Pathogen-reduced cryoprecipitate

Beginning Oct 24, 2022, UCSF Transfusion Service will begin providing pathogen-reduced cryoprecipitate (also known as pathogen reduced cryoprecipitated fibrinogen complex or Intercept® Fibrinogen Complex). Based on availability, Transfusion Service will fill orders using conventional cryoprecipitate or an equivalent dose of pathogen-reduced cryoprecipitate. These products will initially be dispensed only at Parnassus, and over the next 6-12 months, also available at the Mt. Zion and Mission Bay facilities, based on supply.

Pathogen-reduced cryoprecipitate is manufactured using the same psoralen-based technology that is used to manufacture pathogen reduced platelets. This was approved by the FDA in 2020 and is being phased in in several large medical centers. UCSF Transfusion Committee has reviewed the product insert and relevant literature and determined that this FDA- approved product is a safe and effective replacement for conventional cryoprecipitate. Pathogen reduced cryoprecipitate has equivalent levels of fibrinogen, vWF and Factor XIII compared to conventional cryoprecipitate.

Indications for use of pathogen reduced cryoprecipitate are the same as conventional cryoprecipitate:

- Treatment and control of bleeding, including massive hemorrhage, associated with fibrinogen deficiency
- Control of bleeding when recombinant and/or specific virally inactivated preparations of factor XIII or von Willebrand factor (vWF) are not available
- Control of uremic bleeding after other treatment modalities have failed

Limitations: Pathogen reduced cryoprecipitate should not be used for replacement of factor VIII

Advantages of using pathogen reduced cryoprecipitate:

- Pathogen reduction reduces the risk of transfusion-transmitted infection in cryoprecipitate recipients
- Unlike thawed cryoprecipitate (shelf-life of only 4-6 hours), pathogen reduced cryoprecipitate has a 5-day postthaw shelf life, significantly decreasing wastage of thawed cryoprecipitate

Providers: *no change in ordering. Please continue to order cryoprecipitate as usual, using existing APeX blood order sets.*

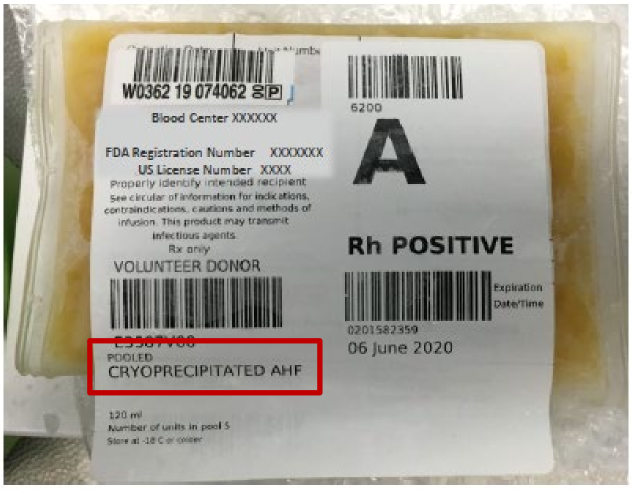
Nursing: *no changes to cross-check/verification of product or to administration procedures.*

ADMINISTRATION OF PATHOGEN REDUCED CRYOPRECIPITATE

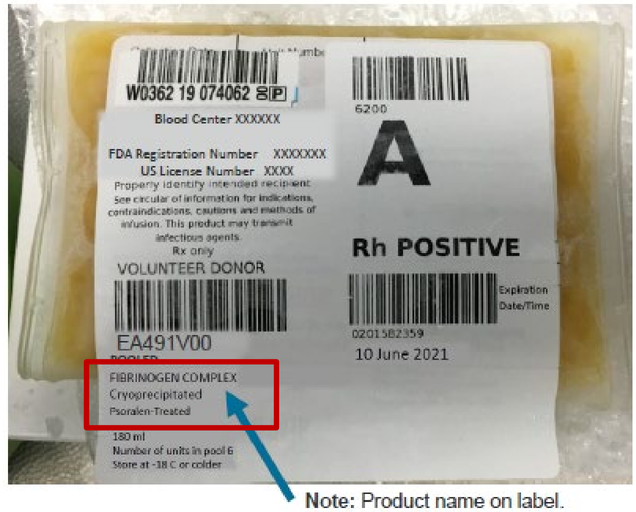
- Administer using standard blood administration sets and follow same instructions as recommended in blood administration procedure for infusion of conventional cryoprecipitate
- Patients can receive both conventional cryoprecipitate and pathogen reduced cryoprecipitate
- Pathogen reduced cryoprecipitate can be transfused in the same line as conventional cryoprecipitate
- Per procedure, please return unused bags promptly to the Blood Bank and DO NOT place bags in coolers as clumps form at colder temperature, leading to wastage of returned product

APPEARANCE OF PATHOGEN REDUCED CRYOPRECIPITATE BAGS

CONVENTIONAL CRYO BAG LABEL



New Pathogen Reduced CRYO BAG LABEL



Additional information is available on the Lab Medicine website

[Transfusion Medicine Guide | UCSF Clinical Laboratories] cerus

Be Ready. When Minutes Matter.

Pathogen Reduced Cryoprecipitated Fibrinogen Complex

prepared from the

INTERCEPT® Blood System for Cryoprecipitation

INTERCEPT Pathogen Reduced Cryoprecipitated Fibrinogen Complex is available for immediate use for up to 5 days when stored liquid; and when stored frozen requires thawing prior to use.

INTERCEPT®

Pathogen Reduced Cryoprecipitated Fibrinogen Complex

Breakthrough Device for Treating Uncontrolled Bleeding

The ready-to-use INTERCEPT® Fibrinogen Complex* is approved specifically for the treatment and control of bleeding, including massive hemorrhage, associated with fibrinogen deficiency.

- Pathogen Reduced Cryoprecipitated Fibrinogen Complex is prepared from the INTERCEPT Blood System for Cryoprecipitation
- Immediate, enriched source of key factors in effective hemostasis[1–3]
  - Fibrinogen
  - von Willebrand Factor
  - Factor XIII
  - Other vital clotting proteins

FDA Breakthrough Device
INTERCEPT® Blood System for Cryoprecipitation

Day 1 | Day 2 | Day 3 | Day 4 | Day 5

TRANSFUSION READY: 5-Day Post-Thaw Shelf Life at Room Temperature

Thaw

Transfuse With the First Blood Products*

Approved for empirical use

PRODUCT	LONG-TERM STORAGE	IMMEDIATE AVAILABILITY	MTP[4] ROUND 1	MTP[4] ROUND 2	MTP[4] ROUND 3
INTERCEPT® Fibrinogen Complex	Frozen ≤ 12 Months	**Room Temp ≤ 5 Days***	✓	✓	✓
— OR —					
Cryoprecipitated AHF[5]	Frozen ≤ 12 Months	**Room Temp ≤ 4-6 Hours**	Availability delayed due to time to thaw-on-demand, and establishment into later rounds of MTPs[4]		✓
Platelets	Room Temp ≤ 5-7 Days	Room Temp ≤ 5-7 Days	✓	✓	✓
Plasma	Frozen ≤ 12 months	Refrigerated ≤ 5 Days	✓	✓	✓
RBC	Refrigerated ≤ 42 Days	Refrigerated ≤ 42 Days	✓	✓	✓

*INTERCEPT Fibrinogen Complex is available for immediate use for up to 5 days when stored liquid; and when stored frozen requires thawing prior to use.

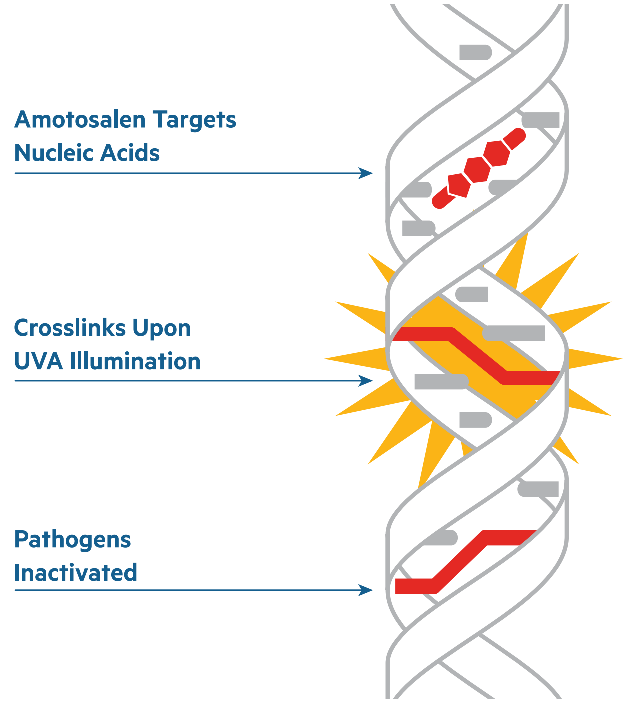
Pathogen Reduction

INTERCEPT® Fibrinogen Complex is produced from plasma treated by the INTERCEPT Blood System.

- Provides broad spectrum transfusion transmitted infection (TTI) risk reduction, including viruses, bacteria, and emerging pathogens[6,7]

INTERCEPT® treated plasma has 20 years of clinical and post-market surveillance experience

INTERCEPT® Blood System for Plasma Mechanism of Action



Upon UVA illumination, amotosalen cross-links nucleic acids to block replication and inactivates pathogens

Improve Order-to-Transfusion Times

TRANSFUSION READY

- **Thawed in advance**
- **Ready-to-deploy with first blood products**
- **No additional labelling or preparation required**

CONVENIENT DOSING

- **Single-use hemostatic doses**
- **Pre-pooled high doses available***

MINIMIZE WASTE

- **5-day post-thaw shelf life**
- **Return to inventory if not transfused**
- **Broad spectrum TTI risk reduction**

**Pooling facilitates transfusion of high doses of fibrinogen from a single container. Fibrinogen content of Fibrinogen Complex depends on donor plasma fibrinogen levels.*

INTERCEPT®

Pathogen Reduced Cryoprecipitated Fibrinogen Complex

Availability

Ready for Immediate Use!

Once thawed, may be stored at room temperature for up to 5 days.

- Provided in single-use containers
- Components may be purchased as single or pre-pooled units

Catalog #	Description	Average Fibrinogen (mg)*
FC10	Pooled Fibrinogen Complex 1.0, Cryoprecipitated, Psoralen Treated	740
FC15	Pooled Fibrinogen Complex 1.5, Cryoprecipitated, Psoralen Treated	1,457
FC20	Pooled Fibrinogen Complex 2.0, Cryoprecipitated, Psoralen Treated	2,220**
FC30	Pooled Fibrinogen Complex 3.0, Cryoprecipitated, Psoralen Treated	3,117
FC40	Pooled Fibrinogen Complex 4.0, Cryoprecipitated, Psoralen Treated	3,700**

* Fibrinogen content depends on donor plasma fibrinogen levels
** Calculated based on pooling of FC10

Intended Use

- Treatment and control of bleeding, including massive hemorrhage, associated with fibrinogen deficiency
- Control of bleeding when recombinant and/or specific virally inactivated preparations of factor XIII or von Willebrand factor (vWF) are not available
- Second-line therapy for von Willebrand disease (vWD)
- Control of uremic bleeding after other treatment modalities have failed

Limitations of Use: Pathogen Reduced Cryoprecipitated Fibrinogen Complex should not be used for replacement of factor VIII.

Hemorrhage is a Leading Cause of Preventable Death[8]

Trauma is the	Of trauma deaths	Hours until death
#1	**~40%**	**~1.6**
cause of death in adults <45 years old[9]	from hemorrhage[9]	from exsanguination*[10]

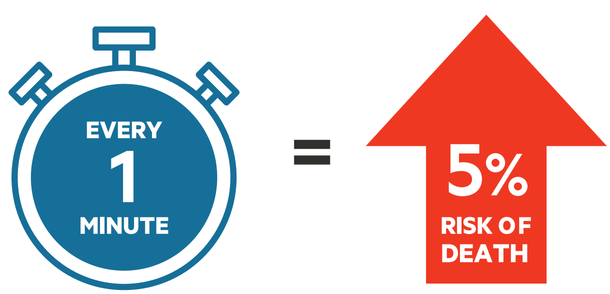
Hemorrhage increases mortality in:

Trauma[11,12]

Postpartum Hemorrhage[13]

Cardiac (CV) Surgery[14]

Combat[15,16]



DELAY INCREASES MORTALITY[17]

Faster is Better[17]

Massive Transfusion Protocols (MTP) were developed to improve hemorrhage outcomes by delivering blood products quickly.

- Every minute of delay between the activation of an MTP and the arrival of the first blood products, results in a 5% increase in the odds of mortality.
- Timely delivery of blood products is an important metric, similar to "door-to-balloon" time.

**Severe loss of blood*

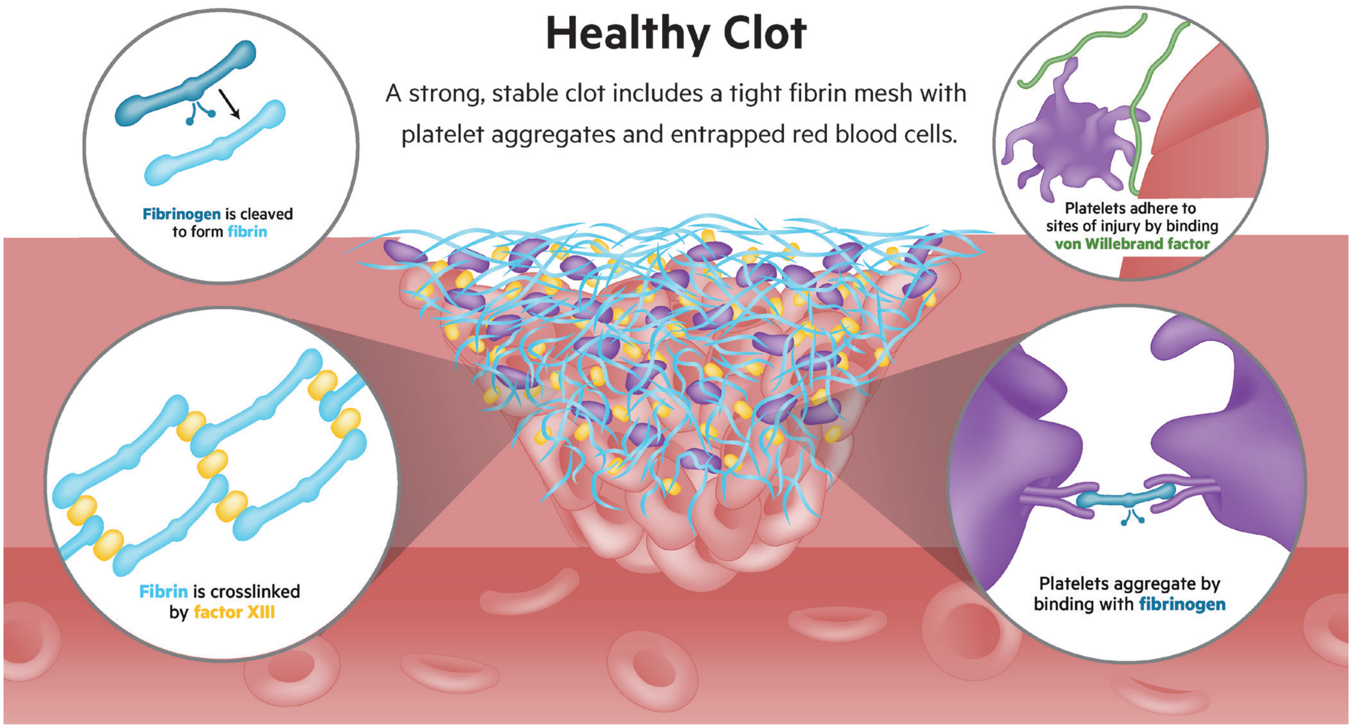
Effective Treatment: Restoring Fibrinogen & Other Clotting Factors

Early fibrinogen supplementation restores clot strength, reduces blood loss, and lowers mortality[12]

- Fibrinogen is the most critical protein needed for stable clot formation and hemostasis[12,18]
- Factor XIII adds strength and stability to clot formation[19,20]

Healthy Clot

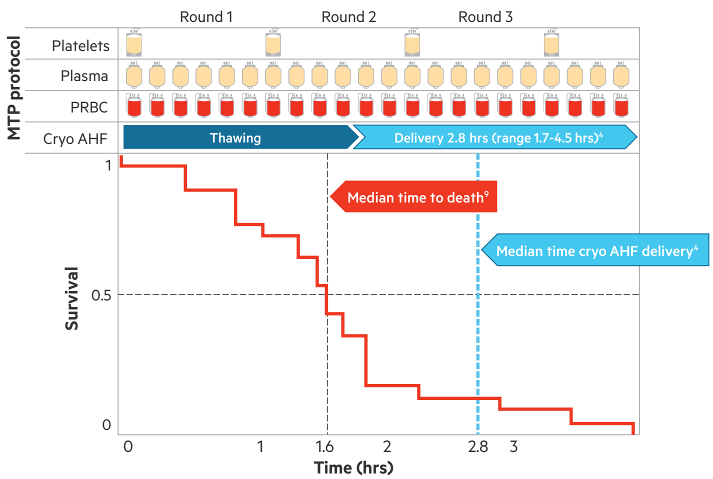
A strong, stable clot includes a tight fibrin mesh with platelet aggregates and entrapped red blood cells.



Fibrinogen, **factor XIII** and **von Willebrand factor**
add the clotting strength needed to achieve stable clot formation and restore hemostasis.[21]

Early delivery of fibrinogen and other vital clotting factors add the clotting strength needed to achieve stable clot formation and restore hemostasis[12,18]

MTPs Lack Critical Components from the Start



Cryoprecipitated Antihemophilic Factor (cryo AHF): source of clotting factors for the treatment of coagulopathy in hemorrhage[5,19]

In **>75%** of U.S. exsanguination cases, cryo AHF arrives too late to be medically efficacious[22]

Cryoprecipitated AHF Inventory Challenges

LONG WAIT TIMES

15 min – 2.8 hours[4,5]

Stored frozen and typically thawed in round 2 or 3 of MTP[23]

SHORT SHELF LIFE

4 – 6 hours[24]

Post thaw due in part to infectious risk

HIGH WASTAGE RATES

7 – 33%[23]

Thawed cryo AHF is wasted

Contraindications

Contraindicated for preparation of blood components intended for patients with a history of hypersensitivity reaction to amotosalen or other psoralens.

Contraindicated for preparation of blood components intended for neonatal patients treated with phototherapy devices that emit a peak energy wavelength less than 425 nm, or have a lower bound of the emission bandwidth <375 nm, due to the potential for erythema resulting from interaction between ultraviolet light and amotosalen.

Warnings and Precautions

Only the INTERCEPT Blood System for Cryoprecipitation is approved for use to produce Pathogen Reduced Cryoprecipitated Fibrinogen Complex.

For management of patients with vWD or factor XIII deficiency, Pathogen Reduced Cryoprecipitated Fibrinogen Complex should not be used if recombinant or specific virally-inactivated factor preparations are available. In emergent situations, if recombinant or specific virally-inactivated factor preparations are not available, Pathogen Reduced Cryoprecipitated Fibrinogen Complex may be administered.

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Rx only. There is no pathogen inactivation process that has been shown to eliminate all pathogens. Certain non-enveloped viruses (e.g., hepatitis A virus (HAV), hepatitis E virus (HEV), parvovirus B19 and poliovirus) and *Bacillus cereus* spores have demonstrated resistance to the INTERCEPT process.

INTERCEPT® Blood System for Cryoprecipitation Package Insert

For the manufacturing of Pathogen Reduced Cryoprecipitated Fibrinogen Complex

INTERCEPT® Blood System for Cryoprecipitation Package Insert

For the manufacturing of Pathogen Reduced Cryoprecipitated Fibrinogen Complex

Rx Only

Caution: Federal law restricts this device to sale by or on the order of a licensed healthcare practitioner.

January 20, 2021

INTENDED USE

The INTERCEPT Blood System for Cryoprecipitation is intended to provide a functionally closed system for the production of Pathogen Reduced Cryoprecipitated Fibrinogen Complex.

Pathogen Reduced Cryoprecipitated Fibrinogen Complex is indicated for:

- Treatment and control of bleeding, including massive hemorrhage, associated with fibrinogen deficiency.
- Control of bleeding when recombinant and/or specific virally inactivated preparations of factor XIII or von Willebrand factor (vWF) are not available.
- Second-line therapy for von Willebrand disease (vWD).
- Control of uremic bleeding after other treatment modalities have failed.

Limitations of Use

Pathogen Reduced Cryoprecipitated Fibrinogen Complex should not be used for replacement of factor VIII.

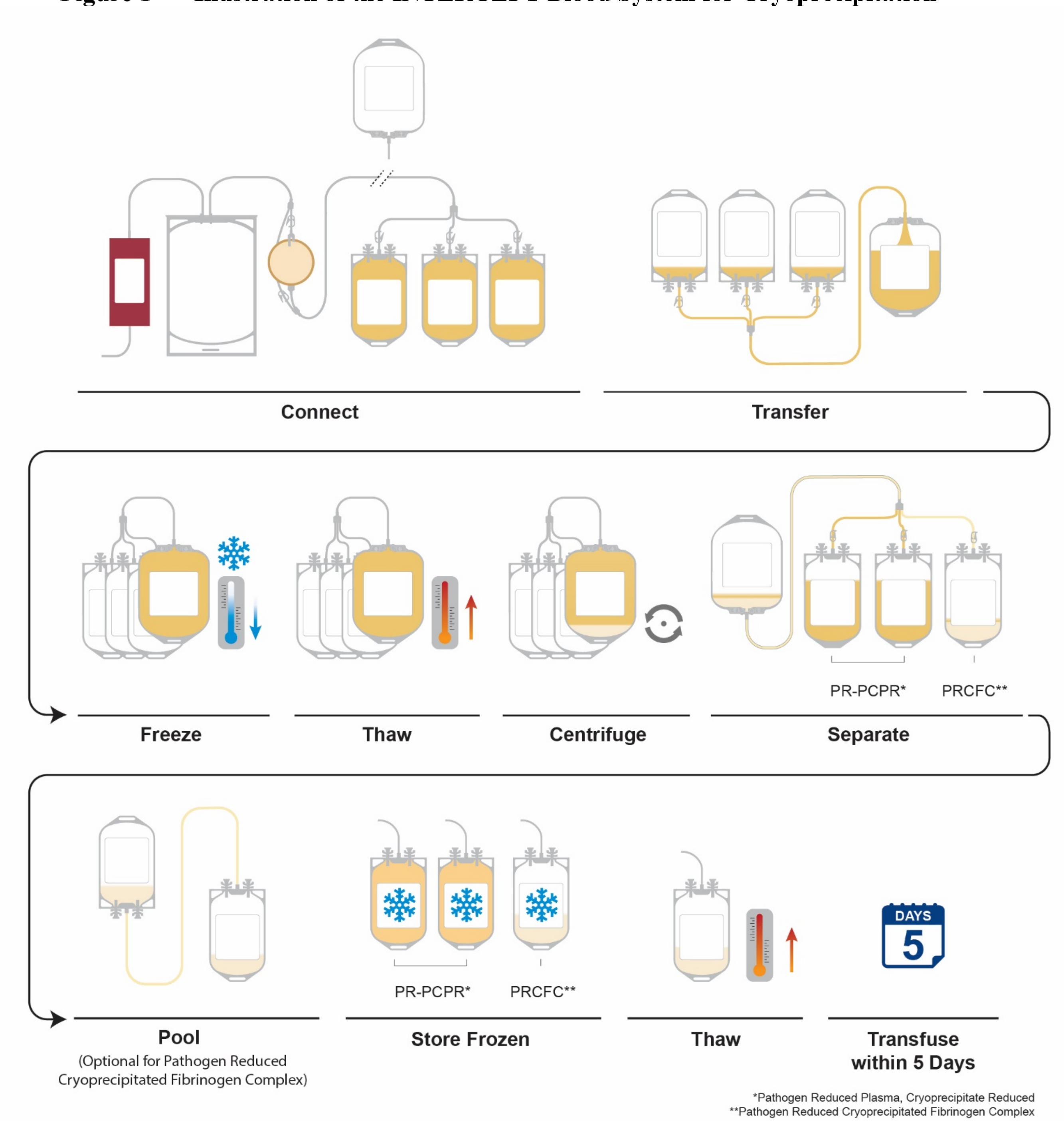
DEVICE DESCRIPTION

The INTERCEPT Blood System for Cryoprecipitation contains a sterile, non-pyrogenic, single-use, fluid path processing container – the FIBRICEPT™ Processing Container – (INT3230) for use in production of Pathogen Reduced Cryoprecipitated Fibrinogen Complex.

The operating principle for the INTERCEPT Blood System for Cryoprecipitation is illustrated in **Figure 1**. INTERCEPT Blood System processed plasma is transferred to the INT3230 processing container and frozen at -18°C or colder within 24 hours of blood draw for pooled whole blood-derived plasma, or within 8 hours of apheresis collection. The INT3230 processing container remains frozen for up to 30 days, at which time the INTERCEPT processed plasma is thawed and centrifuged. After centrifugation, the supernatant is transferred to two of the three final storage containers and the cryoprecipitate pellet is reconstituted into remaining supernatant and transferred to the third final storage container. All three blood components may be frozen and stored at -18°C or colder until thaw prior to transfusion. Components of the INTERCEPT Blood System for Cryoprecipitation may be pooled into a single final storage container using sterile docking up to a maximum of 325 mL prior to freezing.

Pathogen inactivation of plasma using the INTERCEPT Blood System, and processing in a functionally closed system, enables up to 5 days of post-thaw storage of Pathogen Reduced Cryoprecipitated Fibrinogen Complex at room temperature.

Figure 1 Illustration of the INTERCEPT Blood System for Cryoprecipitation



DEVICE PERFORMANCE

Pathogen Reduced Cryoprecipitated Fibrinogen Complex is prepared using the INTERCEPT Blood System for Cryoprecipitation from plasma that has been processed with the INTERCEPT Blood System for Plasma.[1] The INTERCEPT Blood System inactivates a broad spectrum of viruses, gram-positive and gram-negative bacteria, spirochetes, parasites and leukocytes (see **Table 1**).[1-8] There is no pathogen inactivation process that has been shown to eliminate all pathogens. Certain non-enveloped viruses (e.g., hepatitis A virus (HAV), hepatitis E virus (HEV), parvovirus B19 and poliovirus) and *Bacillus cereus* spores have demonstrated resistance to the INTERCEPT process.

Table 1 Pathogen Inactivation Efficacy of INTERCEPT Processed Plasma Used to Prepare Pathogen Reduced Cryoprecipitated Fibrinogen Complex

Pathogen	Log Reduction
Virus (Enveloped)[1-4]	
HIV-1 IIIB, cell-associated	≥6.2
HIV-1 IIIB cellfree	≥6.1
DHBV[a]	4.4 to 4.5
BVDV[b]	>4.3
HTLV-I	≥4.1
HTLV-II	≥4.7
West Nile virus	>5.5
SARS-Associated Coronavirus	≥4.0
Chikungunya virus (CHIKV)	6.5
Influenza A virus (H_5N_1 Avian Influenza)	≥5.7
Virus (Non-Enveloped)[1,4]	
Parvovirus B19	1.8
Bluetongue virus	4.2
Adenovirus 5	≥5.6
Bacteria[1,5]	
Klebsiella pneumoniae	>6.0
Enterobacter cloacae	≥6.7
Pseudomonas aeruginosa	>6.8
Yersinia enterocolitica	≥6.6
Staphylococcus epidermidis	>6.8
Staphylococcus aureus	>6.2
Treponema pallidum	≥5.4
Borrelia burgdorferi	≥9.9
Anaplasma phagocytophilum (HGE agent)	≥3.6
Protozoan Parasite[6,7]	
Plasmodium falciparum	>6.5
Babesia microti	≥4.9
Trypanosoma cruzi	>6.7

[a]DHBV model virus for HBV
[b]BVDV model virus for HCV

Using a limiting dilution assay (LDA), plasma processed with the INTERCEPT Blood System exhibited a 4 log_{10} reduction of viable T cells.[9] Using a DNA modification assay, plasma processed with the INTERCEPT Blood System demonstrated an average of one amotosalen adduct every 83 base pairs in leukocytes.[10]

Pathogen Reduced Cryoprecipitated Fibrinogen Complex serves as an enriched source of fibrinogen, factor XIII, vWF, and other constituents. The focus of the evaluation for Pathogen Reduced Cryoprecipitated Fibrinogen Complex was based on retention of critical functional activities, including 5 days post thaw, that have shown a high level of correlation with therapeutic efficacy. Fibrinogen, vWF, and factor XIII are key constituents in effective hemostasis and functional levels correlate with risk of bleeding, morbidity and mortality.[11-13]

The average (±SD) fibrinogen content (mg) in a unit of Pathogen Reduced Cryoprecipitated Fibrinogen Complex from 2 whole blood-derived plasma units immediately post thaw, and after 120 hours of storage at 20 – 24°C, were 740 ±166 mg, and 686 ±165 mg, respectively (**Table 3**). Functional fibrinogen activity was retained during 5-day post-thaw storage.

Assessment of thrombin generation by measurement of endogenous thrombin potential (ETP) demonstrated 99 ±4% conservation of thrombin generation, an integrated assessment of overall hemostatic capacity. ETP was retained during 120 hours of storage post thaw. Fibrin clot quality was assessed by viscoelastography (ROTEM) after activation of Pathogen Reduced Cryoprecipitated Fibrinogen Complex. Pathogen Reduced Cryoprecipitated Fibrinogen Complex retained Maximum Clot Firmness (mm) measured by a modified, non-whole blood, ROTEM assay (**Table 2**).

In Vitro Characterization of Pathogen Reduced Cryoprecipitated Fibrinogen Complex from 2 Units of Whole Blood-Derived Plasma

In an n=80 *in vitro* study, two ABO-matched whole blood-derived plasma units were combined per replicate and processed with the INTERCEPT Blood System for Plasma within 18 to 22 hours of collection. The INTERCEPT processed plasma was frozen at -18°C or colder. After 26-28 days of storage, the INTERCEPT processed plasma was thawed, centrifuged, and the Pathogen Reduced Cryoprecipitated Fibrinogen Complex was recovered and frozen at -18°C or colder for 14-23 days before final thaw. The thawed components were stored at 20-24°C for 120 hours.

In vitro characterization of the thawed Pathogen Reduced Cryoprecipitated Fibrinogen Complex components is presented in **Table 2** and **Table 3**.

Table 2 *In Vitro* Factor Concentration Characterization of Pathogen Reduced Cryoprecipitated Fibrinogen Complex, per 2 Whole Blood-Derived Plasma Inputs

Characteristic	Result at Thaw	Result at 120 hours Post Thaw
Fibrinogen (mg/mL)	9.22 ± 2.26 [4.75 - 16.65]	8.59 ± 2.39 [4.20 - 17.25]
Factor VIII (IU/mL)	2.83 ± 0.80 [1.12 - 5.09]	2.58 ± 0.72 [0.99 - 4.52]
Factor XIII Antigen (mg/dL)	5.2 ± 1.6 [2.7 - 8.3]	5.2 ± 1.6 [2.8 - 8.4]
vWF ristocetin cofactor activity (IU/dL)	622 ± 233 [250 - 1610]	574 ± 206 [200 - 1160]
vWF Antigen (IU/dL)	647 ± 208 [260 - 1260]	659 ± 213 [260 - 1340]
Viscoelastography (ROTEM) Maximum Clot Firmness (mm)*	55 ± 10 [31 - 76]	56 ± 10 [34 - 79]

*Modified, non-whole blood, ROTEM analysis

Mean ±SD [range], n = 80

Table 3 *In Vitro* Factor Content Characterization of Pathogen Reduced Cryoprecipitated Fibrinogen Complex, per 2 Whole Blood-Derived Plasma Inputs

Characteristic	Result at Thaw	Result at 120 hours Post Thaw
Volume (mL)	81 ± 8 [60 - 102]	ND
Fibrinogen content (mg)	740 ± 166 [405 - 1349]	686 ± 165 [369 - 1311]
Factor VIII content (IU)	226 ± 57 [103 - 375]	206 ± 51 [91 - 315]
Factor XIII Antigen content (mg)	4.3 ± 1.4 [1.8 - 7.1]	4.2 ± 1.4 [1.8 - 6.8]
vWF ristocetin cofactor activity (IU)	494 ± 159 [255 - 1095]	456 ± 144 [204 - 916]
vWF Antigen (IU)	514 ± 141 [248 - 964]	523 ± 142 [248 - 898]

Mean ±SD [range], n = 80

ND = not done

In Vitro Characterization of Pathogen Reduced Cryoprecipitated Fibrinogen Complex from Pooled Whole Blood-Derived Plasma

In two *in vitro* studies, two ABO-matched whole blood-derived plasma units were combined per replicate and processed with the INTERCEPT Blood System for Plasma within 18 to 22 hours of collection. The INTERCEPT processed plasma was frozen at -18°C or colder. After 1-25 days of storage, the INTERCEPT processed plasma was thawed, centrifuged, the Pathogen Reduced Cryoprecipitated Fibrinogen Complex was recovered and frozen at -18°C or colder before final thaw. Pooled components were prepared from 2 or 4 single Pathogen Reduced Cryoprecipitated Fibrinogen Complex components (sourced from 4 or 8 whole blood-derived plasma units, respectively). The thawed components were stored at 20-24°C for 120 hours.

In vitro characterization of the thawed pooled Pathogen Reduced Cryoprecipitated Fibrinogen Complex components is presented in **Table 4** and **Table 5**.

Table 4 *In Vitro* Factor Concentration Characterization of Pooled Pathogen Reduced Cryoprecipitated Fibrinogen Complex: Pools of 2 and 4 Components

Characteristic	Result at Thaw		Result at 120 hours Post Thaw	
	Pool of 2	Pool of 4	Pool of 2	Pool of 4
Input units of WB derived plasma	4	8	4	8
Fibrinogen (mg/mL)	9.82 ± 1.34 [7.70 - 11.77]	10.90 ± 1.98 [8.69 - 14.83]	9.11 ± 1.41 [6.92 - 11.04]	10.15 ± 2.04 [7.11 - 13.74]
Factor VIII (IU/mL)	3.55 ± 0.78 [2.30 - 4.67]	3.13 ± 0.76 [1.85 - 3.92]	3.18 ± 0.78 [2.20 - 4.38]	3.05 ± 0.75 [1.90 - 3.99]
Factor XIII Antigen (mg/dL)	6.0 ± 0.9 [4.6 - 7.0]	6.2 ± 1.2 [4.9 - 8.0]	5.9 ± 1.0 [4.4 - 7.1]	6.2 ± 0.9 [4.8 - 7.3]
vWF ristocetin cofactor activity (IU/dL)	513 ± 259 [285 - 1030]	371 ± 158 [225 - 697]	404 ± 147 [255 - 735]	395 ± 166 [225 - 712]
vWF Antigen (IU/dL)	746 ± 178 [488 - 979]	711 ± 128 [457 - 831]	765 ± 203 [475 - 1059]	706 ± 135 [455 - 831]
Viscoelastography (ROTEM) Maximum Clot Firmness (mm)[a]	58 ± 6 [49 - 64]	59 ± 6 [50 - 65]	59 ± 6 [49 - 67]	60 ± 7 [46 - 68]

Mean ±SD [range]

n = 8 of each pool size which were derived from different plasma inputs

[a]Modified, non-whole blood, ROTEM analysis

Table 5 ***In Vitro*** **Factor Content Characterization of Pooled Pathogen Reduced Cryoprecipitated Fibrinogen Complex: Pools of 2 and 4 Components**

Characteristic	Result at Thaw		Result at 120 hours Post Thaw	
	Pool of 2	Pool of 4	Pool of 2	Pool of 4
Input units of WB derived plasma	4	8	4	8
Volume (mL)	148 ± 13 [130 - 167]	286 ± 20 [257 - 306]	ND ND	ND ND
Fibrinogen content (mg)	1457 ± 243 [1169 - 1801]	3117 ± 568 [2285 - 3811]	1353 ± 250 [1057 - 1689]	2907 ± 601 [1870 - 3531]
Factor VIII content (IU)	529 ± 135 [354 - 729]	907 ± 269 [492 - 1175]	474 ± 136 [324 - 683]	883 ± 264 [505 - 1185]
Factor XIII Antigen (mg)	8.9 ± 1.7 [6.0 - 10.6]	17.8 ± 3.6 [12.9 - 23.8]	8.8 ± 1.7 [5.7 - 10.5]	17.9 ± 3.1 [12.6 - 21.7]
vWF ristocetin cofactor activity (IU)	766 ± 409 [400 - 1576]	1062 ± 480 [668 - 2133]	601 ± 234 [383 - 1132]	1147 ± 539 [599 - 2179]
vWF Antigen (IU)	1108 ± 286 [673 - 1527]	2051 ± 479 [1216 - 2476]	1137 ± 326 [656 - 1652]	2039 ± 505 [1210 - 2501]

Mean ±SD [range]
n = 8 of each pool size which were derived from different plasma inputs
ND = not done

Table 6 describes average fibrinogen content of single or pools of 2 or 4 Pathogen Reduced Cryoprecipitated Fibrinogen Complex components based on *in vitro* studies described in Device Performance section. See blood center production quality control data for additional fibrinogen content detail.

Compatibility testing is not required. ABO-compatible Pathogen Reduced Cryoprecipitated Fibrinogen Complex is preferred. Rh type need not be considered when using this product.

Table 6 Average Fibrinogen Content Per Container of Single or Pooled Pathogen Reduced Cryoprecipitated Fibrinogen Complex

Number of pooled Pathogen Reduced Cryoprecipitated Fibrinogen Complex components per container	Fibrinogen content at thaw* - mg	Fibrinogen content at the end of 5 days post thaw* - mg
1 (prepared from 2 whole blood-derived plasma units)	740 (166)	686 (165)
2 (prepared from 4 whole blood-derived plasma units)	1457 (243)	1353 (250)
4 (prepared from 8 whole blood-derived plasma units)	3117 (568)	2907 (601)

*Mean (±SD) from Pathogen Reduced Cryoprecipitated Fibrinogen Complex prepared from whole blood-derived plasma frozen within 24 hours after phlebotomy (PF24) plasma.
See *Device Performance* section for details.

One Pathogen Reduced Cryoprecipitated Fibrinogen Complex component can be prepared from single donor apheresis plasma, or a pool of two whole blood-derived plasma units, within the volume range (585-650 mL) of the INTERCEPT Blood System for Plasma. Within the volume limits of the pooling container, pools of 1 to 5 Pathogen Reduced Cryoprecipitated Fibrinogen Complex components can be prepared containing estimated fibrinogen content based on multiples of individual Pathogen Reduced Cryoprecipitated Fibrinogen Complex components. Pooling facilitates transfusion of high doses of fibrinogen delivered from a single container for administration to patients with bleeding.

Pathogen Reduced Cryoprecipitated Fibrinogen Complex may be administered empirically.

CONTRAINDICATIONS

- Contraindicated for preparation of blood components intended for patients with a history of hypersensitivity reaction to amotosalen or other psoralens.
- Contraindicated for preparation of blood components intended for neonatal patients treated with phototherapy devices that emit a peak energy wavelength less than 425 nm, or have a lower bound of the emission bandwidth <375 nm, due to the potential for erythema resulting from interaction between ultraviolet light and amotosalen.

NOTE: include information about these contraindications in the labeling provided with transfusable blood component products prepared using the INTERCEPT Blood System.

WARNINGS AND PRECAUTIONS

- Only the INTERCEPT Blood System for Cryoprecipitation is approved for use to produce Pathogen Reduced Cryoprecipitated Fibrinogen Complex.
- For management of patients with vWD or factor XIII deficiency, Pathogen Reduced Cryoprecipitated Fibrinogen Complex should not be used if recombinant or specific virally-inactivated factor preparations are available. In emergent situations, if recombinant or specific virally-inactivated factor preparations are not available, Pathogen Reduced Cryoprecipitated Fibrinogen Complex may be administered.

NOTE: include these “Warnings and Precautions” in the labeling provided with transfusable blood component products prepared using the INTERCEPT Blood System.

INSTRUCTIONS FOR USE

These instructions are for the use of the INTERCEPT Blood System for Cryoprecipitation to produce Pathogen Reduced Cryoprecipitated Fibrinogen Complex and Pathogen Reduced Plasma, Cryoprecipitate Reduced. A single 60-100 mL component of Pathogen Reduced Cryoprecipitated Fibrinogen Complex, and two components of Pathogen Reduced Plasma, Cryoprecipitate Reduced, are made from each INTERCEPT Blood System for Plasma set input defined here.

Pathogen Reduced Cryoprecipitated Fibrinogen Complex is produced from cryoprecipitation of cold, insoluble proteins from plasma that has been processed with the INTERCEPT Blood System for Plasma. Final components are produced using the INTERCEPT Blood System for Cryoprecipitation. The supernatant from this process is Pathogen Reduced Plasma, Cryoprecipitate Reduced.

Input Plasma

Input for this process requires plasma that has been processed with the INTERCEPT Blood System for Plasma but not yet frozen in the final storage containers. The plasma may be from one unit of apheresis or two units of whole blood-derived plasma.

The INTERCEPT process must be initiated to allow freezing of INTERCEPT processed plasma within 24 hours after collection of the first unit in the pool for whole blood-derived plasma or within 8 hours of apheresis collection.

Initial Setup

Equipment Provided: One (1) INTERCEPT Blood System for Cryoprecipitation

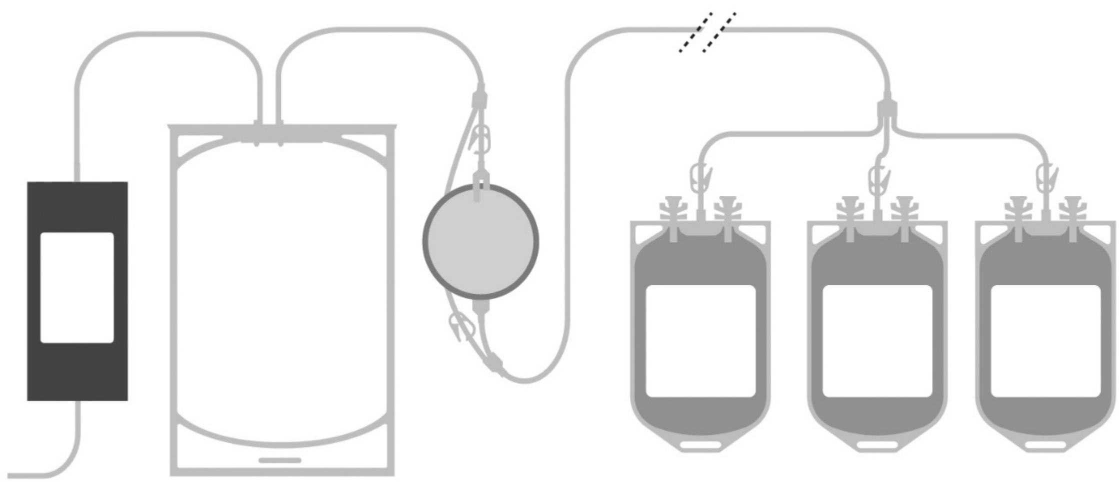
Equipment Required But Not Provided: sterile connecting device (SCD), tube sealer, plasma freezer, centrifuge, top-pan balance and/or scale, labels for final storage containers, label printer, temperature controlled circulating water bath or refrigerator

Processing

I. Preparations Prior to Freezing the Plasma

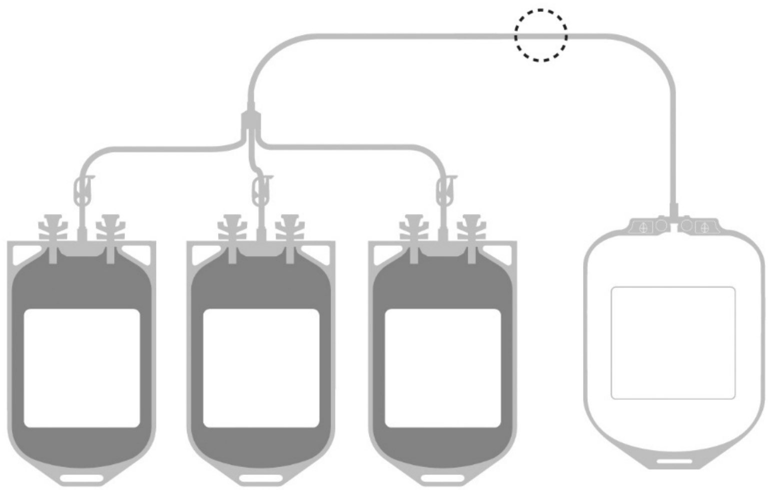
1. Refer to SPC 00818-AW, INTERCEPT Blood System for Plasma. Complete the steps for making INTERCEPT processed plasma, Section III, Step 1 through Step 11. **Do not** re-distribute plasma volume, **do not** disconnect individual storage containers, and **do not** freeze the containers. (i.e., Do not complete Step 12 through Step 16.)
2. Disconnect the storage containers from the plasma set by heat sealing above the 3-way junction of the 3 storage containers (**Figure 2)**.

Figure 2



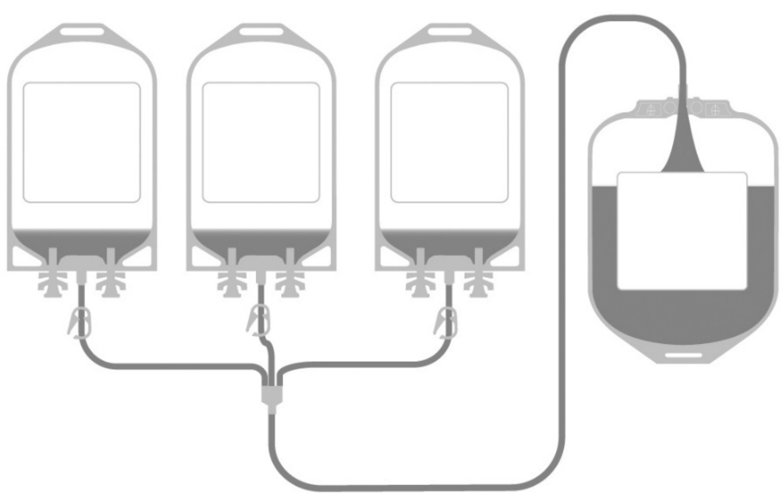
3. Remove the INTERCEPT Blood System for Cryoprecipitation from its packaging.
4. Label the INTERCEPT Blood System for Cryoprecipitation with the donation identification number (DIN).
5. Sterile connect the INTERCEPT Blood System for Cryoprecipitation to the INTERCEPT processed plasma storage containers containing INTERCEPT processed plasma (**Figure 3**).

Figure 3



6. Open the clamps and transfer the INTERCEPT processed plasma to the INTERCEPT Blood System for Cryoprecipitation via gravity flow. The tubing and 3 storage containers should remain connected (**Figure 4**).

Figure 4

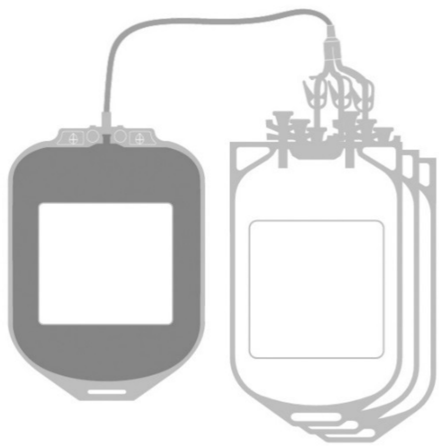


7. After the plasma is transferred, express air from the INTERCEPT Blood System for Cryoprecipitation into the 3 plasma storage containers as needed.
8. Close the clamp on the lines of each of the plasma storage containers. Do not disconnect any of the containers at this point.

II. Freezing INTERCEPT Processed Plasma in the INTERCEPT Blood System for Cryoprecipitation

1. Organize the INTERCEPT Blood System for Cryoprecipitation, tubing, and connected containers. The INTERCEPT Blood System for Cryoprecipitation and the 3 containers should remain connected during freezing (**Figure 5**).

Figure 5



2. Place tubing between the INTERCEPT Blood System for Cryoprecipitation and the connected storage containers to minimize tubing exposure and movement.
3. Place in a freezer that is -18°C or colder.
4. Store at -18°C or colder for no more than 30 days.

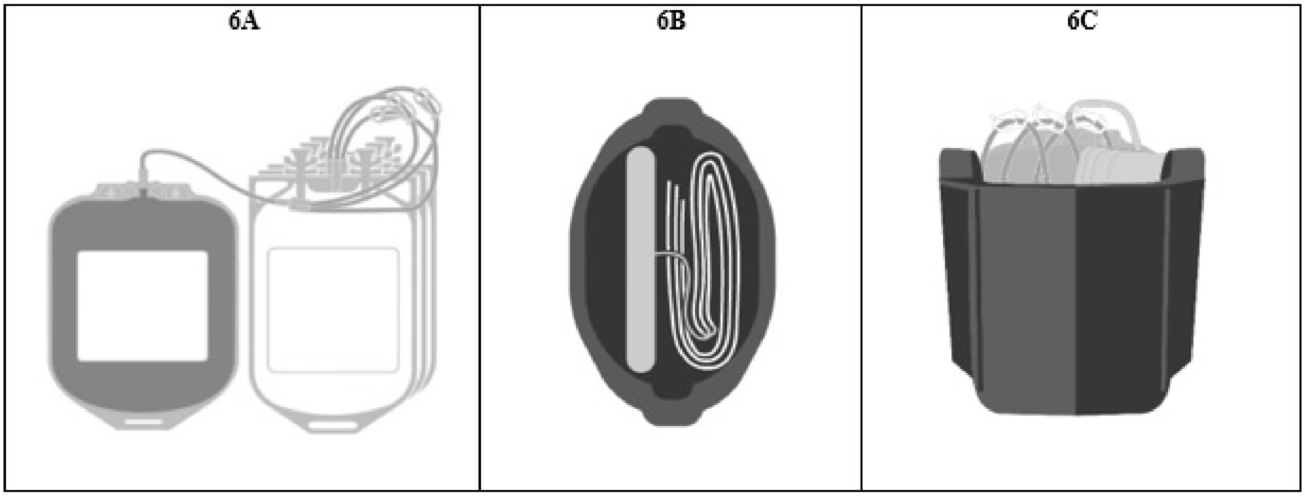
III. Thawing INTERCEPT Processed Plasma in the INTERCEPT Blood System for Cryoprecipitation

1. Carefully remove the INTERCEPT Blood System for Cryoprecipitation, tubing, and connected containers from the freezer.
2. After removal from the freezer, allow sufficient time at ambient temperature for the tubing to thaw sufficiently to regain flexibility.
3. Place the INTERCEPT Blood System for Cryoprecipitation and connected containers at 1°C to 6°C until the plasma is sufficiently thawed.
   NOTE: Thaw time and specific thawing practices must be characterized by the blood center.
4. When the plasma has completely thawed, remove the INTERCEPT Blood System for Cryoprecipitation, tubing, and connected containers from the water bath or refrigerator.

IV. Centrifugation

1. Organize and place the INTERCEPT Blood System for Cryoprecipitation, tubing, and containers in a centrifuge liner. An example is shown below of the contents (**Figure 6A**) and placement (**Figure 6B** - top view, **Figure 6C** - side view). White clamps should be positioned prior to folding to avoid compression during centrifugation (**Figure 6A**). NOTE: method of loading in the centrifuge liner and clamp placement must be established by the blood center.

Figure 6



2. Place the liner into the centrifuge bucket and balance with any other liners following centrifuge manufacturer's instructions.
3. Centrifuge at 1°C to 6°C using a hard spin. NOTE: Centrifuge time and settings must be characterized by the blood center.
4. Carefully remove the INTERCEPT Blood System for Cryoprecipitation, tubing, and connected containers from the liner.
5. Inspect to ensure cryoprecipitate pellet is visible and there are no breaks or leaks. Take care not to disturb the pellet during handling.
6. If separation is not performed immediately, store the items at 1°C to 6°C until ready for separation.

V. Separation into Components

1. Open the clamps leading to any two of the final storage containers. One clamp on the tubing leading to the third storage container will remain closed.
2. Drain or express the Pathogen Reduced Plasma, Cryoprecipitate Reduced supernatant from the INTERCEPT Blood System for Cryoprecipitation into two open final storage containers. Retain 60 mL to 100 mL of cryoprecipitate and supernatant within the INTERCEPT Blood System for Cryoprecipitation.
3. Expel air from the two final storage containers containing Pathogen Reduced Plasma, Cryoprecipitate Reduced into the INTERCEPT Blood System for Cryoprecipitation, as needed.
4. Clamp off INTERCEPT Blood System for Cryoprecipitation with hemostat or clamp.

5. Distribute the Pathogen Reduced Plasma, Cryoprecipitate Reduced evenly as needed between the two final storage containers. Each storage container can hold up to a maximum of 325 mL.
6. Disconnect the two final storage containers with the Pathogen Reduced Plasma, Cryoprecipitate Reduced by heat sealing below the 3-way junction. Allow sufficient tubing length for segments if needed. Discard the white clamps.
7. Apply blood center label for Pathogen Reduced Plasma, Cryoprecipitate Reduced to each disconnected container.
8. Resuspend the cryoprecipitate in the residual supernatant in the INTERCEPT Blood System for Cryoprecipitation.
9. Open the clamp leading to the remaining empty final storage container.
10. Transfer the Pathogen Reduced Cryoprecipitated Fibrinogen Complex from the INTERCEPT Blood System for Cryoprecipitation into the final storage container.
11. Expel air from the final storage container back into the INTERCEPT Blood System for Cryoprecipitation, as needed.
12. Disconnect the final storage container by heat sealing below the 3-way junction. Allow sufficient tubing length for segments if needed. Discard the white clamp.
13. Apply blood center label for Pathogen Reduced Cryoprecipitated Fibrinogen Complex to the final storage container or label after pooling multiple Pathogen Reduced Cryoprecipitated Fibrinogen Complex components into one final storage container. Each storage container can hold up to a maximum of 325 mL.
14. Organize components into packaging for freezing and storage.
15. Freeze immediately following blood center procedures.
16. Store all three components at -18°C or colder.
17. Discard the INTERCEPT Blood System for Cryoprecipitation as Biohazardous Waste.

NOTE: Pathogen Reduced Cryoprecipitated Fibrinogen Complex must be stored in one of the INTERCEPT Blood System for Plasma storage containers.

NOTE: Multiple Pathogen Reduced Cryoprecipitated Fibrinogen Complex components may be pooled into one INTERCEPT Blood System for Plasma storage container. Each storage container can hold up to a maximum of 325 mL of Pathogen Reduced Cryoprecipitated Fibrinogen Complex.

NOTE: Pathogen Reduced Cryoprecipitated Fibrinogen Complex may be stored at -18°C or colder for up to 12 months from the date of collection of the first donation in the input plasma pool.

STORAGE AND HANDLING

INTERCEPT Blood System for Cryoprecipitation

- The INTERCEPT Blood System for Cryoprecipitation is designed to be a functionally closed system for use with the INTERCEPT Processing Set for plasma. Pathogen Reduced Cryoprecipitated Fibrinogen Complex must be stored in one of the three final storage containers of the INTERCEPT Processing Set for plasma.
- The INTERCEPT Blood System for Cryoprecipitation is for single use only. Do not reuse.
- Do not use the INTERCEPT Blood System for Cryoprecipitation if the container or its packaging is damaged or shows any sign of deterioration.
- Protect the packaging, container, and tubing from sharp objects.
- Do not store processing set above 25°C.
- Do not freeze prior to use.

Pathogen Reduced Cryoprecipitated Fibrinogen Complex

- Pathogen Reduced Cryoprecipitated Fibrinogen Complex may be stored at -18°C (-0.4°F) or colder for up to 12 months.
- Thaw according to institutional procedures. If using a waterbath for thawing Pathogen Reduced Cryoprecipitated Fibrinogen Complex, place in liquid-impermeable plastic overwrap. Do not allow product to contact water. Do not refreeze post thaw.
- Do not administer Pathogen Reduced Cryoprecipitated Fibrinogen Complex if there is evidence of container breakage or of thawing during frozen storage.
- If Pathogen Reduced Cryoprecipitated Fibrinogen Complex is pooled or aliquoted post thaw without using an FDA-cleared sterile connection device, transfuse within 4 hours of pooling or aliquoting.
- Pathogen Reduced Cryoprecipitated Fibrinogen Complex may be stored at room temperature for up to 5 days post thaw.
- Discard unused, thawed Pathogen Reduced Cryoprecipitated Fibrinogen Complex at the end of 5 days post thaw as medical waste according to institutional and local regulations.

NONCLINICAL TOXICOLOGY

Nonclinical toxicology studies have not been performed with the INTERCEPT Blood System for Cryoprecipitation.

Pathogen Reduced Cryoprecipitated Fibrinogen Complex is prepared from INTERCEPT processed plasma. *In vitro* studies using whole blood-derived plasma frozen within 24 hours after phlebotomy (PF24) were used to evaluate the concentration of amotosalen in precursor plasma Pathogen Reduced Cryoprecipitated Fibrinogen Complex fractions. The average concentrations in precursor plasma and Pathogen Reduced Cryoprecipitated Fibrinogen Complex were comparable and demonstrate that there is no enrichment of amotosalen in any fraction; and thus the safety data from the nonclinical, clinical, and post-marketing studies with INTERCEPT processed plasma are informative about the safety of Pathogen Reduced Cryoprecipitated Fibrinogen Complex.

Nonclinical studies were conducted in mice, rats and dogs to evaluate the potential toxicity of single and repeated exposures to amotosalen, the synthetic psoralen derivative used in the INTERCEPT process to cross-link DNA and RNA. A single, intravenous injection of amotosalen alone resulted in mortality in rats at doses equal to or greater than 35,000-fold the anticipated human exposure from INTERCEPT Blood System processed plasma, on a dose per kilogram body weight basis. Lower doses (4,000- or 20,000-fold greater than the human exposure in dogs and rats, respectively) were not lethal, and resulted in transient clinical signs of toxicity (i.e., piloerection, inactivity, hunched posture and abnormal breathing in rats, and excessive salivation, convulsions, and non-lethal cardiac arrhythmias in dogs). No target organ toxicities were noted at necropsy.[14]

Animal experiments provided no indication of an increased toxicological risk for the use of plasma processed with amotosalen using the INTERCEPT Blood System, as compared to dosing with equivalent volumes of either homologous unprocessed plasma, or saline or buffer control. Single-dose studies with INTERCEPT processed plasma in dogs were non-toxic at amotosalen doses of 6,000-fold the expected clinical exposure, and repeated daily dosing in rats and dogs for 28 days with homologous plasma processed with the INTERCEPT Blood System showed no evidence of toxicity at 5,000-fold the expected amotosalen clinical exposure.[14]

Amotosalen was rapidly eliminated following intravenous dosing in mice and rats, with an initial plasma $t_{½}$ of less than one hour. There was no evidence of amotosalen accumulation after repeated exposures over periods as long as 13 weeks. The primary route of excretion of amotosalen and its photo-byproducts was fecal.

No effects on fertility parameters were noted in male or female rats repeatedly dosed with amotosalen. In studies evaluating the effects of amotosalen dosing of pregnant rats or rabbits on embryo-fetal or peri-postnatal development, and in one study of neonatal rats dosed with amotosalen, there was no evidence of teratogenicity, or other reproductive or developmental toxicities.[15] No evidence of genotoxicity or mutagenicity was observed in the *in vitro* or *in vivo* mutagenicity studies of amotosalen[16]. In transgenic mice heterozygous for the p53 tumor suppressor gene, there was no evidence of carcinogenicity after repeated, three times weekly dosing for 6 months with amotosalen in plasma, at cumulative weekly doses approximately 150 times the human exposure from a single infusion of INTERCEPT processed plasma.[14]

CLINICAL STUDIES

Pathogen Reduced Cryoprecipitated Fibrinogen Complex is intended to provide fibrinogen, factor XIII, and vWF for management of massive bleeding or risk of massive bleeding due to fibrinogen deficiency and as second-line therapy for vWD, factor XIII deficiency and bleeding associated with uremia.[17,18] No *in vivo* clinical studies have been performed with Pathogen Reduced Cryoprecipitated Fibrinogen Complex.

Efficacy of fibrinogen provided by Pathogen Reduced Cryoprecipitated Fibrinogen Complex

The primary indication for Pathogen Reduced Cryoprecipitated Fibrinogen Complex with 5-day post-thaw storage is control of massive bleeding associated with fibrinogen deficiency. The effective fibrinogen dose for transfusion of Pathogen Reduced Cryoprecipitated Fibrinogen Complex is dependent on the clinical presentation of bleeding, the clinical setting, and the risk and magnitude of bleeding associated with demonstrable or clinically suspected fibrinogen deficiency. The higher levels of fibrinogen content in pooled doses of Pathogen Reduced Cryoprecipitated Fibrinogen Complex provides feasibility to transfuse a large dose of fibrinogen in a tolerable volume (**Table 6**).

Clinical efficacy of vWF and factor XIII replacement provided by Pathogen Reduced Cryoprecipitated Fibrinogen Complex

Pathogen Reduced Cryoprecipitated Fibrinogen Complex contains therapeutic levels of vWF RCF activity and factor XIII. Each of these factors retained functional activity or antigenic levels over 5 days of post-thaw storage at room temperature.[19]

vWF RCF activity in Pathogen Reduced Cryoprecipitated Fibrinogen Complex was retained 94 ± 21% over 5 days post thaw (**Table 5**). Treatment of vWD requires doses ranging from 20 – 60 IU/kg, which for a 60 kg patient would require a total dose of 1200 to 3,600 IU. The levels in Pathogen Reduced Cryoprecipitated Fibrinogen Complex support clinically feasible dosing of vWF when other products are not available or as second-line therapy for vWD (**Table 5**).

Summary of Safety of Pathogen Reduced Cryoprecipitated Fibrinogen Complex

There are no specific clinical safety studies for Pathogen Reduced Cryoprecipitated Fibrinogen Complex.

Pathogen Reduced Cryoprecipitated Fibrinogen Complex is prepared from INTERCEPT processed plasma and contains the comparable concentrations of residual amotosalen as INTERCEPT processed plasma.

The safety data from the nonclinical, clinical, and post-marketing studies with INTERCEPT processed plasma are informative about the safety of Pathogen Reduced Cryoprecipitated Fibrinogen Complex.

Studies with Pathogen Reduced Cryoprecipitated Fibrinogen Complex in pregnant women or pediatric patients have not been conducted. Pathogen Reduced Cryoprecipitated Fibrinogen Complex is produced from INTERCEPT processed plasma, which has been used in the treatment of pregnant and pediatric patients, including neonates. No unexpected adverse events associated with transfusion of INTERCEPT processed plasma to pregnant women or children have been reported.[20] Assessment of safety for INTERCEPT processed plasma has relied on validated nonclinical studies in appropriate animal models, controlled clinical trials, and post-marketing surveillance studies, including in countries with active hemovigilance programs, such as France. The nonclinical studies in reproductive animal models and neonatal animal models established high safety margins in these populations using platelet and plasma components.

INTERCEPT processed plasma has been in clinical use in the European Union for 15 years for treatment of congenital coagulopathy including fibrinogen deficiency, acquired coagulopathy including liver transplant, and for therapeutic plasma exchange (TPE). Each of these indications was supported by clinical trials. TPE is of specific interest because this requires large volume exposure to plasma processed with amotosalen. Long-term surveillance studies of TPE patients have demonstrated no excess treatment related morbidity indicative of safety.[21-24] Post-marketing surveillance studies that have included neonatal and children to age 18 have not detected any adverse events specifically related to INTERCEPT processed plasma transfusion; and these studies have included longitudinal exposures for many of these patients including liver transplant.[25-27] On the basis of the multi-year clinical experience with INTERCEPT processed plasma, there are no safety signals indicative of excess treatment related morbidity.[20]

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CIRCULAR OF INFORMATION

FOR THE USE OF HUMAN BLOOD AND BLOOD COMPONENTS

This *Circular* was prepared jointly by AABB, the American Red Cross, America's Blood Centers, and the Armed Services Blood Program. The Food and Drug Administration recognizes this *Circular of Information* as an acceptable extension of container labels. *Federal Law prohibits dispensing the blood and blood components described in this circular without a prescription.*

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Armed Services Blood Program

REVIEW THIS PAGE FOR IMPORTANT INFORMATION FROM THE BLOOD SUPPLIER AND UPDATES REQUIRED BY FDA

THIS DOCUMENT IS POSTED AT THE REQUEST OF FDA TO PROVIDE A PUBLIC RECORD OF THE CONTENT IN THE DECEMBER 2021 CIRCULAR OF INFORMATION.

THIS DOCUMENT IS INTENDED AS A REFERENCE AND PROVIDES:

- GENERAL INFORMATION ON WHOLE BLOOD AND BLOOD COMPONENTS
- INSTRUCTIONS FOR USE
- SIDE EFFECTS AND HAZARDS

THIS DOCUMENT DOES NOT SERVE AS AN EXTENSION OF LABELING REQUIRED BY FDA REGULATIONS AT 21 CFR 606.122.

REFER TO THE CIRCULAR OF INFORMATION WEBPAGE AND THE MARCH 2022 FDA GUIDANCE FOR IMPORTANT INFORMATION ON THE CIRCULAR.

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Notice to All Users

The *Circular of Information for the Use of Human Blood and Blood Components* (hereafter referred to as *Circular*) is an extension of container labels, as the space on those labels is limited.

Blood and blood components are biological products and living human tissue intended for use in patient treatment. Professional judgment based on clinical evaluation determines the selection of components, dosage, rate of administration, and decisions in situations not covered in this general statement.

This *Circular*, as a whole or in part, cannot be considered or interpreted as an expressed or implied warranty of the safety or fitness of the described blood or blood components when used for their intended purpose. Attention to the specific indications for blood components is needed to prevent inappropriate transfusion.

Because of the risks associated with transfusion, physicians or prescribing health care professionals should be familiar with alternatives to transfusion. Blood banks and transfusion services are referred to the AABB *Standards for Blood Banks and Transfusion Services* for additional information and policies, especially in the areas of recipient sample identification, compatibility testing, issue and transfusion of blood and blood components, investigation of transfusion reactions, and proper record-keeping practices. Transfusionists are referred to the AABB *Technical Manual* for applicable chapters on adult and pediatric transfusion.

The specific product manufacturer's instructions for use should be reviewed for information pertaining to the use of transfusion devices (eg, filters, blood administration sets, and blood warmers).

This *Circular* is supplied to conform with applicable federal statutes and regulations of the Food and Drug Administration (FDA), United States Department of Health and Human Services. The blood components in this *Circular* marked with the symbol "Ω" are blood components for which the FDA currently has not received data to demonstrate that they meet prescribed requirements of safety, purity, and potency, and therefore are not licensed for distribution in interstate commerce.

General Information for Whole Blood and All Blood Components

Donors

Blood and blood components described in this *Circular* are collected from blood donors for use in patients (allogeneic transfusions) or from patients donating for themselves (autologous transfusions). Most allogeneic donations are from volunteer blood donors and the components are labeled "volunteer donor." If donors receive monetary payment for a blood donation, the components must be labeled as "paid donor."

All blood donors have satisfactorily completed a health assessment that includes a medical history questionnaire on past and present illnesses and have satisfied minimum physiologic criteria. Allogeneic donors have been questioned about risk factors for transmissible infectious agents and have been given instructions to call the blood center after donation if they develop illness or have concerns that their blood may not be safe to give to another person.

Autologous donations are collected from patients who anticipate requiring blood transfusions. Donor-safety screening criteria and testing procedures applicable to collection from allogeneic donors do not always apply to these components. All units intended for transfusion to the donor/patient must be labeled "AUTOLOGOUS DONOR." The unit must be labeled "FOR

AUTOLOGOUS USE ONLY" if the donor fails to meet donor eligibility requirements or has reactive or positive test results for evidence of infection.

Required Testing of Blood Donations

Testing of a sample of donor blood is performed before units of blood or blood components are distributed for routine transfusion. The donor's ABO group and Rh type have been determined, including testing for the presence of weak D antigen.

A sample from each donation intended for allogeneic use has been tested by FDA-licensed tests and found to be:

1. Nonreactive for antibodies to:
   - human immunodeficiency virus (anti-HIV-1/2),
   - hepatitis C virus (anti-HCV),
   - human T-lymphotropic virus (anti-HTLV-I/II),
   - hepatitis B core antigen (anti-HBc), and
   - *Trypanosoma cruzi* either on the current donation or at least one previous donation.
2. Nonreactive for hepatitis B surface antigen (HBsAg).
3. Nonreactive when tested using licensed nucleic acid tests (NAT) for:
   - hepatitis B virus (HBV) deoxyribonucleic acid (DNA),
   - hepatitis C virus (HCV) ribonucleic acid (RNA),
   - human immunodeficiency virus (HIV-1) RNA, and
   - West Nile virus (WNV) RNA.
4. Nonreactive when tested using a licensed NAT for *Babesia* (RNA and DNA) for blood collected in states where *Babesia* testing is required by FDA.
5. Nonreactive when tested using a licensed serologic test for *Treponema pallidum* (syphilis).

A blood collector may perform additional testing for pathogens; such additional testing may be performed under an FDA-approved investigational new drug (IND) application, using language for component labeling and/or revisions to the *Circular*, as required in the approved IND and provided by the IND sponsor.

For units labeled "FOR AUTOLOGOUS USE ONLY," infectious disease testing requirements vary, depending on whether the unit will be drawn in one facility and infused in another facility and whether the unit might be made available for allogeneic transfusion. Infectious disease testing may be omitted for autologous units drawn, stored, and infused at the same facility. Autologous units for which testing has not been performed are labeled "DONOR UNTESTED." Autologous units with reactive test results may be used for transfusion to the donor-patient with appropriate physician authorization. A biohazard label will be applied to all autologous units that are tested for evidence of relevant transfusion-transmitted infections as listed above and determined to be reactive. If the units labeled "FOR AUTOLOGOUS USE ONLY" are infused at a different facility, at a minimum the first donation from the donor-patient in each 30-day period is tested for evidence of infection as listed above. Subsequent units that are not tested will be labeled as "DONOR TESTED WITHIN THE LAST 30 DAYS." A biohazard label is required if these units have a reactive relevant transfusion-transmitted infection test result within the last 30 days.

In addition, if these units are untested, they must be labeled as "DONOR UNTESTED." If a facility allows for autologous units to be crossed over for inclusion in the general blood inventory, the donors and units must be subjected to the same donor eligibility and donation suitability requirements and test requirements as allogeneic donors and units.

Tests for unexpected antibodies against red blood cell antigens (red cell) have been performed on samples from all donors. The results of these tests are negative or have been determined to be clinically insignificant unless otherwise indicated on the label. Other tests may have been performed on donor blood as indicated by information that has been provided by the blood bank or transfusion service on an additional label or tie tag, or in a supplement to this *Circular*.

Bacterial Risk Control Strategies for Platelets

Consistent with the December 2020 FDA recommendations to control the risk of bacterial contamination, platelet components stored at room temperature have been:

1. tested and found negative for bacterial contamination using FDA recommended bacterial risk control strategies and FDA-cleared or approved devices, or
2. treated using FDA-approved pathogen reduction technology.

Note: Certain bacterial testing strategies include secondary or rapid testing performed prior to transfusion.

Blood and Component Labeling

All **Components Available** identified in this *Circular* are listed using the International Society of Blood Transfusion 128 (ISBT 128) product name.

Blood and blood component labels will contain the following information:

1. The proper name, Whole Blood or blood component, including an indication of any qualification or modification.
2. The method by which the blood component was prepared, either by whole blood or apheresis collection.
3. The temperature range in which the blood component is to be stored.
4. The preservatives and anticoagulant used in the preparation of the blood or blood components, when appropriate.
5. The standard contents or volume is assumed unless otherwise indicated on the label or in *Circular* supplements.
6. The number of units in pooled blood components.
7. The name, address, registration number, and US license number (if applicable) of the collection and processing location.
8. The expiration date, including the day, month, and year, and, if the dating period for the product is 72 hours or less, including any product prepared in a system that might compromise sterility, the hour of expiration. When the expiration time is not indicated, the product expires at midnight.
9. The donation (unit or pool) identification number.
10. The donor category (paid or volunteer, and autologous, if applicable).
11. ABO group and Rh type, if applicable.
12. Special handling information, as required.
13. Statements regarding proper recipient identification, this *Circular*, infectious disease risk, and prescription requirement.
14. Any sedimenting agent used during cytapheresis, if applicable.

Instructions for Use

The following general instructions pertain to Whole Blood and all the blood components described in this *Circular*:

1. All blood and blood components must be maintained in a controlled environment and stored under appropriate conditions as described in the AABB *Standards for Blood Banks and Transfusion Services*.
2. The intended recipient and the blood container must be properly identified before the transfusion is started.

3. Aseptic technique must be employed during preparation and administration. If the container is entered in a manner that violates the integrity of the system, the component expires 4 hours after entry if maintained at room temperature (20-24 C) or 24 hours after entry if refrigerated (1-6 C).
4. All blood components must be transfused through a filter designed to remove clots and aggregates (generally a standard 150- to 260-micron filter).
5. Blood and blood components should be mixed thoroughly before use.
6. Blood and blood components must be inspected immediately before use. If, upon visual inspection, the container is not intact or the appearance is abnormal (presence of excessive hemolysis, a significant color change in the blood bag as compared with the tubing segments, floccular material, cloudy appearance, or other problems), the blood or blood component must not be used for transfusion and appropriate follow-up with the transfusion service must be performed.
7. No medications or solutions may be added to or infused through the same tubing simultaneously with blood or blood components, with the exception of 0.9% Sodium Chloride, Injection, United States Pharmacopeia (USP), unless: 1) they have been approved for this use by the FDA, or 2) there is documentation available to show that the addition is safe and does not adversely affect the blood or blood component.
8. Lactated Ringer's Injection USP or other solutions containing calcium should never be added to or infused through the same tubing with blood or blood components containing citrate.
9. Blood components should be warmed, if clinically indicated, for situations such as exchange or massive transfusions, or for patients with cold-reactive antibodies. Warming must be accomplished using an FDA-cleared warming device.
10. Life-threatening reactions may occur after the infusion of only a small volume of blood or blood components. Therefore, unless otherwise indicated by the patient's clinical condition, the rate of infusion should initially be slow.
11. Periodic observation and recording of vital signs should occur before, during, and after the transfusion to identify suspected adverse reactions. If a transfusion reaction occurs, the transfusion must be discontinued immediately, and appropriate therapy initiated. The infusion should not be restarted unless approved by transfusion service protocol.
12. Specific instructions concerning possible adverse reactions shall be provided to the patient or a responsible caregiver when direct medical observation or monitoring of the patient will not be available after transfusion.
13. Transfusion should be started before component expiration and completed within 4 hours after entering the container.
14. All adverse events related to transfusion, including possible bacterial contamination of blood or a blood component or suspected disease transmission, must be reported to the transfusion service according to its local protocol.

Refer to the Section on **Further Processing** for additional information on:

- Pathogen Reduction Technology
- Leukocyte Reduction
- Irradiation
- Washing and Volume Reduction.

Refer to the Section on **Additional Testing** for additional information on:

- Identification of CMV-Seronegative Blood.
- Identification of Low Titer Anti-A and/or Anti-B Blood Products.

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Side Effects and Hazards for Whole Blood and All Blood Components

Transfusion-related adverse events may be voluntarily reported to the National Healthcare Safety Network (NHSN) hemovigilance program (https://www.cdc.gov/nhsn/index.html) unless there is a state requirement to report. The NHSN Biovigilance Component Hemovigilance Module Surveillance Protocol (https://www.cdc.gov/nhsn/pdfs/biovigilance/bv-hv-protocol-current.pdf) provides case classification criteria for Centers for Disease Control and Prevention-defined transfusion-associated adverse reactions.

Immunologic Complications, Immediate

1. *Hemolytic transfusion reaction*, the immune destruction of red cells, is typically the result of the exposure of transfused red cells to incompatible recipient plasma. The transfusion of blood components containing plasma which is incompatible with the recipient's red cells rarely results in clinically relevant hemolysis. Further details are discussed in the section on components containing red cells and in the platelet section.
2. *Immune-mediated platelet destruction*, one of the causes of refractoriness to platelet transfusion, is the result of alloantibodies in the recipient to human leukocyte antigen (HLA) or platelet-specific antigens on transfused platelets. This is described in more detail in the section on platelets.
3. *Febrile nonhemolytic reaction* is typically manifested by a temperature elevation of ≥1 C or 1.8 F occurring during or within 4 hours after a transfusion and in the absence of any other pyretic stimulus or active warming. This may reflect the action of antibodies against white cells or the action of cytokines either present in the transfused component or generated by the recipient in response to transfused elements. Febrile reactions may occur in less than 1% of transfusions of leukocyte-reduced red cell components and about 5% of leukocyte-reduced apheresis platelet components. Febrile reactions occur more frequently in patients receiving non-leukocyte-reduced components and those previously alloimmunized by transfusion or pregnancy. No routinely available pre- or posttransfusion tests are helpful in predicting or preventing these reactions. Antipyretics usually provide effective symptomatic relief. Patients who experience repeated, severe febrile reactions may benefit from receiving leukocyte-reduced components. If these reactions are caused by cytokines in the component, prestorage leukocyte reduction may be beneficial.
4. *Allergic reactions* frequently occur (ie, with 1-3% of plasma-containing components) as mild or self-limiting urticaria or wheezing that usually responds to antihistamines. More severe manifestations, including respiratory and cardiovascular symptoms, are more consistent with anaphylactoid/anaphylactic reactions and may require more aggressive therapy (see below). No laboratory procedures are available to predict these reactions.
5. *Anaphylactoid/anaphylactic reactions*, characterized by hypotension, tachycardia, nausea, vomiting and/or diarrhea, abdominal pain, severe dyspnea, pulmonary and/or laryngeal edema, and bronchospasm and/or laryngospasm, are rare (<10/100,000 transfused units) but dangerous complications requiring immediate treatment with epinephrine and supportive care. While these reactions have been reported in IgA-deficient patients with anti-IgA antibodies and patients with haptoglobin deficiency, most reactions are idiosyncratic and not associated with a specific serum protein deficiency, polymorphism, or identifiable cause. In certain circumstances, patients may benefit from the use of washed cellular components to prevent or reduce the severity of allergic reactions not minimized by treatment with medication alone.

6. *Transfusion-related acute lung injury* (TRALI) is characterized by the acute onset of hypoxemia and noncardiogenic pulmonary edema within 6 hours of a blood or blood component transfusion in the absence of other causes of acute lung injury or circulatory overload. Various stimuli in blood components, most commonly white cell antibodies from donors sensitized during pregnancy or prior transfusion or transplantation, or proinflammatory molecules that accumulate in stored blood components, may cause TRALI. These mechanisms may not be mutually exclusive and may act synergistically with underlying patient factors to lead to a final common pathway of acute lung injury. These stimuli may trigger an inflammatory response, granulocyte activation and degranulation, and injury to the alveolar capillary membrane and the development of permeability pulmonary edema. Although most TRALI cases are associated with donor antileukocyte antibodies, rare cases have implicated recipient antileukocyte antibodies that reacted with donor leukocytes. Widespread leukoreduction of blood components has likely mitigated this latter risk. Laboratory testing of blood donors for antileukocyte antibodies or blood components for biological mediators does not alter management of this reaction, which is diagnosed on clinical and radiographic findings. Treatment of TRALI involves aggressive respiratory support, and often mechanical ventilation. The preferential use of plasma collected from male donors or female donors who have tested negative for the presence of HLA Class I and/or II antibodies has been associated with a significant reduction in the number of reported TRALI cases and associated fatalities. Transfusion services should immediately report suspected TRALI to the blood collection facility to facilitate the retrieval of other components associated with the involved donation(s) or prior donations.

Immunologic Complications, Delayed

1. *Delayed hemolytic reaction* is described in detail in the section on components containing red cells.
2. *Alloimmunization* to antigens of red cells, white cells, platelets, or plasma proteins may occur unpredictably after transfusion. Blood components may contain certain immunizing substances other than those indicated on the label. For example, platelet components may also contain red cells and white cells. Primary immunization does not become apparent until days or weeks after the immunizing event and does not usually cause symptoms or physiologic changes. If components that express the relevant antigen are subsequently transfused, there may be accelerated removal of cellular elements from the circulation and/or systemic symptoms. Clinically significant antibodies to red cell antigens will ordinarily be detected by pretransfusion testing. Alloimmunization to antigens of white cells, platelets, or plasma proteins can be detected only by specialized testing.
3. *Posttransfusion purpura* is a rare syndrome characterized by the development of dramatic, sudden, and self-limited thrombocytopenia, typically 7 to 10 days after a blood transfusion, in a patient with a history of sensitization by either pregnancy or transfusion. Although the immune specificity may be to a platelet-specific antigen the patient lacks, both autologous and allogeneic platelets are destroyed. High-dose Immune Globulin, Intravenous (IVIG) may correct the thrombocytopenia.
4. *Transfusion-associated graft-vs-host disease* (TA-GVHD) is rare but has a fatality rate of nearly 100% due to overwhelming infection in the setting of pancytopenia. This condition occurs when viable T lymphocytes in the transfused component engraft in the recipient and react against recipient tissue antigens. TA-GVHD can occur if the host does not recognize and reject the foreign transfused cells, and it can follow transfusion of any component that contains even very small numbers of viable T lymphocytes. Immunologically normal recipients who are heterozygous for a tissue antigen haplotype for which the donor is homozygous are at risk. Recipients with severe cellular immunodeficiency (except for HIV infection) are also at

greatest risk (eg, fetuses receiving intrauterine transfusions, at-risk neonates, recipients of hematopoietic progenitor cell transplants, and selected patients with severe immunodeficiency conditions). Patients with oncologic and rheumatologic diseases receiving purine analogues (eg, fludarabine, cladribine) or certain other biological immunomodulators (eg, alemtuzumab, antithymocyte globulin) may be at risk for TA-GVHD, depending on clinical factors and the source of the biological agent. TA-GVHD remains a risk with leukocyte-reduced components because they contain sufficient residual T lymphocytes. Irradiation of the component renders T lymphocytes incapable of proliferation. Pathogen reduction technology may also be used as an alternative to irradiation to prevent TA-GVHD if the pathogen reduction technology has been shown to inactivate residual lymphocytes.

Nonimmunologic Complications

Because Whole Blood and blood components are made from human blood, they may carry a risk of transmitting infectious agents [eg, viruses, bacteria, parasites, the variant Creutzfeldt-Jakob disease (vCJD) agent, and, theoretically, the Creutzfeldt-Jakob disease agent (CJD)]. Also, septic and toxic reactions can result from transfusion of bacterially contaminated blood and blood components. Careful donor selection, available laboratory tests, and pathogen reduction technology do not totally eliminate these hazards. Such complications are infrequent but may be life-threatening. Infectious disease transmission may occur despite careful selection of donors and testing of blood. Donor selection criteria are designed to screen out potential donors with increased risk of infection with HIV, HTLV, hepatitis, and syphilis, as well as other agents (see section on Required Testing of Blood Donations). For *other infectious agents* (eg, *Plasmodia* spp.) there are no licensed tests available for donor testing; however, other screening measures for possible exposure or history of malaria, or use of pathogen reduction technology may mitigate the risk of transfusion-transmitted infections. Transfusion services should immediately report infections that may be related to the blood donor or to the manufacture of the blood components to the collection facility.

1. *Cytomegalovirus* (CMV) may be present in white-cell-containing components from donors previously infected with this virus, which can persist for a lifetime despite the presence of serum antibodies. Up to 70% of donors may be CMV seropositive. Transmission of CMV by transfusion may be of concern in low-birthweight (≤1200 g) premature infants born to CMV-seronegative mothers and in intrauterine transfusions and/or certain other categories of immunocompromised individuals such as hematopoietic progenitor cell or solid organ transplant patients, if they are CMV seronegative. For at-risk recipients, the risk of CMV transmission by cellular components can be reduced by transfusing CMV-seronegative or leukocyte-reduced components, or pathogen-reduced components when applicable.
2. *Bacterial sepsis* occurs rarely but can cause acute, severe, sometimes life-threatening effects. Onset of high fever (≥2 C or ≥3.5 F increase in temperature), severe chills, hypotension, or circulatory collapse during or shortly after transfusion should suggest the possibility of bacterial contamination and/or endotoxin reaction in the transfused products. Although platelet components stored at room temperature have been implicated most frequently, previously frozen components thawed by immersion in a water bath and red cell components stored for several weeks at 1 to 6 C have also been implicated. Platelet components are controlled for bacterial contamination, however this does not completely eliminate the risk.

   Both gram-positive and gram-negative organisms have been identified as causing septic reactions. Organisms capable of multiplying at low temperatures (eg, *Yersinia enterocolitica*) and those using citrate as a nutrient have been associated with components containing red cells. A variety of pathogens, as well as skin contaminants, have been found in platelet components. Multiplication of gram-negative bacteria in blood components has also caused endotoxemia in recipients.

Prompt recognition of a possible septic reaction is essential, with immediate discontinuation of the transfusion and aggressive therapy with broad-spectrum antimicrobials and vasopressor agents, if necessary. In addition to prompt sampling of the patient's blood for cultures, investigation should include examination of material from the blood container by gram stain, and cultures of specimens from the container and the administration set. It is important to report all febrile transfusion reactions to the transfusion service for appropriate investigation. If posttransfusion sepsis is suspected, the transfusion service should immediately report the reaction to the blood collection facility to facilitate retrieval of other potentially contaminated components associated with the collection.

3. *Transfusion-associated circulatory overload* (TACO) is a frequent complication of transfusion leading to cardiogenic (hydrostatic) pulmonary edema and can occur after transfusion of excessive volumes or at excessively rapid rates. This is a particular risk in individuals with underlying cardiopulmonary or renal disease, the very young and the elderly, and in patients with chronic severe anemia in whom low red cell mass is associated with high plasma volume. Small transfusion volumes can precipitate symptoms in at-risk patients who already have a positive fluid balance.

   Pulmonary edema should be promptly and aggressively treated, and infusion of colloid preparations, including plasma components and the supernatant fluid in cellular components, reduced to a minimum.
4. *Hypothermia* carries a risk of cardiac arrhythmia or cardiac arrest and exacerbation of coagulopathy. Rapid infusion of large volumes of cold blood or blood components can depress body temperature, and the danger is compounded in patients experiencing shock or surgical or anesthetic manipulations that disrupt temperature regulation. A blood warming device should be considered if rapid infusion of blood or blood components is needed. Warming must be accomplished using an FDA-cleared blood warming device so as not to cause hemolysis.
5. *Metabolic complications* may accompany large-volume transfusions, especially in neonates and patients with liver or kidney disease.
   a. Citrate "toxicity" reflects a depression of ionized calcium caused by the presence in the circulation of large quantities of citrate anticoagulant. Because citrate is promptly metabolized by the liver, this complication is rare. Patients with severe liver disease or those with circulatory collapse that prevents adequate hepatic blood flow may have physiologically significant hypocalcemia after rapid, large-volume transfusion. Citrated blood or blood components administered rapidly through central intravenous access may reach the heart so rapidly that ventricular arrhythmias occur. Standard measurement of serum calcium does not distinguish ionized from complexed calcium. Ionized calcium testing or electrocardiogram monitoring is more helpful in detecting physiologically significant alteration in calcium levels.
   b. Other metabolic derangements can accompany rapid or large-volume transfusions, especially in patients with preexisting circulatory or metabolic problems. These include acidosis or alkalosis (deriving from changing concentrations of citric acid and its subsequent conversion to pyruvate and bicarbonate) and hyper- or hypokalemia.

Fatal Transfusion Reactions

Reporting requirements can be found on the FDA's webpage, Transfusion/Donation Fatalities:

"Section 606.170(b) of Title 21, Code of Federal Regulations [21 CFR 606.170(b)], requires that facilities notify the Food and Drug Administration (FDA), Center for Biologics Evaluation and Research (CBER), Office of Compliance and Biologics Quality (OCBQ), as soon as possible after confirming a complication of blood collection or transfusion to be fatal. The collecting facility is to report donor fatalities, and the compatibility testing facility is to report recipient fatalities. The regulation also requires the reporting facility to submit a report of the investigation within 7 days after the fatality."

FDA's August 2021 Guidance, Notifying FDA of Fatalities Related to Blood Collection or Transfusion; Guidance for Industry, provides recommendations and additional information, including this clarification:

"We recommend that you submit the initial notification by email, if possible, and if you do so, you will receive an email confirmation receipt from us. If email is not feasible, please notify us by telephone or facsimile. We cannot access notification outside of customary working hours unless you use email or telephone."

When reporting a fatality during or outside of regular business hours, the reporting facility may submit initial notification by leaving a voice message or sending an email or facsimile to the Division of Inspections and Surveillance.

- Email: fatalities2@cber.fda.gov
- Telephone/voice-mail number: 240-402-9160
- Fax number: 301-837-6256, Attn: CBER Fatality Program Manager
- Express mail address: See below

FDA will contact you as soon as possible to obtain more detailed information. This does not replace the 7-day written report regarding the fatality and all related information as described in 21 CFR 606.170(b).

The 7-day follow-up report may be submitted by email, facsimile, or express mail.

Express mail address for 7-day follow-up reports:

U.S. Food and Drug Administration
Office of Compliance and Biologics Quality/CBER
Attn: Fatality Program Manager
10903 New Hampshire Ave.
Bldg. 71, Rm. 3128
Silver Spring, MD 20993-0002

Refer to FDA's website for information (https://www.fda.gov/vaccines-blood-biologics/report-problem-center-biologics-evaluation-research/transfusiondonation-fatalities) and August 2021 Guidance for Industry, Notifying FDA of Fatalities Related to Blood Collection or Transfusion.

Whole Blood

Overview

Whole Blood is transfused to increase oxygen-carrying capacity in patients whom physiologic compensatory mechanisms are inadequate to maintain normal tissue oxygenation. Whole Blood may be transfused in an emergency situation or other clinical setting that necessitates delivery of multiple blood components simultaneously.

Description

A single whole blood donation typically contains either 450 mL (±10%) or 500 mL (±10%) of blood collected from allogeneic blood donors with a minimum hematocrit of 36% to 38% (females) or 39% (males), drawn in a sterile container that includes an anticoagulant solution licensed for this component. Whole Blood is prepared in an aseptic manner in a ratio of 14 milliliters (mL) of anticoagulant-preservative solution per 100 mL of whole blood targeted for collection.

Whole Blood contains approximately 5.5×10^{10} platelets. The volume of plasma in Whole Blood is about 170 mL or greater and contains nonlabile clotting factors.

Whole Blood must be stored at 1-6 C for an interval ("shelf life") determined by the properties of the anticoagulant-preservative solution (see Table 1).

Refer to the Section on **Further Processing** for additional information on:

- Leukocyte Reduction

Refer to the Section on **Additional Testing** for additional information on:

- Identification of CMV-Seronegative Blood
- Identification of Low Titer Anti-A and/or Anti-B Blood Products

Actions

Whole Blood increases the recipient's oxygen-carrying capacity by increasing the mass of circulating Red Blood Cells. In addition to Red Blood Cells, Whole Blood provides plasma and platelets which provide volume expansion and may contribute to hemostasis.

Indications

Whole Blood may be indicated in life-threatening hemorrhage where oxygen-carrying capacity, nonlabile coagulation factors, platelets, and volume expansion are needed.

Contraindications

Whole Blood should not be used solely for volume expansion or to increase oncotic pressure of circulating blood.

Dosage and Administration

Whole Blood contains enough hemoglobin to increase the hemoglobin concentration in an average-sized adult by approximately 1 gram/ deciliter (g/dL) (increase hematocrit by 3%).

Whole Blood must be ABO group-specific with the recipient. In life-threatening situations, group O Whole Blood may be administered to non-O patients provided facilities have policies and procedures to define titer cut-offs for anti-A and anti-B titers.

The transfusing facility must have policies and procedures in place addressing specific indications for use, product specifications, administration instructions, and a defined maximum number of units to be transfused to each patient.

The initial portion of each unit transfused should be infused cautiously and with sufficient observation to detect onset of acute reactions. Thereafter, the rate of infusion can be more rapid, as tolerated by the patient's circulatory system. It is undesirable for components that contain red cells to remain at room temperature longer than 4 hours.

Side Effects and Hazards

Hazards that pertain to all transfusion components are described in the earlier section titled Side Effects and Hazards for Whole Blood and All Blood Components. Listed below are additional hazards that apply specifically to components that contain red cells.

1. **Hemolytic transfusion reaction** is the immunologic destruction of transfused red cells, nearly always the result of incompatibility of antigen on the transfused cells with antibody in the recipient's circulation (see item 4 below for discussion of nonimmunologic hemolysis). The most common cause of severe, acute hemolytic reactions is transfusion of ABO-incompatible blood, resulting from identification errors occurring at some point(s) in the transfusion process. Serologic incompatibility undetected during pretransfusion testing is a much less common cause of acute hemolysis. If a hemolytic transfusion reaction is suspected, the transfusion must be stopped, and the transfusion service laboratory notified immediately. Information identifying the patient, the transfusion component, and associated forms and labels must be reviewed promptly to detect possible errors. A postreaction blood sample, preferably

Table 1. Contents of Anticoagulant-Preservative Solutions*

Anticoagulant-Preservative (g/L)	Trisodium Citrate	Citric Acid	Monobasic Sodium Phosphate	Dextrose	Adenine	Shelf Life (Days)
Anticoagulant citrate-dextrose A (ACD-A)†	22.0	8.0	0	24.5	0	21
Citrate-phosphate dextrose (CPD)	26.3	3.27	2.22	25.5	0	21
Citrate-phosphate-dextrose-dextrose (CP2D)	26.3	3.27	2.22	51.1	0	21
Citrate-phosphate-dextrose-adenine (CPDA-1)	26.3	3.27	2.22	31.9	0.275	35

*63 mL/450 mL collection, 70 mL/500 mL collection.
†ACD is used for apheresis components.

drawn from a site other than the transfusion access, must be sent to the laboratory along with the implicated unit of blood and administration set.

Acute hemolytic reactions characteristically begin with an increase in temperature and pulse rate; symptoms may include chills, dyspnea, chest or back pain, abnormal bleeding, or shock. Instability of blood pressure is frequent, the direction and magnitude of change depending upon the phase of the reaction and the magnitude of compensatory mechanisms. In anesthetized patients, hemoglobinuria, hypotension, and evidence of disseminated intravascular coagulopathy (DIC) may be the first signs of incompatibility. Laboratory findings can include hemoglobinemia and/or hemoglobinuria, followed by elevation of serum indirect bilirubin. The direct antiglobulin test (DAT) result is usually positive, with rare exceptions (ie, complete hemolysis of incompatible red cells). Treatment includes measures to maintain or correct arterial blood pressure; correct coagulopathy, if present; and promote or maintain renal function. Lack of symptoms does not exclude an acute hemolytic reaction.

Delayed hemolytic reactions occur in previously red-cell-alloimmunized patients in whom antigens on transfused red cells provoke anamnestic production of antibody. The anamnestic response reaches a significant circulating level while the transfused cells are still present in the circulation; the usual time frame is 2 to 14 days after transfusion. Signs may include unexplained fever, development of a positive DAT result, and unexplained decrease in hemoglobin/hematocrit. Hemoglobinemia and hemoglobinuria are uncommon, but elevation of lactate dehydrogenase or bilirubin may be noted. Most delayed hemolytic reactions have a benign course and require no treatment.

Hemolytic transfusion reactions in patients with sickle cell anemia may be particularly severe, with destruction of autologous as well as transfused red cells, resulting in a lower hemoglobin level after transfusion. This is suggestive of hyperhemolysis syndrome. In such patients, serologic investigations may not reveal the specificity of the causative antibody. Immediate treatment may include steroid use, IVIG, and avoiding transfusions, if possible. Consultation with a transfusion medicine specialist is required in these cases. Prospective matching for Rh and Kell antigens may decrease risk.

2. Antigens on transfused red cells may cause red cell **alloimmunization** of the recipient. Clinically significant antibodies to red cell antigens will usually be detected in pretransfusion antibody screening tests. For most patients, red cell antigen matching beyond ABO and Rh is unnecessary.
3. **TACO** can accompany transfusion of any component at a rate more rapid than the recipient's cardiac output can accommodate. Whole Blood creates more of a risk than Red Blood Cell components (RBCs) because the transfused plasma adds volume without increasing oxygen-carrying capacity. Patients with chronic anemia have increased plasma volumes and are at increased risk for circulatory overload.
4. **Nonimmunologic hemolysis** occurs rarely but can result from: 1) introduction of hypotonic fluids into the circulation; 2) effects of drugs coadministered with transfusion; 3) effects of bacterial toxins; 4) thermal injury by freezing or overheating; 5) metabolic damage to cells, as from hemoglobinopathies or enzyme deficiencies; or 6) mechanical injury or osmotic stresses. Examples of situations capable of causing nonimmune red cell hemolysis include exposure to excessive heat when using warming devices not cleared or approved by FDA, mixture of blood with hypotonic solutions, or transfusion under high pressure through small-gauge or defective needles.

Components Available

WHOLE BLOOD is prepared from 400-550 mL of blood collected into the appropriate volume of anticoagulant solution.

WHOLE BLOOD LEUKOCYTES REDUCED is prepared from Whole Blood by a method resulting in a final product containing $<5.0 \times 10^6$ leukocytes and $\geq 85\%$ of the original Whole Blood content. Leukocyte-reduced Whole Blood may be prepared using a platelet-sparing leukocyte reduction filter.

Red Blood Cell Components

Overview

RBCs are transfused to increase oxygen-carrying capacity in patients whom physiologic compensatory mechanisms are inadequate to maintain normal tissue oxygenation. Red cells contain hemoglobin and serve as the primary agent for transport of oxygen to tissues. The primary red-cell-containing transfusion component is RBCs. This component is prepared by centrifugation or sedimentation of Whole Blood to remove much of the plasma. RBC components can also be prepared by apheresis methods.

Description

Depending upon the collection system used, a single whole blood donation typically contains either 450 mL (±10%) or 500 mL (±10%) of blood collected from allogeneic blood donors with a minimum hematocrit of 36% to 38% (females) or 39% (males), withdrawn in a sterile container that includes an anticoagulant solution licensed for this component. In the case of autologous adult blood donors, a hematocrit minimum as low as 33% is acceptable. Occasionally, units of other volumes are collected, and those volumes are stated on the label.

Red-cell-containing components can be stored at 1-6 C for an interval ("shelf life") determined by the properties of the anticoagulant-preservative solution (see Table 1). Whole Blood units are prepared in an aseptic manner in a ratio of 14 milliliters (mL) of anticoagulant-preservative solution per 100 mL of Whole Blood targeted for collection. Apheresis components are collected into anticoagulants as recommended by the manufacturer.

After plasma is removed, the resulting component is RBCs, which has a hematocrit between 65% to 80% and a usual volume between 225 mL and 350 mL. Red Blood Cells additive solutions (AS) may be mixed with the red cells remaining after removal of nearly all of the plasma to extend the shelf life (see Table 2). The typical hematocrit of AS RBCs is 55% to 65%, and the volume is approximately 300 to 400 mL. AS RBCs have a shelf life of 42 days. Descriptions of specific components containing red cells are given at the end of this section.

Refer to the Section on **Further Processing** for additional information on:
- Pathogen-Reduction Technology
- Leukocyte Reduction
- Irradiation
- Washing and Volume Reduction

Refer to the Section on **Additional Testing** for additional information on:
- Identification of CMV-Seronegative Blood
- Identification of Low Titer Anti-A and/or Anti-B Blood Products

Actions

RBC components increase the recipient's oxygen-carrying capacity by increasing the mass of circulating red cells. Processing and/or storage deplete the component of virtually all potential therapeutic benefit attributable to the functions of white cells and platelets; however, cellular elements remain in these blood components and may cause adverse immunologic or physiologic conse-

Table 2. Contents of Red Blood Cells Additive Solutions*

Additive Solution (mg/100 mL)	Dextrose Mono-hydrate	Adenine	Monobasic Sodium Phosphate	Dibasic Sodium Phosphate	Mannitol	Sodium Bicarbonate	Sodium Chloride	Sodium Citrate	Citric Acid	Shelf Life (Days)
AS-1 (Adsol)	2200	27	0	0	750	0	900	0	0	42
AS-3 (Nutricel)	1100	30	276	0	0	0	410	588	42	42
AS-5 (Optisol)	900	30	0	0	525	0	877	0	0	42
AS-7 (SOLX)	1585	27	0	170	1000	218	0	0	0	42

*100 mL AS/450 mL collection, 110 mL AS/500 mL collection.

quences. Residual plasma in the component provides the recipient with volume expansion and nonlabile plasma proteins to the extent that residual plasma is present in the preparation. Depending on the method of production, RBCs may contain approximately 20 to 100 mL of residual plasma. RBCs prepared with AS are the most used red cell product and have limited residual plasma.

Indications

Red-cell-containing components are indicated for treatment of symptomatic or critical deficit of oxygen-carrying capacity. They are also indicated for red cell exchange transfusion.

Contraindications

Red-cell-containing components should not be used to treat anemias that can be corrected with specific hematinic medications such as iron, vitamin B12, folic acid, or erythropoietin.

RBCs should not be used solely for volume expansion or to increase oncotic pressure of circulating blood.

Dosage and Administration

Each unit of RBCs contains enough hemoglobin to increase the hemoglobin concentration in an average-sized adult by approximately 1 gram/deciliter (g/dL) (increase hematocrit by 3%). Smaller aliquots can be made available for use with neonatal or pediatric patients, or adults with special transfusion needs.

The ABO group of all red-cell-containing components must be compatible with ABO antibodies in the recipient's plasma.

Serologic compatibility between recipient and donor must be established before any red-cell-containing component is transfused. This may be accomplished by performing ABO/Rh typing, antibody screening, and crossmatching by serologic technique or use of a computer crossmatch. In cases when delay in transfusion will be life-threatening, uncrossmatched group O RBCs or ABO group-specific RBCs may be transfused before completion of pretransfusion compatibility testing.

The initial portion of each unit transfused should be infused cautiously and with sufficient observation to detect onset of acute reactions. Thereafter, the rate of infusion can be more rapid, as tolerated by the patient's circulatory system. It is undesirable for components that contain red cells to remain at room temperature longer than 4 hours. If the anticipated infusion rate must be so slow that the entire unit cannot be infused within 4 hours, it is appropriate to order smaller aliquots for transfusion.

See Table 3 for pediatric dosage information.

Side Effects and Hazards

Hazards that pertain to all transfusion components are described in the earlier section titled Side Effects and Hazards for Whole Blood and All Blood Components. Listed below are additional hazards that apply specifically to components that contain red cells.

1. **Hemolytic transfusion reaction** is the immunologic destruction of transfused red cells, nearly always the result of incompatibility of antigen on the transfused cells with antibody in the recipient's circulation (see item 5 below for discussion of nonimmunologic hemolysis). The most common cause of severe, acute hemolytic reactions is transfusion of ABO-incompatible blood, resulting from identification errors occurring at some point(s) in the transfusion process. Serologic incompatibility undetected during pretransfusion testing is a much less common cause of acute hemolysis. If a hemolytic transfusion reaction is suspected, the transfusion must be stopped, and the transfusion service laboratory notified immediately. Information identifying the patient, the transfusion component, and associated forms and labels must be reviewed promptly to detect possible errors. A postreaction blood sample, preferably drawn from a site other than the transfusion access, must be sent to the laboratory along with the implicated unit of blood and administration set.

Table 3. Suggested Pediatric (Patients <50 kg) Dosing (adapted from Mo Y, Roseff SD, Wong ECC, eds. Pediatric hemotherapy data card. 5th ed. Bethesda, MD: AABB, 2020)

Component	Attributes	Dosage	Expected Increment
Red Blood Cells (RBCs)	CPD, CPDA-1 (65-80% Hct)	5-15 mL/kg	3 g/dL rise in Hb
	AS-1, AS-3, AS-5, AS-7 (55-65% Hct)	10-15 mL/kg	2 g/dL rise in Hb
Washed RBCs	70-80% Hct, suspended in normal saline	10-15 mL/kg	3 g/dL rise in Hb
Plasma components*	Near-normal levels of coagulation factors, citrate anticoagulant	10-15 mL/kg	15-20% rise in factor level (assume ideal recovery)
Platelets	Whole-blood-derived platelets: $\geq 5.5 \times 10^{10}$ platelets suspended in 25-50 mL of plasma	5-10 mL/kg OR 1 unit/10 kg (patients >10 kg)	50,000-100,000/µL rise in platelet count (assume ideal recovery)
	Apheresis platelets: $\geq 3.0 \times 10^{11}$ platelets in 250-300 mL plasma, equivalent to approx. 6 units of whole-blood-derived platelets	Same as above	Same as above (assume ideal recovery)
Cryoprecipitated AHF	≥150 mg fibrinogen/single donor ≥80 units Factor VIII/unit, von Willebrand Factor (vWF), Factor XIII	1-2 units /10 kg (volume of a unit will vary, maximum to 15 mL) or 2-3 mL/kg	60-100 mg/dL rise in fibrinogen
Granulocytes†	Apheresis or pooled from whole blood buffy coats	10-15 mL/kg (1×10^9 to 2×10^9 polymorphonu-clear cells/kg) for neonates. For older children, minimum of 1×10^{10} granulocytes.	None. Administered daily until an adequate neutrophil count is maintained and/or the patient shows clinical improvement.

*See Table 7 for specific components.

†Roseff SD, Luban NL, Manno CS. Guidelines for assessing appropriateness of pediatric transfusion. Transfusion 2002;42:1398-413; Wong ECC, Roseff SD, Bandarenko N, eds. Pediatric transfusion: A handbook. 5th ed. Bethesda, MD: AABB, 2020; Price TH, Boeckh M, Harrison RW, et al. Efficacy of transfusion with granulocytes from G-CSF/dexamethasone-treated donors in neutropenic patients with infection. Blood 2015;126:2153-61 In: Cohn CS, Delaney M, Johnson ST, Katz LM, eds. Technical manual. 20th ed. Bethesda, MD: AABB, 2020:688-9.

CPD = citrate-phosphate-dextrose; CPDA = citrate-phosphate-dextrose-adenine; Hct = hematocrit; Hb = hemoglobin; AS = additive solution; AHF = antihemophilic factor.

Acute hemolytic reactions characteristically begin with an increase in temperature and pulse rate; symptoms may include chills, dyspnea, chest or back pain, abnormal bleeding, or shock. Instability of blood pressure is frequent, the direction and magnitude of change depending upon the phase of the reaction and the magnitude of compensatory mechanisms. In anesthetized patients, hemoglobinuria, hypotension, and evidence of disseminated intravascular coagulopathy (DIC) may be the first signs of incompatibility. Laboratory findings can include hemoglobinemia and/or hemoglobinuria, followed by elevation of serum indirect bilirubin. The direct antiglobulin test (DAT) result is usually positive, with rare exceptions (ie, complete hemolysis of incompatible red cells). Treatment includes measures to maintain or correct arterial blood pressure; correct coagulopathy, if present; and promote or maintain renal function. Lack of symptoms does not exclude an acute hemolytic reaction.

Delayed hemolytic reactions occur in previously red-cell-alloimmunized patients in whom antigens on transfused red cells provoke anamnestic production of antibody. The anamnestic response reaches a significant circulating level while the transfused cells are still present in the circulation; the usual time frame is 2 to 14 days after transfusion. Signs may include unexplained fever, development of a positive DAT result, and unexplained decrease in hemoglobin/hematocrit. Hemoglobinemia and hemoglobinuria are uncommon, but elevation of lactate dehydrogenase or bilirubin may be noted. Most delayed hemolytic reactions have a benign course and require no treatment.

Hemolytic transfusion reactions in patients with sickle cell anemia may be particularly severe, with destruction of autologous as well as transfused red cells, resulting in a lower hemoglobin level after transfusion. This is suggestive of hyperhemolysis syndrome. In such patients, serologic investigations may not reveal the specificity of the causative antibody. Immediate treatment may include steroid use, IVIG, and avoiding transfusions, if possible. Consultation with a transfusion medicine specialist is required in these cases. Prospective matching for Rh and Kell antigens may decrease risk.

2. Antigens on transfused red cells may cause red cell **alloimmunization** of the recipient. Clinically significant antibodies to red cell antigens will usually be detected in pretransfusion antibody screening tests. For most patients, red cell antigen matching beyond ABO and Rh is unnecessary.
3. **TACO** can accompany transfusion of any component at a rate more rapid than the recipient's cardiac output can accommodate. Patients with chronic anemia have increased plasma volumes and are at increased risk for circulatory overload.
4. **Iron overload** is a complication of chronic RBC transfusion therapy. Each transfusion contributes approximately 250 milligrams (mg) of iron and significant accumulation can occur after 10 to 20 RBC transfusions. Patients requiring multiple transfusions due to decreased red cell production or increased RBC destruction are at far greater risk than patients transfused for hemorrhagic indications, because blood loss is an effective means of iron excretion. Patients with predictably chronic transfusion requirements should be considered for treatment with iron-chelating agents, a program of exchange transfusion therapy, or therapeutic phlebotomy, if applicable.
5. **Nonimmunologic hemolysis** occurs rarely but can result from: 1) introduction of hypotonic fluids into the circulation; 2) effects of drugs coadministered with transfusion; 3) effects of bacterial toxins; 4) thermal injury by freezing or overheating; 5) metabolic damage to cells, as from hemoglobinopathies or enzyme deficiencies; or 6) mechanical injury or osmotic stresses. Examples of situations capable of causing nonimmune red cell hemolysis include exposure to excessive heat when using warming devices not cleared or approved by FDA,

mixture of blood with hypotonic solutions, or transfusion under high pressure through small-gauge or defective needles.

Components Available

RED BLOOD CELLS are prepared from blood collected into any of the anticoagulant-preservative solutions approved by the FDA and separated from the plasma by centrifugation or sedimentation. Separation may be done at any time during the allowable shelf life. RBCs may contain from 160 to 275 mL of red cells (50-80 g of hemoglobin) suspended in varying quantities of residual plasma.

RED BLOOD CELLS ADENINE SALINE ADDED are prepared by centrifuging Whole Blood to remove as much plasma as possible and replacing the plasma with usually 100 to 110 mL of an AS that contains some combination (see Table 2) of dextrose, adenine, sodium chloride, sodium bicarbonate, monobasic or dibasic sodium phosphate, or mannitol; the hematocrit is usually between 55% and 65%. RBCs in an AS have lower viscosity than RBCs, and flow through administration systems in a manner more comparable to that of Whole Blood. RBCs stored with an AS have an extended shelf life.

RED BLOOD CELLS LEUKOCYTES REDUCED and RED BLOOD CELLS ADENINE SALINE ADDED LEUKOCYTES REDUCED are prepared from a unit of Whole Blood (collected in anticoagulant-preservative solution as noted above) containing ≥1 to 10×10^9 white cells. In general, leukocyte reduction is achieved by filtration: 1) soon after collection (prestorage) or 2) after varying periods of storage in the laboratory. Leukocyte reduction will decrease the cellular content and volume of blood according to characteristics of the filter system used. RBCs Leukocytes Reduced must have a residual content of leukocytes $<5.0 \times 10^6$. Leukocyte reduction filters variably remove other cellular elements in addition to white cells. The leukocyte-reduced component contains ≥85% of the original red cell content.

APHERESIS RED BLOOD CELLS are red cells collected by apheresis. This component must be collected in an approved anticoagulant. The red cell volume collected, and the anticoagulant used are noted on the label. Aside from the automated collection method used, the component is comparable to whole-blood-derived RBCs in all aspects. The dose can be calculated, as for RBCs, from the red cell content of the product. Apheresis RBCs contain approximately 60 g of hemoglobin per unit.

APHERESIS RED BLOOD CELLS LEUKOCYTES REDUCED and APHERESIS RED BLOOD CELLS ADENINE SALINE ADDED LEUKOCYTES REDUCED are collected by apheresis methods. Leukocyte reduction is achieved by filtration during the manufacturing process resulting in a final product containing $<5.0 \times 10^6$ leukocytes and ≥85% of the target red cell content.

RED BLOOD CELLS, LOW VOLUME are prepared when 300 to 404 mL of Whole Blood is collected into an anticoagulant volume calculated for 450 mL ± 45 mL or when 333 to 449 mL of Whole Blood is collected into an anticoagulant volume calculated for 500 mL ± 50 mL. These products reflect a collection with an altered ratio of anticoagulant to red cells and may not be an indication of a lower dose of hemoglobin. Plasma and platelet components should not be prepared from low-volume collections.

FROZEN RED BLOOD CELLS and FROZEN REJUVENATED RED BLOOD CELLS are prepared by adding glycerol to red cells as a cryoprotective agent before freezing at -65 C or colder. The glycerol must be removed from the thawed component before it is infused. Frozen RBCs can be stored for up to 10 years. Some rare units may be stored frozen beyond 10 years, provided there is exceptional medical need for the units. Frozen storage is especially suitable for red cells with unusual antigenic phenotypes.

DEGLYCEROLIZED RED BLOOD CELLS is the form in which cryopreserved red cells (Frozen RBCs) are made available for infusion. Glycerol is added to red cells as a cryoprotective agent before freezing and must be removed from the thawed component before it is infused.

Deglycerolized RBCs contain 80% or more of the red cells present in the original unit of blood and have approximately the same expected posttransfusion survival as RBCs. Glycerol is removed by washing the cells with successively lower concentrations of Sodium Chloride, Injection USP; the final suspension is in 0.9% Sodium Chloride, Injection USP, with or without small amounts of dextrose. Small amounts of residual-free hemoglobin may cause the supernatant fluid to be pink-tinged.

Deglycerolized RBCs provide the same physiologic benefits as RBCs, but their use is usually restricted to situations in which standard transfusion components are inappropriate or unavailable. Deglycerolized RBCs may be useful for transfusions to patients with previous severe allergic transfusion reactions because the process efficiently removes plasma constituents.

In addition to the side effects and hazards of RBC transfusion, Deglycerolized RBCs carry a risk of intravascular hemolysis if deglycerolization has been inadequate.

Deglycerolized RBCs must be transfused within 24 hours after thawing if prepared in an open system. If prepared in a closed system, they can be stored at 1-6 C and infused within a 2-week interval after thawing and as directed by the manufacturer's instructions for use.

REJUVENATED RED BLOOD CELLS may be prepared from red cells stored at 1-6 C and prepared with citrate-phosphate-dextrose (CPD) and CPD Adenine Solution (CPDA-1) up to 3 days after expiration. RBCs stored in CPD/AS-1 or CP2D/AS-3 may be rejuvenated up to, but not exceeding 42 days of uninterrupted storage at 1-6 C. Addition of an FDA-approved solution containing inosine, phosphate, and adenine restores 2,3-diphosphoglycerate and adenosine triphosphate to levels approximating those of freshly drawn cells. These products must be washed before infusion to remove the inosine, which may be toxic. Rejuvenated RBCs may be prepared and transfused within 24 hours or frozen for long-term storage.

DEGLYCEROLIZED REJUVENATED RED BLOOD CELLS is the form in which rejuvenated, cryopreserved red cells (Frozen Rejuvenated RBCs) are made available for infusion. For additional information, see sections on Rejuvenated RBCs and Deglycerolized RBCs above.

Plasma Components

Overview

Plasma is the fluid part of blood and can be derived from the separation of a whole blood collection or by apheresis collection. Important elements in plasma include albumin, coagulation factors, fibrinolytic proteins, immunoglobulin, and other proteins. Once plasma is collected, it can be maintained in the liquid state or stored frozen and subsequently thawed and kept in a liquid state. If Fresh Frozen Plasma (FFP) is thawed at 1 to 6 C, and the insoluble cryoprecipitate (see Cryoprecipitated Components) is removed by centrifugation, the supernatant plasma can be refrozen and labeled as Plasma Cryoprecipitate Reduced. Labile coagulation factor levels vary based upon ABO group, storage conditions, and/or further processing (see Tables 4 and 5).

Refer to the Section on **Further Processing** for additional information on:

- Pathogen Reduction Technology and Components Available

Refer to the Section on **Additional Testing** for additional information on:

- Identification of Low Titer anti-A and/or anti-B Blood Products

Fresh Frozen Plasma

Description

FFP is prepared from a whole blood or apheresis collection and frozen at –18 C or colder within the time frame as specified in the manufacturer's instructions for use of the blood collection, processing, and storage system. The anticoagulant solution used, and the component volume are indicated on the label. On average, units contain 200 to 250 mL, but apheresis-derived units may contain as much as 400 to 600 mL. FFP contains plasma proteins, including all coagulation factors. FFP contains normal levels of the labile coagulation factors, Factors V and VIII.

FFP should be infused immediately after thawing or stored at 1 to 6 C. After 24 hours, the component must be discarded or, if collected in a functionally closed system, may be relabeled as Thawed Plasma Ω (see Thawed Plasma).

Actions

FFP serves as a source of plasma proteins for patients who are deficient in or have defective plasma proteins.

Indications

FFP is indicated in the following conditions:

1. Management of preoperative or bleeding patients who require replacement of multiple plasma coagulation factors (eg, liver disease, DIC).
2. Patients undergoing massive transfusion who have clinically significant coagulation deficiencies.
3. Patients taking warfarin who are bleeding or need to undergo an invasive procedure before vitamin K could reverse the warfarin effect or who need only transient reversal of warfarin effect.
4. Transfusion or plasma exchange in patients with thrombotic thrombocytopenic purpura (TTP).
5. Management of patients with selected coagulation factor deficiencies, congenital or acquired, for which no specific coagulation concentrates are available.
6. Management of patients with rare specific plasma protein deficiencies, such as C1 inhibitor, when recombinant products are unavailable.

Contraindications

1. When coagulopathy can be corrected more effectively with specific therapy, such as vitamin K and prothrombin complex concentrate (PCC) for urgent Vitamin K Antagonist (VKA) reversal, Cryoprecipitated AHF or Pathogen-Reduced Cryoprecipitated Fibrinogen Complex for hypofibrinogenemia, or specific coagulation factor concentrates when available. Specific reversal agents should be used for non-VKA anticoagulants (eg, Idarucizumab for Dabigatran or Andexanet for Factor Xa inhibitors such as rivaroxaban- and apixaban-related life-threatening bleeding).
2. When blood volume can be safely and adequately replaced with other volume expanders.

Relative Contraindications

1. To correct a minimally elevated international normalized ratio (INR). An INR value between 1.5 - 1.7 represents at least 30% of coagulation factor levels, which should allow for normal hemostasis. Transfusion of a standard dose of plasma [~15 mL/kilogram (kg)] to a patient with an INR of 1.7 may not normalize the INR.

Table 4. Coagulation Factor Activity in FFP and PF24 (wholeblood) at the Time of Thaw and after 120 Hours of 1 to 6 C Storage (adapted from Table 1. Scott EA, et al. Transfusion 2009;49:1584-91)

Analyte	Thaw, mean ± SD (range) by product		120 hr, mean (range) by product		% Change after 120 hr at 1 to 6 C	
	FFP (n=20)	PF24 (n=14)*	FFP (n=20)	PF24 (n=14)*	FFP	PF24
FII (IU/dL)	97 ± 10 (83-125)	97 ± 8 (80-113)	95 ± 10 (82-126)	96 ± 11 (74-120)	3‡	1
FV (U/dL)	85 ± 13 (63-104)	86 ± 16 (54-124)	67 ± 19 (17-92)	59 ± 22 (15-109)	21‡	31‡
FVII (IU/dL)	105 ± 25 (50-163)	89 ± 22 (54-145)	70 ± 18 (34-102)	77 ± 27 (50-159)	33‡	14‡
FVIII (IU/dL)§	81 ± 19 (47-117)	66 ± 17 (30-100)†	43 ± 10 (27-60)	48 ± 12 (26-73)	47‡	28‡
F IX (IU/dL)	82 ± 13 (62-108)	88 ± 13 (70-105)	80 ± 12 (64-107)	84 ± 12 (65-99)	2	4‡
FX (IU/dL)	94 ± 10 (71-112)	94 ± 11 (72-112)	87 ± 11 (65-111)	91 ± 12 (67-114)	7‡	3‡
vWF:Ag (IU/dL)§	98 ± 27 (57-156)	132 ± 41 (78-211)	97 ± 30 (48-150)	127 ± 40 (79-224)	1	4
vWF:RCo (IU/dL)§	101 ± 26 (61-152)	123 ± 47 (58-238)	93 ± 30 (48-149)	102 ± 38 (50-191)	8‡	17‡
Fibrinogen (mg/dL)	280 ± 52 (223-455)	309 ± 70 (211-500)	278 ± 50 (223-455)	303 ± 50 (205-490)	1	2‡
Antithrombin (IU/dL)	97 ± 9 (85-118)	97 ± 11 (77-110)	100 ± 10 (85-131)	101 ± 14 (73-116)	3	4‡
Protein C (IU/dL)	107 ± 20 (74-148)	88 ± 16 (65-120)†	107 ± 19 (77-148)	89 ± 17 (65-115)†	0	2
Protein S (IU/dL)	97 ± 18 (61-123)	92 ± 18 (54-121)	90 ± 22 (52-134)	78 ± 19 (46-114)†	7‡	15‡

*N = 25 for FII, FV, FVIII, fibrinogen, vWF:RCo, and Protein S.
†p <0.05 compared with mean activity in FFP of the same age.
‡p <0.05 when comparing mean activity at thaw to mean activity after 120 hours of 1 to 6 C storage.
§Only results from group O products were used for statistical comparisons of Factor VIII, vWF:Ag, and vWF:RCo activities.
FFP = Fresh Frozen Plasma; PF24 = Plasma Frozen Within 24 Hours After Phlebotomy; SD = standard deviation; FII = Factor II; vWF:Ag = von Willebrand Factor antigen; vWF:RCo = von Willebrand Factor ristocetin cofactor.

Table 5. Statistically Significantly Different Coagulation Factor Activity in FFP and PF24RT24 (apheresis) after 24 Hours at 1 to 6 C Storage after Thawing [adapted from Tables 2 and 3 of the 102nd Meeting of the Blood Products Advisory Committee (May 16, 2012)]

	Sponsor A			Sponsor B		
	Mean ± SD (range) by product		Mean difference:	Mean ± SD (range) by product		Mean difference:
Analyte	FFP (n=52)	PF24RT24 (n=52)	PF24RT24 – FFP (95% CLs)	FFP (n=54)	PF24RT24 (n=54)	PF24RT24-FFP (95% CLs)
FV (IU/dL)	101 ± 18 (52-138)	100 ± 17 (52-136)	–1.1 (–2.1, –0.1)*	90 ± 19 (35-136)	89 ± 18 (35-131)	–1.0 (–2.6, 0.6)
FVIII (IU/dL)	81 ± 25 (37-163)	73 ± 24 (36-157)	–7.3 (–9.4, –5.2)†	99 ± 32 (49-193)	86 ± 27 (40-156)	–13.2 (–16.0, –10.5)†
Protein S (IU/dL)	94 ± 20 (53-161)	83 ± 19 (48-145)	–10.6 (–12.7, –8.5)†	82 ± 18 (29-124)	73 ± 14 (47-109)	–9.0 (–11.7, –6.2)†

*p = <0.05.
†p = <0.0001.
FFP = Fresh Frozen Plasma; PF24RT24 = Plasma Frozen Within 24 Hours After Phlebotomy Held At Room Temperature Up To 24 Hours After Phlebotomy; SD = standard deviation; CLs = confidence limits; FV = Factor V.

Dosage and Administration

Compatibility tests prior to transfusion are not necessary. Plasma must be ABO compatible with the recipient's red cells. Compatibility with RhD is not necessary in plasma transfusion. The volume transfused depends on the clinical situation and patient size, and may be guided by laboratory assays of coagulation function.

FFP must be thawed in a water bath at 30 to 37 C or in an FDA-cleared device. If a water bath is used, thaw the component in a protective plastic overwrap using gentle agitation.

See Table 3 for pediatric dosage information.

Side Effects and Hazards

Do not use FFP if there is evidence of container breakage or of thawing during storage.

Hazards that pertain to all transfusion components, including FFP, are described in the earlier section on Side Effects and Hazards for Whole Blood and All Blood Components.

Components Available

FRESH FROZEN PLASMA

APHERESIS FRESH FROZEN PLASMA

Plasma Frozen Within 24 Hours After Phlebotomy

Description

Plasma Frozen Within 24 Hours After Phlebotomy (PF24) is prepared from a whole blood or apheresis collection. The anticoagulant solution used, and the component volume are indicated on the label. On average, PF24 contains 200 to 250 mL, but apheresis-derived units may contain as much as 400 to 600 mL. This plasma component is a source of nonlabile plasma proteins. Plasma proteins such as albumin; a disintegrin and metalloprotease with thrombospondin type 1 motifs 13 (ADAMTS13); fibrinogen; and Factors II, VII, IX, X, and XI remain at levels similar to FFP. Levels of Factor VIII and Protein C are reduced, and levels of Factor V and other labile plasma proteins are variable compared with FFP.

PF24 should be infused immediately after thawing or stored at 1 to 6 C. After 24 hours' storage, the component must be discarded or, if collected in a functionally closed system, may be relabeled as Thawed Plasma Ω (see Thawed Plasma).

Actions

PF24 serves as a source of nonlabile plasma proteins for patients who are deficient in or have defective plasma proteins. Some coagulation factor levels may be lower than those of FFP, especially labile coagulation Factors V, VIII, and Protein C.

Indications

For Plasma Frozen Within 24 Hours After Phlebotomy *Indications* see Fresh Frozen Plasma *Indications*, page 20.

Contraindications

For Plasma Frozen Within 24 Hours After Phlebotomy *Contraindications* see Fresh Frozen Plasma *Contraindications* and *Relative Contraindication*, page 20. In addition, this product is not indicated for treatment of deficiencies of labile coagulation factors, including Factors V and VIII, and Protein C.

Dosage and Administration

For Plasma Frozen Within 24 Hours After Phlebotomy *Dosage and Administration* see Fresh Frozen Plasma *Dosage and Administration*, page 23.

Side Effects and Hazards
For Plasma Frozen Within 24 Hours After Phlebotomy *Side Effects and Hazards* see Fresh Frozen Plasma *Side Effects and Hazards*, page 23.

Components Available
PLASMA FROZEN WITHIN 24 HOURS AFTER PHLEBOTOMY is prepared from a whole blood collection and must be separated and placed at –18 C or colder within 24 hours from whole blood collection.

APHERESIS PLASMA FROZEN WITHIN 24 HOURS AFTER PHLEBOTOMY is prepared from apheresis and stored at 1 to 6 C within 8 hours of collection and frozen at –18 C or colder within 24 hours of collection.

Plasma Frozen Within 24 Hours After Phlebotomy Held At Room Temperature Up To 24 Hours After Phlebotomy

Description
Plasma Frozen Within 24 Hours After Phlebotomy Held At Room Temperature Up To 24 Hours After Phlebotomy (PF24RT24) is prepared from whole blood or an apheresis collection. The product can be held at room temperature for up to 24 hours after collection and then frozen at –18 C or colder. The anticoagulant solution used, and the component volume are indicated on the label. On average, PF24RT24 contains 200 to 250 mL, but apheresis-derived units may contain as much as 400 to 600 mL. This plasma component is a source of nonlabile plasma proteins. Plasma proteins such as albumin; ADAMTS13; fibrinogen; and Factors II, VII, IX, X, and XI remain at levels similar to FFP. Levels of Factor V, Factor VIII, and Protein S are reduced, and levels of other labile plasma proteins are variable compared with FFP.

PF24RT24 should be infused immediately after thawing or stored at 1 to 6 C. After 24 hours, the component must be discarded or, if collected in a functionally closed system, may be relabeled as Thawed Plasma Ω (see Thawed Plasma).

Actions
This plasma component serves as a source of nonlabile plasma proteins for patients who are deficient in or have defective plasma proteins. Some coagulation factor levels may be lower than those of FFP, especially labile coagulation Factors V and VIII, and Protein S.

Indications
For Plasma Frozen Within 24 Hours After Phlebotomy Held At Room Temperature Up To 24 Hours After Phlebotomy *Indications* see Fresh Frozen Plasma *Indications*.

Contraindications
For Plasma Frozen Within 24 Hours After Phlebotomy Held At Room Temperature Up To 24 Hours After Phlebotomy *Contraindications* see Fresh Frozen Plasma *Contraindications* and *Relative Contraindications*. In addition, this product is not indicated for treatment of deficiencies of labile coagulation factors, including Factors V and VIII, and Protein S.

Dosage and Administration
For Plasma Frozen Within 24 Hours After Phlebotomy Held At Room Temperature Up To 24 Hours After Phlebotomy *Dosage and Administration* see Fresh Frozen Plasma *Dosage and Administration*.

Side Effects and Hazards
For Plasma Frozen Within 24 Hours After Phlebotomy Held At Room Temperature Up To 24 Hours After Phlebotomy *Side Effects and Hazards* see Fresh Frozen Plasma *Side Effects and Hazards*.

Components Available
PLASMA FROZEN WITHIN 24 HOURS AFTER PHLEBOTOMY HELD AT ROOM TEMPERATURE UP TO 24 HOURS AFTER PHLEBOTOMY

APHERESIS PLASMA FROZEN WITHIN 24 HOURS AFTER PHLEBOTOMY HELD AT ROOM TEMPERATURE UP TO 24 HOURS AFTER PHLEBOTOMY

Plasma Cryoprecipitate Reduced

Description
Plasma Cryoprecipitate Reduced is prepared from whole-blood-derived or apheresis-collected FFP (frozen at –18 C or colder within 8 hours of collection) after thawing and centrifugation and removal of the cryoprecipitate. The remaining product is plasma that is reduced in fibrinogen, Factor VIII, Factor XIII, vWF and cryoglobulin. This supernatant plasma must be refrozen within 24 hours of thawing at –18 C or colder. Proteins such as albumin, ADAMTS13, and Factors II, V, VII, IX, X, and XI remain in levels similar to FFP. High-molecular-weight forms of vWF (multimers) are significantly decreased during production; however, smaller multimers are retained.

Plasma Cryoprecipitate Reduced should be infused immediately after thawing or stored at 1 to 6 C. This product can be stored at 1 to 6 C for up to 4 days after the initial 24-hour postthaw period has elapsed, but must be relabeled as Thawed Plasma Cryoprecipitate Reduced Ω.

Actions
This component serves as a source for plasma proteins except for fibrinogen, Factor VIII, Factor XIII, and vWF.

Indications
Plasma Cryoprecipitate Reduced is used for transfusion or plasma exchange in patients with TTP. It may be used to provide clotting factors except fibrinogen, Factor VIII, Factor XIII, and vWF for transfusion support of patients with appropriate clinical indications when specific plasma concentrates and/or other plasma products are not available.

Contraindications
Plasma Cryoprecipitate Reduced is contraindicated for the repletion of coagulation factors known to be depleted in this product: fibrinogen, vWF, Factor VIII, and Factor XIII. This component should not be used as a substitute for FFP, PF24, PF24RT24 or Thawed Plasma.

Dosage and Administration
For Plasma Cryoprecipitate Reduced *Dosage and Administration* see Fresh Frozen Plasma *Dosage and Administration*, page 23.

Side Effects and Hazards
For Plasma Cryoprecipitate Reduced *Side Effects and Hazards* see Fresh Frozen Plasma *Side Effects and Hazards*, page 24.

Components Available
PLASMA CRYOPRECIPITATE REDUCED

APHERESIS PLASMA CRYOPRECIPITATE REDUCED

Thawed Plasma Ω

Description
Thawed Plasma is derived from FFP, PF24, or PF24RT24 prepared using aseptic techniques (functionally closed system). It is thawed at 30 to 37 C and maintained at 1 to 6 C for up to 4 days after the initial 24-hour postthaw period has elapsed. The volume is indicated on the label. Thawed Plasma contains stable coagulation factors such as Factor II and fibrinogen in concentrations clinically similar to those of FFP, but variably reduced amounts of other factors (see Table 4).

Actions
This component serves as a source of nonlabile plasma proteins. Levels and activation state of coagulation proteins in thawed plasma are variable and change over time.

Indications
For Thawed Plasma *Indications* see Fresh Frozen Plasma *Indications,* page 20.

Contraindications
For Thawed Plasma *Contraindications* see Fresh Frozen Plasma *Contraindications* and *Relative Contraindications*. Do not use Thawed Plasma as the treatment for isolated coagulation factor or specific plasma protein deficiencies where other products are available with higher concentrations of the specific factor(s) or proteins.

Dosage and Administration
For Thawed Plasma *Dosage and Administration,* see Fresh Frozen Plasma *Dosage and Administration,* page 23.

Side Effects and Hazards
For Thawed Plasma *Side Effects and Hazards,* see Fresh Frozen Plasma *Side Effects and Hazards*, page 23.

Components Available
THAWED PLASMA Ω

Thawed Plasma Cryoprecipitate Reduced Ω

Description
Thawed Plasma Cryoprecipitate Reduced is derived from Plasma Cryoprecipitate Reduced. It is thawed at 30 to 37 C and maintained at 1 to 6 C for up to 4 days after the initial 24-hour postthaw period has elapsed. The volume is indicated on the label. Thawed Plasma Cryoprecipitate Reduced is deficient in fibrinogen, Factor VIII, Factor XIII, vWF, and cryoglobulin, and contains variable levels of albumin, ADAMTS13, and Factors II, V, VII, IX, X, and XI.

Actions
For Thawed Plasma Cryoprecipitate Reduced *Actions,* see Plasma Cryoprecipitate Reduced *Actions,* page 25.

Indications
For Thawed Plasma Cryoprecipitate Reduced *Indications,* see Plasma Cryoprecipitate Reduced *Indications* page 25.

Contraindications
For Thawed Plasma Cryoprecipitate Reduced *Contraindications,* see Plasma Cryoprecipitate Reduced *Contraindications,* page 25.

Dosage and Administration
For Thawed Plasma Cryoprecipitate Reduced *Dosage and Administration,* see Fresh Frozen Plasma *Dosage and Administration* page 23.

Side Effects and Hazards
For Thawed Plasma Cryoprecipitate Reduced *Side Effects and Hazards,* see Fresh Frozen Plasma *Side Effects and Hazards,* page 23.

Components Available
THAWED PLASMA CRYOPRECIPITATE REDUCED Ω

Liquid Plasma

Description
Liquid Plasma is prepared from Whole Blood and stored at 1-6 C. Liquid Plasma expires 5 days from the end of the Whole Blood dating period.

The profile and activity of plasma proteins involved in coagulation of Liquid Plasma are not completely characterized. Levels and activation state of coagulation proteins in Liquid Plasma are dependent upon and change with time in contact with cells, as well as the conditions and duration of storage. This product contains viable lymphocytes that may cause graft-versus-host reactions in susceptible patients.

Actions
This component serves as a source of plasma proteins. Levels and activation state of coagulation proteins are variable and change over time.

Indications
Liquid Plasma is indicated for the initial treatment of patients who are undergoing massive transfusion because of life-threatening trauma/hemorrhages and who have clinically significant coagulation deficiencies.

Contraindications
For Liquid Plasma *Contraindications,* see Fresh Frozen Plasma *Contraindications*. Do not use Liquid Plasma as the treatment for coagulation factor deficiencies where other products are available with higher factor concentrations.

Dosage and Administration
For Liquid Plasma *Dosage and Administration,* see Fresh Frozen Plasma *Dosage and Administration,* page 23.

Side Effects and Hazards
For Liquid Plasma *Side Effects and Hazards,* see Fresh Frozen Plasma *Side Effects and Hazards,* page 23.

Components Available
LIQUID PLASMA

Cryoprecipitated Antihemophilic Factor

Description
Cryoprecipitated Antihemophilic Factor (AHF) is prepared by thawing whole-blood-derived or apheresis FFP between 1 and 6 C and recovering the precipitate. The cold-insoluble precipitate is

placed in the freezer at –18 C or colder within 1 hour after removal from the refrigerated centrifuge. Cryoprecipitated AHF contains fibrinogen, Factor VIII, Factor XIII, and vWF. Each unit of Cryoprecipitated AHF should contain ≥80 International Units (IU) of Factor VIII and ≥150 mg of fibrinogen in approximately 5 to 20 mL of plasma.

If the label indicates "Pooled Cryoprecipitated AHF," several units of Cryoprecipitated AHF have been pooled. The volume of the pool is indicated on the label and, if used, the volume of 0.9% Sodium Chloride, Injection USP may be separately listed. To determine the minimum potency of this component, assume 80 IU of Factor VIII and 150 mg of fibrinogen for each unit of Cryoprecipitated AHF indicated on the label.

Actions

Cryoprecipitate serves as a source of fibrinogen, Factor VIII, Factor XIII, and vWF.

Indications

This component is used in the control of bleeding associated with fibrinogen deficiency, and when recombinant and/or virally inactivated preparations of fibrinogen, Factor VIII, Factor XIII, or vWF are not readily available. It is also indicated as second-line therapy for von Willebrand disease (vWD) and hemophilia A (Factor VIII deficiency). Coagulation factor preparations other than Cryoprecipitated AHF are preferred for management of vWD, Factor VIII deficiency, and Factor XIII deficiency. Every effort must be made to obtain preferred factor concentrates for hemophilia A patients before resorting to the use of Cryoprecipitated AHF. Use of this component may be considered for control of uremic bleeding after other modalities have failed.

Contraindications

Do not use this component unless results of laboratory studies indicate a specific hemostatic defect for which this product is indicated. Cryoprecipitated AHF should not be used if virus-inactivated specific factor concentrates or recombinant factor preparations are available for management of patients with vWD, hemophilia A, or Factor XIII deficiency.

Dosage and Administration

Compatibility testing is unnecessary. ABO-compatible material is preferred. Rh type need not be considered when using this component.

The frozen component is thawed in a protective plastic overwrap in a water bath at 30 to 37 C up to 15 minutes (thawing time may be extended if product is pooled before freezing). This component should not be given if there is evidence of container breakage or of thawing during storage. Do not refreeze after thawing. Thawed Cryoprecipitated AHF should be kept at room temperature and transfused as soon as possible after thawing, within 6 hours if it is a single unit (from an individual donor, or products pooled before freezing or prior to administration using an FDA-cleared sterile connecting device), and within 4 hours after entering the container (eg, to attach an administration set or to pool) without using an FDA-cleared sterile connecting device.

Cryoprecipitated AHF may be transfused as individual units or pooled. For pooling, the precipitate in one or more concentrates should be mixed well with 10 to 15 mL of diluent to ensure complete removal of all material from the container. The preferred diluent is 0.9% Sodium Chloride, Injection USP. Serial use of each bag's contents to resuspend the precipitate into subsequent bags may be used to efficiently pool cryoprecipitate into a single bag.

The recovery of transfused fibrinogen is 50% to 60%. When used to correct hypofibrinogenemia, Cryoprecipitated AHF may be dosed at one bag per 7 to 10 kg body weight to raise plasma fibrinogen by approximately 50 to 75 mg/dL. Thrombosis alters fibrinogen kinetics; therefore, patients receiving cryoprecipitate as fibrinogen replacement in conditions associated with increased fibrinogen turnover should be monitored with fibrinogen assays.

For treatment of bleeding in patients with hemophilia A when Factor VIII concentrates are not available, rapid infusion of a loading dose expected to produce the desired level of Factor VIII is usually followed by a smaller maintenance dose every 8 to 12 hours. To maintain hemostasis after surgery, a regimen of therapy for 10 days or longer may be required. If circulating antibodies to Factor VIII are present, the use of larger doses, activated concentrates, porcine-derived concentrates, or other special measures may be indicated. To calculate cryoprecipitate dosage as a source of Factor VIII, the following formula is helpful: Number of bags = (Desired increase in Factor VIII level in % × 40 × body weight in kg) / average units of Factor VIII per bag. Good patient management requires that the Cryoprecipitated AHF treatment responses of Factor VIII-deficient recipients be monitored with periodic plasma Factor VIII assays.

For treatment of vWD, smaller amounts of Cryoprecipitated AHF will correct the bleeding time. Because the vWF content of Cryoprecipitated AHF is not usually known, an empiric dose of 1 bag per 10 kg of body weight has been recommended. Patients receiving this treatment should be monitored by appropriate laboratory studies to determine the frequency of Cryoprecipitated AHF administration.

See Table 3 for pediatric dosage information.

Side Effects and Hazards

Hazards that pertain to all transfusion components are described in the earlier section on Side Effects and Hazards for Whole Blood and All Blood Components.

If a large volume of ABO-incompatible Cryoprecipitated AHF is used, the recipient may develop a positive DAT.

Components Available

CRYOPRECIPITATED AHF

APHERESIS CRYOPRECIPITATED AHF

POOLED CRYOPRECIPITATED AHF

Platelet Components

Overview

Platelet transfusions are administered to treat patients with thrombocytopenia, dysfunctional platelet disorders, active platelet-related bleeding, or administered prophylactically to patients at serious risk of bleeding. This section applies to all platelet components stored at room temperature 20-24 C, in plasma or platelet additive solution (PAS), including platelets manufactured by automated methods (apheresis platelets), as well as whole-blood-derived single and pooled (prestorage and poststorage) platelet components.

Refer to the Section on **Further Processing** for additional information on

- Pathogen Reduction Technology and Components Available
- Leukocyte Reduction
- Irradiation
- Washing and Volume Reduction

Refer to the Section on **Additional Testing** for additional information on:

- Identification of CMV-Seronegative Blood
- Identification of Low Titer anti-A and/or anti-B Blood Products

Description

Platelets for transfusion are manufactured using automated collection by apheresis ("Apheresis Platelets") or from whole blood collections ("WBD platelets"). One unit of WBD platelets typically contains $\geq 5.5 \times 10^{10}$ platelets suspended in 40 to 70 mL of plasma. WBD platelets may be transfused as single units or as a pool. WBD platelets may be pooled prestorage using a closed system or poststorage using an open system. A pool of approximately 6 units of WBD platelets is considered the therapeutic equivalent of one unit of apheresis platelets which usually contains $\geq 3.0 \times 10^{11}$ platelets.

Platelet components may contain a varying number of leukocytes depending upon the manufacturing method. Some units may contain more than the trace amounts of red cells usually present and will appear pink to salmon in color. This occurs more frequently with WBD platelets than with apheresis platelets.

Platelet products are stored at room temperature, 20-24 C with continuous gentle agitation. Platelet products stored in plasma at room temperatures contain near-normal levels of stable coagulation factors.

To control the risk of bacterial contamination, platelets are either pathogen reduced or tested for bacteria. FDA has provided recommendations for bacterial risk control strategies in the December 2020 Final Guidance, "Bacterial Risk Control Strategies for Blood Collection Establishments and Transfusion Services to Enhance the Safety and Availability of Platelets for Transfusion. Based on the strategy used, platelets may either have a 5-, 6-, or 7-day expiration. Note that certain testing strategies may require secondary testing prior to transfusion.

For more information on bacterial contamination risk refer to *Side Effects and Hazards* section below and FDA Guidance titled "Bacterial Risk Control Strategies for Blood Collection Establishments and Transfusion Services to Enhance the Safety and Availability of Platelets for Transfusion."

Actions

Platelets are essential for normal hemostasis. Complex reactions occur between platelets, vWF, collagen in the walls of disturbed vasculature, phospholipids, and soluble coagulation factors, including thrombin. These changes induce platelet adherence to vessel walls and platelet activation, which leads to platelet aggregation and formation of a primary hemostatic plug. The therapeutic goal of platelet transfusion is to provide adequate numbers of normally functioning platelets for the prevention or cessation of bleeding.

Indications

Platelet transfusions may be given to patients with thrombocytopenia, dysfunctional platelet disorders (congenital, metabolic, or medication-induced), or active platelet-related bleeding, or patients at serious risk of bleeding (ie, prophylactic use). Patients with the following medical conditions may require platelet transfusion: leukemia, myelodysplasia, aplastic anemia, solid tumors, congenital or acquired platelet dysfunction, and central nervous system trauma. Patients undergoing extracorporeal membrane oxygenation or cardiopulmonary bypass may also need platelet transfusion, and platelets may be indicated in massive transfusion protocols. Thrombocytopenia is unlikely to be the cause of bleeding in patients with platelet counts of at least 50,000/microliter (μL). Higher transfusion thresholds may be appropriate for patients with platelet dysfunction. For the clinically stable patient with an intact vascular system and normal platelet function, prophylactic platelet transfusions may be appropriate at <5,000 to 10,000/μL.

Prophylactic platelet transfusion may not be of therapeutic benefit when thrombocytopenia is related to destruction of circulating platelets secondary to autoimmune disorders [eg, immune thrombocytopenic purpura (ITP)]; however, transfusion may be indicated for active bleeding in these patients.

Platelets Leukocytes Reduced or Apheresis Platelets Leukocytes Reduced are indicated to decrease the frequency of recurrent febrile nonhemolytic transfusion reaction, HLA alloimmunization, and transfusion-transmitted CMV infection (see sections on **Further Processing** and **Additional Testing).**

Contraindications

Do not use this component if bleeding is unrelated to decreased numbers of, or abnormally functioning, platelets. Platelets should not be transfused when the platelet count is greater than 100,000/µL unless there is documented or suspected abnormal function. Prophylactic transfusion is generally not indicated in nonbleeding patients on antiplatelet medications, or when platelet dysfunction is extrinsic to the platelet, such as in uremia, certain types of vWD, and hyperglobulinemia. Patients with congenital surface glycoprotein defects should be transfused conservatively to reduce the possibility for alloimmunization to the missing protein(s).

Do not use in patients with activation or autoimmune destruction of endogenous platelets, such as in heparin-induced thrombocytopenia (HIT), TTP, or ITP, unless the patient has a life-threatening hemorrhage.

Dosage and Administration

Compatibility testing is not necessary in routine platelet transfusion. Except in unusual circumstances, the donor plasma should be ABO compatible with the recipient's red cells when this component is to be transfused to infants, or when large volumes are to be transfused. The number of platelet units to be administered depends on the clinical situation of each patient. An apheresis platelet unit, transfused to an average-sized relatively healthy recipient, would be expected to result in a 1-hour posttransfusion increase in platelet count of approximately 30,000 to 60,000/uL. One unit of WBD platelets would be expected to increase the platelet count of a 70-kg adult by 5000 to 10,000/µL and increase the count of an 18-kg child by 20,000/µL. The therapeutic adult dose is 1 unit of apheresis platelets or 6 units of WBD platelets, either of which usually contains $\geq 3.0 \times 10^{11}$ platelets. For prophylaxis, this dose may need to be repeated in 1 to 3 days because of the short life span of transfused platelets (3 to 4 days). Platelet components must be examined for abnormal appearance before administration. Units with excessive aggregates should not be administered. Transfusion, using a standard platelet administration set, may proceed as quickly as tolerated, but must take less than 4 hours after entering the container.

The corrected count increment (CCI) is a calculated measure of patient response to platelet transfusion and is not directly correlated with bleeding risk. CCI adjusts for the number of platelets infused and the size of the recipient, based upon body surface area (BSA):

CCI = (postcount – precount) × BSA / platelets transfused

where postcount and precount are platelet counts (/µL) after and before transfusion, respectively; patient BSA(meter^2); and platelets transfused is the number of administered platelets ($\times 10^{11}$). The CCI is usually determined 10 to 60 minutes after transfusion. For example:

A patient with acute myelogenous leukemia with a nomogram-derived BSA of 1.40 m^2 is transfused with a unit of Apheresis Platelets (a platelet dose of 4.5×10^{11}). The pretransfusion platelet count is 2000/µL. The patient's platelet count from a sample of blood collected 15 minutes after platelet transfusion is 29,000/µL. The CCI is calculated as (29,000 – 2000) × 1.4 / 4.5 = 8400/µL per 10^{11} per m^2.

In an afebrile, nonbleeding patient, the CCI is typically greater than 7500 at 10 minutes to 1 hour after transfusion and remains above 4500 at 24 hours for conventional platelets. A lower CCI may be expected following transfusion with platelet components that have been further manufactured (pathogen reduced, irradiated, or washed) or in patients that have been multiply transfused. Both immune and nonimmune mechanisms of platelet destruction may contribute to reduced platelet recovery and lower CCIs. Along with supportive serologic test results, a CCI of less than 5000 at 10 minutes to 1 hour after transfusion may indicate an immune-mediated refractory state to platelet therapy (refer to Platelet Alloimmunization, below). With nonimmune mechanisms, platelet recovery within 1 hour may be adequate, although survival at 24 hours is reduced.

See Table 3 for pediatric dosage information.

Side Effects and Hazards

Hazards that pertain to all transfusion components are described in the section on Side Effects and Hazards for Whole Blood and All Blood Components. Listed below are **additional** hazards or hazards more often associated with platelet components.

1. **Bacterial Contamination:** Room-temperature-stored platelets are associated with a higher risk of sepsis and related fatality than any other transfusable blood component. Platelet products have undergone bacterial detection testing as described above or have undergone treatment using pathogen reduction technology approved/cleared by the FDA. Although methods to limit and detect bacterial contamination have been implemented for platelet components, risk of bacterial contamination remains a hazard of platelet transfusion, and platelets remain the most likely blood components to be contaminated with bacteria. Gram-positive skin flora are the most commonly recovered bacteria. Symptoms may include, but are not limited to, high fever (≥2.0 C or ≥3.5 F increase in temperature), severe chills, hypotension, or circulatory collapse during or immediately after transfusion. In some instances, symptoms, especially when associated with contamination by gram-positive organisms, may be delayed for several hours following transfusion. Prompt management should include broad-spectrum antibiotic therapy along with cultures from the patient, suspected blood component(s), and administration set. Consider gram stain, culture or other rapid detection method of the suspected contaminated unit(s) whenever possible.
2. **Platelet Alloimmunization:** Platelets bear a variety of antigens, including Class I HLA and platelet-specific antigens. In the setting of platelet transfusion, patients may develop Class I HLA and/or human platelet antigen (HPA) antibodies potentially leading to refractoriness to transfused platelets. When platelets are transfused to a patient with an antibody specific for an expressed antigen, the survival time of the transfused platelets may be markedly shortened. Medication should be considered as a cause of immune or nonimmune thrombocytopenia. Nonimmune events may also contribute to reduced platelet survival. It may be possible to distinguish between immune and nonimmune platelet refractoriness by assessing platelet recovery soon after infusion (ie, a 10- to 60-minute CCI). In immune refractory states secondary to serologic incompatibility, there is poor recovery in the early postinfusion interval resulting in a CCI <7500. In nonimmune mechanisms (eg, splenomegaly, sepsis, fever, intravascular devices, and DIC), platelet recovery within 1 hour of infusion may be adequate while longer-term survival (ie, 24-hour survival) is reduced. Serologic tests may confirm the presence of alloimmunization. Laboratory tests (HLA typing and antibody identification, HPA antibody identification, or a platelet crossmatch) may also be helpful in selecting platelets with acceptable survival.
3. **Red Blood Cell Alloimmunization:** Immunization to red cell antigens may occur because of the presence of residual red cells in Platelets. Red cell compatibility testing is necessary only if the platelet component is prepared by a method that results in the component containing 2 mL or more of red cells, making the unit appear pink to salmon in color. This occurs more frequently with WBD platelets than apheresis platelets.

   Rh(D)-positive platelet transfusions to Rh(D)-negative individuals are common. The risk of Rh(D) alloimmunization is higher with WBD platelets and is very low with apheresis platelets. Providers may consider the use of Rh Immune Globulin to mitigate this risk in select patient populations.

4. **Hemolysis:** Platelet components that are not ABO identical with the recipient's blood group may contain incompatible plasma and when transfused may cause a positive DAT and possibly hemolysis. Platelet transfusions from ABO incompatible donors with high-titer isohemagglutinins (anti-A or anti-B) may cause acute hemolytic reactions in susceptible patients.

Components Available

This information is divided into sections by component type:

- Whole-Blood-derived platelets
- Apheresis platelets

Whole-Blood-Derived Platelet Components:

PLATELETS are a concentrate of platelets separated from a single unit of Whole Blood also referred to as WBD. One unit of Platelets should contain $\geq 5.5 \times 10^{10}$ platelets suspended in 40 to 70 mL of plasma. This component is usually provided as a pool. See below.

POOLED PLATELETS may be prepared using aseptic technique as an open or closed system. The number of units of Platelets in the pool will be indicated on the label. To determine the minimum potency of this component, assume 5.5×10^{10} platelets per unit of Platelets indicated on the label. See the label for the approximate volume.

PLATELETS LEUKOCYTES REDUCED may be prepared using an open or closed system. One unit of Platelets Leukocytes Reduced should contain $\geq 5.5 \times 10^{10}$ platelets and $<8.3 \times 10^5$ leukocytes. This component is usually provided as a pool. See below.

POOLED PLATELETS LEUKOCYTES REDUCED may be prepared using aseptic technique as an open or closed system by pooling and filtering Platelets or pooling Platelets Leukocytes Reduced. The number of units in the pool will be indicated on the label. To determine the minimum potency of this component, assume 5.5×10^{10} platelets per unit of Platelets Leukocytes Reduced indicated on the label and $<5 \times 10^6$ leukocytes in the pool. See the label for the approximate volume.

Apheresis Platelet Components:

APHERESIS PLATELETS are an effective way to collect a therapeutic adult dose of platelets from a single donor. Apheresis Platelets should contain $\geq 3.0 \times 10^{11}$ platelets. One unit of Apheresis Platelets may be equivalent to 6 units of WBD Platelets. The product volume is variable and indicated on the label. The number of leukocytes contained in this component varies depending upon the blood cell separator and protocol used for collection. Apheresis Platelets are supplied in one or more connected bags to improve platelet viability during storage by providing more surface area for gas exchange. Anticoagulant Citrate Dextrose-Solution A is the anticoagulant solution currently used for the collection and preservation of Apheresis Platelets.

APHERESIS PLATELETS LEUKOCYTES REDUCED can be leukocyte reduced during the collection process or may be prepared by further processing using leukocyte-reduction filters. Apheresis Platelets Leukocytes Reduced should contain $\geq 3.0 \times 10^{11}$ platelets and $<5.0 \times 10^6$ leukocytes. When Apheresis Platelets Leukocytes Reduced are prepared during further processing, these may be labeled Apheresis Platelets Leukocytes Reduced provided the requirement for residual leukocyte count is met and the platelet recovery is at least 85% of the prefiltration content. The volume, anticoagulant-preservative, and storage conditions for Apheresis Platelets Leukocytes Reduced are the same as those for Apheresis Platelets.

APHERESIS PLATELETS PLATELET ADDITIVE SOLUTION ADDED LEUKOCYTES REDUCED are platelets collected by apheresis and suspended in variable amounts of plasma and an approved PAS. See Table 6. One unit of platelets should contain $\geq 3.0 \times 10^{11}$ platelets and $<5.0 \times 10^{6}$ leukocytes. The volume in the product is variable and indicated on the label. Plasma proteins, including coagulation factors present in the plasma, are diluted in proportion to the PAS added.

Granulocyte Components

Apheresis Granulocytes Ω

Description

Apheresis Granulocytes contain numerous leukocytes and platelets as well as 20 to 50 mL of red cells. The number of granulocytes in each concentrate is usually $>1.0 \times 10^{10}$. The number of platelets varies in each product. Various modalities may be used to improve granulocyte collection, including donor administration of granulocyte colony-stimulating factor and/or corticosteroids. The final volume of the product is 200 to 300 mL including anticoagulant and plasma as indicated on the label.

Red cell sedimenting agents approved by the FDA, such as hydroxyethyl starch (HES), are typically used in the collection of granulocytes. Residual sedimenting agents will be present in the final component and are described on the label. Apheresis Granulocytes should be administered as soon after collection as possible because of well-documented deterioration of granulocyte function during short-term storage. If stored, maintain at 20 to 24 C without agitation, for no more than 24 hours.

Actions

Granulocytes migrate toward, phagocytize, and kill bacteria and fungi. A quantitative relationship exists between the level of circulating granulocytes and the prevalence of bacterial and fungal infection in neutropenic patients. The ultimate goal is to provide the patient with the ability to fight infection. The infusion of a granulocyte component may not be associated with a significant increase in the patient's granulocyte count and is dependent on multiple factors, including the patient's clinical condition.

Indications

Granulocyte transfusion therapy is controversial. Apheresis Granulocytes are typically used in the treatment of patients with documented infections (bacterial and fungal) unresponsive to antimicrobial therapy in the setting of neutropenia [absolute granulocyte count $<0.5 \times 10^{9}$/L (500/µL)] with expected eventual marrow recovery. A trial of broad-spectrum antimicrobial agents should be used before granulocyte transfusion therapy is initiated. If the intended recipient is CMV seronegative and severely immunosuppressed (eg, a marrow transplant recipient), serious consideration should be given before administration of CMV-seropositive granulocytes. In addition to neutropenic patients, patients with hereditary neutrophil function defects (such as chronic granulomatous disease) may be candidates for granulocyte transfusion therapy.

Contraindications

Prophylactic use of granulocytes in noninfected patients is not routinely recommended. Patients with HLA and/or human neutrophil antigen (HNA) antibodies may not derive full benefit from granulocyte transfusion and may have a higher risk of pulmonary reactions. Antigen-matched or HLA-matched components, if available, may be considered in these patients.

Table 6. Contents of Platelet Additive Solutions

Additive Solution (mg/100 mL)	Sodium Chloride	Sodium Citrate	Sodium Gluconate	Sodium Acetate	Dibasic Sodium Phosphate	Monobasic Sodium Phosphate	Monobasic Potassium Phosphate	Potassium Chloride	Magnesium Chloride	Shelf Life (Days)
PAS-C (Intersol)	452	318 (dihydrate)		442 (trihydrate)	305 (anhydrous)	93 (monohydrate)				5
PAS-F (Isoplate)	530		500	370 (trihyidrate)	12 (heptahydrate)		0.82	37	30 (hexahydrate)	5

PAS = platelet additive solution.

Dosage and Administration

Transfuse as soon as possible. A standard blood infusion set is to be used for the administration of Apheresis Granulocytes. Do not administer using leukocyte-reduction filters. Depth-type microaggregate filters and leukocyte-reduction filters remove granulocytes.

The red cells in Apheresis Granulocytes must be ABO compatible. Once granulocyte transfusion therapy is initiated, support should continue at least daily until infection is cured, defervescence occurs, the absolute granulocyte count returns to at least 0.5×10^9/L (500/µL), or the physician in charge decides to halt the therapy.

Because most patients receiving these products are severely immunosuppressed and may be at risk for TA-GVHD, Apheresis Granulocytes should be irradiated (see sections on Further Processing and Additional Testing).

See Table 3 for pediatric dosage information.

Side Effects and Hazards

Hazards that pertain to all transfusion components are described in the section on Side Effects and Hazards for Whole Blood and All Blood Components. Listed below are hazards that apply specifically to Apheresis Granulocytes.

1. **Febrile Nonhemolytic Reactions:** These reactions are frequently noted in patients receiving granulocyte transfusions. Fever and chills in patients receiving granulocyte components may be avoided or mitigated by slow administration and recipient premedication.
2. **Allergic Reactions:** Allergic reactions to HES and other red cell sedimenting solutions may occur during granulocyte transfusion.
3. **Pulmonary Reactions:** Granulocyte transfusion can cause worsening of pulmonary function in patients with pneumonia, and rarely severe pulmonary reactions, especially in patients receiving concomitant amphotericin B. Patients who have pulmonary reactions should be tested for HLA and HNA antibodies.
4. **Alloimmunization:** Immunization to HLA antigens frequently occurs with granulocyte transfusion and can cause refractoriness to platelet transfusion.

Components Available

APHERESIS GRANULOCYTES Ω

Further Processing

This section addresses further processing of previously described blood components. The processes described in this section are pathogen reduction technology, leukocyte reduction, irradiation, washing, and volume reduction. A component may undergo one or more of these processes.

Pathogen Reduction Technology

Description

Pathogen reduction is an ex-vivo process intended to reduce the risk of certain transfusion-transmitted infections (TTI), including sepsis and may also be used as an alternative to irradiation to prevent TA-GVHD if the pathogen reduction technology has been shown to inactivate residual lymphocytes. There is no pathogen inactivation process that has been shown to eliminate all pathogens; eg, hepatitis A (HAV), hepatitis E (HEV), human parvovirus B19, poliovirus, and *Bacillus cereus* spores have shown resistance to some processes.

A current pathogen reduction procedure uses a chemical photosensitizer that is added to the plasma or platelet product and then transferred into a container that is placed inside an illumination device for UVA treatment. Unreacted photosensitizer and free photoproducts are subsequently removed with a compound adsorption device.

Products currently approved by FDA for pathogen reduction technology include apheresis platelets and whole-blood-derived (WBD) plasma or apheresis plasma. Pathogen-reduced plasma may be further manufactured, using a system approved by FDA for this purpose, into Pathogen Reduced, Cryoprecipitated Fibrinogen Complex (PRCFC) and Pathogen Reduced Plasma, Cryoprecipitate Reduced (PRPCR). Pathogen reduction technology may apply to other products in the future.

Consistent with the **Notice to All Users** section on page 1, refer to the manufacturer's instructions for use of components prepared using a pathogen-reduction device for all components listed in this section.

- **Refer to the Platelet Section beginning on page 29 or the Plasma Section beginning on page 19** for the corresponding *Description, Actions, Indications, Contraindications, Relative Contraindications, Dosage and Administration,* and *Side Effects and Hazards* as applicable to pathogen-reduced platelet components, and frozen and thawed pathogen-reduced plasma components.
- NOTE: *Additional Contraindications* for pathogen-reduced platelet and plasma components include:
    1. Contraindicated for preparation of pathogen-reduced components intended for patients with a history of hypersensitivity reaction to amotosalen or other psoralens.
    2. Contraindicated for preparation of pathogen-reduced components intended for neonatal patients treated with phototherapy devices that emit a peak energy wavelength less than 425 nm, or have a lower bound of the emission bandwidth <375 nm, due to the potential for erythema resulting from interaction between ultraviolet light and amotosalen.
- NOTE: Additional *Warnings and Precautions* for pathogen reduced platelet and plasma components include:

    Platelet Components:
    Amotosalen-treated platelets may cause the following adverse reaction:
    Pulmonary Events:
    Acute Respiratory Distress Syndrome (ARDS). An increased incidence of ARDS was reported in a randomized trial for recipients of INTERCEPT processed platelets, 5/318 (1.6%), compared to recipients of conventional platelet components (0/327). Monitor patients for signs and symptoms of ARDS.

    Plasma Components:
    Amotosalen-treated plasma may cause the following adverse reaction:
    Cardiac Events:
    In a randomized controlled trial of therapeutic plasma exchange (TPE) for TTP, five patients treated with INTERCEPT Blood System processed plasma and none with conventional plasma had adverse events in the cardiac system organ class (SOC) reported. These events included angina pectoris (n=3), cardiac arrest (n=1), bradycardia (n=1), tachycardia (n=1) and sinus arrhythmia (n=1). None of these events resulted in documented myocardial infarction or death. Monitor patients for signs and symptoms of cardiac events during TPE for TTP.

Components Available

APHERESIS PLATELETS LEUKOCYTES REDUCED PSORALEN-TREATED

APHERESIS PLATELETS PLATELET ADDITIVE SOLUTION ADDED LEUKOCYTES REDUCED PSORALEN-TREATED

APHERESIS FRESH FROZEN PLASMA PSORALEN-TREATED

POOLED FRESH FROZEN PLASMA PSORALEN-TREATED

POOLED PLASMA FROZEN WITHIN 24 HOURS AFTER PHLEBOTOMY PSORALEN-TREATED

APHERESIS PLASMA CRYOPRECIPITATE REDUCED PSORALEN-TREATED

POOLED PLASMA CRYOPRECIPITATE REDUCED PSORALEN-TREATED

THAWED APHERESIS PLASMA PSORALEN-TREATED

THAWED POOLED PLASMA PSORALEN-TREATED

THAWED PLASMA CRYOPRECIPITATE REDUCED PSORALEN-TREATED

Pathogen Reduced Cryoprecipitated Fibrinogen Complex

Description

Pathogen Reduced Cryoprecipitated Fibrinogen Complex (PRCFC) is prepared from plasma that has been processed with an FDA-approved pathogen reduction device. The PRCFC process includes thawing pathogen-reduced plasma between 1 and 6 C and recovering the precipitate. The cold-insoluble precipitate is placed in the freezer at –18 C or colder.

Actions

PRCFC serves as an enriched source of fibrinogen, Factor XIII, von Willebrand Factor (vWF), and other constituents. The 5-day postthaw shelf life of PRCFC is based on retention of critical functional activities that have shown a high level of correlation with therapeutic efficacy and the reduced pathogen risk associated with pathogen inactivation.

PRCFC is not intended to be used for replacement of Factor VIII.

Indications

PRCFC is indicated for:

1. Treatment and control of bleeding, including massive hemorrhage, associated with fibrinogen deficiency.
2. Control of bleeding when recombinant and/or specific virally inactivated preparations of Factor XIII or vWF are not available.
3. Second-line therapy for vWD.
4. Control of uremic bleeding after other treatment modalities have failed.

Limitations of Use: PRCFC should not be used for replacement of Factor VIII.

Contraindications

1. Contraindicated for preparation of blood components intended for patients with a history of hypersensitivity reaction to amotosalen or other psoralens.
2. Contraindicated for preparation of blood components intended for neonatal patients treated with phototherapy devices that emit a peak energy wavelength less than 425 nm, or have a lower bound of the emission bandwidth <375 nm, due to the potential for erythema resulting from interaction between ultraviolet light and amotosalen.

Warnings and Precautions

1. For management of patients with vWD or Factor XIII deficiency, PRCFC should not be used if recombinant or specific virally-inactivated factor preparations are available. In emergent situations, if recombinant or specific virally-inactivated factor preparations are not available, PRCFC may be administered.

Dosage and Administration

1. Compatibility testing is not required. ABO-compatible PRCFC is preferred. Rh type need not be considered when using this product.
2. Thaw according to institutional procedures and manufacturer's instructions for use of PRCFC. If using a water bath, for thawing PRCFC, place in liquid-impermeable plastic overwrap. Do not allow product to contact water. Do not refreeze postthaw.
3. Do not administer PRCFC if there is evidence of container breakage or of thawing during frozen storage.
4. If PRCFC is pooled or aliquoted postthaw without using an FDA-cleared sterile connection device, transfuse within 4 hours of pooling or aliquoting.

PRCFC may be transfused from a single or multiple containers. For in-hospital pooling, the precipitate in one or more containers may be mixed well with 10 to 15 mL of diluent to allow complete removal of all material from the container. The preferred diluent is 0.9% Sodium Chloride, Injection (USP). Serial use of each container's contents to resuspend the precipitate into subsequent containers may be used to efficiently pool PRCFC into a single container.

Thrombosis alters fibrinogen kinetics; therefore, patients receiving PRCFC as fibrinogen replacement in conditions associated with increased fibrinogen turnover should be monitored with fibrinogen assays.

When used to correct hypofibrinogenemia, PRCFC may be dosed based on the clinical presentation and expected fibrinogen content of the product. For example, a unit of PRCFC prepared from 2 whole-blood-derived plasma units will contain about 740 ±166 mg fibrinogen immediately postthaw, and 686 ±165 mg fibrinogen after 120 hours.

Side Effects and Hazards

Hazards that pertain to all transfusion components are described in the earlier section on Side Effects and Hazards for Whole Blood and All Blood Components.

Components Available

POOLED FIBRINOGEN COMPLEX CRYOPRECIPITATED PSORALEN-TREATED

APHERESIS FIBRINOGEN COMPLEX CRYOPRECIPITATED PSORALEN-TREATED

APHERESIS POOLED FIBRINOGEN COMPLEX CRYOPRECIPITATED PSORALEN-TREATED

Leukocyte Reduction

Description

A unit of whole blood generally contains ≥ 1 to 10×10^9 white cells. Leukocyte reduction will decrease the cellular content and volume of blood according to characteristics of the technology used. RBCs Leukocytes Reduced, Apheresis RBCs Leukocytes Reduced, Apheresis Platelets Leukocytes Reduced and Pooled Platelets Leukocytes Reduced must have $<5.0 \times 10^6$ residual leukocytes per unit. Platelets Leukocytes Reduced (single unit WBD) must have $<8.3 \times 10^5$ residual leukocytes per unit. Leukocyte reduction may be performed using in-process collection methods. Leukocyte reduction may be performed using additional postcollection processing steps to permit labeling as a leukocytes reduced component: 1) soon after collection (prestorage), 2) after varying periods of storage in the laboratory, or 3) at the bedside as directed by manufacturer's instructions. The methods used by the laboratory for leukocyte reduction are subject to quality control testing; leukocyte-reduced components prepared at the bedside are not routinely subjected to quality control testing. Leukocyte-reduction technologies variably remove other cellular elements in addition to white cells. Washing is not a substitute for leukocyte reduction. Leukocyte reduction is not a substitute for irradiation.

Indications

Leukocyte-reduced components are indicated to decrease the frequency of recurrent febrile nonhemolytic transfusion reaction. They have also been shown to reduce the risk of transfusion-transmitted CMV and to reduce the incidence of HLA alloimmunization.

Contraindications

Leukocyte-reduced components do not prevent TA-GVHD.

Leukocyte-reduction filters are not to be used in the administration of Apheresis Granulocytes.

Side Effects and Hazards

The use of blood components that are leukocyte reduced at the bedside may cause unexpected severe hypotension in some recipients, particularly those taking angiotensin-converting enzyme inhibitor medication.

Specific Leukocyte-Reduced Components

All components resulting from the leukocyte reduction process will bear the labeling attribute "leukocytes reduced."

Irradiation

Description

Blood components that contain viable lymphocytes may be irradiated to prevent proliferation of T lymphocytes, which is the immediate cause of TA-GVHD. Irradiated blood is prepared by exposing the component to a radiation source. The standard dose of gamma or X-ray irradiation is 2500 centigray (cGy) targeted to the central portion of the container with a minimum dose of 1500 cGy delivered to any part of the component.

Indications

Irradiated cellular components are indicated for use in patient groups that are at risk for TA-GVHD. At-risk groups include fetal and neonatal recipients of intrauterine transfusions, selected immunocompromised recipients, recipients of cellular components known to be from a blood relative, recipients who have undergone peripheral blood progenitor cell transplantation, recipients of cellular components whose donor is selected for HLA compatibility and recipients of granulocyte transfusions. Transfused patients receiving purine analogues (eg, fludarabine, cladribine) or certain other biological immunomodulators (eg, alemtuzumab, antithymocyte globulin) may be at risk for TA-GVHD, depending on clinical factors and the source of the biological agent.

Side Effects and Hazards

Irradiation induces erythrocyte membrane damage. Irradiated red cells have been shown to have higher supernatant potassium levels than nonirradiated red cells. Removal of residual supernatant plasma before transfusion may reduce the risks associated with elevated plasma potassium. The expiration date of irradiated red cells is changed to 28 days after irradiation if remaining shelf life exceeds 28 days. There are no known adverse effects following irradiation of platelets; the expiration date is unchanged.

Specific Irradiated Components

All components that have been irradiated will bear the labeling attribute "irradiated."

Washing

Description
Washed components are typically prepared using 0.9% Sodium Chloride, Injection USP with or without small amounts of dextrose. Washing removes unwanted plasma proteins, including antibodies and glycerol from previously frozen units. There will also be some loss of red cells and platelets, as well as a loss of platelet function through platelet activation. The shelf life of washed components is no more than 24 hours at 1 to 6 C or 4 hours at 20 to 24 C. Washing is not a substitute for leukocyte reduction, and only cellular components should be washed.

Indications
Washing may be used to reduce exposure to plasma proteins, acellular constituents or additives (such as mannitol). It is indicated to reduce exposure to antibodies targeting known recipient antigens (such as an Apheresis Platelet unit containing incompatible plasma collected from a mother for the treatment of neonatal alloimmune thrombocytopenia), or to remove constituents that predispose patients to significant or repeated transfusion reactions (eg, removal of IgA-containing plasma in providing transfusion support for
an IgA-deficient recipient or in rare recipients experiencing
anaphylactoid/anaphylactic reactions to other plasma components).

Specific Washed Components

WASHED RED BLOOD CELLS

WASHED APHERESIS RED BLOOD CELLS

WASHED PLATELETS Ω

WASHED APHERESIS PLATELETS Ω

WASHED APHERESIS PLATELETS PLATELET ADDITIVE SOLUTION ADDED LEUKOCYTES REDUCED Ω

Volume Reduction

Description
Volume reduction is a special manipulation of cellular blood products using centrifugation to remove plasma and storage media in order to concentrate the product. It is typically performed immediately prior to issuing the product for patient administration. The process involves the aseptic removal of a portion of the supernatant, containing plasma and storage medium. Volume reduction removes excess plasma, thereby reducing unwanted plasma proteins, including antibodies. It is more commonly used in pediatric and intrauterine transfusions. There will be some loss of platelet function through platelet activation as a result of volume reduction. The shelf life of volume-reduced components is no more than 24 hours at 1 to 6 C or 4 hours at 20 to 24 C.

Indications
Reducing the plasma volume of cellular components is indicated in cases where consequences of hypervolemia are of concern, (such as in infants with compromised cardiac function). Component volume reduction is also used to mitigate adverse transfusion reactions such as TACO, severe allergic reactions, and ABO incompatibilities.

Contraindications
Volume reduction is not a substitute for washing or for dosing with small aliquots.

Specific Volume-Reduced Components

RED BLOOD CELLS PLASMA REDUCED Ω

RED BLOOD CELLS SUPERNATANT REDUCED Ω

APHERESIS RED BLOOD CELLS PLASMA REDUCED Ω

APHERESIS RED BLOOD CELLS SUPERNATANT REDUCED Ω

PLATELETS PLASMA REDUCED Ω

APHERESIS PLATELETS PLASMA REDUCED Ω

APHERESIS PLATELETS PLATELET ADDITIVE SOLUTION ADDED LEUKOCYTES REDUCED SUPERNATANT REDUCED Ω

Additional Testing

This section addresses additional testing performed on previously described blood components. The testing described in this section includes identification of CMV-seronegative blood, and identification of low titer anti-A and/or anti-B blood products.

Identification of CMV-Seronegative Blood

Description

CMV-seronegative blood is selected by testing for antibodies to CMV. Transmission of CMV disease is associated with cellular blood components specifically those containing mononuclear leukocytes from donors with a history of CMV infection. Plasma, cryoprecipitate, and other plasma-derived blood components are not associated with CMV transmission. Therefore, CMV testing is not necessary for these components.

Indications

In the latently infected donor, CMV is exclusively associated with mononuclear leukocytes. Current studies indicate that transfusion of prestorage, leukocyte-reduced blood products safely reduces the risk of CMV transmission to levels not significantly different to transfusion with CMV-seronegative blood. Thus prestorage, leukocyte-reduced components are considered a suitable alternative to CMV-seronegative transfusion.

Transfusion of prestorage leukocyte-reduced or CMV-seronegative blood is indicated in CMV-seronegative recipients who are at risk for severe CMV infections. These at-risk groups include pregnant women and their fetuses, low-birthweight infants, hematopoietic progenitor cell transplant recipients, solid-organ transplant recipients, severely immunosuppressed recipients, and HIV-infected patients.

Identification of Low Titer Anti-A and/or Anti-B Blood Products

Description

Plasma, apheresis platelets, and whole blood products containing defined titers of anti-A and/or anti-B may reduce the risk of hemolytic transfusion reactions when transfusing ABO-incompatible blood products. Titers considered "low" are not standardized; there is no "safe" titer because hemolytic reactions have been observed at even low titers, with no direct correlation of titer and risk of reactions. Facilities must have policies and procedures to define cut-offs for anti-A and/or anti-B titers for ABO-incompatible blood components.

Refer to the United States Industry Consensus Standard for Uniform Labeling of Blood and Blood Components Using ISBT 128 (https://www.fda.gov/regulatory-information/search-fda-guidance-documents/united-states-industry-consensus-standard-uniform-labeling-blood-and-blood-components-using-isbt-128) for labeling recommendations. Options include placing the titer value on a tie tag.

Indications

Group O Whole Blood and group A plasma tested for anti-A and/or anti-B may be used as an initial resuscitation fluid for an acutely bleeding patient prior to determining the recipient blood group.

The transfusing facility must have policies and procedures in place addressing specific indications for use, product specifications, administration instructions, and a defined maximum number of units to be transfused to each patient.

Contraindications

ABO-incompatible products should not be transfused when an appropriate product that is ABO compatible is readily available, or when the risk of administering ABO-incompatible blood components outweighs the potential therapeutic benefit.

Table 7. Summary Chart of Blood Components

Category	Major Indications	Action/Recipient Benefit	Not Indicated for	Special Precautions	Hazards*	Rate of Infusion
Red Blood Cells	Symptomatic anemia; red cell exchange transfusion.	Increases oxygen-carrying capacity.	Pharmacologically treatable anemia. Volume expansion.	Must be ABO compatible.	Infectious diseases. Hemolytic, septic/ toxic, allergic, febrile reactions. Iron overload. TACO. TRALI. TA-GVHD.	As fast as patient can tolerate but less than 4 hours.
Deglycerolized Red Blood Cells	See Red Blood Cells. IgA deficiency with anaphylactoid/ anaphylactic reaction.	See Red Blood Cells. Deglycerolization removes plasma proteins. Risk of allergic and febrile reactions reduced.	See Red Blood Cells.	See Red Blood Cells.	See Red Blood Cells. Hemolysis due to incomplete deglycerolization can occur.	See Red Blood Cells.
Red Blood Cells Leukocytes Reduced	See Red Blood Cells. Reduction of febrile reactions, HLA alloimmunization and CMV infection.	See Red Blood Cells.	See Red Blood Cells. Leukocyte reduction should not be used to prevent TA-GVHD.	See Red Blood Cells.	See Red Blood Cells. Hypotensive reaction may occur if bedside leukocyte-reduction filter is used.	See Red Blood Cells.
Washed Red Blood Cells	See Red Blood Cells. IgA deficiency with anaphylactoid/ anaphylactic reaction.	See Red Blood Cells. Washing reduces plasma proteins. Risk of allergic reactions is reduced.	See Red Blood Cells. Washing is not a substitute for leukocyte reduction.	See Red Blood Cells.	See Red Blood Cells.	See Red Blood Cells.

	Recurrent severe allergic reactions to unwashed red cell products.					
Whole Blood	Symptomatic anemia with large volume deficit.	Increases oxygen-carrying capacity.	Condition responsive to specific component.	Must be ABO identical or as defined by local policies and procedures.	See Red Blood Cells.	As fast as patient can tolerate but less than 4 hours.
	Treat the massively bleeding patient.	Increases blood volume. Variably contributes plasma coagulation factors and platelets.	Treatment of coagulopathy.			
Fresh Frozen Plasma (FFP)	Clinically significant plasma protein deficiencies when no specific coagulation factor concentrates are available. TTP.	Source of plasma proteins, including all coagulation factors.	Volume expansion. Coagulopathy that can be more effectively treated with specific therapy. Correcting a minimally elevated INR.	Must be ABO compatible.	Infectious diseases. Allergic, febrile reactions. TACO. TRALI.	Less than 4 hours.
Plasma Frozen Within 24 Hours After Phlebotomy (PF24)	Clinically significant deficiency of stable coagulation factors when no specific coagulation factor concentrates are available. TTP.	Source of non-labile plasma proteins. Levels of Factor VIII are significantly reduced and levels of Factor V and other labile plasma proteins are variable compared to FFP.	Volume expansion. Deficiencies of labile coagulation factors including Factors V and VIII and Protein C. See FFP.	Must be ABO compatible.	See FFP.	Less than 4 hours.

(Continued)

Table 7. Summary Chart of Blood Components (Continued)

Category	Major Indications	Action/Recipient Benefit	Not Indicated for	Special Precautions	Hazards*	Rate of Infusion
Plasma Frozen Within 24 Hours After Phlebotomy Held at Room Temperature Up to 24 Hours After Phlebotomy (PF24RT24)	Clinically significant deficiency of stable coagulation factors when no specific coagulation factor concentrates are available. TTP.	Source of nonlabile plasma proteins. Levels of Factor V, Factor VIII, and Protein S are significantly reduced, and levels of other labile plasma proteins are variable compared with FFP.	Volume expansion. Deficiencies of labile coagulation factors including Factors V and VIII and Protein S. See Fresh Frozen Plasma (FFP)	Must be ABO compatible.	See FFP.	Less than 4 hours.
Plasma Cryoprecipitate Reduced	TTP.	Plasma protein replacement for plasma exchange in TTP. Deficient infibrinogen, vWF, Factors VIII and XIII. Deficient in high-molecular-weight vWF multimers as compared to FFP.	Volume expansion. Deficiency of coagulation factors known to be depleted in this product: fibrinogen, vWF, Factors VIII and XIII.	Must be ABO compatible.	See FFP.	Less than 4 hours.
Thawed Plasma Ω	Clinically significant deficiency of stable coagulation factors when no specific coagulation factor concentrates are available. TTP.	Source of plasma proteins. Levels and activation state of coagulation proteins in thawed plasma are variable and change over time.	Not indicated as treatment for isolated coagulation factor deficiencies or specific plasma protein deficiencies.	Must be ABO compatible.	See FFP.	Less than 4 hours.

Thawed Plasma Cryoprecipitate Reduced Ω	TTP.	Plasma protein replacement for plasma exchange in TTP. Deficient in fibrinogen, vWF, Factors VIII and XIII.	Volume expansion. Deficiency of coagulation factors known to be depleted in this product: fibrinogen, vWF, Factors VIII and XIII. See FFP.	Must be ABO compatible.	See FFP.	Less than 4 hours.
Liquid Plasma	Initial treatment of patients undergoing massive transfusion.	Coagulation support for life-threatening trauma/ hemorrhages. The profile of plasma proteins in Liquid Plasma is not completely characterized. Levels and activation state of coagulation proteins are dependent upon production methods and storage.	Not indicated as treatment for coagulation factor deficiencies where other products are available with higher factor concentrations. See FFP.	Must be ABO compatible.	See FFP.	Less than 4 hours.

(Continued)

Table 7. Summary Chart of Blood Components (Continued)

Category	Major Indications	Action/Recipient Benefit	Not Indicated for	Special Precautions	Hazards*	Rate of Infusion
Cryoprecipitated AHF; Pooled Cryoprecipitated AHF	Hypofibrinogenemia. Factor XIII deficiency. Second-line therapy of von Willebrand disease, hemophilia A, and uremic bleeding.	Provides fibrinogen, vWF, Factors VIII and XIII.	Not indicated if specific concentrates are available. Deficiency of any plasma protein other than those enriched in Cryoprecipitated AHF.		Infectious diseases. Allergic, febrile reactions.	Less than 4 hours.
Platelets/Apheresis Platelets	Bleeding due to thrombocytopenia or platelet function abnormality including antiplatelet drugs. Prevention of bleeding from marrow hypoplasia.	Improves hemostasis. Apheresis platelets may be HLA (or other antigen) selected.	Plasma coagulation deficits. Some conditions with rapid platelet destruction (eg, ITP, TTP) unless life-threatening hemorrhage.	Should only use platelet-compatible filters (check manufacturer's instructions).	Infectious diseases. Septic/toxic, allergic, febrile reactions. TACO. TRALI. TA-GVHD.	Less than 4 hours.
Platelets Leukocytes Reduced/ Apheresis Platelets Leukocytes Reduced	See Platelets. Reduction of febrile reactions, HLA alloimmunization and CMV infection.	See Platelets.	See Platelets. Leukocyte reduction should not be used to prevent TA-GVHD.	See Platelets.	See Platelets.	See Platelets.
Apheresis Platelets Platelet Additive Solution Added Leukocytes Reduced	See Platelets Leukocytes Reduced.	See Platelets.	See Platelets Leukocytes Reduced.	See Platelets.	See Platelets.	See Platelets.

Apheresis Granulocytes Ω	Neutropenia with infection, unresponsive to appropriate antibiotics.	Provides granulocytes and platelets.	Infection responsive to antibiotics, eventual marrow recovery not expected.	Must be ABO compatible.	Infectious diseases. Hemolytic, allergic, febrile reactions. TACO. TRALI. TA-GVHD.	One unit over 2-4 hours. Closely observe for reactions.
				Use only filters specifically approved by a manufacturer for granulocyte transfusions (check manufacturer's instructions).	Maintain caution. Pulmonary reactions may occur in patients receiving concomitant amphotericin B.	

*For all cellular components there is a risk the recipient may become alloimmunized and experience rapid destruction of certain types of blood products. Red-cell-containing components and thawed plasma (thawed FFP, thawed PF24, thawed PF24RT24, or Thawed Plasma) should be stored at 1-6 C. Platelets, Granulocytes, and thawed Cryoprecipitate should be stored at 20-24 C. Disclaimer: Please check the corresponding section of the *Circular* for more detailed information.
TACO = transfusion-associated circulatory overload; TRALI = transfusion-related acute lung injury; TA-GVHD = transfusion-associated graft-vs-host disease; CMV = cytomegalovirus; TTP = thrombotic thrombocytopenic purpura; AHF = antihemophilic factor; ITP = immune thrombocytopenic purpura; vWF = von Willebrand Factor; HLA = Human Leukocyte Antigen; IUT = intrauterine transfusion.

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Efficacy of a new pathogen-reduced cryoprecipitate stored 5 days after thawing to correct dilutional coagulopathy in vitro

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BACKGROUND: Fibrinogen supplementation during bleeding restores clot strength and hemostasis. Cryoprecipitate, a concentrated source of fibrinogen, has prolonged preparation time for thawing, a short shelf life resulting in frequent wastage, and infectious disease risk. This in vitro study investigated the efficacy of a new pathogen-reduced cryoprecipitate thawed and stored at room temperature for 5 days (PR Cryo) to treat dilutional hypofibrinogenemia, compared to immediately thawed standard cryoprecipitate (Cryo) or fibrinogen concentrate (FC).

STUDY DESIGN AND METHODS: Ten phlebotomy specimens from healthy volunteers were diluted 1:1 with crystalloid and supplemented with PR Cryo and Cryo (at a dose replicating transfusion of two pooled doses [10 units]) and FC at a dose replicating 50 mg/kg. Changes in clot firmness (thromboelastometry) and in coagulation factor activity were assessed at baseline, after dilution, and after supplementation.

RESULTS: Clinical dosing was used, as described above, and consequently the FC dose contained 24% and 36% more fibrinogen versus PR Cryo and Cryo, respectively. At baseline, subjects had a median FIBTEM maximum clot firmness of 13.5 mm, versus 6.5 mm after 50% dilution ($p = 0.005$). After supplementation with PR Cryo, a median FIBTEM maximum clot firmness of 13 mm was observed versus 9.0 mm for Cryo ($p = 0.005$) or 16.5 mm for FC ($p = 0.005$). Median factor XIII was higher after PR Cryo (64.8%) versus Cryo (48.3%) ($p = 0.005$). Fibrinogen activity was higher after FC (269.0 mg/dL) versus PR Cryo (187.0 mg/dL; $p = 0.005$) or Cryo (193.5 mg/dL; $p = 0.005$); the difference between PR Cryo and Cryo supplementation ($p = 0.445$) was not significant.

CONCLUSION: PR Cryo used 5 days after thawing effectively restores clot strength after in vitro dilution.

Acquired hypofibrinogenemia due to consumption of coagulation factors or dilutional coagulopathy occurs in a variety of clinical settings, such as trauma, postpartum hemorrhage, and major surgeries. Supplementation of fibrinogen during severe bleeding in patients with hypofibrinogenemia helps to restore clot strength, reduce blood loss, and thus lower mortality.[1–4] As fibrinogen is one of the first coagulation factors to become critically low during the development of coagulopathy,[5] early administration of fibrinogen plays a crucial role in acute bleeding management. Available sources of concentrated fibrinogen include cryoprecipitate and fibrinogen concentrate (FC).

Cryoprecipitate contains fibrinogen, factor VIII, factor XIII, von Willebrand factor, and fibronectin. According to

ABBREVIATIONS: Cryo = standard cryoprecipitate; EXTEM = extrinsically activated test using tissue factor as activator; FC = fibrinogen concentrate; FIBTEM = fibrin-based extrinsically activated test with tissue factor and cytochalasin D; ICPC = INTERCEPT Cryo Processing Container; MCF = maximum clot firmness; PR Cryo = pathogen-reduced cryoprecipitate; VWF:Ag = von Willebrand factor antigen; VWF:RCo = von Willebrand factor ristocetin cofactor activity.

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AABB standards, each nonpooled unit of cryoprecipitate must have a minimum content of 150 mg of fibrinogen and 80 international units of factor VIII. However, actual fibrinogen content can be highly variable (3–30 g/L) depending on donors and the manufacturing process.[6] Although quality control for cryoprecipitate includes only fibrinogen and FVIII, it is very likely that the other components also play an important part in treating severe coagulopathies. FXIII deficiencies can occur during exsanguination and require supplementation to achieve hemostasis.[7] In addition, FXIII plays an important role in clot stabilization to avoid hyperfibrinolysis.[8] Von Willebrand factor has a central role in primary hemostasis where it mediates platelet adhesion to damaged vascular subendothelium and subsequently platelet aggregation[9]; thus, it is also likely that the concentrated source of von Willebrand factor in cryoprecipitate enhances its impact on restoring hemostasis. One of the major obstacles for the use of cryoprecipitate is that it must be thawed by the hospital transfusion service after the order is placed, which delays availability by at least 30 to 45 minutes.

In a recently published cohort trial, the median (interquartile range [IQR]) time to issue cryoprecipitate was 2.5 hours (1.2–4.3 hours) from time of commencement of massive transfusion.[10] Once cryoprecipitate has been thawed, it can be stored between 4 and 6 hours at room temperature before expiration, depending on national guidelines and the pooling process. Pooling may lead to the introduction of infectious agents into the final product, and thus a shortened shelf life is required after this component modification. The short shelf life leads to a high wastage rate, which is reported in the range of 28%.[11] Each pooled cryoprecipitate dose is sourced from multiple donors, thus carrying an increased risk of infectious disease transmission.[12] This has led to withdrawal of cryoprecipitate from the market in many European countries.

Fibrinogen concentrate is a purified, pooled plasma derivative with a high fibrinogen content (approximately 20 g/L) and insignificant levels of other plasma proteins. It can be stored up to 5 years at room temperature (storage times vary by product and country) and can be quickly reconstituted within 5 to 10 minutes for timely administration. Although fibrinogen concentrate is produced from an even larger pool of donors, its manufacturing process includes stringent steps for pathogen reduction.[12] The cost of fibrinogen concentrate is approximately four to five times more per gram of fibrinogen compared to cryoprecipitate.[6] A systematic review of the current literature could make no overall recommendations with regard to which product is superior.[13]

There is a need for an improved cryoprecipitate product with decreased risk of transfusion-transmitted infections, rapid availability, and an extended shelf life to decrease product wastage. Numerous pathogen reduction processes, including solvent/detergent pathogen reduction technology,[14] methylene blue plus visible light reduction technology,[15] and amotosalen or riboflavin plus ultraviolet light technologies ,[16–18] have been applied to cryoprecipitate. In the past, some pathogen reduction steps in manufacturing cryoprecipitate have been reported to have a negative impact on coagulation factor activity.[12,13]

Prolonged shelf life of cryoprecipitate for up to 5 days after thawing has shown no significant decrease in factor content.[19] The main impediment to the use of cryoprecipitate for longer than 6 hours after thawing is the risk of bacterial contamination in a product stored at room temperature. A product manufactured using pathogen-reduced plasma and contained within a closed system throughout storage and thawing would pose very little risk for microbial transmission.

The aim of this study was to investigate the hemostatic effectiveness of a new pathogen-reduced cryoprecipitate stored thawed at room temperature for 5 days in the treatment of dilutional hypofibrinogenemia compared to both standard pooled cryoprecipitate thawed immediately before use and FC using an in vitro model.

MATERIALS AND METHODS

Volunteer donors

This prospective experimental study was approved by the Weill Cornell Medicine Institutional Review Board (IRB#1802018950). After obtaining written informed consent, blood samples were drawn from 10 healthy volunteers. Male and female healthy adult volunteers were included. The screening process encompassed a short verbal survey about bleeding, pregnancy, recent infection, and medication history.

Exclusion criteria were positive personal or family history for bleeding or prothrombotic disorders, recent infection, or current intake of medications that affect coagulation or platelet function.

Blood withdrawal was performed by puncture of an antecubital vein using a 23G needle. For each subject, one 10-mL blood sampling tube (S-Monovette 10 mL, Sarstedt) containing buffered sodium citrate solution (0.105 M ≈ 3.2%) was prepared and labeled.

Pathogen-reduced cryoprecipitate

In this study, a newly developed pathogen-reduced cryoprecipitate was investigated and compared to standard cryoprecipitate and FC.

Pathogen-reduced cryoprecipitate was manufactured at Cerus Corporation (Concord, CA). The starting material was prepared from a pool of 15 units of whole blood–derived group A plasma that was split into individual units (~595 mL plasma) and processed using the INTERCEPT Blood System for plasma according to the package insert. Following the pathogen inactivation treatment, the INTERCEPT Cryo Processing Container (ICPC) was attached to the plasma storage bags by sterile docking and the plasma transferred to the ICPC, which was then frozen within 24 hours of draw in a freezer at −30°C. The pathogen-reduced plasma was stored frozen at −30°C for 3 days.

Pathogen-reduced cryoprecipitate was produced by placing the plasma in the ICPC in a temperature-controlled 2 to 6°C refrigerator until completely thawed over 24 hours. The thawed component in the ICPC was centrifuged for 15 minutes to sediment the cryoprecipitate per the following settings: 4150 revolutions per minute, accumulated centrifugal effect 9.35×10^7, $4600 \times g$, temperature 1 to 6°C, brake value 7. The cryoprecipitate-poor supernatant was removed by gravity flow into the still-attached plasma storage containers, leaving 58.8 mL of residual supernatant in the ICPC with the precipitate. The cryoprecipitate was resuspended in the residual supernatant, aliquoted into 1.5-mL Eppendorf tubes and refrozen on dry ice within 1 hour. The tubes were shipped frozen on dry ice to NewYork-Presbyterian Hospital–Weill Cornell Campus, where it was stored for 1 month in a −20°C temperature-monitored freezer within the blood bank.

Five days before collecting samples from each volunteer, 1.5-mL aliquots of PR Cryo were thawed at 37°C in a water bath for 3 minutes and kept at room temperature on a shelf in the temperature-monitored blood bank. All PR Cryo aliquots were used between 96 and 120 hours (4–5 days) from the time of thaw.

Standard cryoprecipitate

Group A cryoprecipitate (Cryo) was manufactured at the New York Blood Center in the standard manner (sterile pooling of five units of cryoprecipitate made from five individual units of fresh frozen plasma). However, instead of freezing in one bag (approximately 110–130 mL), per standard manufacturing, the product was mixed well and aliquoted into 10-mL conical tubes. The aliquots of the standard pooled cryoprecipitate were thawed at 37°C in a water bath for 10 minutes on the day of investigation and used within 6 hours. Quality control testing performed at the New York Blood Center on standard cryoprecipitate pooled by a sterile method at the time of manufacture revealed that each pool contains between 1729 and 2169 mg of fibrinogen by the Clauss assay.

Fibrinogen concentrate

The FC (RiaSTAP, CSL Behring) was reconstituted before starting the study according to the manufacturer's instructions by adding 50 mL of sterile water to the powder (final concentration of 20 mg/mL). Aliquots containing 1 mL each were kept frozen (−80°C) until the day of the investigation. Before use, vials were thawed at 37°C for 3 minutes in a water bath and used within 6 hours. The dose for FC was chosen to replicate a dose commonly used in the clinical setting (50 mg/kg).[20] Based on the available quality control data for standard cryoprecipitate, we hypothesized that the fibrinogen content in the chosen doses would be similar for the three products.

Thromboelastometry

All thromboelastometry tests were performed by one trained operator to capture the A10 value (clot amplitude at 10 minutes after start of clot initiation) and were stopped after the maximum clot firmness (MCF) was determined. Testing was performed using a validated rotational thromboelastometry device (ROTEM Delta, Instrumentation Laboratory) with internal and external quality control performed in compliance with regulatory requirements. Technical details have been previously described.[21]

Within 3 hours after blood withdrawal, all thromboelastometry (fibrin-based extrinsically activated test with tissue factor and cytochalasin D [FIBTEM] and extrinsically activated test using tissue factor as activator [EXTEM]) was performed on whole blood. The EXTEM test reflects the contribution of all coagulation factors and platelets on clot building and clot strength. The FIBTEM test eliminates the contribution of platelets by adding cytochalasin D, thus assessing fibrinogen/fibrin polymerization. The FIBTEM and EXTEM tests were performed using lyophilized reagents according to the manufacturer's recommendations by mixing 300 μL of citrated blood with the reagents (EXTEM test: star-tem reagent [recalcification] plus ex-tem reagent [extrinsic activator]; FIBTEM test: ex-tem reagent [extrinsic activator] plus fib-tem reagent [cytochalasin D/platelet inhibitor]; all from Instrumentation Laboratory).

Factor activity levels

Platelet-poor plasma samples were prepared to test for baseline plasma fibrinogen activity (Clauss assay, based on a thrombin-induced clotting time; HemosIL QFA Thrombin [Bovine], Instrumentation Laboratory); factor XIII antigen (latex enhanced immunoassay; HemosIL Factor XIII Antigen; Instrumentation Laboratory), von Willebrand factor antigen (VWF:Ag; latex enhanced immunoassay, HemosIL von Willebrand Factor Antigen; Instrumentation Laboratory) and von Willebrand factor ristocetin cofactor activity (VWF:RCo; Glycoprotein Ib receptor-specific latex enhanced immunoassay, HemosIL von Willebrand Factor Activity; Instrumentation Laboratory), as well as coagulation FVIII activity (using a synthetic phospholipid reagent for determination of aPTT (HemosIL SynthASil; Instrumentation Laboratory) and FVIII-deficient plasma (Congenital Factor VIII Deficient Plasma, George King Bio-Medical, Inc.). All tests were performed on coagulation analyzers (ACL TOP 700 CTS [fibrinogen] or ACL TOP 700 ROT analyzer; Instrumentation Laboratory) using a validated assay protocol. All assays on subject samples and VWF:Rco, VWF:Ag, FVIII activity, and FXIII antigen assays on Cryo, PR Cryo, and FC were performed directly, with validated onboard instrument dilution performed as needed. Fibrinogen assays on the Cryo, PR Cryo, and FC were performed on a prediluted specimen (1:3).

In vitro supplementation

After the baseline thromboelastometry measurement was performed and an aliquot was set aside for testing factor levels, a model of dilutional coagulopathy was induced by adding 7 mL of a balanced crystalloid solution (Plasma-Lyte A, Baxter International) to 7 mL of citrated whole blood, inducing a 50% hemodilution. Diluted blood samples were tested by all assays. Next, the diluted blood specimens were aliquoted into three prepared tubes (3 mL each) for further in vitro supplementation. The in vitro supplementation was performed by adding 227 μL of each cryoprecipitate preparation (PR Cryo or Cryo) to each tube to administer an in vitro dose approximating the transfusion of two pooled doses (10 units) of cryoprecipitate in a patient. Likewise, 165 μL of FC were added to the third diluted test tube at a dose approximating an in vivo dose of 4 g (50 mg/kg). In vitro doses were calculated based on the plasma content in vivo by using the following formula: plasma volume = 0.070 × kg (1 – hematocrit).[22]

Thromboelastometry testing was performed within 15 minutes after Cryo or fibrinogen supplementation of the diluted blood. Plasma samples were prepared and frozen at −80°C for additional laboratory testing as previously described. The study design displaying all preparation steps and measurements for primary outcome parameters are shown in Fig. 1.

To assess the ability of each product to treat dilution-dependent weakening of fibrinogen polymerization, improvement of the FIBTEM MCF after dilution/substitution was assessed as the primary endpoint in the study.

Statistics

SPSS software package (Version 25.0, IBM Corporation) was used for statistical analyses. The Kolmogorov–Smirnov test was applied to test for nonparametric distribution. Friedman's test analysis was used to test for significant differences in FIBTEM MCF before and after supplementation among the three tested fibrinogen-containing products. When an overall significant difference was detected, a pairwise comparison using the Wilcoxon test between each supplement was performed. The same statistical tests were applied for all other parameters assessed. Data are presented as median and 25th and 75th percentiles (IQR).

RESULTS

Coagulation factor concentrations in products

Fibrinogen, FVIII, VWF:Ag, VWF:Rco (activity), and FXIII levels were measured in all three blood products used in the study (Table 1). The median level of fibrinogen was 1616 mg/dL in fibrinogen concentrate, 948 mg/dL in PR Cryo and 864 mg/dL in Cryo. This equated to the addition of 2.67 mg of fibrinogen from FC, 2.15 mg of fibrinogen from PR Cryo and 1.96 mg of fibrinogen from Cryo to the diluted patient specimens. Thus, there was 24% more fibrinogen added using FC than PR Cryo and 36% more than Cryo. There was 11% more fibrinogen added for PR Cryo than Cryo. The median level of FVIII in PR Cryo was 99.6% and in Cryo 410%. The median level of VWF:Rco in PR Cryo was 459% and in Cryo 593%. The median level of VWF:Ag in PR Cryo was 663% and 904% in Cryo. The median level of FXIII antigen was 269% in PR Cryo, and 224% in Cryo, and 48% in FC.

Subjects

All consented subjects were eligible and enrolled. Laboratory results from all 10 volunteers were used for the final analysis. After induction of a 50% dilution in vitro, parameters of clot strength were significantly deteriorated compared to undiluted baseline samples (Table 2). Resulting fibrin/fibrinogen polymerization as detected by FIBTEM MCF decreased significantly to a median (IQR) MCF of 6.5 mm (3.8–8.3 mm;

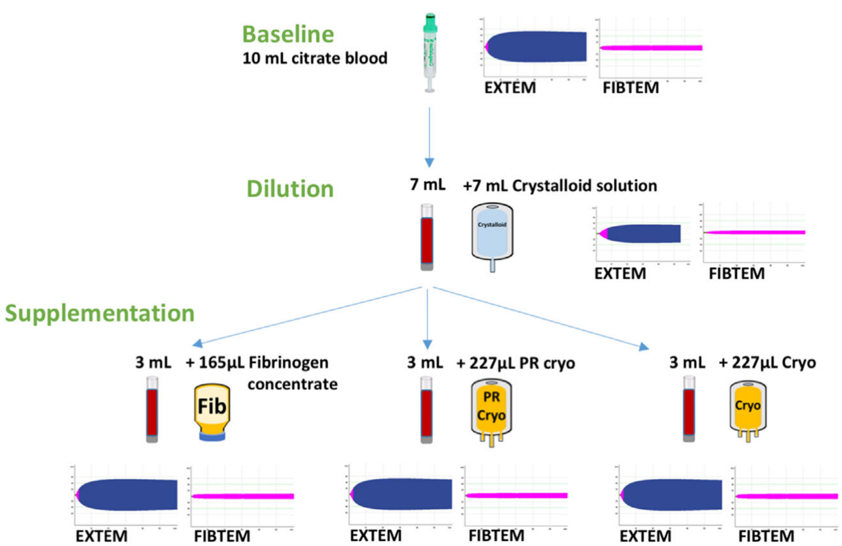

Fig. 1. Preparation of tested blood samples and assessment of primary endpoint (FIBTEM MCF). [Color figure can be viewed at wileyonlinelibrary.com]

p = 0.005), which would indicate the immediate need for administration of a concentrated fibrinogen product in a bleeding patient. After in vitro supplementation with Cryo at a dose that replicates two pooled doses (10 units), the FIBTEM MCF increased significantly as compared to the diluted sample, but still remained significantly lower than baseline levels (Table 3) (Fig. 2). Supplementation with PR Cryo at the same dose significantly increased FIBTEM MCF closer to the range of predilution baseline levels. In vitro supplementation with FC at a dose that replicated a dose of 4 g in an 80-kg person (50 mg/kg) increased FIBTEM MCF to levels significantly higher than baseline levels (16.5 mm [14.8–20.3 mm]; p = 0.035), and significantly higher than resulting PR Cryo levels (13.0 mm [2.0–14.3 mm]; p = 0.005) and Cryo levels (9.0 mm [8.0–11.3 mm]; p = 0.005) (Fig. 2). The difference between PR Cryo and Cryo supplementation was not significant (p = 0.445).

While FIBTEM A10 and FIBTEM MCF were the highest after supplementation with FC, the MCF in the EXTEM assay was significantly higher following supplementation with PR Cryo compared to Cryo (p = 0.01), and showed no difference compared to FC (Fig. 2).

All measured factor levels and activities increased significantly following supplementation with PR Cryo and Cryo (Table 3). Supplementation with Cryo led to significantly higher von Willebrand factor levels and activity compared to PR Cryo, while FXIII levels were significantly higher using PR Cryo. After supplementation with FC, the fibrinogen activity was restored to the range of baseline plasma levels. After supplementation with PR Cryo or Cryo, levels were still significantly lower than baseline levels but significantly higher than levels after dilution.

TABLE 1. Comparison of coagulation measurements in blood products

Measurement	Standard Cryo	PR Cryo	Fibrinogen concentrate
Fibrinogen activity (mg/dL)	864	948	1616
VWF:Ag (%)	904	663	346
VWF:Rco (%)	593	459	104
Factor VIII (%)	410	99.6	11
Factor XIII (%)	224	269	48

VWF:Ag = von Willebrand factor antigen assay; VWF:RCo = von Willebrand factor ristocetin cofactor activity.

DISCUSSION

To our knowledge, this is the first reported investigation of a new PR Cryo stored at room temperature for 5 days, simulating how this novel product would compare in the clinical setting with the current worldwide standards of care: Cryo, used within 6 hours after thawing, and FC.

The main finding of our study is that cryoprecipitate derived from pathogen-inactivated plasma, thawed for 5 days, has the ability to fully restore fibrinogen/fibrin clot strength (FIBTEM MCF) in an in vitro dilutional model. In addition, the FIBTEM MCF was significantly stronger compared to supplementation with the same dose of Cryo used within 6 hours of thawing. However, FC yielded the largest increase in fibrinogen/fibrin clot formation. The overall clot firmness, as measured by the EXTEM test, showed equivalence between FC and PR Cryo, while Cryo achieved slightly inferior results to both.

Notably, supplementation with PR Cryo led to significantly stronger FIBTEM results compared to Cryo in the dilutional model. In contrast, no difference in plasma fibrinogen activity levels was observed when substitution with Cryo versus PR Cryo was compared. The higher FIBTEM response to PR Cryo could be explained by the higher fibrinogen and FXIII levels in PR Cryo compared to Cryo. Results from previous in vitro studies have shown a synergistic positive effect of FXIII and fibrinogen on enhancing FIBTEM clot firmness in a hemodilution model, while FXIII alone did not improve clot firmness.[23,24] The supplementation with FC led to the highest fibrinogen levels and FIBTEM MCF compared to either of the other cryoprecipitate preparations used. This difference may be explained by differences in fibrinogen content added in the product doses used in this in vitro model. This occurred because the design of this study was to compare clinical dosing rather

TABLE 2. Comparison of subject coagulation measurements at baseline and after 50% dilution in vitro

Measurement	Baseline	50% dilution	p value
Fibrinogen activity (mg dL^{-1})	261.5 (205.8–320.3)	112.0 (91.2–134.0)	0.005
VWF:Ag (%)	108.9 (71.4–133.4)	42.2 (27.4–51.9)	0.005
VWF:Rco (%)	89.8 (66.9–102.2)	37.2 (22.6–42.0)	0.005
Factor VIII (%)	84.1 (39.4–106.6)	25.8 (17.3–33.3)	0.005
Factor XIII (%)	101.9 (80.4–109.3)	32.8 (28.4–44.5)	0.005
EXTEM A10 (mm)	51.5 (45.8–57.8)	36.5 (33.0–41.8)	0.004
EXTEM MCF (mm)	59.5 (55.5–64.5)	46.0 (42.5–49.5)	0.004
FIBTEM A10 (mm)	13.5 (10.3–17.5)	6. 0 (4.0–8.3)	0.005
FIBTEM MCF (mm)	13.5 (10.3–18.3)	6.5 (3.8–8.3)	0.005

Data are presented as median (IQR).
EXTEM = extrinsically activated test using tissue factor as activator; FIBTEM = fibrin-based extrinsically activated test with tissue factor and cytochalasin D; MCF = maximum clot firmness; VWF:Ag = von Willebrand factor antigen; VWF:Rco = von Willebrand ristocetin cofactor activity.

TABLE 3. Comparison of subject EXTEM and FIBTEM measurements and factor activity levels after in vitro supplementation

Measurement	Standard cryo	PR cryo	Fibrinogen concentrate
EXTEM A10 (mm)	43.0 (39.8–46.3)	44.0 (41.8–48.0)*	42.5 (38.3–44.5)‡
EXTEM MCF (mm)	51.0 (48.8–54.5)	53.5 (49.8–55.8)*	52.5 (49.0–56.3)
FIBTEM A10 (mm)	9.0 (8.0–11.0)	12.0 (11.0–13.3)*	15.0 (13.8–18.8)†‡
FIBTEM MCF (mm)	9.0 (8.0–11.3)	13.0 (12.0–14.3)*	16.5 (14.8–20.3)†‡
Factor VIII (%)	61.2 (23.1–80.1)†	48.1 (38.4–57.7)‡	21.6 (14.9–31.3)
VWF:Ag (%)	119.2 (107.6–128.6)†*	110.4 (100.2–127.1)‡	62.2 (47.7–72.1)
VWF:Rco (%)	95.4 (88.0–100.6)†*	80.4 (72.2–88.0)‡	48.9 (40.9–52.1)
Factor XIII (%)	48.3 (42.5–54.3)†*	64.8 (61.0–71.6)‡	37.0 (31.4–43.1)
Fibrinogen activity (mg dL^{-1})	193.5 (181.5–213.3)	187.0 (182.5–211.5)	269.0 (244.8–310.5)‡†

Data are presented as median (IQR).
EXTEM = extrinsically activated test using tissue factor as activator; FIBTEM = fibrin-based extrinsically activated test with tissue factor and cytochalasin D; MCF = maximum clot firmness; VWF:Ag = von Willebrand factor antigen; VWF:Rco = von Willebrand ristocetin cofactor activity.
* Significant difference between Cryo and PR Cryo.
† Significant difference between Cryo and fibrinogen.
‡ Significant difference between PR Cryo and fibrinogen.

than dosing matched by fibrinogen content of the products; therefore, the final concentration in the FC contained 24% and 36% more fibrinogen versus PR Cryo and Cryo, respectively. Notably, a recent systematic review did not find evidence that either cryoprecipitate or FC was superior in terms of efficacy and safety.[13] Both FC and cryoprecipitate have been successfully used to treat acquired hypofibrinogenemia in various settings.[10,25]

Finally, it was interesting to note that in the EXTEM test, which evaluates the overall clot firmness, PR Cryo and fibrinogen supplementation led to equivalent results, and PR Cryo was superior to Cryo. These results may differ from the FIBTEM results because there could be a synergistic effect of both the higher FXIII and fibrinogen levels in PR Cryo versus Cryo and the fact that VWF:Rco (activity) was maintained in PR Cryo. Although it is conceivable that an increase in VWF may enhance the platelet contribution to clot firmness, neither the supplementation of VWF alone nor the combination of VWF and FVIII have previously been shown to increase clot firmness in an in vitro assay.[26,27] As such, these findings and their explanation require further exploration in larger studies.

Previous publications have assessed other formulations of pathogen-reduced cryoprecipitate. In general, two different manufacturing processes to reduce pathogen activity in plasma are available: solvent/detergent treatment or the addition of a photosensitizer that inactivates DNA and RNA upon ultraviolet or long wavelength visible light exposure.[28]

The intrinsic effects of pathogen inactivation on fibrinogen structure or function are poorly understood. Backholer and colleagues[15] published one of the first studies directly comparing the cryoprecipitate made from amotosalen-treated plasma and cryoprecipitate made from methylene blue–treated plasma to cryoprecipitate made from untreated plasma. All cryoprecipitate in the Backholer study was made from pools of six ABO-matched plasma units. In that study, fibrinogen activity in both PR Cryo products was significantly decreased compared to cryoprecipitate made from untreated plasma as measured by the Clauss assay and by thromboelastometry. The thromboelastometry MCF was significantly higher using the amotosalen method compared to the methylene blue method; no difference was observed between the products in fibrinogen activity. Those results are in agreement with a study published in 2013 by Cid et al.,[16] where pooled units (three donors each) of fresh frozen plasma were split into two aliquots; one of the aliquots was not treated, and the other was treated with amotosalen and ultraviolet A light. The treated units showed a reduction in fibrinogen activity (modified Clauss assay) between 18% and 40% compared to cryoprecipitate prepared from nontreated plasma. In that study, FVIII and ADAMTS13 levels were likewise decreased following pathogen reduction, while the quantity and quality of VWF (including VWF multimer patterns) were not altered. Other methods of pathogen reduction in cryoprecipitate have demonstrated a similar decrease in fibrinogen content.[29–31] The solvent/detergent method resulted in a decrease in fibrinogen content by 28%,[32] while riboflavin and ultraviolet light treatment showed an average reduction of fibrinogen in a range of 14% to 15%.[17]

The results in our study showed equivalence in fibrinogen activity and overall contribution to clot firmness between PR Cryo and untreated Cryo. This is likely different from the Cid et al. study[16] because a different technique was used to make PR Cryo and the plasma sources and plasma pool sizes were different. In addition, in the Cid study the plasma was manufactured from individual whole blood units that were held overnight at 20 to 24°C for buffy coat processing.

Hemostatic properties and fibrinogen levels of thawed cryoprecipitate held at ambient temperature (18–24°C) are preserved up to 120 hours.[19] The stability of thromboelastometry clot firmness has also been demonstrated in thawed pooled cryoprecipitate units held at room temperature for up to 72 hours.[33] Our study confirmed the hemostatic effect after storage at room temperature for 5 days is preserved for PR Cryo as well.

Undeniably, the fibrinogen concentration within each unit of cryoprecipitate varies widely.[12] Anderson et al.[34] investigated the variability between donors in 11 units of cryoprecipitate and found a range from 3.2 to 8.2 g/L. This variability

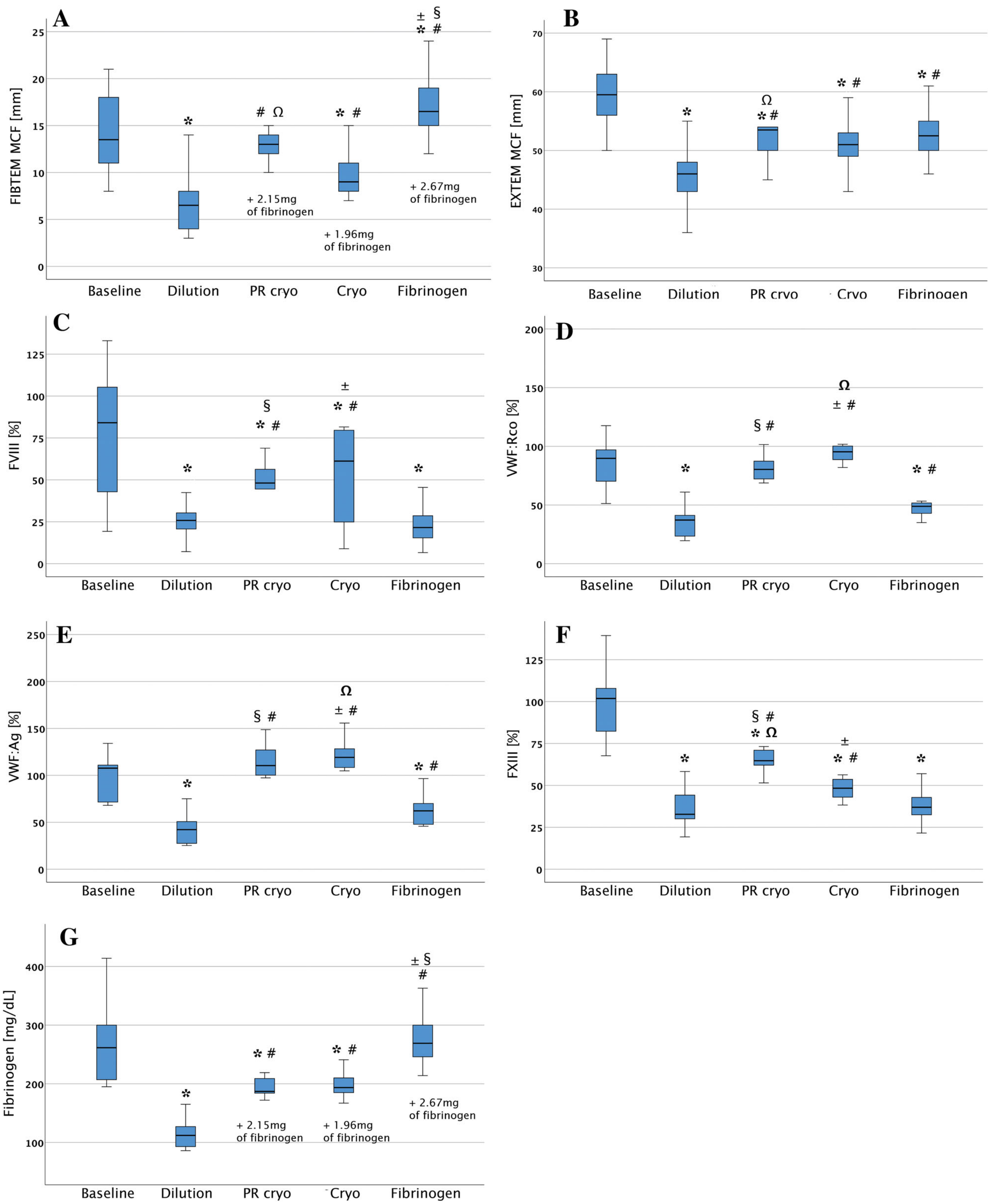

Fig. 2. FIBTEM and EXTEM MCF and factor activity levels at baseline, after dilution, and after supplementation. * Significant difference to baseline, # significant difference to dilution, § significant difference fibrinogen versus PR Cryo, ± significant difference fibrinogen versus Cryo, Ω significant difference Cryo vs PR Cryo. [Color figure can be viewed at wileyonlinelibrary.com]

may have led to differences between the two types of cryoprecipitate preparation in the present investigation and in other studies of cryoprecipitate.

There are a few limitations of this study that need to be considered. First, it is an in vitro analysis. As such, it does not reflect all the dynamic and intricate processes required for clot building, such as the effect of endothelial adhesion and consumption of cellular and plasma components during bleeding. Second, the true efficacy of a blood component should be determined in a clinical setting to assess improvement of hemostasis. In our study, we chose to assess clot firmness using thromboelastometry as a primary endpoint, as this methodology is used to guide fibrinogen replacement therapy.[24,35–37] Third, our study included only a small sample size of blood from healthy subjects who were not bleeding, and results may differ in larger clinical studies with bleeding patients. Fourth, the study only compared a single representative pooled PR Cryo product to a single representative pooled Cryo product. Results could differ depending on product variability. It is anticipated that PR Cryo products will have less variability than Cryo products, as there will be a limited number of PR Cryo manufacturing blood centers with shared standard operating policies. Furthermore, a larger pool of plasma units will be used as the starting material rather than individual units, thus minimizing individual donor variability. Fifth, the cryoprecipitate and fibrinogen were prepared by the standard methods, but the storage was in smaller aliquots than usual, which could potentially impact the function of the product. Finally, we chose to use a dosing strategy similar to that used in clinical practice, 10 units for Cryo and 50 mg/kg for FC, rather than matching the dose by fibrinogen content. This resulted in 24% and 36% more fibrinogen in the FC dose versus PR Cryo and Cryo, respectively.

In conclusion, our study shows that cryoprecipitate derived from pathogen reduced plasma, used 5 days after thawing, is as effective as FC and standard cryoprecipitate used within 4 to 6 hours of thawing at restoring clot strength after 50% in vitro dilution. Further studies are needed to confirm these findings in vivo.

CONFLICTS OF INTEREST

MC is a consultant for Cerus Corporation, Instrumentation Laboratory, and Octapharma. TH has received lecturer's fees and travel support from Octapharma and Instrumentation Laboratory and is a consultant for Octapharma. LA has received lecturer's fees and travel support from CSL Behring and Instrumentation Laboratory.

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