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Sørensen &amp; Bevan

*Cryoprecipitate versus Fibrinogen concentrate*

# A critical evaluation of cryoprecipitate for replacement of fibrinogen

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## Summary

Maintaining the plasma fibrinogen concentration is important to limit excessive perioperative blood loss. In this review, we consider the evidence for this statement, and question the justification for using cryoprecipitate rather than virus-inactivated fibrinogen concentrate to support plasma fibrinogen levels. Haemophilia was historically treated with cryoprecipitate, but specific coagulation factor concentrates are now preferred. In contrast, primary fractions of allogeneic donor blood, including cryoprecipitate, are still commonly used to treat perioperative bleeding.

When compared with cryoprecipitate and fresh-frozen plasma (FFP), freeze-dried fibrinogen concentrate offers standardised fibrinogen content, faster reconstitution and improved efficacy. Pasteurisation and purification processes employed in the preparation of fibrinogen concentrate reduce the risk of pathogen transmission and immune-mediated complications, in comparison with cryoprecipitate and FFP. When all costs associated with administration are taken into consideration, the cost of fibrinogen concentrate is not substantially different to that of cryoprecipitate.

In conclusion, wider availability and use of fibrinogen concentrate may improve the management of perioperative bleeding. Further benefits may accrue from more rapid and accurate techniques for monitoring fibrinogen levels. Clinical studies are needed to evaluate methods of measuring fibrinogen and assessing fibrin polymerisation, and to define critical haemostatic plasma fibrinogen concentrations in different perioperative situations.

Word count: 197

## Introduction

In patients without pre-existing haemostatic disorders, coagulation defects that occur during surgery and/or massive haemorrhage are caused by loss, consumption and dilution of coagulation factors, collectively referred to as 'dilutional coagulopathy'. Some types of surgery disturb haemostasis in other ways: during cardiopulmonary bypass (CPB), interactions with the extracorporeal circuit activates the coagulation and fibrinolytic systems, resulting in platelet dysfunction, which is exacerbated by parallel induction of an inflammatory enzymatic cascade (Dietrich 2000). In liver surgery, portal hypertension results in splenic platelet sequestration and thrombocytopenia (Gorlinger 2006).

Current responses to severe perioperative bleeding include transfusion of allogeneic blood products such as red blood cell concentrates, fresh frozen plasma (FFP), platelets, and, in a few countries, cryoprecipitate. Transfusion of fibrinogen concentrate is not yet a standard component of such protocols in either the UK or the USA. In the past 5 years, several studies, which are reviewed below, have revealed the importance of supplementing fibrinogen levels in correcting coagulopathy associated with surgery. Fibrinogen plays an important role in the coagulation process and clot stabilisation via its cleavage by thrombin to form fibrin polymers capable of binding factor XIII (Velik-Salchner, *et al* 2007), with consequent cross-linkage to form a robust fibrin network. In addition, it induces platelet activation and aggregation by binding to the platelet fibrinogen receptor, the  $\alpha_2\beta_3$  integrin GPIIb/IIIa.

Cryoprecipitate is a good source of fibrinogen prepared by controlled thawing of frozen plasma to precipitate high molecular weight proteins. These include factor VIII, von Willebrand factor (vWF), and fibrinogen. The precipitated proteins are separated by centrifugation, resuspended in a small volume of plasma (typically 10–20 mL) and stored frozen at  $-20^{\circ}\text{C}$  (Poon 1993). In those countries that still use cryoprecipitate, the current rationale is solely to provide fibrinogen. Although cryoprecipitate is prepared as single units, these are pooled prior to administration – a typical adult dose is 10 units (Stanworth 2007). Alternatively, pasteurised human fibrinogen concentrates are available. In Europe, fibrinogen concentrate is well established for treatment of congenital fibrinogen deficiency, and is increasingly

used for acquired fibrinogen deficiency (i.e. the management of perioperative bleeding) (Bundesaertzekammer 2009).

As initially stated almost a decade ago (Bevan 1999), the use of cryoprecipitate in the treatment of perioperative bleeding represents a double standard since it is contraindicated for the treatment of haemophilia, in preference for recombinant and pathogen-reduced plasma-fractionated products when available, on safety grounds. The present manuscript aims to explore: the historic reasons behind the discrepancy between treatment of acquired and hereditary bleeding disorders; the factors influencing the choice between cryoprecipitate and fibrinogen concentrate; and the potential for future improvements in perioperative bleeding management.

## History of the development of blood products

### Haemophilia

Haemophilia A and B are caused by deficiency of factors VIII and IX, respectively (Figure 1). The first successful treatment of perioperative bleeding in a haemophiliac using blood transfusion was reported as early as 1840, but modern transfusion history really began in 1900 when Landsteiner discovered ABO histocompatibility antigens (Starr 2002).

Figure 1 shows a timeline of developments in the treatment of haemophilia. In the 1940s and 50s, transfusion for haemophilia involved the use of 'antihaemophilic globulin', a crude preparation of fibrinogen and factor VIII. This was followed by the development of cryoprecipitate (Pool, *et al* 1964, Pool and Shannon 1965), which allowed an effective dose of factor VIII in a tolerable volume and led to a dramatic increase in life expectancy (Josephson and Abshire 2006).

However, treatment with plasma-derived products brought infection with diseases such as hepatitis, with multiple transfusions increasing the risk of infection (Alter and Klein 2008). In 1982, three cases of acquired immunodeficiency syndrome (AIDS) were observed among patients with haemophilia A in whom transfusion was the most likely source of infection. It is estimated that, tragically, around 90% of concentrate-treated patients with severe haemophilia were already infected with the human immunodeficiency virus (HIV) before the first case of AIDS was recognised in 1981 (Alter and Klein 2008). Assays to screen blood for contamination with HIV

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3 were introduced in 1985, significantly reducing the risk of transfusion-transmitted  
4 HIV (Alter and Klein 2008).  
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8 Although reduced by more rigorous donor screening and more sensitive viral  
9 detection tests such as polymerase chain reaction testing for viral genomes, the  
10 residual risk of viral transmission by plasma-derived products drove the  
11 development of more purified preparations of factor VIII with better safety profiles  
12 (Poon 1993). A method to produce virally-inactivated factor VIII concentrates was  
13 developed in 1985 (Heimburger 2002). Most recently in the development of  
14 haemophilia A treatments, recombinant factor VIII products became available in the  
15 early 1990s. The World Federation of Hemophilia supports use of coagulation factor  
16 concentrates in preference to cryoprecipitate, because cryoprecipitate is not subjected  
17 to viral inactivation procedures (World Federation of Hemophilia 2005).  
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### 26 **Perioperative bleeding**

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28 Initially, whole blood was used in the management of perioperative bleeding, but  
29 this evolved to the use of blood components including red blood cells, FFP,  
30 cryoprecipitate and platelets. It was the needs of those wounded in war that led to  
31 advances in blood transfusion: blood storage was introduced during World War I;  
32 and fractionation of blood during World War II. Primary allogeneic blood  
33 components remain the mainstay of therapy for perioperative bleeding. At the same  
34 time, there is general agreement that transfusion of blood components, in particular  
35 plasma-rich blood components, should be avoided if possible (The Serious Hazards  
36 of Transfusion Steering Group 2004). Crystalloid and colloid solutions can be used to  
37 provide volume, and concentrates are available for replacement of coagulation  
38 factors (fibrinogen concentrate, factor XIII concentrate, and prothrombin complex  
39 concentrates containing three or four coagulation factors). Other ongoing  
40 developments include haemoglobin- or perfluorocarbon-based artificial oxygen  
41 carriers (Henkel-Honke and Oleck 2007).  
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54 During the era of whole-blood transfusion, thrombocytopenia was the first  
55 haemostatic abnormality observed during blood loss. However, in the modern era of  
56 intravenous fluids and red cell concentrates, fibrinogen deficiency is the first defect  
57 observed (Hiippala, *et al* 1995). In a pig model of dilutional coagulopathy, even with  
58 moderate loss (35% of blood volume), the limited increase in fibrinogen synthesis  
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cannot compensate for the concomitantly increased breakdown (Martini, *et al* 2005). Necessary fluid replacement using crystalloid and colloid solutions not only further reduces fibrinogen concentration by dilution, but colloids such as hydroxyethyl starch also impair fibrin polymerisation (Fenger-Eriksen, *et al* 2009b, Fries, *et al* 2002, Innerhofer, *et al* 2002).

A further indication of the importance of fibrinogen comes from the observation that patients with high fibrinogen levels experience fewer bleeding complications than those with low levels (Blome, *et al* 2005, Fries, *et al* 2005, Pothula, *et al* 2004, Ucar, *et al* 2007a). Thus, the threshold level for treatment may be substantially higher than the 'historical' 1 g/L, particularly in patients suffering from postpartum bleeding [4 g/L; (Charbit, *et al* 2007)] or excessive blood loss during cardiac surgery [3.8 g/L; (Karlsson, *et al* 2008)]. Low preoperative levels of fibrinogen are associated with increased postoperative blood loss (Blome, *et al* 2005, Karlsson, *et al* 2008, Ucar, *et al* 2007b). In postpartum bleeding, low levels of fibrinogen are associated with severe bleeding, with a positive predictive value of 100% (Charbit, *et al* 2007). Based on this work, some current guidelines recommend transfusing fibrinogen concentrate in massive bleeding. Administration of fibrinogen is supported by recent studies including one prospective clinical trial (Fenger-Eriksen, *et al* 2009a, Fenger-Eriksen, *et al* 2009b).

In a porcine model of uncontrolled haemorrhage (induced by inflicting a standardised liver injury), administration of fibrinogen concentrate improved clot firmness and slowed down blood loss (Fries, *et al* 2006, Fries, *et al* 2005). In this model, fibrinogen concentrate was significantly more effective than platelet concentrate transfusion in the presence of thrombocytopenia [average platelet count =  $30 \times 10^9/L$ ; (Velik-Salchner, *et al* 2007)]. Thus, substitution of fibrinogen may act at more than one level in clot formation, compensating for low thrombin generation and decreased platelet function. High fibrinogen levels may compensate for a low concentration of thrombin because it only takes a single thrombin molecule to cleave up to 1,680 molecules of fibrinogen (Elodi and Varadi 1979). Similarly, the number of platelets present may not be the limiting factor in clot formation if fibrinogen levels are high as there are 40,000–80,000 copies of GPIIb/IIIa receptors on a single activated platelet (Kestin, *et al* 1993). This is supported by the observation that the effect of platelet-blocking substrates like clopidogrel can be antagonised by



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3 increasing the concentration of fibrinogen (Li, *et al* 2001). In patients undergoing  
4 thoracoabdominal aortic aneurysm surgery, fibrinogen supplementation with  
5 concentrate was more effective than transfusion of FFP and platelet concentrate in  
6 achieving effective haemostasis and reducing postoperative bleeding (Rahe-Meyer, *et*  
7 *al* 2009b).

### 13 **Current sources of fibrinogen**

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15 Today's therapeutic options for supplementing plasma fibrinogen are FFP,  
16 cryoprecipitate and fibrinogen concentrate. FFP is the most widely available source  
17 of fibrinogen, but it has several significant drawbacks such as extended  
18 administration time, transfusion-related complications and questionable efficacy  
19 (Stanworth 2007). Blood group matching is required and, as FFP is stored at -20°C,  
20 thawing time needs to be taken into account. High volumes are needed for effective  
21 fibrinogen supplementation as the concentration in FFP is low (typically around 2.5  
22 g/L (O'Shaughnessy, *et al* 2004), although this is variable). These factors all  
23 contribute to extending the time for administering FFP, a clear disadvantage in the  
24 setting of massive haemorrhage. Also, the low concentration limits the extent to  
25 which the fibrinogen level can be raised. FFP is not typically subjected to viral  
26 inactivation procedures, so there are risks of viral transmission. Treatment with  
27 methylene blue or solvent-detergent can be employed, but this can reduce the level  
28 of fibrinogen in the end-product (particularly in the case of methylene-blue  
29 treatment, where the reduction is around 30%) (Cardigan, *et al* 2009). Other potential  
30 complications associated with the use of FFP include volume overload and  
31 transfusion-related acute lung injury (TRALI) (Stanworth 2007). Perhaps the most  
32 notable consideration with FFP, however, is the lack of robust evidence supporting  
33 its efficacy (Heim, *et al* 2009, Stanworth 2007).

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35 Cryoprecipitate contains a higher concentration of fibrinogen than FFP, typically  
36 around 15 g/L (Stinger, *et al* 2008). However, it shares many of the disadvantages of  
37 FFP. The risk of viral transmission is similar to that with FFP, the fibrinogen  
38 concentration is variable, and blood group matching is needed (Danes, *et al* 2008).  
39 Time is also required for thawing cryoprecipitate. The product was withdrawn from  
40 most European countries some years ago, on the basis of safety concerns, though it  
41 remains available in the UK and the USA. Cryoprecipitate is unsuitable for pathogen  
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3 reduction steps, but it can be produced from plasma that has undergone treatment  
4 with methylene blue or psoralen/ultraviolet light. However, as previously  
5 mentioned, these methods can reduce functional fibrinogen content.  
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10 In contrast to FFP and cryoprecipitate, viral inactivation steps are routinely included  
11 in the manufacturing process for fibrinogen concentrate, therefore the risk of viral  
12 transmission is minimal (Groner 2008). The concentration of fibrinogen is  
13 standardised, and the administration volume is low (Fenger-Erikson, *et al* 2009). The  
14 administration time is short as there is no requirement for thawing (Rahe-Meyer, *et al*  
15 2009a). Fibrinogen concentrate has been shown to be effective and well tolerated, in a  
16 variety of clinical settings. The risk of thrombosis has been shown in a 22-year  
17 pharmacovigilance study to be low (Dickneite, *et al* 2008).  
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### 24 25 **The choice between cryoprecipitate and fibrinogen concentrate in** 26 **therapy of congenital fibrinogen disorders** 27

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29 In addition to its important role in perioperative bleeding, fibrinogen  
30 supplementation is also indicated for congenital deficiencies. Inherited disorders that  
31 result in fibrinogen deficiency and/or aberrant function are rare but challenging  
32 therapeutic problems.  
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37 In afibrinogenaemia, homozygous or double heterozygous inheritance of lesions in  
38 the FGA, FGB or FGG genes encoding the paired A $\alpha$ , B $\beta$  and  $\gamma$  chains that form the  
39 hexameric fibrinogen molecule result in profound quantitative deficiency of  
40 fibrinogen (plasma concentration <0.1 g/L). This results in an episodic, sometimes  
41 life-threatening bleeding disorder. Replacement of fibrinogen is required to treat  
42 spontaneous bleeding (mucosal, cerebral, musculoskeletal, ovarian); to prevent  
43 bleeding after surgery (including poor wound healing); and in pregnancy, including  
44 prevention of early foetal loss. Afibrinogenaemia can also be associated with  
45 thrombosis, an unexplained complication possibly connected to the role of fibrin in  
46 binding and localising thrombin. There is marked heterogeneity in the frequency of  
47 these symptoms, but prophylactic fibrinogen replacement is clearly indicated in  
48 some individuals and is favoured by a long half-life of infused fibrinogen. The  
49 median plasma elimination half-life of Haemocomplettan® P (CSL Behring, Marburg,  
50 Germany) is 2.7 days (range: 2.5–3.7), with a median clearance of 0.91 ml/h/kg  
51 (range; 0.84 – 1.22) (Kreuz, *et al* 2005).  
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5 Hypofibrinogenaemia and dysfibrinogenaemia (usually associated with  
6 hypofibrinogenaemia, but sometimes with a normal plasma level) is caused by  
7 heterozygous inheritance of genes associated with afibrinogenaemia, and a wide  
8 variety of other mutations. Bleeding and/or poor wound healing usually follows  
9 surgical challenge, but venous and arterial thrombosis can occur spontaneously. In  
10 dysfibrinogenaemia, abnormal fibrin clot structure and delayed or disordered  
11 fibrinolysis can contribute to thrombogenesis. Simply elevating the plasma  
12 fibrinogen is enough to prevent bleeding and normalise wound healing, but effective  
13 treatment of thrombosis also requires suppression of endogenous synthesis and/or  
14 secretion of the thrombogenic dysfibrinogen. Many variants of dysfibrinogen are  
15 associated with hypofibrinogenaemia due to impaired hepatocytic secretion of the  
16 mutant protein.  
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28 Transfusion strategies and dose calculations in fibrinogen replacement and  
29 prophylaxis demand an infusion product that delivers a known, standardised  
30 content of fibrinogen. This is difficult to achieve with cryoprecipitate, in which  
31 fibrinogen content varies widely between samples (manual pooling before infusion  
32 may add to this variability). In contrast, freeze-dried fibrinogen concentrate provides  
33 a known quantity of fibrinogen (900–1400 mg per vial).  
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40 In terms of safety, cryoprecipitate retains, to a degree, the statistically low risk of  
41 pathogen transmission entailed by its single-donor origin. However, a mini-pool of  
42 10–12 units has to be assembled to make a single effective dose of fibrinogen, and in  
43 an inherited disorder, cumulative exposure obviates this advantage compared to  
44 large pool-derived fibrinogen concentrates treated with standard pathogen-reduction  
45 methods. For all these reasons, appropriately treated fibrinogen concentrate, if  
46 available, offers clear advantages over cryoprecipitate as therapy for inherited  
47 deficiencies and disorders of fibrinogen.  
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56 The development of inhibitory antibodies in response to treatment with fibrinogen has  
57 been reported in three cases of afibrinogenemia: two cases following the use of  
58 cryoprecipitate (Bronnimann 1954, Ra'anani, *et al* 1991) and one case following  
59 treatment with Cohn fraction I (De Vries, *et al* 1961). These inhibitors reduced the  
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3 recovery and half-life of fibrinogen so that continuous infusion was required to  
4 maintain haemostasis. The patient who received Cohn fraction I developed  
5 anaphylaxis and giant urticaria, and eventually died as a result of anaphylaxis  
6 following subsequent infusion with whole blood (De Vries, *et al* 1961).  
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## 10 11 12 **The choice between cryoprecipitate and fibrinogen concentrate for** 13 **the management of perioperative bleeding** 14 15

### 16 17 **Efficacy** 18

19 There is a clear consensus that treatment with FFP is inappropriate in cases of severe  
20 fibrinogen deficiency as it contains insufficient concentrations of fibrinogen  
21 (Chowdhury, *et al* 2004, Danes, *et al* 2008). Although scientific evidence regarding the  
22 clinical efficacy of fibrinogen concentrate is limited, this is even more the case for  
23 cryoprecipitate (Danes, *et al* 2008), with no published studies specifically addressing  
24 the efficacy of cryoprecipitate in the management of perioperative bleeding.  
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30 There is evidence for the efficacy and safety of fibrinogen concentrate in congenital  
31 fibrinogen deficiency (Aygoren-Pursun, *et al* 2007, Kreuz, *et al* 2005, Rodriguez, *et al*  
32 1988), and data on its use in patients with acquired deficiencies in a variety of  
33 surgical settings is beginning to emerge (Danes, *et al* 2008, Fenger-Eriksen, *et al* 2008,  
34 Fenger-Eriksen, *et al* 2009a, Haas, *et al* 2008, Heindl, *et al* 2005, Rahe-Meyer, *et al*  
35 2009a, Rahe-Meyer, *et al* 2009b, Weinkove and Rangarajan 2008). In an observational  
36 study of 69 patients suffering from various forms of acquired severe  
37 hypofibrinogenaemia, most (62%) had consumptive hypofibrinogenaemia (Danes, *et*  
38 *al* 2008). After a median dose of 4 g of fibrinogen concentrate, a mean absolute  
39 increase of 1.09 g/L of plasma fibrinogen was measured. Coagulation parameters, PT  
40 and aPTT, were significantly improved ( $p < 0.001$ ) at 24 hours and 72 hours after  
41 fibrinogen concentrate administration (Danes, *et al* 2008). Furthermore, there was an  
42 association between plasma fibrinogen concentrations after treatment and 7-day  
43 patient survival. In another retrospective study of 43 patients, a similar increase in  
44 fibrinogen levels (1.01 g/L) was achieved with half the average dose of fibrinogen  
45 (Fenger-Eriksen, *et al* 2008). This may reflect differences between the two study  
46 populations including underlying clinical conditions and proportion of paediatric  
47 patients.  
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There are no published studies comparing the efficacy of fibrinogen concentrate with cryoprecipitate. The specification for cryoprecipitate in the UK requires that 75% of units contain at least 140 mg of fibrinogen, in other words, there can be wide variation in fibrinogen content between units (O'Shaughnessy, *et al* 2004). This confounds dose calculations in comparative studies.

### Safety

In the past, nearly all patients with haemophilia who received factor VIII concentrates were exposed to transfusion-transmitted viruses, due to factor VIII being unable to withstand heating at 60°C during the standard pasteurisation process. The same is true for fibrinogen. In 1985, CSL Behring (then called Behringwerke), invented a pasteurisation process using stabilisers to protect fragile proteins (Heimburger 2002). A sterile filtration step also removes pathogens (Figure 2). As a result, the fibrinogen concentrate available today has a superior viral safety over cryoprecipitate, despite being plasma-derived. The overall reduction of titres during the production of fibrinogen concentrate is shown for some representative viruses in Table 1 (Groner 2008).

The introduction of viral testing of plasma has greatly reduced the risk of viral transmission with cryoprecipitate. It has been estimated that in the UK, where FFP is not manufactured from first-time or lapsed donors, the residual risks from a single unit of FFP are 1 in 10 million for HIV, 1 in 50 million for hepatitis C virus and 1 in 1.2 million for hepatitis B virus (Williamson, *et al* 2003). However, in the absence of pathogen inactivation processes, the potential remains for contamination of plasma with an emerging, potentially lethal agent, for example variant Creutzfeld-Jakob disease (vCJD) in the UK, and West Nile virus (WNV) in the USA. The first case of possible transmission of vCJD as a result of transfusion was reported in 2004 (Pincock 2004). Countermeasures taken to minimise the risk of vCJD transmission by transfusion, such as the use of leucocyte-depleted blood components and sourcing of FFP for neonates and children born after 1 January 1996 from outside the UK (O'Shaughnessy, *et al* 2004), increase the cost of blood products. By 2002, four transplant-associated cases and 23 transfusion-transmitted symptomatic cases of WNV had been identified. A test to detect genomic material of WNV was developed very rapidly, and transfusion-related transmission of WNV has been very rare since the implementation of testing in 2003 (Alter and Klein 2008).

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There are two main methods available for viral inactivation of plasma: treatment with solvent/detergent or methylene blue. However, at present, cryoprecipitate available in the UK is all derived from untreated FFP (O'Shaughnessy, *et al* 2004). The use of methylene blue for viral inactivation of plasma was first described in 1991. Reactive oxygen species that are generated when methylene blue is exposed to visible light inactivate viruses. However, it is well documented that methylene blue treatment also reduces coagulation factor levels, with fibrinogen one of the factors most sensitive to depletion. Compared with cryoprecipitate derived from untreated plasma, the loss of fibrinogen in methylene blue-inactivated cryoprecipitate ranged from 18 to 41% (Aznar, *et al* 2000, Hornsey, *et al* 2000, Seghatchian and Krailadsiri 2001). A retrospective analysis of blood product use before and after the introduction of methylene blue-inactivated plasma in a University hospital in Spain found that the demand for plasma and cryoprecipitate increased across all diagnostic categories (Atance, *et al* 2001). The authors proposed compensation for low fibrinogen content as the most plausible explanation for this increase. No loss of coagulation factors is associated with solvent/detergent treatment of plasma, but there have been batch withdrawals due to possible contamination with parvovirus B19 (O'Shaughnessy, *et al* 2004). Both the methylene-blue and solvent/detergent methods of inactivation are primarily effective against enveloped viruses. Therefore, agents that are inactivated by pasteurisation or removed by filtration during the processing of fibrinogen concentrates may still be transmitted by cryoprecipitate prepared from virally-inactivated plasma.

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Aside from the risk of viral transmission, the same immune-mediated risks associated with transfusion of plasma exist for cryoprecipitate (MacLennan and Barbara 2006). These risks include anaphylactic or anaphyloid reactions, allergic reactions, haemolysis, and transfusion-related lung injury (TRALI). However, the non-specific allergic reactions associated with FFP transfusion are rarely seen with cryoprecipitate as only a small volume of plasma is used to resuspend the cryoprecipitated proteins (Ahrons, *et al* 1970, Reese, *et al* 1975). TRALI is believed to be caused by donor leukocyte antibodies, which are produced mainly as a result of pregnancy. Although it is under-diagnosed (Wallis 2003), not least because the same clinical features are seen in acute lung injury resulting from other causes such as sepsis, trauma and shock, TRALI is a common cause of transfusion-related death.

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3 The UK's National Blood Service announced its decision not to supply FFP from  
4 female blood donors in an effort to reduce the risk of TRALI in 2003 (Anonymous  
5 2003). A recent summary of 10 years of haemovigilance reports of TRALI in the UK  
6 suggested that this policy has been effective in reducing the incidence of TRALI due  
7 to FFP (Chapman, *et al* 2008). However, the report also found that, although low, the  
8 risk from cryoprecipitate seems to have increased (from 4.3 cases per 10<sup>6</sup>  
9 cryoprecipitate components issued from 1999–2004 to 9.6 cases per 10<sup>6</sup> from 2004–  
10 2006). This could be because there is now a greater proportion of female donor  
11 plasma being used to prepare cryoprecipitate (Chapman, *et al* 2008).  
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20 A further safety concern in the management of perioperative bleeding is the risk of a  
21 thrombogenic event occurring. Solvent/detergent-treated plasma has reduced  
22 activity of the anticoagulant protein S, and has been associated with deep vein  
23 thromboses when used to treat patients with thrombotic thrombocytopenic purpura  
24 (PLAS+SD®, VI Technologies, Melvin, NY, USA) (Flamholz, *et al* 2000). Increased  
25 fibrinogen levels are associated with increased risk of coronary heart disease and  
26 myocardial infarction (MI). However, there is evidence to suggest that in this  
27 instance fibrinogen is acting as a marker rather than a mediator (Reinhart 2003). For  
28 example, there is no increased risk of MI in people that have a polymorphism in the  
29 fibrinogen gene resulting in high fibrinogen levels (Reinhart 2003). There have been  
30 nine reports of thromboembolic events in patients with congenital or acquired  
31 afibrinogenaemia during postmarketing surveillance of a fibrinogen concentrate  
32 (Dickneite, *et al* 2008). Although the patients had additional risk factors in most of the  
33 cases, a causal relationship could not be definitely excluded. Nonetheless, fibrinogen  
34 concentrate appears to have a very low risk of thrombogenicity, corresponding to  
35 one case report for every 13,655 treatments of 8 g (Dickneite, *et al* 2008). Thrombin  
36 generation in plasma is inhibited by formation of fibrin (hence fibrin has been  
37 referred to as antithrombin I), and increased thrombin generation in  
38 afibrinogenaemic patients can be normalised by fibrinogen supplementation (Korte  
39 and Feldges 1994, Mosesson 2003). Cryoprecipitate is not subject to the same  
40 postmarketing surveillance as fibrinogen concentrate, but has been associated with  
41 thrombotic events (Nizzi, *et al* 2002). Administration of cryoprecipitate to substitute  
42 fibrinogen could cause thrombosis as a result of supraphysiological levels of other  
43 proteins present in the precipitate (e.g. von Willebrand factor).  
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### Cost and availability

Fibrinogen concentrate is often perceived as much more expensive than cryoprecipitate. However, the true cost of cryoprecipitate may not be seen by operating theatre staff. Savings are made with fibrinogen concentrate as there is no need for compatibility testing or thawing and administration is simpler, meaning the net cost is not necessarily higher (Weinkove and Rangarajan 2008). Cryoprecipitate is not available in most European countries (Haas, *et al* 2008) but is still used in the US and the UK whereas fibrinogen concentrate is far more widely available than cryoprecipitate in Central Europe. These factors naturally affect treatment decisions.

### Future improvements in management of perioperative bleeding

General uptake of fibrinogen concentrate in place of cryoprecipitate for the management of perioperative bleeding would bring about the benefits described above and summarised in Table 2. There is also scope for further improvement through clarification of critical fibrinogen levels and more rapid and reliable diagnostic tests.

Although fibrinogen levels of around 1 g/L are widely cited as a threshold for triggering supplementation, dating back to the late 1980s (Ciavarella, *et al* 1987), the optimal value for this is not clear (O'Shaughnessy, *et al* 2004, Stainsby, *et al* 2006). The critical threshold may vary with the clinical situation and patient characteristics, for example, normal fibrinogen levels increase with age (Balleisen, *et al* 1985, Coppola, *et al* 2000, Ishikawa, *et al* 1997, Laharrague, *et al* 1993, Oswald, *et al* 1983). Several authors consider a threshold of 1 g/L to be too low when blood loss is continuing (Haas, *et al* 2008). In an *in vitro* study, there was no clot formation at <0.5 g/L fibrinogen and at 0.75 g/L only weak clots were formed (Nielsen, *et al* 2005). In a study of postpartum haemorrhage (PPH), fibrinogen concentrations less than 2 g/L had a 100% positive predictive value for severe PPH (Charbit, *et al* 2007).

Point-of-care monitoring may further improve the management of patients with perioperative bleeding. Certainly, evidence is growing that haemostasis management guided by thromboelastographic techniques is associated with a lower requirement for allogeneic transfusions (Kozek-Langenecker 2007, Royston and von Kier 2001, Shore-Lesserson, *et al* 1999, Spalding, *et al* 2007). Recently, assays that specifically measure the contribution of fibrinogen to clot formation by inhibiting platelets have



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been developed for both available point-of-care systems – the TEG<sup>®</sup> Coagulation Analyzer and the ROTEM<sup>®</sup> Whole Blood Haemostasis Analyser. These methods provide faster results than the standard laboratory tests and also offer greater accuracy. The Clauss method for measuring fibrinogen may give falsely high fibrinogen levels if colloids have been used for volume replacement because they impair fibrin polymerisation (Fries, *et al* 2002, Hiippala 1995, Innerhofer, *et al* 2002, Mardel, *et al* 1998, Mittermayr, *et al* 2007).

## Conclusions

There is evidence that effective fibrinogen supplementation in patients with perioperative bleeding can: reduce blood loss, lower the requirement for transfusion of other blood components such as FFP and platelet concentrates, restore coagulation, and improve survival. Where cryoprecipitate is still used, replacement with fibrinogen concentrate would offer improvements in efficacy and safety, bringing the standard of treatment for surgical patients in line with that offered to haemophilia patients. Additional improvements to perioperative bleeding management may be attained by the introduction of more rapid and reliable tests for monitoring fibrinogen levels, and by clarification of the level of fibrinogen at which therapy should be initiated.

In congenital fibrinogen deficiencies, the argument for using current pathogen-reduced fibrinogen concentrates as replacement therapy, in preference to cryoprecipitate, is very strong, although the current unlicensed status of this product in the UK is a significant impediment.

## References

- Coagulation management in trauma-related massive bleeding. Recommendations of the Task Force for Coagulation of the Austrian Society of Anesthesiology, Resuscitation and Intensive Care Medicine (ÖGARI).
- Ahrons, S., Glavind-Kristensen, S., Drachmann, O. & Kissmeyer-Nielsen, F. (1970) Severe reactions after cryoprecipitated human factor VIII. *Vox Sanguinis*, **18**, 182-184.
- Alter, H.J. & Klein, H.G. (2008) The hazards of blood transfusion in historical perspective. *Blood*, **112**, 2617-2626.
- Anonymous (2003) International Blood. *Plasma News*, **21**, 70.
- Atance, R., Pereira, A. & Ramirez, B. (2001) Transfusing methylene blue-photoinactivated plasma instead of FFP is associated with an increased demand for plasma and cryoprecipitate. *Transfusion*, **41**, 1548-1552.
- Aygoren-Pursun, E., Martinez Saguer, I., Rusicke, E., Louwen, F., Geka, F., Ivaskevicius, V., Oldenburg, J., Klingebiel, T. & Kreuz, W. (2007) Retrochorionic hematoma in congenital afibrinogenemia: resolution with fibrinogen concentrate infusions. *American Journal of Hematology*, **82**, 317-320.
- Aznar, J.A., Bonanad, S., Montoro, J.M., Hurtado, C., Cid, A.R., Soler, M.A. & De Miguel, A. (2000) Influence of methylene blue photoinactivation treatment on coagulation factors from fresh frozen plasma, cryoprecipitates and cryosupernatants. *Vox Sanguinis*, **79**, 156-160.
- Balleisen, L., Bailey, J., Epping, P.H., Schulte, H. & van de Loo, J. (1985) Epidemiological study on factor VII, factor VIII and fibrinogen in an industrial population: I. Baseline data on the relation to age, gender, body-weight, smoking, alcohol, pill-using, and menopause. *Thrombosis and Haemostasis*, **54**, 475-479.
- Bevan, D.H. (1999) Cardiac bypass haemostasis: putting blood through the mill. *British Journal of Haematology*, **104**, 208-219.
- Blome, M., Isgro, F., Kiessling, A.H., Skuras, J., Haubelt, H., Hellstern, P. & Saggau, W. (2005) Relationship between factor XIII activity, fibrinogen, haemostasis screening tests and postoperative bleeding in cardiopulmonary bypass surgery. *Thrombosis and Haemostasis*, **93**, 1101-1107.
- Bronnimann, R. (1954) [Congenital afibrinogenemia; report of a case with multiple bone cysts and formation of a specific antibody (anti fibrinogen) following blood transfusion.]. *Acta Haematol*, **11**, 40-51.
- Bundesaertzekammer (2009) Cross-sectional guidelines for therapy with blood components and plasma derivatives. 4th edition.
- Cardigan, R., Philpot, K., Cookson, P. & Luddington, R. (2009) Thrombin generation and clot formation in methylene blue-treated plasma and cryoprecipitate. *Transfusion*, **49**, 696-703.
- Chapman, C.E., Stainsby, D., Jones, H., Love, E., Massey, E., Win, N., Navarrete, C., Lucas, G., Soni, N., Morgan, C., Choo, L., Cohen, H. & Williamson, L.M. (2008) 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*, **49**, 440-452.
- Charbit, B., Mandelbrot, L., Samain, E., Baron, G., Haddaoui, B., Keita, H., Sibony, O., Mahieu-Caputo, D., Hurtaud-Roux, M.F., Huisse, M.G., Denninger, M.H. & de Prost, D. (2007) The decrease of fibrinogen is an early predictor of the

- 1  
2  
3 severity of postpartum hemorrhage. *Journal of Thrombosis and Haemostasis*, **5**,  
4 266-273.
- 5  
6 Chowdhury, P., Saayman, A.G., Paulus, U., Findlay, G.P. & Collins, P.W. (2004)  
7 Efficacy of standard dose and 30 ml/kg fresh frozen plasma in correcting  
8 laboratory parameters of haemostasis in critically ill patients. *British Journal of*  
9 *Haematology*, **125**, 69-73.
- 10  
11 Ciavarella, D., Reed, R.L., Counts, R.B., Baron, L., Pavlin, E., Heimbach, D.M. &  
12 Carrico, C.J. (1987) Clotting factor levels and the risk of diffuse microvascular  
13 bleeding in the massively transfused patient. *British Journal of Haematology*, **67**,  
14 365-368.
- 15  
16 Coppola, L., Caserta, F., De Lucia, D., Guastafierro, S., Grassia, A., Coppola, A.,  
17 Marfella, R. & Varricchio, M. (2000) Blood viscosity and aging. *Archives of*  
18 *Gerontology and Geriatrics*, **31**, 35-42.
- 19  
20 Danes, A.F., Cuenca, L.G., Bueno, S.R., Mendarte Barrenechea, L. & Ronsano, J.B.  
21 (2008) Efficacy and tolerability of human fibrinogen concentrate  
22 administration to patients with acquired fibrinogen deficiency and active or  
23 in high-risk severe bleeding. *Vox Sanguinis*, **94**, 221-226.
- 24  
25 De Vries, A., Rosenberg, T., Kochwa, S. & Boss, J.H. (1961) Precipitating  
26 antifibrinogen antibody appearing after fibrinogen infusions in a patient with  
27 congenital afibrinogenemia. *Am J Med*, **30**, 486-494.
- 28  
29 Dickneite, G., Joch, C. & Bergman, G.E. (2008) The evaluation of a prothrombotic risk  
30 in a human fibrinogen concentrate. *American Society of Hematology Annual*  
31 *Meeting Abstracts*, **112**, 4064.
- 32  
33 Dietrich, W. (2000) Cardiac surgery and the coagulation system. *Current Opinion in*  
34 *Anaesthesiology*, **13**, 27-34.
- 35  
36 Elodi, S. & Varadi, K. (1979) Optimization of conditions for the catalytic effect of the  
37 factor IXa-factor VIII complex: probable role of the complex in the  
38 amplification of blood coagulation. *Thrombosis Research*, **15**, 617-629.
- 39  
40 Fenger-Eriksen, C., Lindberg-Larsen, M., Christensen, A.Q., Ingerslev, J. & Sorensen,  
41 B. (2008) Fibrinogen concentrate substitution therapy in patients with massive  
42 haemorrhage and low plasma fibrinogen concentrations. *British Journal of*  
43 *Anaesthesia*, **101**, 769-773.
- 44  
45 Fenger-Eriksen, C., Midtgaard Jensen, T., Kristensen, B.S., Jensen, K.M., Tonnesen, E.,  
46 Ingerslev, J. & Sorensen, B. (2009a) Fibrinogen substitution improves whole  
47 blood clot firmness after dilution with hydroxyethyl starch in bleeding  
48 patients undergoing radical cystectomy: a randomized placebo-controlled  
49 clinical trial. *J Thromb Haemost*, **7**, 795-802.
- 50  
51 Fenger-Eriksen, C., Tonnesen, E., Ingerslev, J. & Sorensen, B. (2009b) Mechanisms of  
52 hydroxyethyl starch-induced dilutional coagulopathy. *J Thromb Haemost*, **7**,  
53 1099-1105.
- 54  
55 Fenger-Erikson, C., Ingerslev, J. & Sorensen, B. (2009) Fibrinogen concentrate - a  
56 potential universal haemostatic agent. *Expert Opinion on Biological Therapy*, **9**,  
57 1325-1333.
- 58  
59 Flamholz, R., Jeon, H.R., Baron, J.M. & Baron, B.W. (2000) Study of three patients  
60 with thrombotic thrombocytopenic purpura exchanged with  
solvent/detergent-treated plasma: is its decreased protein S activity clinically  
related to their development of deep venous thromboses? *Journal of Clinical*  
*Apheresis*, **15**, 169-172.
- Fries, D., Haas, T., Klingler, A., Streif, W., Klima, G., Martini, J., Wagner-Berger, H. &  
Innerhofer, P. (2006) Efficacy of fibrinogen and prothrombin complex

- concentrate used to reverse dilutional coagulopathy--a porcine model. *British Journal of Anaesthesia*, **97**, 460-467.
- Fries, D., Innerhofer, P., Klingler, A., Berresheim, U., Mittermayr, M., Calatzis, A. & Schobersberger, W. (2002) The effect of the combined administration of colloids and lactated Ringer's solution on the coagulation system: an in vitro study using thrombelastograph coagulation analysis (ROTEG). *Anesthesia and Analgesia*, **94**, 1280-1287.
- Fries, D., Krismer, A., Klingler, A., Streif, W., Klima, G., Wenzel, V., Haas, T. & Innerhofer, P. (2005) Effect of fibrinogen on reversal of dilutional coagulopathy: a porcine model. *British Journal of Anaesthesiology*, **95**, 172-177.
- Gorlinger, K. (2006) Coagulation management during liver transplantation. *Hamostaseologie*, **26**, S64-76.
- Groner, A. (2008) 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*, **93**, e24-26.
- Haas, T., Fries, D., Velik-Salchner, C., Oswald, E. & Innerhofer, P. (2008) Fibrinogen in craniostomosis surgery. *Anesthesia and Analgesia*, **106**, 725-731.
- Heim, M.U., Meyer, B. & Hellstern, P. (2009) Recommendations for the use of therapeutic plasma. *Curr Vasc Pharmacol*, **7**, 110-119.
- Heimburger, N. (2002) From cryoprecipitate to virus-safe high-purity concentrate. *Seminars in Thrombosis and Hemostasis*, **28 Suppl 1**, 25-30.
- Heindl, B., Delorenzo, C. & Spannagl, M. (2005) [High dose fibrinogen administration for acute therapy of coagulopathy during massive perioperative transfusion]. *Anaesthesia*, **54**, 787-790.
- Henkel-Honke, T. & Oleck, M. (2007) Artificial oxygen carriers: a current review. *AANA Journal*, **75**, 205-211.
- Hiippala, S.T. (1995) Dextran and hydroxyethyl starch interfere with fibrinogen assays. *Blood Coagulation & Fibrinolysis*, **6**, 743-746.
- Hiippala, S.T., Myllyla, G.J. & Vahtera, E.M. (1995) Hemostatic factors and replacement of major blood loss with plasma-poor red cell concentrates. *Anesthesia and Analgesia*, **81**, 360-365.
- Hornsey, V.S., Krailadsiri, P., MacDonald, S., Seghatchian, J., Williamson, L.M. & Prowse, C.V. (2000) Coagulation factor content of cryoprecipitate prepared from methylene blue plus light virus-inactivated plasma. *British Journal of Haematology*, **109**, 665-670.
- Innerhofer, P., Fries, D., Margreiter, J., Klingler, A., Kuhbacher, G., Wachter, B., Oswald, E., Salner, E., Frischhut, B. & Schobersberger, W. (2002) The effects of perioperatively administered colloids and crystalloids on primary platelet-mediated hemostasis and clot formation. *Anesthesia and Analgesia*, **95**, 858-865.
- Ishikawa, S., Kario, K., Nago, N., Kayaba, K., Hiraoka, J., Matsuo, H., Goto, T., Miyamoto, T., Tsutsumi, A., Nakamura, Y., Shimada, K., Inoue, K. & Igarashi, M. (1997) Factor VII and fibrinogen levels examined by age, sex, and other atherosclerotic risk factors in a Japanese population. The Jichi Medical School Cohort Study. *Thrombosis and Haemostasis*, **77**, 890-893.
- Josephson, C.D. & Abshire, T.C. (2006) Clinical uses of plasma and plasma fractions: plasma-derived products for hemophilias A and B, and for von Willebrand disease. *Best Practice & Research. Clinical Haematology*, **19**, 35-49.
- Karlsson, M., Ternstrom, L., Hyllner, M., Baghaei, F., Nilsson, S. & Jeppsson, A. (2008) Plasma fibrinogen level, bleeding, and transfusion after on-pump

- 1  
2  
3 coronary artery bypass grafting surgery: a prospective observational study.  
4 *Transfusion*, **48**, 2152-2158.
- 5  
6 Kestin, A.S., Valeri, C.R., Khuri, S.F., Loscalzo, J., Ellis, P.A., MacGregor, H.,  
7 Birjiniuk, V., Ouimet, H., Pasche, B., Nelson, M.J. & et al. (1993) The platelet  
8 function defect of cardiopulmonary bypass. *Blood*, **82**, 107-117.
- 9  
10 Korte, W. & Feldges, A. (1994) Increased prothrombin activation in a patient with  
11 congenital afibrinogenemia is reversible by fibrinogen substitution. *Clin*  
12 *Investig*, **72**, 396-398.
- 13  
14 Kozek-Langenecker, S. (2007) Management of massive operative blood loss. *Minerva*  
15 *Anesthesiologica*, **73**, 401-415.
- 16  
17 Kreuz, W., Meili, E., Peter-Salonen, K., Haertel, S., Devay, J., Krzensk, U. & Egbring,  
18 R. (2005) Efficacy and tolerability of a pasteurised human fibrinogen  
19 concentrate in patients with congenital fibrinogen deficiency. *Transfusion and*  
20 *Apheresis Science*, **32**, 247-253.
- 21  
22 Laharrague, P.F., Cambus, J.P., Fillola, G. & Corberand, J.X. (1993) Plasma fibrinogen  
23 and physiological aging. *Aging (Milano)*, **5**, 445-449.
- 24  
25 Li, Y.F., Spencer, F.A. & Becker, R.C. (2001) Comparative efficacy of fibrinogen and  
26 platelet supplementation on the in vitro reversibility of competitive  
27 glycoprotein IIb/IIIa (alphaIIb/beta3) receptor-directed platelet inhibition.  
28 *American Heart Journal*, **142**, 204-210.
- 29  
30 MacLennan, S. & Barbara, J.A. (2006) Risks and side effects of therapy with plasma  
31 and plasma fractions. *Best Practice & Research Clinical Haematology*, **19**, 169-189.
- 32  
33 Mardel, S.N., Saunders, F.M., Allen, H., Menezes, G., Edwards, C.M., Ollerenshaw,  
34 L., Baddeley, D., Kennedy, A. & Ibbotson, R.M. (1998) Reduced quality of clot  
35 formation with gelatin-based plasma substitutes. *British Journal of Anaesthesia*,  
36 **80**, 204-207.
- 37  
38 Martini, W.Z., Pusateri, A.E., Uscilowicz, J.M., Delgado, A.V. & Holcomb, J.B. (2005)  
39 Independent contributions of hypothermia and acidosis to coagulopathy in  
40 swine. *Journal of Trauma*, **58**, 1002-1009.
- 41  
42 Mittermayr, M., Streif, W., Haas, T., Fries, D., Velik-Salchner, C., Klingler, A.,  
43 Oswald, E., Bach, C., Schnapka-Koepf, M. & Innerhofer, P. (2007) Hemostatic  
44 changes after crystalloid or colloid fluid administration during major  
45 orthopedic surgery: the role of fibrinogen administration. *Anesthesia and*  
46 *Analgesia*, **105**, 905-917.
- 47  
48 Mosesson, M.W. (2003) Antithrombin I. Inhibition of thrombin generation in plasma  
49 by fibrin formation. *Thromb Haemost*, **89**, 9-12.
- 50  
51 Nielsen, V.G., Cohen, B.M. & Cohen, E. (2005) Effects of coagulation factor deficiency  
52 on plasma coagulation kinetics determined via thrombelastography: critical  
53 roles of fibrinogen and factors II, VII, X and XII. *Acta anaesthesiologica*  
54 *Scandinavica*, **49**, 222-231.
- 55  
56 Nizzi, F.A., Sapatnekar, S. & Blick, R.L. (2002) Hereditary coagulation protein defects.  
57 In: *Disorders of thrombosis and haemostasis* (ed. by Blick, R.L.), pp. 117-138.  
58 Lippincott Williams & Wilkins.
- 59  
60 O'Shaughnessy, D.F., Atterbury, C., Bolton Maggs, P., Murphy, M., Thomas, D.,  
Yates, S. & Williamson, L.M. (2004) Guidelines for the use of fresh-frozen  
plasma, cryoprecipitate and cryosupernatant. *British Journal of Haematology*,  
**126**, 11-28.
- Oswald, M.W., Hunt, H.H. & Lazarchick, J. (1983) Normal range of plasma  
fibrinogen. *The American Journal of Medical Technology*, **49**, 57-59.

- 1  
2  
3 Pincock, S. (2004) Patient's death from vCJD may be linked to blood transfusion.  
4 Committee to discuss need for further precautions to prevent possible vCJD  
5 transmission through blood. *Lancet*, **363**, 43.
- 6  
7 Pool, J.G., Gershgold, E.J. & Pappenhagen, A.R. (1964) High-potency antihaemophilic  
8 factor concentrate prepared from cryoglobulin precipitate. *Nature*, **203**, 312.
- 9  
10 Pool, J.G. & Shannon, A.E. (1965) Production of high-potency concentrates of  
11 antihemophilic globulin in a closed-bag system. *New England Journal of*  
12 *Medicine*, **273**, 1443-1447.
- 13  
14 Poon, M.C. (1993) Cryoprecipitate: uses and alternatives. *Transfusion Medicine*  
15 *Reviews*, **7**, 180-192.
- 16  
17 Pothula, S., Sanchala, V.T., Nagappala, B. & Inchiosa, M.A., Jr. (2004) The effect of  
18 preoperative antiplatelet/anticoagulant prophylaxis on postoperative blood  
19 loss in cardiac surgery. *Anesthesia and Analgesia*, **98**, 4-10.
- 20  
21 Ra'anani, P., Levi, Y., Varon, D., Gitel, S. & Martinowitz, U. (1991) [Congenital  
22 afibrinogenemia with bleeding, bone cysts and antibodies to fibrinogen].  
23 *Harefuah*, **121**, 291-293.
- 24  
25 Rahe-Meyer, N., Pichlmaier, M., Haverich, A., Solomon, C., Winterhalter, M.,  
26 Piepenbrock, S. & Tanaka, K.A. (2009a) Bleeding management with  
27 fibrinogen concentrate targeting a high-normal plasma fibrinogen level: a  
28 pilot study. *British Journal of Anaesthesia*, **102**, 785-792.
- 29  
30 Rahe-Meyer, N., Solomon, C., Winterhalter, M., Piepenbrock, S., Tanaka, K.,  
31 Haverich, A. & Pichlmaier, M. (2009b) Thromboelastometry-guided  
32 administration of fibrinogen concentrate for the treatment of excessive  
33 intraoperative bleeding in thoracoabdominal aortic aneurysm surgery. *Journal*  
34 *of Thoracic and Cardiovascular Surgery*, **138**, 694-702.
- 35  
36 Reese, E.P., McCullough, J.J. & Craddock, P.R. (1975) An adverse pulmonary reaction  
37 to cryoprecipitate in a hemophiliac. *Transfusion*, **15**, 583.
- 38  
39 Reinhart, W.H. (2003) Fibrinogen--marker or mediator of vascular disease? *Vasc Med*,  
40 **8**, 211-216.
- 41  
42 Rodriguez, R.C., Buchanan, G.R. & Clanton, M.S. (1988) Prophylactic cryoprecipitate  
43 in congenital afibrinogenemia. *Clinical Pediatrics*, **27**, 543-545.
- 44  
45 Royston, D. & von Kier, S. (2001) Reduced haemostatic factor transfusion using  
46 heparinase-modified thrombelastography during cardiopulmonary bypass.  
47 *British Journal of Anaesthesia*, **86**, 575-578.
- 48  
49 Seghatchian, J. & Krailadsiri, P. (2001) What's happening? The quality of methylene  
50 blue treated FFP and cryo. *Transfusion and Apheresis Science*, **25**, 227-231.
- 51  
52 Shore-Lesserson, L., Manspeizer, H.E., DePerio, M., Francis, S., Vela-Cantos, F. &  
53 Ergin, M.A. (1999) Thromboelastography-guided transfusion algorithm  
54 reduces transfusions in complex cardiac surgery. *Anesthesia and Analgesia*, **88**,  
55 312-319.
- 56  
57 Spalding, G.J., Hartrumpf, M., Sierig, T., Oesberg, N., Kirschke, C.G. & Albes, J.M.  
58 (2007) Cost reduction of perioperative coagulation management in cardiac  
59 surgery: value of "bedside" thrombelastography (ROTEM). *European Journal of*  
60 *Cardiothoracic Surgery*, **31**, 1052-1057.
- Stainsby, D., MacLennan, S., Thomas, D., Isaac, J. & Hamilton, P.J. (2006) Guidelines  
on the management of massive blood loss. *British Journal of Haematology*, **135**,  
634-641.
- Stanworth, S.J. (2007) The evidence-based use of FFP and cryoprecipitate for  
abnormalities of coagulation tests and clinical coagulopathy. *Hematology*  
*American Society of Hematology Educational Program*, **2007**, 179-186.

- 1  
2  
3 Starr, D. (2002) *Blood: an epic history of medicine and commerce*. Harper Collins, New  
4 York.  
5  
6 Stinger, H.K., Spinella, P.C., Perkins, J.G., Grathwohl, K.W., Salinas, J., Martini, W.Z.,  
7 Hess, J.R., Dubick, M.A., Simon, C.D., Beekley, A.C., Wolf, S.E., Wade, C.E. &  
8 Holcomb, J.B. (2008) The ratio of fibrinogen to red cells transfused affects  
9 survival in casualties receiving massive transfusions at an army combat  
10 support hospital. *J Trauma*, **64**, S79-85.  
11  
12 The Serious Hazards of Transfusion Steering Group (2004) Serious Hazards of  
13 Transfusion annual report 2004.  
14  
15 Ucar, H.I., Oc, M., Tok, M., Dogan, O.F., Oc, B., Aydin, A., Farsak, B., Guvener, M.,  
16 Yorgancioglu, A.C., Dogan, R., Demircin, M. & Pasaoglu, I. (2007a)  
17 Preoperative fibrinogen levels as a predictor of postoperative bleeding after  
18 open heart surgery. *The Heart Surgery Forum*, **10**, E392-396.  
19  
20 Ucar, H.I., Tok, M., Atalar, E., Dogan, O.F., Oc, M., Farsak, B., Guvener, M., Yilmaz,  
21 M., Dogan, R., Demircin, M. & Pasaoglu, I. (2007b) Predictive significance of  
22 plasma levels of interleukin-6 and high-sensitivity C-reactive protein in atrial  
23 fibrillation after coronary artery bypass surgery. *Heart Surg Forum*, **10**, E131-  
24 135.  
25  
26 Velik-Salchner, C., Haas, T., Innerhofer, P., Streif, W., Nussbaumer, W., Klingler, A.,  
27 Klima, G., Martinowitz, U. & Fries, D. (2007) The effect of fibrinogen  
28 concentrate on thrombocytopenia. *Journal of Thrombosis and Haemostasis*, **5**,  
29 1019-1025.  
30  
31 Wallis, J.P. (2003) Transfusion-related acute lung injury (TRALI)--under-diagnosed  
32 and under-reported. *British Journal of Anaesthesia*, **90**, 573-576.  
33  
34 Weinkove, R. & Rangarajan, S. (2008) Fibrinogen concentrate for acquired  
35 hypofibrinogenaemic states. *Transfusion Medicine*, **18**, 151-157.  
36  
37 Williamson, L.M., Cardigan, R. & Prowse, C.V. (2003) Methylene blue-treated fresh-  
38 frozen plasma: what is its contribution to blood safety? *Transfusion*, **43**, 1322-  
39 1329.  
40  
41  
42  
43  
44  
45  
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Table 1. Mean reduction of virus titres during the production of Haemocomplettan® P/Riastap (CSL Behring, Marburg, Germany). Adapted from (Groner 2008)

Virus	Mean reduction of titre (log <sub>10</sub> )
Human immunodeficiency virus	≥9.6
Bovine viral diarrhoea virus <sup>a</sup>	≥11.2
Herpes simplex virus 1	≥9.1
Hepatitis A virus	≥7.6
Canine parvovirus <sup>b</sup>	6.1

<sup>a</sup>Model virus for hepatitis C virus; <sup>b</sup>model virus for human parvovirus B19.

For Peer Review



Table 2. Attributes to consider when choosing between cryoprecipitate and fibrinogen concentrate for management of perioperative bleeding.

Attribute	Cryoprecipitate	Fibrinogen concentrate
Immunological reactions	Risk of ABO incompatibility, TRALI and severe anaphylaxis, albeit low because resuspended in small volume of plasma.	Negligible risk of immunological reactions because purification steps during preparation remove donor antibodies
Risk of viral/pathogen transmission	Usually not virally inactivated. Viral inactivation using MB or SD not as effective as pasteurisation	Manufacturing process includes pasteurisation* and filtration steps that minimise the risk
Accuracy of dosing	Inconsistent fibrinogen content between units. Reduced fibrinogen content in cryoprecipitate from MB-treated plasma	Standardised fibrinogen content
Number of units/vials required to provide 4g dose	29 units (based on 140 mg/unit)	4 vials
Reconstituted volume of 4g dose	Approximately 375 mL (based on 15 g/L)	200 mL
Time to administration	Must first be thawed in a water bath	Can be reconstituted rapidly
Cost	Perceived to be cheaper than fibrinogen concentrate	Cost-effective and overall cost may be similar to cryoprecipitate
Availability	Not available in many European countries. Mainly used in UK and USA	More widely available than cryoprecipitate in most European countries

MB, methylene blue; SD, solvent/detergent; TRALI, transfusion-related lung injury

\*in Haemocomplettan® P/Riastap only

**Figure 1. Timeline of developments in treatment of haemophilia**

1803	First modern description of haemophilia
1828	First use of term 'haemophilia'
1840	First successful blood transfusion
1946	Antihaemophilic globulin (AHG)
1952	Haemophilia B described
1964	Cryoprecipitate revolutionised treatment of haemophilia A
1968	First commercially available FVIII concentrate
1982	First reports of AIDS in haemophilia patients
1985	Virally-inactivated factor concentrates became available
1989	Hepatitis C virus identified
1991	Viral inactivation of plasma with methylene blue described
1992	First recombinant FVIII products became available

Figure 2. Schematic of production of pasteurised fibrinogen concentrate from frozen plasma.

