

Clinical Use of Plasma for Transfusion

Irma Szymanski, MD

Professor of Pathology, Emerita

**University of Massachusetts
Medical School**

PLASMA PRODUCTS FOR TRANSFUSION

Fresh Frozen Plasma (FFP)

Thawed Plasma

Plasma Frozen within 24 hours of Collection (FP24)

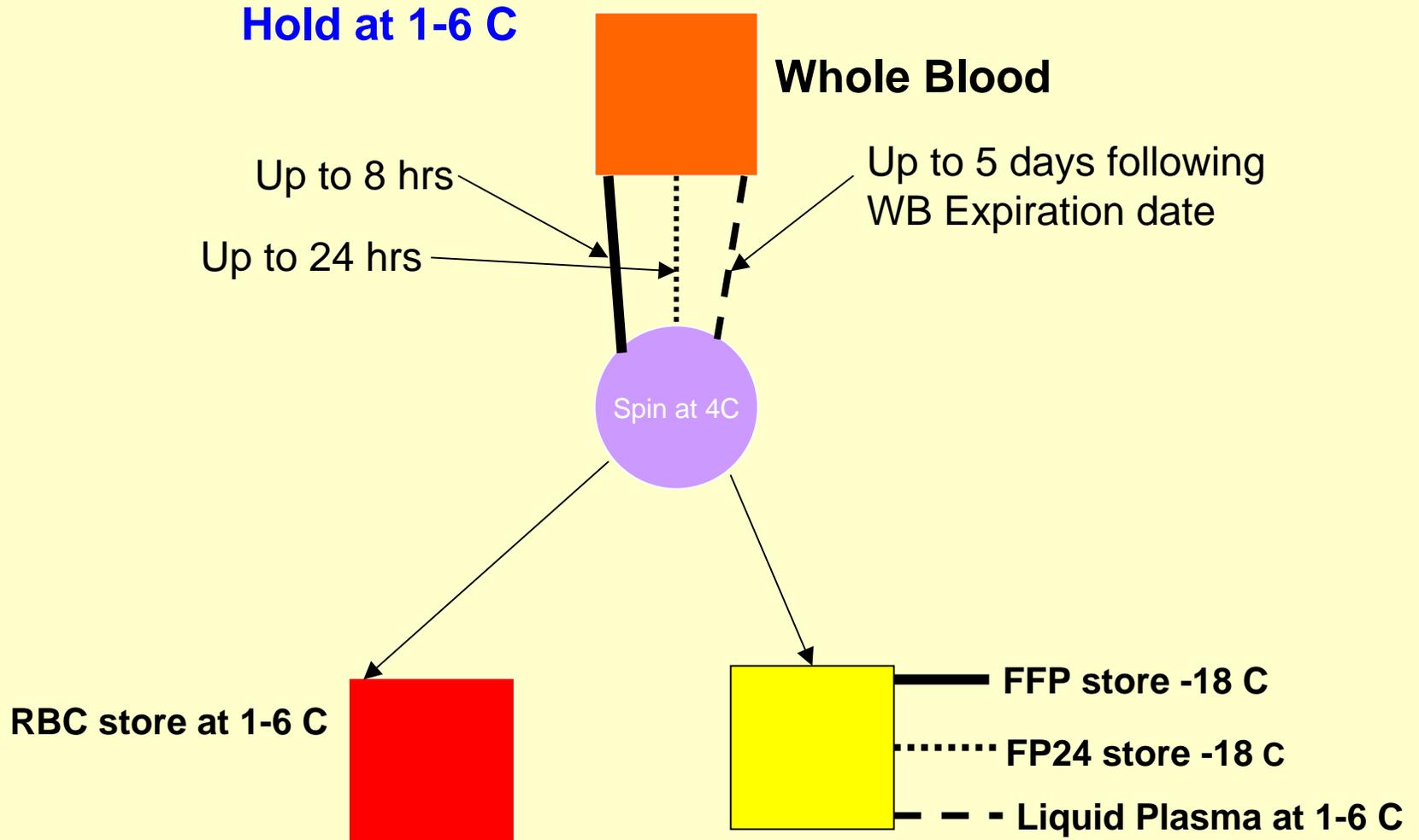
Liquid Plasma

Plasma, Cryoprecipitate Reduced (Cryo-poor Plasma)

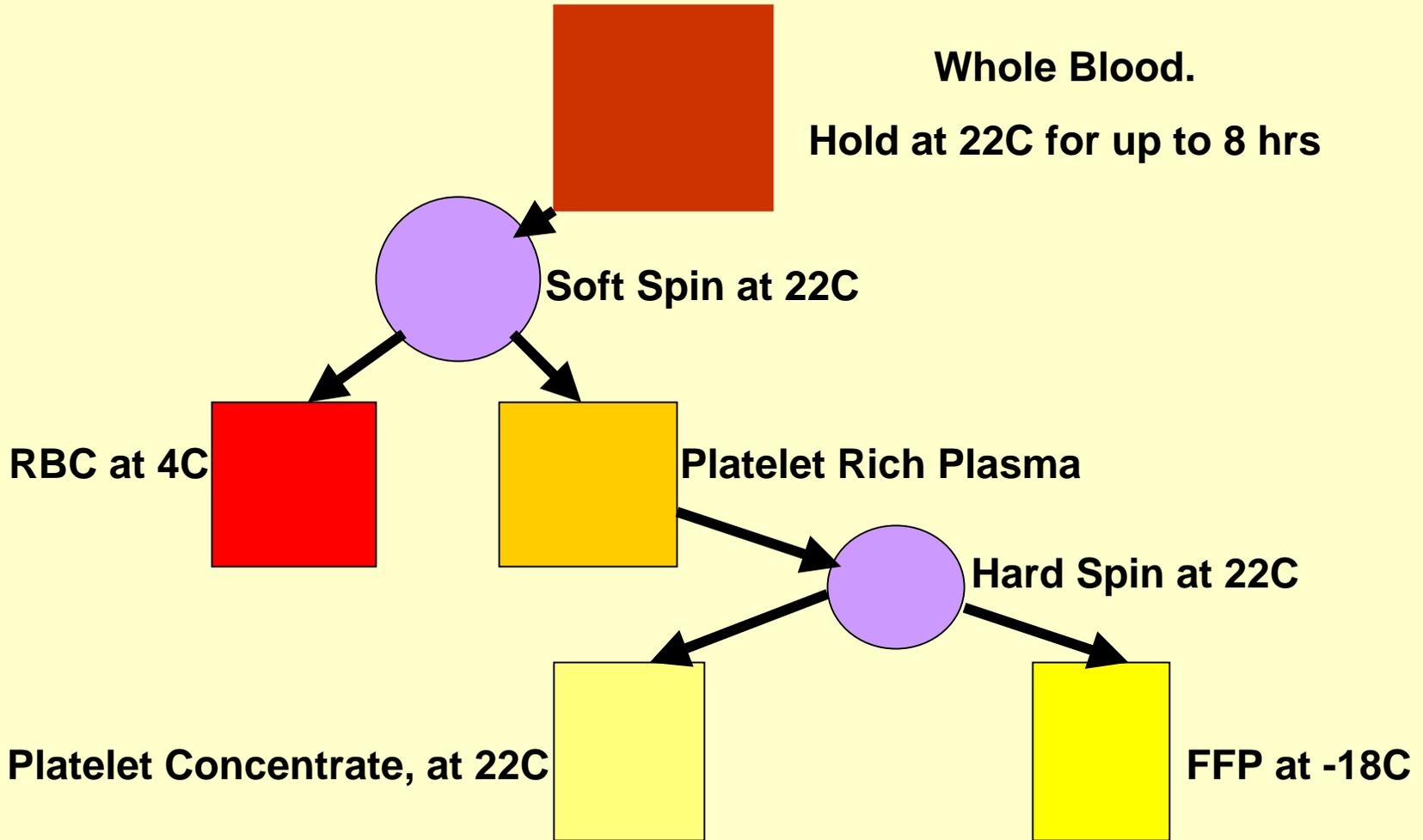
Cryoprecipitated AHF (Cryoprecipitate, Cryo)

Fibrin Glue

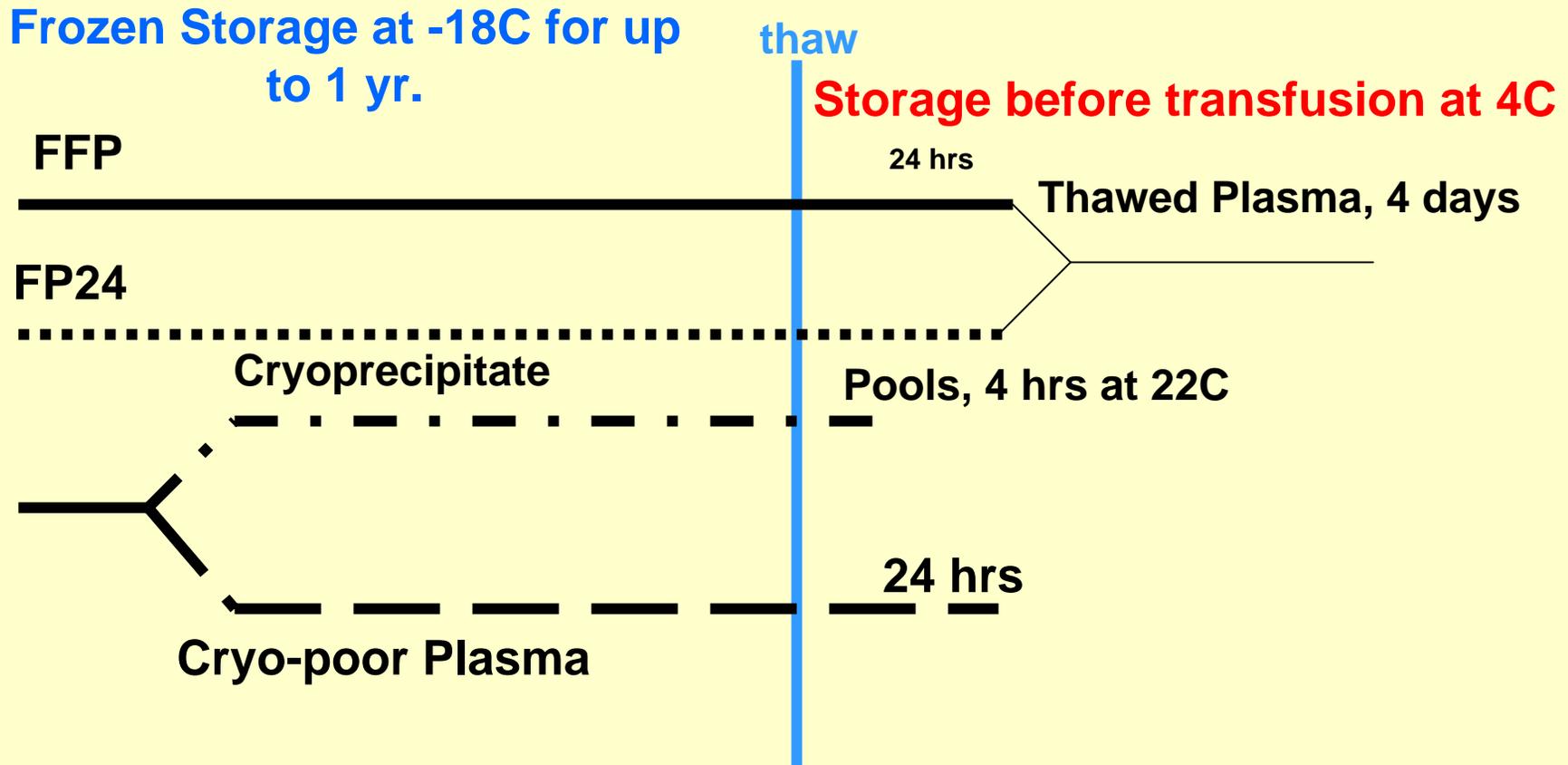
Preparation of RBC, FFP, FP24, and Liquid Plasma



Preparation of RBC, FFP, and Platelets



Outdates of FFP, FP24, Thawed Plasma, Liquid Plasma, Cryoprecipitate and Cryo-poor Plasma



**Which factors
influence the
recovery of proteins
in plasma separated
from whole blood?**

Anticoagulants

Temperature and Length of Hold

Rate of cooling to the temperature of the Hold

Rate and Temperature of freezing plasma

Length and Temperature of frozen storage

Temperature and Length of Storage after thaw

Chemicals in the Currently used anticoagulants (mg in 63 mL) added to 450 mL of whole blood (AABB Technical Manual)

| Anticoagulant | CPD | CP2D | CPDA-1 |
|-------------------------------|-------------|-------------|-------------|
| Chemical | | | |
| Sodium citrate | 1660 | 1660 | 1660 |
| Citric acid | 188* | 188* | 188* |
| Dextrose | 1610 | 3220 | 2010 |
| Monobasic Na phosphate | 140 | 140 | 140 |
| Adenine | 0 | 0 | 17.3 |

* 206 mg stated on the
label of bags

What affects the recovery of factors V and VIII in plasma separated from RBC?

- When WB is kept at 4C for 8 hours, FV decreases very little, but FVIII...(according to A. Farrugia, PhD)

| Cooling temperature | FVIII, IU/mL |
|----------------------------|---------------------|
| 0 – 4 C (n=9) | 0.45 ± 0.05 |
| 20 C (n=9) | 0.84 ± 0.1 |

Delayed blood processing. Percentage of FVIII remaining when blood kept at 4C or 22C *

| Length of the delay (hours) | Blood at 22C | Blood at 4C |
|-----------------------------|--------------|-------------|
| 6 | 90 | 84 |
| 12 | 80 | 68 |
| 18 | 65 - 70 | 56 |

* Hughes et al. Transfusion 1988;28:566-70

Table IV. Haemostatic factor content of thawed fresh-frozen plasma (FFP), and after storage at 4°C. A typical unit of 300 ml includes (IU/ml), except fibrinogen (g/l).

| | Levels when freshly thawed | Levels at 24 h | Levels at 5 d |
|------------------|-------------------------------|-------------------|------------------|
| Fibrinogen | 2.67 | 2.25 | 2.25 |
| FII | 80 | 80 | 80 |
| FV | 80 | 75 | 66 |
| FVII | 90 | 80 | 72 |
| FVIII | 92 | 51 | 41 |
| FIX | 100 | | |
| FX | 85 | 85 | 80 |
| FXI | 100 | | |
| FXII | 83 | | |
| FXIII | 100 | | |
| Antithrombin III | 100 | | |
| VWF | 80* | | |

These values were determined in the Pathology Laboratories of Southampton University Hospitals Trust.

Protein C and antithrombin levels are in the 'normal range'.

*With some loss of HMW multimers, particularly if SD-treated.

Cryoprecipitated AHF (Cryoprecipitate)

- Cryoprecipitate is **the cold insoluble portion of plasma** that remains when FFP is thawed at 1-6 C. **The supernate (Cryo-poor Plasma)** is removed by centrifugation and the cryoprecipitate, in a small volume of plasma (about 15 mL), is refrozen and stored at -18C.
- Different **technical variables** of separating plasma from whole blood, such as the temperature and length of whole blood storage before separation, as well as the method of freezing (temperature, rate of freezing) influence **the amount of cryoprecipitable proteins** in the cryoprecipitate.
- CFR states that each bag of cryoprecipitate shall contain no less than **80 units of FVIII per bag**.

Cryoprecipitated AHF (Cryoprecipitate). Total amount of different proteins per bag prepared in different centers.

| Protein | Center A, ARC, NE | Center B, Puget Sound | Center C, ARC, PA* | Center D, Inst. Tx. Med |
|--------------------------------|------------------------------|----------------------------------|-------------------------------|------------------------------------|
| FVIII, IU/bag | 80 – 100 | 100 | 197 | 80 – 100 |
| vWF, IU/bag | Significant | 100 | 197 | 80 – 100 |
| Fibrinogen, mg/bag | 150 – 200 | 150 – 200 | 445 | 150 – 250 |
| FXIII, IU/bag | Significant | Some | Not done | 50 – 100 |
| Fibronectin, mg/bag | Not stated | Some | Not done | 50 - 60 |

*** Flash freezing used**

Cryoprecipitated AHF (Cryoprecipitate)

- **Uses for:**
- Treatment of Bleeding in **Congenital hypo- or dysfibrinogenemia.**
- Not used for treatment of hemophilia A or vWD because purified products are available.
- Recommended for treatment of **congenital FXIII deficiency.** Purified product, Fibrogammin P (Aventis (Behring)) is available in Europe.
- **Source Material** for purification of coagulation factors.

Fibrin Glue

- **Definition:** Fibrin glue is a **biological tissue adhesive** used by surgeons; it initiates the final stages of coagulation, when a solution of human fibrinogen is activated by thrombin.
- Fibrin glue is prepared during **surgery** by combining equal volumes of **cryoprecipitate** (usually one or two bags) and **thrombin** solution containing **CaCl₂** and sometimes **antifibrinolytic agents** (Tranexamic acid* or epsilonaminocaproic acid, EACA). The concentrations of the ingredients vary in different reports.
- **Commercial preparation "Tisseel VH"** (Baxter Healthcare) is available.

*Not available in USA

Fibrin Glue

Used to seal:

- potential leaks in dura mater
- Large traumatized bleeding surfaces in life-threatening conditions, e.g., liver trauma, cardiac surgery, leaking vascular suture lines
- Middle ear or microsurgical procedures
- Plastic surgery

Problems:

- Use of bovine thrombin may cause immunization to thrombin and FV.

Human thrombin is used in Europe, recombinant human thrombin is going to be available in future in the USA.

FFP/FP24 transfusions. Role of the blood group.

ABO group of the FFP should be **identical** to that of the patient.

The next choice is to give **“compatible FFP”**, the isoagglutinins of which do not sensitize patient's RBC.

It is said that Rh group identity is not important. However, I want to bring to your attention, that

Rh negative patients, who have anti-D, may develop autoimmune hemolysis when given Rh+ FFP.

This is because FFP may contain some RBC stroma.

*IO Szymanski, V Smith. Transfusion 2003;43, No 9S, S75-040A

Immediate Transfusion Reactions to Plasma

Allergic

Usually mild urticaria. Exact cause often not known.
Sometimes patient has high levels of IgE.
??Storage-induced changes in plasma proteins.

Anaphylactic

Usually patient has antibodies to IgA.
Needs FFP without IgA.

Febrile non-hemolytic

Reason: recipient suspected to have WBC antibodies.
Reactions not eliminated by WBC-poor blood products
Why?? (Release of pyrogens from WBC during Hold?)

TRALI

Donor plasma contains antibodies to recipient's WBC.

Are FFP and FP24 infused correctly?

- Although guidelines for transfusion of plasma products have been published, **UK** data indicate that between 1993 and 2000, **34% of FFP transfusions were outside the guidelines.**
- In the **USA**, Dr. Dzik et al. reported in 2004 that at the Massachusetts General Hospital, **about 30% of the FFP transfusions were given to “prepare” patients with an increased INR for an invasive procedure.** The authors could not find any published evidence that such transfusions reduce bleeding at the time of the procedures.

Clinical Indications for FFP Transfusions

Category A: In patients with a single coagulation factor or plasma protein deficiency, whenever purified, virus-reduced, components are not available

- **A1, Congenital FV deficiency, Rare, autosomal, recessive disorder**
- **FFP** recommended for **bleeding**
- **Bleeding due to inhibitors to FV:**
 - Platelets (contain FV), immunosuppression, maybe PEX

Indications for FFP/FP24 Transfusions, Category A, cont.

- **A2, Congenital F XI deficiency**, autosomal recessive inheritance, occurs mostly in Ashkenazy Jews. Mild to moderate bleeding tendency related to trauma. Severity of bleeding site-related, because FXI prevents clot lysis.
- **FFP or FP24** should be given for **major surgery** at sites with high local fibrinolytic activity (**dental, urological**), together with antifibrinolytic agents.
- Dental extraction does not require replacement therapy, only antifibrinolytic agents.
- Virus-inactivated FXI concentrates (exist in Europe) are not used because of a chance of DIC.

Indications for FFP/FP24, Category A, cont.

- **A3, Thrombotic Thrombocytopenic Purpura (TTP)**
- **Definition:** This is a serious condition resulting in over 90% mortality if not treated correctly.
- **Cause:** Congenital or acquired **deficiency of the vWF metalloprotease, ADAMTS13**, which may also be at low levels because of autoantibodies to ADAMTS13.
- **Treatment:** Plasma exchange therapy with a replacement solution containing ADAMTS13.

A3, Thrombotic Thrombocytopenic Purpura, (TTP)

- Which is the best replacement solution?
- Some recommend the use of **Cryo-poor Plasma**, because it contains less vWF multimers than **FFP**. Recent data, however, show that FFP and Cryo-poor Plasma are equally effective*.
- **SD/FFP** contains practically no vWF multimers, and causes less allergic reactions, but because of reduced level of Protein S, its use has been associated with **thrombosis**.
- I have found the following protocol very useful: during PEX replace the first half of patient's plasma with 5% albumin, and the last 50% with FFP or with Cryoprecipitate Reduced Plasma.

Indications for FFP/FP24, Category A, cont.

A4, C-1 esterase inhibitor deficiency

**FFP is recommended to treat angioedema
Or prevent angioedema
during airway manipulation.**

**A purified concentrate, “Cetor”, exists,
Not yet available in the USA.**

Indications for FFP/FP24 Transfusions, Category B: Multiple coagulation factor deficiencies.

- **B1; Disseminated Intravascular Coagulation (DIC)**
- **Causes:** various causes may trigger the hemostatic system. It can be only a laboratory abnormality or result in microvascular bleeding or microvascular thrombosis. Platelets and all coagulation factors are depleted.
- **Treatment:** Treat the primary cause, but when **bleeding occurs**, blood component therapy is indicated. This includes platelets, **Cryoprecipitate, FFP (or FP24?)**, with careful clinical and coagulation test follow-up q 8 hr.
- Replacement therapy in the absence of bleeding is not necessary

Indications for FFP/FP24 Transfusions, Category B, cont.

B2, Liver disease

- ↓Clotting factor synthesis, ↑PT, aggravated by dysfibrinogenemia, thrombocytopenia, and fibrinolysis. Bleeding occurs due to a trigger, i.e. surgery, liver biopsy, or variceal rupture.
- If **bleeding** occurs, transfusion of FFP (?FP24) and cryoprecipitate is indicated. Prothrombin Complex Concentrates may confer a risk of DIC.
- Many clinicians do not want to attempt liver biopsy without FFP infusions if PT is more than 4 sec. over normal. However, there is no evidence that this is beneficial.
- Before and during liver transplantation, large amounts of FFP are transfused.

Indications for FFP/FP24 Transfusions, Category B, cont.

B3, Massive Transfusions (MT).

- Replacement formulae should be avoided.
- **Fibrinogen deficiency** is the first coagulation factor deficiency which develops after the loss of about 150% of blood volume*.
- If bleeding occurs, Cryoprecipitate, FFP (or FP24), (and platelet) **transfusions should be guided by coagulation tests** to reach a PT and PTT ratios of 1.5 and fibrinogen concentration above 100 mg/dL.

* Hiippala ST et al. Anesthesia and Analgesia 1995;81:360-65

Indications for FFP/FP24 Transfusions, Category B, cont.

B4, Open heart surgery

- Most patients do not need any transfusions. The large amount of heparin used during surgery is usually well handled by anesthesiologists. In our hospital, **ATIII** may be requested when **heparin** alone does not produce sufficient anticoagulation.
- We have observed **fibronectin consumption** in patients during CABG surgery when they need transfusions.
- Post operative bleeding from chest tube could indicate surgical blood loss rather than coagulation factor deficiency.

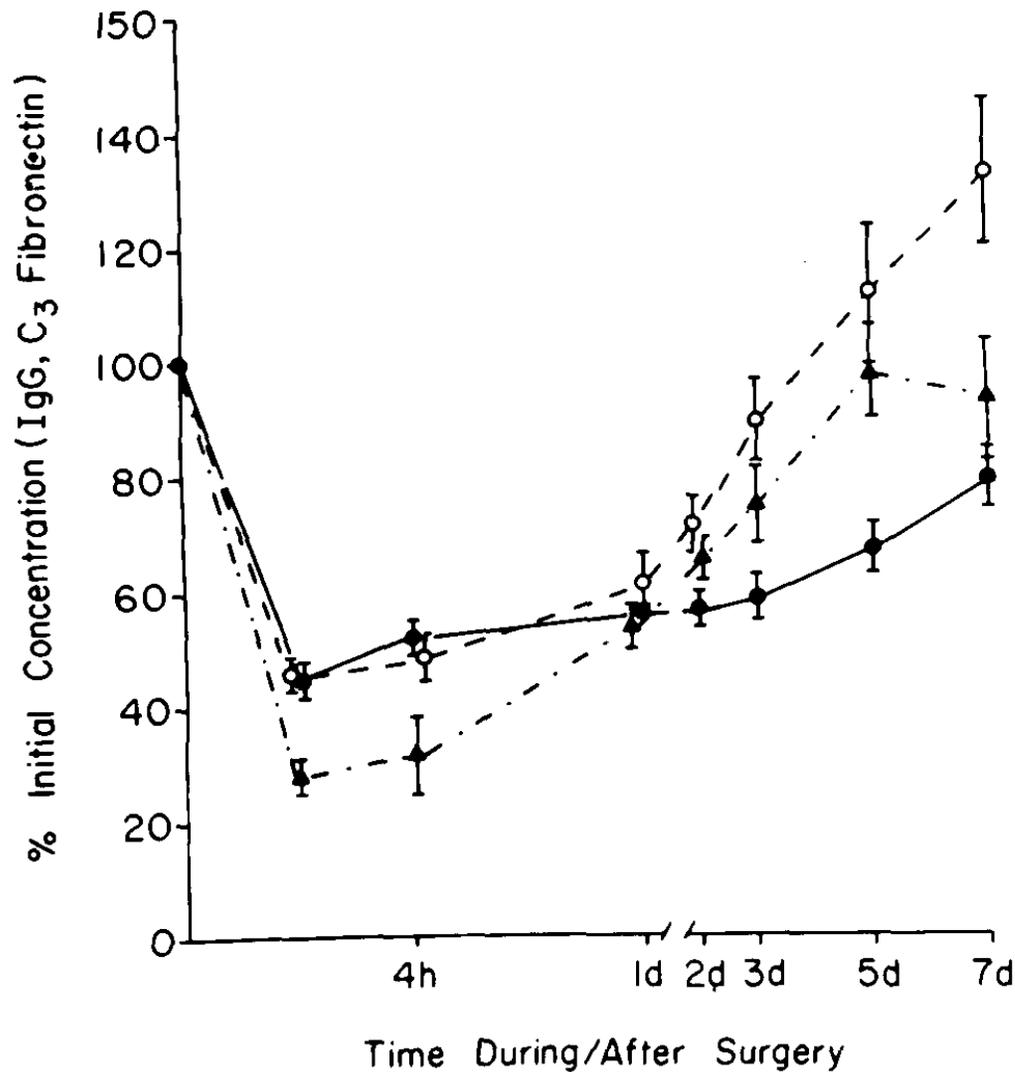


FIG. 1. Plasma concentrations of IgG, C3, and fibronectin expressed as a percent of the respective preoperative values during and after cardiac surgery in 12 patients. Mean \pm SEM are shown. \bullet — \bullet , IgG; \blacktriangle — \blacktriangle , fibronectin; \circ — \circ , C3. The zero value on the abscissa represents the preoperative value.

Indications for FFP/FP24 Transfusions, Category B, cont.

- **B5, Reversal of Warfarin Effect**
- Anticoagulation by Warfarin is caused by inhibition of vitamin K-facilitated carboxylation of **FII, FVII, FIX and FX**, and **Proteins C and S**.
- **Overanticoagulation** causing **INR of 10 or more and/or bleeding**, or when patient requires **urgent surgery**, is treated by **1. withdrawal of the drug, 2. Vitamin K p.o. or s.c., and 3. FFP or FP24.**
- **? rFVIIa.**

Summary

- The **purpose** of plasma transfusions is to correct **deficiencies** of plasma proteins and coagulation factors causing **serious, even life-threatening symptoms**.
- For purposes of **preparation and storage of Plasma Products** the optimum methods should be **defined on the basis of current knowledge and accurate data** on the specific protein content - eventually, also ADAMTS13- in the final products prepared by the current and newly described methods (including flash freezing).

Summary, cont.

- Since the current use of Plasma Products deviates from the guidelines established worldwide, more **research** about the effectiveness of **Plasma Transfusions** should be conducted to provide data for clear guidelines, acceptable to physicians both in clinical and laboratory specialties.
- To guide **clinicians** in Plasma transfusion therapy, they **need to know the content of specific proteins in Plasma Products** and use **point of care tests** to monitor the effectiveness of therapy.