

# New Advances in Transfusion

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# Objectives

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To discuss the terminology, components, transfusion risks, and dosing guidelines for plasma

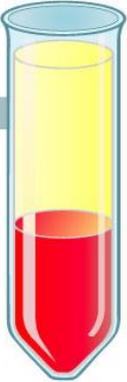
To review the common indications for plasma transfusion, including new recommendations for reversing warfarin

To examine the latest advances in plasma and platelet transfusion, including:

- New shelf-life and post-thaw storage times for solvent detergent plasma (Octaplas)
- Recent FDA approval of psoralen and UV-treated plasma and platelets (Intercept)
- New guidelines for platelet transfusion
- FDA approval of platelet additive solutions

To learn the benefits of additive solution 7, recently approved by the FDA

Plasma (55%)	
Constituent	Major functions
Water	Solvent for carrying other substances
Salts (ions) Sodium Potassium Calcium Magnesium Chloride Bicarbonate	Osmotic balance, pH buffering, and nerve and muscle function
Plasma proteins  Fibrinogen  Immunoglobulins (antibodies)	Osmotic balance and pH buffering  Clotting  Immunity
Substances transported by blood Nutrients (e.g., glucose, fatty acids, vitamins) Waste products of metabolism Respiratory gases (O <sub>2</sub> and CO <sub>2</sub> ) Hormones	



Centrifuged blood sample

# Plasma terminology

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## FFP

- Frozen at  $-18^{\circ}\text{C}$  within 6-8 hours of collection
- High levels of FV and FVIII
- Thawed at  $30-37^{\circ}\text{C}$  and transfused within 24 hours of thaw

## FP24

- Frozen at  $-18^{\circ}\text{C}$  within 24 hours of collection
- Decreased levels of FV and FVIII, but still adequate for most indications

## Thawed plasma

- FFP or FP24 thawed at  $30-37^{\circ}\text{C}$  and stored at 1 to  $6^{\circ}\text{C}$  for up to 5 days
- FVIII levels moderately decreased, but still adequate for most indications



# Plasma terminology

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## Cryopoor plasma

- FFP thawed at 1-6°C, separated by centrifugation, and remaining plasma is refrozen at -18°C within 24 hours
- Significantly decreased levels of FVIII, FXIII, fibrinogen, and VWF
- Equally effective for treatment of TTP

## Liquid plasma

- Separated from whole blood and stored at 1-6°C, never frozen
- Shelf life is 5 days after expiration of whole blood (26 or 40 days)
- Significant decline in FVIII, FV, FVII, and protein S after 15 days
- Contains viable lymphocytes (GVHD), may transmit CMV or result in alloimmunization

# Risks of plasma transfusions

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## Transfusion reactions

- Allergic
- Transfusion associated circulatory overload (TACO)
- Transfusion related acute lung injury (TRALI)

## Infections

- Window period for screened infections
- Unscreened and emerging infections
  - Chikungunya, denge, ebola

# Group A plasma for emergency release

Group AB is universal donor plasma

Due to shortages of AB plasma, some hospitals have switched to group A plasma for emergency release when blood type is unknown

Some hospitals check anti-B titers first, but no known “safe” threshold

Currently no adverse events reported in the small number of patients who have received incompatible group A plasma

Plasma								
Patient Blood Type	Can Receive ✓							
	O+	O-	A+	A-	B+	B-	AB+	AB-
O+	✓	✓	✓	✓	✓	✓	✓	✓
O-	✓	✓	✓	✓	✓	✓	✓	✓
A+			✓	✓			✓	✓
A-			✓	✓			✓	✓
B+					✓	✓	✓	✓
B-					✓	✓	✓	✓
AB+							✓	✓
AB-							✓	✓

[http://www.mc.vanderbilt.edu/documents/vmcpathology/files/TRUTH%20TABLE%20CARDS\(1\).pdf](http://www.mc.vanderbilt.edu/documents/vmcpathology/files/TRUTH%20TABLE%20CARDS(1).pdf)

# Plasma dosing

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Plasma donor units vary from 150 to 300mL, and are then diluted by anticoagulant

The potency of each coagulation factor per mL may vary 50% to 150% of a pooled standard control

- FVIII and VWF levels in blood group O donors average 30% less

FVIII and FV levels decrease rapidly during processing and storage

Standardized dosing is limited by variation in volume and potency between units, many use 10-20 mL/kg as an estimate, which will be expected to increase coagulation factors by 20-30%

# Indications for plasma transfusions

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1. Coagulation factor replacement in patients with a deficiency of multiple clotting factors
  - Decreased production (liver disease) IF actively bleeding or planned procedure
  - Consumption (DIC)
  - Dilution (massive blood loss, repeated plasma exchange procedures)
2. Replacement of a single coagulation factor when factor concentrates are not available
3. Replacement fluid during therapeutic plasma exchange for thrombotic thrombocytopenic purpura (TTP)

# Plasma transfusion guidelines

**Table 1**  
**Fresh Frozen Plasma Transfusion Guidelines**

Author	Year	Laboratory Criteria	Dose (mL/kg)
National Institutes of Health <sup>1</sup>	1985	None given	None given
Hong Kong Government Blood Banking Advisory Committee <sup>2</sup>	1990	PT/INR >1.5 times normal	10-15
British Committee for Standards in Haematology <sup>3</sup>	1992	PT/PTT >1.5 times normal; PT >1.8 times normal with liver disease	12-15
Committee Report <sup>4</sup>	1994	PT/PTT >1.5 times normal	15
College of American Pathologists <sup>5</sup>	1994	PT >1.5 times midpoint of normal; PTT >1.5 times upper normal; factor level <25%	2 U (6-7 mL/kg)
American Society of Anesthesiologists <sup>6</sup>	1994	PT/INR >1.5 times normal; factor level <30%	10-15
American College of Obstetrics and Gynecology <sup>7</sup>	1994	PT/PTT >1.5 times normal	2 U (6-7 mL/kg)
Canadian Medical Association Expert Working Group <sup>8</sup>	1997	Significantly increased coagulation time; PT >2.0 with liver disease	10-15
Japanese Ministry of Health and Welfare <sup>9</sup>	1999	PT/PTT >1.5 times normal; factor level <30%	8-12
North Ireland Clinical Resources Efficiency Support Team <sup>10</sup>	2001	PT/PTT >1.5 times normal	12-15
Australia National Health and Medical Research Council <sup>11</sup>	2001	Abnormal coagulation	5-20
American Red Cross <sup>12</sup>	2002	PT/PTT >1.5 times normal	None given
South African National Blood Service <sup>13</sup>	2003	Disturbed coagulation	15-20
British Committee for Standards in Haematology <sup>14</sup>	2004	Multiple factor deficiencies	10-15
New York State Council on Human Blood and Transfusion Services <sup>15</sup>	2004	PT/PTT >1.5 times normal	10-20

INR, international normalized ratio; PT, prothrombin time; PTT, partial thromboplastin time.

# When NOT to transfuse plasma

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Hypovolemia

Plasma exchange (exception: TTP)

Wound healing/Burns

Immunodeficiency states

Non-bleeding patients with liver disease and prolonged INR

Non-bleeding ICU patients with coagulopathy prior to invasive procedure



# Warfarin reversal

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If patient is not actively bleeding and does not require an urgent surgical procedure, treat with vitamin K

If patient is actively bleeding or requires urgent reversal of a surgical procedure, treat with prothrombin complex concentrates (PCC)

- If PCC is not available, treat with plasma transfusion



<http://www.kcentra.com/>

Transfusion. 2015;55(1).  
Medical Letter. 2013;55(1420).

# Updates on plasma and platelet transfusion

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# Solvent detergent-treated plasma (Octaplas)

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New shelf life and post-thaw storage times

# Solvent detergent-treated plasma

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Multiple manufacturers with different processes

Pooled units (100-2500) treated with a solvent and detergent, processed to remove the solvent and detergent, concentrated, and stored frozen

Causes physical disruption of the membrane of enveloped viruses and bacteria

One product, PLAS+SD, had lower levels of citrate, protein S, and antitrypsin activity compared to other products and was withdrawn from the market due to an increased association with venous thrombosis

# S/D plasma (Octaplas)

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First marketed in US in 1992, current version marketed in 2009.

FDA approved in January 2013 for replacement of multiple coagulation factors in patients with acquired deficiencies due to liver disease, cardiac surgery, or liver transplantation

Each lot is tested for coagulation factor levels and is only released if levels meet thresholds



<http://www.medicalpress.es/wp-content/uploads/2013/01/Octaplas.jpg>

Transfusion. 2012;52(s1).

# S/D plasma (Octaplas)

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## Advantages

- Numerous studies show that it is safe and effective in treating patients with coagulation factor deficiencies and TTP
- S/D process destroys most enveloped viruses (HIV, Hepatitis C, West Nile), bacteria, protozoa, and cellular fragments
- Reduced risk of allergic reactions due to dilution of individual antibodies and allergens
- No reported cases of TRALI
- Competitive pricing (~\$58/unit mean cost of plasma in 2011; ~\$95/unit cost for Octaplas in 2015)

Transfusion. 2012;52(s1).  
2011 National Blood Collection  
and Utilization Survey.

# S/D plasma (Octaplas)

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## Disadvantages

- Does not destroy non-enveloped viruses (parvovirus B19 and hepatitis A, donors are pre-screened)
- Loss of FV, FVIII,  $\alpha$ 1-antitrypsin, and  $\alpha$ 2-antiplasmin; can't be used for treating factor VIII deficiency
- Can not be used for cellular products

## Octapharma USA, Inc.: FDA Approves Octaplas License Supplement, Increasing Post Thaw Permitted Storage Time

3/9/2015 10:27:43 AM

HOBOKEN, N.J.--(BUSINESS WIRE)--Octapharma USA today announced the U.S. Food and Drug Administration (FDA) has approved revised product labeling for Octaplas™ [Pooled Plasma (Human), Solvent/Detergent Treated Solution for Intravenous Infusion], which provides a significant increase in available time span between product thawing and patient administration of the biological therapy.<sup>1, 2</sup>

“Octaplas™ features a multi-step manufacturing process expressly designed to minimize pathogen transmission and reduce the risk of adverse events such as transfusion related acute lung injury (TRALI), and allergic reactions.”

The newly approved product label indicates thawed Octaplas™ can now be used within 24 hours if refrigerated (between 1°C and 6°C/33.8°F to 42.8°F) or within 8 hours if stored at room temperature (between 20°C and 25°C/68°F to 77°F). Previous product information had directed that thawed product should be used within 12 hours if stored between 2°C and 4°C (35.6°F to 39.2°F) or within three hours if stored between 20°C and 25°C (68°F to 77°F).<sup>1, 2</sup>

In January 2013, Octapharma USA, a subsidiary of global human protein products manufacturer Octapharma AG, received approval for Octaplas™, the only FDA-licensed pooled, solvent/detergent (S/D) treated plasma for transfusion. The FDA classifies the therapy as a biologic and, therefore, tests every product batch to ensure quality and consistency measures are met before released for sale.<sup>1-4</sup>

The new labeling also significantly increases the product's shelf life. Octaplas™ can be stored frozen, =-18°C (-0.4°F), for three years from the date of manufacture as opposed to the earlier labeling of two years. Octaplas™ is made from plasma frozen within eight hours of collection in order to preserve labile coagulation factors.<sup>1, 2</sup>

# Octaplas: Summary

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Octaplas now has extended frozen and thawed shelf-life, potentially increasing the flexibility of use for this pathogen reduced plasma product

# Psoralen and UV light-treated plasma and platelets (Intercept)

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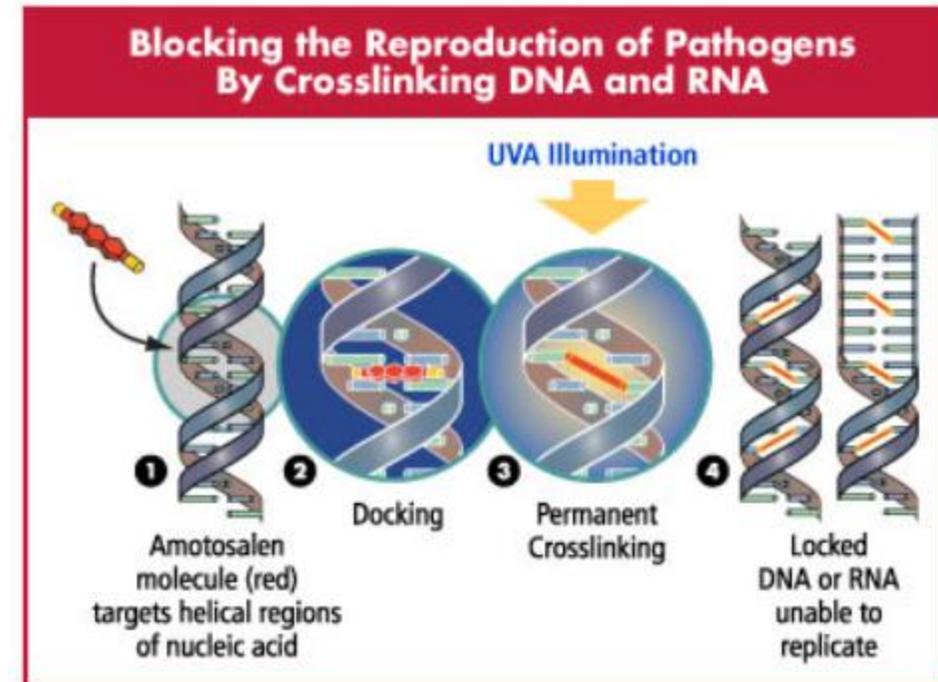
Recent FDA approval for use in reducing transfusion transmitted infections (TTI)

# Psoralen and UV light-treated plasma and platelets (Intercept)

Pooled units (2-3 or 1 jumbo apheresis unit) are treated with amotosalen and UVA light, filtered to remove the amotosalen and breakdown products, and frozen in 200 mL aliquots within 8 hours of collection.

Psoralens cross cell membranes and intercalate DNA and RNA, UVA light causes crosslinking which prevents replication/division

Red blood cells, platelets, and plasma don't have DNA or RNA



<http://interceptbloodsystem.com/product-overview/amotosalen-mechanism-of-action>

PRESS RELEASE

# FDA Approves INTERCEPT Blood System for Plasma

By

Published: Dec 16, 2014 5:31 p.m. ET



*Cerus' Blood Safety Technology is Indicated to Reduce the Risk of Transfusion-Transmitted Infections from Plasma Components*

CONCORD, Calif., Dec 16, 2014 (BUSINESS WIRE) -- Cerus Corporation **CERS, -2.19%** today announced that the U.S. Food and Drug Administration (FDA) has approved the INTERCEPT Blood System for plasma. The INTERCEPT plasma system is approved for ex vivo preparation of plasma in order to reduce the risk of transfusion-transmitted infection (TTI) when treating patients requiring therapeutic plasma transfusion.

The INTERCEPT Blood System inactivates a broad spectrum of enveloped viruses, non-enveloped viruses, Gram-positive and Gram-negative bacteria, spirochetes and parasites.

# FDA approves pathogen reduction system to treat platelets

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**For Immediate  
Release**

December 19, 2014

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## **Release**

The U.S. Food and Drug Administration yesterday approved the Intercept Blood System for platelets, the first pathogen reduction system to treat single donor apheresis platelets. The system is for use by blood establishments that collect and manufacture blood and blood components to prepare pathogen reduced platelets for transfusion to reduce the risk of transfusion-transmitted infections.

On Dec. 16, the FDA also approved the Intercept Blood System for the preparation of plasma to reduce the risk of transfusion-transmitted infections.

The Intercept System for platelets has been shown to reduce the number of a broad range of viruses, bacteria and other pathogens that may contaminate platelets. Examples of some of the pathogens that may be reduced using the Intercept Blood System include HIV, hepatitis B and C viruses, West Nile virus and gram-negative and gram-positive bacteria. The Intercept process also reduces the number of T cells (a type of white blood cell) to a level that lowers the risk of transfusion-associated graft-versus-host disease (TA-GvHD). TA-GvHD is a rare, but often fatal, complication of blood transfusion in which the donor's T cells attack the recipient's tissues.

# Intercept

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## Advantages

- Effective for both plasma and platelets
- Over 2 million components produced, with no cases of TTBI or TAGVHD
- No carcinogenic or toxic effects have been found in safety studies
- Inactivates many enveloped and nonenveloped viruses, bacteria, and protozoa
  - In Europe, has replaced CMV testing and has allowed platelet shelf life to be extended to 7 days in some countries
  - Would satisfy AABB requirement 5.1.5.1 as an alternate to bacterial detection
- Inactivates white blood cells
  - In Europe, has replaced gamma irradiation
- Levels of FV, FVII, FVIII and FX are reduced by only 13-33%, and antithrombotic factors are preserved (much of the factor loss is attributed to volume loss from removing the psoralen)

# Intercept

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## Disadvantages

- Hepatitis A virus, spore-forming bacteria, and prions are resistant to treatment
- Adverse reaction rate similar to conventional plasma
- Not effective for PRBCs, because the density of the unit inhibits UVA penetration
- Cost???

# Cost

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## Cost of Intercept unknown at this time

- Cost of current infectious disease screening (~\$44/donation), bacterial culture for platelet units, and irradiation may potentially be eliminated
- Additional donors may potentially become eligible (ex: recent travel to malaria endemic area)
- Platelet storage period may potentially be expanded to 7 days

# Intercept: Summary

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Intercept has been FDA approved for plasma and platelets. The psoralen and UV light treatment eliminates white blood cells and infectious elements, which may reduce or eliminate the need for certain infectious disease testing or irradiation.

# Platelet transfusion guidelines

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New platelet transfusion guidelines from AABB

# Adverse reactions from platelets

**Table 1.** Approximate Per-Unit Risks for Platelet Transfusion in the United States

<b>Adverse Event</b>	<b>Approximate Risk per Platelet Transfusion</b>	<b>Reference</b>
Febrile reaction	1/14	6
Allergic reaction	1/50	7
Bacterial sepsis	1/75 000	8
TRALI*	1/138 000	9
HBV infection	1/2 652 580	Personal communication†
HCV infection	1/3 315 729	Personal communication†
HIV infection	0 (95% CI, 0 to 1/1 461 888)	Personal communication†

HBV = hepatitis B virus; HCV = hepatitis C virus; TRALI = transfusion-related acute lung injury.

\* The overall risk for TRALI from all plasma-containing blood products is currently estimated to be approximately 1/10 000 (10).

† Notari E, Dodd R, Stramer S.

# AABB Recommendations

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## **Clinical Setting 1: Hospitalized Adult Patients With Therapy-Induced Hypoproliferative Thrombocytopenia**

### ***Recommendations***

Recommendation 1: The AABB recommends that platelets should be transfused prophylactically to reduce the risk for spontaneous bleeding in adult patients with therapy-induced hypoproliferative thrombocytopenia.

The AABB recommends transfusing hospitalized adult patients with a platelet count of  $10 \times 10^9$  cells/L or less to reduce the risk for spontaneous bleeding.

The AABB recommends transfusing up to a single apheresis unit or equivalent. Greater doses are not more effective, and lower doses equal to one half of a standard apheresis unit are equally effective.

Quality of evidence: moderate; strength of recommendation: strong.

# AABB Recommendations

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## **Clinical Setting 2: Adult Patients Having Minor Invasive Procedures**

### ***Recommendations***

Recommendation 2: The AABB suggests prophylactic platelet transfusion for patients having elective central venous catheter placement with a platelet count less than  $20 \times 10^9$  cells/L.

Quality of evidence: low; strength of recommendation: weak.

Recommendation 3: The AABB suggests prophylactic platelet transfusion for patients having elective diagnostic lumbar puncture with a platelet count less than  $50 \times 10^9$  cells/L.

Quality of evidence: very low; strength of recommendation: weak.

# AABB Recommendations

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## **Clinical Setting 3: Adult Patients Having Major Elective Nonneuraxial Surgery**

### ***Recommendations***

Recommendation 4: The AABB suggests prophylactic platelet transfusion for patients having major elective nonneuraxial surgery with a platelet count less than  $50 \times 10^9$  cells/L.

Quality of evidence: very low; strength of recommendation: weak.

Recommendation 5: The AABB recommends against routine prophylactic platelet transfusion for patients who are nonthrombocytopenic and have cardiac surgery with cardiopulmonary bypass (CPB). The AABB suggests platelet transfusion for patients having CPB who exhibit perioperative bleeding with thrombocytopenia and/or with evidence of platelet dysfunction.

Quality of evidence: very low; strength of recommendation: weak.

# AABB Recommendations

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## **Clinical Setting 4: Adult Patients Receiving Antiplatelet Therapy Who Have Intracranial Hemorrhage (Traumatic or Spontaneous)**

### ***Recommendations***

Recommendation 6: The AABB cannot recommend for or against platelet transfusion for patients receiving antiplatelet therapy who have intracranial hemorrhage (traumatic or spontaneous).

Quality of evidence: very low; strength of recommendation: uncertain.

# AABB platelet transfusion guidelines: Summary

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The new guidelines are in line with most existing guidelines, with the exception of a lower recommended platelet count of 20,000/ $\mu$ L prior to central venous catheter insertion, and the emphasis that a single unit is equivalent to greater doses or half-units when transfusing chemotherapy patients with platelet counts below 10,000/ $\mu$ L.

# Platelet additive solutions

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FDA recently approved the use of apheresis platelets stored in platelet additive solution comprising a mixture of 35% plasma/65% PAS

# Platelet additive solutions

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Apheresis platelets are currently stored in anticoagulated plasma

Platelet additive solution is a saline based nutrient media that replaces a portion of the plasma

## Advantages

- Reduced allergic transfusion reactions by 46%
  - Cost saving for hospitals if additional charge is less than \$9.14
- No significant reduction in corrected count increment at 12-24 hours post-transfusion
  - Equivalent to concentrated apheresis platelets and superior to washed apheresis platelets
- Possible reduction in TRALI, bacterial contamination, and hemolytic reactions
- Residual plasma may potentially be used for manufacturing or transfusable product

# Platelet additive solutions

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## Disadvantages

- May not want to use for trauma or patients with low levels of coagulation factors
- Less effective at reducing allergic transfusion reactions than concentrating or washing
  - Concentrating platelets reduces ATRs by 73% and washing platelets reduces ATRs by 95%

# Platelet additive solutions: Summary

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Platelet additive solutions reduce allergic transfusion reactions with minimal effect on count increment

# Additive solution 7

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Recent FDA approval of AS-7 for RBC storage

# AS-7

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AS-7 (SOLX) is a new alkaline RBC storage solution that contains additional bicarbonate and phosphate compared to currently licensed additive solutions

Designed to improve RBC metabolism by increasing the range and capacity of pH buffering.

First new AS approved in the US in 25 years

# AS-7 vs AS-1: RBCs

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## FDA standards

- Mean 24-hour post transfusion in vivo red cell recovery at end of storage of at least 75%
- Hemolysis less than 1.0%

	AS-1 (42 days)	AS-7 (42 days)	AS-7 (56 days)
Hemolysis	0.39 +/- 0.21%	0.29 +/- 0.11%	0.42 +/- 0.17%
24 hour RBC recovery	82 +/- 7%* 76 +/- 5%*	88 +/- 5%	82 +/- 3%
Half-life survival	28-35 days*	33 +/- 10 days	31 +/- 9 days

# AS-7: Overnight hold

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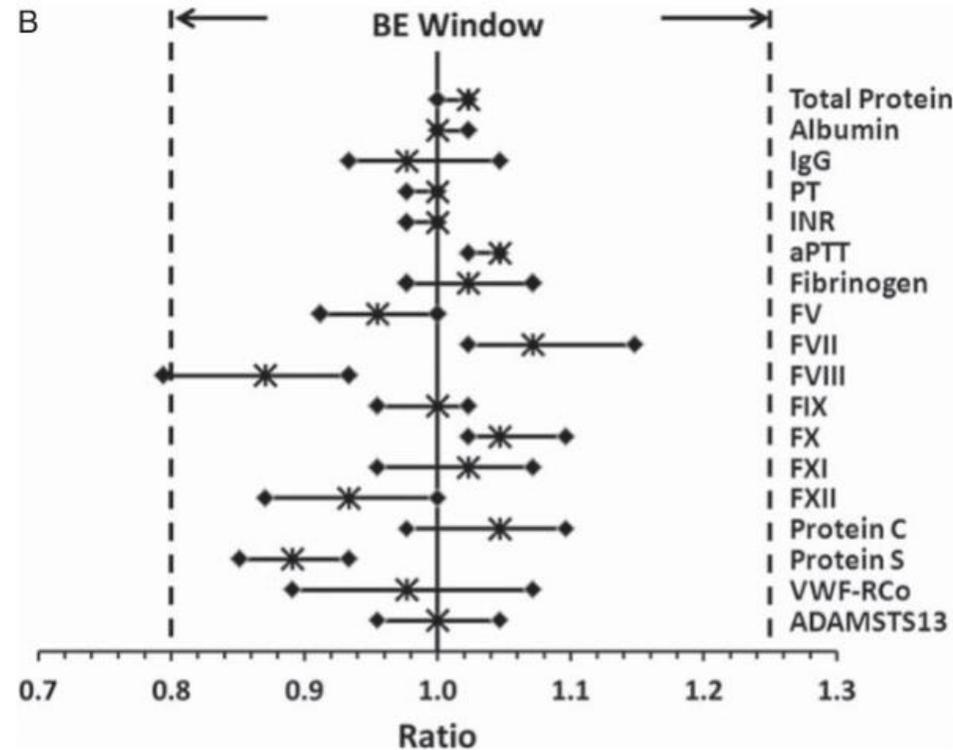
Whole blood was held at room temperature for 18 hours, then RBCs were processed in AS-7 within 24 hours of collection

AS-7 units	ONH, 42 day storage	ONH, 56 day storage	8 hour processing, 56 day storage
Hemolysis < 1.0%	60/60 units	58/60 units	Not reported
24 hour recovery >75%	27/27 subjects	21/28 subjects	13/13 subjects

Overnight storage of whole blood at room temperature before processing met current regulatory requirements for red cells after 42 day storage

# Overnight hold for AS-7: Plasma

Plasma separated after 20 hour room temperature whole blood storage was bioequivalent to plasma prepared and frozen within 8 hours of collection, with the exception of factor VIII activity



# AS-7: Summary

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AS-7 allows for increased RBC shelf life up to 56 days

AS-7 RBCs stored for 42 days meet FDA requirements when processed after overnight hold of whole blood

Overnight hold plasma is bioequivalent to FFP after 12 months, with the exception of a slight decrease in factor VIII which is expected to be of “minimal significance”

This may potentially lead to extended shelf life for RBCs, increased flexibility in whole blood transport and processing, and increased collection of plasma and platelets from whole blood donors

# Questions?

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