Prophylactic correction of the international normalized ratio in neurosurgery: a brief review of a brief literature

A review

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Prophylactic fresh-frozen plasma (FFP) transfusion is often undertaken in hemodynamically stable patients with a minimally elevated international normalized ratio (INR) prior to invasive procedures, despite little evidence in support of this practice. The authors review the current literature in an attempt to clarify best clinical practice with regard to this issue. Although the activated partial thromboplastin time and prothrombin time–INR are useful laboratory tests to measure specific clotting factors in the coagulation cascade, in the absence of active bleeding or a preexisting coagulopathy, their utility as predictors of overall bleeding risk is limited. Several studies have shown an imperfect correlation between mild elevations in the INR and subsequent bleeding tendency. Furthermore, FFP transfusion is not always sufficient to achieve normal INR values in patients who have mild elevations (<2) to begin with. Finally, there are risks associated with FFP transfusion, including potential transfusion-associated [disease] exposures as well as the time delay imposed by laboratory testing and transfusion administration prior to initiation of procedures. The authors propose that the current concept of a “normal” INR value warrants redefinition to make it a more meaningful clinical tool. Based on their review of the literature, the authors suggest that in a hemodynamically stable patient population there is a range of mildly prolonged INR values for which FFP transfusion is not beneficial, and is potentially harmful. (DOI: 10.3171/2010.7.JNS091857)

Key Words • coagulation • neurosurgery • transfusion • prothrombin time–international normalized ratio • fresh-frozen plasma

Abbreviations used in this paper: aPTT = activated partial thromboplastin time; FFP = fresh-frozen plasma; GCS = Glasgow Coma Scale; HMWK = high-molecular-weight kininogen; ICP = intracranial pressure; INR = international normalized ratio; ISI = international sensitivity index; PCC = prothrombin complex concentrate; PK = prekallikrein; PT = prothrombin time; RBC = red blood cell; rFVIIa = recombinant activated factor VII; TBI = traumatic brain injury.
sis, factor XIII deficiency, primary hemostatic disorders (von Willebrand disease), and defects in the extrinsic pathway of secondary hemostasis (factor VII deficiency). Furthermore, the degree to which the aPTT is prolonged does not correlate with the severity of bleeding.48

Similarly, the PT, which is less sensitive to alterations in the common pathway factors than it is to the extrinsic pathway, is best interpreted as a measure of factor VII activity, and not as an overall marker of bleeding risk.

The PT is often expressed in terms of the INR, which was developed to account for variability due to different thromboplastin reagents. Commercial reagents are measured and adjusted against international standards; these standards have been developed using plasma obtained in patients taking vitamin K antagonists to generate a regression line, the slope of which represents the ISI. The INR is calculated with the following formula: INR = (patient PT/mean normal PT)ISI. The “mean normal PT” is the geometrical mean of the PT values for healthy, normal individuals. Thus, if the ISI = 1, the PT-INR is simply the PT ratio. The values defined as the “normal range” (more correctly, the “reference range”) is the range of values encompassing 95% of healthy individuals. This usually consists of INR values of approximately 0.8–1.2 for most coagulation analyzer/reagent systems. This means that 5% of normal, healthy individuals will have values outside the “normal” range.

The PT-INR was initially used only to standardize

**Fig. 1.** During primary hemostasis, platelet adhesion is mediated by interactions of the platelet surface proteins GPIb and GPIa/IIa with exposed von Willebrand factor (VWF) and collagen on the endothelial surface. Platelets then aggregate via fibrinogen binding with multiple platelet GPIb/IIIa surface proteins to form the initial platelet plug.
laboratory values for monitoring patients taking vitamin K antagonists, and some have argued that it should only be applied to this patient population. However, because the INR is only an arithmetic transformation of the PT, it is no less valid than the PT in seconds or the PT ratio. However, it should be noted that the INR is most reliable in the range of 1.5–4.5, with the variability of results increasing dramatically at higher values.

Both the PT and aPTT results can be influenced by numerous pretest variables such as hematocrit, fasting state of the patient, time from sample collection, and citrate concentration. For example, a sample with an elevated hematocrit (RBC mass) has a proportionately reduced volume of plasma (supernatant), and as a result the effective ratio of anticoagulant to plasma is increased, resulting in an artificially prolonged bleeding time. Lipemic, icteric, and hemolyzed plasma have increased turbidity, interfering with the light transmittance used for clot detection and thereby potentially altering PT and aPTT values.

Despite these issues, it has become common practice to monitor the PT and aPTT as indicators of bleeding risk, and to attempt to correct “abnormal” values before undertaking invasive procedures. Fresh-frozen plasma is the acellular component of blood and contains all of the soluble clotting factors. This product is commonly transfused in an attempt to “correct” INR values between 1.1 and 1.5. However, this practice is based on little scientific evidence, and is shaped by 2 assumptions: first, that the INR is a reliable predictor of bleeding; and second, that administration of FFP will correct an abnormal INR. Our goal is to review the recent literature with respect to the question of whether a mild elevation in INR warrants FFP transfusion prior to invasive procedures in patients who have no history of abnormal bleeding and who are not actively bleeding.

### Does a Mild Elevation in Preprocedural INR Indicate a Significant Risk of Bleeding?

The question of whether a mild elevation of INR indicates significant bleeding risk in patients undergo-
Can FFP Effectively Correct a Mild Elevation in INR?

The issue of whether mild elevations in INR truly need to be corrected remains controversial, and at the same time, the efficacy of using FFP to do so has been called into question.

In a prospective study by Abdel-Wahab et al., changes in coagulation laboratory values after FFP transfusion were followed for a group of patients with initial INR values between 1.1 and 1.85. The authors surveyed a variety of medical and surgical patients receiving FFP transfusion at Massachusetts General Hospital over a 10-month period. Eligibility requirements included an initial INR between 1.1 and 1.85, followed by a repeat INR assessment within 8 hours of product administration. These investigators found that only 0.8% of 121 total patients obtained a normal INR (defined as < 1.1) after FFP transfusion, and just 15% had changes in magnitude of the INR that brought values at least halfway to normal. There was no relationship between the extent of PT prolongation and the degree of normalization achieved, and no differences were observed in patients who were actively bleeding versus those who were not. Furthermore, when the change in INR was analyzed with respect to the amount of FFP transfused, a dose-response effect was lacking. Together, these results suggest that for a patient population with mildly elevated INR, this value is only partially normalized in a small subset of patients, and that normalization is achieved in a manner that is unrelated to degree of INR prolongation, bleeding status, or amount of FFP used.

A second study, by Holland and Brooks, included 250 adult and pediatric patients, and also found that FFP treatment was minimally effective in correcting mild elevations in INR (< 1.7). Patients from 3 institutions were included in the study if they had received FFP transfusion and had documented pre- as well as posttransfusion INR values. The laboratory values were obtained at a median interval of 5.5, 2.2, and 1.5 hours prior to transfusion at the 3 institutions, whereas posttransfusion INR values were checked at a median of 4.8, 1.7, and 1.4 hours. Administration of FFP alone failed to show a significant reliable change in the INR; instead, the investigators found that the most effective way to treat a mildly elevated INR was to treat the underlying medical condition. The authors proposed that in illness, factors such as dehydration, increased bleeding tendency, and the management of neurosurgical patients, because a delayed time to intervention tends to correlate with a worse outcome. The authors concluded that the transfusion of plasma to “normalize” the PT-INR was not warranted in patients with an INR ≤ 1.6, and only served to delay monitor placement.

In a prospective study published in 2008, patients undergoing liver transplantation were divided into 2 groups: INR < 1.5 (97 patients) or ≥ 1.5 (103 patients). None of the patients received FFP, and the need for intraoperative RBC transfusion was assessed. Blood product transfusion was required by 83.5% of the group with an INR < 1.5 and by 79.6% of the group with an INR ≥ 1.5, a difference that was not statistically significant. The authors concluded that there was no correlation between INR and intraoperative bleeding.

Remarkably, in this study 46 patients had an INR < 2, and 13 had an INR > 3, yet none required FFP to prevent a life-threatening hemorrhage. Of the 13 patients with an INR > 3, RBCs (1 U each) were administered in 3 patients. One must use caution, however, in extrapolating the results of a study conducted in patients with cirrhosis to those undergoing neurosurgery. The PT-INR measurements reflect only procoagulant activity. With impaired liver function, a patient with cirrhosis has decreased synthesis of both pro- and anticoagulant factors. Thus, the PT-INR is prolonged due to reduced procoagulant activity, yet the patient may be able to maintain a delicate hemostatic balance because anticoagulant levels are similarly reduced. However, this study does not demonstrate a finding that can be more universally applied, which is the imperfect correlation between INR and bleeding risk.

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is predictive of the response to FFP. However, this correlation is strongest for INR values > 2, and not for mildly elevated INR.

Additional evidence comes from the study of ICP monitors discussed above.14 In this study, 20 patients did receive FFP before ICP monitor insertion, after which 8 had elevated INR levels (> 1.7) and 10 had borderline values (1.3–1.6), with only 2 normalizing completely (INR < 1.3). Of the 6 patients with borderline INR values (1.3–1.6) to begin with, only 1 obtained an INR within the normal range (decreased from 1.5 to 1.0), whereas 1 experienced an increase in INR (increased from 1.5 to 2.5), and the other 4 remained in the borderline range (1.3–1.9) after FFP administration. Of the 13 patients with INR values > 1.6, 7 still had values > 1.6, 5 had INRs that decreased to borderline range, and only 1 corrected to a normal value with FFP. The 1 patient with an INR of 2.5 who experienced hemorrhage had been treated with FFP, which had failed to correct the INR.

In a retrospective cohort study, change in INR in response to FFP transfusion was examined in critically ill, nonbleeding medical patients.13 Of 115 patients, 44 (38.3%) received FFP over a wide range of INR values (median 2.7, range 1–22). The INR decreased to < 1.5 in just 36% of those treated with FFP (16 of 44 patients). Of note, however, the median dose of FFP was higher in the group whose INR decreased to < 1.5 than in those whose INR did not decrease below this level (17 ml/kg vs a median of 10 ml/kg), a finding that was statistically significant (p = 0.018). Also of interest, when compared with an equivalent group of 71 patients not receiving FFP who had no statistically significant differences in multiple factors, including INR, there were no differences in bleeding episodes, hospital deaths, or length of stay in the intensive care unit. However, the group receiving FFP transfusion had a significantly greater incidence of new-onset acute lung injury.

The apparent inability of FFP transfusion to “correct” a marginally prolonged PT- INR in published studies is probably related to 2 factors: 1) a consumptive process may continue to deplete factors at a greater rate than they are replaced by transfusion; and 2) an inadequate dose of FFP is commonly used. Doses of approximately 15 ml/kg are often given, but a dose closer to 30 ml/kg may be required to raise coagulation factors reliably enough to normalize clotting assays in critically ill patients.10 Transfusion of 2 U of FFP (approximately 400–450 ml or 6 ml/kg in a 70-kg patient) would only be expected to increase coagulation factor levels slightly (by approximately 6%, based on the data of Chowdhury et al.14), and would be unlikely to change the PT significantly.

**Prophylactic Use of FFP in TBI**

Traumatic brain injury has been associated with both hyper- and hypocoagulable states. The CNS is unique in that it has high levels of tissue factor, which can lead to excessive activation of the coagulation system in response to head trauma.20,24 Ultimately, this can result in diffuse fibrin deposition, depletion of coagulation factors and platelets, and a bleeding diathesis.24 The incidence of coagulation disorders in TBI has been reported to be anywhere from 10% to 97.5%, depending on the specific patient population and the definition of coagulopathy used.24 When it was defined as an INR value > 1.3, coagulopathy was found in 17% of patients with TBI, with a relative risk of 2.9.67 A second study with a very limited range of “normal” INR (0.92–1.10) defined patients as suffering from coagulopathy if they exhibited a clinical condition frequently associated with this disorder, plus a platelet count < 100,000 and/or INR > 1.1. With this approach, 36% of patients with TBI were classified as having coagulopathy.67

Some authors advocate administration of FFP to prevent hemorrhage following TBI, and some support an approach of FFP transfusion based on the GCS score. Prophylactic transfusion has been suggested for patients with TBI whose GCS scores were < 6.67 However, recent evidence suggests that routine prophylactic transfusion of FFP may not be as effective as previously thought, and in fact may contribute to overall patient morbidity. For example, a double-blind randomized controlled trial was undertaken to compare prophylactic transfusion of FFP versus saline in patients with severe head injury (GCS score < 8) and no history of coagulopathy. Outcomes were worse in patients receiving FFP transfusion, with an increase in death and delayed traumatic intracerebral hematoma.18 The authors hypothesize that FFP transfusion may in fact promote thrombosis, leading to vascular ischemia and exacerbation of cerebral edema and delayed traumatic intracerebral hematoma.

These studies suggest that the routine use of FFP in patients with TBI who have mild elevations in INR may not be warranted, and may in fact be harmful. In the same way that mildly elevated INR does not appear to be a reliable indicator of the need for FFP transfusion in patients undergoing procedures, the circumstances may be similar in the case of TBI. Although activation of the coagulation pathway may result in factor consumption and thrombosis, significant hemorrhage may need to be treated; perhaps the trigger point for treatment should be reanalyzed. The majority of the studies of TBI define normal INR as ranging from < 1.1 to 1.3; as we will discuss, this number may be lower than is clinically warranted.

**Adverse Effects of FFP**

Although the use of FFP when clinically indicated can certainly be of benefit, its administration is not Without risks. Among these risks are acute lung injury, transfusion-transmitted infections, allergic and anaphylactic reactions, and fluid overload.22,40

Reports from the US FDA show that between the fiscal years 2005 and 2008, transfusion-related acute lung injury was the leading cause of transfusion-associated death (35%–65% of fatalities), with FFP being the most commonly transfused product in these cases.9 Transfusion-related acute lung injury is estimated to occur in between 1:100 and 1:5000 plasma-containing transfusions, with a mortality rate of 6%–23%.52 Indeed, of all blood component products, plasma is most strongly implicated, with a 5- to 7-fold increased risk of transfusion-related acute lung injury developing.58

Because FFP is a blood component, its administra-
tion carries a small but real risk of transfusion-related infection. In the United Kingdom, residual virus risks for FFP transfusion are estimated at 1:90,000 for hepatitis B virus, 1:8 million for HIV, and 1:30 million for hepatitis C virus. In addition to transmitting infectious agents, it has been suggested that FFP may have adverse immunomodulatory effects, making patients more susceptible to infection in general, although the mechanisms are unclear. Virus-inactivated preparations such as methylene blue–treated and solvent detergent–treated plasma are now being offered; however, virus inactivation is also associated with a decrease in coagulation factor levels.

Bacterial contamination of FFP is rare, as are transmission of cytomegalovirus and human T-lymphotropic virus due to FFP transfusion.

Anaphylactic and allergic reactions are not infrequent in response to FFP, and have been estimated to occur in 1%–3% of plasma transfusions. Although generally not severe, such reactions contribute to overall morbidity and may necessitate termination of transfusion, leading to blood product wastage. Fluid overload due to FFP transfusion is relatively uncommon, with published estimates of 0.1–2.06 per 10,000 transfusions in some European countries.

Data show that over the last 20 years the amount of FFP used has been steadily rising in the US, and that the US in particular uses a disproportionate amount of FFP when compared with other countries with similar health care provisions. For example, between 1979 and 2001, the number of units of FFP given per unit of packed RBCs rose from 1 per 6.6 to 1 per 3.6. The number of units of FFP per 1000 people in the US in 2001 was 13.9, compared with 4–8.7 U per 1000 people in countries such as France, the United Kingdom, New Zealand, and Norway. This is associated with significant costs to the health care system.

Comparison of liberal and conservative approaches to blood transfusion in critically ill patients has established that liberal transfusion provides no additional benefit and may in fact be harmful to recipients. These studies have helped redefine the hemoglobin threshold at which RBC transfusion should be undertaken for that particular patient population. In considering the need to transfuse, defining the patient population of interest is key. In contrast to critical care studies, there is a body of literature in the trauma field supporting a more liberal and aggressive approach to transfusion, which coagulation parameters are prolonged, but rather the reason for prolongation that matters. Although it is certainly important to identify patients preoperatively who may sustain life-threatening hemorrhages, relying on the PT and aPTT may not be an effective way to do so. Furthermore, if screening INR values are < 1.5, there are no data to support FFP transfusion. In fact, there is little evidence to support transfusion, even for an isolated elevation of the INR in the range of 1.6–2.0.

What Should we do When the Patient is Bleeding?

The primary goal of this review was to discuss the available data on the prophylactic administration of FFP in the nonbleeding patient. However, the management of treatment in the bleeding patient with abnormal coagulation test results deserves mention. The most common such scenario is the reversal of anticoagulation in the patient receiving coumadin therapy who has evidence of intracranial bleeding. Nearly 20% of spontaneous intracranial hemorrhage is associated with therapeutic anticoagulation. The risk of bleeding increases with INR values above the therapeutic range: the incidence of bleeding in patients on coumadin therapy rises 4-fold with INRs over 4.5, and each 0.5 increase in the INR increases the risk of intracranial bleeding by 1.43. Bleeding in this setting requires rapid and effective correction of the coumadin-induced coagulopathy.

Several treatment options are available to provide urgent reversal of anticoagulation in the patient on coumadin therapy (these are summarized in Table 1). No well-designed clinical trials clearly support the superiority of any one treatment strategy, so opinion is divided about the best approach. Intravenous vitamin K is the
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<table>
<thead>
<tr>
<th>Blood Product</th>
<th>Indication</th>
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<tbody>
<tr>
<td>vitamin K</td>
<td>used alone for non-urgent reversal of coumadin effect; used in combination with other modality for urgent reversal</td>
</tr>
<tr>
<td>FFP</td>
<td>urgent reversal of coumadin effect for active bleeding or invasive procedure</td>
</tr>
<tr>
<td>rFVIIa</td>
<td>severe bleeding in patients who do not respond to FFP/cryoprecipitate/platelet transfusion; urgent reversal of coumadin effect for active bleeding or invasive procedure, alone or as adjunct to FFP</td>
</tr>
<tr>
<td>PCC</td>
<td>urgent reversal of coumadin effect for active bleeding or invasive procedure, in combination with vitamin K or as adjunct to FFP</td>
</tr>
</tbody>
</table>

* The following indications for transfusion of various blood components for urgent reversal of coumadin anticoagulation, including vitamin K, FFP, rFVIIa, and PCCs, are based on evidence derived from published literature and have been adopted at the Durham Veterans Administration Medical Center. These are criteria for transfusion without further review. Transfusion of any blood product should ultimately be based on the clinical picture.

Coagulation factor products collectively called PCCs can rapidly provide many or all of the vitamin K–dependent coagulation factors. Some of these have been approved to manage bleeding in patients with hemophilia A (factor VIII deficiency) with antibody inhibitors. Theoretically these products would be the ideal therapy for reversing coumadinization, because they replace specifically those factors that are decreased by coumadin. They are more commonly used for this purpose in Europe than in the US, and are recommended by guidelines from several national organizations. However, not all PCCs have the same content of clotting factors, especially factor VII and the antithrombotic factors proteins C and S. Prothrombin complex concentrates have been shown to speed coumadin reversal when given in concert with FFP, but it is not clear that all PCCs products are equivalent in this regard. It is also not clear whether the use of different PCCs results in different levels of risk of thrombosis. Clearly, PCCs have the advantage that they are a concentrated source of coagulation factors, so replacement can be achieved more rapidly than with FFP and without the risk of volume overload. Optimal therapy has been suggested to combine administration of PCCs with vitamin K, or as an adjunct to FFP. The possibility of thrombotic complications of PCCs has not been well addressed, and deserves further study in this population.

Developed as a “bypassing” agent to manage bleeding in hemophiliacs with antibody inhibitors, rFVIIa is approved for that use in the US, Europe, Japan, and other countries. It has also been extensively used “off label” to manage bleeding in a wide variety of patients who did not respond to transfusion therapy. This factor has also been used for coumadin reversal, alone or as an adjunct to FFP. In a retrospective chart review study, reversal was accomplished in a mean time of approximately 32 hours with FFP and vitamin K, but it took approximately 9 hours when rFVIIa was added to the regimen. Although good clinical trials are lacking, the guidelines proposed at the Seventh American College of Chest Physicians Conference recommend the consideration of rFVIIa for the acute reversal of warfarin-induced bleeding events. In contrast to the administration of PCCs, rFVIIa is not given only to replace a deficient factor. Supraphysiologic levels of rFVIIa compensate for a deficiency of other factors by enhancing platelet surface thrombin generation. Unlike PCCs, rFVIIa has the potential to enhance thrombin generation in the presence of heparins as well as vitamin K antagonists. Although rFVIIa can enhance hemostasis in the setting of anticoagulation treatment, the therapeutic effect of rFVIIa cannot be monitored using the PT-INR. At the high concentrations of rFVIIa used therapeutically, it artifactually shortens the PT-INR. Lower levels of rFVIIa are needed to shorten the INR than are needed for a hemostatic effect. Thus, correction of the INR by administration of rFVIIa does not necessarily mean that hemostasis has been corrected in the patient. Unfortunately, at this time no good test is available to monitor rFVIIa therapy, nor is the optimal dose clear. The risk of thrombosis has also not been well defined. It seems likely to us that rFVIIa is best used in patients who are not responding as expected to FFP, or who cannot tolerate the volume required for full correction with FFP.

Finally, one more use of rFVIIa relevant to neurosurgery deserves mention. There is evidence that rFVIIa can reduce intracranial hematoma expansion in patients who are not receiving anticoagulation therapy. A phase IIb randomized clinical study showed that rFVIIa reduced hematoma expansion in patients without coagulopathy in whom hemorrhagic stroke was diagnosed within 3 hours of the onset of symptoms. There was a suggestion that outcomes, as measured by death and degree of disability, were improved in the rFVIIa-treated patients. However,
there was also a suggestion that arterial thrombotic events were increased in the rFVIIa-treated groups. A follow-up phase III trial confirmed the reduction in hematoma expansion, but not the improved outcomes. At the present time, it is unclear what role rFVIIa may play in management of intracerebral hemorrhage (not related to concurrent anticoagulation). It seems likely that a subset of patients may benefit from such hemostatic therapy, or that rFVIIa, along with optimization of other factors, may be of more general benefit in patients with hemorrhagic stroke.

Conclusions

We focused primarily on the question of mildly elevated INR values in patients who were otherwise hemodynamically stable, and we could find little convincing evidence that prophylactic FFP transfusion was necessary prior to neurosurgical procedures. The PT and aPTT do give information about coagulation factor levels. However, minimal prolongation of these values does not necessarily indicate that a clinically significant bleeding risk is present.

Furthermore, there is mounting evidence that the harm from FFP transfusion may outweigh its benefit. This harm is 2-fold. First, there are risks associated with blood component transfusion, such as transfusion-related acute lung injury and infection. Second, the processes of laboratory testing and transfusion may impose a significant delay on necessary procedures. Thus, attempts to correct a marginally prolonged PT may not only be futile, but may delay urgently needed interventions.

Specifically, we propose that an INR value of < 1.5, in the absence of bleeding, does not require attempted correction prior to invasive procedures. In fact, as we discuss in this paper, there is mounting evidence that the threshold for plasma administration should be at least 1.5, if not even higher. However, none of these statements are meant to discourage plasma transfusion in a patient with bleeding or coagulopathy when it is clinically indicated.

There are certain clinical situations in which transfusion or other hemostatic therapy should unquestionably be undertaken, especially in unstable and actively bleeding patients. However, there are numerous situations in which the decision to transfuse is not as clear cut, requiring analysis of the complete clinical picture, which includes laboratory values as well as the patient’s signs and symptoms. In these cases in which thoughtful review is required, we have developed a set of guidelines for blood component transfusion that are based on published literature as well as institutional experiences (Table 2). These guidelines have been adopted at the Durham Veterans Administration Medical Center and may help provide guidance to other institutions as well.

Disclosure

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| TABLE 2: Guidelines for blood component transfusions* |
|--------------------------------|--------------------------------|
| Blood Component | Transfusion Indications |
| RBCs | Hb/Hct <7.0/21%; Hb/Hct <8.0/24% if: documented pulmonary disease, difficulty oxygenating, profound MI, stroke, symptomatic PVD, EKG evidence of disturbed ventricular function; evidence of tissue ischemia: ST wave changes, unexplained tachycardia |
| platelets | platelets <10,000/µL; active bleeding & patient has recently received antiplatelet agent; minor surgery & platelets <50,000/µL; major surgery & platelets <100,000/µL |
| FFP | active bleeding or invasive procedure & INR >1.5 or aPTT >50 sec; coagulopathy after transfusion of >10 U RBCs; antithrombin deficiency; urgent reversal of warfarin effect |
| cryoprecipitate | active bleeding & fibrinogen <100 mg/dl; active bleeding in patient w/ uremia; von Willebrand disease w/ no other available/effective therapy |

* The following indications for transfusion of various blood components, including FFP, platelets, RBCs, and cryoprecipitate, are based on evidence derived from published literature and have been adopted at the Durham Veterans Administration Medical Center. These are criteria for transfusion without further review. Transfusion of any blood product should ultimately be based on the clinical picture. Abbreviations: EKG = electrocardiographic; Hb = hemoglobin; Hct = hematocrit; MI = myocardial infarction; PVD = peripheral vascular disease.

Author contributions to the study and manuscript preparation include the following. Conception and design: Adamson, Hoffman. Analysis and interpretation of data: Adamson, Hoffman. Drafting the article: West. Critically revising the article: Adamson, Hoffman. Reviewed final version of the manuscript and approved it for submission: all authors.

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