessed using a multiple risk reduction model. *Transfusion* 2010; **50**: 2461–73

118 Mittermayr M, Streif W, Haas T, *et al.* Hemostatic changes after crystalloid or colloid fluid administration during major orthopedic surgery: the role of fibrinogen administration. *Anesth Analg* 2007; **105**: 905–17

Handling editor: J. G. Hardman