Use of Blood Products and Factor Concentrates for Coagulation Therapy

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ABBREVIATIONS: APTT = activated partial thromboplastin time; DIC = disseminated intravascular coagulation; FFP = fresh frozen plasma; HIT = heparin-induced thrombocytopenia; ITP = idiopathic thrombocytopenic purpura; PT = prothrombin time; TTP = thrombotic thrombocytopenic purpura.

INDEX TERMS: Activated prothrombin complex concentrate; cryoprecipitate; factor replacement concentrates; fresh frozen plasma; platelet concentrate.

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Appropriate replacement therapy can be life-saving for patients with hemorrhage due to coagulation disorders. Effective treatment depends on accurate diagnosis of the hemostatic defect, choosing the appropriate therapeutic agent, and monitoring the patient's clinical and laboratory response. A variety of traditional blood components and newer factor concentrates are available, each with its own advantages and limitations for use. Indiscriminate use of blood products should be avoided, as it is costly, wastes resources, subjects the patient to unnecessary risks, and produces limited or no clinical benefit.

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BLOOD COMPONENTS

Fresh frozen plasma

Fresh frozen plasma (FFP) is the plasma from a unit of whole blood separated by centrifugation and frozen within eight hours of collection from the donor. It is stored at –18 °C or lower for up to 12 months, thawed at 30 to 37 °C and kept at 1 to 6 °C for no longer than 24 hours. FFP contains an average of 1 IU/mL of all the coagulation proteins, including the labile factors V and VIII. (An IU is defined as the amount of coagulation factor present in one mL of normal plasma.)

FFP is primarily used to treat bleeding due to acquired multiple factor deficiencies that occur in liver disease, vitamin K deficiency, disseminated intravascular coagulation (DIC), and massive transfusion. Less frequently, it may be used to treat the rare congenital single factor deficiencies of II, V, VII, X, or XI, or deficiencies of protein C or S. (Because of its short half-life of three to six hours, factor VII deficiency is difficult to treat with FFP without volume overload.) FFP may be used for immediate short-term reversal of over-anticoagulation with coumadin. Both FFP and cryoprecipitate reduced plasma are used as replacement components in therapeutic plasma exchange for thrombotic thrombocytopenic purpura (TTP).

A dose of 10 to 20 mL of FFP/kg of body weight will usually increase the factor level by 20% to 30%.[1] Frequency of transfusion depends on the half-life of the deficient factor(s), shown in Table 1.

The use of FFP is not indicated unless the prothrombin time (PT) or activated partial thromboplastin time (APTT) is >1.5 times the mean of the normal range. FFP should not be used as a volume expander, or to 'correct' a mildly prolonged PT or APTT. A patient may have a mildly prolonged PT or APTT and yet have hemostatically stable levels of coagulation factors.

Cryoprecipitate

Cryoprecipitate is the protein precipitate left after FFP is thawed at 4 °C and most of the supernatant liquid plasma removed. Cryoprecipitate is refrozen and stored at –18 °C or lower for up to 12 months. After thawing at 30 to 37 °C, it is kept at 20 to 24 °C for no longer than six hours, or if pooled, no longer than four hours. It contains a minimum of 80 IU of factor VIII, vWF, 150 to 250 mg of fibrinogen, and 50 to 75 IU of factor XIII.[2,3]

Cryoprecipitate is most commonly infused to replace fibrinogen, for either acquired deficiencies due to DIC or thrombolytic therapy, or for congenital hypofibrinogenemia or dysfibrinogenemias. Currently, cryoprecipitate is the only source of concentrated fibrinogen available. A fibrinogen level of 50 to 100 mg/dL is considered hemostatically effective, and can be achieved using a general guideline of infusing one bag cryo/seven kg of body weight.[4] Fibrinogen has a half-life of 100 to 150 hours.[1]

Cryoprecipitate is also used to treat the rare congenital or acquired deficiency of factor XIII. Factor XIII has a long half-life, seven to twelve days, so the recommended treatment for factor XIII deficiency is one bag of cryo/ten kg of body weight every seven days.[5]

Although factor VIII and vWF are present in cryoprecipitate, cryo is no longer recommended for replacement therapy for hemophilia A or von Willebrand's disease because of the risk of disease transmission. Recombinant or virally inactivated FVIII concentrates are the preferred treatment.

Platelets

Two types of platelet components are used for platelet replacement therapy:

- 'Platelets', also called random donor platelets, are pooled concentrates prepared from whole blood donations by centrifugation. Each unit in the pool should have a minimum of 5.5×10^{10} platelets. Usually a pool consists of four to eight units, for an adult dose of one unit/ten kg of body weight.[6]
- 'Platelets Pheresis', or single donor platelets, are prepared by apheresis of one donor, and contain a minimum of 3×10^{11} platelets.[6]

Both random donor platelets and apheresis platelets are stored for five days at 20 to 24 °C with constant agitation.

Therapeutic platelet transfusions are given to treat bleeding due to defects in platelet production or platelet function. Transfusion of platelets is contraindicated for diseases in-

Table 1. Coagulation factor replacement therapy

Clotting factor	Half-life	Hemostatic level	Replacement therapy
Fibrinogen (Factor I)	3-4 days	50-100 mg/dL	Cryoprecipitate
Factor II	60 hours	20%	FFP or PCC
Factor V	16 hours	25%	FFP
Factor VII	3-6 hours	20%	FFP, PCC (with FVII), recombinant VIIa
Factor FVIII	12 hours	30%	FVIII concentrate
Factor IX	18-24 hours	30%	FIX concentrate
Factor X	30 hours	25%	FFP, some PCCs
Factor XI	2-3 days	25%	FFP
Factor XIII	7-10 days	2-3%	Cryoprecipitate
FVIII with inhibitor			FEIBA or Autoplex, porcine FVIII, high dose FVIII, PCCs, recombinant VIIa
FIX with inhibitor			FEIBA or Autoplex, PCCs, recombinant VIIa
VonWillebrand factor			FVIII concentrate with vWF: Humate P, Alphanate

volving thrombotic consumption of platelets, including thrombotic thrombocytopenic purpura (TTP), heparin-induced thrombocytopenia (HIT), and active DIC. Platelet transfusions are not usually effective in immune-mediated thrombocytopenias, such as idiopathic thrombocytopenic purpura (ITP), although there may be some benefit in life-threatening situations.

Indications for prophylactic platelet transfusions are less definitive. It is difficult to establish a specific platelet count threshold for prophylactic transfusion since the patient's clinical condition, and the risk, presence, and cause of bleeding are individualized. Complicating factors affecting the response to platelet transfusion include fever, sepsis, consumption, bleeding, ABO incompatibility between patient and platelets, splenomegaly, platelet count of the donor(s), medications, presence of other hemostatic defects, and immune refractoriness.[7,8] Nevertheless, a threshold of 10 x 10^9/L to 20 x 10^9/L is commonly used as an indication for prophylactic platelet transfusion.

Ideally, effectiveness of platelet transfusions will be shown by cessation of bleeding. If there are no complicating factors affecting response as listed above, a unit of platelets should increase the recipient's platelet count by 5 x 10^9/L to 10 x 10^9/L, and a unit of 'Platelets Pheresis' should increase the count by 30 x 10^9/L to 50 x 10^9/L. Many multi-transfused patients do not show the expected increment response to platelet transfusion. The most common method to determine if the recipient is refractory to platelet transfusion is to measure the platelet count within one hour posttransfusion and calculate the corrected count increment (CCI), shown below.[7]

CCI = (post transfusion platelet count – pretransfusion platelet count) X body surface area (m^2) ÷ number of platelets transfused (multiples of 10^{11})

A CCI above 7500 indicates an adequate response to platelet transfusion.

For patients who are immunized to HLA antigens and are refractory to platelet transfusion, HLA-matched or crossmatch-compatible platelets may be effective. These units should be irradiated to prevent transfusion-associated graft-versus-host disease.[9]

Platelet refractoriness in multi-transfused patients has been shown to be related to the presence of Class II HLA antigens on contaminating leukocytes, rather than to the number of donor exposures.[10,11] Therefore, leukocyte-reduced platelets are recommended to reduce the incidence of HLA immunization in patients receiving frequent platelet transfusions.

PLASMA AND NON-PLASMA FACTOR CONCENTRATES

A variety of factor concentrates are available to treat hemophilia A (FVIII deficiency), hemophilia B (FIX deficiency), and von Willebrand's disease (vWF deficiency), as described below.

Plasma derived factor concentrates

These concentrates (Table 2) are prepared by fractionation of large pools of thousands of units of donor plasma. They are processed to inactivate contaminating viruses, using pasteurization techniques, solvent/detergent treatment, or immunoaffinity column purification. Although they are considered quite safe, they are not totally risk free, in that they could potentially transmit nonlipid viruses such as hepatitis A and human parvovirus 19.

Intermediate purity FVIII

Humate-P® and Alphanate® contain factor VIII and von Willebrand factor. Humate-P® is licensed to treat both hemophilia A and von Willebrand's disease. Clinical trials using Alphanate® for treatment of von Willebrand's disease have not yet been done; therefore Alphanate® is only approved for treatment of hemophilia A.

Immunoaffinity high purity FVIII concentrate

These products are prepared by monoclonal antibody column purification and do not contain vWF. Examples of licensed products are Monarch-M®, Hemofil-M®, Monoclate®, and Koate-HP®.[3,6]

Porcine FVIII

Hemophiliacs who have produced inhibitors against human FVIII may be successfully treated with porcine FVIII. Hyate-C® is the licensed product and the recommended initial dose is 100 U FVIII/ten kg of body weight.[5]

Immunoaffinity High Purity FIX Concentrate

These FIX concentrates are prepared using monoclonal antibody affinity columns. Examples are AlphaNine SD® and Mononine®.[3,6]

Prothrombin complex concentrate (PCC)

Prothrombin complex concentrates consist of factors II, IX, and X. Factor VII may also be present depending on the method of production. PCCs may produce allergic or thrombotic side effects, and are indicated for treatment of rare de-

ficiencies of II, VII, or X. They may also be beneficial in treatment of hemophiliacs with factor inhibitors. They are not recommended for treatment of FIX deficiency. Examples of licensed products are Proplex T® (contains FVII), Konyne®, Profilnine HT®, and Bebulin®.[3,6]

Activated prothrombin complex concentrates (APCC)

Activated complex products are prothrombin complex concentrates in which the coagulation proteins are activated. They are used to treat hemophiliacs with inhibitors by bypassing FVIII or FIX activation. The recommended dose is 50 to 100 IU/kg. Repeat doses may be given at 6-, 8-, 12- or 24-hour intervals depending on the extent of the bleeding. To avoid thrombotic complications, the amount given should not exceed 200 IU/kg/24 hours. Examples of APCCs are FEIBA® and Autoplex®.[3,5]

Table 2. Plasma derived coagulation factor concentrates

Type	Product	Deficiency/Therapeutic Use
Intermediate purity FVIII	Humate-P	FVIII and vWF
	Alphanate	FVIII
High purity FVIII	Monarch-M	FVIII
	Hemofil-M	FVIII
	Monoclate	FVIII
	Koate-HP	FVIII
Porcine FVIII	Hyate-C	FVIII w/inhibitor
High purity FIX	AlphaNine SD	FIX
	Mononine	FIX
Prothrombin complex concentrate (PCC)	Proplex	FVIII or FIX w/inhibitor, FII, FVII, and FX
	Konyne	FVIII or FIX w/inhibitor, FII, and FX
	Profilnine-HT	FVIII or FIX w/inhibitor, FII, and FX
	Bebulin	FVIII or FIX w/inhibitor, FII, and FX
Activated prothrombin concentrate (APCC)	FEIBA	FVIII or FIX w/inhibitor
	Autoplex	FVIII or FIX w/inhibitor

Non-plasma recombinant factor concentrates

Factor concentrates produced by recombinant DNA technology (Table 3) have the highest purity and level of safety but are more costly than virally inactivated plasma products. Because they are not produced from plasma they do not transmit diseases.

FVIII concentrate

Examples are Recombinate®, Kogenate®, Bioclate®, Helixate®, and ReFacto®.[3,6]

FIX concentrate

BeneFIX® is the licensed recombinant FIX product.[3]

FVIIa concentrate

NovoSeven® is recombinant activated factor VII which was developed to treat patients with factor inhibitors. The recommended dose is 90 μg/kg body weight.[3] Due to the short half-life of factor VII, the dose should be repeated every two to three hours. Therapy with recombinant FVIIa is safe and effective; however the costs of therapy are enormous.

FACTOR CONCENTRATES THERAPY

The therapeutic target for hemostasis in FVIII or FIX deficiency is 30% to 100% (0.3 to 1.0 IU) depending on the site of the bleeding, as shown in Table 4.[3,6]

Factor VIII replacement

To calculate the initial or loading dose of factor VIII:

Blood volume = weight (kg) X 70 mL/kg
Plasma volume = blood volume X (1.0 – hematocrit)
Required Units of FVIII = (desired level – initial level) X plasma volume

The maintenance dose is 50% of the initial dose, and is administered every 12 hours, since the half-life of FVIII is 12 hours.

Factor IX replacement
Therapy for FIX deficiency is determined using the same formula as FVIII, except that the calculated dose is doubled since factor IX diffuses into the extravascular fluid. The half-life of FIX is 18 to 24 hours, so repeat doses of half of the initial loading dose are administered once daily.

vWF replacement
For treatment of von Willebrand's disease, the usual therapeutic target is 50%, or 0.5 IU, of vWF. The dosage is calculated using the same formula for FVIII shown above. The maintenance dose is 50% of the initial dose, and is administered every 12 hours, since the half-life of vWF is 12 hours.

SUMMARY

Therapy of coagulation disorders has evolved from early use of fresh whole blood and plasma, to sophisticated recombinant factor concentrates. Although current testing protocols and viral inactivation methods ensure that transfusion of components is safer than ever, the potential for new threats continually exists, e.g., West Nile virus. Effective therapy depends on treating the specific deficiency with the safest and most appropriate replacement product, in the proper dose.

Table 3. Non-plasma coagulation factor concentrates

Type	Product	Deficiency/Therapeutic Use
Recombinant FVIII	Recombinate	FVIII
	Kogenate	FVIII
	Bioclate	FVIII
	Helixate	FVIII
	ReFacto	FVIII
Recombinant FIX	BeneFIX	FIX
Recombinant VIIa	NovoSeven	FVIII or FIX with inhibitor

Table 4. Guidelines for hemophilia treatment by bleeding site

Site of Bleed	Desired Factor VIII or IX activity	Days Duration
Intracranial; trauma with bleeding	100%	10-14
Intramuscular	80-100%	1-3
Major surgery	80-100%	5-14 days post-op
Hematuria	50%	1-3
Gastrointestinal	50%	1-3
Single joint	30-50%	1-3
Minor surgery	30% to	3-4 days post-op
Mucosal, severe epistaxis	30%	1-2

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