

Plasma and PCCs

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Plasma

- Constitutes 55% of blood volume
- Has many functions
- Coagulation

Plasma

- Frozen Plasma
- Fresh Frozen Plasma

Frozen Plasma

- Difference

Fresh Frozen Plasma

- Components

FP/FFP

- *Plasma transfusion should be considered for patients with acquired multiple coagulation factor deficiencies under the following circumstances:*

FFP uses

- a. Plasma is recommended when serious bleeding has occurred or when preparing for an emergency surgical or in patients with vitamin K deficiency or on warfarin therapy with significantly increased PT, INR or PTT.

FFP uses

- *b.* Plasma is recommended when there is actual bleeding in patients with liver disease and increased PT, INR or PTT. Plasma may be administered to prepare for surgery or liver biopsy when the results of PT, INR or PTT or other appropriate coagulation assays are deemed sufficiently abnormal.

FFP indications

- Plasma is recommended in patients with acute disseminated intravascular coagulation with active bleeding associated with increased PT, INR or PTT, provided that the triggering condition can also be treated effectively.

FFP indications

- Plasma should be administered in the context of massive transfusion (more than 1 blood volume) if there is microvascular bleeding associated with a significantly increased PT, INR or a PTT. If the PT, INR or PTT cannot be measured quickly, plasma may be transfused in an attempt to stop diffuse nonsurgical bleeding.

- Plasma should be used in patients with congenital or acquired deficiencies of a single coagulation factor only when DDAVP or appropriate factor concentrates are ineffective or unavailable. Plasma should be used in these patients only when bleeding has occurred or is reasonably expected to occur from surgery or other invasive procedures. Plasma may be used depending on the specific factor involved.

Misuse

- Nutritional Support

Complications of FP/FFP Use

- Donor
- ABO
- Patient Issues
- Special issues: TRALI, TACO,

Risks

- Disease transmission,
- Allergic reactions,
- Trali
- Allergic reactions
- Transfusion Associated Cardiac Overload
- Alloimmunisation

Table 1

Condition	Description
INR above therapeutic range but < 5.0; no significant bleeding	Decrease dose or omit dose, monitor more frequently, and resume at lower dose when INR is therapeutic; if only minimally above therapeutic range, no dose reduction may be required. (grade 1C)
INR ≥ 5.0 but < 9.0; no significant bleeding	Omit next one or two doses, monitor more frequently, and resume at an appropriately adjusted dose when INR is in therapeutic range. Alternatively, omit dose and give vitamin K ₁ (1–2.5 mg orally), particularly if at increased risk of bleeding. (grade 1C) If more rapid reversal is required because the patient requires urgent surgery, vitamin K ₁ (≤5 mg orally) can be given with the expectation that a reduction of the INR will occur in 24 h. If the INR is still high, additional vitamin K ₁ (1–2 mg orally) can be given. (grade 2C)
INR ≥ 9.0; no significant bleeding	Hold warfarin therapy and give higher dose of vitamin K ₁ (2.5–5 mg orally) with the expectation that the INR will be reduced substantially in 24–48 h. (grade 1B) Monitor more frequently and use additional vitamin K ₁ if necessary. Resume therapy at an appropriately adjusted dose when INR is therapeutic.
Serious bleeding at any elevation of INR	Hold warfarin therapy and give vitamin K ₁ (10 mg by slow intravenous infusion), supplemented with fresh frozen plasma, prothrombin complex concentrate, or recombinant factor VIIa, depending on the urgency of the situation; vitamin K ₁ can be repeated every 12 h. (grade 1C)
Life-threatening bleeding	Hold warfarin therapy and give fresh frozen plasma, prothrombin complex concentrate, or recombinant factor VIIa supplemented with vitamin K ₁ (10 mg by slow intravenous infusion); repeat if necessary, depending on INR. (grade 1C)
Administration of vitamin K	In patients with mild to moderately elevated INRs without major bleeding, give vitamin K ₁ orally rather than subcutaneously. (grade 1A)

If continuing warfarin therapy is indicated after high doses of vitamin K₁, heparin or low-molecular-weight heparin can be given until the effects of vitamin K₁ have been reversed and the patient becomes responsive to warfarin therapy. It should be noted that international normalized ratio (INR) values greater than 4.5 are less reliable than values in or near the therapeutic range. Therefore, these guidelines represent an approximate guide for high INRs.

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Perioperative Hemostatic Management of Patients Treated with Vitamin K Antagonists²

Levy, Jerrold H.; Tanaka, Kenichi A.; Dietrich, Wulf
Anesthesiology. 109(5):918-926, November 2008.
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Table 1. Recommendations for Treating Oral Anticoagulation Patients Who Need Their INR Decreased Because of Actual or Potential Bleeding

Dose

- No good randomised trials
- Most published consensus documents recommended 10-15ml/kg
- Essential to monitor efficacy
- Repeat

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		

Is FFP clinically effective? A systematic review of randomised controlled trials.

- Dr S J Stanworth, John Radcliffe Hospital, Oxford, UK.
- Bloodmed

Epidemiology

- FDA(2004):the leading cause of transfusion-related death in the United States
 - ▶ Mortality rate:5-8%
 - ▶ Incidence: not well established
 - Underrecognition and underreporting
 - ▶ All plasma-containing blood and blood compartments
 - 1/5,000 blood & blood component
 - 1/2,000 plasma-containing component
 - 1/7,900 units of FFP
 - 1/432 units of whole blood derived platelets

Clinical Presentation

- Sudden onset, within 6 hours, but usually begin within 1~2 hours, of respiratory distress after transfusion

Table 1. Clinical features of transfusion-related acute lung injury

Clinical Features	Frequency
Dyspnea/respiratory distress requiring oxygen support	Virtually all
Requiring mechanical ventilation	~70%
Documented hypoxemia	Virtually all
Cyanosis	Very common
Hypotension	Majority
Fever	Very common
Hypertension	Unusual

Risk Factors

- No definite risk factors for TRALI

Implicated in some, not all:

- prolonged storage of transfused products
 - administration of fresh FFP
 - an underlying condition such as recent surgery
 - cytokine treatment
 - Thrombocytopenia
 - massive blood transfusion
 - active infection
- Dose **not** correlate with the **volume** of plasma infused or the titer of the anti-leukocyte antibody

Prevention

- Producing FFP only from male donors
- Screening previously-pregnant and previously-transfused apheresis donors for HLA antibodies
- Improving tests for the detection of white blood cell antibodies

Prothrombin Complex Concentrates

- Produced by fractionation
- Rich in Vitamin K dependant clotting factors: II, VII, IX, X as well as the anticoagulants Protein C and S.
- For most of the last 40 years PCCs were the mainstay for the treatment of Haemophilia B
- Activated PCCs are used in the treatment of Haemophilia A patients with inhibitors.

Processing of FP/FFP

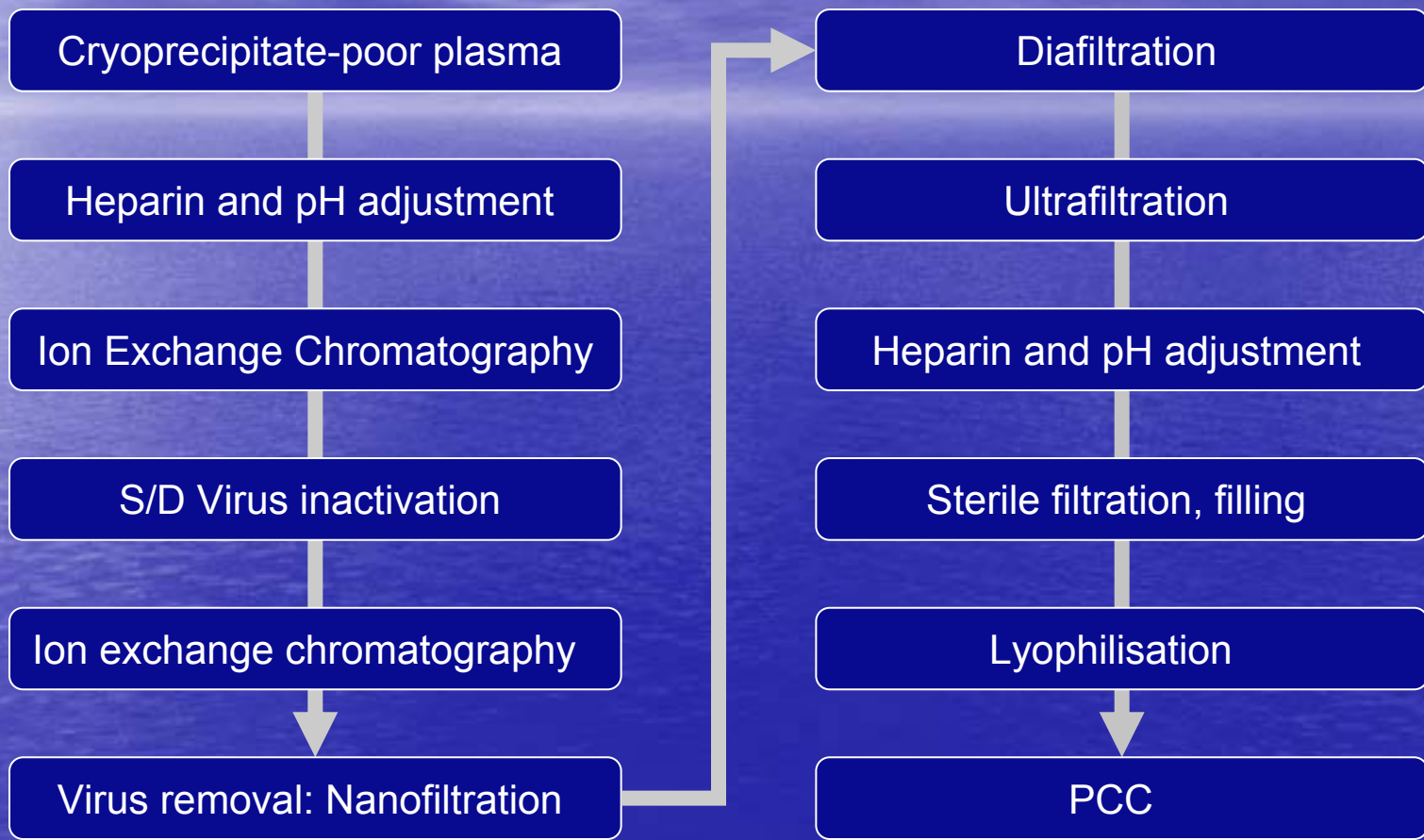


Table 3

Table 3. Studies Comparing PCCs with FFP for Anticoagulation Reversal					
Study	Study Design	Inclusion Criteria	Study Interventions	Number of Patients	Key Outcomes
Cartmill <i>et al.</i> , ⁵² 2000	Prospective for PCC group, retrospective for FFP group	Life-threatening intracranial hemorrhage necessitating urgent reversal of warfarin therapy	PCC (50 U/kg) plus vitamin K (10 mg) vs. FFP (4 units, 800 ml; 2 patients received a further 4 units) and vitamin K (10 mg intravenous)	12 (6 received PCC, 6 received FFP)	Mean preoperative INR in the PCC group was 4.86; this was reduced to 1.32 after treatment. Corresponding values in the FFP group were 5.32 and 2.30. All patients in the PCC group had posttreatment INR below the recommended value of 1.5, compared with one in the FFP group. The mean clinical correction time was 41 min in the PCC group vs. 115 min in the FFP group.
Fredriksson <i>et al.</i> , ⁵³ 1992	Retrospective analysis	Anticoagulant-related intracranial hemorrhage	PCC (mean dose 32 ml, 1,930 U) vs. FFP (mean dose 600 ml); all patients also received vitamin K (10–20 mg intravenous)	17 (10 received PCC, 7 received FFP)	The mean INR improved from 2.83 to 1.22 over a period of 4.8 h in the PCC group, compared with 2.97 to 1.74 (7.3 h) in the FFP group. The rate of improvement was 4.6 times greater after PCC than after FFP ($P < 0.001$). Symptoms and signs of intracerebral hemorrhage, measured on an eight-graded Reaction Level Scale, progressed 0.2 grades in patients given PCC vs. 1.9 grades in those given FFP ($P < 0.05$).
Makris <i>et al.</i> , ⁴⁹ 1997	Not defined	Hemorrhage relating to anticoagulation, or other requirement for urgent reversal of anticoagulation	PCC (25–50 U/kg) vs. FFP (4 units, 800 ml); all patients also received vitamin K (1–5 mg intravenous)	41 (29 received PCC, 12 received FFP)	Mean preoperative INR in the PCC group was 5.8; this was reduced to 1.3 after treatment. Corresponding values in the FFP group were 10.2 and 2.3. “Complete” INR correction (<i>i.e.</i> , < 1.5) was observed in 28 of 29 patients treated with PCC vs. none of the patients treated with FFP.
Huttner <i>et al.</i> , ²⁸ 2006	Retrospective analysis	Anticoagulant-related intracranial hemorrhage	PCC (alone or in combination with FFP or vitamin K) vs. FFP (alone or in combination with vitamin K) vs. vitamin K alone (doses of FFP and PCC adjusted according to body weight; vitamin K dose: 5–20 mg)	55 (31 received PCC, 18 received FFP, 6 received vitamin K)	The incidence and extent of hematoma growth were significantly lower in patients receiving PCC (19%/44%) compared with FFP (33%/54%) and vitamin K (50%/59%). However, the difference between PCC and FFP was not present among patients whose INR was completely reversed within 2 h of treatment.

FFP = fresh frozen plasma; INR = international normalized ratio; PCC = prothrombin complex concentrate.

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Complications

Author, year (reference)	Study design	Inclusion criteria	N. of patients	Thromboembolic events (%)
Evans, 2001 (37)	Prospective non-randomised	Major bleeding and INR > 14	10	0/10
Preston, 2002 (38)	Prospective non-randomised	Major bleeding or need for urgent reversal of anticoagulation	42	1/42 (2.4)
Lorenz, 2007 (39)	Prospective cohort	Need for urgent reversal of anticoagulation	8	0/8
Pabinger, 2008 (40)	Prospective multicentre	Emergency anticoagulation reversal	43	1/43 (2.3)
Bruce, 2008 (41)	Retrospective analysis	Severe bleeding	24	0/24
Schick, 2008 (42)	Retrospective	Major bleeding or urgent anticoagulation reversal	50	0/50
Staudinger, 1999 (43)	Prospective	Overt bleeding or planned invasive procedures in critically ill patients	16	0/16
Lorenz, 2003 (44)	Prospective multicentre	Acute bleeding or surgical/invasive procedures in patients with liver disease	22	0/22
Total			165	2/215 (0.9)

Word of Caution

- Many case reports in literature in which patients with severe Haemophilia B have developed thrombotic events.
- Blamed on the “cocktail” nature of PCCs.
- New indications are to treat patients who already have one or more prothrombotic risk factors.

PCCs today

- New recombinant FIX concentrates are available
- The use in Haemophilia B is waning
- Vitamin K antagonists

Table 2

Perioperative Hemostatic Management of Patients Treated with Vitamin K Antagonists²

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Table 2. Constituents of Commercially Available PCCs (Based on Product Labeling*)

Product (Manufacturer); International Availability	Factor Content								Antithrombotic Content				
	II		VII		IX		X		Protein C				
	Label U/ml	Ratio, %	Label U/ml	Ratio, %	Label U/ml	Ratio, %	Label U/ml	Ratio, %	C Label U/ml	S Label U/ml	Z Label U/ml	ATIII Label U/ml	Heparin Label U/ml
Beriplex P/N (CSL Behring); major western European countries	20–48	133	10–25	69	20–31	100	22–60	161	15–45	13–26	Not in label	0.2–1.5	0.4–2.0
Octaplex (Octapharma); major western European countries	11–38	98	9–24	66	25	100	18–30	96	7–31	7–32	Not in label	Not in label	Not in label
Prothromplex Total/S-TIM 4 Immuno (Baxter); Sweden, Germany, Austria	30	100	25	83	30	100	30	100	>20	Not in label	Not in label	0.75–1.5	<15
Prothromplex TIM 3 (Baxter); Italy, Austria	25	100	Not in label	—	25	100	25	100	Not in label	Not in label	Not in label	Not in label	3.75
Cofact/PPSB SD (Sanquin/CAF); Netherlands, Belgium, Austria, Germany	≥15	75	≥5	25	≥20	100	≥15	75	Not in label	Not in label	Not in label	Present, not quantified	Not in label
Kaskadil (LFB); France	40	160	25	100	25	100	40	160	Not in label	Not in label	Not in label	Not in label	Present, not quantified
Uman Complex D.J. (Kedrion); Italy	25	100	Not in label	0	25	100	20	80	Not in label	Not in label	Not in label	Present, not quantified	Present, not quantified
PPSB-human SD/Nano (Octapharma); Germany	25–55	130	7.5–20	45	24–37.5	100	25–55	130	20–50	5–25	Not in label	0.5–3	0.5–6
Profilinone (Grifols); USA	Present	≤150	Present	35	Present	100	Present	100	Not in label	Not in label	Not in label	Not in label	Not present
Bebulin (Baxter); USA	Present	—	Present (low)	—	Present	100	Present	—	Not in label	Not in label	Not in label	Not in label	0.15 U per U of factor IX
FEIBA (Baxter); USA	Present, not quantified (nonactivated)		Present, not quantified (activated)		500, 1,000, or 2,500 U per vial (nonactivated)		Present, not quantified (nonactivated)		Not in label	Not in label	Not in label	Not in label	Not present

Factor content ratios are based on the content of factor IX.

* In Europe, ranges are usually given on the product label, in accordance with the European Pharmacopoeia; single values are generally from older, national registrations.

PCC = prothrombin complex concentrate.

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Table 2. Constituents of Commercially Available PCCs (Based on Product Labeling)

Table I

Brand (Company)	Purification	Viral inactivation	Clotting factors (U/mL)				Anticoagulant proteins (U/mL)			
			II	VII	IX	X	PC	PS	AT	Heparin
Uman Complex D.I. (Kedrion)	Ion-exchange chromatography	Solvent/detergent + 100°C for 30 min	25	-	25	20	-	-	NQ	NQ
Prothromplex TIM 3 (Baxter)	Ion-exchange chromatography	Vapour heat 60°C for 10 h, 80°C for 1 h	30	-	30	30	-	-	-	0.5
Confidex (CSL Behring)	Ion-exchange chromatography	Pasteurization 60°C for 10 h + nanofiltration (75 nm-35 nm)	20- 48	10- 25	20- 31	22- 60	15- 45	13- 38	0.6	0.5

PCCs vs FFP

- Rapid reversal of INR
- Small volume
- Contains Heparin
- Pooled product and therefore exposure to hundreds of donors
- Dual viral inactivation steps (do not cover unencapsulated viruses)
- Small cost
- Paid donors (some PCCs)
- Delay in thawing
- Once thawed, limited shelf life
- Large volumes required
- ABO blood group required.
- No viral inactivation steps
- Reduced donor exposure
- TRALI
- Lower thrombotic potential
- Traceability of donors
- Most centres have experience using FFP.