The Evidence-Based Use of FFP and Cryoprecipitate for Abnormalities of Coagulation Tests and Clinical Coagulopathy

Simon J. Stanworth

National Blood Service, Oxford Radcliffe Hospitals, University of Oxford, Oxford, United Kingdom

There continues to be a general but unfounded enthusiasm for fresh frozen plasma (FFP) or frozen plasma (FP) usage across a range of clinical specialties in hospital practice. Plasma for transfusion is most often used where there are abnormal coagulation screening tests, either therapeutically in the face of bleeding, or prophylactically in nonbleeding patients prior to invasive procedures or surgery. Little evidence exists to inform best therapeutic transfusion practice, and most studies describe plasma use in a prophylactic setting. Laboratory abnormalities of coagulation are considered by many clinicians to be a predictive risk factor for bleeding prior to invasive procedures or in other clinical situations where bleeding risk exists, and plasma for transfusion is presumed to improve the laboratory results and reduce this risk. However, most guideline indications for the prophylactic use of plasma for transfusion are not supported by evidence from good-quality randomized trials. Arguably, the strongest randomized controlled trial (RCT) evidence indicates that prophylactic plasma for transfusion is not effective across a range of different clinical settings, and this is supported by data from nonrandomized studies in patients with mild to moderate abnormalities in coagulation tests. There is a need to undertake new trials evaluating the efficacy and adverse effects of plasma, both in bleeding and non-bleeding patients, to understand whether the *presumed* benefits outweigh the *real* risks. In addition, new hemostatic tests that better define the risk of bleeding and monitor the effectiveness of the use of FFP should be validated. Last, there is an opportunity to develop effective educational strategies aimed at addressing understanding and compliance with recommendations in guidelines.

What Is Plasma for Transfusion?

Frozen plasma (FP) is human donor plasma, either recovered from a single whole-blood donation or obtained by plasmapheresis, frozen within a specific time period after collection and then stored at a defined temperature, typically –30°C. Plasma frozen within 8 hours is called fresh frozen plasma (FFP); plasma frozen at slightly longer intervals (typically up to 24 hours) after collection is referred to as frozen plasma (known as F24 in the U.S.). Levels of the labile coagulation factors V and VIII may be slightly lower in FP in comparison with FFP. Although both components (FFP and F24) are largely considered clinically equivalent by physicians, and for the purposes of this review will be covered (interchangeably) by the common term FP, evidence for equivalence has not been documented. After thawing, FP contains near-normal levels of most plasma proteins, including procoagulant and inhibitory components of the coagulation system, acute phase proteins, immunoglobulins and albumin, although all levels are diluted by the citrate anticoagulant solution. Factor VIII (FVIII) is typically the only plasma protein whose level is quality controlled in the specification of the product, and as required by UK[1] and EU guidelines (but not AABB standards); this level needs to be met for a proportion of units (typically 75%). Overall coagulation factor content is well maintained in thawed FFP stored at 1°C to 6°C for up to 5 days (with evidence of a fall in Factors V and VIII). A typical unit of plasma derived from a collection of whole blood has a volume of just under 300 mL, and local and national guidelines for usage generally specify a dose of around 10 to 20 mL/kg.

Although clinicians tend to assume approximate equivalence in clinical effectiveness among units of FP, it is likely that there is heterogeneity, reflecting biological variation in factor levels among individual donors (for example levels of von Willbrand factor (VWF) and FVIII levels are ABO blood group related), and differences in processing, storage and preparation for administration. **Figure 1** shows data for procoagulant factor content from 66 U of FFP.[2,3]

Such variation among transfused units is less marked for pooled plasma components such as solvent detergent FP. This component is prepared from pools of 300 to 5000 plasma donations and is one of the pathogen-inactivated preparations of plasma available for clinical use. Pathogen inactivation technology represents an additional safety measure to reduce the risk of transfusion-transmitted infection. The main methods applied to plasmas are solvent-detergent treatment, in which pooled plasma is exposed to a solvent and detergent; methylene-blue treatment, in which single-donor units are treated with methylene blue (a phenothiazine dye) and light; and amotosalen treatment in which a group of compounds called psoralens (which have been developed for their virus- and bacteria-killing prop-

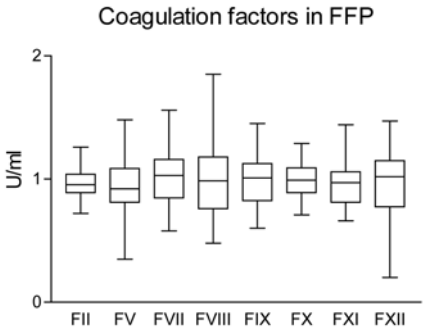

Figure 1. A box and whisker plot for the 25th and 75th centiles, with median and error bars as range, for normal plasma (white-cell–reduced fresh frozen plasma [FFP]).

erties) are added to plasma prior to exposure to UVA light. Although the methods offer good virus protection and can reduce microbial infectivity, they are associated with altered or loss of coagulation factor content, and the implications of this will be discussed later.[4,5] Pathogen-inactivated plasma is more widely used in Europe, and none of these methods are currently widely available in the U.S., although solvent detergent treatment has been licensed by the Food and Drug Administration (FDA).

As well as FP, plasma can be used to produce more purified constituents, including concentrates of coagulation factors and fibrin sealant, immunoglobulins (normal or specific, e.g., Rh-immune globulin), anticoagulants (e.g., antithrombin, protein C), complement-related proteins (C1-esterase inhibitor), and albumin. Further discussion of these components is beyond the scope of this article.

What Is Cryoprecipitate?

Cryoprecipitate represented the first practical preparation of a concentrated form of anti-hemophiliac factor. It is prepared by controlled thawing at 1°C to 6°C of FP to precipitate higher molecular weight proteins, including FVIII, VWF and fibrinogen. In many Western countries, cryoprecipitate is mainly transfused as a concentrated source of fibrinogen. An adult dose of around 10 single bags of cryoprecipitate derived from units of whole blood typically raises the plasma fibrinogen level by up to 1 g/L (60-100 mg/dL). The product remaining after the removal of cryprecipitate is called cryosupernatant (cryopoor or cryoreduced plasma) and has been used in the treatment of thrombotic thrombocytopenic purpura (TTP) because of the theoretical benefit of its reduced content of VWF high-molecular-weight multimers. This benefit of cryosupernatant use in TTP remains unproven in large clinical trials.[6]

Which Patients Receive FP?

Clinical use of FP has grown steadily in the last two decades in many countries. There is also evidence of variation in usage among countries—use in England and Wales may be proportionately less per patient than current levels of usage in the U.S.[7] In a subset of Finnish hospitals, over 6000 FP units were tracked to 1159 patients who received transfusions, revealing that FP was transfused most often to surgery patients, especially cardiac.[8] Findings from local audits in many countries identify those recipients of FP as including patients with liver disease, those undergoing cardiovascular surgery or reversal of warfarin over-anticoagulation, or patients with disseminated intravascular coagulation (DIC), massive transfusion, or TTP. These broad groupings of FP recipients mirror those addressed in most national guidelines[1,9-11] and form the basis of this review.

Defining Abnormal Coagulation Screening Tests and Clinical Coagulopathy.

Given the role of laboratory results for coagulation screening tests to direct transfusion decisions for FP, it is necessary to first review the limitations of these tests. For many clinicians, coagulation is envisioned as proceeding through either an intrinsic pathway (triggered by a negatively charged surface) or by an extrinsic pathway (triggered by tissue factor). But the reality is that *in vivo* the coagulation processes are more interrelated, with initiation of coagulation occurring through the extrinsic pathway (dependent on the tissue factor–FVIIa complex) and propagation through factors in the intrinsic pathway (the intrinsic factor tenase and the prothrombinase complexes). The activated partial thromboplastin time (APTT) and prothrombin time (PT) laboratory tests were developed to investigate coagulation factor deficiencies in patients with a bleeding history by providing an end-assessment of thrombin generation by fibrin formation. However, their applied value in clinical practice continues to be debated.[12] PT and APTT results are dependent on reagent and laboratory quality controls and processes, and may be outside reference range for a number of reasons not associated with bleeding risk, including normal variation for some individuals or the presence of a lupus anticoagulant. In addition, coagulation tests vary in sensitivity for reduced levels of coagulation factor levels. For example, the APTT will be significantly prolonged with only small reductions in the levels of some intrinsic coagulation factors. The PT is sensitive to mild deficiencies of *multiple* procoagulants, as is often seen in clinical practice,[13] but this is of less clinical significance.

Many laboratories report the international normalized ratio (INR), and physicians then base decisions to transfuse on results above a certain threshold, typically 1.5 times the control. The INR is based on PT and was developed to monitor warfarin therapy by standardizing results to account for different sensitivities of thromboplastins. It has been argued that the extrapolation of PT to INR is really only valid for those patients stably anticoagulated with vitamin K antagonists, and may not be valid for patients with, for example, liver disease.[14] Many thromboplastins now have a lower International Sensitivity Index (ISI) than found in the past, but corresponding changes in general levels of INRs may not always be appreciated by clinicians

when reviewing the literature.[15] An INR of 1.5 is also not equivalent to a PT of 1.5 times midpoint of reference range, although it may approximate to this measure as the ISI value moves closer to 1.0. An important study by Deitcher[16] showed that over the INR range of 1.3–1.9 inclusive, mean factor levels ranged from 31% to 65% (FII), 40% to 70% (FV), and 22% to 60% (FVII). All of these levels are consistent with adequate concentrations of factors to support hemostasis.

In a systematic review Segal and Dzik[17] addressed the problems of relating the standard *in vitro* tests to *in vivo* hemostasis by asking whether abnormalities in coagulation tests correlate with an increased risk of clinical bleeding. All relevant publications describing bleeding outcomes in patients with abnormalities in coagulation tests prior to invasive procedures were assessed. Their analysis focused on one controlled trial (of liver biopsies) and 24 observational studies (of which about half had a comparison group) covering a range of procedures. Overall, the published studies did not support evidence for a predictive value of PT/INR for bleeding. For example, in one recent large retrospective (nonrandomized) study of central line placement in consecutive patients prior to cardiac surgery, no evidence was found that hemorrhagic complications were increased in heparin-anticoagulated patients.[18] In another more direct assessment, Ewe[19] reported on a "liver bleeding time" in patients after laparoscopic liver biopsy and found no correlations between bleeding time and variables including coagulation testing and platelet count.

Given the understanding that overall hemostasis depends on a complex inter-relationship among endothelium, platelets, other inflammatory cells, fibrinolysis, and inhibitors as well as procoagulant factors, it is not surprising perhaps that an abnormality in one component, coagulation screening, is not a sensitive marker of clinical hemostasis. A more composite approach to individual bleeding risk would seem more appropriate for clinical use. However, laboratory tests to monitor this are not readily available at present, and whether newer tests of global hemostasis (e.g., thromboelastogram, thrombin generation tests[20]) can better predict clinical bleeding risk is beyond the scope of this review. It will be important to validate these newer tests in large prospective studies that measure clinical outcomes. Finally, reference ranges for any tests need to be clinically appropriate. As an example, ranges for APTT (and PT to a lesser degree) are wider in neonates than adult or older childhood ranges.

Evidence For and Against the Effectiveness of FP

The clearest evidence for a direct beneficial effect of FP would be expected to come from randomized controlled studies of FP compared with no FP. Studies of interventions comparing FP with a non-blood product (e.g., solutions of colloids and/or crystalloids) may also assess effectiveness, but such studies would need to be separately evaluated given that these solutions have variable effects on *in vivo* or *in vitro* coagulation themselves.[21] Out of a total of 57 identified published RCTs (up to 2004) on the use of FP identified in another systematic review, only 17 compared FP with no FP or to a colloid/crystalloid solution in adults.[22] Many enrolled small numbers of patients and provided inadequate information on the ability of the trial to detect, without bias, meaningful differences in outcomes between the two patient groups. When considering all RCTs evaluating prophylactic usage across a range of settings (including cardiac, neonatal, and other clinical conditions) as a group, the results failed to document evidence for the effectiveness of prophylactic FP for a range of clinical and laboratory outcomes.

In two large well-conducted trials, evidence for a lack of benefit for prophylactic use of FP was reported. Both were designed to evaluate the effectiveness of FP in a large group of patients and provided information about the sample sizes required to allow adequate power to detect clinically important differences between the groups of patients. One was in neonates, in which the Northern Neonatal Nursing Initiative (NNNI) Trial Group randomized 776 neonates and compared FP with volume expanders (gelofusin or dextrose-saline) in the prevention of intraventricular hemorrhage.[22,23] Allocation concealment and blinding of outcome assessors in monitoring clinically relevant long-term developmental outcomes were described. Of note, the study did not include measurement of coagulation tests. In the other trial, the effectiveness of FP was evaluated in patients with acute pancreatitis,[22,24] and 275 patients (in total) were randomized to receive either FP or a colloid solution, again with no evidence of benefit for plasma.

Specific information about additional selected clinical groups is discussed below.

Cardiac surgery

Epidemiologic evidence indicates that much FP is given during cardiac surgery, and a number of published RCTs have assessed benefit. However, RCTs comparing prophylactic use of FP with either no FP or a non-plasma product after cardiopulmonary bypass (CPB) have not shown evidence of a consistent significant effect on blood loss or transfusion requirements.[22] A meta-analysis of the results from these trials has also failed to establish evidence for any benefit.[25] The hemostatic changes related to cardiac bypass are multifactorial, including contact with synthetic surfaces, use of heparin, hypothermia, thrombocytopenia and defects in platelet function, and not solely related to coagulation factor deficiency.

Intensive care

In the ICU setting, there are few prospective data on the frequency with which FP is given as prophylaxis, for example prior to central venous cannulation or other invasive procedures. Dara et al reported a single-center retrospective cohort study of FP use in medical ICU patients.[26] They identified patients in whom an INR $\geq$ 1.5 was found during ICU stay and evaluated FP use in the subgroup who

were not actively bleeding. In addition to variability in FP transfusion practice, the authors observed that patients who received FP had a similar rate of hemorrhage to matched cases but had a higher incidence of "acute lung injury" during the 48 hours after transfusion (18% vs 4%; $P = .02$). This association raises the possibility that critically ill patients, many with concurrent inflammatory problems, may be more susceptible to transfusion-related acute lung injury (TRALI) after receiving plasma, although distinguishing TRALI from other clinical problems such as volume overload remains problematic. These findings do not prove cause and effect, but emphasize a need for concern about the use of FP when evidence of efficacy is at best questionable.[27]

Liver disease

The coagulopathy of liver disease is complex, with abnormalities of platelets, fibrinolysis and inhibitors of coagulation as well as coagulation factor deficiencies. One randomized trial[28] has tried to assess the effects of regular prophylactic transfusions of FP in patients with paracetamol overdose by comparison with a control group in which patients received no FP. Twenty patients were evaluated in this small study and no differences in clinical outcomes between the two groups were observed. Other studies to investigate FP transfusion practice in patients with liver disease have been uncontrolled and observational. Youssef et al[29] reported the effects of FP transfusion in 100 patients with liver disease, and found that it was difficult to correct abnormalities of coagulation screening tests unless large volumes of FP were transfused and that the effects of transfusion were short-lived. Lack of evidence for an association between bleeding and laboratory tests of coagulation in liver disease has also been reported in a number of studies, for example, the retrospective studies of McVay and Toy.[30] Although these studies contain no control group data, there is a consistent theme of lack of evidence for clinical benefit for FP when transfused to patients with liver disease. The lack of bleeding in cirrhotic patients despite diminished procoagulant synthesis (and abnormal PT/APTT) may be explained by a parallel reduction in the production of anticoagulant proteins, such as proteins C and S, leading to equivalent thrombin generation potential on activation of both pro- and anti-coagulant pathways.[20]

Reversal of warfarin effect

In the absence of major bleeding associated with over-anticoagulation due to vitamin K antagonists, primary treatment should be initiated with oral/intravenous vitamin K. In addition to vitamin K, guidelines recommend FP or prothrombin complex concentrates (PCC) for reversal of over-anticoagulation, but only in patients with major bleeding.[31] However, there is continuing controversy over which component is preferable, and this, in part, reflects a lack of clinical trials comparing the two components. PCC are virally inactivated and produced by fractionation of pooled plasma and contain coagulation factors II, VII, IX and X at a significantly higher concentration than FP. But not all PCC are the same, and in particular the levels of FVII vary between concentrates from different manufacturers. Although there is evidence that some PCC achieve more rapid and complete reversal of abnormalities of coagulation screening tests than FFP,[32] further evaluation is required to ascertain whether the more rapid improvements in coagulation screening tests translate into clinical benefit, without an increased risk of thromboembolic complications.

Therapeutic apheresis—TTP

FP may be used as a replacement fluid in patients undergoing therapeutic apheresis procedures.[33] Based on the findings of one RCT,[34] plasma exchange with FP has been recommended as the first-line treatment of choice for TTP,[35] the FP providing a source of ADAMTS13 (a disintegrin and metalloprotease with thrombospondin type 1 motif 13). However, randomized studies to define the optimal dose and schedule of FP or type of plasma (e.g., solvent detergent–treated) for therapeutic apheresis in patients with TTP have not been undertaken. Of interest, early studies investigating plasma exchange for conditions other than TTP have reported that despite repeated procedures with coagulation factor–free replacement fluids, no bleeding complications occurred, even though marked reductions of coagulation factor levels were seen.[36]

Massive transfusion and DIC

Very few trials have evaluated the effects of therapeutic FP in patients with bleeding who have multiple or global deficiencies of coagulation factors, e.g., DIC or massive transfusion, presumably in part reflecting the difficulties of trial design in this setting. From a pathophysiologic perspective, use of FP in this setting seems clinically appropriate. One study tried to address the effectiveness of FP in DIC in a group of neonates, using defined criteria for a diagnosis of DIC.[37] In this small three-way controlled trial, neonates were randomly allocated to receive either exchange transfusion (using whole blood), FP (and platelet) infusions or no plasma in a control group. Although there were no differences in rates of improvement for coagulation tests or in survival in either treatment group, the size of the trial was small (a total of 33 patients across three arms). Further consideration of transfusion support in massive transfusion, including discussion of (the potentially important) early use of FP,[38] is beyond the scope of this article.[39]

Is There an Optimal Dose for Plasma?

Questions about appropriate or optimal dose for FP transfusion generally presuppose that evidence of (dose-dependent) effectiveness in correcting abnormalities of coagulation tests exists. Much of the evidence for informing appropriate dose comes from a mathematic analysis of physiologic assessments of coagulation factor content and ef-

fects of plasma infusion.[40] However, FP may be ineffective in correcting mild to moderate abnormalities of coagulation screen tests. Abdel-Wahab et al prospectively evaluated the effects of plasma transfusions on PT/INR in hospital patients.[41] They followed patients with a pretransfusion PT between 13.1 seconds and 17 seconds (INR equivalent, 1.1-1.85). A total of 324 plasma units were evaluated in 121 patients. Fewer than 1% of patients had normalization of PT/INR after transfusion, and only 15% demonstrated a correction of half way to normal. There was no meaningful correlation with clinical bleeding, as recorded retrospectively by patient chart review. In addition, when all cases of transfusion were reviewed for correction, there was little evidence for dose-response effect. In a smaller study, 22 critically ill adult patients were allocated in consecutive groups to receive FP in one of two dosages (one group received median volume 12.2 mL/kg, the other 33.5 mL/kg).[42] Many patients who received the lower (standard) dose, but not larger dose, FP failed to achieve the target level of coagulation factor replacement. Another study[40] reported on 103 adult patients with minimally prolonged INRs and found that adding FP to their treatment failed to accelerate the decrease in INR that occurred over time. When other studies or trials do report apparent "correction," the overall absolute or mean changes again appear very small. For example, in one RCT of patients with liver disease the median reduction in INR attained after FFP was 0.2 (range, 0-0.7).[43]

FP—A Treatment with an Adverse Risk Profile

Crucial to recommendations in guidelines is the need for a clear understanding of the risk of harm. FP is not without risk, and indeed may be among the most "high risk" of all blood components.[44] The most immediate serious complication (including mortality) is TRALI, although there are ongoing issues of reporting and diagnosis of this condition that make accurate estimation of prevalence difficult.[45] Other risks are transfusion-transmitted infection, including an unquantifiable risk of prion disease, and fluid overload, which may be a greater issue if larger doses of FP are transfused to attempt full reversal of abnormal coagulation tests. Allergic reactions to FP are relatively common, with a frequency of around 1% to 3% of all transfusions, and can be extremely troublesome and sometimes life threatening for some multitransfused patients. In the U.K., an association between cases of TRALI and female donors has been identified through the Serious Hazards of Transfusion hemovigilance scheme, and male donors are now used as much as possible for production of FFP.[46] Similar trends to switching to all-male FP are being considered by transfusion services in U.S.

Understanding the risks of FP transfusion is particularly important when considering use of FP as prophylaxis (previous sections). A prophylactic policy is only justified if the risk of bleeding is greater than the risk of harmful effects. Without evidence of benefit, a policy aimed at preventing uncommon bleeding complications could involve transfusing potentially harmful FP to a large number of patients, many of whom might not bleed even if prophylactic FP were not given.

Efficacy Trials of Pathogen-Inactivated Plasma

Pathogen-inactivated formulations are increasingly finding their way into clinical practice. In the U.K., plasma is sourced from the U.S. for children and neonates up to the age of 16 years because of the perceived lower risk of variant Creutzfeldt-Jacob disease transmission. It is pathogen inactivated (methylene blue–treated) because of concern about the higher background level of viral markers in the U.S. population compared to the U.K. There are studies of efficacy comparing pathogen-inactivated product with standard FP.[47] However, it may be argued that assessing the clinical efficacy of these pathogen-inactivated variants of FP is very difficult when evidence of benefit for the standard product is thin. Although newer pathogen-inactivation processes are aimed at reducing the real but low risk of infection transmission, they may paradoxically have altered clinical effectiveness—for example, because of lower coagulation factor content—at the cost of marginally increased safety. Solvent/detergent plasma is known to have lower levels of some inhibitors of coagulation (e.g., protein S), and there are case reports suggesting an increased incidence of thrombosis in patients with TTP receiving this product compared with standard FP.[48] Transfusion of pathogen-inactivated FP has also been associated with a need for a greater volume in at least one retrospective study,[49] although the reasons for this are unclear.

Cryoprecipitate

FP contains fibrinogen at near-normal plasma levels and so will correct low fibrinogen levels if the volumes for infusion are adequate. Cryoprecipitate should not be considered for transfusion solely as a more concentrated form of FP (for example, where there are concerns about fluid overload), as it only contains significant levels of FVIII, VWF, fibronectin, FXIII and fibrinogen. Cryoprecipitate is not a source of all coagulation factors and therefore is not appropriate replacement therapy in patients with global coagulation factor deficiencies, for example, with liver disease. Cryoprecipitate use should be reserved for patients with documented isolated hypofibrinogenemia, but there are few prospective trial data to define the optimal use of cryoprecipitate. There is evidence that the use of cryoprecipitate is rising in many countries, although the exact reasons for this remain unclear. A specific purified fibrinogen concentrate is available, and it may represent a safer concentrate for direct fibrinogen replacement in isolated deficiencies, such as inherited hypofibrinogenemia (although transfusable fibrinogen concentrates are not widely available in the U.S.).

Dissemination of the Evidence

Although practice guidelines for FP transfusion are readily available in many countries, there are important limitations in the strength of the RCT evidence on which to base recommendations for its use. Existing published data, including nonrandomized clinical studies, do not provide evidence-based guidance for the prophylactic transfusion of FP to patients with mild to moderate abnormalities in coagulation tests. The evidence that exists, both from randomized and non-randomized studies, seems to consistently point to the lack of evidence for benefit for prophylactic FP. But understanding the evidence base for FP is one side of the coin; the other side is the effective dissemination of the evidence to clinicians.

Evidence for variation in practice and inappropriate practice can be drawn from many local and national audits and sources. Many physicians presumably believe that FP infusions will correct a prolonged coagulation result, and thereby minimize any hemostatic risk.[50] In other words, it seems that physicians continue to use an often ineffective intervention for which in many clinical situations (e.g., mild-moderate derangements of coagulation) there is at best frank uncertainty of benefit but also for which there is evidence of harm.[51] Perhaps a more systematic approach is required to understand the determinants of this prescribing pattern and barriers to practice change,[41] including identification of better strategies for delivery and uptake of evidence-based health care. These are all clearly demonstrated as unpredictable for FP. Indeed, a recent systematic review of the RCT evidence for the effectiveness of different educational strategies operating in transfusion medicine has pointed out the very weakness of the evidence itself for the success of these approaches to deliver sustained and effective behavioral change.[42]

What Are Alternatives to Donor Plasma?

This review has focused on FP because it is by far the most commonly used intervention to manage abnormalities of coagulation tests and clinical coagulopathy in clinical practice. Alternative options to FP exist, both generally to promote overall hemostasis or more specifically (e.g., variants of ADAMTS13). Recombinant factor VIIa (rFVIIa) is a novel procoagulant that is licensed for use in patients with hemophilia A or B and inhibitory alloantibodies. Off-license use in patients anticipated to be at risk of major bleeding (prophylactic) or who have major and uncontrolled bleeding (therapeutic) has been increasing. A number of RCTs have now been published that assess both prophylactic and therapeutic indications and cover a variety of medical and surgical settings, but the analysis of these RCTs indicates little firm evidence to indicate a beneficial effect for this drug in any situation.[54] There are also concerns about the risk of thromboembolic events in patients who are not hemophiliacs. In contrast to newer drugs such as rFVIIa, other pharmacological agents have been used for many years in patients in whom there are an expected high level of transfusion requirements, including serine protease inhibitors (e.g., aprotinin), antifibrinolytics (e.g., tranexamic acid), and DDAVP (desmopressin). Understanding how to use these drugs more appropriately is important, but beyond the scope of this review.

Summary and Looking Ahead

Hematologists and other transfusion medicine specialists are all too familiar with the problems of trying to question or justify the benefits of using FP in discussions with other physicians. What might be done to improve this situation? There should be more open recognition of the limitations of current standard coagulation screening tests and appreciation that *in vitro* abnormalities of coagulation screening tests may not equate with an *in vivo* failure of clinical hemostasis and the presence of clinical coagulopathy. The opportunity now exists for the newer generation of global tests of hemostasis to be assessed and validated in clinical studies. There is a pressing need to undertake new trials of efficacy of FP transfusion to define which groups of patients really benefit from FP. New studies need to take account of the extent to which adverse effects might negate the benefits of treatment with FP. It is also important to understand more about the identity of the constituents in plasma that are providing the most benefit in individual situations (e.g., ADAMTS13 in TTP).

Prior to design of trials of efficacy, it may be valuable to understand more about actual current FP transfusion practice and the clinical justifications for transfusion via multicentered surveys, since a recurring theme for many of the studies discussed in this review is the lack of detailed prospective information about clinical decisions regarding transfusion. For example, in one recent study, indications for plasma transfusion were not provided for more than 50% of patients,[42] and in another, the indications for transfusion of FFP were questionable in a significant number of patients.[43]

Perhaps a general enthusiasm for FP usage has been perpetuated over the years, since intuitively this blood component appears to be such an appropriate product to replace or supplement plasma constituents in patients with abnormal coagulation tests. In other words, it appears to be a readily available source of many plasma proteins, including coagulation factors that are believed by physicians to be of value in the management of sick patients. This intervention has over time become so accepted in practice that paradoxically it has not been subjected to the clinical research scrutiny required to demonstrate effectiveness now demanded in the world of evidence-based transfusion practice. There may also be a failure to acknowledge the results from prophylactic clinical studies that point to a lack of effect for a blood component that has a finite risk of adverse events. Perhaps guidelines should focus as much on when *not* to use FP as when to use FP, and with a greater emphasis on a fuller documentation and rationale for prescription by the physician.

Correspondence
Simon Stanworth, MD, National Blood Service, Level 2, John Radcliffe Hospital, Headley Way, Headington, Oxford OX3 9BQ United Kingdom; phone +44 (1865) 447976; fax +44 (1865) 447957; simon.stanworth@nbs.nhs.uk

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